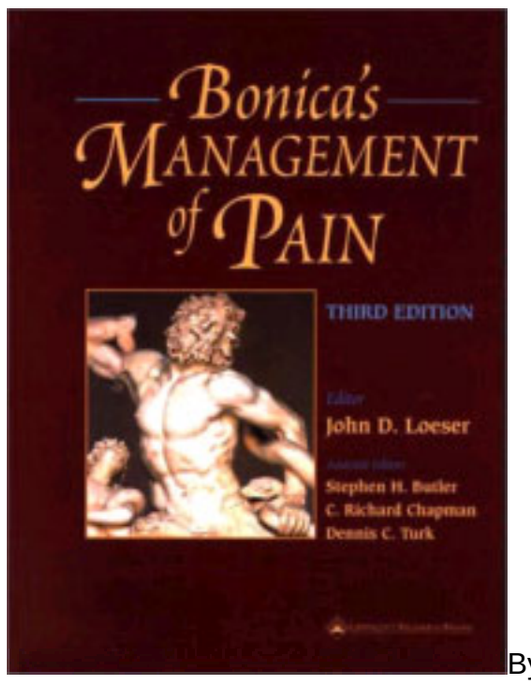
Bonica's Management of Pain 3rd edition (January 15, 2001): By John D. Loeser (Editor), Steven H. Butler (Editor), C. Richard Chapman (Editor), PhD Dennis C. Turk (Editor) By Lippincott Williams & Wilkins Publishers



By OkDoKeY

Bonica's Management of Pain

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PART IV

Regional Pains

PART V

Methods for Symptomatic Control

Editor

John D. Loeser, M.D.
Professor of Neurological Surgery and Anesthesiology
Former Director, Multidisciplinary Pain Center
University of Washington School of Medicine
Seattle, Washington

Associate Editors

Stephen H. Butler, M.D.
Associate Professor of Anesthesiology
Acting Director, Multidisciplinary Pain Center
University of Washington School of Medicine
Seattle, Washington

C. Richard Chapman, Ph.D.
Professor of Anesthesiology,
Psychology, Psychiatry, and Behavioral Sciences
University of Washington School of Medicine
Member, Fred Hutchinson Cancer Research Center
Seattle, Washington

Dennis C. Turk, Ph.D.
John and Emma Bonica Professor of Anesthesiology and Pain Research
University of Washington School of Medicine
Seattle, Washington
Adjunct Professor of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Illustrator

Marjorie Domenowske

132 Contributing Authors

This book is dedicated to the memory of John J. and Emma L. Bonica. John was the inspiration and guiding force behind the pain movement that began with the first edition of this book; Emma made his contributions possible. We miss them both, but the momentum they created is rapidly accelerating, and the memories of their goodness will be with all who study pain and its management.

John D. Loeser, M.D.

Contributing Authors

Roger J. Allen, Ph.D., P.T.
Multidisciplinary Pain Center
University of Washington Medical Center
Seattle, Washington
Chapter 20, Complex Regional Pain Syndromes?Type I: Reflex Sympathetic Dystrophy, and Type II: Causalgia

Edward E. Almquist, M.D.
Clinical Professor of Orthopaedics
Department of Orthopaedics
University of Washington School of Medicine
Seattle, Washington
Chapter 59, Painful Conditions of the Forearm, Wrist, and Hand

Kenneth M. Alo¢, M.D.
Pain and Health Management Center, PA
Houston, Texas
Chapter 73, Pelvic and Perineal Pain of Urologic Origin

Gunnar B. J. Andersson, M.D., Ph.D.
Professor and Department Chairman
Department of Orthopedic Surgery
Rush-Presbyterian-St. Luke's Medical Center
Chicago, Illinois
Chapter 76B, Low Back Pain: Role of Surgery in the Treatment of Low Back Pain and Sciatica

John G. Arena, Ph.D.
Professor of Psychiatry and Health Behavior
Medical College of Georgia
Director, Pain Evaluation and Intervention Program
Department of Veterans Affairs Medical Center
Augusta, Georgia
Chapter 90, Biofeedback Therapy for Chronic Pain Disorders

Michael A. Ashburn, M.D.
Professor of Anesthesiology
Director, Pain Management Center
University of Utah Health Sciences Center
Salt Lake City, Utah
Chapter 41, Postoperative Pain

Misha-Miroslav Backonja, M.D.
Associate Professor of Neurology and Anesthesiology
University of Wisconsin Center for Health Sciences
Madison, Wisconsin
Chapter 19, Painful Neuropathies

Joseph Barber, Ph.D.
Clinical Professor of Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 91, Hypnosis

Alexander B. Baxter, M.D.
Department of Radiology
University of Washington School of Medicine
Seattle, Washington
Chapter 14, Imaging Pain Patients

Charles B. Berde, M.D., Ph.D.
Professor of Anaesthesia and Pediatrics
Harvard Medical School
Director, Pain Treatment Service
Senior Associate in Anesthesia
Children's Hospital, Boston
Boston, Massachusetts
Chapter 44, Pain and Its Management in Children

Stanley J. Bigos, M.D.
Professor of Orthopedic Surgery and Environmental Health
University of Washington Schools of Medicine and Public Health
Seattle, Washington
Chapter 76A, Low Back Pain: Primary Care Approach to Acute and Chronic Back Problems: Definitions and Care

Edward B. Blanchard, Ph.D.
Distinguished Professor of Psychology
State University of New York at Albany
Albany, New York
Chapter 90, Biofeedback Therapy for Chronic Pain Disorders

Andrew R. Block, Ph.D.
Department of Psychiatry
Division of Psychology
University of Texas Southwestern Medical Center at Dallas
Dallas, Texas
Director, The WellBeing Group
Plano, Texas
Chapter 76D, Low Back Pain: Psychological Screening of Spine Surgery Candidates: Risk Factors for Poor Outcome

John J. Bonica, M.D., D.Sc., D.Med.Sc. (Hon.), F.F.A.R.C.S. (Hon.) (Deceased)
Professor and Chairman Emeritus, Department of Anesthesiology
Director Emeritus, Multidisciplinary Pain Center
University of Washington School of Medicine
Seattle, Washington
Founder and Honorary President, International Association for the Study of Pain
Chapter 1, History of Pain Concepts and Therapies; Chapter 3, Peripheral Pain Mechanisms and Nociceptor Plasticity; Chapter 4, Spinal Mechanisms and Their Modulation; Chapter 5, Supraspinal Mechanisms of Pain and Nociception; Chapter 8, Applied Anatomy Relevant to Pain; Chapter 9, General Considerations of Acute Pain; Chapter 29, Myofascial Pain Syndromes; Chapter 46, General Considerations of Pain in the Head; Chapter 49, Facial and Head Pain Caused by Myofascial and Temporomandibular Disorders; Chapter 54, General Considerations of Pain in the Neck and Upper Limb; Chapter 60, General Considerations of Pain in the Chest; Chapter 65, General Considerations of Abdominal Pain; Chapter 67, Painful Diseases of the Liver, Biliary System, and Pancreas; Part V: Methods for Symptomatic Control, Section E Implanted Electrical Stimulators, Introduction

William Breitbart, M.D.
Professor of Psychiatry
Weill Medical College of Cornell University
Chief, Psychiatry Service
Department of Psychiatry and Behavioral Sciences
Attending Psychiatrist
Pain and Palliative Care Service
Department of Neurology
Memorial Sloan-Kettering Cancer Center
New York, New York
Chapter 39, Pain in Human Immunodeficiency Virus Disease

Eduardo Bruera, M.D.
Palliative Care Program
Grey Nuns Community Health Centre
Edmonton, Alberta
Chapter 40, Palliative Care

F. Peter Buckley, M.B., F.R.C.A.
Associate Professor of Anesthesiology
Department of Anesthesiology
University of Washington School of Medicine
Seattle, Washington
Chapter 102, Regional Anesthesia with Local Anesthetics

Kim J. Burchiel, M.D.
John Raaf Professor and Chairman, Department of Neurological Surgery
Oregon Health Sciences University
Portland, Oregon
Chapter 107, Surgical Treatment of Trigeminal Neuralgia

Jeffrey A. Burgess, D.D.S., M.S.D.
Clinical Associate Professor of Oral Medicine
University of Washington School of Dentistry
Seattle, Washington
Chapter 49, Facial and Head Pain Caused by Myofascial and Temporomandibular Disorders; Chapter 50, Pain of Dental and Intraoral Origin

Stephen H. Butler, M.D.
Associate Professor of Anesthesiology
Acting Director, Multidisciplinary Pain Center
University of Washington School of Medicine
Seattle, Washington
Chapter 97, Acupuncture; Chapter 104, Neurolytic Blockade and Hypophysectomy

Margaret R. Byers, Ph.D.
Research Professor, Department of Anesthesiology
University of Washington School of Medicine
Seattle, Washington
Chapter 3, Peripheral Pain Mechanisms and Nociceptor Plasticity; Chapter 50, Pain of Dental and Intraoral Origin

René Cailliet, M.D.
Professor Emeritus, Department of Physical Medicine and Rehabilitation
University of Southern California School of Medicine
Professor of Medicine
Section of Physical Medicine and Rehabilitation
University of California, Los Angeles, UCLA School of Medicine
Los Angeles, California
Chapter 54, General Considerations of Pain in the Neck and Upper Limb

James N. Campbell, M.D.
Professor of Neurosurgery
Johns Hopkins University School of Medicine
Baltimore, Maryland
Chapter 105, Lesions of Primary Afferents and Sympathetic Efferents as Treatments for Pain

Charles Chabal, M.D.
Associate Professor of Anesthesiology
University of Washington School of Medicine
Veterans Affairs Puget Sound Healthcare System
Seattle, Washington
Chapter 98, Transcutaneous Electrical Nerve Stimulation

C. Richard Chapman, Ph.D.
Professor of Anesthesiology, Psychology, Psychiatry, and Behavioral Sciences
University of Washington School of Medicine
Member, Fred Hutchinson Cancer Research Center
Seattle, Washington
Chapter 6, Psychological Aspects of Pain; Chapter 15, Measurement of Pain; Part III: Generalized Pain Syndromes, Section B Psychological Contributions to Pain,

Introduction; Chapter 24, The Psychophysiology of Pain; Chapter 35, Cancer Pain: Assessment and Diagnosis; Part V: Methods for Symptomatic Control, Section C Psychological Techniques, Introduction; Chapter 97, Acupuncture; Chapter 110, Building the Future

J. Edmond Charlton, M.B., B.S.
Department of Anaesthesia
Pain Management Services
Royal Victoria Infirmary
Newcastle upon Tyne, United Kingdom
Chapter 104, Neurolytic Blockade and Hypophysectomy

Eric H. Chudler, Ph.D.
Research Associate Professor,
Department of Anesthesiology
University of Washington School of Medicine
Seattle, Washington
Chapter 5, Supraspinal Mechanisms of Pain and Nociception

John M. Clark, M.D., Ph.D.
Associate Professor of Orthopaedics
University of Washington School of Medicine
Seattle, Washington
Chapter 78, Pain in the Hip

David R. Clawson, M.D.
Clinical Assistant Professor of Physical Medicine and Rehabilitation
University of Washington School of Medicine
Harborview Medical Center
Seattle, Washington
Chapter 31, Treatment of Acute Musculoskeletal Pain

Barbara A. Coda, M.D.
Associate Professor of Anesthesiology
University of Washington School of Medicine
Assistant Member?Clinical Division
Fred Hutchinson Cancer Research Center
Seattle, Washington
Chapter 9, General Considerations of Acute Pain

Craig V. Comiter, M.D.
Department of Urology
University of California, Los Angeles, UCLA School of Medicine
Los Angeles, California
Chapter 68, Painful Diseases of the Kidney and Ureter

Marshall A. Corson, M.D.
Associate Professor of Medicine
University of Washington School of Medicine
Cardiology Section Chief
Harborview Medical Center
Seattle, Washington
Chapter 61, Cardiac and Aortic Pain

Joseph M. Czerniecki, M.D.
Associate Professor of Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 75, General Considerations of Pain in the Low Back, Hips, and Lower Extremities

E. Patchen Dellinger, M.D.
Professor and Vice Chairman, Department of Surgery
University of Washington School of Medicine
Chief, Division of General Surgery
University of Washington Medical Center
Seattle, Washington
Chapter 69, Abdominal Pain Caused by Other Diseases

Richard A. Deyo, M.D., M.P.H.
Professor of Medicine and Health Services
University of Washington School of Medicine
Seattle, Washington
Chapter 82, Clinical Trials

Todd G. Dray, M.D.
Department of Otolaryngology, Head and Neck Surgery
Permanente Medical Group
Santa Clara, California
Chapter 52, Pain in the Ear, Midface, and Aerodigestive Tract

Samuel F. Dworkin, D.D.S., Ph.D.
Professor Emeritus, Department of Oral Medicine
University of Washington School of Dentistry
Professor Emeritus, Department of Psychiatry and Behavioral Sciences
University of Washington School of Medicine
Washington Dental Foundation Distinguished Professor of Dentistry
Seattle, Washington
Chapter 49, Facial and Head Pain Caused by Myofascial and Temporomandibular Disorders

W. Thomas Edwards, M.D., Ph.D.
Associate Professor of Anesthesiology
University of Washington School of Medicine
Director, Pain Relief Service
Harborview Medical Center

Seattle, Washington
Chapter 43, Posttrauma Pain

Mark L. Elliott, Ph.D.
Ohio State Pain Control Center
Ohio State University College of Medicine and Public Health
Columbus, Ohio
Chapter 72, Gynecologic Pain Syndromes

Joel B. Epstein, D.M.D., M.S.D., F.R.C.D.(C)
Professor and Head, Division of Hospital Dentistry
Faculty of Dentistry
University of British Columbia
Medical/Dental Staff
British Columbia Cancer Agency
Head, Department of Dentistry
Vancouver Hospital and Health Sciences Centre
Vancouver, British Columbia
Research Associate Professor, Department of Oral Medicine
University of Washington School of Dentistry
Seattle, Washington
Chapter 38, Oral Mucositis in Cancer Patients

Miklavz Erjavec, M.D., F.R.C.P.C.
Acting Assistant Professor of Anesthesiology
University of Washington School of Medicine
Seattle, Washington
Chapter 76E, Low Back Pain: Epidural Steroids for Low Back Pain

Dermot R. Fitzgibbon, M.B, B.Ch.
Assistant Professor of Anesthesiology
Adjunct Assistant Professor of Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 35, Cancer Pain: Assessment and Diagnosis; Chapter 36, Cancer Pain: Management

Wilbert E. Fordyce, Ph.D.
Professor Emeritus, Department of Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 25, Learned Pain: Pain as Behavior; Chapter 88, Operant or Contingency Therapies

Bradley S. Galer, M.D.
Associate Professor of Neurology
Albert Einstein College of Medicine
Department of Pain Medicine and Palliative Care
Beth Israel Medical Center
New York, New York
Chapter 20, Complex Regional Pain Syndromes?Type I: Reflex Sympathetic Dystrophy, and Type II: Causalgia; Chapter 87, Topical Medications

Jason E. Garber, M.D.
Neurosurgical Resident
Baylor College of Medicine
Houston, Texas
Chapter 106, Neurosurgical Operations on the Spinal Cord

Gregory C. Gardner, M.D.
Associate Professor, Division of Rheumatology
Adjunct Associate Professor of Orthopaedic Surgery and Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 27, Arthritis and Periarthritic Disorders

Jonathan R. Gavrin, M.D.
Associate Professor of Anesthesiology
Adjunct Associate Professor of Medicine
University of Washington School of Medicine
Harborview Medical Center
Seattle, Washington
Chapter 64, Chest Pain from Other Disorders Including Cancer

Saadi Ghatan, M.D.
Acting Instructor, Department of Neurological Surgery
University of Washington School of Medicine
Seattle, Washington
Chapter 55, Neck Pain

Bruce C. Gilliland, M.D.
Professor of Medicine and Laboratory Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 27, Arthritis and Periarthritic Disorders

Ian H. Gilron, M.D., M.Sc., F.R.C.P.(C)
Associate Medical Director, Pain Research Clinic
Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research
National Institutes of Health
Bethesda, Maryland
Chapter 85, Antidepressants, Muscle Relaxants, and N-*Methyl-D-Aspartate Receptor Antagonists*

Kenneth R. Goldschneider, M.D.
Department of Anesthesia

Division of Pain Management
Children's Hospital Medical Center
Cincinnati, Ohio
Chapter 44, Pain and Its Management in Children

Barry Goldstein, M.D., Ph.D.
Department of Rehabilitation Medicine
Veterans Affairs Puget Sound Health Care System
Seattle, Washington
Chapter 57, Musculoskeletal Upper Limb Pains; Chapter 75, General Considerations of Pain in the Low Back, Hips, and Lower Extremities

Robert Goodkin, M.D.
Associate Professor of Neurological Surgery
University of Washington School of Medicine
Veterans Affairs Puget Sound Health Care System
Seattle, Washington
Chapter 55, Neck Pain

D. David Graham, M.D.
Fellow, Pediatric Surgery
Children's Hospital and Medical Center
Seattle, Washington
Chapter 67, Painful Diseases of the Liver, Biliary System, and Pancreas

Daniel O. Graney, Ph.D.
Professor, Department of Biological Structure
University of Washington School of Medicine
Seattle, Washington
Chapter 60, General Considerations of Pain in the Chest; Chapter 65, General Considerations of Abdominal Pain

C. Chan Gunn, M.D.
Clinical Professor of Anesthesiology
University of Washington School of Medicine
Seattle, Washington
Chapter 28, Neuropathic Myofascial Pain Syndromes

Jan M. Gybels, M.D., Ph.D.
Professor Emeritus of Neurology and Neurosurgery
Catholic University of Leuven
Leuven, Belgium
Chapter 99, Peripheral Nerve Stimulation

Stephen W. Harkins, Ph.D.
Professor of Gerontology, Psychiatry, and Biomedical Engineering
Psychophysiology/Memory Laboratory
Virginia Commonwealth University School of Medicine
Richmond, Virginia
Chapter 45, Aging and Pain

Samuel J. Hassenbusch, M.D., Ph.D.
Associate Professor of Neurosurgery
University of Texas?Houston Medical School
M. D. Anderson Cancer Center
Houston, Texas
Chapter 106, Neurosurgical Operations on the Spinal Cord

Stanley A. Herring, M.D.
Clinical Professor, Departments of Rehabilitation Medicine and Orthopaedics
University of Washington School of Medicine
Puget Sound Sports and Spine Physicians
Seattle, Washington
Chapter 96, Basic Concepts in Biomechanics and Musculoskeletal Rehabilitation

Irene Higginson, B.Med.Sci, B.M.B.S. F.F.P.H.M., Ph.D.
Head, Department of Palliative Care and Policy
King's College School of Medicine and Dentistry
St. Christopher's Hospice
London, United Kingdom
Chapter 40, Palliative Care

Louis Jacobson, M.D.
Associate Professor of Anesthesiology
University of Washington School of Medicine
Veterans Administration Puget Sound Health Care System
Seattle, Washington
Chapter 10, General Considerations of Chronic Pain

Nora A. Janjan, M.D., F.A.C.P., F.A.C.R.
Professor of Radiation Oncology
University of Texas?Houston Medical School
M. D. Anderson Cancer Center
Houston, Texas
Chapter 37A, Radiotherapeutic Management of Symptomatic Disease

Mark P. Jensen, Ph.D.
Professor of Rehabilitation Medicine
Department of Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington

Chapter 94, Motivating the Pain Patient for Behavioral Change

Kaj H. Johansen, M.D.
Department of Surgical Education
Providence Medical Center
Seattle, Washington
Chapter 33, Pain Due to Vascular Disease; Chapter 69, Abdominal Pain Caused by Other Diseases

Donna Kalauokalani, M.D., M.P.H.
Assistant Professor
Anesthesiology, Division of Pain Management
Internal Medicine, Division of General Medical Sciences
Washington University School of Medicine
St. Louis, Missouri
Part IV: Regional Pains, Introduction

Michael B. Kimmey, M.D.
Professor of Medicine
Department of Gastroenterology
University of Washington School of Medicine
Seattle, Washington
Chapter 66, Painful Diseases of the Gastrointestinal Tract

Joseph C. Langlois, M.D.
Clinical Associate Professor of Dermatology
University of Washington School of Medicine
Seattle, Washington
Chapter 32, Pain of Dermatologic Disorders

Roger V. Larson, M.D.
Associate Professor of Orthopaedic Surgery
University of Washington School of Medicine
Seattle, Washington
Chapter 79, Painful Disorders of the Thigh and Knee

Susan G. Leckband, B.S., R.Ph., B.C.P.P.
Psychiatric Clinical Pharmacy Specialist
Veterans Affairs San Diego Healthcare System
San Diego, California
Chapter 84, Systemic Opioid Analgesics

Linda LeResche, Sc.D.
Research Professor, Department of Oral Medicine
University of Washington School of Dentistry
Seattle, Washington
Chapter 7, Gender, Cultural, and Environmental Aspects of Pain

Bengt Linderoth, M.D., Ph.D.
Department of Neurosurgery
Karolinska Hospital
Stockholm, Sweden
Chapter 100, Spinal Cord Stimulation; Chapter 101, Brain Stimulation: Intracerebral and Motor Cortex Stimulation

John D. Loeser, M.D.
Professor of Neurological Surgery and Anesthesiology
Former Director, Multidisciplinary Pain Center
University of Washington School of Medicine
Seattle, Washington
Part I: Basic Considerations of Pain, Introduction; Chapter 1, History of Pain Concepts and Therapies; Chapter 8, Applied Anatomy Relevant to Pain; Chapter 11, Multidisciplinary Pain Programs; Part II: Evaluation of the Pain Patient, Introduction; Chapter 12, Medical Evaluation of the Patient with Pain; Chapter 18, Multidisciplinary Pain Assessment; Part III: Generalized Pain Syndromes, Section A Neuropathic Pains, Introduction; Chapter 21, Pain after Amputation: Phantom Limb and Stump Pain; Chapter 22, Herpes Zoster and Postherpetic Neuralgia; Part III: Generalized Pain Syndromes, Section C Vascular, Cutaneous, and Musculoskeletal Pains, Introduction; Chapter 34, Pain in Spinal Cord Injury Patients; Part III: Generalized Pain Syndromes, Section D Pain in Malignant Diseases, Introduction; Part III: Generalized Pain Syndromes, Section E Acute Pains, Introduction; Part IV: Regional Pains, Introduction; Chapter 46, General Considerations of Pain in the Head; Chapter 47, Cranial Neuralgias; Chapter 54, General Considerations of Pain in the Neck and Upper Limb; Chapter 56, Cervicobrachial Neuralgia; Chapter 69, Abdominal Pain Caused by Other Diseases; Chapter 74, Pelvic and Perineal Pain Caused by Other Disorders; Chapter 76, Low Back Pain, Introduction; Chapter 77, Pain of Neurologic Origin in the Hips and Lower Extremities; Part V: Methods for Symptomatic Control, Section A General Considerations, Introduction; Part V: Methods for Symptomatic Control, Section B Pharmacologic Therapies, Introduction; Part V: Methods for Symptomatic Control, Section D Physical Therapeutic Modalities, Introduction; Part V: Methods for Symptomatic Control, Section E Implanted Electrical Stimulators, Introduction; Part V: Methods for Symptomatic Control,
Section F Regional Anesthesia/Analgesia, Introduction; Part V: Methods for Symptomatic Control, Section G Ablative Neurosurgical Operations, Introduction; Part V: Methods for Symptomatic Control, Section H Multidisciplinary Multimodal Pain Management Programs, Introduction; Chapter 109, Multidisciplinary Pain Management; Chapter 110, Building the Future

Deon F. Louw, M.B.Ch.B., F.R.C.S.(C)
Consultant Neurosurgeon
Department of Clinical Neurosciences
University of Calgary Faculty of Medicine
Foothills Hospital
Calgary, Alberta
Chapter 107, Surgical Treatment of Trigeminal Neuralgia

Thomas J. Mancuso, M.D.
Instructor in Anaesthesia
Harvard Medical School
Associate Director, Acute Pain Treatment Service
Director, Sedation Service
Associate in Anesthesia
Children’s Hospital, Boston
Boston, Massachusetts
Chapter 44, Pain and Its Management in Children

Kenneth R. Maravilla, M.D.
Professor of Radiology and Neurological Surgery
University of Washington School of Medicine
Seattle, Washington
Chapter 14, Imaging Pain Patients

Anthony J. Mariano, Ph.D.
Clinical Assistant Professor of Psychiatry and Behavioral Sciences
Codirector, Pain Clinic
University of Washington School of Medicine
Veterans Administration Puget Sound Health Care System
Seattle, Washington
Chapter 10, General Considerations of Chronic Pain

Frederick A. Matsen III, M.D.
Professor and Chair, Department of Orthopaedics
University of Washington School of Medicine
Seattle, Washington
Chapter 58, Shoulder, Arm, and Elbow Pain; Chapter 95, Orthopedic Management of Pain

Mitchell B. Max, M.D.
Senior Investigator
Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research
National Institutes of Health
Bethesda, Maryland
Chapter 85, Antidepressants, Muscle Relaxants, and N-*Methyl-D-Aspartate Receptor Antagonists*

John S. McDonald, M.D.
Professor and Chairman of Anesthesiology
Professor of Obstetrics and Gynecology
Harbor-University of California, Los Angeles Medical Center
Torrance, California
Chapter 70, General Considerations; Chapter 71, Pain of Childbirth; Chapter 72, Gynecologic Pain Syndromes; Chapter 73, Pelvic and Perineal Pain of Urologic Origin; Chapter 74, Pelvic and Perineal Pain Caused by Other Disorders

Harold Merskey, D.M., F.R.C.P.
London Psychiatric Hospital
London, Ontario
Chapter 93, Psychotherapy in the Management of Chronic Pain

Michael H. Metcalf, M.D.
Department of Orthopaedics
University of Washington School of Medicine
Seattle, Washington
Chapter 79, Painful Disorders of the Thigh and Knee

Björn A. Meyerson, M.D., Ph.D.
Department of Neurosurgery
Karolinska Hospital
Stockholm, Sweden
Chapter 100, Spinal Cord Stimulation; Chapter 101, Brain Stimulation: Intracerebral and Motor Cortex Stimulation

H. Richard Miyoshi, B.S., R.Ph.
Clinical Associate Professor
University of Washington School of Pharmacy
Department of Psychiatry and Behavioral Sciences
Harborview Medical Center
Seattle, Washington
Chapter 83, Systemic Nonopioid Analgesics; Chapter 84, Systemic Opioid Analgesics

Michael J. Moskal, M.D.
Clinical Instructor of Orthopaedic Surgery
University of Washington School of Medicine
Seattle, Washington
Chapter 58, Shoulder, Arm, and Elbow Pain; Chapter 95, Orthopedic Management of Pain

J. Cameron Muir, M.D.
Assistant Professor of Medicine
Section of Palliative Medicine
Division of Hematology/Oncology
Northwestern University Medical School
Medical Director, Palliative Care and Home Hospice Program
Northwestern Memorial Hospital
Chicago, Illinois
Chapter 37B, Chemotherapeutic Management of Symptomatic Disease

Gerd Müller, M.D.
Department of Orthopaedics
Allgemeines Krankenhaus Barmbek
Hamburg, Germany
Chapter 76A, Low Back Pain: Primary Care Approach to Acute and Chronic Back Problems: Definitions and Care

Catherine M. Neumann, M.Sc.
Division of Palliative Care Medicine
University of Alberta
Grey Nuns Community Health Centre
Edmonton, Alberta
Chapter 40, Palliative Care

Richard B. North, M.D.

Professor of Neurosurgery, Anesthesiology, and Critical Care Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland
Chapter 76C, Low Back Pain: Failed Back Surgery Syndrome

Bart J. Nuttin, M.D., Ph.D.
Assistant Professor of Neurosurgery
Catholic University of Leuven
Leuven, Belgium
Chapter 99, Peripheral Nerve Stimulation

Anne Louise Oaklander, M.D., Ph.D.
Assistant Professor of Anesthesiology and Neurology
Harvard Medical School
Assistant in Anesthesiology and Neurology
Massachusetts General Hospital
Boston, Massachusetts
Chapter 76C, Low Back Pain: Failed Back Surgery Syndrome

Akiko Okifuji, Ph.D.
Assistant Professor of Anesthesiology
University of Washington School of Medicine
Seattle, Washington
Chapter 2, Pain Terms and Taxonomies of Pain

John E. Olerud, M.D.
George F. Odland Professor of Medicine
University of Washington School of Medicine
Head, Division of Dermatology
University of Washington Medical Center
Seattle, Washington
Chapter 32, Pain of Dermatologic Disorders

James C. Orcutt, M.D., Ph.D.
Professor of Ophthalmology
Adjunct Professor of Otolaryngology, Head and Neck Surgery
University of Washington School of Medicine
Seattle, Washington
Chapter 51, Ocular and Periocular Pain

Parag G. Patil
Department of Neurosurgery
Johns Hopkins University School of Medicine
Baltimore, Maryland
Chapter 105, Lesions of Primary Afferents and Sympathetic Efferents as Treatments for Pain

David R. Patterson, Ph.D., A.B.P.P., A.B.P.H.
Professor of Rehabilitation Medicine, Surgery, and Psychology
University of Washington School of Medicine
Harborview Medical Center
Seattle, Washington
Chapter 42, Burn Pain

Karin L. Petersen, M.D.
Postdoctoral Fellow
Pain Clinical Research Center
Department of Neurology
University of California, San Francisco School of Medicine
San Francisco, California
Chapter 86, Anticonvulsants and Local Anesthetic Drugs

Robert R. Phillips, M.D.
Division of Cardiology
University of New Mexico Health Sciences Center
Albuquerque, New Mexico
Chapter 61, Cardiac and Aortic Pain

Charles E. Pope, Jr., M.D.
Professor Emeritus
Department of Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 63, Chest Pain of Esophageal Origin

Joel M. Press, M.D., F.A.C.S.M.
Medical Director, Center for Spine, Sports and Occupational Rehabilitation
Rehabilitation Institute of Chicago
Chicago, Illinois
Chapter 96, Basic Concepts in Biomechanics and Musculoskeletal Rehabilitation

David D. Ralph, M.D.
Associate Professor of Medicine
Department of Pulmonary/Critical Care Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 62, Painful Disorders of the Respiratory System

Andrea J. Rapkin, M.D.
Professor of Obstetrics and Gynecology
University of California, Los Angeles, UCLA School of Medicine
Los Angeles, California

Chapter 70, General Considerations

Shlomo Raz, M.D.
Professor of Urology
University of California, Los Angeles, UCLA School of Medicine
Los Angeles, California
Chapter 68, Painful Diseases of the Kidney and Ureter

L. Brian Ready, M.D.
Professor of Anesthesiology
University of Washington School of Medicine
Director, University of Washington Medical Center Pain Service
Seattle, Washington
Chapter 41, Postoperative Pain; Chapter 103, Regional Analgesia with Intraspinal Opioids

James P. Robinson, M.D., Ph.D.
Clinical Assistant Professor of Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 17, Evaluation of Function and Disability

Joan M. Romano, Ph.D.
Associate Professor of Psychiatry and Behavioral Sciences
University of Washington School of Medicine
Seattle, Washington
Chapter 16, Psychological and Psychosocial Evaluation; Chapter 89, Cognitive-Behavioral Therapy for Chronic Pain

Michael C. Rowbotham, M.D.
Associate Professor of Neurology and Anesthesia
University of California, San Francisco School of Medicine
University of California, San Francisco Pain Clinical Research Center
San Francisco, California
Chapter 86, Anticonvulsants and Local Anesthetic Drugs

I. J. Russell, M.D., Ph.D.
Associate Professor of Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas
Chapter 30, Fibromyalgia Syndrome

Bruce J. Sangeorzan, B.S., M.D.
Professor of Orthopaedics
University of Washington School of Medicine
Harborview Medical Center
Seattle, Washington
Chapter 80, Pain in the Leg, Ankle, and Foot

Mark M. Schubert, D.D.S., M.S.D.
Associate Professor of Dentistry
Department of Oral Medicine
University of Washington School of Dentistry
Seattle, Washington
Chapter 38, Oral Mucositis in Cancer Patients

Lauren Schwartz, Ph.D.
Clinical Assistant Professor of Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 20, Complex Regional Pain Syndromes?Type I: Reflex Sympathetic Dystrophy, and Type II: Causalgia

Sam R. Sharar, M.D.
Associate Professor of Anesthesiology
University of Washington School of Medicine
Harborview Medical Center
Seattle, Washington
Chapter 42, Burn Pain

Anders E. Sola, M.D.
Clinical Assistant Professor of Anesthesiology
University of Washington School of Medicine
Seattle, Washington
Chapter 29, Myofascial Pain Syndromes

Walter C. Stolov, M.D.
Professor and Chair Emeritus, Department of Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 13, Electrodiagnostic Evaluation of Acute and Chronic Pain Syndromes

Mark D. Sullivan, M.D., Ph.D.
Associate Professor of Psychiatry
Department of Psychiatry and Behavioral Sciences
University of Washington School of Medicine
Seattle, Washington
Chapter 26, Psychiatric Illness, Depression, and Psychogenic Pain

Karen L. Syrjala, Ph.D.
Associate Professor of Psychiatry and Behavioral Sciences
University of Washington School of Medicine
Director and Associate Member

Department of Biobehavioral Sciences
Fred Hutchinson Cancer Research Center
Seattle, Washington
Chapter 15, Measurement of Pain; Chapter 92, Relaxation and Imagery Techniques

Ronald R. Tasker, M.D.
Professor Emeritus of Neurosurgery
University of Toronto Faculty of Medicine
The Toronto Western Hospital
Toronto, Ontario
Chapter 23, Central Pain States

Gregory W. Terman, M.D., Ph.D.
Associate Professor, Department of Anesthesiology and the Graduate Program in Neurobiology and Behavior
University of Washington School of Medicine
Seattle, Washington
Chapter 4, Spinal Mechanisms and Their Modulation

Richard W. Tobin, M.D.
Clinical Assistant Professor of Medicine
Departments of Internal Medicine and Gastroenterology
University of Washington School of Medicine
Seattle, Washington
Chapter 66, Painful Diseases of the Gastrointestinal Tract

Edmond L. Truelove, D.D.S., M.S.D.
Department of Oral Medicine
University of Washington School of Dentistry
Seattle, Washington
Chapter 49, Facial and Head Pain Caused by Myofascial and Temporomandibular Disorders

Eldon R. Tunks, M.D., F.R.C.P.(C)
Professor Emeritus of Psychiatry
McMaster University
Hamilton Health Sciences Corporation, Chedoke Division
Hamilton, Ontario
Chapter 93, Psychotherapy in the Management of Chronic Pain

Dennis C. Turk, Ph.D.
John and Emma Bonica Professor of Anesthesiology and Pain Research
University of Washington School of Medicine
Seattle, Washington
Adjunct Professor of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania
Chapter 2, Pain Terms and Taxonomies of Pain; Chapter 26, Psychiatric Illness, Depression, and Psychogenic Pain; Chapter 109, Multidisciplinary Pain Management; Chapter 110, Building the Future

Judith A. Turner, Ph.D.
Hughes M. and Katherine G. Blake Professor of Health Psychology
Departments of Psychiatry and Behavioral Sciences and Rehabilitation Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 6, Psychological Aspects of Pain; Chapter 16, Psychological and Psychosocial Evaluation; Chapter 81, Nonspecific Treatment Effects; Chapter 89, Cognitive-Behavioral Therapy for Chronic Pain

Sandip P. Vasavada, M.D.
Assistant Professor of Urology
Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania
Chapter 68, Painful Diseases of the Kidney and Ureter

Douglas B. Villaret, M.D.
Assistant Professor of Otolaryngology
University of Florida College of Medicine
Gainesville, Florida
Chapter 53, Pain Caused by Cancer of the Head and Neck

C. Peter N. Watson, M.D., F.R.C.P.(C)
Assistant Professor of Medicine
University of Toronto Faculty of Medicine
Toronto, Ontario
Chapter 22, Herpes Zoster and Postherpetic Neuralgia

K. M. A. Welch, M.D.
Vice Chancellor for Research
Senior Associate Dean?School of Medicine
University of Kansas Medical Center
Kansas City, Kansas
Chapter 48, Headache

Ernest A. Weymuller, Jr., M.D.
Professor and Chairman, Department of Otolaryngology?Head and Neck Surgery
University of Washington School of Medicine
Seattle, Washington
Chapter 52, Pain in the Ear, Midface, and Aerodigestive Tract;
Chapter 53, Pain Caused by Cancer of the Head and Neck

Stuart E. Willick, M.D.
Assistant Professor of Physical Medicine and Rehabilitation
University of Utah School of Medicine
Salt Lake City, Utah

Chapter 96, Basic Concepts in Biomechanics and Musculoskeletal Rehabilitation

Jeffrey J. Wise, M.D.
Attending Orthopaedic Surgeon
Department of Orthopaedic Surgery
Fauquier Hospital
Warrenton, Virginia
Chapter 76B, Low Back Pain: Role of Surgery in the Treatment of Low Back Pain and Sciatica

Ronald F. Young, M.D.
Neurosciences Institute
Good Samaritan Hospital
Los Angeles, California
Chapter 108, Ablative Brain Operations for Chronic Pain

Alastair S. E. Younger, M.B., Ch.B., M.Sc., Ch.M., F.R.C.S.C.
Clinical Instructor
Department of Orthopaedics
Division of Reconstruction
University of British Columbia Faculty of Medicine
St. Paul's Hospital Foot and Ankle Program
Vancouver, British Columbia
Chapter 80, Pain in the Leg, Ankle, and Foot

Preface

This textbook presents a comprehensive and systematic approach to the sciences basic to the practice of pain management and to all aspects of the diagnosis and treatment of acute and chronic pain. In this respect it resembles the first edition of this book, published in 1953, and the second edition, published in 1990, both under the personal direction of John J. Bonica. My colleagues and I have attempted to meet the standards that Dr. Bonica established in the previous editions and have maintained the same organization and completeness that he developed. The reader will find that we have added new chapters, deleted some of the old topics, and updated every chapter. We have reprinted the Preface from the first edition, as it is one of the key documents in the history of the pain movement in the last half of the twentieth century.

The past 45 years have witnessed an explosion of published materials relevant to the study of pain and the practice of pain management. John J. Bonica was the driving force behind this major change in the way biomedicine approached the problem of pain. Numerous books have been published, at least 25 journals have been established, and educational materials of all types have been developed. No one person can be the author of a contemporary, comprehensive textbook on pain; this is why the second edition of this book had multiple contributors. Few authors or editors have attempted to provide the type of broad yet deep coverage of basic science, acute and chronic pain, cancer pain, and problems related to the young and the old and those with all types of illness.

This book is designed to be a source of information for both pain specialists and those who are seeking information about a specific pain topic. The organization of the chapters reflects our concepts of how the reader can best use these materials. The nature of a book is to fragment information into segments; this does not imply a deviation from the fundamental fact that patients are not a collection of body parts; optimal management of pain patients requires a holistic approach to health care. We do not expect anyone to read it from cover to cover.

The book has five general sections. Part I contains eleven chapters with information basic to an understanding of pain. It begins with the history of pain concepts and theories and definitions and taxonomies of pain. Next are chapters on anatomy and physiology and pharmacology of the peripheral nerves, spinal cord, and brain. The behavioral and social sciences are next, followed by the roles of culture, gender, and social interactions. Applied anatomy and general considerations of acute and chronic pain are then presented. The final chapter in this section addresses the development and characteristics of multidisciplinary pain treatment. Those who wish to develop an overview of all of the issues that provide a cornerstone for pain management should begin with this section.

Part II addresses the evaluation of the patient with pain. The seven chapters cover all phases of the medical and psychological assessment process, including the role and interpretation of imaging studies. Of particular import is the chapter on the evaluation of pain and disability, for this is a major medical, political, and economic problem in all the developed countries. Accurate diagnosis is the cornerstone of optimal treatment. The final chapter describes assessment in a multidisciplinary pain clinic.

Part III consists of 27 chapters focusing on generalized pain syndromes that can cause patients to present with complaints referable to any region of the body. It also contains chapters on pain in the young and the old, for these age groups merit special considerations. Pains related to cancer and to acquired immunodeficiency syndrome are discussed in Part III, as are the issues surrounding acute pain management. Organizing the book in this fashion permits the reader to obtain information about generalized or multifocal pain syndromes in a coherent fashion, without resorting to reading about the pain in every regional chapter to obtain a complete picture of the pains related to this disease.

Part IV addresses pain syndromes on a regional basis, beginning with the head and ending with the foot. Each chapter begins with an overview of the anatomy and physiology of that region and the principles of diagnosis and differential diagnosis in that part of the body. Principles of the management of pain in each area are stressed. Obviously, the discussion of disease processes in each area cannot be as detailed as in texts devoted exclusively to a single system or part of the body. Appropriate references are included to direct the reader to more detailed presentations.

Part V provides an overview of all aspects of the treatment of pain that are currently in use by medical and psychological practitioners. It begins with two new chapters, one on non-specific treatment effects and the other on the construction and evaluation of clinical trials. Both of these subjects are essential for the pain practitioner or clinical research scientist. The principles of pain management, rather than treatment of the underlying disease, are contained in this section. Presumably, any physician would first attempt to eradicate pain by eliminating the disease leading to the pain; in this volume we address the problem of managing pain when the antecedent disease processes cannot be eliminated. Each chapter attempts to place its subject in historical perspective and to indicate the current usage of this type of treatment. Although one could implement the less complex strategies for pain management that are described in each chapter just on the basis of what is written here, none of the chapters describing complex invasive procedures is designed to serve as a “how to do it” for those who are not adequately trained in this form of treatment. For example, the chapters on regional anesthesia and neurologic surgery are intended to provide adequate information for those who are not anesthesiologists or neurosurgeons so that they may understand the rationale and indications for, techniques of, and expected results of these procedures. Those who make management decisions about patients with pain should become aware of all of the treatment options; this is the purpose of Part V of this book.

We have attempted to avoid duplication of data and repetitive discussion of similar issues in multiple places as much as possible. We have also established a consistent style and depth of presentation so that the weighting of each topic is in proportion to its importance in contemporary pain research and management. The references are selected from extensive bibliographies in each area so that the reader can locate key articles or comprehensive texts that will provide in-depth information beyond that which can be offered in this text. We have worked hard to produce a balanced and thorough approach to the world of pain. Inevitably, some will be offended by the amount of space allocated to their favorite topic; we are certain that the subsequent editions of this text will add some new topics and delete old, just as we have done. Tremendous strides in our understanding of the sciences basic to pain have taken place; we hope that Chapters 3 through 7 will capture the excitement of what was accomplished in basic pain research in the 1990s. We expect that the outcomes-based movement that is gaining momentum in Western medicine will lead to superior information about the effects of pain treatments and that this will shape subsequent versions of the treatment sections of the book.

We have selected each of the authors because of his or her expertise and ability to convey information with clarity. To maintain similar format and style, we have edited each chapter. We have spent many hours resolving philosophical and content issues that are common in multiauthored texts such as this. We hope that the third edition of *Bonica’s Management of Pain* will be as valuable to its readers as the first and second editions have proved to be. It is an honor to carry on the tradition started by John J. Bonica.

John D. Loeser, M.D.
Stephen H. Butler, M.D.
C. Richard Chapman, Ph.D.
Dennis C. Turk, Ph.D.
Seattle, Washington

Preface to the First Edition (1953)

The purpose of this book is to present within one volume a concise but complete discussion of the fundamental aspects of pain, the various diseases and disorders in which pain constitutes a major problem, and the methods employed in its management, with special emphasis on the use of analgesic block as an aid in the diagnosis, prognosis, and therapy. Although several books dealing with certain phases of this problem are available, none is complete from the standpoint of the practitioner; for it is necessary for him to consult several texts in order to obtain information regarding the cause, characteristics, mechanisms, effects, diagnosis, and therapy of pain and management of its intractable variety with analgesic block and certain adjuvant methods. The present volume is the product of the author's desire to facilitate the task of the busy practitioner and to supply him easily accessible information with the conviction that this will induce more clinicians to employ these methods of diagnosis and therapy.

One need not elaborate on the reasons for writing on the management of pain, for reflection emphasized that this age-old problem is still one of the most difficult and often vexing phases of medical practice?a fact well appreciated by most physicians. This fact, as well as other reasons, are presented in the introduction and are emphasized throughout the book, particularly in Chapter 5.

I have been motivated to write this volume by a deep feeling for those who are afflicted with intractable pain, and by an intense desire to contribute something toward the alleviation of their suffering. The plan for its writing was germinated almost a decade ago during the Second World War, while I was Chief of the Anesthesia Section of a large Army hospital, where I was afforded the opportunity to observe and manage an unusually large number of patients with severe intractable pain. The gratifying results obtained with analgesic block in some instances impressed me with the efficacy of this method in selected cases. In addition, the fact that these procedures effected relief which frequently was not only dramatic, but outlasted by hours and days the transient physiochemical interruption of nerve impulses, fascinated me and aroused my interest. Perusal of the literature revealed a paucity of material on this subject?a situation which has not changed much since then and which clearly indicated an obvious need for a practical source of information about this perplexing phenomenon and the application of analgesic block to its management.

This book is composed of three parts. *The first part* includes a discussion of the fundamental aspects of pain. While some of the material, on superficial thought, might be considered too detailed or entirely unnecessary, it has been included because of my conviction that in order to manage pain properly its anatomical, physiological and psychological bases must be understood. As is true in all fields of endeavor, a thorough knowledge of fundamental principles is an essential prerequisite without which optimal results are precluded. In order to diagnose and treat it properly, the physician must know the course of pain from its place of origin to the apperception centers in the brain and must be well versed in all the essentials and components of which pain consists; he must know its causes, mechanisms, characteristics, varieties, its localizations and significance, and the mental and physical effects it produces.

The second part deals with methods and technics of managing pain. It was originally planned to include only the method which is the central theme of the book?analgesic block. However, it was soon realized that while this important phase is, to be sure, here treated in a comprehensive manner, it does not present the complete story of the management of pain; because frequently other adjuvant methods are employed in conjunction with nerve blocking. To illustrate the point, trigeminal neuralgia is frequently treated with neurolytic blocks, but sometimes this does not afford sufficiently long relief, and neurotomy is resorted to. The pain associated with malignancy is managed with alcohol nerve block, but roentgen therapy is frequently employed as an adjuvant. Moreover physical and/or psychiatric therapy constitute integral phases of the management of pain without which optimal results cannot be hoped for. After careful consideration, it was decided to include another section in Part II in which are presented methods that are frequently employed in conjunction with analgesic block. It is hoped that such inclusion will give the book a wider scope and greater usefulness.

In the third part are presented various diseases or disorders with painful syndromes which have been and can be managed with analgesic block with or without the aid of other methods. The arrangement of this part is explained in detail on page 671. It is suggested that the reader refer to that page before proceeding further to read any on the pain syndromes. Though the material in this part mainly represents my observations, clinical impressions, and opinions, obtained or developed from experience with, and statistical analysis of, many thousands of cases, it also includes unpublished data of several outstanding authorities who have kindly placed them at my disposal. Moreover, it includes the published views and clinical experiences of others, with credit given where it is due.

In writing this comprehensive treatise, which has involved no small amount of time and effort, the one principle which has always been kept in mind and adhered to has been to present the fundamental considerations and principles of the problem before the practical aspects are discussed.

I have endeavored to make this book as complete as possible, and to this end have thoroughly searched the literature, both English and foreign, and have taken from it all that I thought might be valuable to the reader. In order to comply with the aim of completeness and still keep the book concise and within reasonable size, the material has been selected with care and discretion. In a field so vast and complex as pain, it is unavoidable that what might be thought sufficiently important to deserve detailed discussion is presented in an abbreviated manner or entirely omitted. In other instances, mere mention or omission represents a reluctant compliance with the requirements dictated by the size of the volume. Nonetheless, I believe thoroughness and important detail have not been sacrificed. The bibliography represents the most important references, and many excellent articles on each subject were also reluctantly omitted for that reason.

The book is intended for practitioners of every field of medicine, because pain is universal and provides the main reason why patients seek the aid of the doctor. It is hoped that it will prove useful, not only to the anesthesiologist, neurologist, neurosurgeon, orthopedist, and physiatrist to whom especially is relegated the task of caring for patients with intractable pain, but also to the general practitioner, surgeon, internist, psychiatrist, and any other physician who may be confronted with this problem. It is especially intended for general practitioners, particularly those practicing in smaller communities where the services of a specialist in analgesic blocking are not available. With this aim in mind the technics of analgesic block are presented in such a manner that most of them may be effectively accomplished by any physician, even though he may be a novice with regional analgesia. In order to facilitate the task of the busy reader, less relevant facts?material which has been included because of its academic importance, for the sake of completeness, or for consumption by students and those who wish to delve deeper into the problem?are presented in small type. These can be omitted without losing continuity of thought. In this manner, while completeness, detail, and thoroughness are not sacrificed, emphasis is laid on the practical aspects of the problem at hand.

The unusually large number of illustrations, many of which are original and composed from dissected material or clinical cases, have been included with the conviction that these frequently tell the story much better than words.

A book of this nature is made possible only by the contribution of many individuals. The information set forth in the first part of the volume represents the fruition of the joint effort of anatomists, physiologists, pharmacologists, neurologists, neurosurgeons, anesthesiologists, psychiatrists, and many other laboratory and clinical investigators who have spent untold time, labor, and effort to discover the mystery of pain. I am grateful for their elucidating knowledge. To clinicians who have reported their experiences, and to others who have placed at my disposal unpublished data, observations, and opinions, my sincere thanks. I am particularly obliged to General Maxwell Keeler, and Col. Clinton S. Lyter, of Madigan Army Hospital for their continuous cooperation in obtaining much of the clinical data embraced in this volume. I want to express my gratitude to Mr. Harold Woodworth for his friendship, sympathetic understanding and devotion to the cause of medicine. I also want to thank the other members of the Board of Trustees of Tacoma General Hospital, but particularly Mr. Alex Babbit, and Mr. Walter Heath and John Dobyns, Directors of the hospital. Their continuous cooperation has facilitated the activities of the Department of Anesthesia, Nerve Block Clinic, and Pain Clinic.

I am very grateful to Dr. Robert Johnson, Associate Professor of Anatomy of the University of Washington School of Medicine, for his encouragement and criticism of some parts of the manuscript; to Doctor Frederick Haugen for his assistance, criticism and suggestion.

My collaborators, Professor Robert Ripley, Doctors Wendell Peterson, Frank Rigos, John T. Robson, Col. Clark Williams, M.C., and Lieut. Col. Walter Lumpkin, M.D., have my heartfelt thanks for their contributions and cooperation.

My appreciation is extended to Miss Joy Polis, Miss Virginia Coleman, and other artists for the illustrations and to Mr. Kenneth Ollar for the photography; to Mrs. Louise Cameron for her cooperation in obtaining the roentgenograms; to Mrs. Katherine Rogers Miller, Miss Eleanor Ekberg and the late Mrs. Blanch DeWitt of Tacoma, Miss Bertha Hallam, Portland, and Mr. Alderson Fry, Seattle?all librarians whose cooperation has facilitated a difficult task, and to Mr. John Morrison for editorial work.

This preface would be incomplete if I did not acknowledge my indebtedness to my secretaries, Miss Katherine Stryker and Mrs. Dorothy Richmond, for the inestimable

aid they have given me in the preparation of the manuscript.

My appreciation is extended to my publishers for their courtesy, cooperation, and considerateness throughout the preparation of this volume.

John J. Bonica
Tacoma, Washington

Acknowledgments

This book reflects the contributions of many scientists and clinicians. Some have authored the chapters; others have made the research discoveries and clinical observations that have been summarized in our text. We are, of course, deeply indebted to those who contributed their valuable time to write the chapters contained in this volume. We are particularly grateful to John J. Bonica, who wrote so many of the chapters in the second edition. We have updated many of these chapters, particularly those based upon anatomy of each region, and used them as the foundation for the similar chapters in this edition. We have also created many new chapters on topics that were not covered in the second edition.

Marjorie Domenowske has again prepared all of the new illustrations for this edition. Because she did the illustrations for the second edition, we have been able to continue her elegant style for all of our original figures. Her efforts to prepare informative and easily grasped visual images have again been a great contribution to our text.

We thank the John C. Liebeskind History of Pain Collection of the University of California, Los Angeles Biomedical History Library for the loan of illustrations from the second edition of Bonica's *Management of Pain*.

Donna Rowe was the glue that held our work together and made certain that it was always perfect. She acted as executive secretary for this, the third edition, just as she did for the second edition. Without her attention to detail, patience, and desire to make this edition every bit as complete and perfect as the prior one, we could never have succeeded. It is to her that we owe the greatest debt. Finally, Tanya Lazar at Lippincott Williams & Wilkins has been patient and thorough in the preparation and printing of this book.

John D. Loeser, M.D.
Stephen H. Butler, M.D.
C. Richard Chapman, Ph.D.
Dennis C. Turk, Ph.D.

Part I Basic Considerations of Pain - Introduction

John D. Loeser

The chapters in Part I contain basic scientific and clinical information essential to an understanding of the fields of pain research and management as they have evolved since the late 1940s. Chapter 1 contains a historical review of pain concepts and treatment dating back to the earliest recorded time. Chapter 2 presents the definitions and taxonomy of pain as developed and then refined by the International Association for the Study of Pain under the direction of Professor Harold Merskey. We also discuss some of the issues surrounding the development of a taxonomy and the attempts to validate different means of classifying pain syndromes. The syndrome codes created by International Association for the Study of Pain appear in various chapters of Parts III and IV of this book, because they help to standardize nomenclature and facilitate scholarly and clinical interchange.

Chapter 3, Chapter 4 and Chapter 5 present an overview of our current understanding of the anatomy, physiology, biochemistry, and pharmacology of the peripheral nerves, spinal cord, and brain. This section is significantly reorganized from that of the second edition of this text, because we wish to present the information in a more contemporary style. Chapter 6, Psychological Aspects of Pain, and Chapter 7, describing the influences of gender, social, cultural, and environmental factors relevant to pain, deal with all aspects of acute and chronic pain. More detailed information on these topics is found in Chapter 9 and Chapter 10 and in various chapters in Part III.

The next four chapters in this part address the basic issues in clinical pain diagnosis and management. Chapter 8 focuses on applied anatomy; Chapter 9 addresses acute pain; and Chapter 10, chronic pain. Both of the latter chapters provide an overview but do not deal with specific syndromes or treatment strategies. The presence of this type of material at the start of the text obviates the need for such general considerations in Parts III and IV.

The final chapter of Part I begins the discussion of multidisciplinary pain diagnosis and treatment as developed since 1960 by Dr. John J. Bonica and his successors at the University of Washington. Multidisciplinary pain centers and clinics are a direct legacy of Bonica's pioneering efforts throughout the world to bring about improvements in the alleviation of pain and suffering. Their evolution, as typified by the Multidisciplinary Pain Center at the University of Washington, is one of the essential developments of the pain treatment movement since the 1950s. Various aspects of the types of therapies used in such treatment facilities are discussed in Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92, Chapter 93 and Chapter 94 as well as in highly focused sections of the chapters in Part III. For information about outcomes of this type of treatment, consult Chapter 109.

The editors' concepts of pain underlie the selection of topics considered essential for an understanding of pain management and pain research. We believe that knowledge of the history of ideas about pain and methods of classifying it is an important foundation. Along with the traditional biomedical sciences, such as anatomy, physiology, and biochemistry, the sciences of human psychology and behavior are also essential for an adequate understanding of patients with pain. Sociocultural factors also must be given attention, as these influence patients' presentation, understanding, acceptance, and response to treatments. Health care professionals' responses to patients also are influenced by a wide range of sociocultural and economic factors. Finally, the fundamental differences in the phenomena of acute and chronic pain and their management strategies make them appropriate topics for the introductory section of this text.

Part II Evaluation of the Pain Patient - Introduction

John D. Loeser

Chapter References

The seven chapters in this part discuss the components of the evaluation of the patient whose complaint of pain does not readily correspond to a specific pathologic change in some part of the body. In most patients with acute pain, the region of tissue damage is obvious and the patient's complaints clearly stem from the injured region. In patients with pain associated with cancer, the search for an etiology of the patient's pain usually reveals disease, such as metastasis to bone or tissue damage from the attempts to cure the malignancy, such as radiation-induced fibrosis or chemotherapy-induced neuropathy. In patients with chronic pain associated with nonneoplastic diseases, the linkage between specific pathology and the patient's pain behaviors is quite loose, and the search for an explanation of the symptoms requires a comprehensive assessment that is often beyond the skills of any one health care provider. A multidisciplinary team of health professionals who have special knowledge and experience in the evaluation of pain patients can best accomplish this. The interactions between those who perform the assessment are often essential in formulating a meaningful diagnosis and treatment plan.

Bonica stated in the first edition of this text, published in 1953, that all complex patients required multidisciplinary evaluation, but his viewpoint did not gain wide acceptance for at least two decades. He wrote and spoke extensively on this topic, but few physicians understood the complexities of chronic pain patients and most were tied to their own disciplinary approaches to diagnosis and treatment. A second factor was the widespread belief that graduation from medical school qualified one to deal with all aspects of pain diagnosis and treatment. Another problem was the increasing specialization of medical practice and the relative isolation of information into narrow disciplinary areas. A fourth issue was the failure to recognize that chronic pain was not just a by-product of a disease process but was a form of illness that required direct assessment and treatment.

The complex, multidimensional nature of pain was unrecognized—a shortcoming nurtured by the continued widespread teaching and acceptance of the Cartesian concepts of the separation of mind and body and the clockwork mechanisms of body function, by the preeminence of the specificity theory of pain, and by the rapid growth of scientific medicine and the consequent practice of reductionism. Any problem could be understood by analyzing the body in ever smaller units, until the causative diseased part became evident. Human beings, however, are more than the sum of their individual parts.

One of the great triumphs of Bonica's career was that he lived long enough to see his concepts of the multidimensional nature of pain validated and disseminated throughout the world. Advances in our understanding of the complaint of pain have led to much greater appreciation of the complexities associated with the report of pain and the critical roles not only of tissue damage, but also of changes in the nervous system in response to noxious input, and of cognitive, affective, and environmental factors in the genesis, exacerbation, and perpetuation of the complaint of pain. Multidisciplinary assessment of chronic pain patients is now a standard approach. Changes in clinical practice stem from the tremendous increases in our understanding of central nervous system mechanisms that influence the recognition of and response to noxious stimulation. We now recognize the complexities of what was once thought to be a simple, line-labeled information system. Concepts about pain drive the strategies for the evaluation and subsequent treatment of the patient with pain, and it is the conceptual change that Bonica initiated that is his greatest legacy.

Cartesian dualism is dually deficient as a conceptual model for pain. In the first place, one cannot separate mind and body in a living human being. The mind is an emergent property of the human brain. All responses of the organism involve mind and body. More important, what Descartes left out was just as essential as the two factors he included. Mind and body alone do not suffice to predict behavior; the environment is just as potent a force. Human beings are social organisms from the moment of birth. All too often, those who provide health care are oblivious to the major role that environmental factors play in the genesis and perpetuation of chronic pain. Newer conceptual models for pain incorporate the role of learning, cognitive, and affective factors in the genesis of chronic pain. These models overtly state that nociception derived from tissue damage is not the sole determinant of pain and its behavioral expression, and that the nervous system can modulate nociceptive stimuli by physiologic as well as psychological mechanisms.

A conceptual model was published by Loeser (1) in 1982. It has proven to be a useful adjunct in the understanding of the components of pain. According to this model, the phenomenon of human pain can be separated into four nested components: nociception, pain, suffering, and pain behaviors. The model (Fig. II-1) emphasizes that nociception, pain, and suffering are personal, private, internal events that one cannot measure directly in another human being. Their existence can only be inferred by the assessment of pain behaviors. *Nociception* is the detection of tissue damage by transducers in the skin and other tissues and the propagation of this information to the central nervous system by A-d and C fibers in the peripheral nerves. Inflammation or injury is now known to be capable of biasing the nociceptive transducers and lowering their threshold for activation (see Chapter 9). *Pain* is the perception of the nociceptive signaling by neural mechanisms in the spinal cord and brain. Pain can arise from lesions in the peripheral or central nervous system that send impulses to the spinal cord or brainstem and higher centers. When impulses that imply tissue damage reach the nervous system, the brain cannot discriminate a peripheral tissue damage origin from electrical activity generated in the axon, cell body, or central connections of the peripheral nerve.

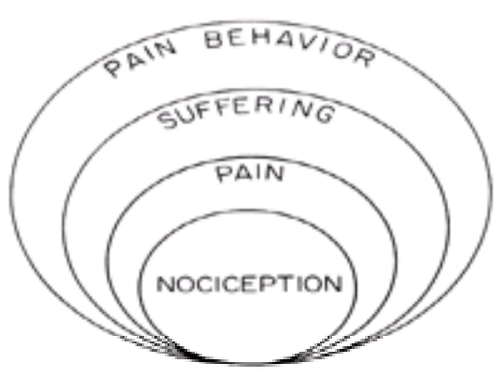

Figure II-1. Loeser's conceptualization of the phenomenon of pain. See text for explication. (From Loeser JD. Concepts of pain. In: Stanton-Hicks M, Boas R, eds. *Chronic low back pain*. New York: Raven, 1982:146, with permission.)

Suffering is a negative affective response generated in the forebrain by pain or by a wide variety of emotional states such as isolation, depression, fear, and anxiety. Suffering reflects a threat to the physical or psychological integrity of the individual, as eloquently presented by Cassell (2). It is true that many physicians and patients use the language of pain to describe suffering of any etiology. Patients who manifest suffering are therefore evaluated as if the only possible etiology was tissue damage. This can lead to unnecessary and inappropriate diagnostic tests and potentially harmful surgical procedures.

Pain behaviors are the actions or inactions of a person that imply the presence of tissue damage, such as saying “ouch,” grimacing, taking pills, lying down, refusing to work, and seeking health care. All pain behaviors are real, for they can all be observed. The proper questions are not about the reality of the patient's symptoms, but instead are the following: What are the roles of nociception, pain, suffering, and pain behaviors in the genesis and perpetuation of the patient's pain complaint? What are the stimuli that lead to the generation of pain behaviors? The originating cause of the pain—for example, trauma—may not be the predominant factor in the perpetuation of the pain behaviors. The diagnostician must be aware of this possibility. Changes in the nervous system in response to massive sensory input or from cognitive and affective factors can lead to alterations in the way sensory information, including nociception, is processed. All pain behaviors can be quantified and used as measures of pre- and posttreatment status to evaluate outcomes. Pain behaviors also follow the general rules of behavior: They are real and they are exquisitely sensitive to environmental consequences, either anticipated or actual (see Chapter 16).

The complex nature of pain makes multidisciplinary assessment a necessity. A physician *pain management specialist* usually takes the lead in the assessment of the

pain patient. Not many people today like the terms coined by Bonica of *dolorologist* or *algologist*. Complex problems may benefit from the knowledge and skills of different types of medical specialists, in addition to the obvious need for psychological and vocational assessment to supplement the medical information. The medical diagnostic workup is described in detail in Chapter 12. Chapter 13 discusses the role of electrodiagnostic testing, and Chapter 14 reviews contemporary imaging studies. The next chapter addresses the critical topic of pain measurement; this has clinical and research implications. Chapter 16 details the psychologist's assessment of the patient and the patient's environment. Multidisciplinary evaluation is also discussed in Chapter 11 of Part I. Chapter 17 considers problems in the evaluation of pain and disability. This topic is included because of the widespread use of physicians as arbiters of whether or not a claimant is able to perform in the workplace. This type of assessment goes far beyond the medical diagnosis of a painful state and is not well grounded on evidence about the validity of this administrative decision-making process. Indeed, there are reasons to question the morality of the physician's role in disability evaluation as well as the accuracy and reliability of such determinations (3). The final chapter describes multidisciplinary pain assessment using the University of Washington model.

This part of our text contains essential information about the conduct of a clinical evaluation of the patient who presents with chronic pain. This material should be mastered by anyone who is going to evaluate chronic pain patients. Even when dealing with acute pain, such as that after burns, trauma, or surgery, the assessment methods described in this part of the text will be of great value to the clinician.

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Section A. Neuropathic Pains - Introduction

John D. Loeser

The 27 chapters in Part III contain comprehensive yet concise discussions of acutely painful conditions and chronic pain syndromes that can occur in different regions of the body. We provide this information here to avoid discussion of these pain syndromes in every region of the body in which they can occur. We hope that this minimizes the discussions of etiology, mechanisms, pathophysiology, symptoms and signs, and therapy for these syndromes in every body region included in Part IV. Chapter 19, Chapter 20, Chapter 21, Chapter 22 and Chapter 23 focus on pains of neuropathic origin. They build upon the basic science information presented in Chapter 3, Chapter 4 and Chapter 5. Chapter 24, Chapter 25 and Chapter 26 discuss pain of psychological origin and supplement the information in Chapter 6, Chapter 7, and Chapter 10. These three chapters provide background for the discussions of the various types of pain that are presented in Part IV.

We devote Chapter 27, Chapter 28, Chapter 29, Chapter 30, Chapter 31, Chapter 32 and Chapter 33 to pains of musculoskeletal, vascular, and cutaneous origin, with particular emphasis on arthritis and myofascial pain syndromes, which are common and poorly understood. Chapter 34 addresses pain after spinal cord injury, a particularly difficult aspect of pain management. The organization of this part generally follows that of group I in the *IASP Taxonomy*.

Chapter 35, Chapter 36, Chapter 37, Chapter 38, Chapter 39 and Chapter 40 address pain related to cancer and acquired immunodeficiency syndrome and the treatments that patients receive in the attempt to eradicate their diseases. We believe that it is necessary to expand the coverage of these topics in this edition. These chapters include a discussion of palliative care, which is becoming an ever-important issue as the population ages. Better treatments for heretofore rapidly lethal diseases have prolonged the lives of those who are likely to suffer from painful afflictions. Chapter 41, Chapter 42 and Chapter 43 consider the acute pain syndromes that follow surgery, burns, and trauma. These, of course, are often the focus of anesthesiologists, but other health care providers need to understand the issues and management principles.

Chapter 44 and Chapter 45 focus on pain in children and pain in the aged. These topics are also relatively new in the pain movement and deserve special attention because of the unique issues related to age and problems associated with the ability to communicate verbally.

Part III contains diagnostic and therapeutic information about specific generalized pain syndromes. More detailed information about treatment technologies for generalized and regional pain syndromes appears in Part V. The reader should consult that portion of the book to learn more about the treatment strategies and their risks, benefits, and outcomes. Although it is convenient to discuss generalized pain syndromes with regard to the organs or tissues that are involved in disease processes, one must remember that the patient is the focal point in the delivery of health care. We address disease processes for ease of presentation; those who treat patients with pain must address all of the issues that interfere with normal health and well-being.

Section B. Psychological Contributions to Pain - Introduction

C. Richard Chapman

Every experienced clinician knows that psychological factors play a central role in chronic pain problems. This is hardly surprising, because pain is a psychological phenomenon: It depends on consciousness, it is a somatic perception with emotional as well as sensory features, and it exists solely in the personal reality of the sufferer. We know of another's pain only when the person in pain speaks of it or emits behaviors consistent with injury or personal discomfort. Moreover, the effect of chronic pain on the patient manifests as a cascade of psychological problems. Pain prevents adequate restorative sleep, causes fatigue, impairs attention to and concentration on the events and demands of daily life, and fosters inactivity. Poor sleep and inactivity, in turn, contribute to a general myalgia and malaise, somatic preoccupation, and negative affect. Most people experiencing chronic pain have difficulty meeting the physical, emotional, and cognitive demands of daily life, and many become partly or wholly disabled. Months or years of chronic pain force habit patterns and adjustments in lifestyle and self-image that lead the person to redefine him- or herself.

Pain management would be straightforward if most chronic pain cases had identifiable and treatable causes. However, many chronic pains by definition defy conventional explanation. More important, even when a patient presents with a detectable and treatable cause, the physician cannot assume that the patient is *self-righting*. Removing the cause of the pain does not necessarily result in the patient's recovery and return to productive living. The secondary myalgia, poor sleep, fatigue, discouragement, and social problems, may remain as a self-perpetuating cycle of misery and disability long after the original injury has healed or responded physiologically to treatment. The real challenge in many chronic pain cases, therefore, is not simply pain relief, but rather rehabilitation. This generally requires a fully integrated team approach that combines psychology and rehabilitation medicine.

The complicating influence of psychological factors sometimes extends beyond the evaluation and rehabilitation of otherwise normal patients with chronic pain. Some patients who develop chronic pain have preexisting psychiatric conditions that greatly befuddle evaluation and impair rehabilitation. Sometimes, these conditions contribute to abnormal illness behavior and excessive health care use. Other patients are predisposed to specific psychiatric problems, such as depression, and these problems manifest only because of the constellation of personal and social stressors that chronic pain creates. Patients with coexisting medical and psychiatric conditions need parallel intervention and treatment for such conditions if rehabilitation for chronic pain is to succeed.

The chapters in this section provide a knowledge base for understanding some of the fundamental psychological factors that determine the experience of pain and that influence and perpetuate chronic pain. The concepts in this section provide the conceptual foundation for the psychological interventions that appear in Part V, Section C. These chapters show that antiquated distinctions between mind and body are of little help in explaining chronic pain, and they offer contemporary explanatory frameworks. The reader seeking further information on the role of psychological factors in pain should consult Chapter 6 and Chapter 81.

Chapter 24 addresses the central mechanisms of the negative emotion that accompanies nociception. Drawing support from brain imaging studies of persons experiencing pain, they show that negative affect and somatic hypervigilance are an intrinsic part of pain. Moreover, during emotional arousal, the brain alters bodily states via autonomic mechanisms, and these in turn influence somatic perception and sense of well-being.

Chapter 25 offers a learning theory explanation for the development of chronicity in patients with pain. Although one would normally consider pain a subjective and private experience, it is equally plausible to consider it a set of behaviors. It is through behavior, after all, that one person perceives that another is experiencing pain. Viewing pain as a behavior opens a powerful explanatory framework and an avenue for intervention. Behavioral patterns, including sick-role behaviors and expressions of distress, develop as a function of contingencies (rewards for specific actions) in the individual's environment, and such patterns change in response to changes in those contingencies. Some chronic pain behavior, therefore, may be learned. Learned pain behaviors stem from environmental contingencies rather than perseverating nociception.

Chapter 26 provides a review of psychiatric disorders that may complicate the evaluation of a chronic pain patient, accentuate abnormal illness behavior, or confound efforts to rehabilitate the patient. The review follows *Diagnostic and Statistical Manual*, Fourth Edition, criteria, discussing psychiatric disorders that appear most commonly in pain clinics. The chapter illustrates how one might view these disorders and their effect on pain and sick-role behavior from different perspectives. Several explanatory models exist for these disorders and how they may affect illness behavior. Chapter 26 briefly describes them.

Section C. Vascular, Cutaneous, and Musculoskeletal Pains - Introduction

John D. Loeser

Chapter Reference

This section is devoted to consideration of the disorders of the musculoskeletal system that produce acute or chronic pain. In the United States and most other industrialized nations, disorders of muscles, tendons, fasciae, bones, joints, and ligaments are the most frequent cause of pain, disability, limitation of activity, and impairment. Issues related to impairment and disability are discussed in Chapter 17. The part of the musculoskeletal system most frequently affected is the back or spine, followed by the lower extremities and hips and then upper extremities and shoulders.

In Chapter 8 it was emphasized that pain caused by disorders of deep somatic structures that make up the musculoskeletal system are associated with localized and referred pain, together with skeletal muscle spasm and tenderness, either locally if the structure is superficial or in the region of the referred pain if the lesion involves deep structures. The tenderness is usually not severe, and, like the pain, is not evenly distributed; one or more areas of maximal tenderness are found over the structures normally more sensitive to pressure. These tender spots in the area of reference should not be confused with the deep tender areas or trigger points that are found in myofascial pain syndromes. Referred tender spots usually correspond to the points of maximal spontaneous pain, whereas trigger points are also located outside the distribution of the pain. Not infrequently, there are also autonomic disturbances, the type depending on the causative lesion.

The chapters in this section are presented in order of clinical importance (incidence, prevalence, and difficulty in diagnosis and treatment) of the disorders. The arthritides are considered first because they afflict approximately 15% of the American population and cause sufficient pain, suffering, and disability to prompt over 25 million Americans to seek medical attention each year.[1] The next chapters are devoted to myofascial pain syndromes, which, although not recognized by many physicians, are a common cause of pain and disability among the general population. Fibromyalgia is, of course an enigmatic musculoskeletal disorder that affects women primarily and often leads to profound disability. The chapter on trauma includes discussion of major and minor trauma and a special discussion of athletic injuries. The next two chapters discuss dermatologic and vascular pain syndromes that are often difficult for the pain physician to diagnose and treat. The final chapter on pain after spinal cord injury is a new addition to this text, as it was not covered in detail in the prior editions. We have tried to include some data on prevalence for each of these conditions, but epidemiologic studies are often scarce.

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Section D. Pain in Malignant Diseases - Introduction

John D. Loeser

We have greatly expanded the discussion of cancer pain in this edition to reflect the dramatic increase in knowledge and concern about the optimal management of patients with pain due to cancer. All of the material in this section is completely new; it is one of the few sections of our text that has virtually no carryover from prior editions.

Chapter 35 and Chapter 36 address general issues in the diagnosis and treatment of cancer pain. Chapter 37 presents information on the use of radiation and chemotherapy for the treatment of pain associated with cancer. Oral mucositis, a common problem in patients receiving bone marrow transplants and in those receiving orofacial radiation therapy, is discussed in Chapter 38.

Pain in acquired immunodeficiency syndrome is the subject of Chapter 39; this protean disease is usually characterized by multiple sites and causes of acute and chronic pain. Finally, palliative care, a new specialty of medical practice that includes much pain management, concludes this section.

Section E. Acute Pains - Introduction

John D. Loeser

Chapter 41, Chapter 42 and Chapter 43 present information on the management of postoperative pain, burn pain, and posttrauma pain as developed at the University of Washington. The mechanisms underlying these acute pain states are probably similar, but the strategies utilized by pain management physicians must be designed for the specific situation. The treatment of postoperative pain begins with the preanesthetic visit and the surgeon's operative and postoperative intentions. Burn and trauma pain do not permit individualized preplanning, but must be dealt with as the patient presents to the treatment facility and during his or her hospitalization and recovery periods. The standards published by the Joint Commission on Accreditation of Healthcare Organizations in 1999 will force American hospitals to focus more on the adequacy of their acute pain management. Bonica would have been thrilled with this development in the war on pain.

Chapter 44 (Pain and Its Management in Children) and Chapter 45 (Aging and Pain) address the special diagnostic and therapeutic needs of people at the beginning and end of life. These chapters include both acute and chronic pain management issues. Unique technical and ethical issues need to be considered when dealing with these groups of patients.

Part IV Regional Pains - Introduction

John D. Loeser and Donna Kalauokalani

Part IV consists of six sections, each of which is devoted to a region of the body. There is also a discussion of epidemiology, included in this introductory section. Each regional section commences with a chapter that provides an overview of the anatomy and physiology, with particular emphasis on the nerve supply of that region. A comprehensive table summarizing the etiology and differential diagnosis of regional pains concludes the first chapter in each section and precedes the individual chapters on painful conditions involving different organ systems in that region. Such a tabular listing of diseases and differential diagnoses was a feature of the first edition of this book and proved to be a valuable feature; we have therefore continued it. The reader can use the table to make a tentative diagnosis based on key features of the pain syndrome and then move to the relevant chapter in each section. The arbitrary system of classifying pain syndromes by region and systems was also a feature of the first edition of this book and proved to be one of Bonica's major contributions to the diagnosis and management of pain. The International Association for the Study of Pain Subcommittee on Taxonomy adopted this scheme in the development of its taxonomy of pain as axes 1 and 2. We continue to use this strategy of classification because it seems to be of heuristic value and to be consistent with the International Association for the Study of Pain taxonomy (see Chapter 2).

Many chapters in Part IV present painful disorders not discussed in Part III, whereas other chapters overlap the discussions of generalized diseases covered in that part. We intend to minimize the redundant material; consequently, the reader should refer to the relevant chapter in Part III to obtain complete information on a regional pain syndrome that could also occur in another part of the body. For example, herpes zoster can occur in the lower extremity and sacral dermatomes, but it is only mentioned in Chapter 77; the reader should consult the discussion of the disease in Chapter 22, in Part III. Similarly, treatment methods may appear in the chapters in Part IV, but detailed discussion of the potential risks and benefits of each form of treatment can be found in Part V. For example, tic douloureux is discussed in Chapter 47, but a detailed description of the surgical management of tic appears in Chapter 107.

Although we have divided the human body into six regions for ease of presentation, no one should assume that we believe that this is an appropriate way to provide comprehensive pain management diagnostic or treatment services. All pain symptoms are the product of electrochemical events within the brain, and that organ responds not only to messages from specific sites within the body, but also to past experiences, the present environment, and anticipated consequences. The physician must address the patient as a person and not as a set of symptoms.

EPIDEMIOLOGY AND PAIN MANAGEMENT

Epidemiology is the study of variance in the occurrence of disease and the reasons for that variation. It is a science of structured observation and appraisal of the nature and strength of inferences drawn from those observations (1). This definition incorporates both descriptions of the contents of the discipline and the purpose for which epidemiologic investigations are carried out. Epidemiology focuses on various measures of disease occurrence and risk used to measure the distribution, determinants, and natural history of disease in a population. Application of epidemiologic principles to the judgments and intuitions that comprise the practice of pain management is important to better understand the distribution and natural history of pain conditions, as well as to improve diagnosis, prognosis, and treatment.

Although this section focuses on epidemiologic concepts, many biostatistical concepts and methods are applied in epidemiologic research. Biostatistical methods are used to measure and explain overall variation (some of which is due to errors); distinguish between random versus meaningful and reproducible variation; and facilitate interpretations of data used for diagnosis, prognosis, and treatment. Three important considerations of data collection and analysis are (a) accuracy and precision, (b) random error and bias, and (c) intra- and interobserver and patient variability. These are discussed briefly as they relate to the discussion of epidemiologic concepts.

For the clinician who treats chronic pain, this section discusses basic epidemiologic concepts and measurements, the study of causation in epidemiologic research, an overview of common research designs, assessment of risk and treatment efficacy, biostatistical methods, and policy implications.

Disease States and Events

Typically, disease is regarded as an adverse health state that characterizes an individual over a period of time. Onset of the disease state is an event that occurs at a particular point in time. This is depicted in Figure IV-1. Some conditions are more naturally regarded as events that occur at a certain point in time with negligible duration—for example, fracture of a femur or rupture of the Achilles tendon. States and events may occasionally be defined in terms of each other—that is, the onset of a disease state is an event that occurs at a particular point in time (e.g., onset of shingles marks a bout of acute herpes zoster) or prior occurrence of a certain event may be required for some conditions (e.g., amputation and phantom limb pain).

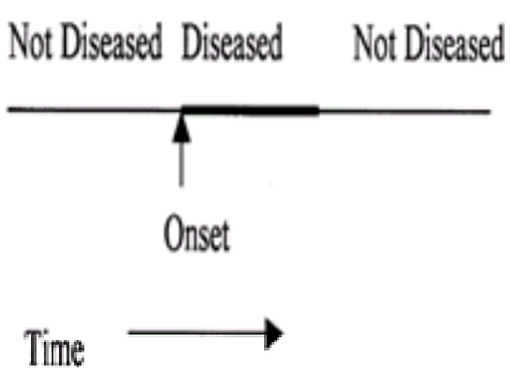

Figure IV-1. Health-related states and events. A disease can be regarded as an adverse health state that characterizes an individual over a certain period of time.

An operational definition is used in deciding whether a given person has the condition. Whether the definition of the condition is simple, complex, or study-specific, the basic approach to quantifying disease frequency remains unchanged. Defining a population requires similar criteria specification for membership. Criteria may involve geographic boundaries, membership in a predefined group, or specification of a time or time interval. In populations monitored over time, it is important to know whether membership in a population can change. If no changes occur, this is called a “fixed cohort.” If membership changes during the observation period, this is called a “dynamic population.” Epidemiologic research on chronic pain aims to investigate pain in populations as a dynamic process characterized by interactions

between the patient, causative agents, and the environment. Von Korff (2) has described a dynamic population model such that, at any given point in time, persons may be pain free or experiencing acute, recurrent, or persistent pains, with or without dysfunction.

Epidemiologic Measures: Frequency and Severity

Frequency

Characteristics of a pain condition to consider in determining its importance are frequency and severity. The frequency of a pain condition is usually measured by its incidence rate and prevalence. *Prevalence* refers to the proportion of a population with a condition at a given point in time. Prevalent cases are persons who have the condition at a specified point in time. Prevalence is a proportion that has no units; people in the numerator are also in the denominator. Hence, the proportion accounts for population size, permitting valid comparisons among populations of different sizes.

The “point in time” used for determining prevalence may refer to any of several scales. For example, one could refer to calendar time to determine the prevalence of low back pain in Seattle on July 1, 1998. This is known as “point prevalence.” Alternatively, age is often used as a time scale, for example, to determine the prevalence of postherpetic neuralgia among 65-year-olds, regardless of when they achieved age 65 in calendar time. Another method is to use the time since an event occurred, for example, to determine prevalence of phantom limb pain among amputees 6 months after amputation. The proportion of persons affected by the condition during a defined period of time is sometimes referred to as “period prevalence,” or if the period of interest is a lifetime, “lifetime prevalence.”

Incidence is the measure of the frequency at which new cases of a disease are occurring in a population over time (3). For different pain states, it is the *onset* of that state whose frequency is measured over time. Incidence is expressed as the ratio of the number of new cases of a condition during the given time period and the population at risk for developing the target condition during the given time period. Thus, it represents the probability, or rate of onset, of a condition among people with no prior history. The denominator does not refer to any specific high-risk group, but includes all members of the population of interest whose probability of becoming a new case is greater than zero. For example, if one is studying the annual incidence of neuropathy among U.S. adults with diabetes mellitus, then the population at risk for developing the target condition is all adult diabetics residing in the United States with the exception of those who already have diabetic neuropathy before the beginning of the study time period.

Severity

Severity is expressed by a variety of measures that are used to estimate severity of the condition and the impact of pain management interventions. Traditional measures of severity include mortality, morbidity, and survival. More recently, outcome measures have been developed that incorporate quality-of-life domains that attempt to capture functional status and preference (4,5). Such measures are important to determine the significance of pain conditions and the impact of interventions. When these measures are combined with an understanding of the prevalence in a defined population, one can quantify the burden of the condition of interest in the population—for example, to help determine the level of health care resources required to meet current needs of people with the condition (6).

Natural History of Disease: Expressing Prognosis

Another objective of epidemiology is to define the natural history of a disease in quantitative terms. Natural history quantifies different aspects of clinical course, such as the interval between exposure to a risk factor and onset of the condition, episode duration, the likelihood of recovery or relapse, the likelihood of death (mortality rates and survival rates), and the likelihood of becoming disabled.

Patients seen in tertiary pain centers represent a small proportion of patients in the general population who experience pain. Therefore, inferences generated about this select group may help in identifying the specific factors or characteristics that place them at high risk and in modifying those factors. In contrast, study of individuals with pain both in and outside of the treatment setting would allow for investigation into the etiology, natural history, and risk factors for pain as distinct from factors associated with seeking treatment.

As new modes of intervention are developed, we can compare results of using such new modalities to the baseline data to see whether the new approaches are truly effective. The new measures of intervention subjected to evaluation may be preventive measures, therapeutic measures, or new modes of health care delivery. Conditions with higher frequencies in specific populations, conditions of greater severity, or those with high cost to society may merit greater attention in terms of preventive efforts, resources, and research (7).

Study of Causation in Epidemiologic Research

Epidemiologic research often seeks to identify causes of disease in the environment, nutrition, lifestyle, or genes of individuals and populations. When such causes are removed or modified, a reduction in disease burden follows. Three fundamental types of causations in order of decreasing causal strength include a sufficient cause, a necessary cause, and a risk factor. A sufficient cause precedes a disease, and if present, the disease will occur. A necessary cause also precedes a disease, and if absent, the disease will not occur. A risk factor is a characteristic that, if present, increases the probability of a particular disease in a group of persons who have the factor compared with an otherwise similar group who do not. A risk factor is neither a sufficient nor a necessary cause of the disease.

Three types of associations between a possible cause (risk factor) and an effect (disease) include a directly causal association, an indirectly causal association, and a noncausal association. If an association is causal, the pathway may be direct or indirect depending on whether there are intermediary factors between the cause and effect. In contrast, the association between a factor and a condition may be statistically strong and yet not be causal. Research to determine causation is complicated, particularly because of the need to rely on observational methods that usually do not have experimental control. Consequently, among the most common challenges encountered in causal research is to deduce differential and nondifferential (random) errors.

Several possible sources of error may obscure true causal relationships. *Bias* is an introduction of error in the measurement or interpretation of data that systematically favors one result. *Random error* produces findings that are too high and too low in approximately equal amounts, owing to random factors. Random error can, but usually does not, introduce bias into the results of an analysis. *Confounding* is confusion of two supposedly causal variables so that part or all of the purported effect of one variable is actually due to the other. *Effect modification* occurs when the strength or direction of the influence of a causal factor on outcome is altered by a third variable, the effect modifier.

Although it is important to appreciate the types of challenges described above, it is also necessary to understand two other concepts related to causation. First, one causal factor may increase the risk for several diseases. For example, diabetes mellitus may be a risk for several pain conditions, including carpal tunnel syndrome and peripheral neuropathy. Second, one disease may have several different risk factors. Although diabetes is a risk factor for carpal tunnel syndrome, it is only one of several contributing factors. Other factors may include occupation and recreational activities that involve repetitive movements. Assessing the relative amount that each factor contributes to a disease, also known as *attributable risk*, is discussed below. Identifying causal factors for diseases and reducing or eliminating exposure to those factors can serve as a basis for prevention programs. Two important epidemiologic study designs used to define factors that are associated with pain conditions are the case control and cohort study designs.

Common Research Designs Used in Epidemiology

Case Control Study

In clinical settings, we often observe patterns across patients and hypothesize about the relationship between exposures or characteristics and the development of a particular condition (Fig. IV-2). In a case control design, both cases and controls are chosen based on a condition or disease rather than on exposures or risk factors. A clinician doing independent medical examinations for patients presenting with upper extremity disorders observes a number of patients with carpal tunnel syndrome. He or she also notes that virtually all patients seen with carpal tunnel syndrome are obese and suggests that there is an association between obesity and the development of carpal tunnel syndrome. Although such observations are interesting, they are difficult to interpret without a comparison group of patients without carpal tunnel syndrome. It is possible, for example, that those patients with and without carpal tunnel syndrome have the same rate of obesity. The question, therefore, is whether the prevalence of obesity is greater in persons with carpal tunnel syndrome (cases) than in persons without carpal tunnel syndrome (controls). To determine the significance of such observation in a group of cases, a comparison or control group is needed. Without such a comparison, these clinical observations would only constitute a case series without a possible conclusion based on comparative observations. The case control study design exemplifies the

comparison component of epidemiologic investigation. It is particularly useful when disease occurrence is rare and generally requires a small study group. This feature makes these studies relatively inexpensive to carry out. This design is often a first step in identifying an association between exposure and a disease or condition. If, in the example above, the apparent association is true, one still cannot be certain whether carpal tunnel syndrome predisposes to obesity, or vice versa, because the temporal sequence of exposure and outcome in a case control study is uncertain. To reach further conclusions regarding the association would require further study. Schlesselman (8) provides an in-depth discussion of this study design.

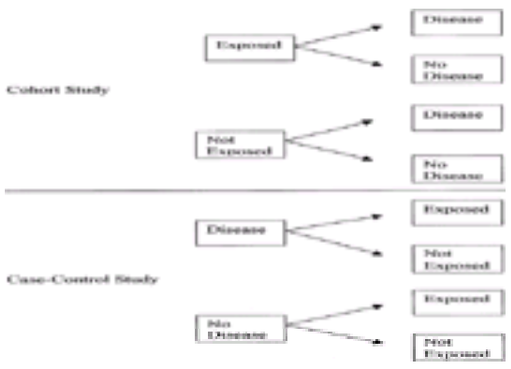

Figure IV-2. Design of cohort and case control studies.

Cohort Study

A cohort study forms groups based on exposure status at the beginning of the study period. Relative sizes of exposed and nonexposed groups may not necessarily reflect true prevalence of exposure in the source population. In contrast to randomized trials, there is no random assignment of subjects to exposure groups, only classification of exposure status. This design allows direct measurement of disease incidence in both groups, permitting comparison in terms of ratios or differences. Thus, cohort studies allow for determining both absolute and relative measures of risk.

The cohort design is most desirable when the exposure of interest is rare. On the other hand, it is impractical for studying rare diseases. Prospective cohort studies have the advantage of demonstrating a better temporal relationship between exposure and outcome and have less potential for recall bias. Among the limitations of the cohort design, however, is that they generally require large sample sizes and therefore tend to be expensive to carry out. Retrospective cohort studies depend on data from the past, often require less time, and are generally less expensive. Among disadvantages for the retrospective cohort design are that the temporal relationship between exposure and disease is often more difficult to establish and enhanced susceptibility to bias both in assessing exposure and outcome (9).

Nested Case Control Study

The nested case control design is a hybrid design in which a case control study is nested in a cohort study. By combining elements of both designs, it offers a number of advantages. Recall bias is eliminated because exposure data are obtained before the disease develops. Exposure data are likely to represent the preillness state, with little assessment bias. Finally, costs are reduced, because data acquisition is needed only for the subjects later chosen as cases or controls (10).

Cross-Sectional Studies

Cross-sectional studies are characterized by the simultaneous collection of exposure and disease outcome data. Comparison is made between the prevalence of the disease in exposed subjects and nonexposed subjects or between the prevalence of exposed subjects with disease and exposed subjects without disease. This design is limited in its ability to determine the temporal relationship between exposure and disease. Although there is limited ability to derive causal inferences, it can provide direction for further research by using one of the aforementioned designs.

Assessment of Disease Risk

Measures of risk compare differences of incidence or prevalence among people differing in a risk factor. Risk factors for developing, enhancing, or detecting a pain condition may be distinct from one another, yet differentiation between these various types of risk factors may be difficult.

Characteristics to consider in determining the importance of a risk factor are its frequency and *magnitude of risk*. A person is at risk for a condition if it is possible for him or her to develop it during a time period of interest. Reasons for a person not being at risk for a condition include the circumstance in which the person already has the condition, was never biologically capable of developing the disease, or has acquired immunity. Analogous to its use for conditions, the frequency of a risk factor or “exposure” is measured by prevalence and incidence.

Distinguishing between those who have a risk factor being studied from those who do not and between those who have a disease from those who do not is seldom simple and is subject to both random error and biases. In addition, the need to analyze several independent variables at the same time (including how they interact) and the need to measure different degrees of strength of exposure, duration of exposure, or both can complicate understanding. Depending on the risk factor, it may be difficult to determine the time of onset of exposure to it. Another problem is the need to measure different levels of disease severity. Despite the complexities, much epidemiologic research relies on the fundamental dichotomies that are commonly presented in the form of the 2 × 2 table, as shown in Table IV-1.

		Disease status		
		Present	Absent	Total
Risk Factor	Present	a	b	a + b
	Absent	c	d	c + d
Status	Total	a + c	b + d	a + b + c + d

Interpretation of the cells:
a, subjects with both the risk factor and the disease; b, subjects with the risk factor but not the disease; c, subjects with the disease but not the risk factor; d, subjects with neither the risk factor nor the disease; a + b, all subjects with the risk factor; c + d, all subjects without the risk factor; a + c, all subjects with the disease; b + d, all subjects without the disease; a + b + c + d, all study subjects.

TABLE IV-1. Standard 2 × 2 table for demonstrating the association between a risk factor and a disease

The magnitude of risk associated with a factor is defined in absolute terms or in relative terms. The method used will depend on the type of the study performed. Whenever possible, it is important to examine both the absolute and relative risks because they provide different information. Absolute risk is the rate of occurrence of the condition in a particular group. Relative and attributable risks are two measures of the association between exposure to a particular factor and a particular outcome. A risk factor can predict the outcome but it may not necessarily “cause” the condition or predict benefit from an intervention.

Relative risk is the incidence of disease among persons with the risk factor compared to the incidence among those without the risk factor. A relative risk of 5 suggests that persons with the risk factor are five times as likely to develop the condition as persons without the risk factor. Relative risk does not measure the

probability that any given person with the risk factor will develop the condition.

Absolute difference in risk is the difference between the risk in the exposed group and the risk in the unexposed group. Also known as the *attributable risk*, it is expressed as AR = [*a*/(*a* + *b*)] – [*c*/(*c* + *d*)] (see Table IV-1 for definitions of *a, b, c,* and *d*). *Relative risk* is the ratio of the risk in the exposed group to the risk in the unexposed group: RR = [*a*/(*a* + *b*)] / [*c*/(*c* + *d*)]. A large relative risk that applies to a small segment of the population may actually produce few cases of disease, whereas a small relative risk that applies to a large segment of the population may produce many cases of disease. The odds ratio (OR) is the odds of exposure in the diseased group divided by the odds of exposure in the nondiseased group: OR = (*a/c*)/(*b/d*) = *ad/bc.* When the disease or condition is rare (i.e., *a* and *c* are small relative to *b* and *d*), the odds ratio is a good estimate of the risk ratio.

Assessing Efficacy of Treatment Measures

The rational evaluation of clinical pattern recognition (symptoms, signs, laboratory tests) demands critical appraisal of how this clinical finding has behaved previously among groups of patients with the same conditions. Similarly, the rational selection of a treatment for each patient requires appraisal of how similar patients have fared with various treatments in the past. If, on average, patients experienced better clinical outcomes and fewer side effects while on one treatment compared with untreated (or differently treated) patients, we will likely prescribe that regimen (other variables and costs being equal).

When exposure cannot be assigned at random, observational studies are relied on or performed. However, randomized studies are superior to observational studies because this experimental form reduces the probability that the results obtained were due to random errors. It does not, however, necessarily prevent systematic errors or bias. Commitment to randomized trials as the standard of proof should be especially strong when the public health implications are great. Clinical trials are discussed in Chapter 82.

Data Collection and Analysis Considerations

As alluded to earlier, biostatistical methods are used to compensate for unavoidable errors in clinical data. Two distinct but related goals of data collection and analysis are to promote both accuracy and precision. *Accuracy* refers to the ability to obtain the correct measure on average, whereas *precision* refers to the ability to provide the same or very similar results with repeated measurements (10). This is also referred to as *reproducibility* or *reliability*. A high degree of precision is not proof of accuracy.

The study of accuracy is important in deciding the usefulness of a medical test as applied to a particular population. Important measures of test function are sensitivity, specificity, and predictive value. Although the definitions of these measures are straightforward, several factors influence whether a test result for a particular patient is accurate and whether the test in general is useful for a particular population. Two such factors are (a) stage of the condition or disease and (b) spectrum of disease or condition in the study population.

Sensitivity refers to the ability of a test to detect a condition when it is present. It is expressed as the proportion of persons with a condition who correctly test positive when screened: *a/a+c*. A test with poor sensitivity will miss many cases and therefore produce a large proportion of false-negative results. *Specificity* refers to the proportion of persons without the condition that correctly test negative when screened: *d/b+d*. A test with poor specificity incorrectly labels persons as having the condition. The incorrect labeling of true negative results produces false-negative cases. False-positive results can produce a whole series of untoward consequences, including psychological problems and a cascade of further tests and procedures.

Predictive values follow a different direction of analysis to answer perhaps a more clinically relevant question—that is, if the patient's test result is positive, what is the probability that the patient has the disease being tested? Positive predictive value indicates what proportion of the subjects who have positive test results have the disease or condition: *a/a+b*. Negative predictive value indicates what proportion of the subjects who have negative test results do not have the condition: *d/c+d*. Both the prevalence of the condition and the specificity of the test affect the predictive value (3).

Measuring Pain: Intervariations and Intravariations

With pain conditions, we are making observations based on a construct (see Chapter 2). There is, as yet, no laboratory test or imaging study that affirms or refutes the patient's report of pain on quantifiable terms (11). Thus, we are bound not only to measure the variation of symptoms *within* individuals—for example, how individuals' bodies may respond differently—but also the variation in patient report *between* individuals—for example, qualitative variation in how patients express their experiences. Issues dealing with the measurement of pain and specific methods used to measure this are discussed in detail in Chapter 15.

It is also important to determine the extent of observer agreement of the same phenomenon. If there is high intraobserver agreement, high interobserver agreement, or both, the data in a study are considered highly reliable and will elicit more confidence.

Evaluation and Policy

Finally, epidemiology can provide the foundation for developing public policy and regulatory decisions relating to environmental problems. For example, which occupations are associated with increased risk of injury and disability in workers? What types of regulations are required? Understanding the burden of disease in the community is crucial for planning health services and facilities and to training future health care providers.

Epidemiologists are concerned with human ecology and, in particular, the impact that health interventions have on disease patterns and on the environment. An ecological perspective suggests that changing only one element in an ecosystem is virtually impossible and that interventions send out ripples of a secondary effect. This is consistent with the biopsychosocial model for pain that is the cornerstone of this text.

By viewing disease patterns ecologically, the interaction between and among diseases may be appreciated (12). Synergy occurs when the impact of two or more diseases on an individual or population is greater than the sum of the separate effects of each individual disease. Just as malnutrition and infection often occur in the same populations and each exacerbates the other, such synergy is observed for chronic pain states and depression (13).

Even with good evidence that an intervention is *efficacious* under *ideal* or controlled conditions, it may be less *effective* in a *routine* practice setting. Potential benefits of an intervention must be weighed against potential harms, costs, and implementation considerations.

CONCLUSIONS

Epidemiologic concepts can be applied to increase understanding of pain conditions. An epidemiologic approach increases understanding through addressing a set of questions. First, what are the extent and magnitude of the problem? Does a certain group of individuals suffer more or less from a given condition compared to other groups? Does variation in sickle cell disease risk among black Americans belonging to different geographic and cultural groups exist? Are these diseases or conditions occurring more or less frequently in recent times compared with the past? Second, what is known about the etiology and pathogenesis of these conditions and are risk factors unique to certain populations? What are relative contributions of environment and genetic risk factors in accounting for the observed frequency and distribution of these diseases? Finally, what prevention and control strategies are available for these diseases and conditions, and has their effectiveness been evaluated? To what extent are described interventions applicable to different populations? In many chronic pain syndromes, social and ecological influences are of particular importance and thus appear to call for an integration of the social sciences (e.g., anthropology, sociology) and epidemiology for future research. The chapters in Part IV all contain some references to epidemiologic information. However, the field of pain management is in need of well-constructed, systematic epidemiologic studies.

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Low Back Pain - Introduction

With Introduction by John D. Loeser

Chapter Reference

Low back pain is a common complaint in any developed nation. It is a major cause of health care consumption and by far the most common reason for disability in the working years (1,2). Although headache may be more common, the impact of low back pain on a society is far greater. The importance of the back in all human endeavors is often overlooked by health care providers, but Melville certainly understood this region of the body. At the height of the phrenology craze he wrote the following:

> For I believe that much of a man's character will be found betoken in the backbone. I would rather feel your spine than your skull, whoever you are. A thin joist of a spine never yet upheld a full and noble soul. I rejoice in my spine, as in the firm audacious staff of that flag which I fling half out to the world.
>
> *Moby-Dick*

This chapter is divided into five sections, each of which focuses on an aspect of the low back pain problem. In addition, the reader is referred to Chapter 17, in which disability and functional assessment are discussed. Section A, by Bigos and Müller, is aimed at the diagnosis and management of acute low back pain. Wise and Andersson, in Section B, have addressed chronic low back pain. Oaklander and North present the problem of failed back surgery syndrome and its management. Although this is primarily an American problem because of our excessive rate of surgery for low back pain, it is not an unknown phenomenon in other countries. In Section D, Block has addressed the issue of using psychological evaluation to predict surgical outcomes. Finally, in Section E, Erjavec discusses the role of epidural corticosteroids in the treatment of low back pain. Although these are five important general issues, an entire book of the size of this text could be written about all the facets of low back pain. Many books have, in fact, been written on this topic, all too often to promote totally unscientific theories and treatment strategies. There is some reason to believe that many of the treatments advocated for back pain are not only ineffective but also may increase disability and health care consumption.

The incidence, prevalence, and costs of low back pain have been the subjects of numerous reports and research projects (3,4 and 5). In addition to the customary epidemiologic issues surrounding such studies, there are inherent difficulties in the ascertainment of low back pain and its costs. First, pain is not a discrete entity that can be exactly measured. There is no tank into which one can insert a dipstick and determine the volume of contents. Second, the researcher is totally dependent on the patient's complaint or behavior. There is no gold standard to measure low back pain. Third, the validity of the patient's complaint is unprovable. There is enough literature on eyewitnesses to give one cause for concern. A patient is, of course, the epitome of an eyewitness. Fourth, low back pain is certainly a condition with heterogeneous precipitating and perpetuating factors. Finally, the legitimacy of extrapolating from one population to another is often unclear, at least in part due to the various etiologic agents that may play a role in low back pain.

The best data currently available suggest that more than three-fourths of all people will have low back pain at some time in their lives. The annual prevalence has been reported to vary from between 15% and 45%. Of course, the severity of an episode is not ascertained in most of the reported studies, and therefore the significance of low back pain remains unclear. Much depends on what a person is expected to do with his or her back, independent of what messages the back is sending to the brain. Back pain is the most common cause of activity limitation in the working years of 18 to 55 in the United States and in every developed country that has yet been studied. It is responsible for 10% to 15% of all work absences in the developed countries. Similarly, between 2% and 8% of the workforce in a developed country is disabled by back pain annually. A variety of interventions designed as primary prevention for low back pain have not been effective.

Health care consumption for low back pain is enormous. In 1990 in the United States there were 15 million office visits to physicians for low back pain, second only to the common cold as a symptomatic reason for a physician visit. This accounts for 2.8% of all office visits to physicians. The number of visits to chiropractors was probably even greater, but reliable data are not available on this topic (6). Similar or even higher rates of office visits are found in the United Kingdom and Sweden (4). Rates of hospitalization for low back pain have decreased in the United States over 20 years, while the rates for surgery have significantly increased (7,8). Indeed, there are wide regional variations within the United States for the surgical management of low back pain and even greater variations in the rate of surgery in 13 countries contrasted with the United States (9). From this type of data one could conclude that the American back was disintegrating at a rate faster than in any other country, but it seems more likely that the large number of surgeons has something to do with the rate of surgery. In fact, with the exception of Sweden, whose neurosurgeons and orthopedists seem to do half as many cases as in 11 other countries, the number of cases done in a country is 11.1 times the number of eligible surgeons and is not as directly related to the population at risk. Clearly, we do not understand the reasons for wide variations in the use of health care in the diagnosis and treatment of low back pain. This would be a fertile arena for health services research.

The natural history of back pain has been studied in many countries; this certainly is a recurrent symptom for most patients, even though each episode has a rather benign prognosis. Approximately 25% of patients have a recurrence within 1 year and 75% in their lifetime. By 6 weeks, 65% of patients have recovered from an episode of low back pain. By 12 weeks, 85% are without significant symptoms. After 12 weeks, recovery is not likely: Fewer than half of those off work for 26 weeks ever return to work and, after 104 weeks, the likelihood of returning to work is virtually nil. Being a participant in a compensation system delays return to work after an episode of low back pain, whether or not an operation was performed and whether or not the injury was work related. In fact, compensation is best thought of as a comorbidity, as it adversely affects many different outcomes measures (10). It is not known whether the failure to return to work is due to events within the patient's back or is more related to workplace and other social, cultural, and economic factors. Predictors of return to work have been shown to include age, educational level, back pain alone rather than sciatica and low back pain, and a variety of job characteristics. As is true for most chronic illnesses, psychological distress and depression are correlated with symptom persistence. We certainly need further studies on the etiologies for low back pain and their successful treatment. It is unlikely that a single strategy for dealing with all patients with low back pain will be forthcoming, as this is certainly a protean disorder that involves multiple systems both within and without the patient's body.

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Section A. General Considerations - Introduction

John D. Loeser

The final part of this text consists of eight sections, each of which has chapters that describe specific therapeutic modalities for the symptomatic control of both acute and chronic pain. We use the word *symptomatic* to emphasize that these treatment strategies are not intended to eliminate the cause of the pain, but rather to reduce the pain, suffering, and pain behaviors without recourse to the underlying disease process. Methods to eliminate the cause of the pain are discussed when appropriate, in the regional pain syndrome chapters in Part IV. We have attempted in this part to present the therapeutic modalities in order of their frequency of usage by all health care professionals and not just specialists. Thus, Sections B and C present noninvasive techniques that physicians apply universally; Sections E, F, and G contain information about more invasive techniques that are not likely to be used by those who do not have specialist training. Section H describes the results of multidisciplinary pain management, which, although certainly not invasive, is a relatively infrequent strategy used in far fewer pain treatment programs than, for example, nerve blocks or surgery.

Section A (Chapter 81 and Chapter 82) contains two new and essential chapters for those who wish to evaluate treatment outcomes and ascertain the roles of nonspecific treatment effects. These chapters appear deliberately at the beginning of this part, and clinicians should start by reading them. The information in these two chapters is basic to an understanding of all types of clinical trials. Those who wish to understand the significance of statements of efficacy for treatments must begin with the methods of assessing outcomes and the ubiquitous nature of nonspecific responses to all forms of treatment.

Section B, Chapter 83, Chapter 84, Chapter 85, Chapter 86 and Chapter 87, discusses the pharmacologic agents commonly used for the management of both acute and chronic pain. We have divided the discussions for convenience into chapters on systemic nonopioid drugs, systemic opioid drugs, psychotropic drugs, anticonvulsant and membrane-stabilizing drugs, and a new chapter on topical drugs. There can be little question that drugs have been, and are likely to continue to be, the mainstay of the treatments of both acute and chronic pain states. New insights into the mechanisms of drug action will likely lead to the introduction of new agents in the immediate future, it is hoped with beneficial results for the patients.

Section C contains Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92, Chapter 93 and Chapter 94, on psychological and psychosocial techniques in the management of chronic pain. These include contingency management, cognitive-behavioral therapy, biofeedback, hypnosis, relaxation therapy, and psychotherapy. A new chapter on the use of psychological strategies to enhance the patient's motivation to change his or her lifestyle and reduce the disabilities associated with chronic pain and its concomitant behaviors concludes this section.

Section D, Chapter 95, Chapter 96, Chapter 97 and Chapter 98, includes discussions of operative and nonoperative orthopaedic procedures for the management of musculoskeletal pains, physical therapy and rehabilitation medicine, acupuncture, and transcutaneous electrical stimulation. It addresses musculoskeletal pain syndromes and pains of uncertain etiology. Section E, Chapter 99, Chapter 100 and Chapter 101, describes methods of implanted electrical stimulation of nerves, spinal cord, and brain, often called “neuroaugmentative” by their proponents. Section F, which contains Chapter 102, Chapter 103 and Chapter 104, describes anesthesiologic techniques for pain management: regional anesthesia with local anesthetic agents, regional analgesia with opioids, and regional analgesia with neurolytic blocks. Section G consists of Chapter 105, Chapter 106, Chapter 107 and Chapter 108, on ablative neurosurgical procedures, with one chapter devoted to the surgical management of tic douloureux. Section H contains Chapter 109, which discusses multidisciplinary pain treatment programs and their outcomes. The final chapter (Chapter 110) presents some of our beliefs and aspirations about the future of pain research and management.

The short introduction that precedes each section puts the treatment modalities into historical perspective. We have edited the chapters to follow a consistent format, with an introduction that assesses the current status of the therapy, an overview of the contents of the chapter, and selected references. Next is a presentation of the basic considerations that describe the rationale for the treatment methodology based upon scientific information and then a discussion of indications for this type of treatment. After a description of the technique itself, the text discusses the results and complications.

When techniques are simple and suitable for use by all physicians managing pain patients, the text provides sufficient detail to allow the physician to base his or her treatment upon what is written here. The presentation of more specialized treatment strategies such as major nerve blocks or surgery provides only enough detail to allow the generalist physician to understand the principles of a procedure and its risks and benefits. With this information, one can counsel patients and reach appropriate management decisions. Those who wish to perform interventional therapies need more instruction than this book can provide before they treat patients. There is, of course, some overlap with the information in Parts III and IV, but this part is designed to contain a comprehensive overview of all of the currently used treatments for pain. It is also important to recognize that cognitive/behavioral strategies require specialized training for their optimal use.

The editors have obviously selected from the almost infinite varieties of treatment methods for both acute and chronic pain. As pain is ubiquitous, so are its treatments. We have focused upon those treatments that currently are offered by physicians and psychologists as well as those who customarily work in conjunction with these professionals. We have not included discussions of what is commonly labeled as *alternative health care*, such as chiropractic, homeopathy, naturopathy, massage therapy, or healing touch, to name just a few, because we believe that the conceptual basis for such therapies falls outside the canons of modern allopathic medical sciences. Moreover, they are rarely used by those who specialize in comprehensive pain management. The exception to this rule is acupuncture, which we include despite its utterly foreign conceptual basis for those trained in Western medicine. Thanks to former President Richard Nixon, acupuncture has swept across the United States (and elsewhere) and is in widespread use.

Those who are offended by our selection strategies would be wise to consider carefully Chapter 81 and Chapter 82 to understand some of our reason to include and exclude treatment modalities and approaches. We identify a progression in the history of pain management that follows upon the evolution of medical thinking from the reductionism of the nineteenth and early twentieth centuries, through the fusion of mind and body, as seen in psychosomatic medicine, to the current behavioral medicine perspective that links the events within a person's body to the surrounding world. Alternative health care strategies are often anachronistic and recidivist; they impede the evolution of new treatment strategies that incorporate the role of the environment in health and illness. On the other hand, the public attraction to many alternative therapies is a sign of the failure of modern medicine to acknowledge the reality of pain and to treat human beings as whole persons existing within a social framework rather than a collection of biological parts. The challenge for those who wish to espouse “alternative” health care is to develop a meaningful conceptual framework and to demonstrate specificity of treatment effects. The challenge for allopathic physicians is to provide compassionate health care that encompasses not only the search for a structural lesion, but also consideration of the patient as a human being. We believe that this part provides a comprehensive overview of the treatments employed by pain management specialists.

Chapter 110 completes this textbook by reviewing the past and present and looking into the new millennium. It provides a new way of looking at pain management concepts and opens a window into the world of ideas about pain.

Section B. Pharmacologic Therapies - Introduction

John D. Loeser

This section is devoted to the use of drugs in the management of pain. We have covered the systemic administration of nonopioids and opioids in Chapter 83 and Chapter 84, psychotropic drugs in Chapter 85, anticonvulsant and membrane-stabilizing drugs in Chapter 86, and topical medications in Chapter 87. The last chapter is a new addition to this text; this subject was not covered in the second edition of this book.

Opioids, of all drugs, probably have the longest known association with humans, for they were described by the ancient Sumerians more than 5,000 years ago. The juice of *Papaver somniferum* was known to the Greeks and the Romans as well as the pre–Christian era Hebrews. The German pharmacist, Friedrich A. W. Serturner, extracted an alkaloid from opium in 1803 that was soon known as *morphine*. Many other alkaloids have been identified and synthetic molecules constructed to mimic the naturally occurring drugs. The use of opioids has greatly expanded in the past 20 years as knowledge about receptors, endogenous opioids, and molecular biology has exploded (Chapter 84).

Nonsteroidal agents also have a long history: Salicylic acid obtained from willow bark was first recognized in Western literature by Stone in the early nineteenth century. The development of synthetic nonsteroidal agents has been prodigious; they are the most commonly used group of pharmacologic agents (Chapter 83).

Psychotropic medications also have a long history, although not exclusively for medicinal purposes. Today, antidepressant medications are frequently used in the management of chronic pain. A wide assortment of other classes of mind- and mood-altering medications is considered in Chapter 85. Anticonvulsants are also used frequently, as discussed in Chapter 86. These medications were once used exclusively for neuropathic pains with shocklike properties such as tic douloureux, but they have been found to be useful for many other types of pain.

Topical medication is a new aspect of pain management whose ultimate utility is not yet determined. Several classes of drugs have been administered this way and are discussed in Chapter 87. It is highly likely that some of the systemic drugs will be found to have useful properties when administered topically.

Pain management must include not only medications but also psychological and physical treatment strategies. Nonspecific treatment effects, discussed in Chapter 81, certainly are important aspects of the use of drugs and all other therapies. We must not overlook the fact that the giver of the pill, as well as the pill itself, is likely to have an impact on the patient. It is also essential to recognize the role of nurses in the administration of pain medications, especially in a hospital or clinic setting. Nursing education has dramatically improved in the past 2 decades in regard to pain treatment; patients have benefited from this development. Drugs are the most common method used to treat pains of all types. Optimal therapy is often denied our patients because of inadequate knowledge of pharmacology, inordinate fear of side effects, governmental policies, and patient reluctance to use effective therapies.

Section C. Psychological Techniques - Introduction

C. Richard Chapman

Pain is a psychological state. It depends on consciousness, it has perceptual and emotional features, and a person's expression of pain is a behavior that exerts a psychological impact on other persons. Chronic pain has become a socioeconomic problem, largely because it causes disability or limits productive behavior and not just because it requires costly, ongoing invasive treatment. One of the frustrating difficulties that pain specialists face in managing pain, particularly chronic pain, is that knowledge of the sensory neurophysiology of a pathologic pain rarely allows one to predict the impact of the pain on the patient's functional capability and quality of life. Moreover, much of the task of managing chronic pain and related disability is psychological rather than medical. Psychological aspects color every aspect of chronic pain management, from patient assessment to treatment adherence and rehabilitation. Given these considerations, it is surprising that well-established psychological interventions for pain play so small a role in the management of most pain patients. This section of the book is intended as a resource for physicians who need a general introduction to psychological techniques in pain management.

Many physicians in community practice continue to overlook the role of psychological factors in response and adaptation to chronic pain as well as the potential contributions of psychological interventions. There are three primary reasons for this. First, traditional medical education, including most continuing medical education, prepares physicians to practice in a monodisciplinary rather than a multidisciplinary manner. The concept of working jointly with a psychologist to address simultaneously the patient's medical and psychological needs is foreign to most practitioners. This is curious because academic medicine has forged many links between clinical health psychology and medical practice. Many departments of anesthesiology (and indeed many departments) in schools of medicine across the United States include psychologists on their faculties, and it is no accident that two of the editors of this book are psychologists. Because of their methodologic skills, psychologists contribute solidly to evidence-based medicine, and they excel in both rigorous patient assessment and measurement of treatment outcome as well as in the delivery of health care. Experience demonstrates that psychologists are invaluable in the pain field, not because they set up alternatives to medical intervention, but because they can enhance medical intervention in a variety of ways.

Second, the practice of medicine has long regarded psychological issues in patient care as marginal or irrelevant dimensions of patient evaluation and treatment. The implicit assumption persists that dysfunctional or disabled persons are self-righting: Remove the cause of the pain (or otherwise prevent the noxious signaling from reaching the brain), and the patient will recover. This assumption becomes increasingly indefensible as knowledge of neuroplasticity grows. Mounting evidence shows that persistent noxious signaling can permanently alter the nervous system in which it occurs in complex ways. Consequently, in many cases in which pain has become chronic, the patient requires rehabilitation as well as a reversal or minimizing of the pathophysiology that may underlie the pain. In cases in which practice dictates medication prescription, issues of medication adherence and outcome assessment are paramount. Psychologists are well prepared to deal with such issues. The varied psychological aspects of pain management are simply too many and too important to ignore.

Finally, many physicians fail to work with psychologists or use psychological methods simply because they know too little about the field of clinical psychology or have an incorrect image of the field. In American society as a whole, the image of folk psychology overshadows that of professional psychology. Self-help books or tapes and self-proclaimed televised experts hold forth on how to take charge of one's life, how to deal with stress, how to become productive, and even how to free oneself of pain. Physicians and patients alike confuse their offerings with those of professional psychologists. Nonetheless, folk psychology is to professional psychology as folk medicine is to professional medicine. The professional psychologist offers evidence-based assessment and practice, including outcome assessment, and many can provide valuable theoretical frameworks that help clarify knotty problems in medical pain management. The negative image of folk psychology, which trivializes the profession, is often a barrier to appropriate use of psychological services.

The chapters in this section introduce several areas of psychological practice. They present varied psychological approaches to pain control and illustrate the application of several traditions in the field of psychology to the challenge of pain management. Fordyce's chapter (Chapter 88) discusses the application of operant conditioning in the rehabilitation of chronic pain patients, an approach that had a revolutionary impact early in the development multidisciplinary patient care. Turner and Romano (Chapter 89) write from the rapidly evolving perspective of cognitive-behavioral therapy, perhaps the dominant framework in clinical psychology today. They call attention to the importance of patient beliefs and thoughts in the search for pain relief and the response to intervention. They describe how the field has evolved and articulates current thinking about pain in the contemporary behaviorist perspective. In Chapter 90, Arena and Blanchard review and describe biofeedback, a technology-based application of psychological principles that helps patients develop and accept control of their own physiologic responses to stressful events or conditions. In Chapter 91, Barber reviews the field of hypnosis and describes its applications for pain control. Syrjala (Chapter 92) addresses short-term psychological interventions that use relaxation and imagery. Because this area is so easily confused with folk psychology, she provides a strong review of the evidence supporting these approaches as well as a description of what they entail. The chapter by Tunks and Merskey (Chapter 93) discusses the classic application of psychotherapy to the care of the patient in pain. It emphasizes that the pain management physician, by virtue of his or her relationship to the patient, can and should take on the role of supportive psychotherapist. Finally, Jensen (Chapter 94) provides a cutting-edge perspective on motivational dimensions of patient management. Successful management of chronic pain entails changes in patient lifestyle, thinking, and functional capability. Some patients are ready and able to change in response to intervention, but others are not. Jensen outlines an approach by which the physician can help bring the otherwise intransigent chronic pain patient to a point where he or she will be willing and able to accept the importance of self-management in response to rehabilitation. This chapter provides an excellent example of how psychology can help improve the “take” of a medical intervention.

One of the benefits of involving psychologists in pain management is that many key psychological ideas and insights diffuse into the thinking of physicians, making them better able to assess and skillfully manage complicated patients. The fundamental goal of psychology in medicine is not to offer an alternative or complementary service to physicians, but rather to integrate progress in psychology into medical practice. In this, everyone benefits. The use of sound psychological principles in patient care can help most patients in some respect and can facilitate the process of care delivery.

The topics covered in this section are by no means an exhaustive list of the ways that psychology can contribute to pain management. In any setting in which pain requires medical management, psychology has skills to offer. Those skills often extend to bettering patient assessment, care delivery, outcome evaluation, and other key aspects of pain management.

Section D. Physical Therapeutic Modalities - Introduction

John D. Loeser

The four chapters in this section deal with subjects that have been arbitrarily labeled physical modalities. Chapter 95 covers orthopedic nonsurgical and surgical procedures for treating musculoskeletal disorders; one of the primary objectives of these procedures is the relief of pain. It contains concise descriptions of the procedures intended to relieve acute and chronic pain and the anatomic and functional bases of these procedures. It includes a short section on the use of orthopedic operations for patients with cancer-related pain.

Chapter 96 provides an overview of various modalities used in physical medicine and rehabilitation for patients with acute and chronic pain. The physiologic bases, indications, side effects, and contraindications of each of the many types of thermotherapy, cryotherapy, electrotherapy, mechanotherapy, therapeutic exercises, traction, manipulation, immobilization, and laser therapy are discussed and the rationales for their utilization as well as outcomes are presented.

Chapter 97 discusses acupuncture for the management of patients with acute and chronic pain. A comprehensive and fair critical review of the methods, indications, side effects, and complications of classical acupuncture as practiced by traditional practitioners, and modern techniques used in various parts of the world, including electroacupuncture, are presented. The scientific knowledge derived from animal studies, human laboratory studies, and clinical studies is reviewed. The efficacy of acupuncture in the management of patients with acute and chronic pain is discussed.

These chapters cover treatment modalities that often have widespread utilization but unclear data for efficacy with modern outcomes research. They often appear to provide symptomatic relief for patients with pathologic processes that are not clearly understood. There are many similarities between acupuncture and transcutaneous electrical nerve stimulation (covered in Chapter 98); the latter has even been labeled *Western acupuncture*. Vast numbers of patients have received this treatment, the efficacy of which is still debated.

Section E. Implanted Electrical Stimulators - Introduction

John D. Loeser and John J. Bonica

Chapter References

This section consists of three chapters devoted to the use of implanted electrical stimulation for the control of chronic pain. In Chapter 99, Gybels and Nuttin discuss the use of peripheral nerve stimulators. In Chapter 100 and Chapter 101, Meyerson and Linderoth describe the use of spinal cord and brain stimulation. All of these chapters are aimed at the nonneurosurgeon, with the goal of elucidating the potentials for this type of neuroaugmentative surgery. Actual surgical techniques can be found in standard texts or the manufacturers' product descriptions.

The resurgence of the use of electricity to treat pain was provoked by publication of the Melzack-Wall gate theory (1). Indeed, the first modern application of this modality, reported by Wall and Sweet (2) in 1967, provided support for the Melzack-Wall gate theory, which emphasized the important role of the dorsal horn of the spinal cord in modulating sensory transmission. The subsequent discovery and eventual detailed description of the anatomic, physiologic, and pharmacologic aspects of the periaqueductal gray and other brainstem sites and the descending inhibitory systems led to the use of deep-brain stimulation.

Although these implantation techniques have been considered an important recent advance in pain therapy, the practice of applying electricity to relieve pain is as old as recorded history (3,4 and 5). Egyptian tombs of the Fifth Dynasty (2750 b.c.) displayed the Nile (electrical) catfish (*Malopterurus electricus*), and the ancient Greeks, including Aristotle, described the numbness caused by the torpedo ray (*Torpedo marmorata*). Among the Romans, Pliny in *Natural History* and Plutarch in *Morales* referred to the numbing effect of the ray (6), and Scribonius (circa a.d. 46) advocated electrotherapy specifically for the relief of “chronic and unbearable headache,” gout, and other conditions (7). At the same time Dioscorides, a Greek army surgeon in the service of Nero, also advocated electrotherapy for a variety of painful and nonpainful disorders (8). A century later Galen, after studying live and dead electrical fish, concluded that the latter had no effect. He wrote the following about application of a live torpedo ray to a patient suffering from headache: “It could be that this remedy is anodyne and could free the patient from pain as do other remedies which numb the senses: This I found to be so” (9). These and other Roman physicians indicated that in order to be effective, the torpedo fish should be placed on the spot where the pain was felt.

The clinical application of the torpedo fish as a therapeutic modality for pain and other conditions continued throughout the Middle Ages, the Renaissance, and well into the nineteenth century. In non-Western cultures, electrical fish are still used for this purpose (6). During the eighteenth century, many improvements were made in an electrostatic apparatus constructed earlier by Von Guericke, including the development of the Leyden jar (5). Consequently, electrotherapy was applied even more widely despite the skepticism and opposition of a number of authorities.

During the nineteenth century, development of the electrical “pile” and the subsequent development of the induction apparatus provided further impetus for electromedical application (10). Voltaic (galvanic) and faradic currents were stronger and/or more easily modulated than was static electricity, and increased efforts were made to use electricity as a surgical anesthetic especially for tooth extraction and other dental therapies (5). In the years just before and after 1860, numerous reports were published on the use of electrical anesthesia for dental surgery and subsequently for surgery on the limbs. In the United States, the most widely known exponents were Francis (11) of Philadelphia, Garratt (12) of Boston, and Oliver (13) of Buffalo. These three individuals became involved in a bitter controversy as to who was the first “discoverer” of electrical anesthesia. Interestingly, this controversy occurred at about the same time as the intense controversy with regard to the discoverer of general anesthesia by demonstrating the anesthetic properties of ether and nitrous oxide.

In England, Althaus (14), a prominent electrotherapist, was the first to adopt and use the new electroanesthesia. In 1859, he applied “interrupted current” transcutaneously to peripheral nerves and eventually convinced his most prominent critic, Benjamin Richardson (who was a friend of John Snow, the patriarch of anesthesiology and epidemiology), of its efficacy to diminish sensation and produce analgesia by stepwise increase of the electrical stimulus to Dr. Richardson's ulnar nerve. Althaus applied these techniques for the relief of neuralgia and found that analgesia was more effective and more readily attained in pathologic conditions than in normal situations (14). Unfortunately, the controversy continued and prompted the appointment of a commission headed by Richardson. After studying the efficacy of electrical anesthesia in patients undergoing tooth extraction, the commission concluded that the technique produced no local anesthetic effect (15).

The use of electroanesthesia in dentistry was introduced to France in 1858, and subsequently reports also were published in Germany and Italy (3). The results obtained in these countries were variable, and toward the end of the century, this modality was virtually abandoned for surgical anesthesia, although a number of workers continued to use it for the treatment of neuralgia and other pain syndromes.

During the first six decades of this century, a number of clinicians attempted to resurrect electroanesthesia for surgical operations, but because it was much less predictable than pharmacologic anesthesia, it never became widely used. Electroanalgesia is considered a curiosity today and is not in general clinical use in the developed countries.

In 1928, Thompson et al. (16) from the University of California at Berkeley noted that “the cutaneous areas supplied by a nerve may be rendered insensible to light touch by subjecting the nerve trunk to the influence of an alternating current.” Increasing the current produced analgesia. With this technique they determined the distribution of all the cutaneous nerves in the forearm of one individual (16). Fourteen years later Paraf (17), using the same technique, reported the successful treatment of 127 patients with sciatic pain, lumbago, postherpetic neuralgia, and tic douloureux.

In 1953 Guenot (18) wrote a thesis on local electrical analgesia in which he described the work of Perrin, Bernard, LeGo, Presle, Wild, and Probst, all of whom used local and regional electroanesthesia. Probst (19) experimented with 50- to 100-Hz monophasic and diphasic waves, which caused initial excitation and paresthesia but soon caused “inhibition” and raised the sensory threshold to the current. Whether or not the effects of intense stimulation leading to nerve impulse blockade are related to the pain relief obtained with modern implanted stimulators that do not produce analgesia remains unclear.

During the 1950s and early 1960s, reports on the use of electrical stimulation of the spinothalamic tract, the thalamus, and other parts of the brainstem for the relief of pain, with varying degrees of success, were published by Mazars et al. (20) and others (see 4 for references). The most recent development is stimulation of the motor cortex for the relief of neuropathic pains. This is not yet an approved treatment in the United States, and clinical experience is limited to a few centers.

The development of safe, compact electrical generating systems and the fabrication of electrodes and lead wires using new, inert materials allowed the application of electricity to deep structures and not just the skin or mucous membranes. For these reasons, electrical therapies entered a new era in the later half of the twentieth century. The focus of electrical stimulation shifted from acute to chronic pain because of these technologic advances. However, we remain ignorant of the mechanistic relationships between skin stimulation and neural stimulation for pain relief. The ultimate place of implanted stimulators will be determined by properly conducted outcomes trials.

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Section F. Regional Anesthesia/Analgesia - Introduction

John D. Loeser

This section addresses regional analgesia and anesthesia in the management of patients with all types of pain, both acute and chronic. Chapter 102 focuses on regional anesthesia with local anesthetics, Chapter 103 discusses regional analgesia with opioids, and Chapter 104 deals with neurolytic blockade. The intended audiences for these chapters are not so much anesthesiologists, who will need far more detailed anatomy and pharmacology to carry out these procedures, but instead other health care providers who need to know the indications for and techniques of regional anesthesia and analgesia as well as their potential complications.

The modern era using nerve blocks for the control of pain, began in the 1850s with the invention of the hollow needle and syringe. Koller first reported on the injection of cocaine to block nerves in 1884. Subarachnoid injection of cocaine was described by Corning in 1886. The first half of the twentieth century was the zenith of the use of nerve blocks in the management of pains of all types. Lytic substances, such as alcohol, as well as new local anesthetics were widely used for both diagnostic and therapeutic purposes. Blocks were also used in research on both anatomic pathways and physiologic states. The enthusiasm for nerve blocks was certainly one reason why anesthesiologists were in the vanguard of the development of the pain movement that Bonica launched in the aftermath of World War II.

However, better clinical trials and increased understanding of the factors that contribute to chronic pain states have combined to lessen the use of nerve blocks in the management of chronic pain. It remains the case that some patients have painful conditions that are treated successfully by local or regional anesthetic techniques. New drugs and new delivery systems may lead to a recrudescence of this approach to pain management.

The first edition of this text, published in 1953, focused on regional anesthesia and nerve block techniques in the management of pain. Indeed, it was this aspect of pain treatment that led Bonica into the new field of pain medicine. His perspective broadened as he gained experience with pain patients; this is what resulted in his desire to write a comprehensive textbook. This subject takes up less space in this, the third edition, for we know much more about the sciences basic to an understanding of pain and the clinical aspects beyond nerve blocks. We have tried to preserve Bonica's wisdom in these areas in the chapters of this section.

Section G. Ablative Neurosurgical Operations - Introduction

John D. Loeser

This section, composed of four chapters, discusses the neurosurgical procedures used for the management of chronic pain. Each chapter contains sections devoted to specific operations, which have been arbitrarily divided into three groups. Thus, Chapter 105 discusses operations on the peripheral nerves, Chapter 106 discusses operations on the spinal cord, Chapter 107 discusses operations for tic douloureux, and Chapter 108 discusses operations on the brain and brainstem. Each chapter contains sections with an up-to-date summary of the fundamental basis of the procedure, indications for its use, the clinical results obtained by the author and others who have had extensive experience with the procedure, a brief description of the operation, and a summary of the possible complications. The material is intended to provide an overview to physicians (and other health professionals) who are not neurosurgeons. As emphasized elsewhere in this book, it is essential for pain management physicians to be knowledgeable about various therapeutic procedures so that they can discuss them objectively with their patients.

This introduction commences with a brief historical perspective on surgery performed to relieve pain and then analyzes the requirements and guidelines for applications of the various operative procedures used to obtain relief of nonmalignant chronic pain and pain caused by cancer. The importance of patient selection is emphasized, and criteria for choosing a particular operation are identified. More detailed discussions of the indications, techniques, and results of neurosurgical procedures for pain relief have been superbly presented by White and Sweet (1), North and Levy (2), and Gybels and Sweet (3). The neuroanatomy, physiology, and biochemistry of the pain systems are discussed in detail in Chapter 3, Chapter 4, and Chapter 5.

HISTORICAL CONSIDERATIONS

In Chapter 1, we presented the concepts and surgical procedures used by the ancients in their attempts to understand and relieve pain. Ambroise Paré recognized in the late sixteenth century that cutting a nerve in the arm could relieve chronic pain secondary to a penetrating wound of the extremity. By the end of the seventeenth century, Maréchal, the surgeon to the court of Louis XIV, was performing peripheral neurotomies for tic douloureux. Modern neurosurgery began in the latter part of the nineteenth century after the advent of anesthesia and Lister's concepts of asepsis. Probably the first procedure to be used was peripheral neurotomy, described in a book published in 1873 by Letievant (4), in which he discussed sectioning of cranial nerves and of nerves supplying the extremities. One of the greatest neurosurgical pioneers was Horsley, who inaugurated surgery on the gasserian ganglion for tic douloureux in 1891. His work was continued by Krause and perfected by Frazier. The first spinal dorsal rhizotomies are accredited to Abbé and to Bennett in 1889. Spiller and Martin performed the first cordotomy in 1912. Förster continued the clinical studies of cordotomy and made many contributions to the surgery of pain (5).

The development of sympathectomy was mainly the work of Leriche, with major contributions by Jonnesco and Gomoiu. Many other great men of early twentieth-century neurosurgery played important roles in the development of neurosurgical procedures for pain relief: Chippault, Jaubolay, Sicard, Van Gehuchten, de Beule, Thiersch, Sjöqvist, Cushing, Dandy, and White all made significant contributions. Horsley and Clark's apparatus for producing lesions in animal brains was brilliantly adapted by Spiegel and Wycis in their pioneering work on human stereotaxis. Certainly, the major neurosurgical treatise on pain relief of the twentieth century was the text by White and Sweet (1), which introduced the modern era of surgical pain relief.

There is little doubt that developments in our understanding of the anatomy, physiology, and psychology of chronic pain will spur the advance of surgical procedures directed at new targets. Events of the past decade have already shown the inventiveness of surgeons in applying both new information and new technological methods to the problems of chronic pain.

Some of the most dramatic changes in the domain of neurologic surgery have occurred in regard to procedures designed to relieve pain. Early neurosurgical operations, in the late nineteenth and early twentieth centuries, involved section of nerves, roots, spinal cord, and then brainstem. The development of frontal lobotomy permitted a new approach—alteration of the suffering component of the patient's complaints rather than interruption of the pain pathways. Surgeons added new stereotaxic procedures for interruption of both specific and diffuse pain pathways at specific sites for the alleviation of suffering. Finally, the development of new theories of the nature of pain and of technological refinements in the electronic industry has led to the use of implanted electrical stimulators to augment rather than reduce sensory input in attempts to relieve pain (Chapter 99, Chapter 100, Chapter 101).

Another important technical development has been the use of controlled radiofrequency current or cold probes to generate a thermally destructive lesion; this has enabled surgeons to make discrete lesions through a needle rather than by a surgical incision. Patients who could not withstand the physical and psychological stress of a surgical operation can now be offered a percutaneous procedure that does not entail significant risk of infection, hemorrhage, or problems with wound healing. Technological developments of the twentieth century continue to add to the surgeon's repertoire for alleviating pain and suffering, and new operations are described regularly. Long-term results are often not included in the initial optimistic appraisal of the value of each procedure, and some caution seems warranted before new procedures are widely used.

OPTIMIZING SURGICAL RESULTS

The role played by the neurosurgeon in the treatment of chronic pain is a function of local patterns of medical care and the success of the patient's interactions with the health care delivery system. The development of multidisciplinary groups and pain clinics has altered the conceptual approach to the patient with chronic pain and has led to more sophisticated approaches for using surgical methods to deal with the patient with chronic pain. Ablative procedures, whether by knife, alcohol, or thermal coagulation, are often not the primary choice for the management of the patient with chronic pain caused by nonmalignant diseases; they are more useful for cancer pain. Unfortunately, far too many have been subjected to destructive surgical procedures that have not provided long-term relief of symptoms.

The neurosurgeon usually is well advised to avoid destructive operations for chronic pain unless the patient is known to have a life-shortening malignancy or has been thoroughly studied, and all other feasible treatments attempted. Of course, the patient with classic tic douloureux who has not responded to intensive medical therapy is an exception, because the response of this disease to various surgical procedures is likely to be favorable. Few other diseases respond well to surgery. Technical success is not always mirrored by patient improvement; reciprocally, the good results ascribed to an operation can be related to events other than the destruction of a portion of the nervous system.

Technical Skill and Experience

The results of an operation are directly related to the surgeon's knowledge and skill. Appropriate training and experience should be prerequisites for performing operative procedures of any type, especially those affecting the nervous system. Most neurosurgeons have the necessary skills, but few have had adequate experience dealing with the many facets of many chronic pain patients. Most errors in the management of these patients do not occur in the operating room but are made during the preoperative and postoperative evaluation of the patients by the surgeon. The operation is often technically adequate, but patients might have been unwisely selected for the procedure.

Experience in Managing Chronic Pain Patients

Few neurosurgery training programs currently offer adequate exposure to the multiple problems of patients with chronic pain; the overall poor therapeutic results are often not known, and short-term successes are considered adequate reasons for major surgery. For example, it is commonly stated that the “success rate” for initial lumbar diskectomy varies from 60% to 85% as a function of the patient population, but long-term follow-up in a 20-year multicenter Veterans Affairs Hospital study did not show an advantage for surgical therapy over conservative treatment (5).

Such data should make the neurosurgeon consider the indications for diskectomy carefully. Other studies have indicated that the natural history of patients with a ruptured disk is not altered by surgery when the patients are followed for 5 years (6). Furthermore, the long-term results after second or third lumbar disk operations have long been known to be dismal, yet surgeons still use this approach to chronic low back pain, often before other less hazardous avenues are explored. These issues are discussed in depth in Chapter 76 in relation to low back pain.

This situation can be ascribed to various aspects of the systems of medical care: I choose to identify inadequate long-term follow-up and feedback to the surgeon as the primary reasons for its continuation, although economics can be a factor. Careful long-term follow-up and increased participation by the neurosurgeon in the overall management of the patient with chronic pain are needed. Major neurosurgical textbooks often describe operative procedures with little or no discussion of long-term success rates. Many operations can be done to alleviate pain and suffering; the tough decision is not which one, however, but whether any destructive procedure is warranted at a specific time in the patient's course.

In contrast to the circumspect attitude that a neurosurgeon should exhibit toward destructive operative procedures for most nonmalignant diseases, certain types of patients should be promptly offered appropriate surgical relief of their pain or suffering. Two common examples of specific conditions are tic douloureux that has not responded to anticonvulsants and the pain resulting from uncontrolled cancer.

Some guidelines for the management of cancer pain are important for the surgeon. If the patient has a short life expectancy (less than 60 to 90 days), it is unwise to consider a major surgical procedure; narcotics or a percutaneous neurolytic procedure is usually more appropriate. The patient who is this close to death rarely has adequate infection resistance, wound healing, or blood coagulation and is a high surgical risk. For the patient who is going to survive more than 6 months, it is unlikely that oral narcotics or percutaneous procedures are optimal, and a surgical procedure is often indicated. Intermediate survival periods are often best managed by percutaneous procedures such as cordotomy, rhizotomy, epidural narcotics, or intrathecal injections of phenol or alcohol.

The patient with cancer is more likely to have a good result from a surgical procedure because the pain most likely is a result of nociception, which is eliminated by ablative procedures, and the patient is not likely to survive long enough for the beneficial effects of the surgical procedure to disappear. Furthermore, I suspect (but cannot prove) that those personality factors that play such a large role in the pain behavior of some patients with chronic pain secondary to a nonmalignant disease process are not usually found in the patient with a malignancy. These factors can predispose a patient with chronic pain of nonmalignant origin to operative failure. It is the younger patient with a vague pain syndrome related to a nonmalignant disease who so often fails to obtain pain relief from an operative procedure that seemed so promising.

Prediction of Long-Term Results

The major problem for the neurosurgeon is the prediction of long-term operative results for individual patients. A few studies of adequate numbers of patients followed for more than 3 months are available, but how can particular patients be related to a larger group? Are any reliable predictors of operative outcome available? For patients with low back pain, several studies now indicate that return to work 1 year after surgery is not related to the preoperative examination or the findings at surgery, but is predictable from preoperative psychological testing results (7). Few, if any, studies for such procedures as cordotomy, myelotomy, and rhizotomy have been done. The latter operation has been the subject of several reviews, which clearly show that spinal rhizotomy does not provide long-term relief for most patients (8,9).

Psychological and Psychiatric Evaluation

A patient with chronic pain not caused by a malignancy is frequently referred to a psychiatrist or psychologist for evaluation. Unfortunately, few of these patients have been evaluated before embarking on a career of chronic pain, so we do not know if the psychological evaluation describes the type of patient who suffers from chronic pain or describes the effects of chronic pain on the patient. It is clearly unwise to perform a major surgical procedure on a psychotic or severely depressed patient, not so much because of the risk of technical failure but because of the patient's inability to handle the stresses of hospitalization and surgery.

Hysterical or somatically preoccupied patients are likely to respond favorably on a short-term basis to any procedure, but little is known about a procedure's long-term efficacy in such patients versus patients with a healthier outlook on life. The indications for surgery in somatically preoccupied patients must be thoroughly scrutinized; these patients seem all too likely to receive more therapies for body ailments than are required. A significant proportion of patients with chronic pain are labeled as having psychological reasons for their pain behavior. With the exception of the malingerer or the overtly emotionally ill, this type of diagnostic evaluation does not seem to influence the therapeutic results. Therapy should be based on the identification of specific factors that indicate the need for operative intervention.

Many surgeons have relied on the Minnesota Multiphasic Personality Inventory (MMPI) as an indicator of the suitability of patients for surgical therapy. No controlled studies have been done to validate this use of the MMPI, but the test does eliminate the problem of observer bias and seems to predict the types of behavior patterns patients manifest and their responses to illness and stress. The MMPI can effectively identify people who have great readiness to convey to others that something is wrong with their body; to the extent that such tendencies are present (hypochondriasis), surgery or any other therapy is unlikely to reduce health care seeking behavior. The MMPI can be used to identify those individuals whose characteristic modes of responding to environmental stresses make it unlikely that any surgical procedure can restore them to a productive lifestyle. This issue is discussed in detail in Chapter 76.

Influence of Compensation and Litigation

Neurosurgeons have long been aware of the roles of compensation and litigation as factors in the determination of therapeutic outcome. I am not sure that these are particularly valid, because their effects have never been separated from such factors as the passage of time and intervening therapies. It is now quite obvious that environmental factors can and do influence pain behavior regardless of the cause of the pain. Compensation and litigation are only two of the many environmental influences impinging on pain patients. Family interactions can perpetuate pain behavior long after healing has occurred. Health care and insurance programs should be designed to offer rewards for recovery—not prolonged illness; some clearly have the opposite effect and lead to unnecessary surgical procedures.

The lack of motivation to “get well” can influence the search for continued medical assistance. Several studies of specific operations, however, failed to show a poorer prognosis for patients receiving compensation for their illness (9). It is too simplistic to consider only economic compensation when psychological and environmental factors can play such large roles in the genesis of pain behavior (10). Issues such as these have made it difficult to assess the results of surgical procedures.

The influences of duration of pain and prior attempts to alleviate pain have not been ascertained. Santayana's statement that “He who is ignorant of the lessons of history must be prepared to repeat them” is probably relevant to patients with chronic pain who fail to respond to many other well-chosen treatment regimens.

Prognostic Nerve Blocks

The role of nerve blocks in the selection of patients for surgical procedures must be scrutinized. The proper use of diagnostic blocks is discussed in Chapter 102 and Chapter 103 and other sections of this book; certain points need to be emphasized for the neurosurgeon. A single nerve block cannot be relied on to provide meaningful information—too many extraneous factors can influence the patient's response. A carefully planned series of blocks is often helpful but does not, as far as I can tell, predict long-term outcome of an ablative procedure except for sympathectomy for causalgia or trigeminal neurectomy for tic douloureux. Nerve blocks can identify the source of pain and the nerves or roots that must be cut to isolate that region of the body from the spinal cord or brainstem. They can also determine whether the patient's responses seem to be related to the duration of the anesthetic agents used and the nerve structure injected; these seem to be important measures of patient reliability. This issue is difficult to clarify, because no results have been reported in regard to operations performed on the patient who does not respond to nerve blocks in the region of the proposed surgery. Another indication for preoperative nerve block involves allowing the patient to experience the

expected numbness on a short-term basis. Some prefer their pain to this numbness.

Managing Narcotics in the Preoperative and Postoperative Periods

The neurosurgeon must have a strategy for dealing with patients who are taking significant amounts of narcotics and are being considered for an operative procedure. If the genesis of the pain has been clearly established as nociception, as in many patients with cancer-related pain, it is reasonable to relieve the pain with an operation and then taper the medications. Patients with an unclear cause of their pain behavior (e.g., associated with nonmalignant diseases) should be converted from short-duration narcotics to a long-acting drug such as methadone and the dosage gradually tapered (11). In many of these patients, the pain behavior diminishes as the narcotic level falls, and no operation is required. In others, a more accurate diagnosis can be made as the narcotic-induced mental impairment clears; surgical indications might then be more clear-cut (11).

Pain relief obtained with a surgical procedure is likely to reduce the patient's tolerance for narcotics dramatically, and consequently respiratory depression and even apnea can develop (Chapter 84). The dosage should be sharply curtailed in the immediate postoperative period while the patient is under close observation and, if respiratory depression becomes evident, incremental doses of naloxone are used.

Informed Consent

Another issue that must be considered concerns informed consent. The patient and family should be thoroughly informed about the therapeutic options and the risks and benefits of alternative treatment strategies. Not only the neurosurgeon but also the patient's primary care physician(s) must be knowledgeable about the likely outcomes from alternative treatments. The patient's primary physician should have a clear idea of what a proposed neurosurgical procedure entails so that this can be discussed with the patient.

The neurosurgeon who deals with patients with chronic pain must recognize that the greatest problems lie in the selection of therapeutic methods rather than in the application of the techniques themselves. Every operation and every other form of therapy has its advantages and disadvantages (10). What is appropriate at one point in time for a patient might not be optimal during any other phase of treatment. Not infrequently, surgical procedures must be performed in conjunction with other modes of therapy if the patient as a total human being is to be rehabilitated. In general, destructive procedures should not be considered until other modes of therapy have been thoroughly evaluated. When indicated, surgical intervention should not be delayed. That decision reflects the art of neurosurgery.

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Section H. Multidisciplinary Multimodal Pain Management Programs - Introduction

John D. Loeser

Chapter References

In contrast to the other sections of this book, this last section has only one chapter. It describes the multidisciplinary/multimodal team approach using multiple therapeutic strategies in the management of patients with complex chronic pain problems. This chapter is the fourth and last in a series that describes chronic pain patients (Chapter 10), the principles of multidisciplinary pain diagnosis and management (Chapter 11), the strategies for diagnostic assessment (Chapter 18), and treatment in multidisciplinary programs (Chapter 109). Of course, the diagnostic and therapeutic strategies described in many other chapters of this book provide the foundations for the multidisciplinary approach. As clearly indicated in Chapter 10, Chapter 11, and Chapter 18, the focus of this series of chapters is on those chronic pain patients who do not have a directly treatable physical or psychological cause for their chronic pain. After assuring themselves that this is indeed the case, the multidisciplinary team turns its attention to improving the patient's functional status and reducing his or her pain complaints (1).

This type of treatment program was one of John Bonica's major accomplishments. He persisted in the pursuit of this new method of treating pain patients despite the intrinsic and extrinsic problems that he encountered during the 1950s and 1960s and the skepticism expressed by some national authorities who were medical traditionalists and did not like the concept of sharing patient responsibility with other health care providers. Fordyce added the behavioral medicine approach, and the multidisciplinary pain management concept rapidly spread throughout the developed world. Twenty-five years of experience have shown that comprehensive pain programs of the type described in Chapter 109 have been successful in returning roughly half of their patients to a productive life. The results reported from a number of such programs are summarized in this chapter, which uses the University of Washington Multidisciplinary Pain Center as its example. The usefulness and value of such programs has been emphasized by two important task groups, one in the United States and the other in Canada. In the United States the prestigious Institute of Medicine appointed the Committee on Pain, Disability, and Chronic Illness Behavior to consider the various aspects of chronic pain and disability (2). In Canada the Quebec Task Force on Spinal Disorders focused on pain in all parts of the spine, with emphasis on the rates of such disorders among workers in Quebec (3). In their reports, both groups encouraged physicians and other health professionals to refer patients with chronic pain who have failed to respond to the usual medical therapy to a multidisciplinary pain team.

The Quebec Task Force suggested that if management by the treating physician and a consultant specialist has not been successful and the patient still has pain after 3 to 6 months, he or she should be referred to a multidisciplinary team, which should focus primarily on psychological and psychosocial elements, on the premise that these factors are primarily responsible for the persistence of pain. Nothing is said of having the team reassess pathologic or pathophysiologic bases for the pain. Persistent pain due to pathologic lesions can cause serious psychological and psychosocial disorders and they should therefore be included in the assessment, but we wish to emphasize that the multidisciplinary team has the responsibility to evaluate the patient for physical and pathologic processes that might have been missed by prior physicians.

Dr. H. La Rocca, then editor-in-chief of the journal *Spine* (in which a summary of the report was published as a supplement), expressed concern about this issue in an editorial (4) in which he stated that “many patients with symptoms of 6 months' duration or more, can still have intractable organic disease without significant psychologic component. Every effort must be made to identify them” (see Chapter 18). Stoeckle and Boyd (5), members of the Institute of Medicine committee, also mention the unresolved problem posed by patients with chronic pain in whom a diagnosis of an underlying physical illness was missed because of inadequate diagnostic assessment or because the assessment was carried out before identification of the disease process was possible. They cite three publications reporting morbidity rates of undiagnosed physical illness presenting as psychiatric disease. As emphasized in Chapter 18, time and effort must be expended to carry out a comprehensive evaluation to diagnose structural pathology that can be eliminated. On the other hand, one should not be oblivious to the data on the low likelihood of identifying a structural disease in patients who consult their primary physicians with a wide variety of symptoms (6).

Most multidisciplinary pain programs focus on patients who manifest chronic pain behavior and disability long after the healing process should have been completed and have no treatable structural pathology. However, the same principles of multidisciplinary diagnosis and management should be applied to patients with obvious chronic pathology that cannot be removed, such as arthritis, cancer, deafferentation pain, and other chronic pain syndromes. Chronic pain that is not adequately relieved causes the patient to develop psychological, psychosocial, and behavioral problems as well as progressive physical deterioration. All patients with unresolved chronic pain are best managed by multidisciplinary teams.

The experiences of cancer and palliative care programs provides impressive evidence that an integrated approach is much more effective in improving the quality of life of patients with incurable, fatal diseases than can be achieved by traditional ways, in which the oncologist alone manages the patient with the support of nurses. In recent years, the difference between the team approach and the traditional care of cancer patients has become more and more appreciated, and most cancer programs offer both multidisciplinary diagnoses and treatments that include psychosocial issues (see Chapter 35 and Chapter 36). Therefore, what is described in Chapter 109 has usefulness beyond the typical chronic pain patient with nonmalignant disease.

We must continue to emphasize to physicians (particularly family physicians), other health care professionals, the consumers of health care, and third-party payers the critical importance of the team approach in managing patients with chronic pain. We encourage treating physicians who have been unsuccessful with the first or at most the second attempt in using surgery or medical therapies in managing complex pain problems to refer such patients to a multidisciplinary pain center that can carry out a coordinated effort to establish a diagnosis and develop an effective treatment strategy.

Although such comprehensive centers in the past have been viewed as “court of last resort” for the treatment of chronic pain, health professionals should refer patients with complex problems early in order to prevent the development of what some improperly refer to as “chronic pain syndrome” and—most important—reduce the suffering among millions of patients with chronic pain. The success rates reported by such programs suggest that increasing use of such facilities is likely to obviate the multiple, often useless, and at times mutilating operations and attendant complications. Multidisciplinary pain management also saves money, as discussed in Chapter 109.

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CHAPTER 1

History of Pain Concepts and Therapies

John J. Bonica and John D. Loeser

> We must all die. But that I can save him from days of torture, that is what I feel as my great and ever new privilege. Pain is a more terrible lord of mankind than even death itself (1).

Thus did Albert Schweitzer, the great humanitarian, physician, and Nobel Laureate, elegantly describe the nature of pain and the obligation and privilege of the physician (and other health professionals) to relieve it. Dr. Schweitzer wrote these sentences in 1931, after nearly two decades' experience of medical practice in the African jungle. Today, as then, proper management of pain remains one of the most important and most pressing issues of society in general and the scientific community and the health professions in particular. This importance stems from the fact that acute and chronic pain afflicts millions upon millions of persons annually, and in many patients with chronic pain and a significant percentage of those with acute pain, it is inadequately relieved. Consequently, pain is the most frequent cause of suffering and disability that seriously impairs the quality of life for millions of people throughout the world. Although accurate statistics from national and international epidemiologic studies are not available, data from a variety of sources suggest that annually in the United States and many other industrialized nations, 15% to 20% of the population have acute pain, and between 25% and 30% have chronic pain. Additional data can be found in Chapter 9 and Chapter 10 and in those chapters dealing with specific pain and pain syndromes.

In most instances, acute painful disorders are correctly diagnosed and effectively treated. Despite improvements since 1990, evidence suggests that all too many patients with severe or very severe postoperative and post-traumatic pain, and severe visceral pain, are not effectively relieved. In addition to needless suffering, in many patients unrelieved pain and perhaps the underlying pathophysiology cause it to progress to chronic pain. Of the patients with chronic pain, one-half to two-thirds are partially or totally disabled for periods of days (e.g., those with headache), some for weeks and months (e.g., those with complex regional pain syndromes), and some permanently (e.g., those with low back pain, cancer pain, and arthritis). Because pain impairs one's ability to have a productive life, pain in general and chronic pain in particular are serious economic and social problems as well as major health issues.

This introductory chapter includes (a) a review of the concept and treatment of pain from primitive times to the middle of the twentieth century; (b) the theories that have evolved from the mid-nineteenth century to the present time; (c) past and current status of pain therapy and reasons for deficiencies; (d) recent advances in pain research and therapy; and (e) goals for improving the management of acute and chronic pain. Because of the extensive literature on these issues and because of limitation of space, only those publications considered essential and references to key review articles are cited. For a more detailed exposition of the history of pain concepts and therapies, the reader is referred to the books by Castiglioni (2), Fulop-Mueller (3), Keele (4), and Sigerist (5), and to the reviews by Bonica (6,7), Dallenbach (8), Macht (9), Procacci and Maresca (10), Tainter (11), and Rey (12).

HISTORICAL PERSPECTIVES

Pain has been a major concern of humankind since our beginnings, and it has been the object of ubiquitous efforts to understand and control it. Indeed, pain is even older, for there is reason to believe that pain is inherent in any life linked with consciousness (3). Evidence exists that humans have been afflicted with this evil since their beginning, for as the records of every race are examined, one finds testimonials to the omnipresence of pain. Prayers, exorcisms, and incantations bearing testimony to the prevalence and scourge of pain are found on Babylonian clay tablets, in papyri written in the days of the pyramid builders, in Persian leathern documents, in inscriptions from Mycenae, and on parchment scrolls from Troy. Such records continue through the ages in every civilization and in every culture.

The unearthing of prehistoric human skeletons added millions of years to human recorded history of several millennia, and with these findings our knowledge of pain has been thrust into the dark chasm of time, back into the eons. Many of these bones were indelibly stamped with signs of painful diseases, giving us evidence of how early were the beginnings of humans' *via dolorosa*. The French surgeon Daetigus wrote, “Were we to imagine ourselves suspended in timeless space over an abyss out of which the sounds of revolving earth rose to our ears, we would hear naught but an elemental roar of pain uttered as with one voice by suffering mankind” (3).

Pain has been one of the greatest factors to affect the course of human events, for scarcely any human has escaped its throes. As classical authors related the lives of heroes, as medieval chroniclers told the legends of saints, and as biographers wrote of philosophers, artists, soldiers, inventors, scientists, and reformers, invariably one chapter of these biographies was entitled “Pain” (3). The emotional and physical consequences of persistent severe pain have been emphasized repeatedly by scientists, writers, and poets. Milton (13) wrote in *Paradise Lost*: “Pain is perfect miserie, the worst/Of evils, and excessive, overturns/All patience.” It is natural that from its beginning our species should have engaged its energies to understand the nature of pain and make attempts to control it.

Primitive Concepts and Therapies

Apparently, primitive humans had little difficulty in understanding pain associated with accidental injury, but were mystified by pain caused by internal disease or inflicted by an arrow or spear. They treated pain from injury by rubbing (massaging) the part or exposing it to the cold water of streams or lakes; the heat of the sun; and, later, the heat of fire (4). Pressure also was used to numb the part and thus lessen the pain, and probably in time primitive humans learned that pressure over certain regions (nerves and arteries) had a more pronounced effect, although they did not know why (2,3).

The cause of painful disease, or pain inflicted by a foreign object, was linked with intrusion of magic fluids, evil spirits, or pain demons into the body (11). Treatment consisted of extracting the intruding object or making efforts to ward off, appease, or frighten away the pain demons with rings worn in the ears and nose, talismans, amulets, tiger claws, and similar charms. In some primitive societies, skin was tattooed with exorcistic signs to keep these evil spirits outside the body. Above all, conjurations, spells, and words of might were used by the injured person, enabling the person to put the pain demons to flight.

When primitive people could not relieve their own suffering, they called the head of the family, who, according to anthropologists, was a woman in prehistoric times, an incarnation of the Great Mother, who acted as priestess and sorceress in one, perhaps because the maternal instinct made her better qualified to protect the life she had given (3). Even in the subsequent patriarchal states, women remained preeminent as healers. The sibyls and pythonesses of the ancients and the blonde Agamede of the Greeks are classical examples of women who wielded the exclusive power of exorcising the demons of illness and pain. Gradually, however, the duties of banishing pain were taken over by the medicine man, conjurer, or shaman of the tribe, who, having no maternal instinct and having the same shape as all other men of the village, had to rely on the art of conjuring. It was therefore necessary for him to change his shape by dressing as an antidemon and to make his house a special medicine hut in which he muttered incantations and fought and wrestled with the invisible pain demons. In some primitive societies, the shaman made small wounds in the patient that allowed bad fluids, spirits, or demons to escape. In others, the shaman sucked the spirit directly from the wound, taking it into himself

and neutralizing it with magic power, a therapy that survives in some countries.

In addition, herbs were used by primitive humans, who, experimenting with various plants as foods, discovered that some of these were efficacious in assuaging pain. Their use was gradually taken over by the medicine man, who surrounded his knowledge of the mystic herbal concoctions handed down to him by sorcerers and magicians with mystery, incantations, and rituals.

Ancient Civilizations

Ancient Babylonia

In Babylonia, physicians were priests, as the Babylonian civilization was structured around religion. Sciences were part of theology; the physician's role was to placate the gods and keep them benevolent. The physician-priest observed the stars, watched a flickering flame, and observed the organs of sacrificed animals to determine the fate of the patient and the therapeutic actions to be taken. Omens were also included in the symptoms of disease. These, too, had to be observed and given meaning. This allowed rational diagnosis and treatment to be established without transgressing the religious attitudes of the culture. Treatments often used incantations, and we have many descriptions of the physician, garbed in a red cloak with a raven in one hand and a falcon in the other, pronouncing an incantation over the patient. Natural remedies were also used. Object intrusion into the body (by demons or by natural means) was the cause of pain. For example, the pain of dental caries was thought to be caused by worms' burrowing into the teeth (4,5).

Ancient Egypt

The ancient Egyptians believed painful afflictions other than wounds were caused by religious influences of their gods or spirits of the dead, which usually arrived in darkness and entered the body through the nostril or the ear. The types and numbers of demons of Egypt were myriad: spirits of dead “Asiatics,” “Negresses,” and “foreign women,” and the gods Sekhamet and Seth were considered the most active in inflicting pain. The Ebers (14) and Berlin papyri (15) mention that the routes of departure of the intruding demons could be through vomit, urine, the sneeze of the nose, or the sweat of the limbs. According to the Ebers papyrus (14), a widely distributed network of vessels called *metu* carried the breath of life and sensations to the heart. This was the beginning of the concept that the heart was the center of sensation (*sensorium commune*), an idea that lasted more than 2,000 years.

Ancient India

The earliest concepts of pain and other medical knowledge in ancient India were attributed to the god Indra, as recorded in the Vedas and Upanishads (16). Buddha, approximately 500 bc, attributed the universality of pain in life to the frustration of desires: “Birth is attended with pain, decay is painful, disease is painful, death is painful. Union with the unpleasant is painful; painful is separation from the pleasant and any craving that is unsatisfied, that too, is painful” (17). Although recognizing pain as a sensation, Buddhist and Hindu thought in general attached far more significance to the emotional level of the experience. As did the Egyptians, the ancient Hindus believed that pain was experienced in the heart, and as late as 100 ad, Charaka, the first of India's great teachers of medicine, stated that all joy and pain were experienced in the heart, which was considered the seat of consciousness (4).

Ancient China

Medical practice in ancient China was codified in the *Huang Ti Nei Ching Su Wen*, the Chinese canon of medicine, traced back to the time of the Yellow Emperor, Huang Ti, who lived approximately 2600 bc. This work, compiled between the eighth and fifth centuries bc, brings medicine from legend into the realm of history and carries it through the centuries to the practice of traditional medicine in modern China (17). According to the Chinese concept, in a normal person, the two opposing unifying forces, the *Yin* (the feminine, negative, passive force) and the *Yang* (the masculine, positive, active force), are in balance and assist the vital energy called the *chi* to circulate to all parts of the body via a network of 14 channels or meridians, each connected to an important internal organ or function to which it branches. Obstruction (deficiency) and outpouring (excess) in the circulation of the chi cause an imbalance of the two forces and thus result in disease and pain. Acupuncture therapy, at one or more of the 365 specific points located along the meridians, corrects the imbalance and thus eliminates the disease and pain (see Chapter 97).

Ancient Greece

The ancient Greeks were intensely interested in the nature of sensory data, and the sense organs of the body found a prominent place in their physiologic speculations (see reference 4 for detailed review). Pythagoras (566 to 497 bc), the first great Greek thinker, who traveled widely to Egypt, Babylon, and India, apparently stimulated his disciple Alcmaeon to carry out intensive study of the senses (4). Alcmaeon, without apparent precedent, produced the idea that the brain, not the heart, was the center for sensation and reason (18). Despite support by Anaxagoras, and subsequently by Diogenes, Democritus, and others, this view did not gain widespread acceptance in ancient Greece, caused in part by the opposition of Empedocles and, above all, Aristotle, for whom the heart constituted the *sensorium commune*. Anaxagoras (500 to 428 bc) saw sensation as a quantitative change in the subject, resulting from the contrast of opposites (4). All sensations, he held, must be associated with pain, and the more the subject and the object are unlike or contrary, the more intense the sensation of pain, which was perceived in the brain (10). In contrast, Empedocles (490 to 430 bc) believed that the capacity for all sensation, especially pain and pleasure, was located in the heart's blood (10).

It is not easy to interpret the thought of Hippocrates, because the *Corpus Hippocraticum* was written by different authors at different times (19). Of main importance was the theory of four humors: blood, phlegm, yellow bile, and black bile. Pain was felt when one of these humors was in deficit or excess (*dyscrasia*). The brain was considered a gland, the center of thought, and perhaps of sensations. Hippocrates' son-in-law Polypus emphasized this concept in his book *The Nature of Man*, when he wrote that “pain is felt when one of the humoral elements is in deficit or excess” (4). It is obvious that this conceptualization of pain was similar to that held by contemporary Chinese physicians.

Plato (427 to 347 bc) believed that sensation in humans resulted from the movement of atoms communicating through the veins to the heart and liver, which were the centers for appreciation of all sensation (20,21). He further believed that pain arose not only from peripheral stimulation, but also as an emotional experience in the soul, which resided in the heart. The function of the brain in sensory processes was not clearly described; this organ was considered mainly active in elaborating the concepts derived from the sensations. He considered pain and pleasure as affections common to the whole body. Plato observed that pleasure often derived from pain relief. In the dialogue *Phaedo*, this concept is exposed by Socrates: When the chain has been taken off his leg, Socrates observes that the disappearance of pain induced pleasure (21). Plato therefore deduced that pain and pleasure, although opposite sensations, are linked as originating from the heart as passions of the soul (21).

Aristotle (384 to 322 bc) elaborated on Plato's concepts on sensations and pain mainly in *De Anima* (on the soul) (22) and in *Nichomachean Ethics* (23). He distinguished five senses: vision, hearing, taste, smell, and touch. For Aristotle, the brain had no direct function in sensory processes; as previously mentioned, the *sensorium commune*, or center of sensory perception, was located in the heart, which he considered the center of all the fundamental life functions and the location of the soul. For Aristotle, the function of the brain was to produce cool secretions that cooled the hot air and blood arising from the heart. Pain sensation was an increased sensitivity of every sensation, but especially touch, caused by excess of vital heat. Like touch, pain arose in end organs of the flesh and was conveyed by blood to the heart. Aristotle appreciated the value of the touch-pain sense, but also emphasized that when it was excessively intense it had a deleterious and indeed destructive effect. This concept was stressed in *De Anima* (22), in which Aristotle wrote that “sensations are pleasant when their sensible extremes such as acid and sweet are brought into their proper ratio, whilst in excess they are painful and destructive.” Like his teacher Plato, Aristotle believed that pain was felt in the heart as a “quale”–a quality or passion of the soul, a state of feeling, the experience opposite to pleasure and the epitome of unpleasantness.

Soon after Aristotle's death, Theophrastus (372 to 287 bc), his direct successor, cast doubt on his master's views, and Straton, who succeeded Theophrastus, propounded the view that the center of sensation, including pain, was in the brain (4). Later, Herophilus (335 to 280 bc) and Erasistratus (310 to 250 bc) of Alexandria provided anatomic evidence that the brain was part of the nervous system and that nerves attached to the neuraxis were of two kinds: those for movement and those for feeling (4). Human dissection was used to advance anatomic knowledge.

Ancient Rome

Celsus (24) considered pain in relation to the phenomenon of inflammation, along with redness, swelling, and heat. Although he recognized the concepts of Herophilus and Erasistratus regarding pain, particularly that of internal disease, he failed to mention their concept about the brain, spinal cord, and motor and sensory

nerves. For nearly four centuries, the work of the Egyptians and Greeks was lost to the Roman world until rescued by Galen (ad 131 to 200) (25).

Galen was educated in Greece and Alexandria and then settled in Rome, where he became court physician to Marcus Aurelius. He carried out extensive studies on sensory physiology and reestablished the importance of the central and peripheral nervous system (25). He clearly established the anatomy of the cranial and spinal nerves and the sympathetic trunks. On the basis of experiments on nerves and discrete section of the spinal cord on newborn pigs, Galen elaborated a complex theory of sensation. He defined three classes of nerves: *soft* nerves, to which he attributed sensory functions; *hard* nerves, which were concerned with motor function; and a third type, related to the lowest form of sensibility, *pain sensation*. Soft nerves contained invisible tubular cavities in which a *psychic pneuma* flowed. These nerves served different senses: Every organ had a nerve supply suited to its physiologic function. The largest nerves subserved the special senses. The center of sensibility was the brain, which was softer than any nerve and received all kinds of sensations.

Despite Galen's great contribution on the function of the nervous system in sensation, the Aristotelian concept of the five senses, and of pain as a “passion of the soul” felt in the heart, prevailed for 23 centuries.

After Galen, writers of the third and fourth centuries summarized concepts expressed by the ancient Greek philosophers with somewhat different interpretations of the sense of touch. Two writers of this period are noteworthy for their concepts of pain: Nemesius first considered the cerebral ventricles as the center for sensory perception, a concept that was accepted by many authors of the Middle Ages and Renaissance (4). Caelius Aurelianus used for the first time the term *passio cardiaca propria* for pain of the heart some 14 centuries before Heberden termed pain in the heart *angina pectoris* and *dolor pectoris* (10).

Ancient Remedies

During ancient times, there was a transition from attributing the cause of pain to evil spirits to the commitment of sins, and the consequent punishment inflicted by an offended deity. As a result, the medicine man was replaced by the priest, servant of the gods. Along with the natural remedies, the priest relied on prayers, usually made at the shrines of the deities, whether these shrines were the ziggurats of the Babylonians and Assyrians, the pyramids of the Pharaohs, the pillared temples of the Greeks, or the teocallis of the Aztecs (2,3). In holy ecstasy, the priests besought deities to enlighten them of the offense committed by the sufferer smitten with a painful illness, using charms and sacrifices to propitiate the immortals. With sacrifices duly made, the gods were ready at times to listen to the supplications of the priests and perhaps to grant relief. Classical medicine was based on such belief, and even Hippocrates believed that “Divinum est opus sedare dolorem” (Divine is the work to subdue pain).

The concept of sin and punishment was also prevalent in the Judeo-Hebraic civilization, which of course believed in only one God. The same concept was adopted in the Christian ethic. The fundamental significance of the word *pain* in English is derived from the Latin word *poena*, meaning punishment, and its relief through prayer. One task of Jesus Christ and His disciples was to heal the sick and to banish pain and suffering (11,25). Consequently, Catholicism laid great stress on and devoted much attention to the alleviation of pain by its clergy through prayer. Faith in prayer could turn every action into a remedy. Its efficacy in relieving pain, probably through psychotherapeutic mechanisms, has long been respected by physicians. However, philosophical and religious concepts often denied the medical significance of pain and the necessity for medical intervention to minimize human suffering.

In addition to prayer, priests, like the medicine men of primitive people, used natural remedies consisting mostly of herbs. The origin of the medicinal use of herbs is lost in antiquity. We are told in the *Rig-Veda* of the ancient Hindus that “such herbs come to us from the most ancient times, three eras before the gods were born” (17). The use of analgesic agents derived from plant life was prominent in all ancient cultures (11). The earliest records relate legends of the pain-relieving effects of such plants as the poppy, mandragora, hemp, and henbane. Aesculapius, the Greek god of medicine, was said to have used a potion made from herbs, called *nepenthe*, to produce relief of pain (3). Perhaps the first written records on the use of analgesia are those contained in ancient Babylonian clay tablets from Nippur, which date back to 2250 bc (15,16). One of these describes the remedy for the pain of dental caries as a cement consisting of henbane seeds mixed with gum mastic, which was applied to the cavity in the tooth (4). The Ebers Papyrus, written approximately 1550 bc, includes an early Egyptian pharmacopoeia with many prescriptions for the use of opium, one of which was a remedy prescribed by Isis for Ra's headaches (14).

The use of analgesics derived from plants and herbs was also widespread in ancient Greece. Among the earlier references to the use of pain-relieving drugs are those found in the writings of Homer, who lived in approximately 800 bc. In his *Odyssey*, Ulysses and his comrades are treated by Helen of Troy, daughter of Zeus, who “cast into the wine whereof they drank, a drug to lull pain and anger and bring forgetfulness to every sorrow” (26). In the *Iliad*, Homer cites the use of an “astringent” anodyne, applied by the physician Petroclus to relieve the pain in Eurypylus, who had been wounded in battle. Hippocrates refers to a substance called *mecon*, to which he attributed a narcotic action, and some believe that this substance was opium (27). The first authentic reference to the use of opium for pain relief is found in the writing of Theophrastus in the third century bc (9).

Celsus, in his *De Medicina*, written during the first century ad, provides one of the first references to analgesic pills (24). At approximately the same time lived Pliny the Elder, Scribonius Largus, and Dioscorides, a Greek army surgeon in the service of Nero, all of whom wrote extensively on the preparation and use of mandragora, opium, henbane, hemp, and other drugs for the relief of pain (9,28). Later Galen (25) wrote enthusiastically about the analgesic efficacy of opium, mandragora, and other substances.

In addition to prayer and pain-relieving drugs, the Assyrians, Babylonians, and particularly the Egyptians used such surgical methods as trephine of the skull for headache and physical procedures such as exercise, heat, cold, and massage. Moreover, the ancient Chinese used not only acupuncture, but also moxibustion, massage, physical exercise, and dietary regimens to relieve painful conditions. In ancient Egypt, Greece, and Rome, electrotherapy in the form of shocks from the Nile electric fish and the torpedo fish was used for the treatment of neuralgia, headache, and other painful disorders (29).

Middle Ages and Renaissance

In the Middle Ages, the philosophy of Aristotle dominated, but the concept of the sensory heart was not accepted by all scientists. During this period, the center of medicine shifted to Arabia, where Avicenna (ad 980 to 1038), “the prince of physicians,” proved to be the dominant figure. Avicenna was particularly interested in pain and the means for relieving it. In his *Canon of Medicine*, in which he codified all available medical knowledge, he distinguished five “external” senses and five “internal” senses, and located the latter in the cerebral ventricles (30). He described the etiology of 15 different types of pain caused by different kinds of humoral changes and suggested such methods for their relief as exercise, heat, and massage, in addition to the use of opium and other natural drugs.

In Europe during the Middle Ages, the shift of the center of sensory perception from the heart to the brain began with the work of Albertus Magnus (3), who located the *sensorium commune* in the anterior cerebral ventricle. According to the *Anathomia* of Mondino de'Liucci (31), a work that remained the fundamental text for more than 200 years in many European medical schools, the brain was not only the site of sensation, but also had the power to cool the heart. In this book, Mondino presents an overlapping of Aristotelian and Galenic thought.

The Renaissance fostered a great scientific spirit to encourage many remarkable advances in chemistry, physics, physiology, and anatomy, especially the anatomy of the nervous system. During this period, Plato's and Aristotle's works were studied, with particular interest in the Greek originals and not in the Arabian translations, and comments were made especially by Marsilio Ficino, Pico della Mirandola, and the other members of the famous Academia Platonica founded in Florence by Lorenzo the Magnificent. The great scientist and artist of the Renaissance, Leonardo da Vinci, considered nerves as tubular structures, and pain sensibility was strictly related to touch sensibility (10). The *sensorium commune* was located in the third ventricle of the brain, and he considered the spinal cord as a conductor that transmitted sensations to the brain. During the sixteenth century other scientists, including Vesalius (32) and Varolius (4), followed Leonardo's concept on the anatomy and physiology of sensations. In their works the brain was considered the center of sensation; the nerves were generally considered as tubular structures.

During the Middle Ages and Renaissance there was virtually no advance in pain therapy. Thus, we find that Paracelsus (1490–1540) still advocated the use of opium and other natural herbs and such physical therapeutic methods as electrotherapy, massage, and exercise (11). During the latter part of the Middle Ages, the somniferant sponge, which was a sea sponge saturated with a concoction of the juices of opium, hyoscine, mandragora, and other plants, became quite popular in Europe for the relief of pain and to produce insensibility to surgical operations. The effects of the sponge were unpredictable and occasionally sleep progressed to death.

Seventeenth and Eighteenth Centuries

During the seventeenth century, additional evidence was acquired on the role of the brain in sensation, but the Aristotelian concept was still accepted by many

authorities. Thus, William Harvey, who in 1628 discovered the circulation of blood, still believed that the heart was the site at which pain was felt (10). In contrast, Descartes (1596–1650), Harvey's contemporary, adhered to Galenic physiology and considered the brain the seat of sensation and motor function. In his book *L'Homme* (Man) published in 1664 (14 years after his death), Descartes described the results of his extensive anatomic studies, including sensory physiology (33). He considered nerves as tubes that contain a large number of fine threads that form the marrow of the nerves and connect the proper substance of the brain with the nerve endings in the skin and other tissues. Sensory stimuli were transmitted to the brain by means of these threads. Figure 1-1 depicts the famous drawing that has been used for over 35 years to indicate that Descartes' concept was the precursor of the specificity theory that was introduced two centuries later.

Figure 1-1. Descartes' (1664) concept of the pain pathway. He writes: “If for example fire (*A*) comes near the foot (*B*), the minute particles of this fire, which as you know move with great velocity, have the power to set in motion the spot of the skin of the foot which they touch, and by this means pulling upon the delicate thread (*c*) which is attached to the spot of the skin, they open up at the same instant the pore (*d,e*) against which the delicate thread ends, just as by pulling at one end of a rope makes to strike at the same instant a bell which hangs at the other end.” (From Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971, with permission.)

The eighteenth century was ushered in with the same concepts on the nature of pain and the same methods for its control as had been advocated during the preceding centuries. Because up to the eighteenth century the main textbooks of medicine contained the works of Hippocrates and Aristotle, the idea of the heart as the *sensorium commune* remained parallel to the theory that the brain was the center of sensory perception. Thus, we note that Erasmus Darwin (34), grandfather of Charles Darwin, following the Aristotelian idea regarding pain as a phase of unpleasantness, said that pain resulted “whenever the sensorial motions are stronger than usual . . . a great excess of light . . . of pressure or distention . . . of heat . . . of cold produces pain.” He apparently anticipated the “intensive” theory of pain, which was to be a subject of great controversy 100 years later. Willis, Borelli, Baglivi, Malpighi, von Haller, and others (3) made significant progress in the knowledge of the anatomy and physiology of various parts of the central nervous system. Moreover, Winslow and others defined the anatomy and some of the physiology of the sympathetic nervous system. During the latter part of the eighteenth century, the new era of analgesia was initiated with Joseph Priestley's discovery of nitrous oxide and the subsequent observation made by Sir Humphrey Davy of the analgesic properties of this gas.

Nineteenth Century

Pain Research

In the early nineteenth century, physiology emerged as an experimental science. This development led to the scientific study of sensation in general and pain in particular. This era was initiated in part by the publications of Bell (35,36) and Magendie (37), who demonstrated with animal experiments that the function of the dorsal roots of spinal nerves is sensory and that of the ventral roots is motor. The impetus to the scientific study of pain was further enhanced by the writings of Johannes Müller, who, in 1840, proposed *The Doctrine of Specific Nerve Energies*, which stated that the brain received information about external objects and body structures only by way of sensory nerves and that the sensory nerves for each of the five senses carried a particular form of energy specific for each sensation (38). Müller recognized only the five classical senses (i.e., sight, hearing, smell, taste, and touch), the sense of touch incorporating, for him, all the qualities of experience that we derive from stimulation of the body including the sensations of itching, pain, heat, and cold. Müller's concept was that the somesthetic sensations are a function of a unitary straight-through system that conveys information from the sensory organ to the brain center responsible for sensation. The publications of Bell, Magendie, and Müller provoked much discussion and research on all aspects of sensation including pain.

Pain Therapy

During the nineteenth century, significant advances were made also in pain therapy, and these are considered in detail in Part V of this book. Among the most important was the isolation of morphine from crude opium by Serturner in 1806, which was followed by the development of techniques of getting pure crystalline drugs from previously crude and uncertain mixtures and of isolating other opium alkaloids, including codeine in 1832. In 1828, Wohler reported the synthesis of urea and Leroux reported the isolation of salin, which led, years later, to the introduction of salicylic acid, sodium salicylate, acetanalid, and acetyl salicylic acid, which came to be marketed as aspirin. A milestone in the prevention and treatment of pain was Morton's public demonstration in 1846 of the anesthetic properties of ether, which led to the development of general anesthesia. In approximately the same period Rynd developed the needle and Wood the syringe, which permitted the injection of analgesics. This development, together with the isolation and pharmacologic studies of cocaine, eventually led to Karl Koller's demonstration of its local anesthetic efficacy in 1884 and the subsequent widespread use of regional analgesia and anesthesia, not only for surgery but also for diagnosis and therapy of nonsurgical pain.

During the nineteenth century, hypnosis for surgery and for nonsurgical pain therapy became widely used and psychotherapeutic methods were developed. The advent of anesthesia and aseptic surgery and the evolution of the specificity theory led to still another method of relieving chronic intractable pain–neurosurgical operations on sensory pathways in peripheral nerves and spinal cord. Advances also were made in physical therapy, including electrotherapy, hydrotherapy, thermotherapy, and mechanotherapy. Finally, the discovery of x-rays by Roentgen ushered in an era of radiation therapy for many painful conditions.

PAIN THEORIES

During the remainder of the nineteenth century, anatomic, physiologic, and histologic studies were undertaken that prompted the explicit formulation of two physiologic theories of pain, the specificity theory and the intensive theory.

Specificity (Sensory) Theory

The specificity theory stated that pain was a specific sensation, with its own sensory apparatus, independent of touch and other senses. This theory, which, as previously mentioned, had been suggested by Galen, Avicenna, and Descartes, and in 1853 by Loetze (8), was definitively formulated by Schiff in 1858 (39) after his analgesic experiments in animals. Noting the effects of various incisions in the spinal cord, he found that pain and touch were independent: Transsection of the gray matter of the spinal cord eliminated pain but not touch, and a cut through the posterior white matter caused touch to be lost, but pain was unaffected. The results of these vivisections were promptly corroborated by clinical evidence as a number of clinicians reported pathologic cases of disease or injured spinal cords with similar sensory defects (3).

Schiff's theory was supported by later experiments by Funke in 1879 (40) and by the classical experiments by Blix (41), Goldscheider (42), and Donaldson, who discovered separate spots for warmth, cold, and touch in the skin between 1882 and 1885 (8). A decade later, von Frey (43) extended these studies to map out pain and touch spots, but he also did histologic examination of skin intended to identify specific end organs responsible for each sensation. On the basis of his findings and some imaginative deductions, von Frey expanded Müller's concept of the sense of touch to four major cutaneous modalities: touch, warmth, cold, and pain.

Intensive (Summation) Theory

The intensive theory, which was implied in Aristotle's concept that pain resulted from excessive stimulation of the sense of touch, was first suggested by Darwin and subsequently embraced by Romberg, Henle, and Volkmann (8) in the 1840s and 1850s. The theory was explicitly formulated by Erb (44) in 1874. He maintained that

every sensory stimulus was capable of producing pain if it reached sufficient intensity. This theory received subsequent support from Wundt (45) and later from Blix (46), Kulpe (47), Titchener (48), and especially Goldscheider. Blix's aforementioned studies in 1882 had led him to believe that pain was a specific sensation, but a year later he discarded this view. Goldscheider also shifted views. At first he did not believe that pain was specific, but by 1885, just as Blix was shifting in the other direction, Goldscheider (42) came to the conclusion that the evidence was in favor of specificity. He held this view until 1891, when he shifted once more (49) because of the results obtained by Naunyn 2 years earlier, which led the latter to conclude that pain was the result of summation (8).

In 1894 Goldscheider (50) fully developed the theory that stimulus intensity and central summation were the critical determinants of pain. This theory suggested that the particular patterns of nerve impulses that evoke pain are produced by the summation of the skin sensory input at the dorsal horn cells. According to this concept, pain results when the total output of cells exceeds a critical level as a result either of excessive stimulation of receptors that are normally fired by nonnoxious thermal or tactile stimuli or of pathologic conditions that enhance the summation of impulses produced by normally nonnoxious stimuli. Goldscheider assumed the long delays and persistent pain observed in pathologic pain states were caused by abnormally prolonged time periods of summation. He further proposed that the spinal "summation path" that transmitted the pain signal to the brain consisted of slowly conducting, multisynaptic fiber chains and that the large fibers that project up the dorsal column pathways carried the tactile discriminative properties of cutaneous sensation (50).

Controversies

Thus, by the end of the nineteenth century, three conflicting concepts existed on the nature of pain. The specificity theory and the intensive theory, which were in opposition to each other, were embraced by physiologists and a few psychologists. These two theories opposed the traditional Aristotelian concept that pain was an affective quality, which at this time was being supported by most philosophers and psychologists, including Lehmann in Germany; Gain, Bradley, Spender, and Ward in England; and Baldwin, Dewey, James, and especially H. R. Marshall in America (8). The latter was the most active proponent of the pleasure–pain theorists and wrote extensively on the subject (51). During the decade between 1886 and 1895, proponents of each of these theories became involved in unprecedented, intensely fierce controversies. In an attempt to reconcile the views of physiologists with those of philosophers and psychologists, Strong, then president of the American Psychological Association, suggested in 1895 that pain consisted of the original sensation and the psychic reaction or displeasure provoked by the sensation (52). This concept was later embraced by others, including Sherrington, who believed that pain was composed of sensory and affective (feeling) dimensions (53).

Pain Theories in the Twentieth Century

During the first six decades of the twentieth century, research on pain continued and the published data acquired were used, in part, to support either the specificity theory or the intensive theory, or a modification of these. The intense controversy between von Frey and Goldscheider continued until the late 1920s (54,55), and each rallied supporters. Thus, Weir Mitchell, Henry Head, and subsequently Adrian, Ranson, Waterston, Bishop, Sherrington, and Wolff and coworkers supported the specificity theory, whereas Lugaro, Leriche, and subsequently Livingston, Nafe, Hebb, Wedell, and Sinclair supported the intensive theory (7,56,57). By midcentury, however, the specificity theory prevailed and became widely taught.

Von Frey's theory, which dealt only with receptors, subsequently prompted others to believe that pain is subserved by specific fibers from the receptors to spinal cord and specific pain pathways in the neuraxis and even suggested the existence of a pain center. Experiments were carried out in peripheral nerves to show there is a one-to-one relationship between receptor type, fiber size, and quality of experience (58). Other animal experiments suggested that the anterolateral quadrant of the spinal cord was critically important for pain sensation, a concept that found support in the early observation by Spiller (59) of analgesia with pathologic lesions of this part of the cord, the early results with anterolateral cordotomy by Spiller and Martin (60), and subsequently by many others (61). In 1920, Head (62) proposed that a *pain center* is located in the thalamus because cortical lesions or excisions rarely abolish pain, but frequently make it worse, suggesting that the cortex exerts inhibitory control to the thalamic pain center.

Pattern Theories

In 1934, Nafe (63) suggested that all cutaneous qualities are produced by spatial and temporal patterns of nerve impulses, rather than by separate modality-specific transmission routes. On the basis of this suggestion and personal studies, Sinclair (64) and Weddell (65), two decades later, proposed a peripheral pattern theory that stated that all fiber endings, apart from those that innervate hair cells, are alike, so that the pattern of pain is produced by intense stimulation of nonspecific receptors. This theory ignored the physiologic evidence that shows a high degree of receptor fiber specialization.

Central Summation Theory

In 1943, Livingston (66) proposed his own theory of central summation in support of the intensive theory. He suggested that the intensive stimulation resulting from nerve and tissue damage activates fibers that project to internuncial neuron pools in the spinal cord, creating abnormal reverberatory activity in closed self-exciting neuron loops. This prolonged, abnormal activity bombards the spinal cord transmission (T) cells, which project to brain mechanisms that underlie pain perception. The abnormal internuncial activity spreads to lateral horn cells and ventral horn cells in the spinal cord, activating the sympathetic nervous system and somatic motor system, respectively, producing vasoconstriction, increased work of the heart, and skeletal muscle spasm. These, in turn, produce further abnormal input, thereby creating a vicious circle. Brain activities such as fear and anxiety evoked by pain also feed into and maintain the abnormal internuncial pool activity.

Eight years later, in 1951, Gerard (67) suggested a theory that is similar in concept but different in hypothetical mechanisms. He proposed that a peripheral nerve lesion may bring about temporary loss of sensory control of firing in spinal cord neurons, which then begin to fire in synchrony. Such synchronously firing pools "could recruit additional units, could move along in the grey matter, could be maintained by impulses different from and feebler than those needed to initiate it, and could discharge excessive and abnormally patterned volleys to the higher centers."

Fourth Theory of Pain

The controversy among the three groups of theorists continued, but by midcentury the specificity theory had prevailed and was taught universally. To take into account the psychological factors that have been shown to influence pain and consolidate these with the specificity theory, Hardy, Wolff, and Goodell (68) in the 1940s reintroduced the concept of the duality of pain that had been proposed by Strong and called it the *fourth theory of pain*. They believed that pain can be separated into two components: the perception of pain and the reaction to pain. The perception of pain, like the perception of other sensations such as temperature and touch, is a neurophysiologic process that has special structural, functional, and perceptual properties and is accomplished by means of "relatively simple and primitive" neural receptive and conductive mechanisms. The reaction to pain, on the other hand, is a complex physiopsychological process involving the cognitive functions of the individual and is influenced by past experience, culture, and various psychological factors that produce great variation in the *reaction pain threshold*. This concept assumes a one-to- one relationship between the intensity of the stimulus and pain perception and relegates the reaction to pain as a secondary response consequent to the sensation achieved in a straight-through push-button or alarm system fashion.

Sensory Interaction Theory

In 1959, Noordenbos (69) proposed the sensory interaction theory. This theory derived from Goldscheider's original concept and also subsequent proposals by Head, Bishop, and others of the existence of two systems involving transmission of pain and other sensory information: a slow system that involved the unmyelinated and thinly myelinated fibers and a fast system that involved the large myelinated fibers. He proposed that the small-diameter slowly conducting somatic afferent fibers and small visceral afferents project into the cells in the dorsal horn of the spinal cord and the summation of inputs from the small fibers produces the neural patterns that are transmitted to the brain to produce pain. The large-diameter fast-acting fibers inhibit transmission of impulses from the small fibers and prevent summation from occurring. Diseases that produce a selective loss of large fibers bring about a loss of inhibition and thereby increase the probability of summation and of abnormal pain phenomena. Noordenbos further proposed that one of the ascending systems that transmit pain signals is the short axon multisynaptic system in the core of the spinal cord.

Figure 1-2 presents schematically the most important conceptual models of pain mechanisms presented between 1900 and 1960.

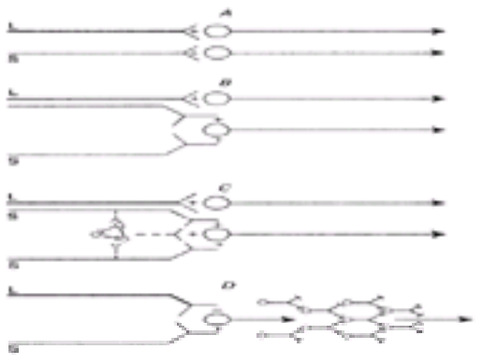

Figure 1-2. Schematic representation of conceptual models of pain mechanisms. **A:** The specificity theory espoused by von Frey, who believed that large fibers (*L*) transmitted touch, and small fibers (*S*) mediated pain impulses in separate, specific, straight-through pathways to touch and pain centers in the brain. **B:** The summation theory, first espoused by Goldscheider, who believed that convergence of small fibers onto a dorsal horn produced pain and that touch was transmitted by large fibers. **C:** Livingston's conceptual model of reverberatory circuits involved in chronic pathologic pain states in which nociceptive impulses initiate prolonged activity in the self-exciting chain of neurons and bombard dorsal horn cells, which then transmit abnormally patterned volleys of nerve impulses to the brain and also to anterior and anterolateral horn cells that become involved in abnormal reflexes, leading to skeletal muscle spasm and sympathetic hyperactivity. **D:** The interaction theory proposed by Noordenbos, who believes that large fibers inhibit (–) and small fibers excite (+) central transmission neurons, which project to a multisynaptic system that leads to the brain. Part of this theory was incorporated into the Melzack-Wall theory depicted in Figure 1-3. (Modified from Melzack R, Wall PD. Psychophysiology of pain. *Int Anesth Clin* 1970;8:3.)

Gate Control Theory

New data acquired during the 1950s led Melzack and Wall to reappraise the specificity and intensive theories in the following decade (70). They concluded that the specificity theory is strongly supported by physiologic evidence of specialization of the nervous system, but its psychological assumption that sensation is achieved via a fixed direct communication from the skin to the brain in a straight-through push-button fashion is its great weakness. The scientific evidence failed to support the assumption of a one-to-one relationship between the intensity of the stimulus and pain perception but instead suggested that the amount and quality of pain perceived are determined by many physiologic and psychological variables. Similarly, the intensive theory is strongly supported by the evidence on central summation and input control but is weakened by ignoring peripheral specificity. The scientific evidence suggests that pain is not caused by neural activity that resides exclusively in nociceptive pathways traditionally considered specific for pain, but is a result of activity in several interacting neural systems, each with its own specialized function. As a result of these considerations, Melzack and Wall published their own theory in 1965 (70) that took into account the evidence of physiologic specialization, central summation, patterning, modulation of input, and the influence of psychological factors.

The original Melzack-Wall theory of pain is illustrated in Figure 1-3. As noted, impulses evoked by peripheral stimulation are transmitted to three systems: the cells in the substantia gelatinosa, the dorsal column fibers that project toward the brain, and the spinal cord transmission (T) cells that mediate information to the brain. The theory is based on the following propositions: (a) The transmission of nerve impulses from afferent fibers to the spinal cord T cells is modulated by a spinal gating mechanism in the dorsal horn. (b) The spinal gating mechanism is influenced by the relative amount of activity in large-diameter (L) and small-diameter (S) fibers; activity in large fibers tends to inhibit transmission (closes the gate), whereas activity in small fibers tends to facilitate transmission (opens the gate). (c) The spinal gating mechanism is influenced by nerve impulses that descend from the brain. (d) A specialized system of large-diameter rapidly conducting fibers labeled the *central control trigger* activates selective cognitive processes that then influence by way of descending fibers the modulating properties of the spinal gating mechanisms. This system carries precise information about the nature and location of the stimulus and conducts so rapidly that it may not only set the receptivity of cortical neurons for subsequent afferent volleys, but also, by way of the descending fibers, influence the sensory input at the segmental gate control system and at other levels of the neuraxis. This rapid transmission makes it possible for the brain to identify, evaluate, localize, and selectively modulate the sensory input before the action system is activated. (e) When the output of the spinal cord transmission (T) cells exceeds a critical level, it activates the action system, those neural areas that underline the complex sequential pattern of behavior and experience characteristics of pain.

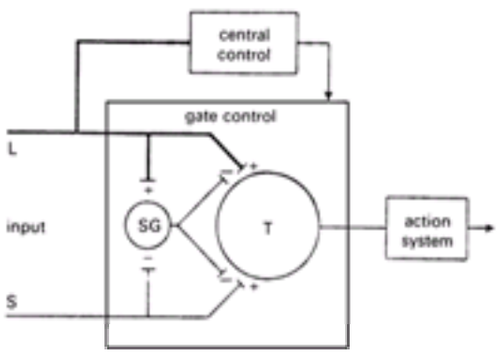

Figure 1-3. Schematic of the gate-control theory of pain (Mark I). L, large-diameter fibers; S, small-diameter fibers. The fibers project to the substantia gelatinosa (SG) and first central transmission (T) cells. The inhibitory effect exerted by the SG on the afferent fiber terminals is increased by activity in L fibers and decreased by activity in S fibers. The central control trigger is represented by a line running from the large-fiber system to the central control mechanisms; these mechanisms, in turn, project back to the gate-control system. The T cells project to the action system. +, excitation; –, inhibition. (From Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971, with permission.)

Three years later, Melzack and Casey (71) expanded the theory by taking into account subsequently acquired knowledge derived from physiologic and behavioral studies that further emphasize the motivational, affective, and cognitive aspects of the pain experience. These pertain to neural systems beyond the gate and involve interaction of the neospinothalamic and paleospinothalamic projecting systems and neocortical processes. They suggested that the neospinothalamic projecting system in the brain serves to process sensory discriminative information about the location, intensity, and duration of the stimulus, whereas impulses that pass through the paleospinothalamic tract and paramedial ascending system activate reticular and limbic structures that provoke the powerful motivational and aversive drive and unpleasant affect that triggers the organism into action. Neocortical higher central nervous system processes, such as evaluation of the input in terms of past experience, exert control over both discriminative and motivational systems.

In 1982, Melzack and Wall (72) modified their theory to take into account information acquired since the original proposal. The new model is depicted in Figure 1-4. As may be noted, this model includes excitatory and inhibitory links from the substantia gelatinosa to the transmission cells as well as descending inhibitory control from brainstem systems. Despite whatever deficiencies the Melzack-Wall-Casey models of pain may have, they have proven to be among the most important developments in the field of pain research and therapy. In addition to providing a comprehensive formulation of pain mechanisms, the theories have stimulated extensive physiologic and psychological research and have provoked the development of new approaches to pain therapy.

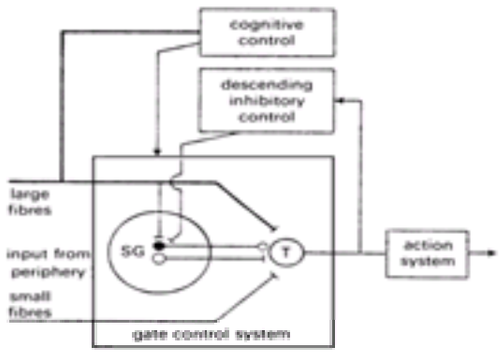

Figure 1-4. The gate-control theory (Mark II). The new model includes excitatory (*white circle*) and inhibitory (*black circle*) links from the substantia gelatinosa (SG) to the transmission (T) cells, as well as descending inhibitory control from brainstem systems. The round knob at the end of the inhibitory link implies that its actions may be presynaptic, postsynaptic, or both. All connections are excitatory, except the inhibitory link from SG to T cell. (Modified from Melzack R, Wall PD. *The challenge of pain*. New York: Basic Books, 1983.)

Psychological and Behavioral Theories

All of the preceding theories have been proposed to explain the mechanisms of pain caused by damage of body tissues or of peripheral nerves, the central nervous system, or both. Since the late 1960s, the literature has increased on chronic pain occurring in the absence of tissue damage or other *organic* pathology. The early reports by Engel and Walters on *psychogenic* pain were followed by studies of Merskey and collaborators and others of the incidence of pain in patients with a neurosis or psychosis and in whom no demonstrable pathology could be found. These studies, summarized in the book by Merskey and Spear (73), suggest that the highest incidence was found in patients with neurotic disorders, especially hysteria, and less frequently with reactive depression and other psychotic disorders.

One of the most important points made by Merskey and Spear (73) and later by Sternbach (74) is that these patients feel and describe their pain in the same terms as patients with demonstrable pathology and that their psychogenic pain is as real to these patients as pain caused by somatogenic disorders. This similarity of describing both types of pain is widely recognized and refutes the Cartesian concept of dichotomy of body and mind. This similarity is emphasized by the definition adopted and published by the Committee on Taxonomy of the International Association for the Study of Pain (IASP) discussed in the next chapter.

As part of the surge in pain research mentioned in the following discussion, studies by psychiatrists and psychologists have markedly expanded our knowledge of the role of learning, personality, culture, and cognition; psychological, emotional, and motivational factors; and environmental influences on pain and pain behavior. This knowledge has led to the development of other hypothesis and concepts to explain chronic pain behavior in patients with minimal or no demonstrable pathology. Among the most important of these are the concept of *chronic abnormal illness behavior*, first proposed by Pilowsky (75) and subsequently adopted by others, and the concept of *operant (behavioral) conditioning* developed by Fordyce (76), which is being applied in many chronic pain therapy programs. These hypotheses are discussed in detail in Chapter 24, Chapter 25 and Chapter 26.

STATUS OF PAIN THERAPY

Throughout the twentieth century, the methods used to treat acute and chronic pain conceived during the nineteenth century underwent remarkable advances. Because these are discussed in detail in Part V of this book, only brief comments on their historical development are made here. During this period, progressively greater advances were made in the development of systemic analgesics made possible by advances in synthetic chemistry. Consequently, a variety of nonnarcotic analgesics were developed, including acetaminophen (paracetamol), phenacetin, and other derivatives of paraminophenols and aminopyrine, phenylbutazone, and a variety of nonsteroidal anti-inflammatory drugs. Equally important advances were made in the development of various narcotic analgesics, including semisynthetic derivatives of morphine such as diacetylmorphine (heroin), hydromorphone (Dilaudid), and oxymorphone (Numorphan); later, wholly synthetic narcotic analgesics were developed, of which meperidine (pethidine, Demerol) was the first. Subsequently, methadone (Dolophine) and morphinan were synthesized, and from these a large number of derivatives that constitute important synthetic opioids were developed. In addition to nonnarcotic and narcotic analgesics, another heterogeneous group of drugs usually labeled adjuvants are used in conjunction with one or both of the other classes. These drugs constitute the most frequently used method for the relief of pain because they are readily available, inexpensive, simple to administer, and if properly used are reasonably effective in relieving various types of pain.

The widespread acceptance of the specificity theory led to the development and widespread use of regional analgesia and neurosurgical operations for the treatment of nonsurgical pain. During the early part of the century, techniques were developed for the injection of local anesthetic into tissues or around virtually every major nerve and various nerve plexuses and into the subarachnoid and epidural spaces to produce nerve block or regional analgesia and anesthesia. Although these procedures were first developed for surgical anesthesia, it was not long before physicians began to use them as diagnostic, prognostic, and therapeutic aids in the management of patients with acute or chronic pain syndromes (57,58). Moreover, the intentional destruction of peripheral nerves or sensory roots of spinal and cranial nerves by injecting alcohol, phenol, or other neurolytic agents became widely used for the relief of severe intractable pain of cancer and other chronic conditions. Similarly, neurosurgical procedures were developed and refined that were intended to interrupt pain pathways in various parts of the peripheral and central nervous system. As is emphasized throughout this book and is considered in detail in Chapter 104, Chapter 105, Chapter 106, Chapter 107 and Chapter 108, more recently acquired information has caused a marked decrease in the use of these destructive chemical and surgical procedures.

During the first decade of the twentieth century, the use of hypnosis for pain therapy underwent periods of enthusiastic acclaim and total neglect. Psychotherapy also was used from time to time in treating persistent pain. Other psychological techniques of controlling pain that have been proposed included relaxation and a variety of cognitive-behavioral procedures, but these did not gain widespread acceptance and application until the pioneering work of Fordyce made multidisciplinary pain management popular after 1970. Moreover, a variety of physical therapeutic techniques and radiation therapy were refined and widely applied for the treatment of acute and chronic pain syndromes.

In the introduction to the first edition of this book, published in 1953 (56), after reviewing the advances in pain theory and pain therapy achieved up to that time, Bonica made the following statement:

> In spite of all the aforementioned achievements, and in spite of the many efforts that have been made by so many investigators regarding all of its phases, we are far from our goal of understanding pain. . . . Moreover, more than superficial thought on this problem reveals that our methods of management, while effective in some patients, are nevertheless not as refined as they can be, and entail procedures which frequently are destructive.

Throughout the book he repeatedly emphasized that many patients with various types of acute pain and most patients with chronic pain were not relieved effectively. Subsequently, he reassessed the status of pain research and therapy at frequent intervals, and each time he found that the statements he made in 1953 continued to be valid (6,7,56,57,77,78,79 and 80).

On each occasion of reassessment, Bonica found impressive evidence that a large percentage of patients with acute postoperative pain, or other post-traumatic pain, and those with severe acute pain associated with visceral disease, and most patients with acute postburn pain were inadequately relieved. Moreover, as detailed in Chapter 10, many patients with nonmalignant chronic pain did not respond to the usual medical therapy and an impressive number have been exposed to the high risks of iatrogenic complications including drug toxicity, drug dependence, and multiple, often useless, and at times mutilating operations. A significant number of these patients gave up medical care and consulted quacks who not only depleted their economic resources, but also did them harm. Patients with cancer pain have often fared no better; indeed there have been numerous reports indicating that many patients with advanced cancer live the last months of their lives in unrelieved severe pain (see Chapter 35, Chapter 36, Chapter 37, Chapter 38, Chapter 39 and Chapter 40). One of the most gratifying events of the 1990s has been the significant improvement in cancer pain and end of life palliative care; this contrasts with the slow progress in the prior 25 years.

Reasons for Deficiencies

On each occasion of reassessing pain diagnosis and therapy, Bonica looked into the reasons for these deficiencies and found them to remain the same. These can

be grouped into three major categories: (a) great voids in knowledge about pain and its mechanisms because of insufficient research; (b) inadequate or improper application of the available knowledge and therapies; and (c) problems with communications. Although he discussed these issues on numerous occasions and in several dozen publications (6,7,56,57; see 80 for other references), they deserve reemphasis here because they serve as an important framework for many of the chapters that follow.

Voids in Knowledge

A careful review and analysis of the history of pain research reveals that, after the surge of interest and activities evidenced during the last part of the nineteenth century and the early part of the twentieth century, the degree of interest and participation in this field was not commensurate with the clinical importance of the problem. Until the 1960s or so, pain research was relatively neglected by the scientific community, and only a few basic and clinical scientists devoted efforts to this field. Moreover, of those basic scientists who studied pain, most did so in the isolation of the animal laboratory, and many were not concerned with clinically relevant issues. The failure to study animals with injuries to somatic tissues or nerves was a major impediment to the development of valid models for clinical pain states, especially those that were chronic. Indeed, almost all studies that purported to be related to pain involved transient stimuli designed to be insufficient to damage tissues. The advent of reasonable animal models in the 1990s has greatly advanced studies of the mechanisms of chronic pain. As previously mentioned, most of the new data acquired during the first half of the twentieth century were used to support either the specificity theory or the intensive theory or subsequent modifications.

Until the early 1970s, the scientific community did not take advantage of great advances in medical research, medical science, and technology and apply them to pain research. This was especially true of the investigation of the mechanisms and pathophysiology of chronic pain states. Perhaps this was caused in part by the fact that most scientists, like most clinicians, did not appreciate differences between acute and chronic pain. Consequently, no effort was devoted to development of animal models for chronic pain. As a result of fragmented independent research efforts on artificially induced acute pain, hypotheses and concepts were developed that, although reasonable for the times and the scientific data available, were not relevant to chronic pain.

The predominant concern with anatomic and physiologic research on pain, consequent to the widespread assumption that pain was a purely sensory experience, caused emotional and psychological factors to be relegated to secondary roles or to be considered by-products of the sensation. These and other factors discouraged experimental and clinical psychologists and behavioral scientists from becoming involved in pain research. Consequently, the crucial roles of psychological and environmental factors in causing chronic pain behavior in a significant number of patients were not studied and defined until recently. In regard to this issue and to the widespread acceptance of the specificity theory by midcentury, Bonica stated in the first edition of this book that: “As a consequence, there has emerged a sketch plan of pain apparatus with its receptors, conducting fibers, its centers of elaboration, and its standard function, which is supposed to be applicable to all circumstances. But . . . in doing so, medicine has overlooked the fact that the activity of this apparatus is subject to a constantly changing influence of the mind.”

As emphasized in Chapter 9 and Chapter 10, a serious research-related deficiency has been the lack of accurate data from large-scale national epidemiologic studies on the incidence and prevalence of various types of pain and their socioeconomic effect. Another critically important reason for the voids in our knowledge of pain has been the lack of research training programs focused on pain of the type that has existed for the study of other important health problems. Consequently, there has been an insufficient number of basic and clinical scientists devoting their time to pain research. Related to these problems has been the meager amount, or total lack, of funds allocated for pain research and research training even in so-called developed and medically advanced countries.

The explosion in neurosciences research in the last quarter of the twentieth century has led to increased understanding of the nervous system in general and mechanisms of acute and chronic pain in particular. Entire laboratories have been established to undertake pain research and have received significant funding from governmental and commercial sources. A significant fraction of the papers at the annual Society for Neurosciences meeting focuses on aspects of pain. Numerous other meetings take place every year that lead to increased communications among pain researchers and attract neuroscientists to this field. Pain research is better funded at the end of the twentieth century than at any time in the past.

Inadequate Application of Available Knowledge and Therapies

Improper or inadequate application of current knowledge and therapies has been caused by a number of interrelated factors including (a) lack of organized teaching of medical students, physicians, and other health professionals involved in the clinical management of patients with acute and chronic pain; (b) inadequate sources of other information, such as books and journals available for the education of students, physicians in training, and practitioners; and (c) the lack of appreciation by investigators, teachers, and clinicians of the differences between acute pain and chronic pain in regard to etiology, function, mechanisms, pathophysiology, and approach to diagnosis and therapy. Consequently, students have been taught to use pain as a diagnostic aid and have been given little, if any, instruction in the basic principles of the management of acute and chronic pain.

As a result of this lack of education, many physicians have treated acute pain and cancer pain in an empiric manner, relying on nonnarcotic and narcotic analgesics and related drugs, not infrequently administering them improperly. A number of studies have shown that house officers and some physicians prescribe narcotics at two-thirds or three-fourths of the dose required to relieve severe pain, and that nurses underadminister drugs by another one-third to one-half (81,82). These studies revealed that the reasons for such underdosing included inadequate knowledge of the pharmacology of these drugs so that physicians underestimated the effective dose range and overestimated the duration of action and that nurses and physicians had an exaggerated opinion of addiction potential and the dangers of respiratory depression. As is emphasized in many parts of this book, these are not valid reasons for underdosing patients with pain.

Inadequate application of available knowledge and therapies has played an even greater role in the improper treatment of patients with chronic pain syndromes. The lack of organized teaching and appreciation of the difference between acute and chronic pain have caused many physicians to apply the same therapeutic modalities that are used in treating acute pain to the management of patients with chronic pain. Moreover, as previously mentioned, until the last quarter of the twentieth century, the critical influence of environmental and psychological factors as primary causes of chronic pain behavior was not known or appreciated. Treatment of patients with chronic pain, caused by such factors, with traditional medical therapy has proved totally ineffective and has often led to iatrogenic complications.

As a result of the deficiencies in teaching and transfer of information, some physicians have not appreciated that, because most patients with chronic pain develop complex emotional and behavioral changes, they require extensive psychological evaluation as well as detailed general physical, neurologic, orthopedic, and other special examinations as discussed in Part II of this book. Finally, many physicians do not have a broad perspective of all the available therapeutic modalities, including their indications and advantages and their disadvantages and complications, essential requisites for their proper application.

The inability (or unwillingness) of some physicians and other health professionals to spend several hours for the initial workup of the patient has probably been caused by the pressure of their large clinical practices and lack of interest in, and knowledge of, chronic pain syndromes. Consequently, a correct diagnosis is not made and the patient is started on a course of empirical therapy that usually ends in drug toxicity and other iatrogenic complications and in an endless series of experiences of hopefulness and then disappointments, frustrations, and hopelessness. Many of the patients seen at the University of Washington Pain Center could have been spared the prolonged suffering and disability if, at the initial contact, the physicians could have spent more time to do a proper workup of the patient, or if the patient had been referred to someone who could do so.

The progressive trend toward specialization has led practitioners in the various specialties to concern themselves only with their own narrow approaches to pain. Thus, the anesthesiologist attempts to treat all patients with chronic pain with nerve blocks, the neurosurgeon by cutting pain pathways, the orthopedic surgeon by surgical operations, the general practitioner and internist by prescribing drugs, and the psychiatrist by traditional psychotherapy. This tunnel vision is particularly likely to occur when a specialist practices alone and sees these patients in the isolation of the office. This approach precludes viewing the pain problem within the perspective of the many diagnostic and therapeutic strategies that may be applicable to the particular problem and choosing which are best for the particular patient.

A related causative factor is that many chronic pain syndromes are composed of such complex arrays of sensory, perceptual, psychological, psychosocial, environmental, and other factors as to require the concerted and well-coordinated efforts of the patient's physician and a number of specialists from different disciplines working as a closely knit team to make a correct diagnosis and develop the most appropriate therapeutic strategy. Although Bonica first conceived and practiced this multidisciplinary team approach to complex pain problems in 1945, and subsequently spoke and wrote extensively about it until the late 1960s and early 1970s (see Chapter 11 for references), the pattern of traditional medical practice was not conducive to such team efforts. This concept is discussed in detail in Chapter 11, Chapter 18, and Chapter 109.

The aforementioned deficiencies are not the fault of physicians, nurses, and other health professionals, but of educators who, because of lack of appreciation and concern about the symptomatic treatment of acute pain, cancer pain, and nonmalignant chronic pain, have not included ample education and training in this subject in

the curricula of undergraduate and graduate (residency) programs and in postgraduate (continuing) educational courses. This thesis is strongly supported in part by the fact that review of the 10 textbooks on medicine and surgery (83,84,85,86,87,88,89,90,91 and 92) and 11 on oncology (93,94,95,96,97,98,99,100,101,102 and 103) published in the United States, which are used as standard texts for medical students, house officers, and practitioners, in 1985 revealed that of a total of nearly 27,000 pages, only 0.6% are devoted to the description of symptomatic therapy of acute and chronic pain (i.e., therapy not directed at removing the cause of the pain by medical or surgical means). Similar deficiencies have existed in texts in other countries. Since 1980, journals and books devoted to pain diagnosis and treatment have dramatically increased in number, both in the English language and in many other languages. Furthermore, many comprehensive textbooks have included chapters on pain management. Although few medical schools provide their students with adequate education about pain, some have developed good curricula. In general, nursing schools have done a better job with this subject matter. In some countries, the government has recognized the discipline of pain management as a bona fide specialty; this has greatly improved educational opportunities for medical students and advanced trainees. Some of the improvements are related to the recognition of palliative care as a medical specialty and the inclusion of pain management as an essential part of palliation of illness.

Communication

A matrix common to all of these causative factors has been the poor, and indeed at times total, lack of communication among investigators and between this group and clinicians. Until the mid-1970s, the usual mechanisms for disseminating new information were publications in highly specialized journals limited to specific fields and meetings generally limited to specific groups. These specialized publications and meetings precluded cross-fertilization of ideas and dissemination of information among the various basic scientists and clinicians. The poor interaction among basic scientists of different disciplines has impaired the application of vitally important new information acquired by biochemists, for example, to the pain research programs of neurophysiologists. Moreover, it has impaired interaction and collaboration between basic and clinical scientists, which is essential to solve clinical problems. This lack of communication also has resulted in a great lag in clinical application of new information useful and pertinent to the care of patients with chronic pain. Other major communication problems have included a lack of an international standard terminology (taxonomy) of pain and pain syndromes, and lack of national and international pain data banks or data pools, essential requisites to optimal communication and evaluation of old and new methods of therapy.

ADVANCES

Since the early 1970s, several developments have taken place that, if sustained and expanded, hold the promise of helping to rectify some of the previously mentioned deficiencies. One has been a surge of interest among many basic scientists concerning the mechanisms of acute and chronic pain syndromes, and in collaborating with clinical investigators and practitioners to begin to solve some of the major clinical problems. This has resulted in the acquisition of much new knowledge on the anatomy, physiology, biochemistry, and psychology of acute pain and some new information on the pathophysiologic, psychological, and environmental substrates of chronic pain, most of which are summarized in this textbook. This new knowledge has changed our concept of sensory processing and sensory coding, and, together with recent clinical experience, it has changed our concepts and approaches to diagnosis and therapy of acute and chronic pain.

An important spin-off of recent research has been to bring into sharper focus a point that Bonica made in the first edition of this book, but which was ignored by many investigators and clinicians: that there are significant differences between acute pain and chronic pain in regard to etiology, mechanisms, pathophysiology, function, diagnosis, and therapy. In a paper published in 1981, Sternbach (74) described the contrasting characteristics of acute pain and those of chronic pain and developed, in an intriguing way and an impressively logical sequence, convincing evidence that whereas in acute pain the pain is a symptom of disease or injury, in chronic pain the pain itself is the disease. These differences are emphasized in the next two sections and throughout the book.

Some progress has also been made in some areas of pain diagnosis and therapy. A number of physicians and other health professionals have manifested interest in acquiring more knowledge about pain and its treatment. This has been reflected in part by the large attendance at numerous postgraduate seminars, international, national, and regional symposia and meetings, and at nine World Congresses on Pain sponsored by the IASP, and by the large number of textbooks on pain published during the 1990s and purchased by health professionals. Another encouraging trend has been the surge of interest in the multidisciplinary approach to diagnosis and therapy of chronic pain and in the hospice concept of managing patients with terminal cancer, two developments that Melzack and Wall (72) believe are the most important advances in patient care. These are discussed further in Chapter 11, Chapter 12, Chapter 40, and Chapter 109.

There has also been some progress with regard to communication and transfer of information. The founding of the IASP in 1974 and publication of its journal *Pain* since 1975 must be considered among the most important developments in the field of pain research and therapy. The goals of the IASP are to foster and encourage research on pain mechanisms and pain syndromes and to help improve the management of patients with acute and chronic pain by bringing together basic scientists, physicians, and other health professionals in various disciplines and backgrounds; to promote education and training in the field of pain; to facilitate dissemination of information; to promote triennial World Congresses; to encourage the formation of national chapters; to develop a classification of pain syndromes; and to encourage development of national and international data banks.

IASP has grown (up to 1999) to a membership of some 7,000 persons representing every biomedical science, clinical discipline, and health profession from 95 countries and has fulfilled most of its purposes. The journal *Pain* has acquired a reputation as a prestigious multidisciplinary international publication that publishes high-quality reports of original pain research and therapy, review articles, and other types of information relative to pain. The first nine World Congresses sponsored by IASP attracted the largest number of scientists and health professionals interested in pain research and therapy ever assembled. Through the scientific programs of these Congresses, publication of *Pain*, and publication of the Congress proceedings, IASP has done much to enhance the dissemination of basic and clinical information of multidisciplinary interest.

Through these programs, the IASP has made major contributions to promoting research and disseminating research knowledge and clinically relevant information. IASP's success in bringing together large numbers of research scientists from many disciplines, all having an interest in pain research and maintaining and promoting the high standards of these research areas, is a major achievement. Equally important has been its effectiveness in bringing together scientists and clinicians, thus bridging the gap that heretofore was partly responsible for the great lag in application of new knowledge to the care of patients. The Committee on Taxonomy completed its original task of developing definitions and a classification of various pain syndromes and an initial revision has been accomplished (presented in the next chapter), and the Committee on Research and Ethical Issues has developed guidelines for animal and human experimentation that have received international acclaim. Moreover, most of the 56 chapters of the association, composed of members from 65 countries, have had impressive growth, are active, and contribute to the achievements of the association. Chapter development and other professional societies also have been important in disseminating clinical information. Many other local, regional, national, international, single discipline, or multidisciplinary societies focusing on pain have been established. Some are purely clinical; others have a research focus. These often sponsor journals and meetings that have brought new interest to the problems of pain mechanisms and treatment. Their existence is a sign of the healthy growth in pain research and management.

If one attempts to characterize the last quarter of the twentieth century in contrast to the prior 5,000 years of study and treatment of pain, it is the cross-fertilization of different domains of thought that has led to dramatic advances. Only since 1975 have physicians, philosophers, psychologists, physiologists, moralists, and others who consider the human condition realized the need to study pain from multiple perspectives to move forward in the reduction of human suffering. We no longer accept the inevitability of pain or the suffering it engenders; scientists and clinicians are determined to develop knowledge of mechanisms of pain and effective diagnostic and treatment strategies. Predicting the future is always perilous, but we seem to be close to major breakthroughs in the relief of pain and suffering. The changes that can be documented since 1975 are in no small measure because of the crusading efforts of John J. Bonica, who first made the study of pain and its treatment a goal for twentieth-century physicians and scientists.

FUTURE NEEDS AND GOALS

We end this chapter with the same theme as the end of the introduction to the first edition of this book (77). What is our present position, and what are our needs and goals in improving the management of patients with pain? In the future, we must not only sustain but also markedly increase the current momentum and rapidly expand the gains we have made. The challenge to the biomedical scientific community, health professionals, and society as a whole is to organize, mount, and support a multipronged program. We must exert greater efforts and expend greater energy to solve the mystery of pain and to carry out more effective therapy. Doing so requires that the anatomist, neurophysiologist, psychologist, pharmacologist, and other laboratory investigators join forces with clinical scientists and clinicians to further elucidate the intimate nature of this most vexing perennial human problem. We must also markedly increase our efforts in the education and training of students, house officers, physicians, nurses, and other health professionals to improve the care of patients suffering from pain. We must concern ourselves with this problem, because pain is the day to day business of most physicians, nurses, and other health professionals. We must apply effectively the available knowledge and therapies so that we can reduce prolonged suffering and disability and thus improve the quality of life and social usefulness of millions of patients with pain. The proper management of patients with pain remains one of the most important responsibilities and obligations and can be the crowning achievement of biomedical

scientists and clinicians. It is hoped that this book will contribute to the attainment of this vital human and professional objective.

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CHAPTER 2

Pain Terms and Taxonomies of Pain

Dennis C. Turk and Akiko Okifuji

The inherent subjectivity of pain presents a fundamental impediment to increased understanding of its mechanisms and control. The language used by two individuals attempting to describe a similar injury often varies markedly, but appropriate communication requires a common language and classification system used in a consistent fashion. Clinicians and clinical investigators commonly use multiple terms that at times have idiosyncratic meanings. Thus, we have two primary goals in this chapter: (a) to provide definitions for many commonly used terms in the pain literature in an effort to bring about consistency and thereby to improve communication, and (b) to describe and discuss different classification systems or taxonomies, in an attempt to improve communication and to bring consistency to research and treatment of patients reporting pain.

DEFINITION OF COMMONLY USED PAIN TERMS

Discussions of pain involve many terms. The meaning and connotation of these different terms may vary widely. Some authors use the term *pain* to relate to a stimulus, others to a thing, and still others to a response. Such inconsistent usage creates difficulties in communication. As Merskey noted (1), it would be most convenient and helpful if there were some consensus on technical meanings and usage. Based on this belief, the editors of the two editions of the *International Association for the Study of Pain (IASP) Classification of Chronic Pain* included a set of definitions of commonly used pain terms (2,3). In the second edition of this text, Bonica reproduced a list of the terms and, in some cases, provided annotations. We adopt a similar strategy. We follow the convention of IASP, begin with the definition of pain, and then proceed alphabetically. Terms followed by an asterisk come directly from the IASP descriptions of pain terms.

*Pain**: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Pain, acute/pain, chronic[†]*:* Definitions of acute, chronic, recurrent, and cancer pain are not included in the IASP list of pain terms. We believe, however, that it is important to clarify these as they are commonly used in the literature.

Traditionally, the distinction between acute and chronic pain has relied on a single continuum of time with some interval since the onset of pain used to designate the onset of acute pain or the transition point when acute pain becomes chronic. The two most commonly used chronologic markers used to denote chronic pain have been 3 months and 6 months since the initiation of pain; however, these distinctions are arbitrary.

Another criterion for chronic pain is “pain that extends beyond the expected period of healing.” This is relatively independent of time because it considers pain as chronic even when it has persisted for a relatively brief duration. Unfortunately, how long the process of healing will (should) take is ambiguous.

Some hold that pain that persists for long periods of time, in the presence of ongoing pathology, should be considered an extended acute pain state. In this case, treatment targets the underlying pathology. This is not to encourage a Cartesian perspective of pain that distinguishes between mind and body. As the IASP definition clearly states, any pain, acute or chronic, regardless of the presence of identifiable tissue damage, is an unpleasant experience, inherently influenced by various cognitive, affective, and environmental factors. We hold that the weighting of the psychological factors is often greater in chronic pain than acute pain.

We propose conceptualizing acute and chronic pain on two dimensions: time and physical pathology dimensions. Figure 2-1 schematically depicts this two-dimensional conceptualization of acute and chronic pain. From this perspective, any case falling above the diagonal line (short duration or high physical pathology) is acute pain, whereas cases falling below the diagonal line (low physical pathology or long duration) are chronic pain. The perspective presented in Figure 2-1 leads to the following definitions of acute and chronic pain.

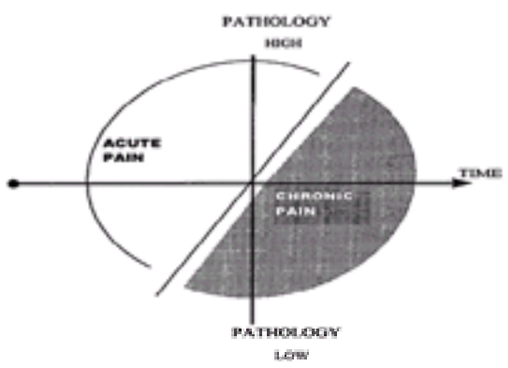

Figure 2-1. Figurative representation of acute and chronic pain.

Acute pain: Pain elicited by the injury of body tissues and activation of nociceptive transducers at the site of local tissue damage. The local injury alters the response characteristics of the nociceptors and perhaps their central connections and the autonomic nervous system in the region. In general, the state of acute pain lasts for a relatively limited time and generally remits when the underlying pathology resolves. This type of pain is often a reason to seek health care, and it occurs after trauma, surgical interventions, and some disease processes.

Chronic pain: It is usually elicited by an injury but may be perpetuated by factors that are both pathogenetically and physically remote from the originating cause. Chronic pain extends for a long period of time, represents low levels of underlying pathology that does not explain the presence and extent of pain, or both. This type of pain prompts patients frequently to seek health care, and it is rarely effectively treated. Because the pain persists, it is likely that environmental and affective factors eventually interact with the tissue damage, contributing to the persistence of pain and illness behaviors. It is also possible that, just as the brain is modified by experience, especially in early life, the brain may alter the way noxious information is processed to reduce or augment its effect on subjective awareness.

Cancer pain: Pain associated with cancer includes pain associated with disease progression as well as treatments. Although some contend that pain associated with

neoplastic disease is unique, we view it as fitting within our description of acute and chronic pain as depicted in Figure 2-1. Moreover, pain associated with cancer can have multiple causes—namely, disease progression, treatment (e.g., neuropathic pain resulting from radiation therapy), and co-occurring diseases (e.g., arthritis). Regardless of whether the pain associated with cancer stems from disease progression, treatment, or a co-occurring disease, it may be either acute or chronic. Thus, we do not advocate a separate classification of cancer pain as distinct from acute and chronic pain.

Recurrent pain: Recurrent pain is episodic or intermittent occurrences of pain, with each episode lasting for a relatively short period of time but recurring across an extended period of time. Our distinction between acute and chronic pain using the integration of the dimensions of time and pathology does not include recurrent pain (e.g., migraine headaches, tic douloureux, sickle cell crisis). In the case of recurrent pain, patients may suffer from episodes of pain interspersed with periods of being completely pain free. Although recurrent pain may seem acute because each pain episode (e.g., sickle cell crisis) is of short duration, the pathophysiology of many recurrent pain disorders (e.g., migraine) is not well understood. Syndromes characterized by recurrent acute pain share features in common with acute and chronic pain. The fact that these syndromes extend over time, however, suggests that psychosocial and behavioral factors, not only physical pathology, may be major determinants of illness behavior.

Transient pain: Transient pain is elicited by activation of nociceptors in the absence of any significant local tissue damage. This type of pain is ubiquitous in everyday life and rarely is a reason to seek heath care. It is seen in the clinical setting only in incidental or procedural pain, such as during a venipuncture or injection for immunization. This type of pain ceases as soon as the stimulus is removed.

Addiction: A behavioral pattern of psychoactive substance abuse, addiction is characterized by overwhelming involvement with the use of a drug (i.e., compulsive use), the securing of its supply, and the high tendency to relapse. The compulsive use of the drug results in physical, psychological, and social harm to the user and use continues despite this harm (see also Physical Dependency).

*Allodynia**: This is pain caused by a stimulus that does not normally provoke pain.

Analgesia: Absence of the spontaneous report of pain or pain behaviors in response to stimulation that would normally be painful. The term implies a defined stimulus and a defined response. Analgesic responses can be tested in animals as well as humans.

*Anesthesia dolorosa**: This refers to spontaneous pain in an area or region that is anesthetic.

*Central pain**: Pain initiated or caused by a primary lesion or dysfunction in the central nervous system.

Central sensitization: This is an increase in the excitability and responsiveness of neurons in the spinal cord.

*Complex regional pain syndrome type 1 (formerly reflex sympathetic dystrophy)**: A syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of edema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia.

*Complex regional pain syndrome type 2 (formerly causalgia)**: A syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor dysfunction and later trophic changes.

Cost-benefit analysis: An evaluation of the costs and effects of an intervention in a common, usually monetary, unit. The standardization of unit has an advantage because it permits comparisons across dissimilar intervention programs. On the other hand, the conversion of treatment effects to monetary units may not always be feasible. Estimation of the cost to outcome ratio is possible, as are comparisons between interventions using the rates of improvement (e.g., return to work) with common denominators.

Cost-effectiveness analysis: An estimation of treatment outcome entails criteria other than monetary terms, such as lives saved or return to work. An intervention is cost effective when it satisfies one of the following conditions: It is more effective than an alternative modality at the same cost; it is less costly and at least as effective as an alternative modality; it is more effective and more costly than an alternative treatment, but the benefit exceeds the added cost; or it is less effective and less costly, but the added benefit of the alternative is not worth the additional cost.

Disability: Any restriction or loss of capacity to perform an activity in the manner or within the range considered normal for a human being, such as climbing stairs, lifting groceries, or talking on a telephone. It is a task-based concept that involves the person and the environment. Disability is essentially a social and not a medical term or classification. Level of disability should be determined only after a patient has reached maximum medical improvement following appropriate treatment and rehabilitation.

*Dysesthesia**: An unpleasant abnormal sensation, whether spontaneous or evoked.

*Hyperalgesia**: An increased response to a stimulus that is normally painful.

*Hyperesthesia**: Increased sensitivity to stimulation, excluding special senses.

*Hyperpathia**: A painful syndrome characterized by increased reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.

*Hypoalgesia**: Diminished pain in response to a normally painful stimulus.

Hypochondriasis: An excessive preoccupation that bodily sensations and fears represent serious disease despite reassurance to the contrary.

Impairment: Any loss of use of, or abnormality of psychological, physiologic, or anatomic structure or function that is quantifiable. It is not equivalent to disability. Impairment is to disability as disease is to illness.

Malingering: A conscious and willful feigning or exaggeration of a disease or effect of an injury in order to obtain a specific external gain. It is usually motivated by external incentives such as financial compensation, avoiding work, or obtaining drugs.

Maximum medical improvement: The state beyond which additional medical treatment is unlikely to produce an improvement in function.

Multidisciplinary (interdisciplinary) pain center: An organization of health care professionals and basic and applied scientists that includes research, teaching, and patient care related to acute and chronic pain. It includes a wide array of health care professionals including physicians, psychologists, nurses, physical therapists, occupational therapists, and other specialty health care providers. Multiple therapeutic modalities are available. These centers provide evaluation and treatment and are usually affiliated with major health science institutions.

*Neuralgia**: Pain in the distribution of a nerve or nerves.

*Neuritis**: Inflammation or a nerve or nerves.

*Neurogenic pain**: Pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system.

*Neuropathic pain**: Pain initiated or caused by a primary lesion or dysfunction in the nervous system.

*Neuropathy**: A disturbance of function or pathologic change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and

bilateral, polyneuropathy.

Nocebo: Negative treatment effects induced by a substance or procedure containing no toxic or detrimental substance.

*Nociceptor**: A receptor preferentially sensitive to tissue trauma or to a stimulus that would damage tissue if prolonged.

Nociception: Activation of sensory transduction in nerves by thermal, mechanical, or clinical energy impinging on specialized nerve endings. The nerve(s) involved conveys information about tissue damage to the central nervous system.

*Noxious stimulus**: A stimulus that is capable of activating receptors for tissue damage.

Pain behavior: Verbal or nonverbal actions understood by observers to indicate that a person may be experiencing pain and suffering. These actions may include audible complaints, facial expressions, abnormal postures or gait, use of prosthetic devices, avoidance of activities, overt expressions, and verbal or nonverbal complaints of pain, distress, and suffering.

Pain clinic: Facilities focusing on diagnosis and management of patients with pain problems. It may specialize in specific diagnoses or pain related to a specific area of the body.

Pain relief: Report of reduced pain after a treatment. It does not require reduced response to a noxious stimulus and is not a synonym for analgesia. The term applies only to humans.

Pain threshold: The least level of stimulus intensity perceived as painful. In psychophysics, pain threshold is defined as a level of stimulus intensity that a person recognizes as painful 50% of the time.

*Pain tolerance level**: The greatest level of noxious stimulation that an individual is willing to tolerate.

Pain sensitivity range: The difference between the pain threshold and the pain tolerance level.

*Paresthesia**: An abnormal sensation, whether spontaneous or evoked.

*Peripheral neurogenic pain**: Pain initiated or caused by a primary lesion or dysfunction or transitory perturbation in the peripheral nervous system.

Physical dependence: A pharmacologic property of a drug (e.g., opioid) characterized by the occurrence of an abstinence syndrome following abrupt discontinuation of the substance or administration of an antagonist. It does not imply an aberrant psychological state or behavior or addiction.

Placebo: A substance or procedure without therapeutic effect that is provided as a treatment. It is frequently used to control patients' expectations for the efficacy in testing a treatment intervention.

Placebo effects: Refers to the positive benefit(s) from a placebo preparation or procedure that is generally achieved only with an active treatment intervention.

Plasticity, neural: Nociceptive input leading to structural and functional changes that may cause altered perceptual processing and contribute to pain chronicity.

Pseudoaddiction: Refers to the perception by observers of drug-seeking behavior in patients who have severe pain and are undermedicated or who have not received other effective pain treatment interventions. Such patients may appear preoccupied with obtaining opioids, but the preoccupation reflects a need for pain relief and not drug addiction. Pseudoaddictive behavior differs from true addictive behavior because when higher doses of opioid are provided, the patient does not use these in a manner that persistently causes sedation or euphoria, the level of function is increased rather than decreased, and that medications are used as prescribed without loss of control over use.

Psychogenic pain: Report of pain attributable primarily to psychological factors usually in the absence of any objective physical pathology that could account for pain. This term is commonly used in a pejorative sense. It often suggests a cartesian dualism and is not usually an effective method of describing a patient.

Rehabilitation: Restoration of an individual to maximal physical and mental functioning in light of his or her impairment.

Residual functional capacity: The capacity to perform specific social and work-related physical and mental activities after rehabilitation related to an impairment or when a condition has reached a point of maximum medical improvement.

Symptom magnification: Conscious or unconscious exaggeration of symptom severity in an attempt to convince an observer that one is truly experiencing some level of pain. It differs from malingering as it is an effort to be believed not necessarily to achieve a positive outcome (i.e., secondary gain) such as financial compensation.

Suffering: Reaction to the physical or emotional components of pain with a feeling of uncontrollability, helplessness, hopelessness, intolerability, and interminableness. Suffering implies a threat to the wholeness of an individual's self-concept, self-identify, and integrity.

Tolerance: A physiologic state in which a person requires an increased dosage of a psychoactive substance to sustain a desired effect.

Wind-up, second pain: Slow temporal summation of pain mediated by C fibers. Repetitive noxious stimulation at a rate less than one stimulus per 3 seconds. It may cause the person to experience a gradual increase in the perceived magnitude of pain.

TAXONOMIES

The lack of a classification of chronic pain syndromes that is used on a consistent basis inhibits the advancement of knowledge and treatment of chronic pain and makes it hard for investigators as well as practitioners to compare observations and results of research. Bonica (4) referred to this language ambiguity as “a modern tower of Babel.”

To identify target groups, conduct research, prescribe treatment, evaluate treatment efficacy, and for policy and decision making, it is essential that some consensually validated criteria are used to distinguish groups of individuals who share a common set of relevant attributes. The primary purpose of such classification is to describe the relationships of constituent members based on their equivalence along a set of basic dimensions that represent the structure of a particular domain. Infinite classification systems are possible, depending on the rationale about common factors and the variables believed to discriminate among individuals. The majority of the current taxonomies of pain are *expert-based* classifications.

Expert-Based Classifications of Pain

Classifications of disease are usually based on a preconceived combination of characteristics (e.g., symptoms, signs, diagnostic test results), with no single characteristic being both necessary and sufficient for every member of the category, yet the group as a whole possesses a certain unity (5). Most classification systems used in pain medicine [e.g., International Classification of Diseases (ICD-10) (6), Classification and Diagnostic Criteria for Headache Disorders, Cranial Neuralgias, and Facial Pain (7), International Association for the Study of Pain Classification of Chronic Pain (2)] and dentistry [i.e., Research Diagnostic Criteria for Temporomandibular Disorders (8)] are based on the consensus arrived at by a group of experts. In this sense they reflect the inclusion or elimination of certain diagnostic features depending on agreement.

Expert-based classifications develop preconceived categories and *force* individuals into the most appropriate one, even if not all characteristics defining the category

are present. Expert-based classification systems do not explicitly state the mathematical rules that should exist among the variables used to assign a case to a specific category.

In an ideal classification, the categories comprising the taxonomy should be mutually exclusive and completely exhaustive for the data to be incorporated. Every element in a classification should fit into one and only one place and no other element should fit into that place. An example of such an ideal, natural taxonomy is the periodic table in chemistry. We can also develop artificial classifications such as a telephone directory. The criterion for the classification—namely, the sequence of letters in the alphabet, has no relation to the people, addresses, and telephone numbers being classified; but it is quite satisfactory for the intended purpose (3). No classification in medicine or dentistry has achieved such aims. For example, the Research Diagnostic Criteria for Temporomandibular Disorders (8) includes eight different diagnoses. In one study, more than 50% of the sample received three or more Research Diagnostic Criteria diagnoses (9). Thus, the classifications or diagnoses are not mutually exclusive.

The most commonly used classification system of pain is the ICD published by the World Health Organization. In the most recent edition, the ICD-10 (6), conditions are classified along a number of different dimensions including causal agent, body system involved, pattern and type of symptoms; and whether they are related to the artificial intervention of an operation, time of occurrence, or grouped as signs, symptoms, and abnormal clinical and laboratory findings. Within major groups there are subdivisions by symptom pattern, the presence of hereditary or degenerative disease, extrapyramidal and movement disorders, location, and etiology. Overlapping occurs repeatedly in such approaches to categorization and thus is not ideal even if they serve a useful function.

Further complications arise when clinicians require a separate coding system. In the United States, for example, in addition to the ICD codes a clinician must select Current Procedural Terminology coding schemes for billing purposes. This has created a tendency whereby the fulfillment of the Current Procedural Terminology coding may dictate the ICD selections to justify the procedures. Such practices often needlessly create many diagnoses and additional treatments for billing purposes.

It is clear that the classification of pain cannot approach the ideal found in chemistry or telephone books, but this is not unique to pain; it characterizes medical classification systems in general. Classification in medicine, dentistry, and psychology is a pragmatic activity. It does not provide absolute truth but rather provides categories with which we can work to identify individuals with similar phenomena, prognoses, or causes (3). Currently, the majority of pain classifications in pain medicine rely on various parameters of pain experience such as anatomy, system, severity, duration, and etiology.

Classification Based on Anatomy

Several pain syndromes are classified by body location. For example, low back pain, pelvic pain, and headache each refer to the specific location of symptoms. However, the extent for which the anatomy-based classification of pain is clinically meaningful is limited, at least partially, because of the lack of anatomically defined specificity in the neurophysiology of pain.

Classification Based on Duration

As previously discussed, one common way to classify pain is to consider it along a continuum of duration. Thus, pain associated with tissue damage, inflammation, or a disease process that is of relatively brief duration (i.e., hours, days, or even weeks), regardless of how intense, is frequently referred to as acute pain (e.g., postsurgical pain). Many pain problems can be classified as chronic. For example, pain that persists for extended periods of time (i.e., months or years), that accompanies a disease process (e.g., rheumatoid arthritis), or that is associated with an injury that has not resolved within an expected period of time (e.g., low back pain, phantom limb pain) are all referred to as chronic. As noted, however, a single dimension of duration is inadequate because pathologic factors may be relatively independent of duration.

Classification Based on the Etiology of Pain

Another way to classify pain is based on etiology. The crudest classification of this kind is simply to distinguish somatogenic pain from psychogenic pain (pain of psychological origin). Simply put, when a range of physical examination, diagnostic imaging, and laboratory tests fail to identify the physical basis for the report of pain, pain is automatically believed to have originated from psychic conflict or psychopathology. Variations on the dichotomous somatogenic versus psychogenic classification exist. For example, Portenoy (10) proposed that three primary categories of pain be used—namely, nociceptive, neuropathic, and psychogenic. In this system, somatogenic pain is subdivided into two subtypes that contrast with psychogenic pain.

It is interesting to note that the processes by which clinicians determine whether pain is somatogenic or psychogenic are distinctive. The classification of somatogenic pain is established by identification of positive organic findings, whereas psychogenic pain is indicated only in the absence of positive signs. We question the utility of such a classification scheme.

Classification Based on Body System

Classification may focus on the body system involved. For example, Fricton (11) proposed the use of five categories—namely, myofascial, rheumatic, causalgic, neurologic, or vascular. In this case patients are assigned to one of five rather than two or three categories. However, the decision regarding classification still is based on a single dimension: system for the experience of pain.

Classification Based on Severity

Frequently, pain is classified unidimensionally on the basis of severity (0- to 10-point scale, with 0 being no pain and 10 being the worst pain that can be imagined). Therefore, regardless of the scale's level of measurement, nominal, ordinal, or interval, the construct involves a single dimension.

Mechanism-Based Classification of Pain

The conventional classifications of pain disorders based on anatomy, duration, and systems have drawn criticism for their deficiency in sensibility for guiding treatment or research (12). Woolf et al. (12) support developing a mechanism-based classification of pain, proposing a potential list of pain mechanisms (Table 2-1). They argue that the list needs to include affective, behavioral, and cognitive factors relevant to pain, although they do not specify what these factors may be.

Transient pain
Nociceptor specialization
Tissue injury pain
Primary afferent
Sensitization
Recruitment of silent nociceptors
Alteration in phenotype
Hyperinnervation
Central nervous system mediated
Central sensitization recruitment, summation, amplification
Nervous system injury pain
Primary afferent
Acquisition of spontaneous and stimulus-evoked activity by nociceptor axons and somata at loci other than peripheral terminals
Alteration in phenotype
Central nervous system mediated
Central sensitization
Deafferentation of second-order neurons
Disinhibition
Structural reorganization

Adapted from Woolf C, Bennett G, Doherty M, et al. Towards a mechanism-based classification of pain. Int J Pain 1998;77:227–229.

TABLE 2-1. Categories of pain and possible mechanisms

The mechanism-based classifications of pain differ from the conventional classification in that the former frees pain from diseases that may accompany pain complaints. Mechanism-based classification groups patients who are homogeneous in pain mechanisms but heterogeneous in disease conditions or diagnoses. Woolf

et al. (12) emphasize that their proposal is not to replace but rather to supplement the current system.

The basic premise underlying the mechanism-based classification of pain is helpful, both in guiding treatment and in bridging research to clinical practice in pain medicine. However, the mechanism-based system is still at the conceptual stage. Ongoing efforts to synthesize findings from various areas of pain research will help to formulate this new classification system.

This approach contrasts with our use of two dimensions, time and severity, to distinguish acute and chronic pain (Fig. 2-1). The description of attempts to develop multidimensional classification systems incorporating features of several of the classifications is reviewed in the next section.

Multidimensional Classification of Pain: International Association for the Study of Pain Taxonomy

An alternative to the unidimensional approaches is a multidimensional approach that uses several relevant dimensions rather than a single dimension as the basis for developing the classification system and for assigning patients to a particular subgroup or diagnosis. The IASP has published an expert-based multiaxial classification of chronic pain (1,2) intended to standardize descriptions of relevant pain syndromes and to provide a point of reference. The published taxonomy classifies chronic pain patients according to five axes based on the best published information and consensus: (a) region of the body (axis I), (b) system whose abnormal functioning could conceivably produce the pain (axis II), (c) temporal characteristics of pain and pattern of occurrence (axis III), (d) patient's statement of intensity and time since onset of pain (axis IV), and (e) presumed etiology (axis V) (Table 2-2).

TABLE 2-2. International Association for the Study of Pain: scheme for coding chronic pain syndromes

This system establishes a five-digit code that assigns a unique number to each chronic pain diagnosis. For example, the code for carpal tunnel syndrome is 204.X6. Thus,

200 = Region: upper shoulder and upper limbs
00 = System: the abnormal functioning is attributed to the nervous system
4 = Temporal characteristics: symptoms occur irregularly
X = Patient's statement of intensity and time since onset: this varies by patient
06 = Etiology: degenerative, mechanical

Table 2-3 contains the IASP scheme developed for the coding of chronic pain diagnoses. The IASP classification is the most comprehensive approach to classification of chronic pain syndromes. By design, the IASP classification is a heuristic, multiaxial guide that emphasizes the consideration of signs and symptoms. It excludes assessment of psychosocial or behavioral data.

Definition
Site
System(s) involved
Main features of the pain including its prevalence, age of onset, sex ratio if known, duration, severity, and quality
Associated features; aggravating and relieving agents
Signs
Laboratory findings
Natural course
Complications
Social and physical disability
Pathology or other contributing factors
Essential features and diagnostic criteria
Differential diagnosis
Code based on the five axes
References (optional)

TABLE 2-3. List of descriptions in each syndrome in the International Association for the Study of Pain Classification

To be useful, any classification system must be reliable and valid, but as yet little published research has evaluated the reliability, validity, or utility of the IASP classification. Existing evidence (13) indicates that, although axis I (body region) demonstrated reliable coding across examiners, axis V (etiology) failed to achieve acceptable interrater reliability. The consistency (test-retest reliability) of the IASP taxonomy has yet to be established. Further research is needed to evaluate the psychometric properties of the classification system and to facilitate refinements of the system.

The classifications we have described are only a few examples and are definitely not exhaustive. Various specialists can arrive at classification categories based on clinical experience, published data, and consensus. However, no single system exists for classifying pain patients that is universally accepted by clinicians or researchers. Furthermore, several problems associated with the current classification systems have generated debates and research concerning an alternative classification of pain. We provide several examples to illustrate different attempts to devise alternative taxonomies of pain and chronic pain patients.

Empirically Based Classifications of Pain

Those who advocate the use of empirically derived taxonomies maintain that quantitative analysis should define the relationships of contiguity and similarity among individuals (i.e., the taxonomic system must reflect clinically relevant characteristics that exist in nature, defined by empirical methods rather than based on expert judgment and consensus).

The American College of Rheumatology provides an empirical diagnosis for the classification of fibromyalgia syndrome (FMS). In a multicenter study (14), a group of FMS experts at several medical centers collected FMS-related variables and used those variables in an attempt to differentiate FMS patients from patients with other types of chronic pain syndromes. The acceptable sensitivity and specificity were achieved by two criteria, presence of widespread pain (i.e., above and below the waist, right and left side of the body, and along the midline) and at least 11 of 18 positive tender points on palpation. Other symptoms commonly reported by FMS patients, such as fatigue and stiffness, did not differentiate between FMS and other types of chronic pain. Since publication, most subsequent research seems to conform to this classification system, making it a bit easier to compare results across studies. Nonetheless, debate remains about the extent that this classification contributes to clinical practice.

Several types of empirical methods statistically (e.g., cluster analysis) can identify categories that share relationships derived directly from data rather than hypothesized relationships. This is the case with more traditional consensus-based deductive systems. The results of identification analyses can lead to explicit,

mathematical categories. Physicians can assign patients to specific categories on an objective basis.

Although quantification, replication, and objectivity are the hallmarks of the inductive approach, it is important to acknowledge that all relevant factors cannot be measured by a single classification system. The use of an inductive approach depends on what the investigator chooses to include within the statistical analysis. Thus, in practice, the inductive approach to classification is not a totally objective process that is completely atheoretical. In light of this notion, some advocate the dual-diagnostic approach, using the two loosely defined domains, biophysiologic and psychosocial domains (8,15). In this framework, physiologically homogeneous patients may exhibit a range of psychosocial heterogeneity.

Multiaxial Classification of Pain

Ever since the gate-control model underscored the importance of cognitive-evaluative and motivational-affective factors in the process of pain experience, the importance of integrating the psychosocial domains in the classification of pain has been proposed by a number of clinical investigators. However, as in other domains of pain medicine, the psychosocial classifications of pain have largely depended on the traditionally defined diagnosis system, in this case, identification of psychopathology. Although the psychiatrically defined classification of pain patients may help identify patients with specific psychiatric disorders, thereby directing treatments for those disorders, psychologists have introduced psychological classification systems to identify the specific psychological components (affective, evaluative, motivational) of pain.

Emory Pain Estimate Model

The Emory Pain Estimate Model (EPEM) was the first attempt to integrate the biophysiologic and psychosocial domains in classifying pain patients (16,17). Brena and colleagues arbitrarily labeled the dimensions *pathology* and *behavior*. The pathology dimension includes the quantification of physical examination procedures (e.g., ratings of joint mobility, muscle strength) as well as assigning numerical indices to reflect the extent of abnormalities determined from diagnostic procedures such as radiographic studies. The behavioral dimension comprises a composite of activity levels, pain verbalizations, drug use, and measures of psychopathology based on the elevations of the Minnesota Multiphasic Personality Inventory scales.

Using median divisions on the pathology and behavior dimensions, the EPEM defines four classes of chronic pain patients (Fig. 2-2). Class I patients are characterized by higher scores on the behavior dimension and lower scores on the pathology dimension. It describes these patients as displaying low activity levels, high verbalizations of pain, prominent social and psychological malfunctions, and frequent misuse of medications. Class II patients are those who display lower scores on the pathology and behavioral dimensions. These patients are described as displaying dramatized pain complaints with ill-defined anatomic patterns. However, they do not display significant behavioral dysfunction. Class III represents patients with higher scores on both dimensions, characterized as showing clear evidence of physical pathology and high-intensity illness behavior. Finally, class IV patients are those who have higher scores on the pathology dimension and lower scores on the behavior dimension and thus demonstrate “competent” coping in the presence of a physical pathologic condition.

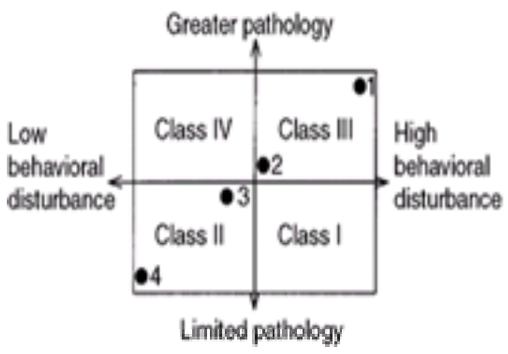

Figure 2-2. The Emory pain estimate model. (From Turk DC, Rudy TE. Classification logic and strategies in chronic pain. In: Turk DC, Melzack R, eds. *Handbook of pain assessment*. New York: Guilford, 1992:409–428, with permission.)

Although Brena and colleagues (16,17) appropriately emphasized the importance of integrating physical and psychological data to develop a classification system for chronic pain patients, some of the basic theoretical and quantitative characteristics of the EPEM are problematic. We see this framework as a conceptual model rather than an adequately operationalized empirical one. For example, from a theoretical standpoint, the inclusion of activity levels, pain verbalizations, and measures of psychopathology under a single dimension labeled *behavioral* is troubling because research shows that little association exists between pain behaviors and psychopathology. Thus, the behavioral dimension is most likely not unidimensional and, therefore, cannot measure behavior directly.

Examination of the empirical aspects of the scoring and classification system used in the EPEM identifies additional problems. For example, the weights assigned to specific medical and physical findings are *a priori* and were not empirically derived. Moreover, applying median divisions to the two dimensions, although intuitively appealing, artificially creates four classes of patients, so no statistical demonstration exists that four nonoverlapping groups of pain patients naturally exist in these data or that, in fact, the pathology and behavioral dimensions are independent. Review of the 2 × 2 grid displayed in Figure 2-2 reveals that within the EPEM extreme scores are treated the same as scores near the medians. For example, the scores of patients 1 and 2, depicted as points in Figure 2-2, would both be assigned to class III, whereas those of patients 3 and 4 would be classified in class II. In reality, however, the scores of patients 2 and 3 are more similar than they are with the scores of patient 1 or patient 4. Thus, this method of establishing classification rules may lead to erroneous or nonindependent patient assignments because it is derived from artificial and external mathematical criteria rather than from divisions or clustering of groups that occur naturally within patients' scores.

Empirically Based Classification of the Psychological Components of Pain

Many taxonomies of pain recognize that the conceptualization and operationalization of cognitive, affective, and behavioral factors associated with pain merit consideration. Numerous instruments assess pain-related psychosocial constructs, but most are unidimensional or inadequate for pain populations, or they lack predictive validity for treatment outcomes. We describe one specific multidimensional psychosocial classification system used primarily with patients with chronic pain conditions.

The Multidimensional Pain Inventory (MPI) (18) consists of a set of empirically derived scales designed to assess chronic pain patients' (a) reports of pain severity and suffering; (b) perceptions of how pain interferes with their lives, including interference with family and marital functioning, work, and social and recreational activities; (c) dissatisfaction with present levels of functioning in family, marriage, work, and social life; (d) appraisals of support received from significant others; (e) perceived life control incorporating perceived ability to solve problems and feelings of personal mastery and competence; (f) affective distress including depressed mood, irritability, and tension; and (g) activity levels. Using the MPI, Turk and Rudy (19) were able to group patients within three relatively homogeneous sets.

Turk and Rudy (19) performed cluster analyses on a heterogeneous sample of chronic pain patients' responses on the MPI scales. Three distinct profiles were identified: (a) dysfunctional (DYS), patients who perceived the severity of their pain to be high, reported that pain interfered with much of their lives, reported a higher degree of psychological distress caused by pain, and reported low levels of activity; (b) interpersonally distressed (ID), patients with a common perception that significant others were not very supportive of their pain problems; and (c) adaptive copers (AC), patients who reported high levels of social support, relatively low levels of pain and perceived interference, and relatively high levels of activity. Reliable, external scales supported the uniqueness of each of the three subgroups of patients. Performing a 12-dimension Bayesian calculation to test goodness of fit can identify the profile that best fits a patient.

In addition to categorical classification that assigns an individual patient to a specific diagnosis, the empirical-statistical approach permits judgments about how well a patient matches the central features of that diagnosis. This is especially useful in complex pain syndromes that involve various clinical characteristics with rather large individual variability, even within a single diagnostic group. Using an empirical method, one can not only establish whether a patient fits the diagnostic classification but also determine how good a fit to the diagnosis the patient is. For example, based on a set of patient characteristics, signs, and symptoms, a prototype for a diagnosis is established. It is possible to determine statistically how close an individual case matches that prototype. Assume that a perfect match to a prototype is

0.99. A particular case may fit within the diagnosis but not be a perfect fit; thus the fit might be 0.80. Some statistical rule can decide the minimum fit to the characteristics of the diagnosis—say, for example, 0.67. Thus, any two individuals with the same diagnosis must share certain characteristics but not necessarily all; the similarity of two patients with the same diagnosis has a statistical definition.

Subsequent testing of the MPI profiles across various pain disorders suggests that the MPI psychosocial classification is independent of the conventionally defined pain syndromes, such as low back pain, migraine headaches, fibromyalgia syndrome, and pain associated with cancer. In other words, two patients whose pain pathologies are likely to differ (e.g., those with cancer and migraine headaches) could have a homogeneous psychological classification of pain. On the other hand, two patients, both having same type of temporomandibular pain, based on the Research Diagnostic Criteria for comparable duration (8), may fare differently in the psychological classification of pain. Clinical trials using the MPI-based classification have consistently yielded differential responses to a cognitive-behavioral approach (20,21). Such results strongly suggest that the psychosocial treatment components need to conform to the psychological classification of pain.

We suggest that disease classification should reflect physical assessment and treatment (e.g., 2) and that a psychosocial-behavioral taxonomy should determine complementary psychological treatment strategies. Physical and psychosocial diagnoses are important in the person suffering from a chronic pain syndrome. Several groups (8,15,22) have proposed the use of a dual-diagnostic approach, whereby two diagnoses are assigned concurrently, physical and psychosocial-behavioral. Treatment could then target both simultaneously. A chronic pain patient might have diagnoses on two different but complementary taxonomies (e.g., IASP and MPI-based classification). Thus, a patient might be classified as having Complex Regional Pain Syndrome, Type 1 (CRPS-1) of the upper extremity (203.X1, Axis I Region = Upper Shoulder and Upper Limbs; Axis II System = Nervous; Axis III Temporal Characteristics of Pain: Pattern of Occurrence = none of the codes listed; Axis IV Intensity and Time of Onset = based on patient report; Axis V Etiology = Trauma) on the IASP taxonomy and be classified DYS on the MPI-based taxonomy. Note not all CRPS-1 patients would be classified as DYS and not all DYS patients would have CRPS-1. A second patient might have the same IASP diagnosis, CRPS-1, but be ID on the MPI-based classification. Conversely, patients might have quite different classifications on the IASP system but have the identical MPI-based classification. The most appropriate treatment for these different groups might vary, with different complementary components of treatments addressing the physical diagnosis (IASP) and the psychosocial diagnosis (MPI-based).

Psychometric Considerations

The general utility of any proposed empirical taxonomy links closely to the psychometric properties (i.e., reliability, validity, and utility) of the measures, scales, or instruments used to derive the classification system. Because these are the building blocks used to generate profiles or clusters, the reliability and validity of the classification system depend, in part, on the psychometric quality of the measures used. Because reliability and validity coefficients are generic terms, the specific psychometric techniques used to evaluate a measure's *psychometric properties* require consideration. Multiple ways exist to demonstrate the reliability and validity of measures. Therefore, the more psychometric support there is for a measure, the more likely it will perform well when used in taxonometric identification and classification procedures. Additionally, replication of classification accuracy on new samples and demonstrating substantial, statistically significant differences across patient profiles for conceptually related measures external to the measures used to develop the profiles are some of the best ways to demonstrate the reliability and validity of empirically derived profiles. Evaluation of any classification should demonstrate reliability, validity, and utility before widespread adoption.

CONCLUDING COMMENTS

Pain management specialists have witnessed rapid advances in the basic sciences and clinical arenas of pain medicine since the 1970s. Many pain-related terms, once a major source of confusion, have received clear definitions, aiding efficient and productive communications among researchers and clinicians. The classification systems that direct our research and clinical practice need to reflect the progress in our understanding of mechanisms, multifactorial integration, and outcome predictability of classification criteria. In this chapter, we reviewed several conventional classifications as well as emerging classification systems that can supplement the conventional ones. The review of various classification systems suggests that the comprehensive taxonomy of pain requires multifactorial assessments (Table 2-4).

Pain parameters
Anatomy/system
Duration/intensity/quality
Associated abnormality (physical/psychological)
Underlying diseases
Signs/symptoms
Pain mechanisms
NEUROPHYSIOLOGIC
Primary afferent involvement
Central nervous system involvement
PSYCHOLOGICAL
Cognitive-affective-behavioral involvement
Cognitive appraisal of pain
Coping
Affect/mood
Environment

TABLE 2-4. Taxonomy of pain based on multifactorial assessment: a proposal

The multiaxial approach to the assessment of pain and dysfunction described earlier appears to be a reasonable strategy to adopt. Given a comprehensive set of physical, psychosocial, and behavioral measures, the strategy of matching patients to existing classification systems could provide a basis for treatment decisions. The use of the dual-diagnostic approach holds promise because it incorporates biomedical, psychosocial, and behavioral data in the assignment of patients to empirically derived categories. Future research needs to relate patient classification to performance on standardized physical capacity assessment protocols, rehabilitation, and ability to engage in gainful employment and regular homemaking activities.

The utility of any classification system depends on application. The important question is whether assignment of an individual to a class truly facilitates treatment decisions or predictions of future behavior. Few of the taxometric systems have demonstrated their utility to predict treatment outcome (15). Preliminary results on the MPI-based classification demonstrate the potential of such an approach (20,21). Research efforts to evaluate the predictive value of any classification of pain need to demonstrate the validity of that classification system or taxonomy.

[†]The discussion describing the distinction between acute and chronic pain reflects on deliberations among the editors of this volume.

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CHAPTER 3

Peripheral Pain Mechanisms and Nociceptor Plasticity

Margaret R. Byers and John J. Bonica

This chapter summarizes the structure, physiology, pharmacology, cytochemistry, molecular biology, tissue interactions, and plasticity of the peripheral nervous system in relation to nociception. Until the early 1980s, the peripheral components of pain have been explained primarily in terms of a specific, twofold wiring system (A-d nociceptors for faster sharper *first* pain, and C fibers for the slower conduction of dull ache or *second* pain). This was based on the concepts of Sherrington (1) and included subdivisions for thresholds and modalities within those two groups, sensitization following injury, sympathetic interactions, and distinctive features for skin, compared with deep, visceral, and articular tissues. However, mismatches between that simple afferent scheme and the complex nature of clinical pain were apparent to pioneers such as Lewis (2) and Bonica (3) in their analyses of chronic pain and conditions such as causalgia and other sympathetically mediated pains. These complexities began to be explained in the 1960s and 1970s (4,5,6,7 and 8) with better understanding of polymodal mechanisms, sympathetic and sensory interactions, endogenous pain modulation, neuronal plasticity, and more detailed information about neural events in the periphery in relation to nociception and pain perception (9,10,11,12,13,14,15,16,17,18,19,20).

Since the 1980s and especially the late 1990s, there have been enormous advances in understanding the cellular interactions, neuroplasticity, and molecular mechanisms that support the nervous system in general. Many of the mechanisms that underlie peripheral aspects of acute nociception, chronic inflammatory and neuropathic pain, sensory neural efferent functions, sympathetic interactions, and sensory contributions to inflammation, immune defense, and wound healing are now becoming clear (21,22,23,24,25,26,27 and 28). The discovery of complex growth factor regulation of nociceptor development and mature function now suggests that two different classes of C fibers exist: (a) the polymodal receptors that are regulated by nerve growth factor (NGF) and (b) the more specific nociceptors that are regulated by glial-derived neurotrophic factor (29), with the former more affected by tissue inflammation and the latter by nerve injury (30,31).

The tidal wave of discovery concerning nociceptive molecular and cellular neurobiology has begun to suggest that the peripheral endings of nociceptors rival the complexity of the dorsal horn for processing afferent information (22,28,32). The nociceptors serve as gatekeepers that survey peripheral information to send to the central nervous system (CNS). Numerous specific molecules in the membranes of the nociceptors affect signal generation, and their actions excite or inhibit the endings, thus providing a composite picture of tissue conditions via the patterns and volume of signals that arrive at the dorsal root ganglion and CNS. For example, nociceptive neurons have specific receptors for excitatory amino acids, capsaicin, adenosine triphosphate (ATP), tachykinins, protons, prostaglandins, opoids, noradrenalin, neurotrophins, and bradykinin (28,32,33) with which they can *read* the tissue and convey an edited report to the CNS. When a tissue becomes inflamed or a nerve is injured, many of those specific molecules change expression or activity, and others, such as the a_2-adrenergic receptor (34) or cyclooxygenase-2 enzyme (35), are inducible.

The C, A-d, and A-b nociceptive neurons each have a repertoire of different functional phenotypes that are elicited by different tissue conditions. Those conditions include the various stages and intensities of inflammation, neuropathic injuries and metabolic disease, or regeneration and healing to provide optimal neural functions and tissue integrations for each of those conditions. Their thresholds and other physiologic and pharmacologic properties differ for each phenotype, so that the CNS can receive different types of information for each condition. One subgroup of the C and A-d primary afferents makes up the polymodal receptors, described in detail in the section Polymodal Receptors, later in this chapter. Those have the widest set of stimulus energies to which they respond, a wide dynamic range, and a variety of phenotypic shifts to match tissue condition. However, most of the rest of the primary afferents involved in pain also respond to multiple types of stimuli, they are affected by injury and inflammation to alter their cytochemistry and function, and they have different phenotypes. Even the mechanically silent nociceptors, which are difficult to activate from healthy tissues but become increasingly active during inflammation, can be considered to have a quiet phenotype related to healthy conditions and an active one for inflammation. Finally, the A-b fibers that are sensitized by inflammation to drive mechanical allodynia have a different phenotype during inflammation when compared with their resting state.

This expansion of our understanding of specific mechanisms of nociceptive pharmacology is leading to important new drugs and strategies for pain management (26,36,37,38,39,40 and 41). In addition, much of the mystery for the efficacy of placebo and alternative medicine procedures is beginning to make sense in relation to modulation of tissue conditions and nociceptors by stress or relaxation, endogenous opiates, endocannabinoids, hormones, nutrition, massage, acupuncture, and exercise (42). Indeed, plasticity of nociceptor mechanisms, the sympathetic and nociceptor interactions after nerve injury compared with those during tissue inflammation, and the powerful effects of complex afferent input (including afferent immune information) on central mechanisms have been major missing pieces of the puzzle of pain. Research during the 1990s is beginning to elucidate this multifaceted story, with significant effects on development of new therapeutic drugs.

In this chapter, we have retained much of Bonica's encyclopedic overview of the anatomy, physiology, biochemistry, and pharmacology of nociception while adding new information from the 1990s that greatly expands our knowledge of the peripheral neural contributions to pain. The chapter is accordingly reorganized into sections on the (a) peripheral nervous system, (b) physiology of nociception, (c) polymodal receptors, (d) pharmacology and modulation of nociception, (e) peripheral mechanisms of persistent pain, including a discussion of experimental models of pain, (f) genetics of pain, and (g) conclusions and therapeutic horizons. The types of afferent electrophysiologic, cytochemical, endocrine, and immune information that flow into the CNS after injury are obviously modulated by interactions in the spinal or medullary dorsal horn before further transmission to the brain (Fig. 3-1 and Fig. 3-2). The specific details of spinal and supraspinal basic mechanisms for pain and plasticity, as well as descending controls and other central modulating systems, are presented in Chapter 4 and Chapter 5. Additional discussion of basic peripheral neural components related to pain, including the autonomic system, can be found in Chapter 8, Chapter 9 and Chapter 10, and in the many chapters on general and regional pain syndromes, especially those that concern neuropathic pains. Much greater detail about this vast and rapidly evolving story is presented in the review by Millan (28).

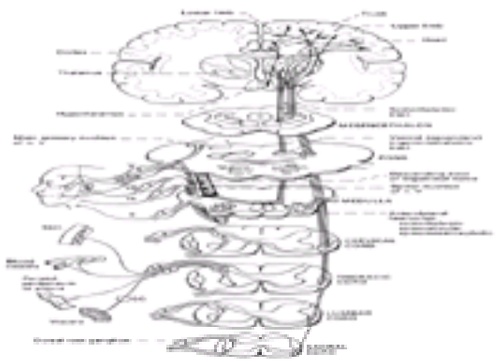


Figure 3-1. Schema of the primary neural pathways for transmission of nociceptive information from various body structures to the brain. The figure forms the basis for detailed discussion of various parts of the *pain* system in Chapter 3, Chapter 4 and Chapter 5. (n., nerve; SG, sympathetic ganglion; V, VII, IX, X, cranial nerves.)

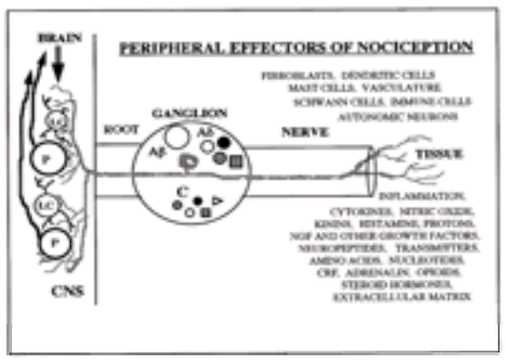


Figure 3-2. Overview of the peripheral cells and factors that modify the flow of information in sensory nerves from tissues through the sensory ganglion (dorsal root, trigeminal, or visceral) and into the central nervous system. Sensory neuronal types that affect pain are represented in each group (A-b, A-d, C) as follows: *Open circles* represent normally mechanoreceptive or thermoreceptive neurons that have altered cytochemistry and activity in inflamed tissue; *black circles*, nociceptive-specific; *gray squares*, silent nociceptors; *gray circles*, polymodal nociceptors; and *open triangle*, GDNF (glial derived neurotrophic factor)-dependent C fibers. Each projection neuron (*P*) is modulated by local circuit (*LC*) neurons and by descending input from supraspinal centers, both of which can also affect primary afferent endings. Many of the key peripheral cell types and factors that affect primary afferent function are listed.

PERIPHERAL SYSTEM

Nociception and Antinociception

Pain is a complex constellation of unpleasant sensory, emotional, and mental experiences and certain autonomic (involuntary) responses and psychological and behavioral reactions provoked by tissue damage. Injury to tissues, whether induced by disease, inflammation, or accident (or provoked by surgical operation or other therapeutic measures) constitutes a noxious stimulus and causes cellular breakdown with liberation of biochemical substances. These activate special receptors on nociceptors that can be sensitive to heat, cold, mechanical stimuli, or chemical mediators. All tissues are also innervated by polymodal C and A-d receptors that have (a) extensive branching of their peripheral endings, (b) a wide range of effective stimuli, (c) a wide dynamic range that includes nonnoxious thresholds, (d) numerous unperceived neuroeffector functions that regulate tissue homeostasis and affect inflammation and wound healing, and (e) a versatile ability to shift their functional and cytochemical phenotype depending on tissue conditions (23). In addition, all tissues also have many afferents that are unresponsive in normal tissues, but that become active during inflammation, called *silent nociceptors* (43,44) as well as some A-b fibers that become chemosensitive during inflammation and affect CNS pain pathways (45). All of these different peripheral nerve fibers exhibit plasticity that can be rapid (seconds) or delayed (hours to days) and is dependent on electrophysiologic properties, growth factors, cytokines, or other tissue factors (see Fig. 3-2).

Although nociceptive impulses are often called *pain* impulses, pain is not experienced until information reaches the brain in normally conscious persons, in which the sensory and emotional experience takes place. Early systems of nociceptor classification used terms such as *acute* versus *chronic pain* or spoke in terms of specific tissues or body regions. However, it has been suggested that nociception categories should be redesigned to reflect basic mechanisms (46). In this chapter, nociceptive activity is subdivided into three levels of injury: *transient* (no significant tissue or nerve damage); *reversible* (moderate damage to tissue, nerve, or both, but healing or regeneration occurs within days or weeks by local defense mechanisms, without persistent pain); and *irreversible* (persistent tissue inflammation, tissue loss, and/or neuropathic injury that induce persisting alterations in peripheral and central nerves and pain mechanisms) (Fig. 3-3). Nociception also is discussed here in terms of various neuronal features: (a) cell body size and cytochemistry, (b) peripheral receptor structure and tissue specificity, (c) physiologic parameters, (d) pharmacology of the peripheral endings, and (e) pharmacology and distribution of the central endings. In addition, polymodal receptor functions are discussed separately.

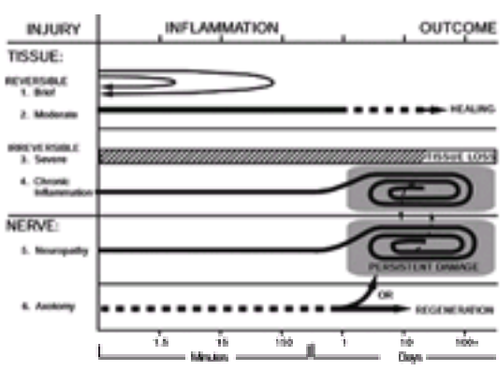


Figure 3-3. Six different outcomes of tissue or nerve injury are diagrammed in relation to a log time scale from minutes to more than 100 days. Reversible tissue injury is either (1) transient, with no long-term effects, or (2) moderate, with successful healing but some scarring and alterations. Irreversible tissue injury includes (3) tissue amputation and (4) persistent damage caused by chronic inflammation. Nerve injury can be reversible (not shown), (5) persistently damaged, or (6) partially or completely regenerated.

Nociceptive and polymodal impulses from tissues below the head are transmitted via fibers in spinal nerves and the vagus nerve that synapse with interneurons or second-order neurons in the dorsal horn of the spinal cord. Afferent information from the head related to pain is carried in fibers that synapse with neurons in the trigeminal sensory nuclei, in particular the spinal subnucleus caudalis (see Fig. 3-1). At this first synapse, the nociceptive impulses are subjected to other influences coming from the periphery, from interneurons of the spinal cord or the trigeminal subnuclei, and from the supraspinal control systems, all of which determine the further processing of these afferent signals of tissue damage. After being subjected to these modulating influences in the dorsal (posterior) horn, some of the nociceptive impulses pass directly or through interneurons to the ventral and ventrolateral horn cells of the same and adjacent spinal cord segments, in which they stimulate somatomotor and preganglionic sympathetic neurons, respectively, and provoke segmental nocifensive reflex responses. Nociceptive impulses also activate other neurons, the axons of which make up the ascending systems that pass cephalad to the brainstem and the brain to provoke suprasegmental reflex responses, the powerful motivational drive and unpleasant affect and other psychological reactions, and activate the motor systems that determine behavior discussed in Chapter

4 and Chapter 5. Pain provoked by injury or disease is the net effect of many simultaneously interacting biochemical, physiologic, and psychological mechanisms that involve activity in most parts of the nervous system concerned with sensory, motivational, and cognitive processes and psychodynamic mechanisms. More recent work also has demonstrated that cytokine signaling from the immune system affects sensory afferents, especially those in the vagus nerve, with important influences on the brain, illness behavior, intensity, and duration of pain (27,47). These interactions are modulated in complex ways during persisting tissue inflammation, neuropathic injury, or metabolic diseases, with profound changes in neural mechanisms in the tissue, nerve, ganglion, root, and central endings (see Fig. 3-2) and at autonomic ganglia, in the afferent immune system, in the dorsal horn or trigeminal nuclei, and in supraspinal and modulatory systems.

Just as the CNS has a range of modulatory systems that either facilitate pain or inhibit it, the peripheral primary afferents not only signal tissue damage and become sensitized by inflammatory mediators, but they also can be inhibited by endogenous analgesic mechanisms. This phenomenon has been called *antinociception*, and several categories of endogenous antinociceptive agents now exist, such as endocannabinoids, opioid peptides, adenosine, and the cytokine leukocyte inhibitory factor (48,49,50,51 and 52). The primary afferents also produce a set of peptides that counteract their own hypersensitivity and excitotoxicity, such as galanin, vasoactive intestinal peptide, and neuropeptide Y (53,54 and 55) . The pharmacology and modulation of peripheral neurons are exceedingly complex, as indicated in Pharmacology and Modulation of Nociception, later in this chapter. The great advances in our understanding of the pharmacology of pain during the 1990s offer a variety of avenues for the management of pain, because each of the excitatory mechanisms can be a target for custom-designed analgesic drugs, and it should be feasible to selectively activate the inhibitory antinociceptive systems for enhanced endogenous analgesia (22,26). Indeed, the efficacy of acupuncture and other alternative medical treatments appears to involve some activation of endogenous antinociceptive pharmacology (42).

Peripheral Nerves

Peripheral nerves consist of somatic motor axons, autonomic axons, and somatic and visceral afferent sensory axons that are connected to the CNS via the dorsal or ventral roots (Fig. 3-4). A cross-section of a peripheral nerve shows various sizes of single myelinated axons (outside diameter ranging from 1.5µ to 20.0 µ) and clustered unmyelinated axons (diameter range, 0.2µ to 2.0µ), each with a basal lamina outside the Schwann cell and collagen of the endoneurium beyond that, plus endoneurial capillaries, and a special perineurium barrier around each fascicle (see Fig. 3-5). The outermost sheath of a peripheral nerve, the epineurium, serves to protect and cushion the nerve, and it contains loose strands of collagenous fascia, blood vessels, fat, and an important neural innervation, the *nervi nervorum* (Fig. 3-5) made up of noradrenergic sympathetic fibers and peptidergic polymodal receptor axons (56,57 and 58). The nervi nervorum play an important role in neuropathic pain conditions and neuritis (59,60). They can have different local pathologic reactions depending on their particular nerve (61), and they also include the sympathetic axons that sprout around sensory cell bodies after peripheral nerve lesions (62,63). Different peripheral nerves have different proportions of nociceptive, polymodal, and nonnociceptive somatic axons, as well as visceral sensory, somatic motor, and autonomic motor axons; those differences confer different peptide expression profiles on normal nerves (64). Thus, an injury affects quite different populations of axons depending on which nerve is involved and where the injury occurs along its course.

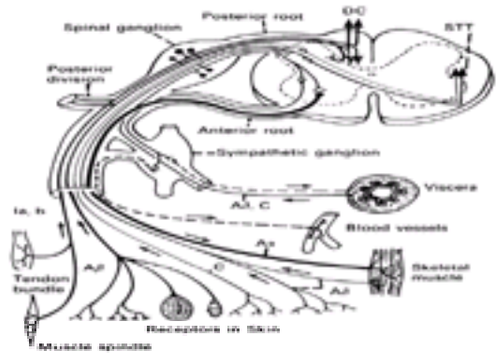


Figure 3-4. A simplified schema of a spinal nerve and the different types of fibers contained therein. (DC, dorsal columns; STT, spinothalamic tract; see Table 3-1 for fiber type.)

Lloyd/Hunt system	Diameter (µm)	Latter system	Conduction velocity (m/sec)	Myelin	Receptor/ending type
Ia*	12-20	–	70-120	+	Muscle spindle primary ending
Ib*	12-20	–	70-120	+	Golgi tendon organ
–	12-20	A_α	70-120	+	Muscle efferents (extrafusal)
II	6-12+	A_β†	30-70	+	Encapsulated ending (Meissner, Ruffini, Pacinian); interfal intrafusal muscle spindle secondary ending
–	3-10	A_γ	15-50	+	Muscle efferents (intrafusal)
III	1-6	A_δ	5-30	+	A_δ specific nociceptors; A_δ polymodal nociceptors; cold receptors; most hair receptors; some visceral receptors
–	<3	B	3-15	+	Preganglionic autonomic
IV	<1.5	C	0.5-2.0	No	C-nociceptors; C polymodal receptors; some visceral receptors; warmth receptors; some mechano-receptors; postganglionic autonomic motor/c nerve fibers

*Data mostly from cats. Velocity in primates and humans has been measured up to 80 m/sec.
†Some afferents in articular joint afferents can conduct up to 17 m/sec. These are sometimes classified as A_α, but sometimes all mammalian afferents are all considered to be A_β.
Adapted from Hulse J. The human brain. St. Louis: Mosby, 1989:213.

TABLE 3-1. Classification Of Fibers In Peripheral Nerves*

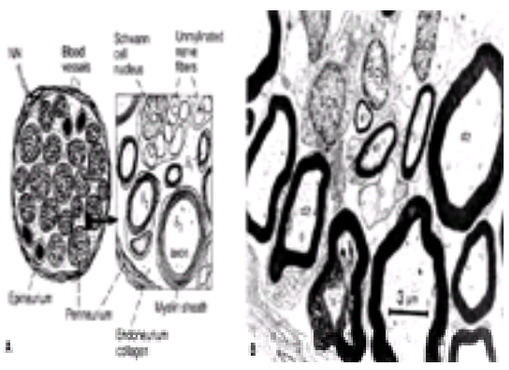


Figure 3-5. **A:** Diagram of a cross-sectioned peripheral nerve showing the many fascicles, each with its own endoneurium collagen and perineurium sheath. The whole nerve has its own innervation of epineurium and vasculature by the nervi nervorum (NN). The higher magnification panel shows details of the ensheathing Schwann cells and their nucleus (SCN) for groups of unmyelinated (C) axons or for single myelinated axons. The A-d axons can be thin and slow (d_1) or larger and faster (d_2). **B:** This electron micrograph of tibial nerve of rat shows a variety of myelinated axon sizes, including small (d1) and larger (d2) A-d fibers, and some bundles of unmyelinated C fibers of various sizes (*). Some of the Schwann cell nuclei are indicated (SCN) (magnification, × 7,000; scale, 3 µm).

A summary of the ranges of conduction velocities and stimulus specificities for axons in peripheral nerves is given in Table 3-1. Within each conduction group (A-a, A-b, A-d, and C) a wide range of rates and corresponding axon calibers occurs (see Fig. 3-5) to give a complex gradient of conduction information. The sensory data are usually recorded from peripheral axons in the proximal part of the nerve in which conduction is fastest. However, sensory axon caliber and conduction velocity decrease markedly in the peripheral branches and preterminal fibers (65), and the central axons are thinner and slower than the peripheral axons, so that there is a set of differing conduction rates along a sensory axon, as well as a range of maximal rates within each group (6). With injury or inflammation, changes in neuropharmacology affect all types of nociceptors (66), including recruitment of A-b fibers into the peripheral mechanisms of hypersensitivity (45). Evidence now

suggests that fundamental neuronal properties, such as duration of action potential (AP), afterhyperpolarization, or conduction velocity shift during inflammation (67), suggesting major changes in membrane channel distribution, type, and regulation (30,31).

Each axon in peripheral nerves requires ensheathment by support cells, called *Schwann cells*, to conduct potentials at the correct rates. Schwann support cells for unmyelinated axons enclose groups of axons, whereas the myelinating Schwann cells only ensheath one axon (Fig. 3-6; see Fig. 3-5). Special Schwann cells are associated with the receptive endings, called *terminal Schwann cells*. Special support cells that are derived from Schwann cells, called *satellite cells*, surround the cell body and its stem axon. Once the axon enters the CNS, it acquires glial sheath cells (Fig. 3-7). During development, the linear relationship between diameter and velocity persists while both increase fourfold, and internodal length is similarly correlated in young and mature animals with animal size (68).

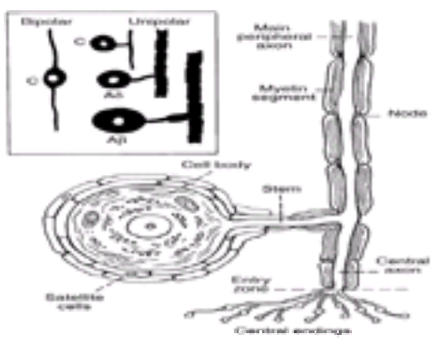


Figure 3-6. The associations of an A fiber with satellite cells, stem axon, peripheral and central branches of the main axon, myelin segments, nodes, and central nervous system entry zone are shown. At the entry zone the central axon switches from Schwann to oligodendroglial support cells (not shown). *Inset*: Primary afferent cell body shape is indicated for bipolar visceral C fibers, and unipolar cell bodies for somatic C, A-d, and A-b sensory neurons.

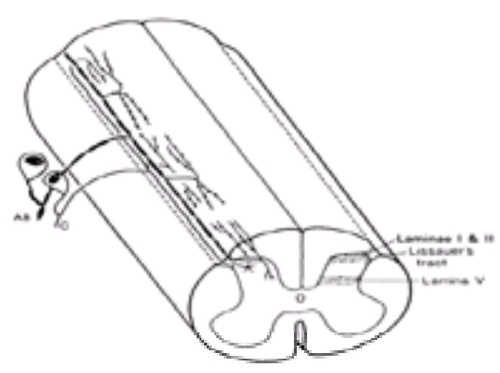


Figure 3-7. Three-dimensional diagram depicting the extensive field of A-d and C fibers after bifurcating at the point of entry in Lissauer's tract. The small-diameter fibers extend for several millimeters before terminating in the superficial dorsal horn (laminae I and II) where they contact dendrites and somas of many hundreds of spinal neurons. The A-dnociceptors and C-visceral afferents also have terminal branches that end in lamina V. (From Fields HL. *Pain*. New York: McGraw-Hill, 1987:45, with permission.)

The somatic motor nerve fibers have multipolar cell bodies located in the ventral (anterior) horn of the spinal cord or the motor nuclei of the cranial nerves, and their axons pass distally via the ventral root of spinal nerves, or the motor roots of the cranial nerves, to their motor end-plates in skeletal muscles (see Fig. 3-4). Skeletal muscle function depends on sensory signals from the annulospiral fibers and secondary sensory receptors in the spindles and the sensory Golgi tendon organs. As might be expected from the intricacy and speed of skeletal muscle reflexes and functions, the main motor fibers and the spindle and tendon sensory fibers are the fastest fibers in the body, conducting up to 120 M per sec, and can have diameters up to 20 µm (Table 3-1). Muscle function also requires gamma efferent motor fibers to the muscle spindles, for adjustment of spindle tension via contraction of the intrafusal muscle fibers, and it requires numerous sensory fibers in the muscle and tendon that include many thin polymodal receptors (Fig. 3-8) (69,70).

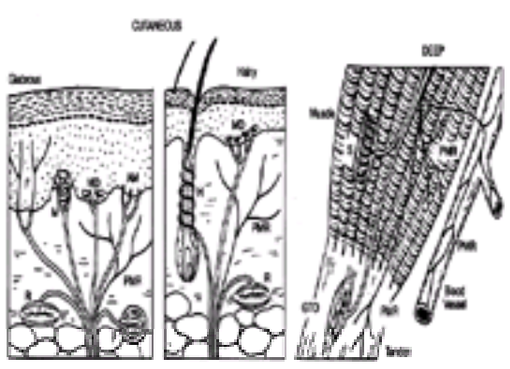


Figure 3-8. Schematic diagrams of the structure and position of various types of sensory receptors in integument (glabrous and hairy cutaneous skin) and a deep tissue (muscle and tendon). All tissues have polymodal receptors (PMR) in addition to their specialized sensory innervation. (AM, intraepithelial A-mechanoreceptors; F, free; GTO, Golgi tendon organ; H, hair mechanoreceptors; M, Meissner corpuscle with attachments to the epithelium; MD, Merkel disks; P, Pacinian corpuscle; R, Ruffini mechanoreceptors with open-ended capsule; S, various types of muscle spindle receptors.)

Autonomic sympathetic preganglionic neurons have their cell bodies in the intermediolateral horn of the thoracolumbar spinal cord and pass distally via the ventral (anterior) root of thoracolumbar spinal nerves and thence sequentially through the formed nerves, the white rami communicantes, and the paravertebral sympathetic ganglion chain to synapse there (or in the prevertebral ganglia) with postganglionic sympathetic neurons. The postganglionic sympathetic axons are unmyelinated and travel in cardiac or splanchnic nerves, via the gray rami to somatic nerves, or via the gray ramus and dorsal root to the vasculature of the sensory ganglia. The sympathetic fibers have extensive interactions with sensory fibers in nociception (34,62), as described below (see Sympathetic Interactions with Primary Afferents). The main parasympathetic preganglionic fibers travel via cranial (III, V, VII, IX, and X) or sacral nerves to their postganglionic neurons in various cranial, visceral, vascular, or urogenital tissues. Also, numerous small parasympathetic clusters of postganglionic neurons exist in some tissues, such as tongue or along blood vessels, and there can be important sensory and parasympathetic interactions in some pain conditions (71). The preganglionic and postganglionic autonomic neurons are multipolar cells that vary in size and form as well as numbers and lengths of their processes. The sympathetic and parasympathetic actions counterbalance each other to promote homeostatic control of involuntary functions such as circulation, respiration, digestion, elimination, and exocrine secretion. In most tissues, the sympathetic vasoregulatory actions are opposed by sensory neuropeptides. The autonomic modulation of nociception is described in greater detail in Pharmacology and Modulation of Nociception, later in this chapter, and in Chapter 8.

The somatic sensory nerve fibers have their unipolar cell body in the dorsal root ganglion of a spinal nerve and send axonal projections to sensory receptors in the periphery (see Fig. 3-8) and to presynaptic terminals in the dorsal horn (see Fig. 3-7). Visceral sensory afferents from cardiopulmonary, gastrointestinal tract, urogenital organs, and solid viscera are major components of the vagus nerve, with the somatic sensory cell bodies for that nerve located in the superior (jugular) ganglion and the numerous visceral sensory cell bodies in the large, inferior (nodose) ganglion. An auxiliary visceral sensory ganglion also is present on the

glossopharyngeal root (inferior ganglion). Other visceral afferent fibers are also part of the facial and trigeminal ganglia, and general visceral afferents make up approximately 10% of dorsal root ganglia.

An additional component of the peripheral nervous system is the enteric system, confined within the walls of the gastrointestinal tract. It contains as many neurons as the spinal cord, and it is primarily concerned with regulation of peristalsis, digestion, nutrient uptake, and fluid exchange. Interactions between the enteric neurons, the immune system, visceral afferents, and vasoregulatory innervation of the gut may contribute in important ways to pain conditions such as irritable bowel syndrome or Crohn's disease and need further research (72).

Finally, paraganglia exist along some peripheral nerves, notably the vagus nerve, that participate in modulation of pain by responding to the cytokines that are released during immune responses, such as interleukin-1b, and then activating afferent fibers either by direct synaptic connections or indirectly to affect pain and illness behavior (27,47). The chromaffin cells of those paraganglia, as well as peripheral cell types, such as mast cells, lymphocytes, and macrophages, function as important modulators or amplifiers of primary afferent neurons, especially during inflammatory or immune responses.

Morphology of Primary Afferent Neurons

Sensory Cell Body

Primary afferent neurons detect conditions outside the nervous system and convert stimuli into signals that reliably inform the CNS to promote survival, maturation, and reproduction of the animal. For the special senses, the receptors are designed to evaluate conditions outside the body, and they convert energy from light, sound, gravity, and airborne or fluid chemicals into meaningful nerve impulses. Somatosensory neurons detect alterations in thermal, mechanical, or chemical conditions in the body's tissues for conversion into nerve impulse information. The cell body of each primary afferent neuron has at least five challenges for maintaining the entire neuron. (a) It must deliver the correct macromolecular traffic from the cell body's synthetic organelles to the different specialized regions (central terminals, central axon in root, axonal branch points, nodes of Ranvier, stem axon and cell body in the ganglion, peripheral axon and branches, preterminal regions, and sensory receptor endings) at the right rates and targeted to the right places. (b) It must maintain correct interactions with the supporting Schwann cells for faithful transmission of signals from periphery to cell body and CNS. (c) It must maintain the correct degree of integration of the sensory receptors with the target tissue, whether that involves full encapsulation, partial separation from the tissue, or completely free endings. (d) It must establish and maintain appropriate central endings, often exceeding 1,000 synaptic boutons (73) distributed over several segments of the cord. (e) It also directs changes in pharmacologic, functional, and structural phenotype as needed to match the conditions of the innervated tissue and the excitatory or inhibitory influences along the axon and at the presynaptic central endings. The cell body learns about events in its distant extensions via APs, axonal transport traffic, and rapid phosphorylation systems. This combined electrophysiologic and cytochemical communication enables it to adjust its gene expression in relation to its far-flung extensions. For nociceptors and polymodal receptors, that adjustment can be extreme, because they express different neuropeptides, growth factors, ion channels, and other molecules, depending on conditions at their target tissue (normal, stressed, injured, inflamed, healing, or permanently damaged) and at their central endings.

Somatic sensory neurons have a bipolar form early in development, but the cell body becomes unipolar (no dendrites) with a short stem connection between the cell body and the main peripheral and central axon branches (see Fig. 3-6). The mature visceral sensory cell bodies often remain bipolar and are either in the spinal and cranial ganglia (making up approximately 2% to 10% of those cells) (62,64) or are in the geniculate ganglion, the distal (petrosal) ganglion, or the distal (nodose) ganglion of the VII, IX, or X cranial nerves, respectively. The sensory cell bodies are located in spinal and trigeminal ganglia or in the proximal ganglia (jugular, superior) of the IX and X cranial nerves, and they are supported by layers of satellite cells at the cell body and Schwann cells on the stem axon (see Fig. 3-6). The satellite cells are derived from the neural crest, and they form overlapping layers around each cell body. The cell bodies vary significantly in size, but can be divided into two general groups. Type A cells are large and light staining, are associated with large-diameter myelinated fibers, and have a cell body diameter of 60 µ to 120 µ. Type B cells are small (10- to 30-µ diameter), are darker staining, and give rise to small-diameter myelinated and unmyelinated primary afferent axons. Of the total population of dorsal root ganglion cells, approximately 60% to 70% are of the small type, a fact that agrees with the preponderance of unmyelinated over myelinated fibers in the dorsal root. Those two groups now also have been shown to have different timetables for programmed cell death during development (74) and different growth factor dependencies (29,75). Immunocytochemistry has shown a complex variety of subtypes in sensory ganglia (64,76,77 and 78), also discussed in Pharmacology and Modulation of Nociception, later in this chapter. Because of the position of the sensory ganglion, the peripheral axon and its branches are a much greater proportion of the neuron than the central axon and endings, and the peripheral axon has a larger caliber (79) and, therefore, a greater volume of axonal transport and faster conduction.

Peripheral Receptor Endings

From the bifurcation of the stem axon, the peripheral process(es) passes distally through the spinal (or cranial) nerves and thence through the somatic nerve branches or autonomic nerves to end as sensory receptors. The peripheral part of a spinal (or cranial) axon takes one of two pathways to reach its sensory endings. Most course through a formed spinal nerve (in its dorsal or ventral division) to reach the sensory endings (receptors) in a somatic tissue such as the skin, subcutaneous tissue, muscles, bones, or joints and are accordingly called somatic sensory fibers. The rest accompany peripheral sympathetic or parasympathetic nerves to reach the viscera or urogenital organs and are known as visceral afferent fibers. Although visceral afferent fibers (including many that mediate pain) use autonomic pathways, their cell bodies are in the spinal dorsal root ganglia, trigeminal ganglion, or the visceral sensory ganglia of the VII, IX, and X cranial nerves.

Peripheral terminations of sensory axons end in the skin and other somatic or visceral tissues by ramifying to varying extents and forming encapsulated, partially covered or free nerve endings. As they near their destinations they branch, shed their perineurial sheaths, and move beyond their myelinated or unmyelinated Schwann cells to associate with specialized terminal Schwann cells (Fig. 3-9 and Fig. 3-10; see Fig. 3-8). The larger myelinated fibers end in specialized encapsulated structures made up of nonneural and neural elements (80,81 and 82) that permit the nerve endings to act as transducers of low-intensity mechanical stimuli.

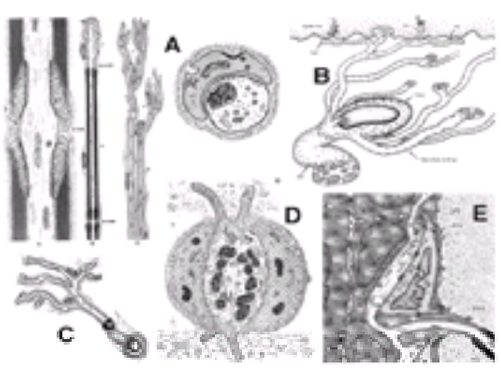


Figure 3-9. Axonal and receptive ending ultrastructure for free endings. **A:** The three left-hand drawings show (A) the complex Schwann and axonal ultrastructure at a node of Ranvier (*arrow*), (B) the last myelin segment and the terminal Schwann cell of a small A fiber, and (C) an unmyelinated fiber bundle and individual endings. The enlargement shows the partial covering of Schwann cell (sz) and a C-fiber receptor terminal, with an extracellular basal lamina separating the ending from the tissue. **B:** Termination of unmyelinated nerve fibers of the penicillate form in human hairy skin. A terminal Schwann cell (T.Sch) is associated with a number of endings and provides them with sheaths for their course through the corium. The endings terminate either in the subepidermal zone (Sub) or intradermally (Int). At intervals, there is attachment (Att) between the basal lamina of the epidermis and the nerve endings. Modified from Cauna N. The free penicillate nerve endings of the human hairy skin. J Anat 1973;115:277–288. **C,D:** Small and large endings of Ruffinilike endings that extend small protrusions or larger fingers to contact the collagen of the tissue. The ultrastructural details of the terminal Schwann cell are shown in **D**, including numerous active caveoli (budding vesicles). **E:** Intraepithelial Merkel ending (pale) contacting a Merkel cell on its right side. [a, axon; ax, axon; r, receptor endings; sy, synapse; sz, Schwann cell; tm, terminal. For other abbreviations in **E**, see Andres and von Düring (80), cited here.] (**A** and **C–E** modified from Andres KH, von Düring M. Morphology of cutaneous receptors. In: Iggo A, ed. *Somatosensory system. Handbook of sensory physiology*. Berlin: Springer-Verlag 1973;II:3– 28, with permission.)

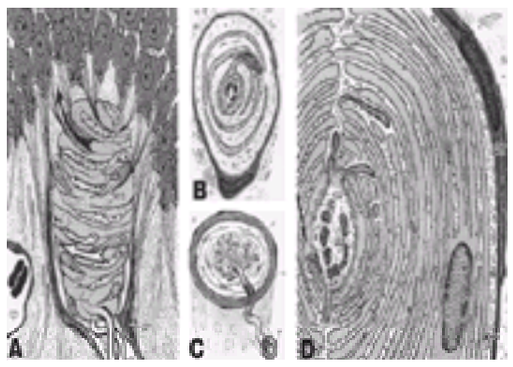


Figure 3-10. Terminal ultrastructure for various encapsulated endings. **A:** The Meissner corpuscle is ensheathed at its base, but its coiled endings are exposed to the tissue near its tip, and extracellular fibers attach it to the epithelium. **B,C:** Two varieties of small corpuscle. **D:** Portion of the central neural ending and layers of support structure within a pacinian corpuscle. [ax, axon; cp, capillary; pn, perineurium; ra, receptor axon; sc, terminal Schwann cell. For other abbreviations, see Andres and von During (80), cited here.] (From Andres KH, von Düring M. Morphology of cutaneous receptors. In: Iggo A, ed. *Somatosensory system. Handbook of sensory physiology*. Berlin: Springer-Verlag 1973;II:3–28, with permission.)

The endings of A-d and C fibers do not make encapsulated receptors in their peripheral tissues, but rather branch extensively and then end with different tissue associations depending on whether they are located in intraepithelial, subcutaneous, musculoskeletal, visceral, vascular, deep, or special target tissues. Many intraepithelial endings are completely free between the epithelial cells, having shed their Schwann cell and basal lamina (see Fig. 3-8 and Fig. 3-9) (83), and those in teeth are also completely free where they end in the dentinal tubules (see Chapter 50). Other intraepithelial nociceptive endings have been shown in serial reconstructions to have only a small exposed ending just after their axon has entered the epithelium (84). A-d axons in deep or visceral tissues can have extensive branching that then shifts to unmyelinated terminal fibers and finally beaded endings with partial Schwann covering, but a basal lamina is usually retained (85,86). Clusters of C fibers that have a single Schwann cell sheath in the main nerve branch to many smaller bundles and often appear to end as small groups of thin axons, still with a Schwann cell and basal lamina (see Fig. 3-9) (60,80,87). Thus, the A-d and C fiber *free nerve endings* usually retain a Schwann and basal lamina barrier between them and the tissue. By contrast, the Ruffini stretch mechanoreceptors form large endings in ligaments, joint sheaths, vessel walls, and deep tissue from which branches extend out to contact the collagen of the tissue (see Fig. 3-10) (80,86,88), so that these appear to have the greatest actual contact with subepithelial tissue.

Central Endings

Dorsal Root. From the stem axon bifurcation, the central axonal process passes through the dorsal (posterior) roots and into the dorsal horn, in which it makes extensive branches, beaded terminal fibers, and many synaptic endings in specific laminae of the dorsal horn (Fig. 3-11 and Fig. 3-12; see Fig. 3-2 and Fig. 3-7). Many sensory axons reach the CNS without branching, but others can form more than one central axon, and in one quantitative study, the number of central processes in the dorsal root exceeded the number of ganglion cells by 43% (89). In many cases, the axon also sends branch(es) into the ventral root, as discussed in the following section. In the nineteenth century, Lissauer and Bechterew noted that the smaller myelinated fibers congregated on the lateral side of the dorsal rootlets as they entered the cord, whereas the larger axons were in the center and medial part of the rootlets (19). Lissauer further noted that the small lateral fibers pass to the apex of the dorsal horn, thus forming the pathway that bears his name, whereas the larger fibers pass centrally to travel in the dorsal columns. In the ensuing half-century, these findings were confirmed in animal studies by Cajal, Ranson, Ingvar, O'Leary and their associates, and others (19), including demonstrations that in experimental animals pain could not be elicited after cutting the lateral bundle. More recently, this notion of segregation of the fibers as the root entry zone was confirmed by some, but disputed by others (90). Snyder (91) and Kerr (90) showed that this segregation does not occur in the cat but does in monkeys, raising the important issue of species variation. Kerr (90) found a random distribution of large and small fibers in a rootlet at 5 mm from the entry zone into the cord that continued until approximately 1 mm from the cord, in which the majority of the small fibers shifted to the periphery of the rootlet, forming a conspicuous marginal ring. Just before joining the cord, however, the fine fibers shifted from the circumferential ring to a clear lateral position and in the cord merged with the tract of Lissauer, in which the medial division was composed of large fibers.

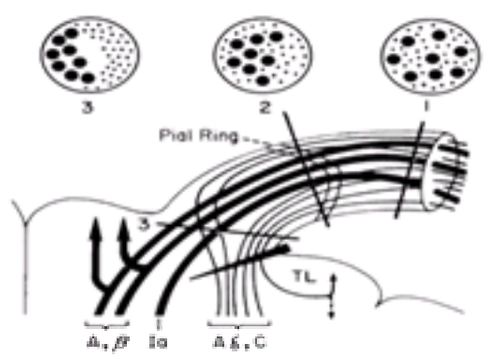


Figure 3-11. Schema of dorsal root entry zone based on anatomic findings. In the peripheral portion of the root (cross-section 1), the large and small fibers are intermingled. At the pial ring (cross-section 2) the fine afferent fibers are situated on the rootlet surface, predominantly in the ventrolateral portion but some dorsomedial. At the entry zone (section 3), the C and A-d fibers cross large myelinated fiber bundles and follow an oblique course to enter the tract of Lissauer (TL) and the dorsal horn. Some of the large A fibers are situated centrally and proceed to the anterior horn, whereas many are medial and proceed toward the dorsal columns. (From Sindou M, Goutelle A. Surgical posterior rhizotomies for the treatment of pain. In: Krayenbühl H, ed. *Advances and technical standards in neurosurgery*. Vol 10. New York: Springer-Verlag, 1983:147–185, with permission.)

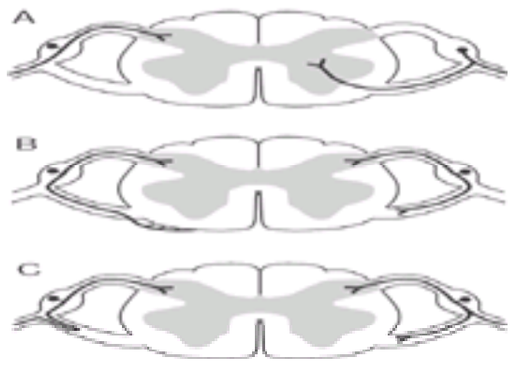


Figure 3-12. Various pathways of primary afferent central axons are diagrammed. **A:** The central axon can follow the dorsal or ventral root into the spinal cord. **B:** Some neurons send their peripheral axon into the ventral root, from which it may innervate the meningeal blood vessels, and in some cases lacks an axon in the peripheral nerve. **C:** Some neurons have a branch into the ventral root as well as a peripheral nerve branch. (Modified from Hildebrand C, Karlsson M, Risling M. Ganglionic axons in motor roots and pia mater. *Prog Neurobiol* 1997;51:89–128.)

In humans, Sindou and colleagues (92) have found that in the rootlet the small and large fibers are randomly situated, but as they near the dorsal root entry zone (DREZ), the small fibers become situated on the surface, mostly in the lateral region, although some are in the medial region. In the DREZ, the small fibers in the

medial aspect cross to join those in the lateral bundle to enter the tract of Lissauer (see Fig. 3-11). These findings have prompted Sindou and associates to develop a *selective posterior rhizotomy* or what is sometimes called *rhizidiotomy* (see Chapter 106).

An interesting challenge for neural regeneration in mature animals after dorsal root injury or avulsion is the difficulty of peripheral fiber regrowth across the mature DREZ into the CNS, because astrocytes and their various cytochemical markers inhibit ingrowth by peripheral fibers in mature animals (93,94 and 95). That barrier can be overcome if peripheral nerves or roots are implanted to provide a conduit across the DREZ, with some success in both afferent and motor regeneration. In some cases, the regenerating afferent central axons bypass the DREZ by following the pia mater from the dorsal root into the CNS (96).

Ventral Root. In the early nineteenth century, Bell and Majendie proposed that ventral roots contain axons of motor fibers and dorsal roots contain axons of sensory fibers. Although most fibers follow this law, evidence has been accumulating for more than a century and a half that afferent fibers also exist in ventral roots. Majendie himself noted that manipulation of the ventral root caused an animal to behave as if it were experiencing pain and that this behavior could be eliminated by section of the dorsal roots, and he labeled this phenomenon *recurrent sensibility*. Frykholm and associates (97) noted that stimulation of ventral roots in conscious humans caused pain, and that this could be abolished by applying a local anesthetic to the dorsal root. Coggeshall and associates (98) have used electron microscopic and electrophysiologic methods to demonstrate that ventral roots in mammals (including humans) contain a large proportion of unmyelinated axons, amounting to 30% of the total fiber count. They clearly demonstrated that many of these ventral root unmyelinated afferents are nociceptors and that most of them have their cell body in the dorsal root ganglion and ultimately enter the cord through the dorsal root. Nerve tracing studies (96) show that many of those fibers end in the sheath of the root and its blood vessels or end blindly. Those endings have neuropeptides consistent with polymodal nociceptor properties. In some cases, the axons may double back and enter the cord at the dorsal root, but some also enter through the ventral root in a variety of different types of pathways (see Fig. 3-12). These findings reinforce the old assumption that such an alternate route accounts for failure of dorsal rhizotomy to relieve pain permanently. Moreover, they have provoked the use of ganglionectomy, alone or in combination with rhizotomy, in the attempt to ensure greater success in relieving pain (see Chapter 106).

The different functions, sources, and pathways of sensory axons in ventral roots are summarized in Figure 3-12, taken from the extensive review by Hildebrand and colleagues (96) in which data supporting each of the suggested possibilities are discussed. Not only do the axons have different physiologic properties and come from somatic and visceral neurons, but some ventral axons also are third branches of a dorsal root afferent, some end in the root and lack a CNS projection, and some come from the ganglion without a branch into the peripheral nerve (99). The blood vessels and pia of the roots receive some of this sensory innervation as well as sympathetic endings, and both types of nerve fibers can branch extensively after nerve injuries. Much of the vascular and nonvascular innervation of the spinal pia appears to derive from sensory afferents in the ventral roots (96,99). The trigeminal nerve presents an unusual case in which some of the sensory unmyelinated fibers in the motor root enter the brainstem via that pathway (100). The ventral root sensory fibers may have important functions in acute and chronic pain conditions, inflammatory and neuropathic pain, and regeneration.

Lissauer's Tract. Lissauer's tract is a tightly packed system of longitudinally running fine fibers that extend from the periphery of the dorsal horn to the cord's surface. Lissauer's original view of the tract was that it consisted chiefly of small primary afferent fibers en route to the synaptic terminals in the dorsal horn, and Ranson (101) proposed that most of these conduct nociceptive impulses. Subsequent degeneration studies indicated that, at most, only 25% of the fibers were afferents located in the most medial part of the tract; the rest were considered propriospinal (19). Detailed anatomic studies (19,102) have shown that (a) primary A-d and C fibers make up two-thirds of the axons in the rat, 50% in cat, and 80% in monkey; (b) the ratio of unmyelinated to myelinated fibers within the tract in rat is 3.8:1; (c) primary afferent fibers ascend several segments in the lumbosacral cord of rat but terminate within a single segment in the thoracic cord; and (d) in monkey there are more primary afferents in the medial part than in the lateral part of the tract. A detailed study of the terminal arbors of individual lectin-labeled and functionally identified visceral afferents found that some axons make terminal presynaptic swellings within Lissauer's tract before reaching the neurons of the dorsal horn (103). The proportions of those endings ranged from 5.9% to 20.3% of the total, with the rest located in specific dorsal laminae. Electrophysiology studies by Wall and colleagues show that specific interactions between fibers in Lissauer's tract and subsets of dorsal horn neurons are the basis for the prolonged depolarizations of the dorsal root potential (104).

Somatic and Visceral Central Terminations. The specific organization of laminae in dorsal horn and typical terminal locations for somatic A-b, A-d, and C fibers are illustrated generally in Figure 3-13, Fig. 3-14, Fig. 3-15 and then considered in detail in the next chapter. The pathways of A-b fibers in dorsal horn are shown in Figure 3-13 with their terminations in laminae III through V and their axonal branches into the dorsal columns. As indicated in Figure 3-14, the nociceptive A-d fibers have a different set of pathways and endings, with their terminations mainly in laminae I, II $_o$, V, and X. Capsaicin-sensitive somatic C nociceptors and thermoreceptors end mainly in lamina II, and visceral C fibers in lamina V (see Fig. 3-15).

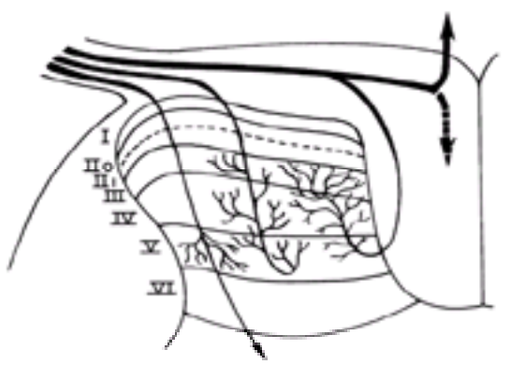


Figure 3-13. Cross-section of the spinal cord showing the course and termination of large beta afferent fibers. On entering the spinal cord these fibers proceed medially and bifurcate into short descending and long ascending branches in the dorsal column. Before entering the dorsal column, they give off the collaterals, some of which penetrate the dorsal horn. Others pass ventrally in the white matter medial to the medial side of the dorsal horn. At the level of lamina IV or V they reverse their direction, enter the gray matter, and pass dorsally as far as lamina III. In this lamina they divide into long (200-µm to 700-µm) ascending and descending branches that give off flame-shaped arborizations that in transverse sections appear to separate the neuropil into lobuli. Although the most dense arborization occurs in lamina III, there are also arborizations in laminae IV and V. The largest sensory afferents from the specialized muscle-stretch receptors have collateral branches that pass ventrally to make synaptic connections with neurons of laminae V, VI, and VII, thus making monosynaptic activation of these possible. Some even penetrate into the ventral horn (laminae VIII and IX), where they terminate directly on motor neurons and form the basis of the monosynaptic reflexes such as the knee jerk.

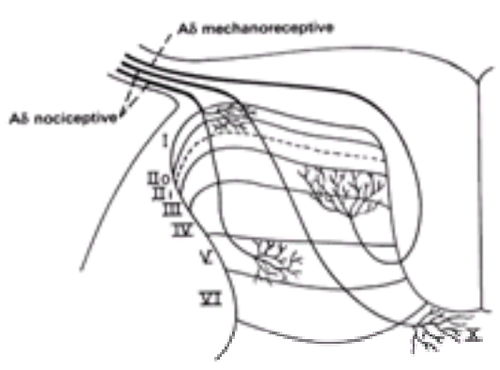


Figure 3-14. A schematic diagram of the course and termination of collaterals of A-d cutaneous fibers in the dorsal horn of the spinal cord.

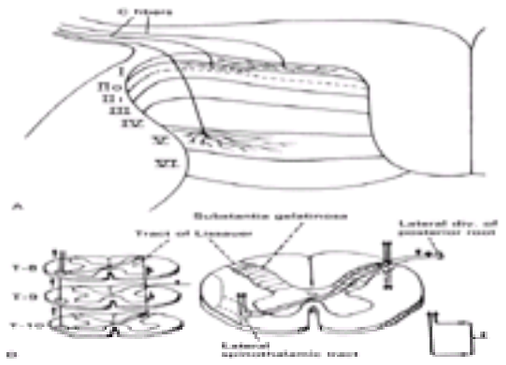


Figure 3-15. Schematic diagrams of the course and termination of collaterals of unmyelinated (C) cutaneous visceral afferents in the dorsal horn. **A:** Simple cross-section. **B:** On entering the spinal cord, the thin fibers divide into short ascending and descending branches and make up Lissauer's tract before they enter the dorsal horn, where they synapse with interneurons and cells of spinothalamic tract fibers. The insets on the left and right are schematic representations of this arrangement. Evidence suggests that C visceral afferents terminate in lamina V. (From Cervero F, *personal communication*, 1989.)

Single cell labeling studies have correlated the physiology of somatic and visceral afferents with the distribution and synaptic ultrastructure of their central presynaptic endings. The rostrocaudal extent, laminar termination fields, ipsilateral endings compared with those with both ipsilateral and contralateral arbors, and the overall shape of the central terminal clusters are different for somatic and visceral fibers, as demonstrated by Sugiura and colleagues (73,103) (Fig. 3-16 and Table 3-2). Individually identified thoracic somatic afferents made approximately 1,400 terminal swellings within its few terminal arbors, whereas individual visceral afferents could form as many as 20 different arbors, with an aggregate total of 5,000 to 6,000 terminal swellings. The challenges for sensory neuronal development and maintenance of such complex central endings for a somatic or visceral afferent fiber are impressive, especially because the pharmacology and functional dynamics are so different for the central endings of primary afferent neurons compared with their peripheral endings (see Pharmacology and Modulation of Nociception, later in this chapter), and because of complex inhibitory mechanisms that shunt APs to only some of the endings (105).

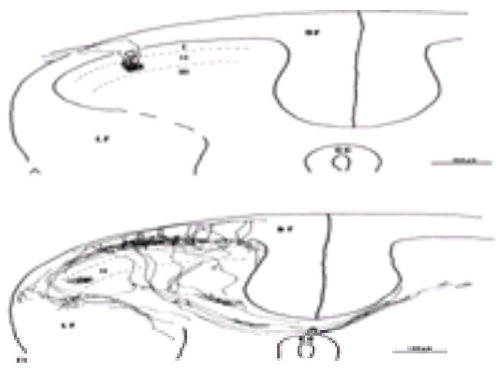


Figure 3-16. The different extents of central terminal fields are shown here for an individual somatic neuron **(A)** and a visceral neuron **(B)** from guinea pigs that were injected with phaseolus vulgaris leucoagglutenin after functional identification. The visceral neuron had many more central branches and numerous arbors that include contralateral projections, whereas the somatic neuron had just one main terminal field. (CC, central canal; DF, dorsal funiculus; LF, lateral funiculus.) [From Sugiura Y, Terui N, Hosoya Y. Difference in distribution of central terminals between visceral and somatic unmyelinated (C) primary afferent fibers. *J Neurophysiol* 1989;62:834–840, with permission.]

Per neuron	Somatic	Visceral
Terminal fields	Narrow	Dispersed
Arbor number	1–2	18–22
Location (%)	I, II	Dorsal funiculus (5–20)
		I (45–60)
		IV and V (5–10)
		X (3)
Boutons		
Type	Large, glomerular	Small, simple
Number	1,400–1,500	5,000–6,000

I, II, IV, V, X represent spinal laminar zones; data from labeled individual fibers: Sugiura Y, Tonosaki Y. Spinal organization of unmyelinated visceral afferent fibers in comparison with somatic afferent fibers. In: Gebhart GF, ed. *Visceral pain. Progress in pain research and management*. Seattle: IASP Press, 1995;5:41–59; and Sugiura Y, Terui N, Hosoya Y. Difference in distribution of central terminals between visceral and somatic unmyelinated (C) primary afferent fibers. *J Neurophysiol* 1989;62:834–840.

TABLE 3-2. Somatic and visceral C-fiber central arbor structure

Trigeminal and Other Cranial Nerves

Nerve impulses encoding head pain originate primarily in the peripheral sensory distribution of four cranial nerves—V (trigeminal), and to a lesser extent VII (facial), IX (glossopharyngeal), and X (vagus)—and also in terminations of the upper three cervical nerves. These nociceptive impulses activate neurons in the trigeminal brainstem nuclei and cervical dorsal horn. Signals are then relayed to other CNS sites, including brainstem reticular nuclei, solitary nucleus, thalamus, and cerebral cortex. In many respects the anatomy, physiology, and biochemistry of cranial nociception and pain pathways are homologous to those involved in transmitting pain signals originating in the body below the head (106,107,108,109,110,111,112,113 and 114) and the main termination region for trigeminal primary afferents is called the medullary dorsal horn.

The sensory input of the trigeminal nerve to the brainstem is diagrammed in Figure 3-17 (also see Chapter 50). The trigeminal mesencephalic nucleus is actually a collection of sensory cell bodies of primary neurons, which instead of being localized in the gasserian ganglion with other somatic cell bodies, have migrated into the midbrain and are thought to be associated functionally with proprioception, especially from oral mucous membrane, temporomandibular joint, masticatory and ocular muscle spindles, and periodontal ligament receptors (88,108,114,115 and 116). The pseudounipolar cell bodies in the mesencephalic nucleus give off peripheral branches that reach the muscles and other structures, and the central branches project to the motor trigeminal nucleus and make monosynaptic contact with somatomotor neurons to complete a two-neuron arc for the jaw-jerk reflex, which is homologous with the spinal reflexes. The other primary afferents of the trigeminal system are like those of the spinal nerves: They are composed of pseudounipolar cell bodies in the gasserian ganglion and have peripheral and central axons. The peripheral axons make up the ophthalmic, maxillary, and mandibular divisions of the ganglion and peripheral nerves, and the central axons make up the sensory root, which becomes attached to the ventral surface of the pons.

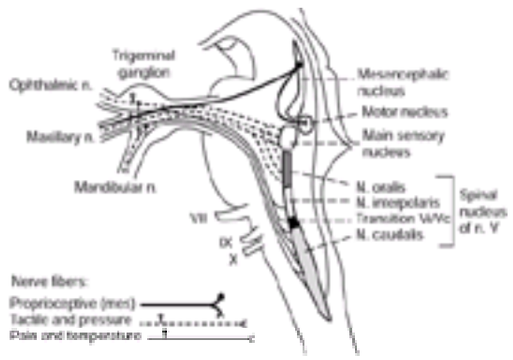


Figure 3-17. Schematic diagram of the neuroanatomy of the trigeminal system in sagittal section. The large A-b fibers, which transmit proprioceptive information from the anterior two-thirds of the head, have their central endings in the motor nucleus and either have their cell body in the gasserian ganglion (not shown), or their cell body is in the mesencephalic nucleus. Tactile and pressure afferents have their cell body in the ganglion and their endings in the main sensory nucleus and the subnuclei oralis and interpolaris. The thin nociceptive and thermoreceptive fibers pass caudally to end in the transition zone between subnuclei interpolaris and caudalis and in the subnucleus caudalis. (n, nerve; N, nucleus; V, VII, IX, X, cranial nerves.)

On entering the brainstem, these central processes pass through the spinal trigeminal tract to terminate in the trigeminal nuclear complex, composed of the main sensory nucleus and the spinal trigeminal nucleus, as well as in auxiliary sites (Table 3-3). The main sensory nucleus is located at the level of the pons, whereas the spinal trigeminal nucleus is deep to the descending trigeminal tract and extends as far caudad as the third or fourth cervical segments (117,118). The spinal subnucleus is further subdivided into three parts: subnucleus oralis, subnucleus interpolaris, and subnucleus caudalis (108,109,110,111,112,113,114 and 115,119). An additional important termination site for nociceptive trigeminal afferents from regions of the head is the overlap *transition* zone between interpolaris and caudalis subnuclei (120,121 and 122). In addition, some trigeminal afferents extend their central axons to the paratrigeminal nucleus, solitary nucleus, and cerebellum; some afferents cross in the caudalis region to terminate on the contralateral side of the brainstem (114,117,118,123,124). On entering the brainstem, the A-d and C fibers pass to the spinal tract and descend in it to terminate mainly within the subnucleus caudalis (see Fig. 3-17). In contrast, the large myelinated fibers divide into short ascending branches that terminate in the main sensory nucleus and long descending branches that pass through the trigeminal tract and give off collaterals to various parts of the underlying spinal nucleus. As these fibers pass caudad and give off collaterals they become smaller, so that by the time they reach the subnucleus caudalis, 75% of them are smaller than 2 µm in diameter, with a consequent progressive slowing of impulse conduction (108).

Trigeminal subnuclei	Auxillary sites
Mesencephalic	Cerebellum
Main (principalis)	Supratrigeminal nerve
Oralis	Trigeminal motor nerve
Interpolaris	Vestibular nerve
Vi/Vc transition zone	Solitary nerve
Caudalis	Reticular parvocellular
Cervical C-1–C-5	Paratrigeminal nerve
	Contralateral C-1–C-5

Data from Pfaller K, Arvidsson J. Central distribution of trigeminal and upper cervical primary afferents in the rat studied by anterograde transport of horseradish peroxidase conjugated to wheat germ agglutinin. *J Comp Neurol* 1988; 268:91–108; and Marfurt CF, Rajchert DM. Trigeminal primary afferent projections to "non-trigeminal" areas of the rat central nervous system. *J Comp Neurol* 1991;303:489–511.

TABLE 3-3. Central distribution of trigeminal afferents

Somatotopic organization is one of the most important and clinically relevant characteristics of the trigeminal system and exists throughout the gasserian ganglion, sensory root, spinal tract, and spinal nucleus. In the ganglion, the cell bodies of the mechanoreceptive and nociceptive afferents within the ophthalmic division are concentrated medially and somewhat anteriorly. Those of the mandibular division are caudal and lateral, and the cell bodies of the maxillary nerve lie between those of the other two divisions. Moreover, cell bodies of neurons that innervate the perioral and oral areas are located more ventrally, whereas those that supply the structures remote from the mouth are located more dorsally. In the sensory root, the afferents are also somatotopically organized in a medial to lateral fashion, such that the central processes of the mandibular division are posteromedially positioned, those of the ophthalmic division are located anterolaterally, and those of the maxillary branch are situated in an intermediate position (108,109,110,111,112 and 113,115,119) (Fig. 3-18). Complementary experimental and clinical studies have shown a similar somatotopic organization in the trigeminal spinal tract.

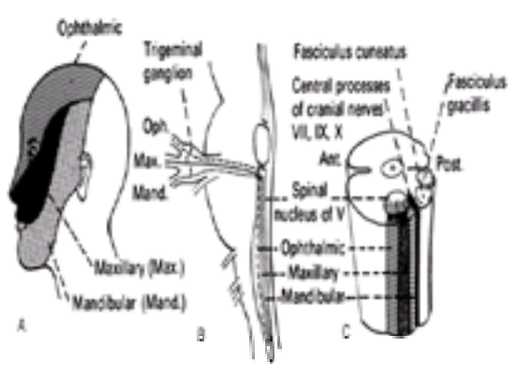


Figure 3-18. **A:** The cutaneous distribution of the three major divisions of the trigeminal nerve. **B:** The somatotopic position of the central processes of the three divisions in the descending trigeminal tract and in the spinal nucleus. **C:** The somatotopic organization of the descending spinal trigeminal tract, and its relation to the spinal nucleus and to the wedge in the medulla that contains the central processes of the VII, IX, and X cranial nerves, located between fasciculus cuneatus and the mandibular division. (Modified from Brodal A. *Neurological anatomy in relation to clinical medicine*, 3rd ed. New York: Oxford University Press, 1981.)

Another important and clinically relevant somatotopic pattern occurs along the rostrocaudal axis of the subnucleus caudalis, showing the *onion peel* pattern first described by Déjérine (125) on the basis of the sensory deficit caused by certain pathologic lesions of the brainstem (Fig. 3-19). Sensory innervation near the midline around the mouth and nose is represented in the most rostral

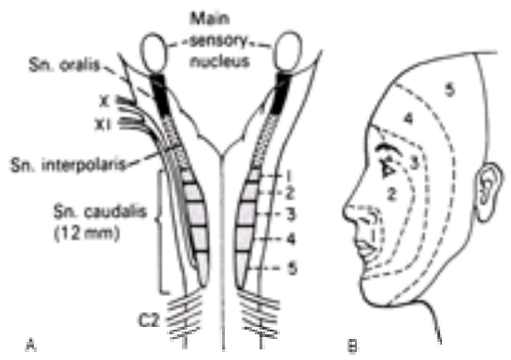


Figure 3-19. **A:** The rostrocaudal somatotopic organization of the subnucleus caudalis. **B:** The relation of the subnucleus caudalis to input from primary afferents on the face. The fibers nearest to the lips and lower nose (area 1) terminate highest in the subnucleus caudalis; the innervation of successively more lateral regions of the face ends progressively in more caudal parts of the subnucleus caudalis. This rostrocaudal somatotopic organization applies to all three divisions of the trigeminal nerves and produces the *onion peel* pattern in the face. (sn, subnucleus.) (Modified from Kunc Z. Significance of fresh anatomic data on spinal trigeminal tract for possibility of selective tractotomies. In: Knighton RS, Dumke PR, eds. *Pain*. Boston: Little, Brown and Company, 1966:351–366.)

part of the subnucleus caudalis, whereas the innervation of successively more lateral regions of the face ends progressively in more caudal parts of the subnucleus caudalis. The most impressive clinical evidence for this has been produced by Kunc (126) based on trigeminal tractotomy for facial pain. This operation, which has been done since 1938, permits the production of analgesia without significant effects on tactile sensation. If the lesion is placed above the upper pole of the subnucleus caudalis, analgesia of the whole ipsilateral trigeminal nerve territory occurs. On the other hand, if the tractotomy is performed more caudally, the analgesia is incomplete, with sensory sparing of the center of the face. With more caudal sections, these areas expand concentrically. These results lead Kunc to conclude that whereas all three divisions of the trigeminal nerve terminate in all segments of the spinal nucleus, the terminations of the primary afferents from the center of the face are most intense in the highest level and those from the periphery in the lowest level. This clinical conclusion was subsequently confirmed by the electrophysiologic studies of Yokota (111). More recent studies have used the expression of the proto-oncogene c-*fos* as an indicator of central neurons that are contacted by trigeminal afferents. Those studies demonstrate some endings in the interpolaris and caudalis transition zone for polymodal nociceptors from all head regions (120,121 and 122).

The classical technique of medullary trigeminal tractotomy can be extended somewhat medially to produce analgesia of the posterior third of the tongue, tonsil, pharynx, tympanic membrane, and external auditory canal. Tactile sensibility in these areas is not noticeably altered after the operation. These results strongly suggest that the central processes of cranial nerves VII, IX, and X end in and synapse with cells of the dorsomedial part of the subnucleus caudalis and the spinal dorsal horn at levels of C-1 and C-2, and sometimes even C-3. The general visceral afferent input traveling in cranial nerves V, VII, IX, and X terminates mainly in the nucleus of the tractus solitarius (115). Although some neurosurgeons believe it is necessary to cut the whole spinal tract to interrupt nociceptive fibers in the other three cranial nerves, Kunc (126) believed it possible to obtain analgesia in the distribution of these nerves and the third division of the trigeminal while sparing the first and second division. He achieved this result by making a precise, narrow incision, extending from the lateral boundary of the cuneate fasciculus to the medial boundary of the spinal trigeminal tract.

Central axons from the spinal afferents ascend and terminate in the subnucleus caudalis. Dorsal root axons from upper cervical nerves can send branches to terminate in the spinal trigeminal nuclei. These overlapping trigeminal and spinal terminations provide a morphologic basis for the substantial interaction between the upper cervical dermatomes and cranial nerve nervatomes revealed after brain lesions or pharmacologic manipulations (110). They also complement evidence indicating a major homology between the trigeminal subnucleus caudalis and the spinal dorsal horn. Finally, the convergence of cranial and upper cervical primary afferents into a common synaptic region in the caudal medullary and upper cervical cord provides a logical explanation for the phenomenon of referred pain from the head to the neck and vice versa.

NOCICEPTOR PHYSIOLOGY

In the preceding section, we have already used several different categorizations for primary afferent neurons: (a) nociceptive subtypes in the ganglion (see Fig. 3-2), (b) conduction velocities (see Table 3-1), (c) type of receptor ending structure (see Fig. 3-8, Fig. 3-9, Fig. 3-10), and (d) central terminal morphology (arbor shape, rostrocaudal extent, ipsilateral and contralateral distribution, and laminar location) (see Fig. 3-13, Fig. 3-14, Fig. 3-15 and Fig. 3-16). To further understand the physiology of nociception, it is important to discuss nociceptor signal detection and integration, information flow in primary afferent neurons, basic physiologic properties of nociception, sensitization and hyperalgesia, reflex activities that affect pain, and tissue specificity of nociception. The special properties of polymodal receptors and their efferent actions are considered in Polymodal Receptors, later in this chapter. The cytochemistry, pharmacology and modulation of the primary afferents are reviewed in the sections on Pharmacology and Modulation of Nociception and Peripheral Mechanisms of Persistent Pain, later in this chapter. Much of the information described here comes from the extensive reviews by Meyer and colleagues, Levine and Taiwo, Rang and colleagues, Woolf, Fitzgerald, Bennett, Yaksh and Malmberg, Dubner and Basbaum, and Devor in the third edition of Wall and Melzack's *Textbook of Pain* (21), as well as more recent reviews by Stein (22), Dray (127), Devor (128), Kumazawa (129), Cesaro and McNaughton (39), Woolf and colleagues (130), Carlton and Coggeshall (32), Dray and Rang (41), Millan (28), Willis (142), and books edited by Kumazawa and colleagues (23), Belmonte and Cervero (131), and Dickenson and Besson (26). The basic principles of neurobiology and neurophysiology that concern pain can be studied further in works by Zigmond and colleagues (132), Nolte (133), Hille (134), Hall (135), and Siegel and colleagues (136).

Detection of cytochemical signals by the peripheral endings is driven by specific molecular systems using ligand-receptor mechanisms or ion channels. The endings are able to respond to many different types of signals, only some of which are allowed to move beyond the endings to reach the cell body and affect gene expression. Thus, it has been proposed that screening of tissue conditions by nociceptors is as sophisticated as that of the dorsal horn for regulating access of peripheral information to the CNS (22,32). Whereas information through-put in the dorsal horn depends on a series of gating and modulating mechanisms at the synaptic connections with central neurons (4), the peripheral signals do not reach the CNS at all unless they exceed physiologic, pharmacologic, and molecular threshold requirements of the peripheral endings, and their access to the CNS may be further regulated within the sensory ganglion (137). The peripheral endings are therefore critical primary *gatekeepers* that select, limit, or enhance access of neural signals to the CNS. In addition, the signal-generating properties of the nociceptive neurons shift to different functional levels or phenotypes depending on whether the tissue is normal, inflamed, invaded by foreign agents, healing, or irretrievably damaged. Those changes in functional and cytochemical phenotype are triggered at the peripheral endings of nociceptors by membrane receptors, ion channels and transporters, G- protein systems, second messenger cascades [cyclic nucleotides, calcium, phosphatidyl inositol, nitric oxide (NO), eicosanoids], various effectors (kinases, phosphatases, enzymatic arrays), and other axonally transported proteins, as described in Pharmacology and Modulation of Nociception, later in this chapter. Whether tissue events produce algesic or analgesic responses depends on how the primary afferent neurons read and respond to their environment, and on how their functions are modulated by neuroinflammatory, neuroimmune, and neuroendocrine interactions.

Information Systems in Peripheral Neurons

The detection systems of primary afferents (whether at their peripheral endings, central endings, along the axon, or at the cell body) are converted into at least four different intraneuronal information pathways (Fig. 3-20): (a) fast electrophysiologic signaling via sensory potentials, conducted APs, and their ion channel mechanisms; (b) the slower cytochemical delivery systems via axonal transport; (c) rapid retrograde phosphorylation signals from nerve endings to cell body; and (d) diffusion of membrane-permeable molecules such as NO. It is the combined effects of the complex messages that are carried by these intraneuronal information systems that underlie phenotypic changes in nociceptive peripheral neurons after injury, at different stages of inflammation and wound healing, and after neuropathic injury.

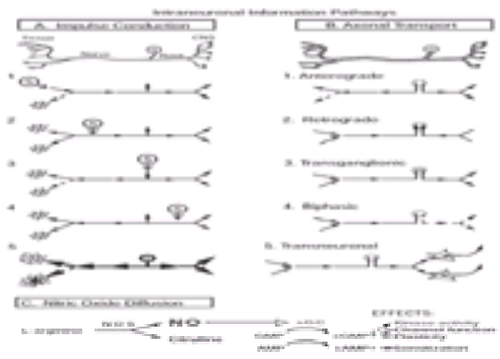


Figure 3-20. Schema depicting the flow of information via action potentials **(A)**, and various types of axonal transport **(B)**. Local intraneuronal signals also involve nitric oxide **(C)**. See text for details.

Electrophysiologic Information

Although the sensory neurons are called primary afferents, their conducted APs can move either in the afferent direction (from the tissue toward the ganglion and CNS) or in the efferent direction (out to the peripheral endings), depending on the type and location of stimulation. Five examples of efferent movement of APs in sensory neurons are shown in Figure 3-20 and include (a) the axon reflex, in which a stimulation of some of the branches of a peripheral arbor reverberate back out to unstimulated branches. (b) Mechanical or electrical stimulation of a nerve can generate APs that move in efferent and afferent directions away from the stimulus. (c) Stimulation of the sensory cell body causes movement of potentials out to the peripheral endings as well as to the central endings. (d) Stimuli to the dorsal horn can generate signals that move back out the peripheral axon, called the *dorsal root reflex*. (e) Endogenous spontaneous signal generation in the sensory cell body sends APs out to the peripheral endings as well as to the central endings. When efferent potentials arrive in the peripheral endings, the voltage change can induce release of neuropeptides that then have paracrine effects on neighboring cells, autocrine effects on the sensory neurons, or both. An interesting feature of AP movement in sensory neurons is that the signals bifurcate to be carried via the stem axon to the cell body when passing through the ganglion, thus enabling the cell body to have a record of the electrical traffic in the main axon and to respond to that traffic with relevant adjustments in gene expression and transcription.

The electrophysiology of nociceptors has some unusual properties. For example, it is now known that conduction velocity increases and AP duration decreases for C and A-d fibers after 2 days of tissue inflammation, and the afterhyperpolarization of A fibers also decreases (67). Many A-d and C fibers have an inflection on the falling phase of their AP and a prolonged afterhyperpolarization, both involving calcium channels. The after-hyperpolarization is enhanced during periods of activity and counterbalanced by excitatory cross- depolarization from adjacent active fibers (138,139) (Fig. 3-21). Evidence suggests that bursts of spontaneous impulse generation occur periodically in normal dorsal root ganglia, and that after nerve injury there are periods of increased frequency followed by periods of suppression and hyperpolarization (128,139). Gradual excitatory summation of low-intensity stimuli in C fibers can cause extended bursts of APs that contribute to central sensitization (140). When antidromic potentials are triggered during dorsal root reflex, they affect all calibers of sensory fiber (141) and can modify sensitivity of peripheral endings as reviewed by Willis (142). For example, one study shows that the peripheral axons to the primary and secondary spindle afferents of muscles are differentially affected by antidromic APs. At low signal frequency, only the secondary afferents are inhibited, but both are affected at high frequency (143), thereby causing different effects on muscle afferent sensitivity depending on the rate of reflex potentials. Release of substance P by C-fiber activity in the ganglion has been shown to vary, depending on tissue condition, and to inhibit subsequent A-fiber AP traffic through the ganglion (137), providing further complexity to passage of electrophysiologic information from the periphery to the CNS.

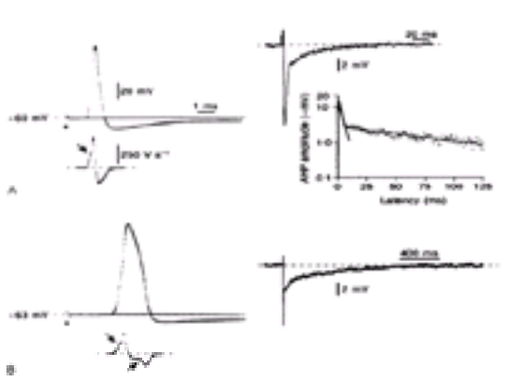


Figure 3-21. Spike waveform and afterhyperpolarization in A fibers. In **(A)** and **(B)** the axon was stimulated (*) just below and just above threshold (single sweeps). **A:** Upper trace shows the spike waveform of A_0 fibers with standard action potentials and the lower trace shows the differentiated voltage signal illustrating spike inflections (*arrows*). **B:** Lower traces show A_{inf} fibers with an extra inflection on the falling phase and prolonged afterhyperpolarization. The higher gain, slower time base records on the right illustrate the two phases of the afterhyperpolarization, including a log plot for the cell in **(A)**, with linear regression plots for the two phases (1.5 and 0.2 mV ms^{-1}). [From Amir R, Devor M. Spike-evoked suppression and burst patterning in dorsal root ganglion neurons of the rat. *J Physiol (Lond)* 1997;501: 183–196, with permission.]

Axonal Transport

Although electrophysiologic signals move from one end of a neuron to another within seconds, the axonally transported cytochemical signaling systems take hours or days to reach their intraneuronal destinations. At least five pathways of axonally transported information in primary afferent neurons exist (see Fig. 3-20): (a) Anterograde transported molecules go from the cell body into the peripheral axon to the receptive endings and into the central axon to the central synaptic terminals. (b) Retrograde transport from the receptors in peripheral tissues travels back to the cell body, or from the presynaptic central terminals back to the cell body. (c) Transganglionic transported materials are picked up by the peripheral endings and move all the way to the central synaptic terminals. (d) Biphasic relay signaling occurs, in which a molecule such as NGF is transported retrograde from a peripheral injury site or from the CNS to the cell body, in which it elicits expression of another neurotrophin [brain-derived neurotrophic factor (BDNF)] that is then conveyed by anterograde transport to peripheral and central endings (144,145). That arrival of BDNF at central terminals may be a key trophic agent in driving persistent plasticity in the dorsal horn, because its expression and delivery only happen when significant injury occurs to drive increased NGF retrograde transport (144). (e) Finally, transneuronal transport occurs when transported materials, such as WGA-HRP (wheat germ agglutinen–bound horseradish peroxidase) or herpes virus, which were picked up in a peripheral tissue, such as cornea or tooth pulp, move into the next neuron in the CNS (146,147). Also, exocytosis and transfer of nerve labels into nonneuronal cells occurs after transport out to the peripheral nerve endings (148).

The anterograde and retrograde systems carry different materials at different rates for different purposes: (a) Rapid anterograde transport carries vesicle-packaged material from the Nissl body endoplasmic reticulum and Golgi organelles to the sensory and synaptic nerve endings or other specialized regions (e.g., nodes of Ranvier), traveling at relatively fast 200 mm per day to 400 mm per day rates, with specific molecular guidance systems to ensure delivery to the correct subcellular domain. (b) Slow anterograde transport moves cytoplasmic cytoskeletal materials such as microtubules and neurofilaments into the axons from the cell body at rates of 1 mm per day to 5 mm per day to resupply and maintains the axon and its endings. (c) Intermediate anterograde transport rates occur for mitochondria and other special cytoplasmic organelles that move within the axon. (d) Retrograde axonal transport carries retrograde signals from the central and peripheral endings back to the cell body at rates of 70 mm per day to 100 mm per day to return exhausted axonal materials to the lysosomal systems of the cell body for recycling or removal. The retrograde signals also trigger altered gene expression for altered nociceptor phenotype.

The extensive mapping of neural pathways in the periphery and CNS that occurred in the 1970s and 1980s (135,149) depended on the discovery of the anterograde and retrograde axonal transport systems in the 1960s and 1970s and on development of the wide variety of general transport labels such as anterograde

radioactive-labeled protein, bidirectional horseradish peroxidase, fluorescent labels, lipophilic hemocyanin dyes such as Di-I, and lectin-labels such as WGA-HRP. Some labels such as biocytin or phaseolus hemoagglutinin lectin have been extremely useful for marking neural form after electrophysiologic recording (see Fig. 3-16). In addition, some labels are specific for axonal subtypes, such as anterograde labeling of small intraepithelial fibers with WGA-HRP but not choleragenoid B-HRP (150) or transganglionic retrograde labeling of terminals of thin fibers by WGA-HRP and of large fibers using choleragenoid-HRP (151). However, combinations of labels can produce puzzling results, such as failure of transganglionic labeling when WGA-HRP is combined with choleragenoid-HRP (151) or failure of herpes virus retrograde transport when combined with Fluoro- Gold label (152); there is still much to learn about the subtleties of axonal transport mechanisms and the targeting of molecular traffic to the correct intraneuronal subcellular regions (153).

Rapid Retrograde Phosphorylation

Until the mid-1990s, the signaling cascades in mature neurons in response to application of ligands such as NGF to the nerve endings have been thought to require retrograde transport of endocytotic vesicles containing ligand and receptor to the cell body (154). However, ultrafast retrograde signaling by phosphorylated tyrosine kinase A (trkA) receptors for NGF has now been demonstrated to produce molecular reactions in the cell body at rates that are at least an order of magnitude faster than possible by standard retrograde transport (155,156). In addition to trkA, other proteins in the cell body also are phosphorylated quickly in response to NGF at the nerve endings. This mechanism appears to bypass internalization of ligand-receptor complexes, a process that requires too much time for the observed effects. Instead it somehow initiates a propagated signal that may involve calcium mechanisms (155). The slower retrograde transport of vesicles that do not have an effect until they reach the cell body many hours later is also important, but would elicit a different set of biologic responses from the ultrafast phosphorylation system.

Intracellular Nitric Oxide

NO is a diffusable gas with numerous local biologic actions that can be intracellular [e.g., stimulation of cyclic guanosine monophosphate (cGMP)–dependent kinases, ion channels, or phosphodiesterase] or extracellular (neurally induced relaxation of vascular smooth muscle, anterograde and retrograde signaling between presynaptic and postsynaptic units, or enhancement of spontaneous discharges in injured neurons involving satellite cell and neuronal interactions) (157,158,159 and 160). NO is generated when the enzyme NO synthase (NOS), in the presence of calmodulin, catalyzes conversion of l-arginine to citrulline, thereby releasing NO. The NO then diffuses short distances in cytosol or through nearby membranes, to activate soluble guanyl cyclase enzymes. These enzymes generate cGMP, thereby promoting cGMP-dependent actions in the donor cell or in nearby target cells, or both (see Fig. 3-20). NO signals are activity dependent, local, and short-lived, with NO amounts regulated first by their production followed by inactivation after binding to guanyl cyclase. More recent work shows that NO also can enhance nociceptor hyperalgesia induced by prostaglandin E_2, adenosine, or serotonin, by activating intracellular cyclic adenosine monophosphate (cAMP)–dependent mechanisms and protein kinase A (161). The NO that is generated at sites of inflammation or ischemia comes from a variety of cell types (neural, endothelial, immune) at different stages of the pathology, and it may potentiate the effects of other agents, such as prostaglandins at low concentration, but have its own direct effects at higher concentrations (161).

Much still remains to be learned about the specific local functions of NO in nociceptive neurons. So far, they involve enhancement of sensitization of peripheral endings (161), increased discharges from ganglia of injured nerves (158), activity-dependent retrograde effects on presynaptic cGMP functions at central endings (162), and inhibition of *N*-methyl-d-aspartate (NMDA)–driven excitotoxicity (159,160). Immunocytochemical studies have found that many visceral afferent neurons normally contain NO synthase, whereas only a few dorsal root ganglia or trigeminal neurons have it, suggesting different functions for NO in normal visceral afferent functions. However, after axotomy, the neurons of nodose, dorsal root, and trigeminal ganglia showed similar upregulation of the enzyme (53). That increased enzyme must then be transported to sites of action, in which it will induce local production of NO. Injured neurons would differ from normal not only in their amount of NO, but also in the specific NO-dependent cGMP or cAMP-driven reactions, and in their axonal transport traffic dynamics.

Basic Physiologic Properties

Chapter 2 defines many terms that are relevant to the neurobiology of pain. Several other physiologic properties are briefly defined here, to facilitate discussion of their contributions to transient, acute, and persistent pain, and the molecular mechanisms of nociceptor modulation and plasticity. These properties occur in primary afferent neurons and in central neurons, but with different mechanisms and significance at each successive level in pain pathways. Further information about fundamental aspects of neurophysiology can be found in reviews and books by Hall (135), Hille (134), Treede and colleagues (163), Meyer and colleagues (164), Devor (128), Nolte (133), Siegel and colleagues (136), Zigmond and colleagues (132), and Willis (142).

Action Potentials

APs are generated when gradual depolarization of the membrane potential causes enough inward sodium current flow through sodium channels to reach threshold for the all-or-none AP. At that time, a transient opening of voltage-gated sodium channels and inward sodium current occur that rapidly shifts the membrane potential to a positive value, followed by closing of the sodium channels and opening of voltage-gated potassium channels. The subsequent outflow of potassium ions brings the membrane potential back to its resting level, with important involvement of calcium and chloride currents in the afterhyperpolarization that precedes resetting of normal resting potential, and of calcium currents for an inflection on the falling phase of some A-d and C-fiber AP (see Fig. 3-21). Successive opening of voltage-gated sodium channels allows an AP to propagate at characteristic rates along the axon, as indicated in Table 3-1. The size of the peripheral axon correlates with conduction velocity to define the A, B, and C components of the compound AP. Primary afferent neurons that contribute to nociception are mostly in A-d and C groups, but some A-b neurons have nociceptorlike properties, and A-bmechanoreceptors in inflamed tissue have altered conduction properties (44,67,78), cytochemistry, and central connections (45). Although voltage and patch clamp technologies have shown that AP mechanisms are roughly similar in all neurons, important variations occur in resting potentials and AP size and shape (67) for different neurons and for different normal physiologic conditions, such as sleep (132,133,134 and 135,165), or after injury. For example, inflammation induces changes in conduction properties of nociceptive C, A-d, and A-b fibers (67), as well as blockade of A-fiber conduction through sensory ganglia if there has been release of substance P by prior C-fiber activity (137). Active fibers may cross-excite many of their neighbors, and neurotrophin growth factors affect conduction properties in some important ways (166,167).

Adaptation

Adaptation denotes the duration of physiologic response by a sensory neuron in relation to the stimulus. Slowly adapting mechanoreceptors continue to fire for the duration of a stimulus to give tonic information, whereas rapidly adapting receptors give phasic information about onset of stimuli (or their cessation). For many of the C fibers, their adaptation is slow and can outlast the stimulus, allowing for the temporal and spatial summation that underlie many of the features of inflammatory and pathologic pain.

Adequate Stimulus

For each somatosensory receptor, there is a preferred type of stimulus energy (mechanical, thermal, cytochemical, or a combination of those modalities) to which the neuron is most sensitive, called the *adequate stimulus*. Specific mechanosensitive and thermosensitive (heat or cold) receptor channels have been identified (164), as well as a variety of chemosensitive receptor mechanisms, such as those driven by bradykinin receptors, capsaicin-sensitive vanilloid receptors, purinergic receptors, or proton-sensitive receptors (127). The adequate stimulus depends on the complement of molecular mechanisms in the membrane of the primary afferents, and it differs for the different functional states (phenotypes) of a nociceptive neuron because the membrane chemistry changes. Each tissue has characteristic adequate stimuli for its custom-designed nociceptive apparatus, as discussed at the end of this section.

Dynamic Range

The range of stimulus intensities to which a sensory neuron responds is called its *dynamic range*. For polymodal receptors, it extends from the innocuous far into noxious levels of stimulation, whereas specific nociceptors have their dynamic range more narrowly confined to the noxious range. The dynamic range for central neurons can be wide or nociceptive specific, and it is affected by unmasking of auxiliary inputs during peripheral inflammation.

Receptive Field

Receptive field indicates the region of the body from which a particular sensory or central neuron is activated. The receptive field of a primary afferent neuron depends on the distribution of its terminals, their receptor properties, the presence or absence of inflammatory agents, and the type and location of the stimulus. The receptive field of a primary afferent expands during inflammation (163,164) (Fig. 3-22). The receptive field of a second-order neuron in spinal cord or brainstem depends on the

types of peripheral inputs and on complex central modulation. The receptive fields of central neurons are much larger than those of the primary afferents, and they expand if their target tissue is inflamed because of integration of many peripheral afferent inputs and central mechanisms. Central receptive fields can be altered within seconds via unmasking of ineffective afferent connections (168).

Spontaneous Discharge

Spontaneous discharge refers to APs that are generated, usually at the sensory cell body, without exogenous stimulation. Those APs then propagate distally and centrally to affect function of the peripheral and central endings. Daily fluctuations in spontaneous discharge rate have been demonstrated in normal conditions, and they are enhanced after neuropathic injury or inflammation (128,138,139). Spontaneous discharges in sensory neurons are often found as bursts of signals with intervening quiescent periods, and the intervals between signal bursts are altered by injury.

Stimulus Modalities

Mechanical, heat, cold, and chemical energy modalities activate sensory neurons via specific ion channels or receptors. Nociceptive C fibers exist that are specific for each of those modalities, as well as a large group that responds to noxious mechanical and heat stimuli [C-fiber mechanoheat nociceptors (CMH)]. Many other C fibers respond to chemical as well as mechanical and heat stimuli and are called *polymodal nociceptors* (see Polymodal Receptors, later in this chapter). The most common type of A-fiber nociceptor responds to high threshold mechanical stimuli in normal skin and becomes sensitive to heat also after injury (A-fiber mechanoheat nociceptors, AMH). Polymodal A-fibers also exist that are responsive to chemicals such as capsaicin in addition to mechanical and or heat sensitivity. Many A-d and C primary afferents cannot be mechanically activated in healthy tissue (mechanically insensitive or *silent* afferents) but become active in inflamed tissue (44,163,164) and might best be considered to be inflammation detectors.

Summation

Changes in the membrane potential at sensory endings (sensory potentials) or at postsynaptic regions (synaptic potentials) do not propagate actively, but dissipate over short distances. Successive potentials can combine to give a progressively more positive (excitatory) or more negative (inhibitory) membrane potential, with the integration of multiple inputs affecting AP generation in the axon. Neurons vary in the duration of their nonpropagating potentials and in the distance over which they can travel. Nociceptive endings have particularly long duration and effective distance, so that temporal and spatial summations are important mechanisms by which the nociceptive endings evaluate the severity of noxious or inflammatory events and titrate their signal frequency accordingly.

Sensitization and Hyperalgesia

Sensitization

Peripheral sensitization occurs when the stimulus threshold of a nociceptive neuron is lowered and the stimulus and response curve shifts to the left (Fig. 3-23). Perl and others (66,164,169) demonstrated that with repeated stimulation, high-threshold polymodal C fibers display enhanced sensitivity, lower stimulus threshold, and prolonged, enhanced afterdischarge. Not only are most C and A-d fibers sensitized by inflammatory mediators (Fig. 3-24), but some A-b fibers also become sensitized (44,45). Other agents, such as endocannabinoids and opioid peptides, decrease nociceptive responsiveness and therefore desensitize the neurons (161,170).

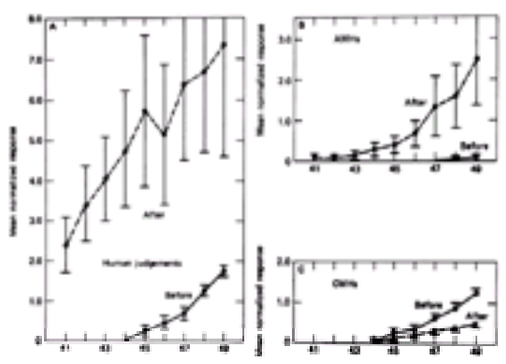


Figure 3-23. Hyperalgesia and nociceptor sensitization after a cutaneous burn injury. Responses to heat stimuli were obtained 5 minutes before and 10 minutes after a 53° C, 30-second burn to the glabrous skin of the hand. The burn resulted in increases in the magnitude of pain (hyperalgesia) in human subjects that were matched by enhanced responses (sensitization) in type I A mechanoheat receptive fibers (AMHs) in monkey. In contrast, C mechanoheat receptive fibers (CMHs) exhibited decreased sensitivity after the burn. **A:** Human judgments of pain (n = 8). **B:** Response of A-fiber nociceptive afferents (type I AMHs) in monkeys (n = 14). **C:** Responses of C-fiber nociceptive afferents (CMHs) in monkeys (n = 15). Because the AMHs did not respond to the 45°C stimulus before the burn, the AMH data were normalized by dividing by the response to the first 45° C after the burn. (From Meyer RA, Campbell JN. Myelinated nociceptive afferents account for the hyperalgesia that follows a burn to the hand. *Science* 1981;213:1527–1529, with permission.)

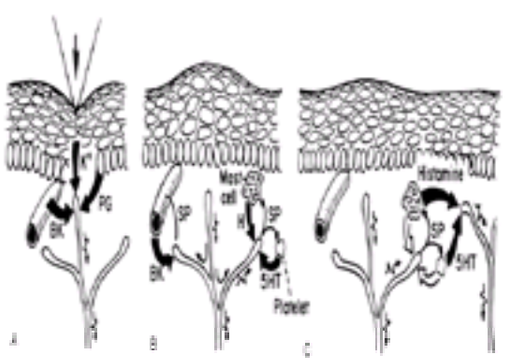


Figure 3-24. Events leading to activation, sensitization, and spread of sensitization of primary afferent nociceptor terminals. **A:** Direct activation of intense pressure and consequent cell damage, which leads to the release of potassium (K^+) and the synthesis of prostaglandins (PG) and bradykinin (BK). Prostaglandins increase the sensitivity of the terminal to bradykinin and other pain-producing substances. **B:** Secondary activation, showing that impulses generated in the stimulated terminal propagate not only to the spinal cord but into other terminal branches, where they induce the release of peptides including substance P (SP). Substance P causes vasodilation and neurogenic edema with further accumulation of bradykinin and also causes release of histamines (H) from mast cells and serotonin (5HT) from platelets. **C:** With continued liberation of substance P, the levels of histamine and serotonin continue to increase in the extracellular fluid and indirectly mildly sensitize nearby nociceptors. Sensitization leads to a gradual spread of hyperalgesia, tenderness, or both. (Modified from Fields HL. *Pain*. New York: McGraw-Hill, 1987:36.)

Central sensitization also occurs after tissue or nerve injury in an activity-dependent fashion (140,171). Both voltage-dependent NMDA receptors and metabotropic (neuropeptide or excitatory amino acid) receptors are involved, and protein kinase C activity is necessary to produce the characteristic increased intracellular calcium (172,173). Repetitive C-fiber stimuli that cause *windup* (increasing amplitude of central neuronal response) drive central sensitization, but other mechanisms that elevate intracellular calcium, such as summation of synaptic potentials below the firing threshold, can also lead to increased intracellular calcium and central sensitization. This is discussed in Chapter 4.

Hyperalgesia

Primary hyperalgesia involves altered physiology and pharmacology of the sensory endings to produce a leftward shift in the stimulus and response curve for injured tissue. It is triggered by inflammatory mediators, persisting noxious stimuli, or both, and it is characterized by lowered threshold, increased rate of APs, spontaneous activity, and increased pain sensation to suprathreshold stimuli. Its specific characteristics depend on the energy that caused the injury (heat has different effects than mechanical injury), on the type of tissue, the energy of the test stimulus, and the time after injury (2,128,163,164). Hypoalgesia is the opposite phenomenon, with increased threshold of primary afferent sensory endings and decreased pain from the stimulated tissue.

Secondary hyperalgesia involves increased pain and allodynia from uninjured tissue surrounding the injury (see Fig. 3-22). It is driven mainly by increased excitability of central neurons via activated NMDA receptors, elevated intracellular calcium, and increased sensitivity to glutamate. The mechanisms for secondary hyperalgesia share many central neuronal plasticity responses with referred hyperalgesia and neuropathic hyperalgesia (163) (see Chapter 4).

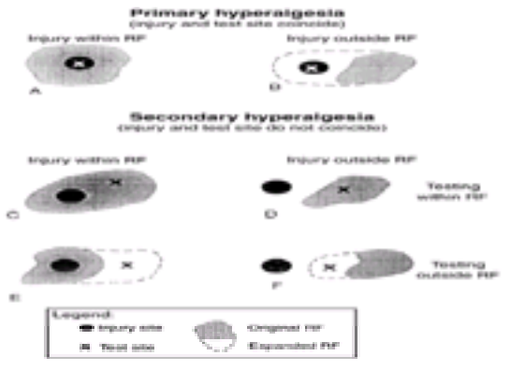


Figure 3-22. Experimental configurations for testing the neural mechanisms of primary and secondary hyperalgesia. For primary hyperalgesia, the site of injury (*filled circle*) and the site of testing (*X*) must coincide. Alterations of the stimulus-response functions within the original receptive field **(A)** or receptive field expansions toward the injury site **(B)** are correlates of primary hyperalgesia. For secondary hyperalgesia, the site of injury and the site of testing must not coincide **(C–F)**. A sensitization of the stimulus-response function revealed by testing within the original receptive field may occur following injuries within **(C)** or outside **(D)** the receptive field. An expansion of the receptive field to include a test site outside the original receptive field may occur for injuries within **(E)** or outside **(F)** the receptive field. (From Treede RD, Meyer RA, Raja SN, et al. Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol* 1992;38:397–421, with permission.)

Reflexes That Affect Nociception

Spinal Motor and Autonomic Reflexes

It has long been known that when tissue damage initiates nociceptive impulses, some of those signals are transmitted to the anterior horn cells to stimulate somatic motor nerves, whereas others are transmitted to the anterolateral horn to stimulate cell bodies of preganglionic neurons (Fig. 3-25). Somatomotor stimulation produces increased tension or spasm of skeletal muscles, which, in turn, can give rise to positive feedback loops that enhance the spasm, which then becomes a new source of nociceptive impulses to reinforce the already existing nociception. Those reflexes can be driven by somatic, visceral, or both kinds of motor spasms. The increase in sympathetic tone leads to peripheral vasoconstriction, with consequent decrease of the microcirculation in the injured tissue and adjacent muscles. That induced ischemia may further enhance sensitization of nociceptors and thus increase nociceptive input. Moreover, this reflex sympathetic response often plays an important role in certain types of persistent pain.

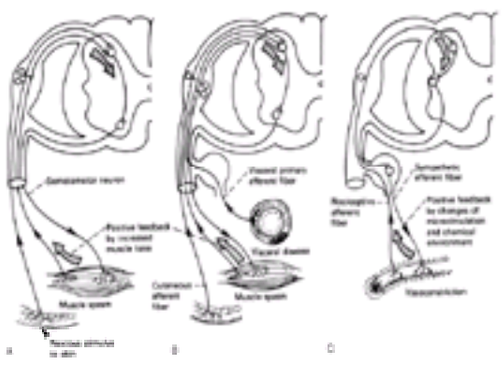


Figure 3-25. Diagram indicating some possible mechanisms of self-excitation nociceptors by spinal reflexes. **A:** A somatomotor reflex induced by stimulation of cutaneous or muscle nociceptors causes reflex contraction of skeletal muscles, which, in turn, act as positive feedback to further excite and sensitize the dorsal and ventral horns' neurons (*arrows*) and to produce an abnormal reflex mechanism, resulting in further increase in tension of the muscle. **B:** A similar mechanism of producing skeletal muscle spasm, initiated by a convergence of cutaneous and visceral primary afferents on viscerosomatic spinothalamic tract neurons. Stimulation of the somatomotor neurons in the anterior horn produces reflex skeletal muscle spasm, which acts as positive feedback to create and sustain a vicious circle. **C:** Noxious stimulation of primary afferent fibers produces nociceptive input, some of which is transmitted to spinothalamic tract neurons. Other impulses go to the anterolateral horn to stimulate sympathetic preganglionic (efferent) fibers, causing vasoconstriction, increased smooth muscle tone, and change in the chemical environment. The latter, in turn, acts as positive feedback to further increase nociceptive input.

The efficacy of relaxation techniques, massage, peripheral vibration, transcutaneous electrical nerve stimulation, and other therapeutic methods that manipulate the peripheral tissues to counteract pain problems must depend in part on inhibiting the reflex muscle spasms and promoting blood flow to counteract sympathetic vasoconstriction. In addition, such activity can affect information processing in the dorsal horn to inhibit the effect of the nociceptive messages and short circuit the positive feedback loops, as proposed originally by Melzack and Wall (4) and modified by the numerous studies of dorsal horn mechanisms since the 1970s (24,26) and discussed in Chapter 4.

Dorsal Root Reflexes

The sensory barrages to the dorsal horn that are triggered by inflammation or neuropathic injury induce reflexive efferent conduction back out the sensory axons in fibers of all size (141,142). The specific efferent effects of dorsal root reflexes on sensory systems need further examination. Those reflexes may play important roles in contralateral sensory sequelae to unilateral injury, such as a mirror-image inflamed knee (174). In addition, it has been shown that sensory fibers of skeletal muscle are differentially affected by dorsal root reflexes, so that they would each acquire a new relationship that would alter the sensory receptor balance in the muscle and, in turn, affect motor reflexes (143).

Neuroimmune Reflexes

Research during the 1990s has shown that important afferent signals to the brain occur via the vagus nerve that drive *illness behaviors* (guarding behavior, hyperalgesia, loss of appetite), physiologic changes such as fever and activation of hypothalamic- pituitary-adrenal system, and cytochemical changes in central neurons. Immune defense after intraperitoneal injections of agents such as lipopolysaccharide causes release of interleukin-1b (IL) or other cytokines such as tumor necrosis factor in the affected tissue, that in turn stimulate paraneurons along the vagus to activate visceral sensory fibers via direct synapses. Subdiaphragmatic

vagotomy completely eliminates the afferent branch of these powerful reflexes, so that all of the central neural cytochemical, physiologic, and behavioral responses except for increased corticosterone are interrupted. This type of experiment shows the importance of the vagus nerve pathway for cytokine-brain communications (27,175,176). When the vagus is intact, it is a conduit for afferent information that has profound effects on pain perceptions and behavioral reactions that in turn affect peripheral tissues. For somatic nerves outside the territory of the vagus nerve, nerve-associated lymphoid tissue can respond to inflammation and then affect nociceptor activity via release of modulators such as IL-1b (177).

Neuroendocrine Reflexes

Tissue injury also induces neuroendocrine responses that feed back to modulate the sensitivity of primary afferent neurons. For example, stress induces release of corticotropin-releasing factor and corticosterone reduces nociceptor sensitivity, as seen during stress-induced analgesia (32). Similarly, increased systemic amounts of opioids and other antinociceptive factors can inhibit activity in nociceptive pathways at central sites and via peripheral opioid receptors. It has been demonstrated that the phospholipid- and calcium- binding protein, annexin I, blocks the phospholipase A_2 pathway and the production of arachidonic acid metabolites such as prostaglandin E_2 and leukotriene B_4 (178). That modulation inhibits the actions of inflammatory mediators such as bradykinin-induced increases in prostaglandin E_2. In addition to inhibitory feedback neuroendocrine reflex modulation of pain, also endocrine enhancement of pain may occur, as during chronic inflammatory conditions, that may elevate systemic NGF (179).

Tissue Specificity of Nociception

The specificity of nociceptive innervation is reviewed here, with emphasis on nerve pathways, types of primary afferent neurons, and adequate stimuli per organ system. The sensory and protective requirements of skin are different from those of muscle or vasculature or gastrointestinal tract or urogenital system or teeth or other tissues, because each tissue has its own types of low and high threshold innervation, adequate natural stimuli, and responses to inflammation. In all cases, there are polymodal receptors with different properties from the specific nociceptors and different functions for different tissues. We know more about skin and joints than some other tissues, because they have been particularly well studied in animal models, but the 1990s have seen many advances in understanding other tissues as indicated throughout this book. In addition to the specific nociceptors and the polymodal receptors, numerous silent nociceptors exist that also are only responsive to experimental stimulation during inflammation (43,164). The polymodal receptors and silent nociceptors have critical importance for persistent inflammatory and neuropathic pain, as described in Peripheral Mechanisms of Persistent Pain, later in this chapter.

Microneurographic recordings from awake humans have given ample evidence that all the general nociceptive properties documented in animals from rat, to cat, to monkey also occur in humans after mechanical, thermal, chemical, or electrical stimulation (180,181). However, some species differences exist in the proportions of each type of nociceptor in particular organs, and there must be some variations within a species that contribute to individual differences in pain threshold and tolerance. Much greater details on the specific nociceptive innervation of skin, joints, muscle, bone, viscera, blood vessels, teeth, temporomandibular joint, and regional pain are considered in the chapters specifically devoted to those areas. Some of the differences in innervation of skin, muscle, and viscera are demonstrated by the different proportions of substance P, calcitonin gene–related peptide (CGRP), and somatostatinlike immunoreactivity of sensory cell bodies labeled by retrograde transport from the saphenous nerve, gastrocnemius nerve, or splanchnic nerve (64) and showing that neuropathic injury affects different sensory neuropeptide subgroups depending on the type of nerve.

Most nociceptive afferent units in uninflamed tissue conduct impulses in the A-d or C-fiber range, although for each type of myelinated nociceptor there are some that conduct up to 50 M per sec, which is well into the A-b range. Some of the nociceptors respond only to intense forms of mechanical stimuli and are known as *mechanical nociceptors*, many of the cutaneous receptors respond to noxious mechanical and heat stimuli and are known as *mechanoheat nociceptors*, and some A-d fibers respond only to intense heat stimuli, called *heat nociceptors*, or to intense cold stimuli, called *cold nociceptors*. Those that respond to noxious mechanical, thermal, and chemical stimuli were initially called *polymodal nociceptors* or, more recently, *polymodal receptors*, (23,129) as discussed in Polymodal Receptors, later in this chapter. Acute nociceptors are characterized by their restricted receptive fields and their ability to respond differentially or exclusively to noxious stimulation. Some nociceptors respond to stimuli that are not noxious or perceived as painful, but are most effectively excited by stimuli in the noxious range. This is not unexpected, because their function is to provoke protective responses that need to be initiated before irreversible tissue damage has occurred. It is thus clear that the afferent units that signal acute tissue injury also signal levels of stimulation that only threaten such damage.

Cutaneous Nociceptors

Skin, subcutaneous tissue, and fascia are supplied by all the categories of nociceptor described previously, with important differences in the distribution and subgroups found in glabrous skin compared with hairy skin (see Fig. 3-8). A-d myelinated mechanical nociceptors, also referred to as *high-threshold mechanoreceptors*, respond only to moderately intense or noxious mechanical stimuli; they do not respond to heat or algesic chemicals. They have been demonstrated in the skin of the body and face of the cat and monkey and in the human forearm (see Fig. 3-22 and Fig. 3-23) (163). They terminate in the epidermis close to the basal keratinocytes (84). Their receptive fields consist of collections of from 3 to 20 discrete spots, each with an area of less than 1 mm^3. These are interspersed among regions unresponsive to equivalent stimuli and are distributed over areas ranging from 1 cm^2 to 8 cm^2 on the body surface and 1 mm^2 to 2 mm^2 on the face. Their stimulus thresholds are 5 to 1,000 times higher than those of the various low-threshold mechanoreceptors. In the absence of stimulation, these receptors are silent, although repeated stimulation leads to a slow background firing that is important for activating central hyperalgesia mechanisms (182). Most high-threshold mechanoreceptor units have axons that conduct in the range of A- d fibers (mean velocity of 15 m/s to 25 m/s, but wide range of 5 m/s to 50 m/s). It is clinically important that approximately 20% of cutaneous high-threshold mechanoreceptors supplying the skin also have receptive fields in the subcutaneous tissue, usually fascia (66,164).

The mechanoheat nociceptors include myelinated AMH fibers and unmyelinated CMH fibers (164). Two types of AMH fibers exist. Type I has high threshold levels of at least 50°C and usually greater than 53°C, with a mean conduction velocity of 30 M per s, and a maximum of 55 M per s. Type II AMH units have lower thresholds and slower conduction velocity (mean, 15 M/s). The CMH mechanoheat nociceptors have the lowest thresholds in the 38° to 50° C range, and their responses increase with stimulus intensity over that temperature range, which includes the pain threshold range for humans. The AMH and CMH fibers have an important role in coding pain intensity.

Some exclusively thermoreceptive nociceptors have been described (163). The cold nociceptors are insensitive to noxious mechanical stimuli and A- and C-caliber groups have been described. They typically are silent over the temperature ranges that excite low-threshold cold receptors. Much of the response to noxious cold stimulation of skin appears to come from vascular receptors, based on ability of local circulating anesthetic to block that pain in humans (164,183). Specific heat nociceptors that have been described are insensitive to mechanical stimulation under normal healthy conditions.

Finally, polymodal nociceptors have variable responses over a range of chemical, mechanical, and thermal noxious stimuli, and they make up a majority of the fibers in many peripheral nerves. They are characterized by their responsiveness to intense mechanical (greater than 1 g), thermal (maximal firing range, 45° to 53°C) and chemical stimuli. Their receptive fields comprise one to two spots in the nonprimates that have been studied, but may be much larger in humans, suggesting extensive peripheral branching (6).

Data from the 1980s and 1990s confirm the earlier suggestion by Zottermann and others that both A-d and C fibers are essential for transient pain (184). The wealth of more recent experiments confirms the century-old concept that brief noxious stimulation to the skin with a pinprick or application of brief noxious heat provokes a double pain response: a fast first pain that has a pricking quality and lasts less than 50 milliseconds, followed by a painless interval of 1 second or longer, after which a slow second pain occurs that has a burning quality and lasts for 1 second or longer. It has long been established that the first pain is mediated by A-d fibers and the second pain by C fibers, and that the double pain response is most easily elicited in the upper and lower limbs and the anterior wall of the trunk below T-3.

The A-d group in skin is mainly specialized for detecting dangerous mechanical or thermal stresses and for triggering a rapid nociceptive response and protective reflexes. The C-polymodal nociceptors also respond to strong mechanical, thermal, and chemical stimuli and are sensitized by chemical agents released in damaged or inflamed skin. Therefore, in addition to reinforcing the immediate response of the A-d fibers to mechanical or thermal stress, the C-polymodal fibers signal the presence of damaged or inflamed tissue, and they contribute to guarding behavior to promotion of healing. The sensitivity of all classes of nociceptor increase following mild injury, and this is a factor in producing primary hyperalgesia, defined previously.

Finally, there have been suggestions that the sensation of itch is simply a different pattern of signals from neurons that can otherwise signal pain (164). However, some specific itch receptors have been identified that react to histamine stimulation of human skin (185).

Noncutaneous Integument

Most of the mucosa of the mouth, nasopharynx and its sinuses (including the middle ear), and mucous membrane of the larynx, upper trachea, and the anal canal are sites of pain consequent to noxious stimulation in the form of extreme cold or heat, chemical, or mechanical stimuli. A high proportion of the nociceptive innervation is of the polymodal receptor type, so inflammation significantly lowers the pain threshold. The oral and nasal mucous membranes have a dense sensory innervation, with a high incidence of polymodal receptors and many fine intraepithelial endings (186,187).

The cornea is innervated by A-d and C fibers that contribute fine axonal terminals that respond readily to mechanical, thermal, and chemical stimuli and can be sensitized by heating (188). Most have characteristics of polymodal receptors. Thus, they are well suited for providing information about potential damaging conditions and are presumably responsible for triggering reflex reactions, such as blinking and tear secretion, as well as transmitting nociceptive impulses, which produce the excruciating pain characteristic of corneal inflammation or injury. Those responses are eliminated in experimental animals by capsaicin treatment, and loss of the blink reflex is the standard indicator of capsaicin denervation in the adult. Trophic efferent actions of corneal polymodal innervation is shown by the persistent keratitis in capsaicin-denervated rats (189).

Other special integument regions, such as tympanic membrane, nails, and external genitalia, have sensory innervation with a high proportion of the polymodal receptors and distinctive pain characteristics (23,60,129).

Visceral Nociceptors

It has long been widely recognized that stimuli that damage skin and deep somatic structures produce pain, but when they are applied to the viscera they usually do not provoke pain. However, Cervero has pointed out that typical cutaneous mechanical or thermal stimuli are not adequate stimuli for viscera, and that one must choose natural stimuli, such as increased biliary pressure, to detect specific nociception in viscera (190) (Fig. 3-26). All of the abdominal and thoracic viscera have afferent innervation associated with parasympathetic or sympathetic nerves, participating in reflex control of cardiopulmonary, gastrointestinal, and genitourinary functions, and changes caused by these reflexes are not perceived. However, when viscera are distended or inflamed, as in the extensive research of the last decade on colorectal pain (191), vaginal and uterine pain (192), or bladder inflammation (193), sophisticated polymodal nociceptive mechanisms are detected.

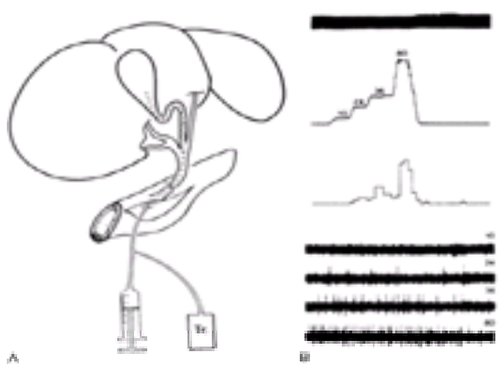


Figure 3-26. Demonstration of the effect of increasing the biliary pressure on high-threshold biliary afferents. **A:** One method of mechanical stimulation of the biliary system. A catheter is inserted through the major duodenal papilla to cannulate the common bile duct, and a ligature is placed around the bile duct to fix the catheter in position. The catheter is connected to a transducer (Tr) and to a syringe for the injection of warm saline into the biliary system. **B:** The response of one high-threshold biliary afferent to increasing biliary pressure. From top to bottom are shown blood pressure, biliary pressure (with numeric values), rate of firing of the afferent, and a recording of electrical activity at different biliary pressures. Activity begins to appear at higher pressures, which evoke transient increases in systemic blood pressure. (From Cervero F. Afferent activity evoked by natural stimulation of the biliary system in the ferret. *Pain* 1982;13:137–151, with permission.)

In general, the afferent fibers from the thoracic and abdominal viscera, except those from the pelvis, run in association with sympathetic fibers. Although the range of fiber size is comparable with that of cutaneous fibers, a considerably higher proportion of C fibers to A fibers exists, with a ratio of approximately 10:1 rather than the 2:1 that is found in cutaneous nerves. Visceral afferents constitute less than 10% of afferent fibers in dorsal roots. However, myelinated and unmyelinated visceral afferents ramify so extensively that there is great overlap between the fields of adjacent dorsal roots. A much larger proportion of the visceral afferents have polymodal receptor properties than is found for cutaneous afferents (23,129,194).

Cardiac. It has long been established that reversible ischemia of ventricular muscle by occlusion of the coronary artery produces pain in humans and in animals via A-d and C visceral afferent fibers that accompany the sympathetic nerves to the heart (195,196). Single-unit recording from the rami communicantes or dorsal roots of sympathetic afferents has shown that activity of A-d and C fibers increases significantly during coronary occlusion. The mechanosensitivity of some slowly responding A-d and C fibers is involved with cardiovascular reflexes. The faster-responding C fibers are chemonociceptors that can be activated by serotonin, histamine, bradykinin, acids, and prostaglandins. It has been suggested that angina results from the combined stimulation of bradykinin and prostaglandins on cardiac polymodal receptors (196).

Respiratory. In the lungs, two types of receptors have been described that probably have nociceptive functions: the type J receptors, with C afferents, and the *lung-irritant receptors*, with afferents in the A-d range, all running in the vagus nerve (197). The type J receptors are located in the interstitial space close to the capillaries, whereas the lung-irritant receptors are in the epithelial lining of the lung and its airways. These are activated by a variety of stimuli that produce mechanical distortion within the lung, such as pulmonary congestion, microembolism, atelectasis, and pneumothorax, and by chemical irritants. The peptide contents of the visceral sensory fibers in lung and airways and their responses to inflammatory mediators suggest that they are in the polymodal receptor category of nociceptor (198).

Gastrointestinal. The gastrointestinal tract has slowly adapting and rapidly adapting mechanoreceptors and chemoreceptors. Sensory impulses from the upper two-thirds of the esophagus are carried by A-d and C fibers in the vagus, whereas in the lower one-third, the afferent fibers travel in sympathetic nerves and enter the cord at T5–8 inclusive (see Chapter 60 and Chapter 65). The stomach, small intestine, and large intestine as far as the splenic flexure are supplied by sympathetic afferents that enter the spinal cord between T-(5)6 and L-2 inclusive. The primary afferents that supply the descending colon and rectum pass through the pelvic nerves and enter the spinal cord via ventral and some dorsal roots of S2–4. Mechanoreceptors of A-d and C fibers are found in smooth muscles of the hollow viscera. Morrison has described splanchnic afferents whose receptive fields contain up to eight punctate mechanosensitive sites distributed along walls of the viscera. They responded not only to light mechanical stimuli but also to tension applied to the peritoneum, to smooth muscle contraction, and to visceral distension. C-polymodal afferents with multiple spotlike receptive fields in the mucosal lining of the rectum and perhaps other parts of the gastrointestinal tract have been found with polymodal properties. For reviews of gastrointestinal and abdominal visceral sensory functions, see Cervero and Morrison (199), Koltzenburg and McMahon (193), and Gebhart (191,194).

Biliary. The gallbladder and bile ducts are supplied by splanchnic afferent units excited by distension and with small receptive fields. Cervero (200) used controlled pressure stimulation to distend the gallbladder and ducts and noted that there were two distinct types of units: low-threshold and high-threshold fibers. The high-threshold groups required pressure in excess of 25 mm Hg, as is likely to occur when obstruction exists in the ductal system, and these responses were accompanied by reflex vascular changes (Fig. 3-26).

Urinary. Visceral afferents that supply the kidney travel via sympathetic nerves and enter the spinal cord at T-10–L-2. Some of these have a nociceptive function because distension of the fascia of the kidney, irritation of distension of the kidney pelvis, or distension of the ureter (kidney stone) causes pain, and extensive peptidergic sensory innervation of kidney and ureter occurs (201). The urinary bladder is supplied by C and A-d fibers that are sensitive to stretch and contraction, some of them passing through the lumbar and sacral splanchnic nerves and others passing through the pelvic nerves (193). As for other viscera, rapid distension, contraction, or pressure of the kidney, ureters, or bladder causes severe pain. The involvement of polymodal receptors in bladder pain is indicated by the peptide

content of bladder afferents and their responses to inflammatory mediators (193).

Peritoneal. Lipopolysaccharide or inflammatory challenge to the peritoneal cavity causes pain and causes immunocytes to release IL-1b. If experimental animals have received a subdiaphragm vagotomy, the pain behavior is reduced, showing involvement of vagal afferents in initiating pain and illness behavior via the nucleus tractus solitarius (27).

Intraabdominal Solid Organs. The liver is supplied with vagal afferents within the parenchyma or along the hepatic arterial system that are primarily concerned with regulating osmotic pressure, glucose concentration, and temperature of the organ. However, they also respond to cytokines such as IL-1b that are produced by the resident immunocytes or by the vagal paraganglia during an immune response (27), and thereby trigger pain-related physiologic responses via their connections with the nucleus tractus solitarius. In addition, afferents that travel via sympathetic nerves innervate the capsule of the liver, and those fibers initiate pain in response to distension of the organ. Similarly, the spleen and the pancreas are innervated by afferents that travel in the sympathetic nerves and that innervate the capsules of the organs and their blood vessels and ductal systems. These mechanoreceptors, like those supplying the other viscera, normally have a reflex function, but in the presence of inflammation their threshold is greatly reduced and their activation causes pain. The sensitivity of visceral afferents from the vagus nerve to inflammatory mediators or to cytokines released by immunocytes in the solid viscera contributes significantly to the quality of pain from these organs (27).

Reproductive Systems

The reproductive systems include integument structures and deeper visceral organs that have complex innervation by visceral, somatic, and autonomic nerves. Those afferents travel in multiple peripheral nerves to enter the CNS through many dorsal roots, and they have extensive divergence of their central arbors, to give a diffuse somatosensory system that is integrated with autonomic and endocrine information (129, 192, 202, 203 and 204). For example, nociceptive and polymodal afferents in women have pathways via (a) the pudendal nerve projecting via L-6–S-2 (for perineal structures), (b) the pelvic nerve and plexuses via S2–4 (for cervix and lower uterine region), (c) the thoracolumbar splanchnic nerves and the cervical, uterine, and inferior hypogastric plexuses and nerves (for upper vagina, cervix, uterine body, inner third of the fallopian tubes and ligaments) that travel via the hypergastric plexus, through the sympathetic chain and then into dorsal roots T-10–L-1, and (d) afferents from the ovary and distal fallopian tube that enter the sympathetic chain at L-4 and then the spinal cord at T9–10 (Fig. 3-27). With increasing study of individual afferents, the richly detailed stimulus characteristics and polymodal properties of these visceral afferents are becoming apparent (23, 129, 192). The mechanisms of acute reproductive pain are becoming clear, but those for chronic pelvic pain have not usually correlated with specific peripheral pathology, suggesting the importance of complex central mechanisms (204) and neuroimmune reflexes via the vagus nerve (27).

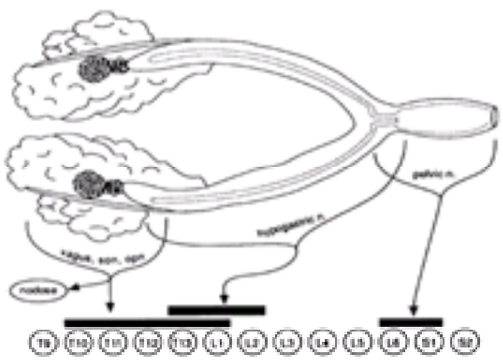


Figure 3-27. Summary of the sensory afferent innervation of female internal reproductive organs in the rat. The upper part of the figure is a diagram of, from left to right, the ovary, oviduct, ovarian ligament, and surrounding fat pads, the uterine horn, cervix, and vaginal canal. The middle part of the figure shows the nerves through which afferent fibers travel from different parts of the reproductive tract to reach nodose and dorsal root ganglia shown at the bottom of the figure. Note overlap of hypogastric and pelvic nerve innervation of the cervix so that primary afferent input from this region enters through two separated sets of dorsal root ganglia (T-13–L-2 and L-6–S-1). (son, superior ovarian nerve; opn, ovarian plexus nerve.) (From Berkley KJ, Hubscher CH. Visceral and somatic sensory tracks through the neuraxis and their relation to pain: lessons from the rat female reproductive system. In: Gebhart GF. *Visceral pain. Progress in pain research and management*. Vol 5. Seattle: IASP Press, 1995:195–216, with permission.)

Deep Somatic Tissues

Skeletal Muscle and Tendon. The stretch receptors of muscle comprise only approximately 25% of the sensory innervation, and the other 75% consists of free endings in fascia of the muscles, between muscle fibers, and in the walls of blood vessels and tendons (see Fig. 3-8) (69, 205). These endings are supplied by thin A-d myelinated axons (group III) and unmyelinated C fibers (group IV). After losing their myelination, the terminal branches of the A-d fibers may extend 1 mm, supplying a field as large as 25 mm × 200 mm. A majority of them respond to inflammatory mediators and also to innocuous to noxious pressure and thermal stimuli and are therefore clearly polymodal receptors (70). They also can be activated by muscle stretch or contraction. Approximately 80% of the C fibers are polymodal (70), but their threshold to mechanical stimuli is higher than that of the A fibers, their receptive fields are small areas within muscle or tendon, adaptation is slow, and few respond to stretch and none to contraction.

Joints. Joints are usually supplied by two types of nerves: articular branches derived directly from major nerves that supply the joint exclusively, and accessory nerves that are short branches from nerves supplying the muscles near or surrounding the joint. The large (group I) and medium (group II) A fibers terminate in mechanoreceptive endings that detect the torque that develops as a joint is extended, flexed, or rotated to the extreme of its range. Most of the A-d (group III) and all of the C fibers (group IV) end as free nerve endings that form a widespread plexus in the joint capsule, ligament, fat pads, and adventitia of blood vessels that supply the joint. The detailed examination of joint innervation in normal and inflamed conditions has been one of the best model systems for understanding polymodal receptors and their functions, including identification of the properties of silent nociceptors, defining the complex variations in chemosensitivity of polymodal receptors, and showing sensitization of some group II thick myelinated fibers by inflammatory agents (44) (Fig. 3-28).

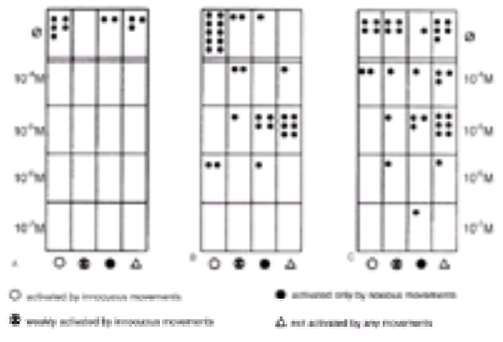


Figure 3-28. Sensitivity to capsaicin of a population of 84 fine afferents recorded from the knee joints of 24 cats. The units were classified based on conduction velocity [**(A)** group III with velocity > 11.3 m/s; **(B)** group III with velocity <11.3 m/s; **(C)** group IV] in regard to their responses to passive movements of the knee joint (left to right in each panel according to the key given at the bottom of the figure). The study included only units that were readily excited by a close intra-arterial bolus injection of 0.3-mL twice isotonic KCl solution. Units that did not respond to a 0.3-mL bolus injection of 10^{-4} M capsaicin were classified as unresponsive (uppermost row in each panel). Notice that many group III fibers with conduction velocity slower than 11.3 m/s were responsive. (From Schmidt RF. The articular polymodal nociceptor in health and disease. In: Kumazawa T, ed. *The polymodal receptor—a gateway to pathological pain. Progress in brain research*. Vol 113. Amsterdam: Elsevier, 1996:53–81; as modified from data in Herbert MK, Schmidt RF. Activation of normal and inflamed fine articular afferent units by serotonin. *Pain* 1992;50:79–88.)

Bone. Among the deep somatic structures, periosteum of bone is a frequent site of pain. Bone is a dynamic tissue capable of responses to injury, stress, and metabolism, and it has sensory innervation that responds to external stimuli and to internal pressure. The periosteum receives nerve endings of thinly myelinated A-d and unmyelinated C fibers, the terminals of which form a plexus that is especially extensive in the periosteum of long bones and that mostly contains neuropeptide-rich polymodal receptors. In the bone, nerve fibers run along with blood vessels in the haversian canals and are mostly vasomotor. The cancellous portion of the bone also receives free nerve endings of C and A-d fibers that are nociceptors, whereas the cortex and marrow of the bone receive mostly vasomotor fibers and normally are not pain sensitive (206).

Teeth and Periodontal Ligament. Teeth are richly innervated by C, A-d, and A-b fibers that are primarily nociceptive, whereas periodontal ligament has both a nociceptive innervation and an elaborate set of Ruffini mechanoreceptors that provide the tooth touch sensitivity, as described in Chapter 50 and several reviews (207,208 and 209). The sharp acute pain from an injured tooth depends on fast A-d and A-b fibers that terminate in dentin and adjacent pulp, whereas the more diffuse pain of toothache depends mainly on capsaicin-sensitive polymodal C and slow A-d fibers in pulp reacting to pulpal damage and inflammatory mediators (209,210). There is also an important A-b innervation of teeth that has the lowest threshold. Those fibers have prepain and vibration-detection functions (211) as well as involvement in dentinal pain (208). Silent nociceptors also have been identified in tooth pulp (209). Much of the dense innervation of teeth is needed to protect against excessive forces that can crack enamel and dentin and to regulate pulpal blood flow and interstitial fluid pressure, in partnership with sympathetic fibers. The nerves in teeth are, therefore, mainly polymodal with important efferent regulatory functions in addition to their responses to injury and inflammation, as discussed in Chapter 50.

Blood Vessels, Meninges, and Pleura. Numerous primary afferents and especially polymodal receptors innervate the blood vessels in all tissues of the body and exert important control over vasodilation via neuropeptide release at arterioles and extravasation of plasma protein and cells at venules after injury. The major vessels of the meninges also receive important sensory innervation, and the trigeminal afferents to the dura have been shown to exhibit sensitization, suggesting their importance for headache pain (212). Many of the nerve endings along the transverse sinus within the dura were found to be A-d or C-fiber mechanically sensitive units, of which subsets also responded to various agents, such as hypertonic sodium chloride, low pH, capsaicin, histamine, serotonin, bradykinin, or prostaglandin E_2, when applied directly or via intravascular infusion. The meningeal afferents also have been shown to induce degranulation of dural mast cells and could be important sources of intracranial neurogenic inflammation (213). The electrophysiologic properties of those meningeal afferents make them likely to respond to the normally innocuous head movements that become painful during conditions that cause headache. Finally, electrophysiologic and structural studies have found many A-d and C polymodal receptors in the pleura with widely distributed receptor arbors that have mechanical and chemical sensitivities as well as responses to noxious cold (214).

POLYMODAL RECEPTORS

Polymodal receptors, also called *polymodal nociceptors* or *neuroeffectors*, participate in regulation of tissue homeostasis, along with autonomic and endocrine systems, via efferent release of neuropeptides and afferent transport of cytokines and growth factors to inform the sensory cell body and CNS about tissue conditions. Organisms need specific nociceptors to detect tissue injury to elicit reflex escape for preservation of tissues and life, and the specific nociceptors that were discussed in the previous section are designed for that type of activity. The polymodal receptor system is quite different in that it interacts with many different cell types to monitor and facilitate local physiology and to shift neural behavior in ways that promote normal health, regeneration, and wound healing (Fig. 3-29). The reflex responses of polymodal receptors to changes in tissue chemistry (whether the minor shifts in efferent neurokine release during normal functions, or the dramatic changes in cytochemistry after injury and during inflammation) contribute to the tissue chemistry, for example, via release of proinflammatory peptides (CGRP, substance P) to cause neurogenic inflammation. Many of the mediators, such as capsaicin, neurotrophins, or inflammatory agents, that affect polymodal receptor function are discussed in Pharmacology and Modulation of Nociception, later in this chapter (Table 3-4,Table 3-5, and Table 3-6), as are the many local and circulating defense systems that amplify polymodal receptor responses to match the extent of injury.

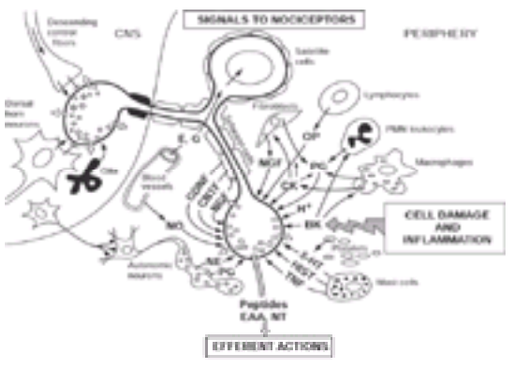


Figure 3-29. Diagram showing *some* of the peripheral cells and factors that interact with nociceptors via specific membrane receptors. Afferent signals to the neuron come from the indicated cells, all of which are affected by efferent release of neuropeptides, excitatory amino acids (EAA), or both and neurotransmitters from the neurons. Systemic hormones such as estrogen (E) or glucocorticoids (G) regulate neural function via receptors in the soma cytoplasm. In the central nervous system there are equally complex interactions with the central neurons and glia as well as with descending control fibers. (BK, bradykinin; CK, cytokines; CNTF, ciliary neurotrophic factor; GDNF, glial-derived neurotrophic factor; H+, protons; Hist, histamine; NE, norepinephrine; NGF, nerve growth factor; NO, nitric oxide; OP, opioid peptides; PG, prostaglandins; TNF, tumor necrosis factor; 5-HT, serotonin.)

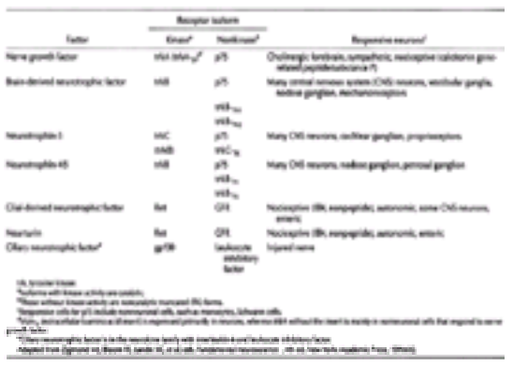
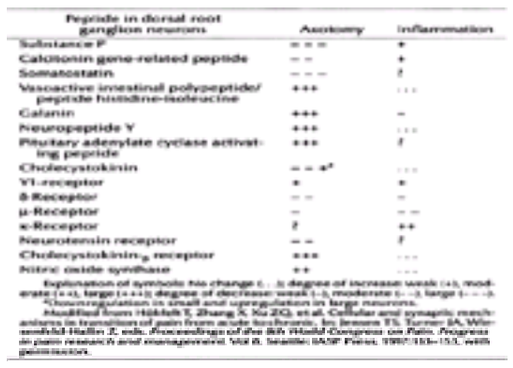


TABLE 3-5. Neurotrophin growth factors and receptors



Peptide in dorsal root ganglion neurons	Axotomy	Inflammation
Substance P	– – –	+
Calcitonin gene-related peptide	– –	+
Somatostatin	– – –	↑
Vasoactive intestinal polypeptide/ peptide histidine-isoleucine	+++	. . .
Galanin	+++	–
Neuropeptide Y	+++	. . .
Pituitary adenylate cyclase activating peptide	+++	↑
Cholecystokinin	– – +*	. . .
V1-receptor	+	+
δ-Receptor	– –	–
μ-Receptor	–	– –
κ-Receptor	↑	++
Neurotensin receptor	– –	↑
Cholecystokinin$_B$ receptor	+++	. . .
Nitric oxide synthase	++	. . .

Explanation of symbols: no change (. . .); degree of increase: weak (+), moderate (++), large (+++); degree of decrease: weak (–), moderate (– –), large (– – –).
*Downregulation in small and upregulation in large neurons.
Modified from Hökfelt T, Zhang X, Xu ZQ, et al. Cellular and synaptic mechanisms in transition of pain from acute to chronic. In: Jensen TS, Turner JA, Wiesenfeld-Hallin Z, eds. *Proceedings of the 8th World Congress on Pain. Progress in pain research and management.* Vol 8. Seattle: IASP Press; 1997:113–153. with permission.

TABLE 3-6. Sensory cytochemical changes with inflammation versus axotomy

The polymodal receptors ordinarily function to prevent or reduce injury and enhance healing, but under some pathologic conditions they may enhance pain and pathology, especially related to chronic pain as described in detail by Kumazawa and colleagues (23,129). The key features of polymodal receptors are (a) widely branched preterminal axons and dispersed endings in the target tissue, (b) wide variety of adequate stimuli, (c) wide dynamic range from nonnoxious to noxious thresholds, (d) numerous efferent (neuroeffector) functions that promote regulation of tissue homeostasis, inflammation, and wound healing via release of neuropeptides, and (e) an ability to shift among different functional phenotypes depending on the conditions of the tissue. Although much research since 1970 has documented the functional flexibility of these neurons, it is only during the 1990s that their close partnership with other defense systems of the body has been appreciated (23,27,129).

The polymodal receptor is especially designed for titrating its electrophysiologic and cytochemical signaling through sensitization or desensitization to mirror the local conditions in the peripheral tissues, thus forming a surveillance system that informs the CNS about the health of the body, while acting to promote survival and healing. Proportions and properties of polymodal receptors in different tissues (e.g., viscera, skin, joints, and muscle) are different (Fig. 3-30) and match the homeostatic and defense needs of each region. In many ways, the polymodal receptor system should be considered to be a dispersed peripheral organ that normally promotes tissue functions but that requisitions altered phenotype in relation to the degree of pathology or healing.

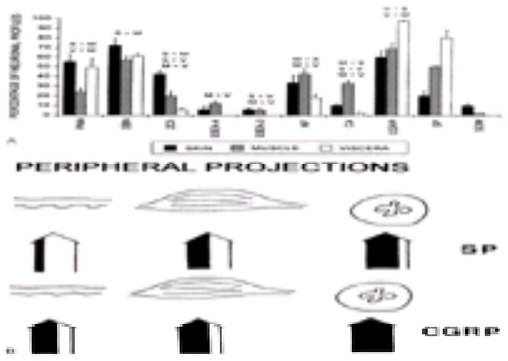


Figure 3-30. **A:** A summary histogram of mean percentages of skin (saphenous nerve), muscle (gastrocnemius nerve), or visceral (splanchnic nerve) afferent neuronal profiles in rat that were labeled by a range of antibodies. Error bars indicate standard error of the mean. Statistical differences and the directions of those differences are shown above the bars for each marker (too few rats for substance P and somatostatin for statistical significance). Specific antibodies identified lectins: PNA (peanut agglutinin), SBA (soybean agglutinin); oligosaccharides: 2C5 (lactoseries), SSEA-3, SSEA-4 (globoseries); neurofilaments (NF); carbonic anhydrase (CA); and neuropeptides: CGRP (calcitonin gene-related peptide), SP (substance P), and SOM (somatostatin). From Perry MJ, Lawson SN. Differences in expression of oligosaccharides, neuropeptides, carbonic anhydrase and neurofilament in rat primary afferent neurons retrogradely labeled via skin, muscle, or visceral nerves. *Neuroscience* 1998;85:293–310, with permission. **B:** Cartoons represent the proportions of dorsal root ganglion neurons of rat that project to skin, muscle, or viscera, as in **A**. The total width of the arrow in each case represents 100% of the retrogradely labeled dorsal root ganglion counted per nerve, whereas the proportion of the width of the arrow filled in black indicates the retrogradely labeled profiles that showed detectable substance P-like or CGRP-like immunoreactivity. Note that neuropeptide content of splanchnic visceral afferent neurons was greater than for muscle afferents, skin had the least proportion of neuropeptide-rich afferents, and higher proportions of neurons projecting to all tissues expressed CGRP-like than substance P-like immunoreactivity. (From Lawson SN. Peptides and cutaneous polymodal nociceptor neurons. In: Kumazawa T, ed. *The polymodal receptor—a gateway to pathological pain. Progress in brain research*. Vol 113. Amsterdam: Elsevier, 1996:369–385, with permission.)

The polymodal receptors were first identified electrophysiologically in skin by their high thresholds to mechanical and heat stimuli plus their sensitivity to algesic chemicals (5). They have since been studied extensively in skeletal muscle, joints, colon, urinary bladder, cornea, and especially in the scrotum, with other investigations in dura, perineurium, vasculature, dental tissues, gastrointestinal tract, gallbladder, andurogenital organs, as described in detail by Kumazawa, Perl, Handwerker, Schmidt, Mense, Gebhart, Mizumura, Kumazawa, and others (23,66,129). The proportion of A- and C-polymodal receptors varies among species and tissues. For example, almost all C fibers in skin are polymodal receptors in humans, but only approximately 70% of cutaneous C fibers are polymodal receptors in rabbits and rats, and only 35% to 40% in cats. By contrast, 90% of the spermatic nerve A and C fibers are polymodal receptors (23,129). Even the articular A-b (group II) fibers sensitize and have some polymodal properties in addition to the large and small A-d group III fibers and the unmyelinated group IV (44).

Within the C-fiber (group IV) axons, a variety of polymodal receptor subtypes exist with different algesic sensitivities and temperatures. For example, some cutaneous C-polymodal receptors are especially sensitive to histamine, whereas others are not (66), and in skeletal muscle or joints, individual units can be especially sensitive to bradykinin but not to serotonin and potassium ions, whereas others are responsive all three agents, and still others are mechanically sensitive and respond to one or more of the algesic compounds (44,70). In addition, fast A-d (group III) fibers differ from slower A-d fibers. Complex subcategories of algesic and mechanical sensitivities exist (44) (see Fig. 3-28), with capsaicin sensitivity demonstrated for the slower A-d fibers that innervate joints (44) and teeth (210). Finally, in the A and C groups there are some polymodal receptors that are mechanically insensitive in healthy tissue, but can be activated by algesic agents, thus providing innervation that only signals to the CNS during inflammation or pathologic conditions (44).

The polymodal receptor neurons release neuropeptides to enhance the functions of many different cells that are important for tissue defense and repair functions, including arterioles (vasodilation), venules (extravasation of plasma proteins and cells), mast cells (histamine release), macrophages (phagocytosis), monocytes (cytokine release), neutrophils (chemotaxis), T lymphocytes (proliferation and cytokine release), fibroblasts (proliferation and scar formation), and visceral and cardiac smooth muscle (contraction or relaxation) (see Fig. 3-29). In addition, they have powerful effects on central neurons (hyperexcitation), as well as on peripheral nerve fibers, both autonomic and sensory, and can have autocrine effects on their own peripheral endings (23,129). These actions are used to coordinate and amplify local inflammatory events at sites of tissue injury and in neighboring regions via the axon reflex.

PHARMACOLOGY AND MODULATION OF NOCICEPTION

Molecular Pharmacology

The phenomenal progress during the 1990s in understanding neurochemistry, neuropharmacology, membrane receptor and ion channel mechanisms, signal transduction, neuronal gene regulation, and neuroplasticity make it clear that all neurons, including peripheral nociceptors, use an enormous molecular repertoire to detect changes in their environment and to respond appropriately. The peripheral endings of nociceptive neurons are continually communicating with inflammatory, vascular, immune, and local cells, as well as analyzing and responding to tissue chemistry (pH, K^+, ATP, cell breakdown products), extracellular matrix, their own products or those of other neurons, and endocrine or other systemic signals. The sensory endings also synthesize, transport, and release neuropeptides and neurotransmitters by specific exocytotic molecular mechanisms that in turn affect their neighbors, with subsequent cellular reactions, alterations in the local environment, and new conditions that further affect the nerve endings. This interactive cytochemical conversation is in constant flux and can operate at different levels depending on the tissue conditions. Of course, the central endings of the sensory neurons are also affecting and responding to the cells of the CNS using similar mechanisms, but via a somewhat different set of agents and membrane receptors and channels. Finally, the primary afferent neurons are also in molecular communication with their different supporting cell types, such as terminal Schwann cells in the periphery, Schwann cells (myelinating or unmyelinated) along their peripheral axons, satellite cells of the ganglion, and CNS glia along their central branches. Each of these different interactions depends on specific mechanisms of signal detection, evaluation, and response, all of which offer possible targets for new drugs to manage pain by blocking excitatory mechanisms or enhancing the inhibitory ones (28,33,37,41,127,215,216).

This section gives a brief overview of signal detection and signal production mechanisms. It also reviews the importance of pharmacologic location, concentration,

timing, and plasticity for nociceptor and polymodal functions that is followed by a discussion of the varieties of nociceptor modulation (excitatory, inhibitory, sensitizing, desensitizing, facilitating, amplifying, or neuroprotective), and by a summary of modulating cells and autonomic and sensory interactions of some of the many ways that neurotrophin growth factors affect inflammation, nociception, and polymodal receptor plasticity. These mechanisms and their pharmacologic manipulation can only be touched on superficially here, and books by Hall (135), Hille (134), Wall and Melzack (21), Dickenson and Besson (26), Zigmond and colleagues (132), and Nolte (133) offer introductions to these topics.

Signal Detection

Membrane Detectors as First Messengers

Receptors. Extracellular agents for which specific receptor molecules have been found so far on nociceptor cell membranes include (a) endogenous chemicals (tissue breakdown products such as protons, ATP, or bradykinin), (b) arachidonic acid metabolites (membrane phospholipase-derived agents such as leukotriene B_4 and prostaglandin E_2), (c) exogenous chemicals (e.g., capsaicin and other vanilloid agents), (d) excitatory agents [glutamate, aspartate, g-aminobutyric acid (GABA), norepinephrine, ATP, histamine, and serotonin], (e) inhibitory agents (opioid peptides), (f) sensitizing agents (IL-1b or IL-6, histamine, serotonin, NGF), or (g) desensitizing agents (leukocyte inhibitory factor, interferon-g, and opioid peptides). Table 3-4 lists some of the specific receptors that have been identified so far, organized by type of ligand. Many of the receptors initiate ion flow after binding their ligand (ionotropic) and are a type of ion channel (see following discussion), whereas others convert extracellular stimuli to intracellular responses by G-protein–driven second messenger systems (metabotropic) or by trk mechanisms that induce a succession of protein phosphorylations (Fig. 3-31). The latter type is found for many growth factors such as the neurotrophin family, described in the following section. Many ligands have ionotropic and metabotropic receptors, and the more recently discovered ones have systematic abbreviations that are indicated by *X* for the ionotropic subtypes and by *Y* for metabotropic (e.g., the $P2X_{1\text{-}n}$ and $P2Y_{1\text{-}n}$ sets of receptors for ATP). However, the nomenclature is less systematic for many ligands discovered earlier; for example, ionotropic glutamate receptors include at least N-methyl- d-aspartate (NMDA)- $_{1,2}$, 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) ($GluR_{1\text{–}3}$) and kainate ($GluR_{4\text{–}7}$) receptors, each of which has distinct ion permeabilities and pharmacologic properties; whereas metabotropic glutamate receptors are designated $mGluR_{1\text{–}4}$ and induce effects via G proteins. For further details see current texts on pharmacology.

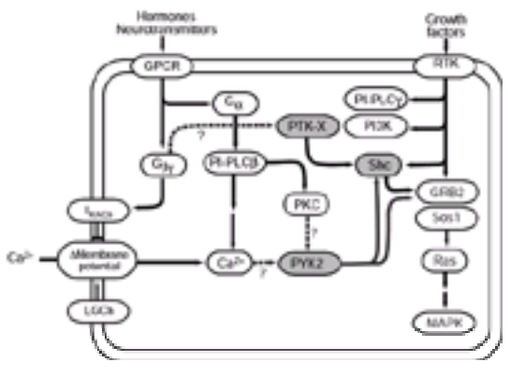


Figure 3-31. Cross-talk between G protein-coupled receptors (GPCR), ligand-gated ion channels (LGCh) and receptor protein tyrosine kinases (RTK). GPCRs, via activation of PTK-X or PYK2, can activate the mitogen-activated protein kinase (MAPK) pathway. LGChs, via an increase in [Ca^{2+}], may also activate PYK2. Note that the key *go-between* molecule is the adaptor protein Shc, which in turn can interact with growth factor receptor-binding protein 2 (GRB2)/son of sevenless (Sos1) to activate the MAPK pathway. Question marks indicate that the pathways of activation still need to be firmly established. (I_{KACh}, inwardly rectifying, acetylcholine-regulated potassium channel; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PI-PLC, phosphoinositide-specific phospholipase C.) (Adapted from Holz RW, Fisher SK. Synaptic transmission and cellular signaling: an overview. In: Siegel GJ, Agranoff BW, Albers RW, et al., eds. *Basic neurochemistry: molecular, cellular and medical aspects*, 6th ed. Philadelphia: Lippincott–Raven, 1999:191–212; as adapted from Bourne HR. Team blue sees red. *Nature* 1995;376:727–729, with permission.)

TABLE 3-4. Some factors that affect nociceptors via membrane receptors*a*

Ion Channels and Ion Transporters. The four main types of voltage-gated ion channels (sodium, potassium, chloride, and calcium) allow ions to flow down their electrochemical gradients when they are open, whereas the transporters actively pump ions against their gradient. The Na, K, and Cl channels induce changes in membrane potential when they are activated electrically, mechanically, or chemically. The altered membrane voltage then affects other voltage-sensitive (voltage-gated) molecules. Ion flow through calcium channels not only affects membrane potential, but also alters calcium concentration, thereby driving most intracellular responses to neuronal stimulation. Calcium is therefore the key transducer of membrane potential changes into specific cellular actions. For each type (*family*) of channel or transporter, many isoforms exist for different tissues and different activation mechanisms, voltages, or types of ion flow. Channel families can be divided into the voltage-gated channels, such as sodium, potassium, and calcium channels, and the ligand-gated ionotropic receptors, such as glycine, $GABA_A$, and glutamate-NMDA receptors. The cloning, pharmacologic analyses, and identified actions of each of the many members of each family of ion channels and their subunits are vast topics of increasing importance for understanding the subtleties of nociception and devising new antinociceptive drugs. Some of the important features of the voltage-gated channels for nociceptor function are summarized here.

Sodium channels, when open, permit the flow of sodium ions into the cell, thereby raising the membrane potential and bringing the neuron closer to its firing threshold. On axonal membranes their brief opening provides the initial positive phase of the all-or-none AP. However, at receptive or postsynaptic membranes they induce local excitatory potentials that extend for variable distances and times before dissipating, and they form the excitatory components of temporal and spatial summation. Neurons that respond to noxious stimulation of normal tissues primarily express the tetrodotoxin-sensitive types of sodium channels (TTXs), whereas inflammation induces the expression of a TTX-resistant variety (SNS/PN3) that is also prominent in the silent nociceptive fibers that are activated by inflammation. Because the lidocaine family of local anesthetics works mainly by blocking sodium channels that are TTX-sensitive, it is clearly important to find new agents that can block the TTX-resistant PN3 type that is so important in nerves responding to inflammation. Analysis of sodium channel subtypes and nociception is progressing rapidly, boosted by molecular and genetic techniques and the avalanche of genome information. For example, a second type of sodium channel (NaN) has been cloned that is preferentially downregulated after axotomy and whose molecular structure predicts it to be voltage dependent and TTX resistant (217).

Potassium channels allow passive flow of potassium ions out of the cell, and their delayed opening after onset of the AP is responsible for bringing axonal membrane potential back to a hyperpolarized negative level that causes a refractory period after each AP before the resting potential is restored. The duration of that afterhyperpolarization is regulated by a variety of potassium channels (134) and can shift its properties during inflammation (67). A large number of potassium channels exist, and they have great importance in controlling the excitability of the neurons during restoration of the resting potential. Many important regulators of nociceptor activity, such as inhibitory mu-opioids, act via interactions between their receptor G proteins and associated potassium channels (218), thereby driving

membrane potential away from threshold and reducing neural activity.

Virtually all cellular responses to ion flow and membrane potential changes involve altered cytoplasmic concentrations of calcium ions, via entry of extracellular calcium or release from intracellular calcium storage compartments. For example, docking of synaptic vesicles with the membrane to allow for exocytosis of neurotransmitters or neuropeptides requires a boost in the local Ca^{2+} concentration, as does the glutamate- or aspartate-driven neuroplasticity via the ionotropic NMDA receptor (134,172). In addition to the many functions of nociceptors that depend on calcium flux, the high-voltage P/Q-type of Ca channel has been implicated in responses of nociceptive neurons to persistent injury (219,220), and responses to substance P and CGRP involve increased Ca influx via voltage-gated Ca channels (221). These observations are just the tip of the iceberg concerning important regulation of and by calcium channels in nociceptor function and plasticity.

Work on ion transporters (molecules that actively pump ions against their electrochemical gradients) has found that membrane conductance is regulated in important ways by transporter activity (216,222) so that modulation of transporter function also could contribute to antinociceptive treatments. Some examples of ion transporters are the Na^+/K^+ pump, the Ca^{2+} pump, the Na^+/Ca^{2+} exchange, and the $Cl–/HCO^{3–}$ exchange (134,135).

Macromolecular Arrays. Most membrane receptors, ion channels, and associated enzymes are clustered and coregulated, as has been found for the NMDA excitatory amino acid receptor and NO synthase, MAP kinase signaling systems, targeting protein PSD-95 and other associated molecules (216,223). Similarly, a newly identified proton-gated ion channel (ASIC-1) appears to interact with other molecules for detection of acidosis by noncapsaicin-type nociceptors (224). Interactions of receptors, G proteins, and second messenger systems can integrate many signals into a single response or convert a single signal into multiple effects (Fig. 3-32). Differential expression of the component molecules and their regulation by growth factors and hormones adds enormous complexity to the ability of the membrane to integrate information and tailor responses to signals in sophisticated ways. Thus, antinociceptive drugs might indirectly target channels or receptors via inhibition of the associated molecules or their regulators.

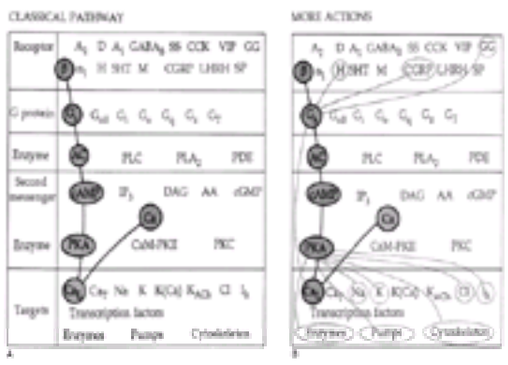


Figure 3-32. Signaling systems arranged as a menu showing at successive levels the abbreviated names of many receptors, G proteins, G-protein–coupled enzymes, second messengers, protein kinases, and target proteins. **A:** Menu filled in with the classical description of b-adrenergic action in the heart leading to the phosphorylation of l-type Ca channels and enhanced Ca^{2+} entry. **B:** A more complete description shows histamine (H), glucagon (CG), and CGRP receptors activating the same pathway, the Gs protein acting on Ca channels directly, and prokininogenase acting on many targets including six kinds of channels. (From Hille B. *Ionic channels of excitable membranes*, 2nd ed. Sunderland, MA: Sinauer Associates, 1992:191. After Hille B. Ionic channels: evolutionary origins and modern roles. *Q J Exp Physiol* 1989;74:785–804, with permission.)

Signal Transduction and Second Messengers. The ionotropic receptors have a conformational change after binding their ligand that then triggers a specific ion flow to produce a local cellular effect (see Fig. 3-31). For example, glutamate binding to the excitatory NMDA receptor causes Ca^{2+} flux into the cell at that site, that in turn initiates neuroplasticity via the protein kinase C-g signal pathway (225). The metabotropic receptors initially induce a conformational change in their associated G-protein structure that causes specific second messenger cascades for specific metabolic responses. Those second messengers include cAMP, cGMP, calcium ions, diacylglycerol, inositol triphosphate, arachidonic acid and its metabolites, and NO. The metabotropic receptors can also induce current flow indirectly by activating associated ion channels, as when the mu-opioid receptor and its G protein trigger potassium flow to inhibit neuronal firing (218). For the trk receptors, binding of the ligand triggers phosphorylation of the trk that then leads to a series of protein phosphorylations via multiple pathways (see Fig. 3-31). An interesting situation in nociception is that many signal cascades that are involved in the development of neuropathic pain funnel through the protein kinase C-gamma pathway. Thus, when protein kinase C-gamma is deleted from mice, neuropathic pain responses are inhibited or missing, even though there is still specific response to acute noxious stimuli (225).

Transcription Factors, the Third Messengers. The ultimate effect of signals that induce alterations in gene expression is the activation of transcription factors that then turn genes on or off. There has been much research during the 1990s of the functions of transcription factors such as c- *fos*, c-*jun*, and NFk B in driving nociceptor and dorsal horn plasticity. Nociceptors shift their functional and cytochemical phenotypes depending on conditions in their target tissue (or in the nerve, the ganglion, or the CNS), and those shifts require activation of transcription factors, as described in more detail by Hall (135) and others (132,133,171,226).

Signal Production

An important aspect of nociceptor function is the efferent delivery of neuropeptide and neurotransmitter signals to the peripheral tissue and to the CNS. This involves synthesis of the signal molecules, packaging into vesicles, targeting and delivery to the right region, regulation of the exocytosis location and timing, and reuptake and recycling. The elegant molecular details of exocytosis are now largely identified (132,135,153), and the importance of Ca^{2+} concentration for triggering the final merging of the vesicle and membrane is clear. The sophistication of signal vesicles was revealed by the demonstration that delta-opioid receptors are clustered inside neuropeptide-containing dense-core vesicles. Those receptors would only be exposed to the external opioid signals when the vesicle has merged with the membrane and so may only function briefly following exocytosis (227). The transient exposure and activity of some receptors reveal an additional complexity to receptor and signal production mechanisms.

Another kind of signaling involves NO. In addition to intracellular signaling (see Fig. 3-20C), it also has important extracellular signaling functions that are activity-dependent, short-lived, and local. NO diffuses readily from donor cells to nearby target cells, and it is a key intercellular regulator of neural, vascular, inflammatory, and immune defense reactions (157,159). In inflammatory pain, the actions of NO depend on the stages of inflammation and the cellular sources and targets. Levels of NO increase quickly in inflamed tissue with activation of the NO synthase enzyme and have complex actions. It is an important agent in sensory neuronal efferent regulation of vasodilation (e.g., in cerebral arteries) (228), so that at early stages of inflammation, neural and endothelial NO have important effects on blood flow and plasma extravasation. The peripheral actions of NO are mostly protective during the first few hours (facilitating blood flow, limiting excitotoxicity and scavenging reactive oxygen species) but become cytotoxic later (oxidative damage, inhibition of energy metabolism, DNA damage) (160). The exact balance of protective and toxic actions would depend on the severity and stages of inflammation and the available targets of NO. The importance of NO signal production is seen in the inhibition of neuropathic pain behavior in various animal models when NO is inhibited pharmacologically (229). The ongoing discharges of dorsal root ganglion neurons that occur after neuroma development in sciatic nerve in rats also appear to be regulated by NO, using mechanisms via signaling between satellite cells and injured neurons (158).

Signal Location, Concentration, Timing, and Plasticity

As is true for all pharmacologic agents, the location and concentration of the receptors and the duration of response are of critical importance. Differential targeting of molecules within the primary afferent neuron is exceedingly complex and specific. These cells can deliver subsets of signal-detection molecules to different regions, such as peripheral endings, axons, cell body, or central endings, or to smaller subregions, such as nodes of Ranvier. The local concentration can differ greatly, as for the 15-fold greater sodium channel density at nodes of Ranvier compared with unmyelinated axons (134), and can be affected in important ways by inflammation or nerve injury. For example, the TTX-resistant sodium channel PN3 expression decreases in large neurons while staying the same or increasing in small neurons affected by paw inflammation, whereas after axotomy the expression stays the same but there is an increased shipment of PN3 out into the axons (41). The complexity of pain pharmacology often includes opposite actions of an agent at different concentrations, as when NO potentiates prostaglandin actions at low concentration while having inhibitory actions at higher concentrations. In other cases, two different agents can affect each other's actions by interactions at the same

second messenger system downstream from their individual receptor binding, as with opioid and adenosine antinociception (161). For each signal, important issues of timing also exist, both for duration of agent activity and duration of neural response. For example, substance P is rapidly degraded in normal tissue by a specific endopeptidase enzyme, so that it is only active for a few minutes. However, if the neuropeptide CGRP is also present, the peptidase is blocked for approximately 30 minutes, thereby prolonging substance P action (230). Not only can the longevity of an agent vary greatly, but the neuronal responses differ depending on which receptors, channels, enzymes, and so forth are constituitively present or induced by inflammation.

Modulation of Nociception

In Table 3-4, we listed some of the types of factors that affect nociceptive peripheral endings via specific membrane receptors. Primary afferent neurons have interactions with other peripheral cells via release of neuropeptides, neurotransmitters, or neurotrophins, or via diffusion of arachidonic acid metabolites or NO to neighboring cells, and via uptake of growth factors, cytokines, and other signals. The nerve fibers are important participants in inflammation, immune responses, vascular regulation, and wound healing via neuroinflammatory, neuroimmune, neurovascular, neurofibroblastic, neuroleukocytic, and neuroendocrine interactions. Nociceptive fibers, and especially the polymodal receptors, are in constant chemical conversation with their neighbors, including some epithelial cells, fibroblasts, dendritic macrophages, mast cells, vascular endothelium, circulating monocytes, immunocytes, paraneurons, other sensory neurons, and Schwann cells. They also respond to signals from extracellular matrix, interstitial fluid and tissue chemistry, circulating agents, hormones, and invading pathogens. This information allows neural participation in coordinated cellular actions to reduce damage and facilitate repair.

The interactions between nociceptive neurons and other cells can be direct, via ligand-receptor mechanisms, or indirect, via an intervening cell that enhances or overrides tissue signals. For example, nociceptive neurons have IL-1 receptors and can respond directly to that cytokine, but the IL-1 also triggers NGF production by monocytes that further stimulate the neuron, or b-endorphin production by invading immunocytes that inhibit the primary afferent neurons (231). With indirect modulation, the intervening cell's amplification contributes to the cytokine portrait of the extent of tissue damage, whereas the inhibitory agents help protect the neurons from excitotoxicity. In addition to the paracrine signals from local and invading cells, important interactions occur with the endocrine and autonomic systems, whose participation and regulation of primary afferents contribute yet another indication of the extent and duration of tissue pathology.

Modulating Nociceptor Membrane Potential

Excitatory and Inhibitory Factors. The peripheral receptive endings of nociceptors do not conduct APs, but their integration of excitatory or inhibitory inputs to their sensory membrane determines whether there is enough summation of positive deflections in the membrane potential for the axon to exceed its depolarization threshold and generate a propagated AP. Depending on the molecular components of the ending and the factors in the extracellular space, the stimulus needed to reach the AP threshold may range from low to high. Excitatory factors that depolarize nociceptive endings at specific receptors include excitatory amino acids, acetylcholine, and ATP. In addition, thermal and polymodal nociceptors are activated by heat or vanilloid compounds at the VR1 receptor. Some of the inflammatory mediators, such as bradykinin, serotonin, NGF, or low pH, also directly excite some of the endings by directly shifting the potential closer to the AP threshold. Inhibitory agents include the opioid peptides whose receptors are linked to potassium channels and cause negative shifts in potential when the opioid receptor binding opens the potassium channels.

Sensitizing and Desensitizing Factors

Other factors induce molecular changes in the endings so that they are more easily (sensitized) or less easily (desensitized) excited. Those effects take minutes or hours to occur and effectively raise or lower the gain of the system. The neuronal membrane threshold remains standard, but the endings shift closer to that threshold when sensitized by inflammatory agents such as serotonin, histamine, prostaglandin, bradykinin, IL-1b, or NGF, or they are moved farther into the hyperpolarized range by factors such as leukocyte inhibitory factor, adenosine, or IL-6. These are mechanisms that help to match the responsiveness of the nociceptive endings to the conditions of their local environment, and the sensitizing and desensitizing agents are augmented or reduced by systemic factors such as gonadal or glucocorticoid steroids or hormones.

Neuroprotective Peptides

With prolonged injury or inflammation, some types of primary afferents increase synthesis of some neuropeptides such as galanin, neuropeptide Y, or vasoactive intestinal peptide that are thought to have neuroprotective functions, while downregulating others (232,233) (Table 3-6). The timing of those changes can be quite variable, as with the transient expression of galanin in large neurons compared with the prolonged increase (many months) in the smaller neurons after neuropathic injury. The neurons also increase production of peptide receptors for circulating agents such as neuropeptide Y (produced by the adrenal and by sympathetic fibers in response to stress), thus giving additional protection to that from its own altered peptide array. The targeting of receptors and detailed local actions at different sites along the neuron are quite sophisticated, as indicated by the concentration of the neuropeptide Y1 receptor at the cell body and the Y2 receptor at endings (232,233,233a).

Sensory-Sensory Interactions

Table 3-4 indicates that the sources of many of the ligands that affect nociceptor function are other nociceptive neurons or autocrine effects by the neuron on itself. These nociceptor-nociceptor interactions follow the exocytotic release of neuropeptides, neurotransmitters, or other agents from normal or injured nerve fibers. They can occur in the periphery following efferent APs (axon reflex or other mechanism; see Fig. 3-20A), along the nerve at sites of damage or neuritis, in the ganglion, or in the central root and dorsal horn. Evidence now exists that neuropeptide release by C fibers during a barrage passing through the ganglion can cause blockage of subsequent A-fiber activity (137), so that the nociceptor-nociceptor interactions during signal propagation in the periphery may be quite complex. That complexity extends into the central branches of the primary afferent in which inhibition of signaling in many terminal branches appears to be a fundamental and powerful mechanism for regulation of the incoming signal traffic (36,234). For some agents, such as CGRP, receptors have not been found on the nociceptive neurons, so that its release may only affect other neurons (or other cells, such as mast cells or vascular smooth muscle). For other agents that are released by the nociceptors (e.g., substance P, glutamate, glycine, GABA, acetylcholine, serotonin, ATP, bombesin, neuropeptide Y, and neurotrophins), receptors are also present and offer the possibility of autocrine regulation (32,235). Data also suggest that specific interactions between A and C fibers in the dorsal horn contribute to dorsal root reflexes that then drive axon reflexes, flare, and pain in areas of tactile allodynia (236).

Sympathetic Interactions with Primary Afferents

It was known for most of the twentieth century that the sympathetic nervous system can initiate or maintain pain after various nerve injuries and during inflammatory pain (2,21). The clinical symptoms of burning pain, allodynia, hyperalgesia, and hyperaesthesia during causalgia and other complex regional pain syndromes clearly had sympathetic involvement, because sympathetic blocks or sympatholytic treatments relieved the conditions, especially if used in the first few months of the initial neuropathic lesion, and noradrenalin exacerbated those pains. The sympathetic-sensory interactions differ for neuropathic and inflammatory pain, and dissection of each of those the molecular mechanisms is leading to much improved clinical treatment, as discussed later in this book. Extensive reviews provide much greater detail than can be given here 34,62,237,238 and 239). The general features of sympathetic modulation of sensory function are summarized in Figure 3-33.

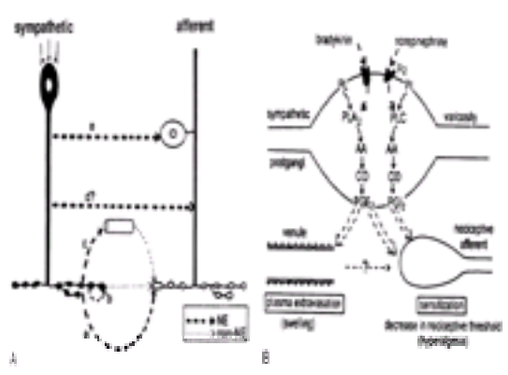


Figure 3-33. **A:** Possible ways of coupling between sympathetic postganglionic neurons and afferent neurons under pathologic conditions. (*a*) Noradrenergic (NE) and possibly also nonnoradrenergic (non-NE) chemical coupling between peripheral endings. This may preferentially occur after nerve lesions. (*b*) Indirect chemical

coupling. As believed by Levine et al. (*Nature* 1986;323:158–160), norepinephrine acts prejunctionally at postganglionic varicosities via a $_2$-adrenoreceptors triggering the release of other substances (e.g., prostaglandins). This may be relevant during states of chronic inflammation. (*c*) Indirect coupling via the vascular bed (change of neurovascular transmission, development of hyperreactivity of the vascular bed). This may occur after various forms of trauma with or without nerve lesion. (*d*) Interaction along the nerve. This may occur after nerve lesions during regeneration and sprouting in the nerve. (*e*) Noradrenergic coupling in the dorsal root ganglion. This may occur after a remote nerve lesion. [From Jänig W, Levine JD, Michaelis M. Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma. In: Kumazawa T, ed. *The polymodal receptor—a gateway to pathological pain. Progress in brain research*. Vol 113. Amsterdam: Elsevier, 1996:161–184; as modified from Jänig and Koltzenburg (237,348).] **B:** Idea on the role of the varicosities of sympathetic postganglionic noradrenergic fibers in venular plasma extravasation and sensitization of nociceptive afferents induced by bradykinin (BK) and in sensitization of nociceptive afferents induced by norepinephrine (NE). Venular plasma extravasation may also contribute to sensitization of nociceptors. Both processes are mediated indirectly via different metabolic arachidonic pathways and are principally independent of the neural activity in the sympathetic neurons: BK reacts with b $_2$-receptors on the varicosities and leads to release of prostaglandin E_2 (PGE_2) via activation of phospholipase A_2 (PLA_2). NE reacts with a_2-adrenoceptors in the varicosities and leads to release of prostaglandin I_2 (PGI_2) via activation of phospholipase C (PLC). Although BK-induced decrease of nociceptive threshold and plasma extravasation occurs in normal tissue, norepinephrine-induced sensitization of nociceptors only occurs in injured tissues. AA, arachidonic acid; CO, cyclooxygenase; PI, phosphatidyl inositol; PL, phospholipid. [From Jänig W, Levine JD, Michaelis M. Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma. In: Kumazawa T, ed. *The polymodal receptor—a gateway to pathological pain. Progress in brain research*. Vol 113. Amsterdam: Elsevier, 1996:161–184; as modified from Levine and Taiwo (169).]

The sympathetic fibers coexist with primary afferents throughout peripheral tissues, especially along the vasculature. The associations are more complex in viscera and in endocrine and exocrine organs in which there are general and special visceral afferents near the sympathetic, parasympathetic, enteric, or all three kinds of nerve fibers. Sensory and sympathetic fibers also exist among the nervi nervorum of the peripheral nerves and ganglia. Most investigators have found that the two systems do not significantly affect one another's electrophysiologic activity in healthy tissues (62). However, they counterbalance each other for efferent regulation of vasculature constriction [norepinephrine (NE) from sympathetics] and dilation (CGRP/substance P from sensory fibers) in many tissues, so that loss of one of the vasoregulatory partners alters the effects of the other on blood flow.

After injury to a peripheral nerve, several different changes occur in sensory-sympathetic interactions, some of which depend on the type of injury. After nerve ligation, A-fiber afferents increase their a_2-adrenoreceptor activity and thereby become sensitized to systemic or local release of noradrenalin (34,62). Initiation or maintenance of some complex regional pain syndromes is primarily via this altered sensory adrenergic receptor activity in large fibers. Those axotomized neurons also attract sprouting intraganglionic sympathetic fibers that form *baskets* of endings around their cell bodies, but it is not clear whether those sprouted sympathetics contribute to sensory activation or have another function (62). When a cut nerve is trapped in a neuroma, many of the sensory sprouts for axons of all sizes develop sensitivity to sympathetic stimulation (240). In partial nerve lesions approximately one-third of the C-polymodal receptor fibers whose fibers are not injured increase their a_2-adrenoreceptor activity to become sensitized to heat and noradrenalin, as demonstrated by their responses to local administration of noradrenalin and inhibition of the effects by a_2-adrenoreceptor antagonists (66). In many neuropathic injuries there would be ligation effects for some fibers, partial injury effects for others, perhaps some small neuromas, and local neuritis for a variety of mechanisms inducing sympathetic activation of sensory fibers. Additional complexities are introduced at the central endings of the primary afferents where there are also a $_2$-receptors; however, their function is mainly inhibited by hyperpolarization responses to descending noradrenergic fibers in the dorsal horn (239).

When a tissue becomes inflamed, a specific set of direct and indirect interactions occurs between sympathetics and the affected primary afferents (see Fig. 3-33). The sympathetic fibers increase their release of norepinephrine, which then has an autocrine feedback effect that stimulates production and release of prostaglandin I_2 from the sympathetic endings, which in turn sensitizes the afferents (62). In addition, the bradykinin in the inflamed tissue stimulates the sympathetic fiber to produce and release prostaglandin E_2, which further sensitizes the afferent, as well as enhancing serum extravasation from postcapillary venules. These direct and indirect actions of sympathetic mediators on primary afferents are the best documented, and undoubtedly others exist (e.g., the hyperpolarizing actions of another sympathetic mediator neuropeptide Y) (232,233).

Parasympathetic Involvement in Pain

Research shows that trigeminal afferents and parasympathetic fibers affect each other during certain kinds of cluster headache and paroxysmal hemicrania (71). Patients with this pain condition, which usually lasts for a few minutes, have typical accompanying lacrimation and rhinorrhea. Evaluation of cranial circulation shows elevated levels of CGRP and vasoactive intestinal polypeptide during the attack, and treatment with indomethacin is successful. Thus, the parasympathetic system also must be included in analyses of neuropathic pain mechanisms for some tissues.

Nerve Growth Factor and Other Neurotrophin Growth Factors

A prolific effort since the mid-1980s has been undertaken to identify the factors that drive neuronal plasticity and persistent pain, especially concerning NGF and other neurotrophin growth factors (30,31,241,242). The role of NGF in stimulating neural outgrowth and survival during development of sympathetic and sensory nerve fibers has been known since the work of Hamburger, Levi-Montalcini, and Cohen in the 1930s to 1950s (243). It is now clear from studies of knockout mice (244,245,246 and 247) that development of each type of peripheral nerve fiber depends on specific members of the neurotrophin growth factor family and their corresponding trk high-affinity receptors, as well as the p75 low-affinity neurotrophin receptor (see Table 3-5). Peripheral neurons shift to somewhat different neurotrophin requirements in mature animals, with some work showing that NGF, BDNF, and glial-derived neurotrophic factor (GDNF) affect different groups of nociceptive primary afferents (75). Those effects include subtle regulations of conduction properties and of sodium channels (30,31,241).

All neurotrophin-dependent neurons also respond to the low-affinity (p75) neurotrophin receptor that also has homologies with the tumor necrosis growth factor family (248). Its functions are still not entirely clear, but, in addition to modulating the functions of the high-affinity receptors, it also initiates apoptosis or survival depending on NGF levels during development, with the proliferative activity involving signaling through the phosphorylated transcription factor NFkB. Its regulatory activities are partly tissue specific, because cutaneous and oral and dental nociceptive afferents are affected differently in p75 knockout mice (244,249).

Many of the neuroplastic effects of nerve injury and inflammation depend on alterations in amount, origin, and distribution of NGF (Fig. 3-34). Nerve injury obviously cuts off NGF and other signals from tissues, and the nociceptive neurons that expresses trkA and neuropeptides substance P and CGRP are most affected after axotomy, and rescued by administration of exogenous NGF. Conversely, inflamed tissues have greatly elevated NGF, made especially by local fibroblasts, which signals the extent of the inflammatory cellular responses when arriving in the sensory ganglion by retrograde transport (241). Altered sodium channel distribution and function are prominent mechanisms in neuropathic pain (250), and work shows that NGF (and GDNF, see following discussion) regulates sodium channel expression and function (30). NGF also has direct involvement in acute pain (179,251,252 and 253), and when animals are depleted of NGF by autoimmunization, they develop thermal hypoalgesia (254,255) under conditions that also alter sodium channels (Fig. 3-35). The effects of NGF on sodium channels differ in rats for sciatic nerve transection (256), tight ligature of L-5/L-6 (257), and carrageenan injections of paw (258), and include effects on the SNS/PN3 and the NaN channel subtypes (30,31). The complexity of neurotrophin effects on nociceptors is seen in the differential effects of estrogen on NGF receptors of dorsal root ganglion (259).

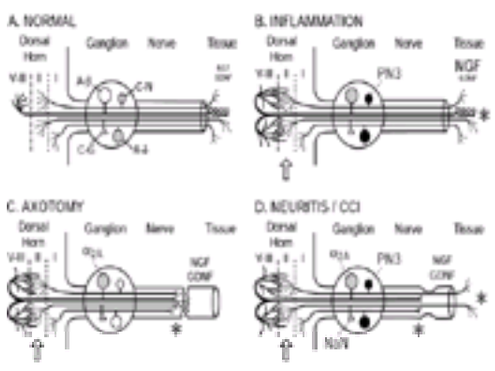


Figure 3-34. Some data support this diagram of four different sensory neurons, (A-b, A-d, C-N [nerve growth factor (NGF)–dependent C fibers], and C-G [glial-derived neurotrophic factor (GDNF)–dependent C fibers]) and their altered peptide expression (gray tone), or expression of the NaN or PN3 tetrodotoxin resistant (TTX-R) sodium channels for four different conditions: **A,** normal; **B,** tissue inflammation; **C,** axotomy; and **D,** chronic nerve constriction with neuritis. The levels of peptide expression in neuronal cell bodies are represented as little or none (*clear*), moderate (*gray*), or high (*dark gray*). The neurons that have the most change in expression or distribution of TTX-R sodium channel are indicated. Altered growth factors at peripheral sites (*) affect neuronal gene expression via axonal transport. Although each of the three pathologic conditions has different combinations of sensory alteration, the sprouting of A-bcentral arbors (*arrow*) into lamina II has been found for all. See text for references.

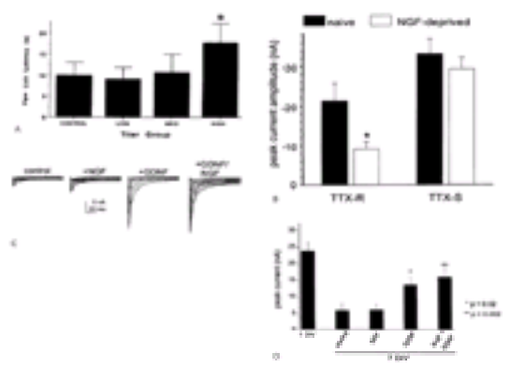


Figure 3-35. **A:** Effects of nerve growth factor (NGF) depletion in rats on heat nociception. High titer animals had a significant hypoalgesia for the paw lick latency test. From Chudler EH, Anderson LC, Byers MR. Nerve growth factor depletion by autoimmunization produces hypoalgesia in adult rats. *Brain Res* 1997;765:327–330. With permission. **B:** Specific effects of NGF depletion in rats on current amplitude for sodium channels of the TTX-R subtype but not TTX-s. From Fjell J, Cummins TR, Fried K, et al. *In vivo* NGF deprivation reduces SNS expression and TTX-R sodium currents in IB4-negative DRG neurons. *J Neurophysiol* 1999;81:803–810, with permission. **C,D:** *In vitro* studies of patch-clamped neurons of the IB4+/glial- derived neurotrophic factor type. Current peaks are affected especially by glial-derived neurotrophic factor (GDNF), not by NGF alone, but with some augmentation of the glial-derived neurotrophic factor effect when NGF is coadministered. (From Fjell J, Cummins TR, Dib-Hajj SD, et al. Differential role of GDNF and NGF in the maintenance of two TTX-resistant sodium channels in adult DRG neurons. *Mol Brain Res* 1999;67:267–282, with permission.)

In addition to the NGF/trkA system that regulates the capsaicin-sensitive, neuropeptide-rich small A-d and C-fiber system, another major set of nociceptive C fibers express the isolectin IB4 that are not neuropeptide-rich, that have specific receptors for GDNF (see Table 3-5), and that make up approximately one-third of the nociceptive population (29,75). GDNF is produced by Schwann cells and is increased after nerve injury, whereas its receptors (a molecular complex of Ret and GDNFRa) are made by the GDNF-dependent neurons and are also affected in injured neurons (260,261). GDNF regulates both the SNS/PN3 and NaN subgroups of sodium channel in the IB4+ neurons (31).

BDNF appears to have different functions in cutaneous and visceral afferents (28). In the former, elevated NGF then stimulates expression of BDNF, as a possible amplification signal when peripheral damage is extensive (262). In visceral afferents, most coexpress trkA and trkB receptors, and many mature visceral neurons express BDNF (263). In addition, BDNF enhances the sensitivity of sensory vagal neurons to capsaicin (264). BDNF exhibits extensive effects on central neural function, but the sprouting of A-fiber central endings into lamina II was not prevented by intrathecal injections of either BDNF or NT3, whereas injections of NGF did prevent that response (265).

Ciliary neurotrophic factor is a neurokine whose molecular structure and actions are similar to the cytokines IL-6 and leukocyte inhibitory factor, and it has important actions via the gp130 receptor after nerve injury and demyelination (28,266,267,268 and 269). Other growth factors are certain to be added to this set of nociceptive modulators in the near future (e.g., the newly described neurturin in the GDNF growth factor family). In addition, to the neurotrophin growth factors there are many others, such as fibroblast growth factors and insulinlike growth factors, that have important regulatory effects on some primary afferents during development, inflammation, and nerve regeneration. The molecular mechanisms of the neurotrophins are critical to regulation of peripheral phenotypes of nociception, and intense research is under way to understand their functions and develop pharmacologic therapies targeted to those mechanisms (28).

PERIPHERAL MECHANISMS OF PERSISTENT PAIN

Experimental Models for Studying Pain

The development of animal models has been an essential step, in combination with molecular and clinical studies, for understanding of pathologic mechanisms of most diseases. The study of pain also has benefited greatly from a variety of animal models, each of which is useful for improving knowledge about and management of particular features of pain and for development of new pharmacologic treatments. Of course, many questions concerning pain mechanisms can be addressed using *in vitro* paradigms such as the isolated skin-nerve preparation (270) or sensory ganglion cell cultures (271,272), and acute studies under general anesthesia or decerebration are conducted without any sensory experience being possible for the animal (273). Indeed, many important molecular mechanisms related to neuroplasticity and pain are being discovered in simple organisms such as the nematode *Caenorhabditis elegans*, in oocytes or other cells *in vitro*, or using patch clamp technology to study ion channels in isolated cell membrane (134,274).

However, studies of pain and analgesia in awake animals also have been necessary to reveal the neurobiology of activity- dependent interactions of the peripheral nervous system and CNS and their effects on behavior *in vivo*. These studies present special challenges for animal care, because some pain is usually unavoidable, and analgesics sometimes cannot be given when their antinociceptive effects counteract the goals of the experiment. The ethical considerations and guidelines for experimental studies of pain in awake animals have been discussed and reviewed in detail (275,276), with special emphasis on the need for careful planning to have an experimental design that allows valid behavioral tests while keeping stress, discomfort, and duration to a minimum. In general, this means that stimulus intensity and duration should give measurable nociceptive responses in comparison with sham controls, but not reach the levels of discomfort that disturb normal eating, drinking, grooming, or other behaviors. Careful attention is needed for choice of species, gender, age, diurnal variations in nociceptive sensitivity, minimal numbers of animals, type of tissue being stimulated, size of stimulus area, and interstimulus interval (277,278,279 and 280). Adaptation of an approved paradigm to a different tissue, species, age group, or gender needs careful scrutiny to be sure that behavioral responses remain in an acceptable range for the new conditions.

Because perception of pain is a psychological event that cannot be directly assessed in animals, its presence must be inferred indirectly from the animal's behavioral responses, and by correlation with parallel studies in human subjects. The investigator has a special responsibility to use adequate behavioral tests and monitoring to ensure that the animal's behavior remains above threshold but well below intolerable levels. Many patients still have intractable persistent pain. However, it is not necessary to duplicate those conditions in an animal, because the properties of neuroplasticity and their reduction by pharmacologic treatment have been shown to occur within the tolerable range (278).

The Committee for Research and Ethical Issues of the International Association for the Study of Pain (281) identified the following guidelines for pain research in conscious animals: (a) Experiments must be reviewed beforehand by scientists and lay persons to clarify the potential benefits for improved understanding of pain, and there must be continuing justification for the investigations. (b) If possible, the investigator should try the pain stimulus on him- or herself. (c) Physiologic and behavioral assessments of any deviations from normal behavior should be measured. (d) The pain stimulus should be the minimum necessary for the purposes of the experiment. (e) Pain-relieving agents or procedures should be used, as long as this does not interfere with the aims of the investigation. (f) Paralytic agents should not be used without a general anesthetic. (g) The duration of the study must be as short as possible, and the number of animals kept to a minimum. Some experimental conditions cannot be self-tested by the investigator, but in most cases there are parallel studies in humans for comparison. In addition, all animal research is monitored by each institution's Animal Care and Use Committee, which has overall responsibility for the humane treatment of animals in research and for minimizing

their discomfort (282).

Development of many animal models for studying acute and persistent pain during the 1980s and 1990s has led to enormous insight into mechanisms of peripheral and central neuroplasticity, especially concerning chronic inflammatory and neuropathic conditions and the phenomena of sensitization, hyperalgesia, allodynia, spontaneous pain, bilateral spread from unilateral lesions, and activity-dependent plasticity. That work has already produced improved treatment for postoperative and inflammatory pain, and a new pharmacology is rapidly emerging for treatment of chronic pain (26,283). In many studies, the animal has control over the intensity and duration of the stimulus by being free to escape it, as in the reflex paw withdrawal or tail-flick tests, or with more complex learned escape responses for which latencies can be measured. In other cases, a persistent pain is initiated (e.g., by intradermal injection of inflammatory agents, moderate distension of hollow viscera, or partial injury to a peripheral nerve), and then the specific features of behavioral, functional, and molecular plasticity are tested. In those cases, keeping the stimulus within the tolerable range can be inferred if the animal maintains normal feeding, grooming, drinking, social behaviors, and mobility (278) or if aversive behaviors provide the end-point for the stimulus (190,194). Combined studies exist in which neuropathy is established *in vivo*, but then the analysis is done with *in vitro* paradigms such as the isolated nerve-skin preparation (284) or patch clamp physiology of labeled sensory ganglion cells (285). Many of the models developed in rats have been successfully adapted to transgenic or knockout mice (225,286).

Important benefits from the animal studies include the detailed testing of syndrome-specific drugs and the development of new treatment strategies to dampen the peripheral barrages that drive CNS plasticity, to discover new anesthetics based on better understanding of peripheral neuroplasticity, and to reduce the effect of immune and endocrine signaling on persistent pain, as described throughout this text and reviewed elsewhere (21,26,287). In addition, sophisticated genetic analyses are now feasible in animals and humans that address important aspects of pain, as discussed in Genetics of Pain, later in this chapter.

Neuropathic Pain

Neuropathic pain syndromes involve injury to the nervous system and have different mechanisms from pain caused by chronic tissue inflammation (see Fig. 3-34). For the latter, the nerve fibers are intact and have reactions to inflammatory mediators and cell breakdown products at their peripheral endings that then alter the afferent and efferent functions of the sensory nerve fibers, both in the periphery and at central connections. For nerve injury, the fibers are disconnected from the periphery and respond to axonal damage, local neuritis, atrophy, altered Schwann cell activity, and their own altered signaling. For inflammatory and neuropathic conditions, there are phenotypic changes in the peripheral nerve cells; increased excitation, disinhibition, or both of dorsal horn and pain pathways; altered immune signals into the CNS; and usually some activation of stress endocrinology and alterations in sensory-sympathetic interactions (46).

For neuropathic injury, important differences exist in symptoms, persistence, and underlying neuroplasticity for each of the animal models, of which more than 30 have been developed so far to address specifically different mechanisms in different nerves and for different causal agents (278,279,288). The main characteristics are summarized in Table 3-7 for (a) the neuroma model for analgesia dolorosa and phantom limb pain (240,289); (b) the chronic constriction injury that causes a partial nerve lesion with neuritis (284,290,291); (c) partial nerve ligation (292); (d) tight ligature and degeneration of the L-5, L-6, or both spinal nerves, but preservation of the L-4 components of the sciatic nerve (293); (e) peripheral neuritis (294); (f) cryoneurolytic injury (295); and (g) diabetic neuropathy (296). In addition, spinal injury models (297) affect the central terminals of the sensory fibers that terminate in the injured spinal segments, and dorsal rhizotomy also destroys central terminals and causes neuropathic behavior. Each of these neuropathic injuries mimics some features of specific clinical conditions, and the differences among the various animal models help us to understand how to devise syndrome-specific pain medications.

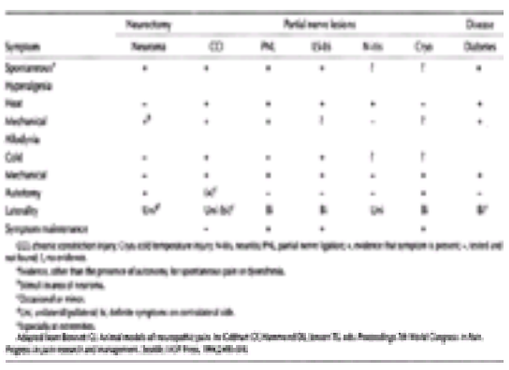


TABLE 3-7. Comparison of animal models of neuropathic pain

Important anatomic considerations exist for neuropathic pain mechanisms. First, the location of injury along a peripheral nerve elicits different intensities of response and types of neuroplasticity depending on whether it is near the periphery, along the nerve, close to the ganglion, in the root, or affecting the central terminals in the cord. Second, different peripheral nerves, such as cutaneous, articular, muscular, or visceral, can have quite different sets of somatosensory fiber types and different proportions of polymodal nerve fibers, as indicated in Figure 3-30 (64), and would therefore have different capacities to react to injury. In addition, special somatic or visceral sensory fibers can exist in the injured group, as well as different access to afferent immune and CNS pathways and different degrees of sympathetic-sensory interaction. Finally, the anatomic location of the pain in humans and animals can differ from the distribution of the injured nerve, including contralateral symptoms for unilateral injury (288). Although that depends on some important central mechanisms, evidence also exists that neighboring uninjured peripheral nerves may contribute to the neuropathy, perhaps by collateral sprouting into the injured territory (298). Chronic pains that become independent of the anatomic triggering site are considered to be maladaptive and tend to persist for long periods and resist standard therapies (46,299)

The physiologic and pharmacologic reactions of peripheral nerves to injury or inflammation have been discussed generally in Nociceptor Physiology, previously in this chapter, and have been reviewed in much more detail elsewhere (21,130,142,232,240,274). Although central plasticity is a key factor in neuropathic pains, many important functional and cytochemical changes in the peripheral nerves help drive the central changes and initiate their own abnormal sensations. The main pathologic changes in the nerves are spontaneous ectopic discharge, increased excitability, and altered pharmacology, and these are driven by different subsets of peripheral fibers during different postinjury times. For example, after the initial injury discharge at experimental neuromas, 10% to 15% of the A fibers have spontaneous discharge at 1 to 2 weeks, subsiding to 2% to 3% by the end of the first month, whereas the C fibers have only 1% to 2% spontaneously active fibers in the first week, gradually increasing to 4% to 6% by 1 month (240). Thus, central sequelae of C-fiber neuropathic activity should intensify during the first month, whereas those related to A-fiber spontaneous discharge should weaken. Other complex abnormal firing patterns that have been recorded from the sensory ganglion include periods of spontaneous bursting followed by suppression of that activity, cross-excitation of quiescent neurons by impulse activity in nearby neighboring neurons possibly via chemical signals, and altered sensory spontaneous activity by sympathetic input after neuropathic injury (138,139,300). These are just a few of the amazingly varied and subtle physiologic changes induced by nerve injury or tissue inflammation, some of which vary for the trigeminal ganglion compared with dorsal root ganglia (301,302).

More recent work has begun to show interesting changes in expression, distribution, and function of specific ion channels, receptors, and other key membrane molecules in primary afferents (30,31 and 32,258,271,303) for each neuropathic condition for each subgroup of nociceptive neuron. The molecules in Table 3-4 and Table 3-5, as well as others not on the list, may all be affected in complex ways depending on the type of nerve injury or tissue conditions. For example, altered expression and distribution of the peripheral type of sodium channel (PN3) is implicated in many neuropathic syndromes, but shows different patterns for different injuries. Some that have been identified so far include downregulation of PN3 after axotomy (217), unaltered PN3 mRNA after chronic constriction injury (CCI) injury but redistribution of the protein from cell body to the injury site for both CCI and axotomy (304), increased expression by 4 days after injections of carrageenan into the rat hind paw (258), and increased expression in large sensory cells after L5-6 ligation (41). These examples of expression plasticity for one sodium channel represent the tip of the molecular iceberg for which current research is intense (Fig. 3-35).

Some of the main changes in expression of neuropeptides, neurotransmitters, and neurotrophin receptors by sensory neurons after axotomy compared with inflammation are indicated in Table 3-6 (232,233,305). Some of those changes are related to protective needs of the injured neurons (upregulation of galanin, vasoactive intestinal peptide, neuropeptide Y), some relate to regeneration (Gap-43, tubulin), some to loss of retrograde signals such as NGF from the target tissue (downregulation of CGRP and substance P), and others could be in response to retrogradely transported inflammatory or vascular agents, immune signals, or Schwann factors generated at the injury site. The smaller fibers can have quite different cytochemical responses from larger ones, and it has been shown that even the A-b fibers begin to express substance P and neuropeptide Y when they become involved in inflammatory pathophysiology (45,306). The sophistication and

molecular intricacy of differences in cytochemical mechanisms for different types of neuropathic pain are just beginning to be appreciated and are the subject of intense current research (41).

Inflammatory Pain

Immediately after tissue injury, sensory nerve endings are suddenly exposed to a variety of cellular breakdown products and inflammatory mediators that trigger acute nociceptive activity. This *inflammatory soup* includes prostaglandins, protons, serotonin, histamine, bradykinin, purines, cytokines, eicosanoids, and neuropeptides that act at specific receptors on the sensory fibers (see Fig. 3-29) and also have important synergistic interactions (233,305). The initial injury and inflammation cause C and A-d fibers to undergo changes such as sensitization, increased activity in normally silent nociceptors, and altered activity of ion channels and membrane receptors (307). If inflammation is short lived, nerve function should return to normal quickly. With increasing severity and duration, those conditions are reflected in the set of growth factors and cytokines produced by the local cells, invading monocytes, and vascular cells that are conveyed to the sensory cell body by retrograde axonal transport. Those then induce myriad changes in neuronal function that are being identified for each subgroup of peripheral axon (see Table 3-6) (233). Some of the most surprising have been the demonstration of substance P production by A-b fibers that normally make little or none of that peptide, the central sprouting of their terminals into lamina II of the dorsal horn (Fig. 3-36), and their increased expression of a $_{2A}$-adrenergic receptors (45,308,309).

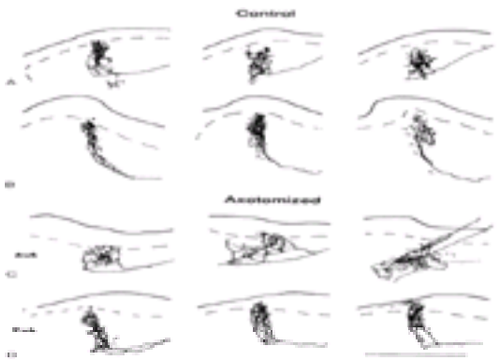


Figure 3-36. Camera lucida reconstructions from transverse sections of the spinal cord of the complex terminal arbors of four single sural Ab afferent fibers. Each row shows three adjacent arbors from a single afferent fiber, two controls (**A** and **B**), and two from axotomized sural nerves (**C** and **D**). Solid line above each drawing is the dorsal-most surface of the dorsal horn; dotted line, the lamina II-III border. Each arbor has a collateral axon arising from a stem axon running longitudinally in the dorsal columns (not shown). This collateral axon for hair follicle afferent fibers terminated in a flame-shaped branching pattern (**A** and **B**). **C** and **D**, arbors that have branching patterns not seen in control animals that extend into the superficial laminae. Scale, 250 µm. (From Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992;355:75–78, with permission.)

This plasticity induced by chronic tissue inflammation differs from neuropathic injury in the types of cytochemical responses (see Fig. 3-34) and because it does not cause ectopic signal generation, increased adrenergic sensitivity of myelinated fibers, sprouting of sympathetic fibers in the ganglion, cell death in the ganglion, or transganglionic degeneration of the central endings (46,305). It is a different challenge to the peripheral nervous system and causes somewhat different reactions in the CNS, although many of the NMDA-based excitatory mechanisms, central modulation, and immune and endocrine responses may be similar. Certainly some of the problems in neuropathic injury are compounded by chronic inflammatory stimulation at the injury site, with important reactions by the local neural innervation (nervi nervorum) that are only just beginning to be appreciated (57,60,287), and other types of persistent pain (cancer pain, postherpetic neuralgia) may involve important combinations of neuritis and neuropathic mechanisms.

Developmental and Aging Aspects

Just as great variation occurs in the response of peripheral nerves to different types of peripheral pathology, much variation exists among individuals in their specific neural reactions and neuroimmune and endocrine responses to injury and inflammation. Those differences are more extreme in infants because of their immature peripheral nervous systems and CNSs. The fetal acute noxious reflex patterns that begin during the first trimester are exaggerated, hypersensitive, whole body responses that continue into the early neonatal period, and gradually become more specific and localized as central and peripheral inhibitory mechanisms become established (310,311). Thresholds to mechanical stimuli increase during the first few weeks, whereas those for noxious chemical or heat stimuli are initially elevated and gradually decrease. The polymodal receptors have fairly mature afferent thresholds and firing patterns at birth in rats, whereas their efferent neurogenic functions take longer to appear, A-d high-threshold fibers take longer to develop, and low-threshold mechanoreceptors are most immature at birth. Establishment of functional central endings for C and A fibers occurs at different rates, development of local circuit neurons extends into the neonatal period, and the important descending inhibitory controls are immature at birth. In addition, the excitatory NMDA mechanisms in the neonatal dorsal horn appear to be hyperactive, and fos responses in the dorsal horn are different (312), so that wind-up and central excitation after C-fiber stimulation may be greater than in adults. Other important pharmacologic aspects of pain, such as opioid and neuropeptide functions, can also be quite different in infants than in adults, and many kinds of receptors are overexpressed initially or occur in areas not found in the adult. Thus, it is not surprising that analgesics have different efficacy for infants than for children and adults.

When infants experience pain from surgeries or prolonged intensive care, there may be persistent changes in neural connections that affect their subsequent acute pain pharmacology and behavior (267). However, it is rare for chronic pain patients to be younger than 20 years, suggesting that nerve injury and tissue inflammation in children elicit central plasticity that easily reverts to normal during peripheral healing. The elderly are also rare among chronic pain populations, but for different reasons. They have been shown to be less stressed emotionally by painful stimuli, to have somewhat reduced acute pain sensations (e.g., during myocardial ischemia), and to have less perception of pain when experiencing dementias (313). In addition, the peripheral nervous system gradually loses some of its fibers with aging and has altered expression and distribution of neuropeptides and growth factor receptors (314), as well as altered protein kinase/phosphatase activities and altered synaptic efficacy (315). If those changes occur at different rates in different fibers, there may be important shifts in the balance among inputs to the CNS, in the capacity of peripheral nerves to drive long-term central plasticity, as well as in central modulatory mechanisms (316).

The prevalence of shingles and postherpetic neuralgia in the elderly (317) may depend primarily on increased longevity with greater opportunity for viral reactivation, but some of the alterations in the aging peripheral nervous system, its proportion of nociceptive subgroups, its interaction with immune and endocrine factors, and its tissue interactions may facilitate that reactivation. Obviously, some changes in tissue chemistry, structure, endocrinology, and circulation occur with age, as well as increased wear and tear, especially for joint and muscle pain.

GENETICS OF PAIN

During the 1990s, there has been extensive interest in genetic approaches to understanding pain mechanisms in animals and humans, as reviewed by Mogil and colleagues (318,319,320,321,322 and 323). The wide variations in clinical pain sensitivity and analgesia (324,325) and evidence for gender differences in pain (319,326,327,328,329 and 330) have shown that there are definite heritable traits for pain. For example, it is now known that five hereditary sensory neuropathies have five different deficits in the peripheral nociceptive apparatus (331) (Table 3-8). One of those neuropathies (type IV, congenital lack of pain sensibility with anhidrosis) has been found to have a defective gene for the high affinity (trkA) NGF receptor (331), which would prevent development of the trkA-dependent nociceptors (see earlier discussion of NGF and peripheral pharmacology of pain). The rapid progress in mapping the human genome, and its associated evolving molecular technologies (332), makes it likely that genetic traits for pain and analgesia, whether they have large phenotypic features as for the conditions mentioned previously or much more subtle properties, may soon be easily detected. When that happens, it should be possible to diagnose an individual's pain-related genes and then custom-design pharmacologic treatment (332).

Type	Characteristics
I. Dominant hereditary sensory neuropathy	Degeneration of dorsal root ganglia
II. Recessive hereditary sensory neuropathy	Loss of myelinated A fibers
III. Dysautonomia	Loss of unmyelinated C fibers
IV. Congenital insensitivity to pain with anhydrosis	Defective tyrosine kinase A gene, loss of C fibers
V. Congenital insensitivity to pain without anhydrosis	Loss of small A-δ fibers

Adapted from Wood JN. No pain, some gain. *Nat Genet* 1996;13:382–383; and Indo Y, Tsuruta M, Hayashida Y, et al. Mutations in the TRKA/NGF receptor gene in patients with congenial insensitivity to pain with anhidrosis. *Nat Genet* 1996;13:485–488.

TABLE 3-8. Peripheral deficits in hereditary sensory neuropathies

Studies in animals using recombinant inbred strains, selective breeding, and targeted or spontaneous mutations have made it clear that some interesting aspects of pain are heritable, such as high or low sensitivity to opiates (319,328,329,333,334), high and low analgesia in swim stress tests (335,336), or high and low autotomy behavior (337). In addition, animal models for other conditions with associated pain problems, such as rheumatoid arthritis, show genetic based traits for severity and chronicity (338). Defects in genes for tissue signals, such as those of IL-6 (286) or b-endorphin and other products of the proopiomelanocortin gene (339) are another way in which peripheral mechanisms of pain are affected by genetic traits.

The extensive work with animal models of persistent pain during the 1980s and 1990s set the stage for the remarkable demonstration that removing the protein kinase C-gamma gene from mice eliminates their neuropathic pain response to partial ligation of the sciatic nerve but does not affect their acute reflexes to noxious thermal or mechanical stimuli (225) (Fig. 3-37). This discovery has stimulated intense research to discover effective treatments based on procedures to either delete appropriate genes, selectively remove key neurons in the dorsal horn that drive neuropathic pain, or design drugs or gene therapies with selective neurotoxic effects (340,341). The mapping of human genetic trait loci, in combination with the animal genetic studies and the new technologies for nucleic acid microarrays (321,322 and 323,332,342) should rapidly change the clinical landscape for pain diagnosis and treatment.

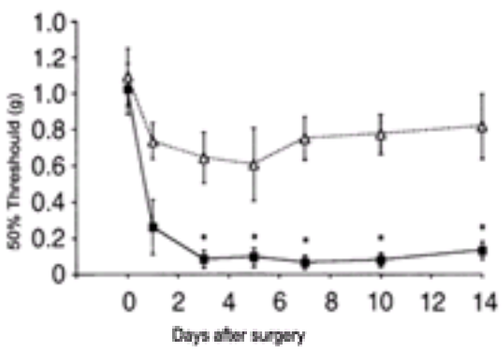


Figure 3-37. Constriction injury to the sciatic nerve produced a significant decrease in paw withdrawal thresholds to von Frey hair stimulation on the injured side in wild-type (n p <.05, Friedman test) but not in PKC-g mutant mice (D p > .05) compared with baseline thresholds. Asterisks indicate significantly lower thresholds on the injured site in wild-type mice compared with the injured side of mutant mice (* p <.05, Mann-Whitney test). No change in withdrawal latency was observed on the contralateral side. (Modified from Malmberg AB, Chen C, Tonegawa S, et al. Preserved acute pain and reduced neuropathic pain in mice lacking PKCg. *Science* 1997;278:279–283, with permission.)

CONCLUSIONS AND THERAPEUTIC HORIZONS

Treatments for peripheral pain mechanisms since the nineteenth century have included inhibitors of inflammation (aspirin, corticosteroids), opiate inhibition of nociceptive pathways in the periphery and CNS (morphine), inhibition of AP signaling (local anesthetics such as cocaine and lidocaine), and use of massage and relaxation therapies to reduce pain. The combined molecular, genetic, animal, clinical, and psychological studies by thousands of pain researchers during the 1980s and 1990s have now opened up new therapeutic possibilities in each of these areas, as summarized in this book. Revolutions in pain management during the 1990s can be expected based on the escalating pace of discovery in the genetics (320,321,322 and 323), pharmacology, and physiology of pain (28,142). Major pharmaceutical efforts to improve anti-inflammatory drugs by making drugs that block membrane receptors, inducible enzymes such as cyclooxygenase 2, membrane ion channels, or that facilitate endogenous antinociceptive mechanisms should soon provide alternatives to the traditional medications for persistent pain. The discoveries of peripheral actions of endorphins, endocannabinoids, and the new orphanin/nociceptin opiate suggest that other endogenous antinociceptive agents and actions are still waiting to be found and brought into service as pain treatments. The many studies on mechanisms of persistent pain have revolutionized knowledge of neuroplasticity and led to the concept of preemptive analgesia and to new strategies for preventing persistent pain or reducing its effect (234,343,344). Precise definition of these phenomena and education of the health professions about their applications for pain management should flourish in the first decade of the new millennium.

The reader is warned that the information presented in this and the next two chapters is a snapshot of the vast topic of basic biologic mechanisms of pain. The database is growing daily, as thousands of neuroscientists tackle the challenge of defining the cellular, molecular, and genetic mechanisms of pain. Many fascinating discoveries of basic and clinical mechanisms are just around the corner. In 1974, at the First World Congress on Pain, Dr. John Bonica encouraged scientists and clinicians to focus their attention on the frustratingly mysterious mechanisms of chronic pain to make its treatment as effective as that for acute pain (8). At that time, the nervous system was thought to have mostly stable wiring and relatively simple neurochemistry, so that mechanisms of neuroplasticity and the complex long- term interactions of the peripheral nervous system and CNS were not even imagined. The remarkable revolution that was set in motion by the vision of Bonica and other pioneers has already achieved much better understanding and treatment for most types of pain, as indicated in this book, and we can anticipate many further improvements as the tidal wave of pain research engulfs and fascinates us.

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CHAPTER 4

Spinal Mechanisms and Their Modulation

Gregory W. Terman and John J. Bonica

This chapter provides an overview of the anatomic and physiologic substrates of nociceptive transmission at the spinal level. The last edition required only a few paragraphs to describe the literature addressing animal models of chronic pain (e.g., inflammatory and neuropathic pain) and the changes that take place in spinal cord physiology and pharmacology as a result of repeated afferent input. This chapter significantly updates this information. Nonetheless, much of the neuroanatomy and neurophysiology described in the last edition pertains, and it is supplemented, not supplanted, here by the extensive research of the 1990s.

Pain is a complex constellation of unpleasant sensory, emotional, and cognitive experiences provoked by real or perceived tissue damage and manifested by certain autonomic, psychological, and behavioral reactions. Thus, this chapter concerning spinal mechanisms attempts to avoid the simplistic and potentially misleading tendency to write about pain in the spinal cord. Nonetheless, the spinal cord is the site of considerable information processing for stimuli normally perceived as painful, termed *nociception*. Injury to tissues, whether induced by disease, inflammation, surgical trespass, or other environmental hazards, constitutes a noxious stimulus and causes cellular breakdown with liberation of biochemical substances from intracellular stores. These, in turn, activate specialized high-threshold receptors, called *nociceptors*, and the primary afferent nerve fibers to which they are attached, to transmit action potentials to the dorsal horn of the spinal cord (or its trigeminal analog above the neck) (see Fig. 3-1). It is here, in the spinal cord dorsal horn, that information from nociceptors is modulated by other incoming primary afferent inputs, descending facilitatory and inhibitory influences from the brain, local interneurons, and the activity-dependent state of *transmission readiness* of the dorsal horn neurons themselves. Moreover, it is likely that in the spinal dorsal horn, information from nonnociceptive specialized receptors in skin (activated by touch, for instance), under certain disease states becomes misinterpreted as noxious and consequently perceived as painful. In this chapter we examine what we know about this process, looking first at the basic anatomy and physiology of the system and then at its remarkable plasticity.

SPINAL CORD ANATOMY

The spinal cord is a long cylindrical structure covered by pial, arachnoid, and dural meninges that lies within the vertebral canal (see Fig. 8-1). It extends from the foramen magnum to the first lumbar vertebra in adult humans. Thirty-one pairs of spinal nerves (one on each side of the body), associated with localized peripheral regions, segregate into dorsal and ventral roots as they approach the spinal cord from the periphery. The entrance of these roots into the spinal cord produces a pseudosegmentation. The spinal cord is the only remaining part of the adult nervous system that retains the segmental features of the developing embryo. Despite this gross appearance, the spinal cord in the adult is not truly segmented, and axon fibers from a particular dorsal root can actually travel to many levels of the spinal cord or brain stem before synapsing. Spinal roots are grouped as cervical, thoracic, lumbar, and sacral/coccygeal roots based on their regions of innervation. Because the spinal cord occupies only the upper two-thirds of the vertebral canal, the lumbar and sacral roots descend for a much longer distance in the cerebrospinal fluid-filled meningeal sac before leaving the vertebral canal via intervertebral foramina. Physicians make use of this offset (see Fig. 8-2) between spinal cord and vertebral levels by placing needles either subarachnoid or epidurally at the lumbar vertebral levels to administer medications or withdraw samples without fear of damaging the spinal cord. For pain management, this offset is important to remember because medications, such as opiates, given at the lumbar vertebral level are some distance from their receptors in the substance of the spinal cord.

The internal structure of the spinal cord comprises the external white matter and internal gray matter, all surrounding the small central canal. The size of the white and gray matter changes as a function of the spinal segment in question. In general, white matter represents the ascending and descending tracts of the spinal cord, communicating with the brain and to a lesser extent between spinal cord segments. Thus, it is not surprising that the white matter is larger the closer to the brain (rostral) one looks (i.e., the more rostral one goes in the spinal cord, the more white matter is present because it represents all of the brain's afferents from and efferents to increasing numbers of caudal spinal segments) (Fig. 4-1). In contrast, the gray matter represents the region of synaptic activity in the spinal cord and thus contains not only neuronal axons but also dendrites and synaptic terminals, supported by a matrix of glia and capillaries. The size of the gray matter, unsurprisingly, is largest in areas in which spinal neural processing is greatest, those segments representing the extremities. The cervical and lumbar enlargements in the human are directly related to the arms and legs, respectively, and the brachial and lumbar and sacral plexes in the periphery (see Fig. 4-1). Gray matter anatomy grossly resembles the shape of the letter H with the dorsal and ventral horns separated by the crossbar of the H and the midpoint of this crossbar representing the central canal. At the microscopic level, gray matter anatomy was, for many years, filled with eponyms and nuclei, and conflicting names for similar locations between, and even within, species. A landmark series of papers by Rexed (1) described a cytoarchitectural organization of the gray matter called laminae in the cat spinal cord. Similar laminar, gray matter divisions have now been described in a variety of species including humans and have provided a framework from which anatomic and physiologic findings within the spinal cord can be compared and contrasted.

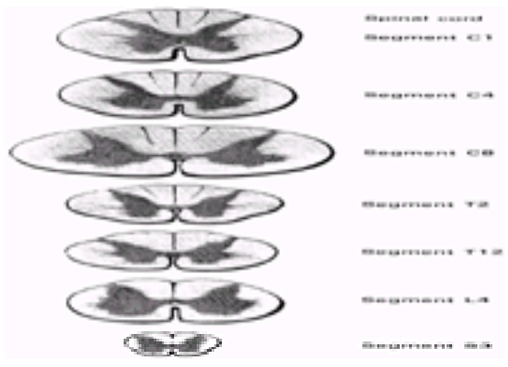

Figure 4-1. Spinal cord segments at different levels of the neuraxis show variations in size and shape of gray and white matter (see discussion in text). (From

Carpenter MB. *Human neuroanatomy*, 7th ed. Baltimore: Williams & Wilkins, 1976:218, with permission.)

Specifically, Rexed (1) divided the spinal gray matter into 10 laminae (Fig. 4-2). Laminae I through VI make up the dorsal horn; laminae VII through IX, the ventral horn; and lamina X is composed of a column of cells clustered around the central canal. We discuss the known differences between the various laminae and their importance in nociceptive processing in the section Dorsal Horn Morphology, later in this chapter. In short, lamina I of the dorsal horn is called the *marginal layer*. This lamina has the largest incidence of cells that send their axons to the thalamus, thereby forming much of the white matter known as the spinothalamic tract (STT). This tract is thought most important for the transmission of nociceptive information from spinal cord to brain. Cells in lamina V are also commonly found to project to the brain via the STT. Lamina II cells rarely project to thalamus or anywhere else outside a particular spinal segment, and are termed *interneurons*. Lamina II and its interneurons are known to modulate the activity of laminae I and V cells. Lamina II, which is subdivided into outer (II_o) and inner (II_i) parts, was originally labeled *substantia gelatinosa* (SG) because of its gelatinous gross appearance. A few authors adhere to Rolando's original description and include laminae I and II as SG, whereas others consider SG as including laminae II and III (2). Rexed's laminae run the entire length of the spinal cord, and the spinal dorsal horn laminae fuse with similar structures in the medulla called the medullary dorsal horn.

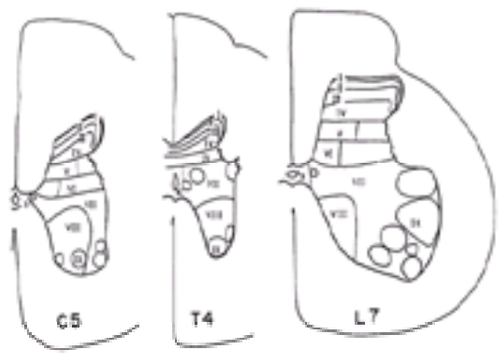

Figure 4-2. Diagrams showing Rexed's laminar histologic organization of the cat spinal cord gray matter at three levels. The dorsal horn corresponds to laminae I through VI inclusive, lamina I being the marginal zone, lamina II the substantia gelatinosa, laminae III and IV the nucleus proprius, and lamina V the neck of the dorsal horn. Lamina VI is more readily demonstrated in the cervical and lumbosacral enlargements of the spinal cord. (From Rexed B. The cytoarchitectonic organisation of the spinal cord in the cat. *J Comp Neurol* 1952;96:415–495, with permission.)

PRIMARY AFFERENT CENTRAL PROJECTIONS

Nociceptive primary afferents (discussed in depth in Chapter 3), whose peripheral processes innervate skin, muscle, or viscera and whose cell bodies are found in a dorsal root ganglion, project centrally via the dorsal root corresponding to that ganglion into the spinal cord. Each dorsal root breaks up into 12 to 15 rootlets that connect with the spinal cord. At the beginning of the twentieth century, Lissauer and Bechterew noted that the smaller myelinated fibers congregate on the lateral side of the rootlets as they enter the cord, whereas the larger axons were in the center and medial part of the rootlets [see (2) for references]. Lissauer further noted that the small lateral fibers pass to the apex of the dorsal horn, thus forming the tract that bears his name, whereas the larger fibers pass centrally to travel in the dorsal columns. In the ensuing half century, these findings were confirmed in animal studies by Cajal, Ranson, Ingvar, O'Leary, and others (2). Ranson (3), agreeing with Lissauer's anatomic studies, also noted that, in experimental animals, pain could not be elicited after cutting the lateral bundle. Snyder (4) and Kerr (5) showed that this segregation does not occur in the cat but does occur in monkeys. Kerr (5) found a random distribution of large and small fibers of a rootlet at 5 mm from the entry zone into the cord that continued until approximately 1 mm from the cord, where the majority of the small fibers shifted to the periphery of the rootlet, forming a conspicuous marginal ring. Just before the rootlet joined the cord, however, the fine fibers shifted from the circumferential ring to a clear lateral position and in the cord merged with the tract of Lissauer, whereas the medial division was composed of large fibers. Similarly, in humans, Sindou and colleagues (6) found small and large fibers to be randomly situated in the rootlet, but that the small fibers shift laterally as they near the dorsal root entry zone. In the dorsal root entry zone, the small fibers in the medial aspect cross to join those in the lateral bundle to enter the tract of Lissauer (see Chapter 3 for more detailed discussion). These findings prompted Sindou and associates to develop a “selective posterior rhizotomy” and others to use dorsal root entry zone lesions as neurosurgical approaches to eliminating certain pain conditions (see Chapter 106).

Lissauer's tract is a tight collection of fine fibers, longitudinally oriented in the spinal cord, that extends between the periphery of the dorsal horn and the cord's surface. Lissauer's original view of the tract was that it consists chiefly of small primary afferent fibers en route to the synaptic terminals in the dorsal horn, and Ranson (3) proposed that most of these conduct nociceptive impulses. Subsequent degeneration studies suggest that as few as 25% of the fibers in the most medial part of the tract are primary afferents, the rest being intersegmental propriospinal fibers (for review see 2). LaMotte (7) found that lesions restricted to Lissauer's tract produced degeneration in laminae I, II, and III of the dorsal horn (Fig. 4-3), the degeneration extending only a few millimeters rostral and caudal to the lesions. The primary afferent fibers are located throughout the tract at the level of their entry, but they shift medially at more rostral and more caudal levels. She concluded that fine primary afferents project to these superficial laminae by way of Lissauer's tract. Coggeshall and colleagues (8) have quantified these studies across species: (a) primary A-d and C fibers make up two-thirds of the axons in rat, 50% in cat, and 80% in monkey; (b) the ratio of unmyelinated to myelinated fibers within the tract in rat is 4:1; (c) primary afferent fibers ascend several segments in the lumbosacral cord of rat, but terminate within a single segment in the thoracic cord; and (d) in monkey there are more primary afferents in the medial part than in the lateral part of the tract.

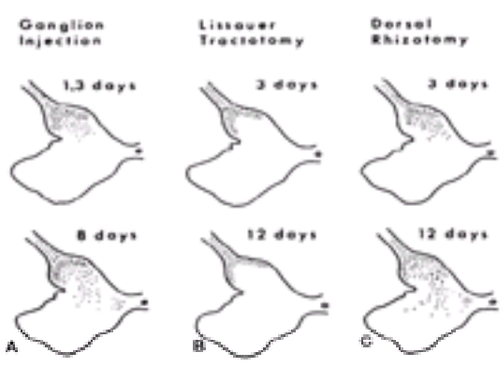

Figure 4-3. Summary diagrams of the results of Lissauer's tractotomy and dorsal rhizotomy in the monkey, suggesting that fine primary afferents pass through Lissauer's tract and terminate in the superficial dorsal horn. **A:** Distribution of radioactive amino acid 1.3 and 8.0 days after injection into the dorsal root ganglion of the monkey showing normal terminations of primary afferents. **B:** Three days after Lissauer's tractotomy, fibers terminating in laminae II and III degenerated, whereas those that terminated in laminae I and II_o required 12 days to degenerate. **C:** Three days after dorsal rhizotomy, dorsal column collaterals to laminae IV through VI and laminae in the ventral horn began to degenerate. The degeneration was prominent by 12 days. (From LaMotte C. Distribution of the tract of Lissauer and the dorsal root fibers in the primate spinal cord. *J Comp Neurol* 1977;172: 529–561, with permission.)

On entering the spinal cord, primary afferents take different courses depending on their size and function. Many dorsal roots, on entering the spinal cord, bifurcate in a Y-shaped fashion into a long ascending and a shorter descending branch. From each of these branches, large numbers of collaterals leave at right angles to enter and distribute in the spinal gray. Although the overwhelming majority of primary afferents terminating in the dorsal horn do so ipsilaterally, some course dorsal to the central canal and terminate in the contralateral horn. As mentioned previously, the small C fibers appear to travel in the most lateral part of the dorsal white matter,

including Lissauer's tract, and large A fibers more medially in the dorsal column. The dorsal root afferents of all sizes issue most collaterals in their segment of entry, but the rostral-caudal spread varies. A-d fibers spread three to six segments rostrally and an equal number caudally, whereas the collaterals of C fibers spread two to three segments above and below the level of entry (Fig. 4-4).

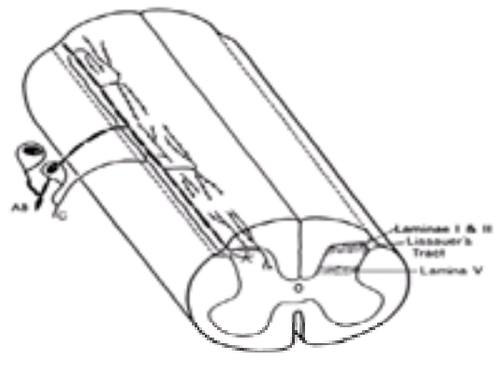

Figure 4-4. Three-dimensional diagram to depict the extensive field of A-d and C fibers after bifurcating at the point of entry into Lissauer's tract. The small-diameter fibers penetrate the spinal gray matter and terminate in the superficial dorsal horn (laminae I and II), and the A-d nociceptors and C visceral afferents also terminate in lamina V. The terminal axons of both types of small-diameter primary afferents are close and have a longitudinal orientation extending for several millimeters in laminae I and II, contacting hundreds of spinal neurons. (From Fields HL. *Pain*. New York: McGraw- Hill, 1987:45, with permission.)

The termination of primary afferents in dorsal horn has been studied by numerous investigators. Light and Perl (9), using the anterograde transport of horseradish peroxidase (HRP), showed that the concentration of fine fibers and their terminals ended in the superficial part of the dorsal horn of rat, cat, and monkey, whereas the large fibers ended in the deeper parts. They examined the number and distribution of HRP-stained terminal enlargements (en passant and boutons) for whole dorsal rootlets and for rootlets whose medial or lateral division had been sectioned. Figure 4-5 shows the results. As noted, the stained terminals in the whole- rootlet preparations were distributed evenly through the gray matter. Section of the lateral division, which contained small primary afferents before application of HRP, caused a dramatic elimination of most of the terminals in the marginal zone and in the SG, whereas the projections to deeper layers remained extensive. Conversely, section of the medial division containing large primary afferents eliminated virtually all terminals in the nucleus proprius and the deeper laminae (most terminals remained unstained), whereas a large number of terminals in the marginal zone and SG were marked.

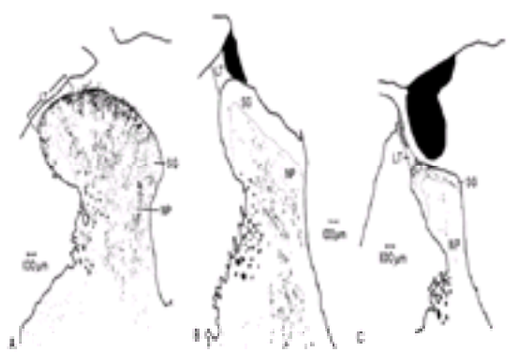

Figure 4-5. Pattern of projection of large and small primary afferent fibers in the spinal cord of rhesus monkey. **A:** Normal distribution. (LT, Lissauer's tract; NP, nucleus proprius; SG, substantia gelatinosa.) **B:** The lateral divisions of the root fibers were cut (lesion shown in solid black) at the junction between the dorsal root and the spinal cord before horseradish peroxidase was applied. Most of the terminals in the marginal zone and the substantia gelatinosa were eliminated, whereas the projection to deeper layers remained extensive. **C:** Lesion of the medial division of the root left most terminals in the nucleus proprius and deeper regions unstained, whereas a large number of terminals were marked in the marginal zone and in the substantia gelatinosa. (Modified from Light AR, Perl ER. Reexamination of the dorsal root projection to the spinal dorsal horn including observations on the differential termination of coarse and fine fibers. *J Comp Neurol* 1979;186:117–131.)

Termination of Collaterals from Large Myelinated (A-b) Fibers

A-b fibers terminate primarily in lamina III but also, to a lesser extent, in laminae IV through IX (including presumed monosynaptic primary afferent–motor neuron contacts) (see Chapter 3 and Fig. 3-13).

Termination of Collaterals of Small Myelinated (A-d) Fibers

The course followed by the fine fibers in the lateral division of the dorsal rootlets is entirely different from that followed by the large fibers. They run laterally into the medial aspect of the tract of Lissauer, in which they divide into short ascending and descending branches that may run for several segments. Collaterals of the A-d nociceptors penetrate the lateral aspect of the dorsal horn and terminate at four sites: lamina I via tortuous paths and ending in terminal arbors in laminae I and II $_{o}$, and others penetrate deeper to end in laminae V and X (see Chapter 3 and Fig. 3-14).

Termination of Collaterals of Small Thinly Myelinated (C) Fibers

Collaterals of C fibers penetrate the dorsal gray matter from the medial Lissauer tract and appear to terminate exclusively in laminae I, II, and V of the dorsal horn (see Fig. 3-15) in two ways: a capping tangential plexus of fibers over the marginal layer oriented longitudinally, and bushy terminal arbors in the SG forming thin sagittally oriented slabs (4). The mediolateral dimension of a C-fiber arbor is much smaller than this dimension of the A-d type B hair fiber. The terminal arbors of C fibers cluster together to make foci curving in their side branches. Figure 4-4 depicts the extensive terminal field of A-d and C fibers along the length of the spinal cord. Studies have described a dichotomy in C-fiber nociceptor anatomy (10). Using immunohistochemical techniques the subpopulation of C fibers terminating in lamina II$_{i}$ have been found to differ biochemically from C fibers terminating elsewhere (e.g., laminae I and II $_{o}$). C fibers terminating in lamina II$_{i}$ do not appear to contain calcitonin gene–related peptide (CGRP) or substance P, instead staining selectively for the enzymes fluoride-resistant acid phosphatase and thiamine monophosphatase as well as the binding site for the lectin IB4 (Fig. 4-6). As discussed in a following section, these two subsets of C-fiber nociceptors have distinct developmental and perhaps functional characteristics as well.

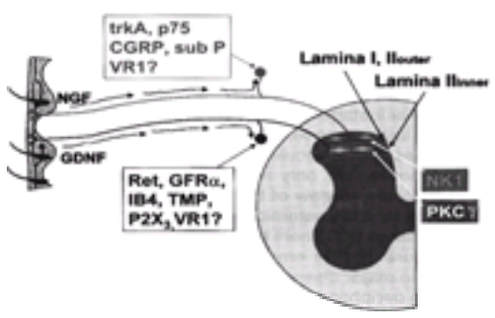

Figure 4-6. Schematic of peripheral and central target fields, trophic factor dependence, and biochemical characterization of two classes of cutaneous C fibers. The class expressing calcitonin gene–related peptide (CGRP) and trkA receptor [a nerve growth factor (NGF) receptor] represents roughly 40% of dorsal root ganglion neurons in rodents. The IB4 lectin binding class represents approximately 30%. Both classes are sensitive to capsaicin probably via the VR1 vanilloid receptor for capsaicin. (GDNF, glial cell line–derived neurotrophic factor; GFRa, GDNF family receptor a; p75, another low-affinity neurotrophin receptor; $P2X_3$, an adenosine triphosphate receptor subtype; PKC, protein kinase C; Ret, receptor tyrosine kinase; sub P, substance P; TMP, thiamine monophosphatase.) (From Snyder WD. Tackling pain at the source: new ideas about nociceptors. *Neuron* 1998;20:630, with permission.)

Termination of Fine Muscle Afferents

Small-diameter muscle afferents (groups III and IV) terminate primarily in dorsal horn laminae and resemble cutaneous small- diameter afferents more than large muscle afferents discussed previously. Mense and associates (11) found that high-threshold myelinated mechanoreceptors (type III) from tail muscle, fascia, and joint capsules sent collaterals to laminae I and V and longer branches to the region of the central canal, as well as to laminae I and V of the contralateral dorsal horn. No terminals were found in laminae III and IV. Craig and Mense (12) have shown that C-fiber muscle afferents terminate in laminae I and V but not in the SG.

Visceral Afferents

Termination of visceral afferents in the spinal cord is of great importance in considering the mechanism of visceral pain. A-d and C afferents, which run with sympathetic autonomic nervous system efferents (termed sympathetic afferents), terminate predominantly in laminae I and V, although they also terminate in laminae IV, VI, VII, and X.

Using the N wave as a signal of the site of afferent termination after stimulation of the sympathetic chain, Selzer and Spencer (13) found that lamina V was the major termination site in the upper two lumbar segments of the cat. Morgan and associates (14), using HRP technique, studied the spinal termination of visceral afferents of the pelvic nerve and noted that the input was largely in S2, less in S1 and S3, still less in L1-4, and contralateral in S1 and S3. The densest staining was in Lissauer's tract, and from this structure two bands of collaterals appeared, one lateral pathway and one medial pathway, thus forming a horseshoe-shaped pattern around the dorsal gray matter. Collaterals from both pathways projected into laminae I, V, VI, and VII, and some from the medial pathway terminated in lamina X (Fig. 4-7). A similar pattern of fiber termination was noted at the L-3 spinal level in the cat after labeling of the sympathetic hypogastric nerve and by Cervero (15) in the cat thoracic cord after splanchnic nerve labeling. None of the visceral afferents was found to terminate in lamina II, a finding whose functional significance is unknown.

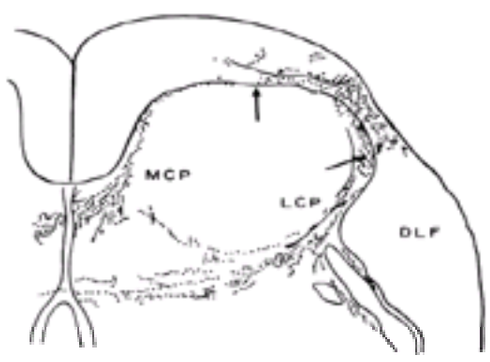

Figure 4-7. Pattern of distribution of collaterals of primary afferents of the pelvic nerve in the S2 segment of cat spinal cord. The pelvic nerve was labeled with horseradish peroxidase, and the ventral roots were cut to eliminate efferent labeling. The densest labeling is in the tract of Lissauer, and from here two bands of collaterals appeared, a lateral pathway (LCP) and a medial pathway (MCP). See text for details. (DLF, dorsolateral funiculus.) (From Morgan C, Nadelhaft I, de Groat WC. The distribution of visceral primary afferents from the pelvic nerve to Lissauer's tract and the spinal gray matter and its relationship to the sacral parasympathetic nucleus. *J Comp Neurol* 1981;201:415–440, with permission.)

Thus, visceral afferents terminate primarily on cells in laminae I, V, and X. Up to 95% of spinal neurons that respond to visceral stimulation, however, also respond to somatic stimuli, thus showing viscerosomatic convergence (16). This convergence was first demonstrated in 1968 by Pomeranz and colleagues (17) in the thoracic cord of cat, and a year later by Selzer and Spencer (13) in the lumbar cord of the same species. Both groups demonstrated that many neurons within the gray matter of the spinal cord responded to electrical stimulation of cutaneous nerves and also could be driven by stimulation of the splanchnic nerve, and, furthermore, that these were visceral A-d and C afferents. Since then, many others have shown this somatovisceral and viscerosomatic convergence at all levels of the spinal cord. Convergence among multiple visceral inputs is also seen, in that stimulation of multiple viscus organs can activate the same lamina I, V, or X neuron (18). These neurons can project to the ventrolateral funiculus of the spinal cord and become part of the spinothalamic and spinoreticular tracts (15). The Willis group has reported a separate visceral ascending pathway in rat (19), monkey (20), and humans (21). Visceral afferents are thought to synapse in the spinal cord (particularly in lamina X) on second-order neurons that then project via the dorsal columns to the dorsal column nuclei and then on to higher brain areas. A lesion of this pathway has been found to inhibit visceral pain behaviors and may underlie the clinical use of myelotomy for visceral pain (see Chapter 106).

Convergence of visceral and cutaneous afferent fibers and muscle and cutaneous afferents onto second-order dorsal horn neurons is the most cited mechanism for referred pain; a phenomenon in which visceral pain is sensed at a somatic site. The site of referral is innervated by the same segmental nerve roots as those innervating the visceral structure (e.g., pain of pleuritic origin referred to the shoulder or angina referred to the chest wall or arm). Although the phenomenon could be explained by single primary afferents innervating both somatic and visceral structures, the low incidence of such primary afferents suggests a central site for referred pain (22). The precise site at which somatic and visceral converging information causes a misrepresentation of pain location is not yet known. The high frequency of somatovisceral convergence in dorsal horn cells may, in fact, argue against the dorsal horn as the critical site because many visceral pains are not referred. The finding of specific visceral nociceptive pathways gives renewed credence to older theories (23) that referred pain is primarily caused by convergence at thalamic or cortical levels at which visceral pain representations, although present (24,25), seem much less detailed than somatic representations.

DORSAL HORN

Enormous advances have been made in knowledge of the complex circuitry, biochemistry, and function of the spinal dorsal horn and its brain stem homologue, the trigeminal subnucleus caudalis (medullary dorsal horn). A number of techniques have made possible physiologic and pharmacologic studies that previously were impossible. For example, the combined use of anatomic (intracellular dyes and ultrastructural analysis) and single cell electrophysiology (*in vitro* and *in vivo*) has permitted precise correlations of structure and function and lent new insight into the synaptic interactions that underlie processing within the dorsal horn. Moreover, immunohistochemical characterization of the dorsal horn has provided a wealth of pharmacologic information including the neurochemical profiles of various sized afferents, their distribution within the dorsal horn, and changes in these profiles with development, activity, or injury (see Chapter 3 for examples in the dorsal root ganglia). This section highlights such work on the morphology, physiology, and biochemistry of the spinal dorsal horn (and its less studied medullary analogue, the medullary dorsal horn). Numerous more specific reviews of the dorsal horn also have been published including those by Wall (26), Cervero (27), Dubner and Bennett (28), Basbaum (29), Yaksh (30), Coderre (31), Coggeshall and Carlton (32), and Millan (33), among others.

Dorsal Horn Morphology

Although it is convenient to subdivide the spinal cord into the various laminae described by Rexed on the basis of shape, size, and distribution of cell bodies, these laminae clearly do not have rigid, exact edges and, furthermore, the dendrites of the cell bodies in one lamina can range widely into neighboring laminae and sometimes into white matter. Nonetheless, we now look more closely at the spinal cord laminae and what is known about their functions as evidenced by their differing cytoarchitecture and electrophysiologic characteristics. Recall that, in this book, lamina I corresponds to the marginal zone, lamina II to the SG, laminae III through V

to the nucleus proprius, and lamina VI to the base of the dorsal horn.

Lamina I

The marginal zone is a thin band that caps the dorsal horn and contains a variety of neuronal types. These include the large cells of Waldeyer, whose dendrites appear parallel to the surface of the lamina. In the cat medullary dorsal horn, Gobel (34) was able to distinguish four types of cells: smooth and spiny pyramidal cells and two types of multipolar neurons. He emphasized that dendrites of these neurons are restricted to the marginal zone and are set to receive direct input from only a restricted population of primary afferent fibers or projections from relay of action of interneurons in deeper laminae. In contrast, Beal and colleagues (35) found in the spinal cord of monkey that the dendrites of cells in the medial part of the marginal zone project ventrally at least to SG and even to lamina III. Therefore, they can receive direct synaptic input from primary afferents that terminate exclusively in marginal zone or SG (as well as presumed relayed activity). Zhang and Craig have looked specifically at lamina I cells projecting to thalamus in cats (36) and monkeys (37,38) and noted three major morphologic types of cells: pyramidal, fusiform, and multipolar. Like Gobel, they noted that the dendritic fields of these cells tended to stay within lamina I (with few exceptions) and emphasized the importance of using horizontal sections, rather than transverse sections, for these morphologic studies (39). Marginal cells located in the lateral part of lamina I often have dendrites that enter into Lissauer's tract. Some of the cell bodies are located within the tract and thus can have synaptic input from axons in the tract (Fig. 4-8).

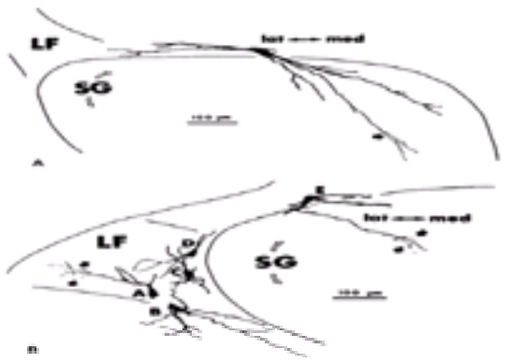

Figure 4-8. Marginal (lamina I) neurons in monkey spinal cord. **A:** The neuron sends a major dendritic projection through lamina II substantia gelatinosa (SG) and into lamina III. **B:** Marginal cells, including a cluster with dendrites extending into Lissauer's tract fibers (LF) (A through D) and a medially located neuron with dendrites (E) descending into the SG. [From Beal JA. The ventral dendritic arbor of marginal (lamina I) neurons in the adult primate spinal cord. *Neurosci Lett* 1979;14:201–206, with permission.]

Lamina I has special function regarding nociception because it is the termination zone of nociceptive afferents and because it contains cells that respond only to noxious stimuli, the so-called nociceptive-specific (NS) neurons (also called *class 3 cells*). Cervero and colleagues (40) reported that marginal NS neurons responding to A-d and C-fiber input from the skin also could be activated by group III and IV muscle afferents, indicating convergence of cutaneous and muscle input. Other neurons in lamina I respond only to innocuous thermal stimuli (class 1), and a third type responds to both noxious and innocuous stimulation and can differentiate between these two by discharging at higher frequency to noxious stimuli. These last cells are called *wide dynamic range* (WDR), *multireceptive*, or *class* 2 neurons. Fewer WDR neurons exist in lamina I than in deeper laminae (particularly lamina V).

Many of the cells in lamina I are projection cells. Many of these have long axons that cross the midline and enter ascending spinal pathways, some projecting to the thalamus, some to the brain stem, and others to the cerebellum. Roughly one-half of the lateral STT, critical for normal pain and temperature sensation, is made up of projecting axons from lamina I cells (37). Other projections interconnect with near and distant spinal segments and are involved in the segmental organization of sensory transmission (41). Attempts to correlate the varied morphology of lamina I cells with their response characteristics (i.e., NS or WDR cells) in lamina I projecting cells has not been very successful, although undertaken by a number of laboratories (39,42,43). In the cat, Craig and colleagues (44) have reported the most success in this regard, recording intracellularly from spinothalamic projecting neurons in lamina I and then morphologically classifying these same cells using biocytin staining. They find a strong correlation between structure and function. Fusiform-shaped cells were found to be NS, responding solely to heat or pinch. Pyramidal-shaped cells were classified as *cold* cells in that they responded to innocuous cooling (and were inhibited by warming). Multipolar cell responses were both NS and polymodal nociceptive, meaning that they responded to cold (called *HPC cells*, signifying responses to heat, pinch, and cold). These interesting structure and function correlations (Fig. 4-9), according to the authors, may have been missed by others because of a failure to test cold responsiveness or because of the use of transverse rather than horizontal spinal cord sections. WDR lamina I spinothalamic cells are rare in the cat and thus were not studied by these authors.

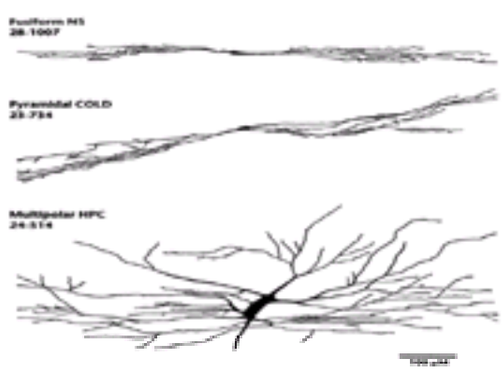

Figure 4-9. Camera lucida reconstructions of examples of three types of morphologically distinct lamina I neurons and their correlated activating stimuli in the cat. Fusiform-shaped cells were found to be nociceptive specific (NS). Pyramidal-shaped cells were *cold* cells in that they responded to innocuous cooling and were inhibited by warming. Multipolar cells were called *HPC cells*, signifying responses to heat, pinch, and cold. Cells and their dendrites were generally contained within two or three serial 50-µm horizontal sections. Rostral is left and medial is up. (From Han ZS, Zhang ET, Craig AD. Nociceptive and thermoreceptive lamina I neurons are anatomically distinct. *Nature Neurosci* 1998;1:223, with permission.)

Lamina II

Most of the neurons in the SG are small, with dendrites arborizing in a rostrocaudal plane. In the early part of the twentieth century, Cajal (45) described two major types of cells in the SG: central cells, which appear to have a radial orientation when viewed in transverse section, a large rostrocaudal orientation in sagittal section, and are found throughout SG; and limotrophe (limiting) cells, which are located in the outer part of the SG (Fig. 4-10). More recently, Gobel (46), on the basis of a detailed study of the cat medullary dorsal horn, described four types of cells: stalked cells, which he believes to be equivalent to Cajal's limiting cells; islet cells, equivalent to Cajal's central cells; arboreal cells; and II to III border cells. Of these, the first two are considered as important dorsal horn nociceptive local-circuit neurons. The stalked cells have cell somata at the border of laminae II and III, dendrites that fan out ventrally in lamina II and occasionally laminae III and IV, and axons that arborize extensively in lamina I among the dendrites of projection neurons (Fig. 4-11). Gobel (46) proposed that they function as excitatory local-circuit neurons, collecting and relaying nociceptive inputs from terminals of primary nociceptive afferents in lamina II to projecting neurons in lamina I. Stalked cell dendrites receive synapses from primary afferents and from dome-shaped axon terminals that resemble the terminals from descending serotonergic axons (28).

Figure 4-10. Transverse section of the dorsal horn of the spinal cord stained with the Golgi technique. C and F are limiting cells, and cells D and H are central cells. (From Cajal SR. *Histologie du systéme nerveux de I'homme et des vertebrés*. Vol 1. Paris: Maloine, 1909, with permission.)

Figure 4-11. A stalked cell of the caudal spinal trigeminal nucleus in the cat. The cell body is in the outer part of lamina II, whereas the dendrites extend into lamina III and even deeper and the axon enters lamina I. The dendrites bear spines and stalklike branches (*arrows*) for which the cells have been named. [From Gobel S. Golgi studies of the neurons in layer II of the dorsal horn of the medulla (trigeminal nucleus caudalis). *J Comp Neurol* 1978;180:395–413, with permission.]

Islet cells, the second major type of local-circuit neurons, are found throughout the SG. Seen in a sagittal section, these have a fusiform cell body and dendritic arbor that is elongated rostral-caudally, and those in lamina II_i extend for well over a millimeter. Islet cell axons are unmyelinated and arborize profusely within and near their dendritic trees. Gobel (46) has proposed that islet cells are inhibitory local interneurons. Some islet cells contain the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and others are enkephalinergic (28,47). Ultrastructural analysis of electrophysiologically characterized and HRP-filled islet cells indicates that their spine heads and dendritic shafts contain aggregates of round and oval synaptic vesicles that synapse with scallop-shaped primary afferent terminals (28,47) (Fig. 4-12). Thus, dendroaxonic synapses may regulate the activity of primary afferent terminals, but the nature of this regulation remains unknown. Islet cell dendrites also synapse on other dendrites, which do not contain vesicles and are thought to come from stalked cells. Islet cells also receive synapses from dome-shaped axon terminals of descending serotonergic axons.

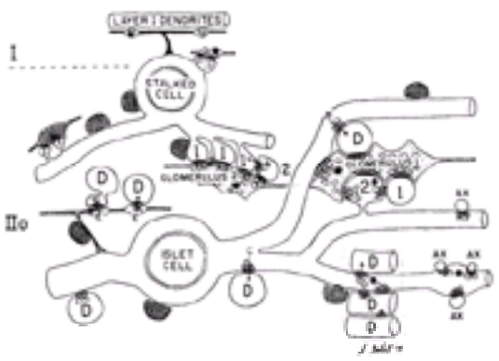

Figure 4-12. Synaptic connections of a lamina II_o islet cell and a stalked cell. Both cells receive axodendritic synapses from primary endings (*stippled*) and nonprimary inputs (*cross-hatched*), which include descending aminergic terminals on their dendrites and cell bodies. The islet cell, with synaptic vesicles in its dendrites, forms dendrodendritic synapses with type I spines and dendritic shafts (D) in glomerulus 1, on dendritic shafts in dendrite bundles (*dotted enclosure*), and with individual dendritic shafts that pass alongside the primary and higher order islet cell dendrites. The islet cell also forms dendroaxonic synapses on the primary ending in glomerulus 1 (*arrowhead*) and on unmyelinated axonal shafts (AX) outside of glomeruli. The islet cell axon (*striped*) receives an axoaxonic synapse on its initial segment from a nonprimary ending, and its endings synapse on dendritic shafts and type I spines. The stalked cell axon (*black*) synapses with layer I dendrites. Potential sites where layer II_o islet cells could synapse with stalked cell dendrites include dendrodendritic synapses with type I spines (*arrow A*) and dendritic shafts (*arrow B*) in glomeruli, with dendritic shafts outside of glomeruli (*arrow C*), and with dendrite bundles (*arrow D*), as well as axodendritic synapses (*arrow E*) at its axonal termination. (From Gobel S, Falls WM, Bennett GJ, et al. An EM analysis of the synaptic connections of horseradish peroxidase filled stalked cells and islet cells in the substantia gelatinosa of adult cat spinal cord. *J Comp Neurol* 1980;194:781–807, with permission.)

The physiologic characteristics of SG cells have been studied by a number of groups. Although both NS and WDR cells have been identified in II_o, only WDR nociceptive cells (48) (and low-threshold mechanical neurons) (28) have been reported in II_i. Of particular value for functional conclusions, in this area containing both excitatory and inhibitory cells, are studies combining anatomic and electrophysiologic methods.

Bennett, Dubner, and coworkers (28), using intracellular HRP techniques, found that both NS and WDR responses were seen in both stalked cells and islet cells in lamina II_o (Fig. 4-13). Islet cells in lamina II_i responded only to innocuous stimuli and no WDR cells in this region were observed in these experiments. The nociceptive inputs could be conveyed by A-d fibers or by A-d and C fibers, whereas the tactile inputs could be mediated by A-d down-hair receptors or A-b guard-hair receptors. They concluded that the patterns of primary afferent excitation of SG neurons were comparable with WDR, NS, and low- threshold mechanoreceptor patterns seen elsewhere in dorsal horn.

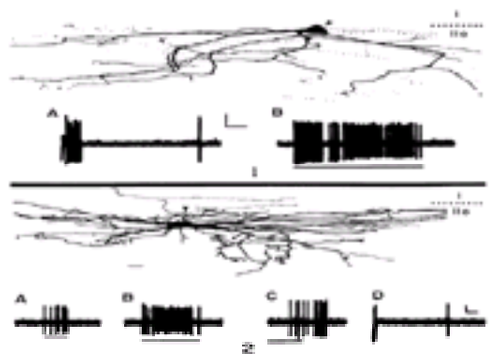

Figure 4-13. Responses of stalked cells and islet cells whose cell bodies are located in the outer part of lamina II $_o$. **1:** Nociceptive-specific stalked cell labeled with intracellular injection of horseradish peroxidase. *Inset A* shows the response of the cell to electrical shocks applied to the receptive field and indicates a convergent input from A-d and C fibers. *Inset B* shows the response to pinch with toothed forceps. **2:** A wide dynamic range islet cell labeled with horseradish peroxidase. *Inset A* shows responses to brushing; *B*, responses to pinching with toothed forceps; *C*, responses to noxious heat; and *D*, responses to electrical shock applied to the skin. (From Bennett GJ, Abdelmoumene M, Hayashi H, et al. Physiology and morphology of substantia gelatinosa neurons intracellularly stained with horseradish peroxidase. *J Comp Neurol* 1980;194:809–827, with permission.)

In other respects, the response of SG neurons to continuous stimulation is quite different from that seen elsewhere in dorsal horn, with many SG neurons showing a powerful habituation to repeated stimuli (28). In addition, Cervero and colleagues (49) reported that SG cells had a tonic discharge that could be inhibited by cutaneous stimulation. A variety of responses were noted: Some cells were inhibited by innocuous mechanical stimuli but excited by noxious input, others were inhibited by both innocuous and noxious stimuli, and still others were inhibited by noxious stimuli but excited by innocuous stimulation. The complexity of the circuitry of this area with its inhibitory and excitatory cells modulating other laminar inputs and outputs has made the functional implications of SG difficult to assess *in vivo*. As noted in the gate-control theory in 1965, the SG seems ideally suited to modulate pain responses. Little evidence of such a role has been demonstrated as yet, however. The development of *in vitro* electrophysiologic techniques applied to spinal cord circuitry may help to unravel the complexity of this region.

Laminae III and IV

Lamina III is distinguished from lamina II by the larger number of myelinated axons and from lamina IV by the appearance of large cell bodies in the latter lamina. Moreover, its anatomy is dominated by the extensive dendritic arbors arising from cells in deeper layers and by *antenna-type* neurons thought to be cells of origin of the spinocervical tract and whose dendrites divide horizontally before pushing dorsally into lamina II (50). Willis and associates (38) found spinothalamic projection cells in laminae III and IV in monkeys that send dendrites through the SG and into lamina I. Beal and Cooper (51) noted that lamina III also contains many central or islet cells that are similar to the neurons found in lamina II. Some small cells have small, low-threshold excitatory receptive fields that make up part of the larger receptive field of the nearest large cell. Although no specific function has yet emerged for lamina III, which may well represent a transition between lamina II and IV, studies by Bennett and colleagues (28) have demonstrated that the cells are particularly responsive to low-threshold afferents that terminate in this region. As we discuss in Modulatory Mechanisms: Structural Reorganization, sprouting of low threshold primary afferent terminals from lamina III into more superficial areas of the dorsal horn (more commonly associated with nociception) may be a mechanism for the development of neuropathic pain (52).

Lamina IV contains some large cells that send dendrites into more superficial layers of the dorsal horn. Many of these neurons project their axons in the dorsal column white matter to the dorsal column nuclei. This lamina also contains small stellate cells. By far the most common cell type is excited only by light mechanical stimuli to the skin, and the response of these cells does not increase with increases in pressure intensity (53). However, several investigators have observed lamina IV WDR cells, and Besson and colleagues noted a few lamina IV cells that are excited by intraarterial injection of bradykinin into the limb (2).

Lamina V

Lamina V is important in nociception and pain because it receives input from A-d and C nociceptors and contains cells whose axons contribute to long ascending tracts, including the spinothalamic and spinomesencephalic, and, to a lesser extent, the spinoreticular tracts (see Ascending Systems, later in this chapter). The most common cells in lamina V are the WDR or multireceptive neurons. By definition they respond to a variety of inputs from low-threshold and high-threshold mechanical, thermal, and chemical stimuli by way of large and small afferent fibers. Evidence exists that these WDR neurons and those in lamina I constitute one-third to one-half of the long ascending nociceptive systems (28). WDR neurons often have large cutaneous receptive fields with a central area responsive to both tactile and noxious stimuli, surrounded by a larger area with ill-defined borders that is responsive only to noxious stimuli. The excitatory receptive field is surrounded by an inhibitory receptive field. Some lamina V neurons have other response properties, including tactile and NS responses.

Certain cells in lamina V respond to A-d and C fibers of visceral origin as well as to cutaneous low- and high-threshold mechanical stimuli, which, as previously mentioned, may constitute the neural substrate of referred pain (17). As we discuss later, the organization of these WDR receptive fields and their responsiveness to different kinds of primary afferent inputs are modulated by descending controls and spinal circuitry. A large body of evidence indicates that WDR neurons contribute to the perception of pain, including the finding that selective activation of human WDR neurons is sufficient to produce pain (28).

Lamina VI

According to Rexed (1), lamina VI cells exist only at certain levels of the spinal cord: They are present in the lumbosacral and cervical enlargements, but not in most of the thoracic cord or lower sacral and coccygeal segments. Lamina VI cells are somewhat smaller than those found in lamina V, and Wall (53) characterized them as responsive to both low-threshold muscle afferents and low- and high-threshold cutaneous afferents. In medullary dorsal horn the homologue to spinal lamina VI consists of neurons (receiving tactile and low-threshold muscle afferents) located at the junction between the subnucleus caudalis and the cuneate nucleus (38,54).

Intermediate Region and Ventral Horn

Cells of the intermediate region and ventral horn contribute a small percentage of axons to nociceptive ascending tracts, including the spinothalamic and spinoreticular (2,26). Lamina VII and VIII make up the majority of the ventral horn and surround clusters of motor neurons (lamina IX). Lamina VII is continuous with the medullary reticular formation. It includes cells with large, often bilateral, receptive fields that are excited (presumably indirectly) by a wide range of stimuli. Many neurons in laminae VII and VIII respond to high-threshold input.

Lamina X

Lamina X consists of a group of specialized cells gathered around the central canal, some of which respond to high-intensity bilateral stimuli and are considered NS. This group of cells may constitute one of the polysynaptic chains linking the entire length of the cord and brain stem that is believed to be involved in transmission of nociceptive information. Lamina X cells have been suggested to be particularly sensitive to visceral nociceptive stimulation (55). However, such selectivity, if it exists, is likely to be a matter of degree only, in that like other lamina of the spinal cord (I and V), a great deal of convergence between somatic and visceral input takes place in lamina X, and a small minority of cells are responsive solely to visceral stimulation (56). Nevertheless, this region does contain neurons that receive input from visceral primary afferents and project cephalad as part of the dorsal column postsynaptic pathway found to be particularly important in transmitting visceral nociceptive information supraspinally (41).

Trigeminal System

Sensory innervation of the face is more highly specialized than any other body region. Like the spinal nerves and the dorsal root ganglia, the primary afferents of the face are pseudounipolar cell bodies in the gasserian ganglion that have peripheral and central processes. The peripheral processes make up the ophthalmic, maxillary, and mandibular trigeminal divisions, and the central processes make up the sensory root, which enters the central nervous system (CNS) on the ventral surface of the pons (see additional discussion in Chapter 3 including Fig. 3-17). On entering the brain stem, these central processes pass through the spinal trigeminal tract to terminate in the trigeminal nuclear complex, composed of the main sensory nucleus and the spinal trigeminal nucleus (see Fig. 3-17). The main sensory nucleus is located at the level of the pons, whereas the spinal trigeminal nucleus is deep to the descending trigeminal tract and extends as far caudad as the second, and often the third, cervical segment (Fig. 4-14). The spinal nucleus is further subdivided into three parts: subnucleus oralis, subnucleus interpolaris, and subnucleus caudalis (57,58,59,60 and 61).

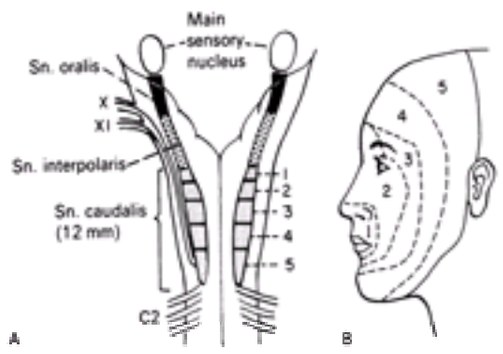

Figure 4-14. **A:** The rostrocaudal somatotopic organization of the subnucleus caudalis. **B:** The relation of the subnucleus caudalis to input from primary afferents on the face. The fibers nearest to the lips and lower nose (area 1) terminate highest in the subnucleus caudalis; the innervation of successively more lateral regions of the face ends progressively in more caudal parts of the subnucleus caudalis. This rostrocaudal somatotopic organization applies to all three divisions of the trigeminal nerves and produces an *onion peel* pattern. (Modified from Kunc Z. Significance of fresh anatomic data on spinal trigeminal tract for possibility of selective tractotomies. In: Knighton RS, Dumke PR, eds. *Pain*. Boston: Little, Brown, 1966:351–366.)

On entering the brain stem, the A-d and C fibers pass to the spinal tract and descend in it to terminate within the subnucleus caudalis (Fig. 4-15). In contrast, the large myelinated fibers divide into short ascending branches that terminate in the main sensory nucleus and long descending branches that pass through the trigeminal tract and give off collaterals to various parts of the underlying spinal nucleus. As these fibers pass caudad and give off collaterals, they become smaller so that by the time they reach the subnucleus caudalis 75% of them are less than 2 µm in diameter, with a consequent progressive slowing of impulse conduction (57).

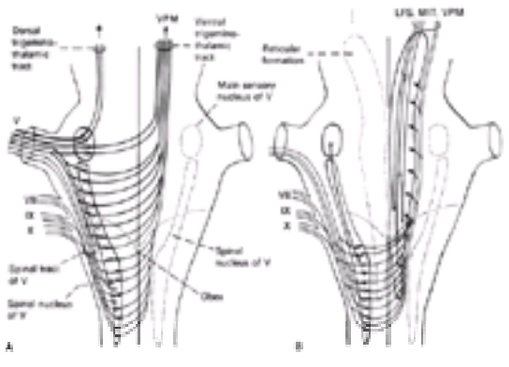

Figure 4-15. **A:** Detailed depiction of primary afferent input into the trigeminal main sensory nucleus and the spinal nucleus, as well as input from primary afferents of the VIIth, IXth, and Xth cranial nerves. The descending fibers from the four cranial nerves make up the descending spinal tract, and their collaterals end in the spinal nucleus, where they synapse with *second-order* neurons. The latter cross to the opposite side to make up the ventral trigeminothalamic tract. Some of the fibers from the main sensory nucleus and subnucleus oralis ascend ipsilaterally as the dorsal trigeminothalamic tract. **B:** Origin and initial course of the paleotrigeminothalamic tract. The fibers cross to the opposite side, and some ascend to reach the thalamic ventroposteromedial (VPM) and medial/intralaminar nuclei (MIT), whereas others pass into the reticular formation, where they synapse with ascending reticulothalamic fibers. (LFS, limbic forebrain structure.)

An important difference between the trigeminal and spinal afferent systems is the separate anatomy of the proprioceptive system of the face. The trigeminal mesencephalic nucleus is actually a collection of cell bodies of primary neurons, which instead of being localized in the gasserian ganglion with other somatic primary cell bodies, have migrated into the midbrain and presumably mediate proprioception from oral mucous membrane, temporomandibular joint, masticatory and ocular muscle spindles, and periodontal ligament receptors (57). The pseudounipolar cell bodies in the trigeminal mesencephalic nucleus give off peripheral branches that reach the muscles and other structures, and the central branches project to the trigeminal motor nucleus. The monosynaptic contact with somatomotor neurons made there completes a two-neuron arc mediating the jaw-jerk reflex and is homologous to monosynaptic spinal reflexes.

Trigeminal Somatotopic Organization. Strict somatotopic organization is one of the most important and clinically relevant characteristics of the trigeminal system and exists throughout the gasserian ganglion, sensory root, spinal tract, and spinal nucleus. In the gasserian ganglion the cell bodies of the mechanoreceptive afferents within the ophthalmic division are concentrated medially and somewhat anteriorly. Those of the mandibular division are caudal and lateral, and the cell bodies of the maxillary nerve lie between those of the other two divisions. Moreover, cell bodies of neurons that innervate the perioral and oral areas are located ventrally in the ganglion, whereas those that supply the structures remote from the mouth are located in the dorsum of the ganglion. In the sensory root, the afferents are also somatotopically organized in a medial to lateral fashion, such that the central processes of the mandibular division are posteromedially positioned, those of the ophthalmic division are located anterolaterally, and those of the maxillary branch are situated in an intermediate position (57) (see additional discussion in Chapter 3 and Fig. 3-18).

Complementary experimental and clinical studies have shown a similar somatotopic organization in the trigeminal spinal tract. The central processes of the ophthalmic division are situated ventrolaterally, those of the mandibular division are situated dorsomedially, and those of the maxillary division lie in between. This somatotopic laminar organization involves myelinated and unmyelinated fibers. Degeneration studies have shown that the collaterals of the myelinated fibers terminate in the underlying main sensory and spinal nucleus, distributed in sharply defined sectors extending deeply into the nucleus and overlapping only slightly with neighboring projections (57). This organization is in contrast to that of the small diameter nociceptive afferents. Although some nociceptive afferent collaterals arise at the level of the subnucleus interpolaris, most nociceptive terminal axonal arbors are found in the subnucleus caudalis (59,62,63).

Another important and clinically relevant somatotopic pattern occurs along the rostrocaudal axis of the subnucleus caudalis. The *onion peel* was first described by Dejerine (63) on the basis of the sensory deficit caused by certain pathologic lesions of the brain stem. Figure 4-14 depicts this pattern in which sensory innervation near the midline around the mouth and nose is represented in the most rostral part of the subnucleus caudalis, whereas the innervation of successively more lateral regions of the face maps to progressively more caudal parts of the subnucleus caudalis. Much of our knowledge of this somatopy comes from electrophysiology studies of Yokota (60). The clinical importance of this somatotopy is seen in the results of trigeminal tractotomy by Kunc for facial pain. Kunc (64) produced lesions at different levels of the subnucleus caudalis and then compared the distribution of the resultant analgesia from the tractotomy with the scheme published by Dejerine. He noted that if the lesion was placed above the upper pole of the subnucleus caudalis, analgesia of the whole ipsilateral trigeminal nerve territory resulted. On the other hand, if the tractotomy was performed more caudally, the analgesia was incomplete, with sensory sparing of the center of the face. With more caudal sections, these areas expanded concentrically. These results led Kunc to conclude that whereas all three divisions of the trigeminal nerve terminate in all segments of the spinal nucleus, the terminations of the primary afferents from the center of the face are most intense in the highest level and those from the periphery are most intense in the lowest level.

Relation of Trigeminal Fibers with Nociceptors in Other Cranial Nerves. The classic technique of medullary trigeminal tractotomy can be extended somewhat medially to produce analgesia of the posterior one-third of the tongue, tonsil, pharynx, tympanic membrane, and external auditory canal. Tactile sensibility in these areas is not noticeably altered after the operation. These results suggest that the central processes of cranial nerves VII, IX, and X terminate and synapse with cells in the dorsomedial part of the subnucleus caudalis and the spinal dorsal horn at levels C1, C2, and perhaps C3 (Fig. 4-16). General visceral afferent input traveling in cranial nerves IX and X relays in nucleus tractus solitarius (65).

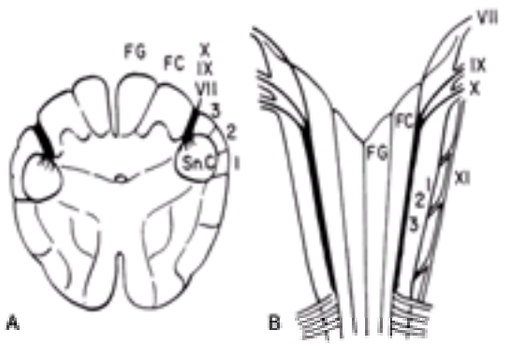

Figure 4-16. Schema depicting the distribution of the central processes of primary afferents of the VIIth, IXth, and Xth cranial nerves, which make up a bundle that is wedged between the fasciculus cuneatus and the mandibular division of the trigeminal nerve. These fibers descend and enter the subnucleus caudalis (SnC), in which they synapse with the second-order trigeminothalamic neurons. **A:** Transverse section. **B:** Dorsal view. (FC, fasciculus cuneatis; FG, fasciculus gracilis; 1, 2, and 3, the divisions of the trigeminal nerve.) See text for details.

Relation of Trigeminal System with Cervical Nerves. Dorsal root fibers from upper cervical nerves also ascend and terminate in the subnucleus caudalis. These overlapping terminations provide a morphologic basis for the substantial interaction between the upper cervical dermatomes and cranial nerve dermatomes revealed after brain lesions or pharmacologic manipulations (59). They also complement evidence indicating a major homology between the trigeminal subnucleus caudalis and the spinal dorsal horn. Finally, this convergence of cranial and upper cervical primary afferents into a common synaptic region in the caudal medulla and upper cervical cord provides a logical explanation for the phenomenon of referred pain in the head and neck.

Morphology of the Medullary Dorsal Horn. On the basis of cytoarchitectonic structure, Olszewski (61) proposed a subdivision of the trigeminal subnucleus caudalis into three layers: the marginal layer, SG, and magnocellular layer. Most investigators (47,59,60,62) now agree that the marginal layer corresponds to Rexed's lamina I; the SG to Rexed's lamina II; and the magnocellular layer, although much expanded, to laminae III and IV of the spinal dorsal horn. The neck region of the dorsolateral gray matter, which is ventromedially adjacent to the magnocellular layer and is part of the lateral reticular formation, is homologous to spinal lamina V, wherein most of the trigeminal WDR neurons are located. This region is the lateral portion of the subnucleus reticularis dorsalis (Fig. 4-17).

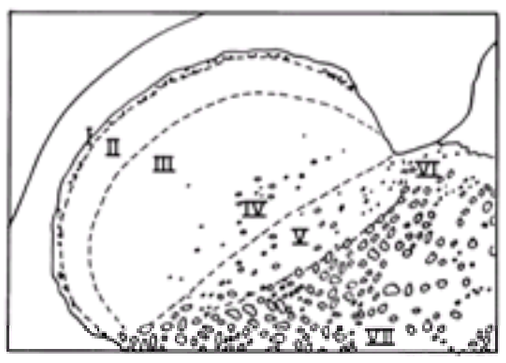

Figure 4-17. Laminar structure of the dorsolateral gray matter of the caudal medulla oblongata at the level of the subnucleus caudalis, more properly called the *medullary dorsal horn*. See text for details. (From Yokota T. Neural mechanism of trigeminal pain. In: Fields HL, Dubner R, Cervero F, eds. *Advances in pain research and therapy*. Vol 9. New York: Raven, 1985:211–232, with permission.)

Neurons receiving tactile and low-threshold muscle afferents, which in the spinal cord are located in lamina VI, in the caudal medulla are located at the junction between the trigeminal subnucleus caudalis and the cuneate nucleus, an area that is continuous with lamina VI of the first cervical segment (60). Finally, the dorsolateral part of the subnucleus reticularis ventralis is probably the homologue of lamina VII of the spinal cord, and this region also contains trigeminal nociceptive neurons (60).

Just above the level of the obex, the subnucleus caudalis makes an abrupt transition to an entirely different structure, which constitutes the subnucleus interpolaris. In contrast, at its caudal end, the subnucleus caudalis and the adjacent reticular formation are directly continuous with the dorsal horn in the cervical spinal cord.

Primary Afferent Input to the Medullary Dorsal Horn. As previously mentioned, the primary afferents projecting to the subnucleus caudalis include myelinated and unmyelinated fibers, the caliber of individual myelinated fibers in the spinal tract decreasing markedly below the level of the obex (57). Both groups of fibers penetrate the subnucleus caudalis from the spinal tract in a spatially ordered radial pattern, in contrast to the terminal projections in the dorsal horn, in which myelinated fibers enter medially (57,59). A-d mechanical nociceptors and C nociceptors terminate in laminae I, II $_o$, and V. A-d low-threshold mechanoreceptive afferents terminate in laminae II$_i$ and III, whereas functionally distinct large A-b low-threshold mechanoreceptive afferents have overlapping distributions in laminae III through VI (62,66).

Intrinsic Neurons of the Medullary Dorsal Horn. Although less studied, the anatomic, physiologic, and pharmacologic characteristics of intrinsic medullary dorsal horn cells are quite similar to those seen in spinal dorsal horn cells. NS (Fig. 4-18) and WDR (Fig. 4-19) cells are evident (34,60,62). Lamina I contains multipolar and fusiform or bipolar trigeminothalamic neurons (34,40,62). The same two major types of dorsal horn local-circuit neurons, the stalked and the islet cells, are found in the SG of the medullary dorsal horn. Multipolar and bipolar thalamic projecting neurons are present in lamina V (62).

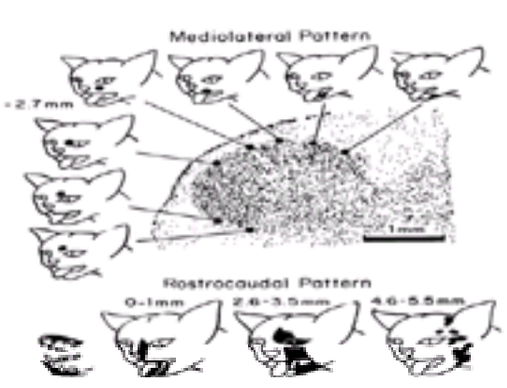

Figure 4-18. Somatotopic organization of nociceptive-specific neurons in the superficial layers of the subnucleus caudalis in the cat. The upper panel shows the locations and receptive fields of marginal layer nociceptive-specific neurons obtained from a transverse section 2.7 mm caudal to the obex. The lower plane shows the receptive fields of nociceptive-specific neurons within the superficial layers at various levels of the subnucleus caudalis. A concentric shift of receptive field representation exists along the rostrocaudal axis of the caudal medulla oblongata. (From Yokota T. Neural mechanism of trigeminal pain. In: Fields HL, Dubner R, Cervero F, eds. *Advances in pain research and therapy*. Vol 9. New York: Raven, 1985, 211–232, with permission.)

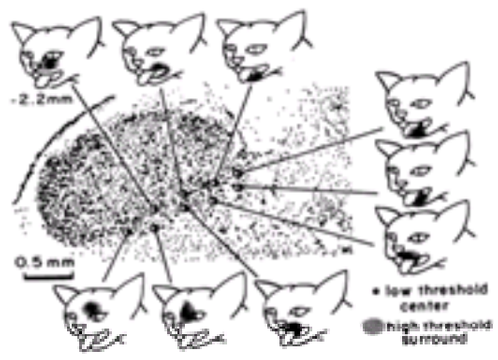

Figure 4-19. Locations and receptive fields of trigeminal wide dynamic range neurons obtained from a transverse section 2.2 mm caudal to the obex in the cat. Trigeminal wide dynamic range neurons are located in the lateral part of the subnucleus reticularis dorsalis and show a somatotopic organization. (From Yokota T. Neural mechanism of trigeminal pain. In: Fields HL, Dubner R, Cervero F, eds. *Advances in pain research and therapy*. Vol 9. New York: Raven, 1985, 211–232, with permission.)

Behavioral and electrophysiologic studies indicate that the more rostral subnuclei of the spinal trigeminal nucleus also receive nociceptive input (57). Terminals of primary afferents and nonnociceptive afferents are found in the subnucleus interpolaris just rostral to the medullary dorsal horn (MDH) (66). A tonic ascending influence of the medullary dorsal horn on more rostral trigeminal neurons has been demonstrated both anatomically and physiologically (47). The afferent neurons projecting rostrally are predominantly from the nucleus proprius (laminae III and IV). These are primarily tactile sensitive neurons that have collateral projections to the thalamus (59). Behavioral studies in cat and monkey suggest that pain sensations from the tooth pulp are intact after trigeminal tractotomy at the level of the obex (67).

Dorsal Horn Nociceptive Physiology

The dorsal horn neurons described previously (summarized in Fig. 4-20) that are excited by natural forms of cutaneous stimulation include (a) low-threshold mechanoreceptive and low-threshold thermoreceptive neurons (class 1); (b) NS neurons (class 3); and (c) WDR or multireceptive neurons (class 2). Low-threshold mechanoreceptor neurons are excited only by touch, hair movement, and other types of innocuous tactile stimulation, whereas low-threshold thermoreceptive neurons are excited by innocuous thermal stimulation. NS (class 3) neurons respond only to stimuli that threaten or actually produce tissue damage, and they are of two types: 3a, which can be excited by A-d nociceptive afferents, and 3b, which can be excited by both A-d and C afferents from the skin and from muscle (40). The WDR (class 2) neurons respond to hair movement and weak mechanical stimuli but respond maximally to intense and potentially tissue-damaging or actually damaging stimuli (Fig. 4-21).

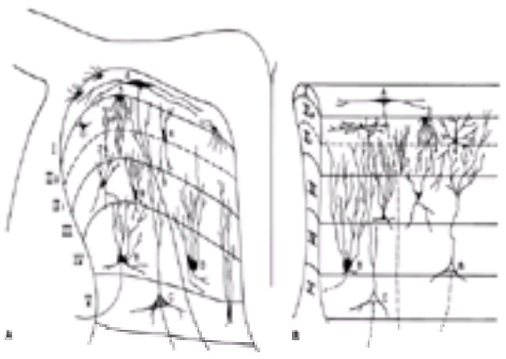

Figure 4-20. A schematic arrangement of various cell types found in the upper five laminae of the dorsal horn of the human spinal cord. **A:** A transverse view. **B:** A sagittal view. Cell types: *A*, a large marginal neuron with output to the anterolateral ascending systems; *B*, two large antenna cells in lamina IV and a smaller one in lamina III, which are low-threshold mechanoreceptive neurons; *C*, a wide dynamic range neuron in lamina V. In the substantia gelatinosa (II_o, II_i), *1* is an islet cell, *2* is a filamentous cell, *3* is a stalked cell, and *4* is a stellate cell. The axons of neurons in **A** are shown solid, whereas in **B** they are indicated by a dotted line. (Modified from Schoenen J. *Organisations Neuronale de la Moelle Epiniére de l'Homme*. Thesis, Faculty of Medicine, Universite de Liége, 1980.)

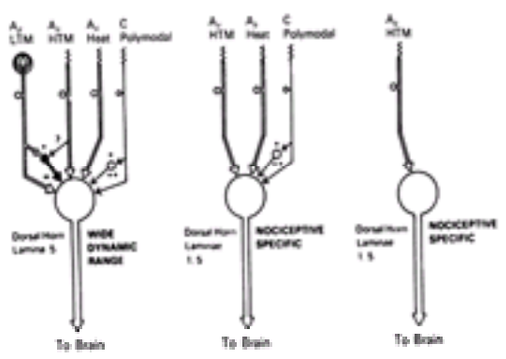

Figure 4-21. Three types of nociceptive cells in the dorsal horn, their inputs from primary afferents, their location in the spinal cord, and their output to ascending systems. Some wide dynamic range neurons are also found in lamina I. Wide dynamic range neurons receive inputs from low-threshold mechanoreceptive primary afferents (LTMs), A-d thermoreceptive afferents, high-threshold mechanoreceptive afferents (HTMs), and C-polymodal nociceptive afferents. The nociceptive-specific dorsal horn neurons receive input exclusively from nociceptive afferents. (From Price DD, Dubner R. Mechanisms of first and second pain in the peripheral and central nervous system. *J Invest Dermatol* 1977;69:167–171, with permission of Blackwell Science, Inc., Oxford, UK.)

Low-threshold thermoreceptive neurons are located in the superficial dorsal horn laminae, whereas low-threshold mechanoreceptor neurons are located in all laminae except lamina I. These low-threshold cells have small receptive fields with sharp boundaries; receptive field characteristics suggest that the cells encode stimulus location. Receptive fields in distal parts are smaller than those in proximal body parts. NS neurons are located mainly in laminae I, II_o, V, and X. NS neurons have receptive fields similar to those of low-threshold groups and therefore presumably also encode stimulus location. WDR or multireceptive neurons have larger and more complex receptive fields with central areas that are responsive to both tactile and noxious stimuli and are surrounded by a larger area with ill-defined borders responsive only to noxious stimuli. The WDR cell excitatory receptive field is often surrounded entirely by an inhibitory receptive field.

Despite these generalities in receptive field properties for nociceptive cells in the spinal cord, it has become clear that receptive field characteristics of a particular cell can change dramatically as a function of pharmacologic and physiologic modulation. Increases in receptive field size, for example, have been correlated with repeated nociceptor activation by tissue injury (68), the mechanisms of which are likely caused by changes in both the peripheral (see Chapter 3) and central (see Central Sensitization, later in this chapter) nervous system. Similarly, it is important to note that anesthetics may change the response properties of nociceptive cells and that most of the studies of spinal cord neurons discussed previously were gathered in anesthetized animals. Collins' group has reported a dramatic effect of barbiturate anesthesia in increasing the incidence of spinal WDR cells in the cat (69). This effect appears to be caused by barbiturate-induced increases in responses to noxious stimuli by cells that normally only respond to low-threshold stimuli (70). An increase in responses of dorsal horn cells to noxious stimuli with low doses of barbiturates

also has been reported in monkeys (71). Spinal or decerebrate preparations, which avoid the need for anesthesia, are no less complicated in that the descending modulation of spinal cord nociceptive cells is considerable. Despite these concerns, Dubner and his colleagues (72) recorded from NS and WDR neurons in awake-behaving monkeys and their results, in general, supported those previously reported in anesthetized and spinalized animals. Indeed, the Dubner group (73), using the same awake-behaving primate model, demonstrated that WDR neurons may be more involved in encoding of the perceived intensity of noxious stimuli than previously thought. Their studies showed that WDR neurons are more precise in detecting small increments of noxious heat intensities than NS neurons. Thus, although an important effect of anesthesia on spinal nociceptive cells cannot be denied, the much more difficult studies in awake animals have thus far not negated the findings in the anesthetized preparation.

Modulation of nociceptive cell activity also may be mediated by small SG cells that receive intrasegmental primary afferent nociceptive input. Moreover, axons from these SG cells project up and down the spinal cord by way of the tract of Lissauer, enabling extrasegmental effects, and to the opposite SG by way of the dorsal commissure. Short propriospinal fibers run in white matter bundles close to the gray matter and may link spinal segments to the brain as well as to each other. Activity in these and other ascending nociceptive systems provoke inhibitory and facilitatory effects on dorsal horn nociceptive responses via descending systems projecting from brain to spinal cord. A number of spinal reflexes can also modulate dorsal horn nociceptive response properties. Direct or indirect peripheral nociceptor activation of anterior and anterolateral horn cells stimulates somatomotor neurons and preganglionic sympathetic neurons, respectively, to provoke autonomic segmental and extrasegmental nocifensive reflex responses (Fig. 4-22). These reflexes, in turn, can give feedback to modulate subsequent nociceptor activity via effects on blood flow or muscle tension (see further discussion in Chapter 3 and Fig. 3-25).

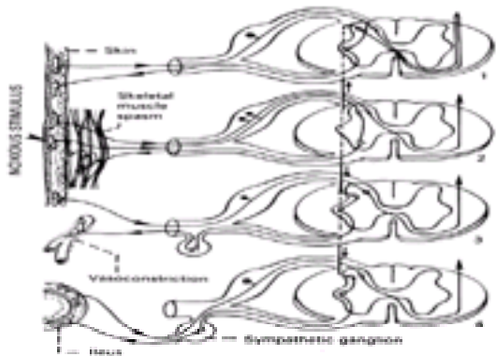

Figure 4-22. Simple diagram to depict the neural pathways for segmental reflex responses to noxious stimulation. Input from the site of injury spreads to the same and adjacent segments of the spinal cord and thus stimulates somatomotor neurons in the anterior horn, which produce skeletal muscle reflex contraction (2). Profound contraction can lead to muscle ischemia and resultant additional nociceptor activation; giving rise to a positive feedback loop referred to as spasm. Other impulses stimulate preganglionic sympathetic neurons in the intermediolateral column to produce vasoconstriction in the skin and splanchnic region (1 and 3). This also produces increased sympathetic tone, which results in an increase in cardiac output and blood pressure and a decrease in the tone of the gastrointestinal tract (4) that may progress to ileus (dashed line indicates normal size of the gut).

Neuropharmacology of Dorsal Horn Inputs

Discussion of the response characteristics of medullary or spinal dorsal horn neurons to noxious stimuli leads naturally into the question of what neurotransmitters mediate or modulate those responses. An explosion of research has investigated the neuropharmacology of nociceptive neurotransmission, particularly that involving the primary afferent (see Chapter 3). Neurochemicals modulating nociception at the level of the dorsal horn could include excitatory and inhibitory agents released by terminals of primary afferents, interneurons of the dorsal horn, and descending axonal projections from supraspinal sites. Minimum criteria necessary for identification of a substance as a neurotransmitter include (a) the candidate neurotransmitter or its *immediate* precursor must be present presynaptically (e.g., within dorsal root ganglion cells or primary afferent terminals); (b) the putative agent must be released by stimulation of a presynaptic terminal (e.g., by a painful stimulus); and (c) the effects of the exogenously applied agent must mimic the effect of the appropriate physiologic stimulus when applied to the terminal field of the unanesthetized animal (e.g., must produce pain behaviors).

An ever-growing list of neuroactive substances has met these criteria for classification as a neurotransmitter in the spinal cord. Probably most important are the excitatory amino acids glutamate and aspartate. However, a number of peptides including substance P, vasoactive intestinal polypeptide, cholecystokinin (CCK), and CGRP also fulfill these criteria. Peptide-mediated effects differ in several ways from more classical, *fast* neurotransmitters (named for their rapid onset and offset of action) such as glutamate. The term *neuromodulation* describes the often slow onset and slow offset effects of a substance, frequently a peptide, that may occur some distance from the place at which it was released (volume transmission). In this way, these neuromodulators resemble hormones in their wide-reaching effects (although the latter term is usually reserved for blood-borne agents). In contemporary neurobiology, these terms are used less frequently as it has become clear that the hormonal, neuromodulator, or neurotransmitter characteristics of a particular released neuroactive substance may vary as a function of site of release, neurochemical environment, and previous stimulus history. In general, onset and offset times of a released neuroactive agent depend on the amount released, its degradation or uptake (e.g., via transporters), its receptor location, and its mechanism of action (e.g., effects on ion channels, enzyme activation, or gene induction). All of these factors can show considerable plasticity in their effects as a result of prior or concurrent neural activity.

Thus, it is likely that numerous substances contained within the central terminals of primary afferents can act as nociceptive neurotransmitters. Moreover, it is now clear that more than one releasable neurotransmitter can coexist in the same or different terminals of a single neuron. This is in contrast to what was believed for many years (Dale's law). For instance, in a single primary afferent terminal at the ultrastructural level both substance P (dense core vesicles that frequently contain peptides) and amino acid transmitters (smaller, clear vesicles) can be identified (74). The release of such primary afferent transmitters may also be modulated by postsynaptically released substances, so-called retrograde neurotransmission. The opioid peptide dynorphin in dendritic vesicles in the hippocampus, for example, can be released by synaptic excitation and retrogradely inhibit further synaptic activity via inhibition of excitatory amino acid release (75). Furthermore, diffusible neurotransmitters (e.g., the gas nitric oxide) can act retrogradely to increase synaptic excitation when synthesized in postsynaptic or other neighboring cells (76). The multiple levels of feedback in tightly regulating neurotransmitter concentrations in the synaptic cleft are further exemplified by the well-known role of presynaptic autoreceptors and their role in inhibiting (or rarely, facilitating) further transmitter release.

Thus, neurotransmission in the CNS is a complex process with multiple mechanisms interacting, all aimed at tightly controlling the release and action of neuroactive substances. The adaptive advantages of pain sensation to the survival of an animal suggests that nociceptive neurotransmission is as tightly regulated as any mechanism. With this overview in mind, we begin to examine the known neuropharmacology of nociception in the spinal dorsal horn. We then look at the modulation of this system by pharmacologic, morphologic, developmental, and descending influences and their hypothesized importance in regulating the perception of pain.

Glutamate Neurotransmission in the Dorsal Horn

Like the majority of excitatory transmission in the CNS, excitatory transmission in the dorsal horn and specifically that involved in nociception is mediated largely via excitatory amino acids (including glutamate and aspartate). Glutamate, in particular, is released from depolarized primary afferent terminals in the dorsal horn; it binds to receptors postsynaptically to depolarize dorsal horn second-order cells and thus transmits the nociceptive signal to the CNS. Glutamate concentrations in the synaptic cleft are tightly controlled by glutamate transporters that quickly remove glutamate from the synapse. The effects of glutamate on neurotransmission are complicated by the variety of characterized receptors that bind glutamate. Much is known about glutamate receptors including their molecular structure, anatomy, physiology, and function in a variety of brain areas. We briefly discuss these receptors as examples of CNS receptors before focusing on their role in pain.

Glutamate receptors, like all receptors, are proteins that bind an agonist and thereby initiate a cellular response. Receptors can be classified on the basis of a number of different structural or functional criteria. With the development of molecular biologic techniques, we now have the ability to describe a large number of glutamate receptor subtypes based on minor alterations in the amino acid sequences or subunit composition of these proteins. Historically, receptors have been classified based more on their pharmacologic properties (i.e., different receptor types bind different drugs, including the ligand in question, with different affinities or with different effects). For example, many years before the opiate receptors were cloned, opiate receptors were subclassified based on responses of animals to different opiate drugs. Similarly, muscarinic and nicotinic acetylcholine (ACh) receptors were defined by differing effects of ACh and the effects being mimicked by two exogenous

chemicals, nicotine and muscarine.

This is clearly a much less precise approach than molecular biology in receptor characterization because one is limited to the pharmacologic tools already available. For instance, the delta opiate receptors were not identified until the endogenous opiates that bind them with high affinity were identified. The pharmaceutical industry, then, is excited about receptor molecular biology because such techniques provide specific targets for their chemical development. Moreover, neuroscientists can, for example, use these molecular targets to grow antibodies specific to various receptor types, ultimately allowing much greater resolution for anatomic localization of receptors than previously possible. Nonetheless, functional end-points, not just binding sites, are important for classification of receptors.

Once the amino acid structure of a receptor is known, physiologists can add these receptors, or the messenger RNA instructions for producing them, to simple systems (frog oocytes or various tumor cell lines) to study their pharmacology or physiology reproducibly and efficiently. More than 30 genes have been identified as important for expressing the various subunits and subtypes that make up the known glutamate receptors (77,78). Minor alterations in the subunits that form a particular receptor in a particular CNS region could allow drug targeting of that receptor in that region with high specificity and a resultant high therapeutic index. Few examples exist of such pharmacologic magic bullets, and most drugs even at the preclinical testing stages are still the result of bioassay rather than molecular biology screening. Nonetheless, the more molecular biology is combined with anatomy and physiology, the more important molecular biologic classification schemes will become in receptor discussion. At present, the classification of glutamate receptors is still largely based on more general functional criteria, as discussed here.

All receptors are loosely classified into two general functional categories, ionotropic and metabotropic (Fig. 4-23). Ionotropic receptors form a channel in the membrane of the cell, and when agonist binds to such receptors a conformational change takes place, allowing ions (e.g., Na^+ or Cl–) to pass through the cell membrane. Such ion movement changes the charge difference across the cell membrane (depolarizing or hyperpolarizing). The size and direction of this depolarization depend on the receptor's permeability to specific ions and on electrical and ion concentration gradients across the cell membrane. Three ionotropic glutamate receptors are named for the compounds that are known to bind them most selectively, kainate, a-amino-3- hydroxy-5-methyl-4-isoxazoleproprionate (AMPA), and *N*-methyl-d-aspartate (NMDA). Kainate and AMPA receptors have been difficult to differentiate pharmacologically until recently because of (a) kainate acting as an agonist at both types of receptors; (b) rapid desensitization of kainate's effects at the kainate receptor, leaving only its AMPA effects to study; and (c) a lack of specific kainate receptor agonists and antagonists. More pharmacologic tools are becoming available to look more specifically at kainate receptors and their role in nociception. Kainate receptors have been localized on C-fiber primary afferent neurons in the dorsal root ganglia (78). Furthermore, kainate receptor-mediated responses from electrical stimulation of primary afferents (particularly C-fiber afferents) have been reported in dorsal horn neurons (79). Finally, intrathecal kainate antagonists have been shown (79,80) to inhibit nociception in laboratory animals (see, however, 81). The possible role of kainate receptors in mediating nociception will likely receive great research attention in the coming years as pharmacologic tools allow.

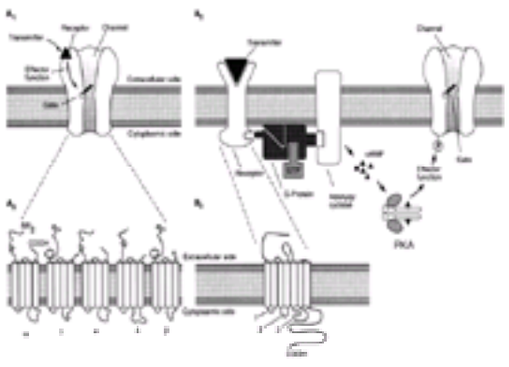

Figure 4-23. Two classes of neurotransmitter receptors. **A:** 1. Ionotropic receptors demonstrate ligand gating of an ion channel that is part of the receptor protein complex. 2. These receptors are composed of four or five subunits, each of which contains four or five membrane-spanning alpha helical regions. **B:** 1. Metabotropic receptors have separate binding and effector complexes. For example, G protein–coupled receptors: The receptor when activated by the transmitter in turn activates a GTP-binding protein (G protein) that transduces a change in an effector molecule (adenylyl cyclase here). In this case, adenylyl cyclase converts ATP to cAMP (a second messenger), which activates cAMP-dependent protein kinase (PKA), which phosphorylates an ion channel (P), leading to a change in channel function. 2. The typical G protein linked receptor is a composed of a single protein with seven membrane-spanning alpha helical regions that bind the ligand within the plane of the membrane. (From Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of neural science*, 3rd ed. New York: McGraw-Hill, 1991:133, with permission.)

Much more information has already been gathered concerning the importance of the AMPA receptor throughout the nervous system in general and in nociceptive processing specifically. This receptor subtype is known to be a common mechanism of excitatory neurotransmission throughout the brain and spinal cord. A number of *in vivo* and *in vitro* studies have demonstrated the importance of glutamate acting at AMPA receptors in mediating fast neurotransmission in laminae I, II, and V electrophysiologically (82,83). Behaviorally, AMPA antagonists have been found to decrease pain behaviors in rats and humans (84), specifically considering the ubiquitous distribution and function of these receptors in the CNS. This could be caused by differences in sensitivity to AMPA antagonists of AMPA receptors in nociceptive pathways or in differences in drug concentrations reaching nociceptive-related receptors in comparison with other receptors (e.g., intrathecal administration might ensure significantly increased concentrations of drug in lamina I compared with lamina IV or IX).

The third ionotropic glutamate receptor, the NMDA receptor, differs in several ways from the other two. Most important, in normal extracellular fluid ionic concentrations and at normal neuronal resting potentials, the NMDA receptor does not allow ions to pass through it even when bound by glutamate because of a block of the ion channel by a magnesium ion. It is only with depolarization that the NMDA receptor becomes unblocked and able to be activated by glutamate. Thus, NMDA effects tend to follow periods of depolarization or several excitatory events in a train of excitatory stimuli. Unlike the majority of kainate and AMPA glutamate receptor actions (in which sodium is the most important ion passing through the receptor), calcium ions are of utmost importance passing through an open NMDA receptor. As we discuss more thoroughly in the section Modulatory Mechanisms: Increases in Synaptic Efficacy, calcium is an important intracellular ionic signal, not only because of its charge but also because of its effects on calcium-dependent enzymes important in the cell's metabolism. The complex structure of the NMDA receptor makes it sensitive to antagonism through several different mechanisms (Fig. 4-24). The first is competitive blockade of the glutamate- (or NMDA) binding site (e.g., AP5). The second is noncompetitive blockade of the ion channel itself (e.g., MK-801 or ketamine). The third is via blockade of the strychnine-insensitive binding site for glycine (e.g., with 5,7-di-Cl-kyurenic acid). Glycine acts as a coagonist at this excitatory receptor unlike the inhibitory effects it has at strychnine-sensitive glycine receptors. Finally, NMDA receptor function can be modulated by several other receptor sites (or their blockers) including proton sensitive sites, re-dox modulatory sites, zinc-binding sites, and polyamine-binding sites. We discuss the extensive evidence for a role of NMDA receptors in nociception in the section Modulatory Mechanisms: Increases in Synaptic Efficacy. As the previous discussion would suggest, these receptors are particularly important in mediating nociceptive responses to repeated noxious stimuli and may be an important mechanism in the development of chronic pain from acute injury.

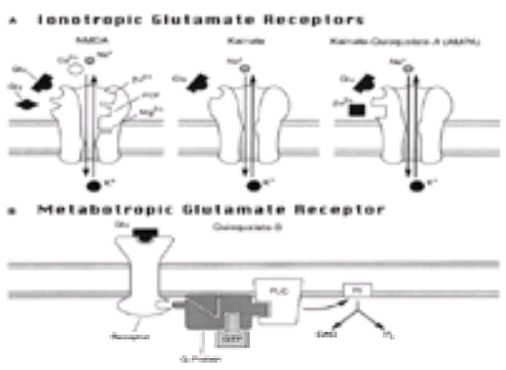

Figure 4-24. Four classes of glutamate receptors. **A:** Ionotropic or ligand gated receptors including *N*-methyl-d-aspartate (NMDA), kainate, and AMPA receptors. The NMDA receptor regulates a channel permeable to Na^+ and Ca^{2+} in particular. It has several different binding sites, including those for glycine, Zn^{2+}, PCP or ketamine, MK801, and Mg^{2+}, which regulate the channel function in separate ways. The kainate and AMPA (also binds kainate) receptors regulate channels primarily permeable to Na^+. **B:** A metabotropic glutamate receptor activated by quisqualate-B activates phospholipase C (PLC), leading to the formation of the second messengers inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) from phosphatidylinositol-4,5-bisphosphate (PI). (From Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of*

neural science, 3rd ed. New York: McGraw-Hill, 1991:157, with permission.)

Such hypotheses and the numerous targets available on the NMDA receptor for antagonism of NMDA effects have raised hopes of finding unique analgesic drugs for chronic pain. Most of the NMDA antagonists investigated thus far produce intolerable side effects in humans, however (e.g., dysphoria). In addition, no differences between spinal cord and supraspinal NMDA receptors have been identified as yet. As mentioned previously, such a difference might allow targeting one site-specific receptor subtype to inhibit spinal nociception without supraspinal dysphoria, for instance; thus increasing the therapeutic ratio for such drugs.

Metabotropic receptors, in contrast to ionotropic receptors, do not directly mediate ionic fluxes across excitable membranes but instead act on intracellular metabolic processes (see Fig. 4-23). This definition suggests the pharmacology of metabotropic receptors is somewhat more complex than with ionotropic receptors. It is much harder to rule out a receptor's interaction with one of many possible metabolic pathways than to rule out its ability to conduct one of a few physiologic ions. Indeed, AMPA glutamate receptors have now been found to have metabotropic effects in addition to and independent of their ionotropic effects (85).

Many metabotropic receptor effects are transduced by guanosine nucleotide-binding proteins (G proteins) acting on an *effector molecule*, often an enzyme such as adenylyl cyclase (see Fig. 4-23). Some metabotropic receptors, such as tyrosine kinase (Trk) receptors for neurotrophins are enzymes themselves. The final cellular target (e.g., an ion channel) may be acted on directly by the effector molecule or via a diffusible second messenger [e.g., cyclic adenosine monophosphate (cAMP) or ionized calcium]. A number of different receptors can use the same G protein and thereby produce the same second messengers, thus integrating complex extracellular pharmacologic activity. However, the same receptor type can also use multiple G proteins and a single G protein can regulate several different effectors. This provides the framework for a complex network of convergent and divergent biochemical interactions, allowing for almost unlimited versatility in cell function regulation.

The metabotropic glutamate receptor has been molecularly classified into eight subtypes. These subtypes have been found to differ dramatically from each other in regard to the effectors to which they couple. Some are coupled to phospholipase C and even receptors in this subgroup differ from one another in the type of G protein used. The phospholipase C activation can produce inositol-1,4,5-trisphosphate and diacylglycerol (see Fig. 4-24), which leads to release of intracellular calcium stores and activation of calcium-dependent protein kinase (PKC), respectively. Phosphorylation (by PKC or other kinases) can alter the conformation of a protein enough to modify the function of an enzyme, a cytoskeletal protein, a channel subunit or a transcription factor (involved in gene expression). Thus, such a metabotropic receptor may have many effects on-cell function after agonist binding with a time course far outlasting the millisecond responses of ionotropic receptors. Glutamate metabotropic receptors also have been linked to other signal transduction pathways, including stimulation and inhibition of adenylyl cyclases with resultant changes in cAMP (e.g., Fig. 4-23) and cAMP-dependent protein kinase (protein kinase A or PKA) as well as phospholipase A_2. A comprehensive review of second messenger systems is beyond the scope of this book and is only described as relates to their increasing relevance to nociception.

Much of the research describing the second messenger effects of metabotropic glutamate receptors are in *in vitro* expression systems in which cells are genetically altered to produce these receptors. It is not yet known whether these effects are relevant to the *in vivo* preparation in which gene expression and biochemical sequelae may be quite different. Moreover, *in vivo* work has been hampered by the lack of specific pharmacologic tools and the related difficulty in knowing the drug concentration that reaches a receptor *in vivo* after either parenteral or intrathecal drug administration. Nonetheless, glutamate metabotropic receptors have been reported to be involved in nociception (86,87,88 and 89). The generally slower effects of these receptors make them more likely to play a role in pain modulation than fast nociceptive transmission *per se*. Thus, glutamate acting at AMPA and, perhaps, kainate receptors is the most likely neurochemical candidate to mediate nociceptive neurotransmission.

Other Excitatory Neurotransmitters

The finding that glutamate excites nearly 100% of dorsal horn neurons involved in nociceptive processing (83,90,91 and 92), via AMPA/kainate, NMDA, or both receptors does not rule out other neurotransmitter involvement. Other known fast excitatory transmitters in the CNS include ACh at nicotinic receptors, serotonin (5-HT) at 5-HT_3 receptors, and adenosine triphosphate (ATP) at P2X receptors.

Acetylcholine. ACh nicotinic receptors, most carefully studied at the neuromuscular junction, have been molecularly characterized and their CNS subtypes have been described. Although all of these channels conduct cations and therefore should be depolarizing, nicotine has been characterized as producing analgesia since 1932. CNS subtype-specific nicotinic agonists also produce analgesia, when administered either peripherally, intrathecally, or in the brain stem (93,94 and 95). Such agonists have been reported to show no analgesic tolerance or dependence in rodents (94). The most likely explanation for antinociceptive effects of a depolarizing compound is in the location of the receptor, either on primary afferent terminals via presynaptic inhibition or on inhibitory interneurons. Indeed, both mechanisms appear to take place in the spinal cord. Presynaptic nicotinic receptors on primary afferent terminals have been well described (96). Acetylcholine-induced increases in the release of the inhibitory neurotransmitter GABA also have been demonstrated (i.e., excitation of inhibitory neurons). In the spinal cord this effect is best documented for ACh acting at its metabotropic, muscarinic receptor, however (97). Discovering the details of ACh physiology in the spinal cord is complicated by its dual receptors, both of which have pain modulatory effects, and by its primarily interneuronal location (98) (and the complex circuitry of these cells). Nonetheless, the finding that interference with ACh metabolism via anticholinesterase inhibitors such as neostigmine produces analgesia in laboratory animals and humans suggests a tonic role of ACh in inhibiting nociception (99). Moreover, other spinal analgesics, including opioids and a $_2$-noradrenergic receptor agonists, may act in part via release of ACh in the cord (99). In any event, no evidence exists that ACh mediates fast nociceptive transmission and indeed ACh receptors seem to be positioned to inhibit such transmission instead.

Serotonin (5-Hydroxytryptamine). 5-HT receptors also have a complex pharmacology, with four major groups of receptors (5-HT 1 through 4) and multiple subtypes within these groups (e.g., 5-HT_{1A} receptor). The only ionotropic serotonin receptor identified thus far is the 5-HT $_3$ receptor. Like nicotinic receptors, 5-HT_3 receptors are fairly nonselective cation channels and depolarize neurons. Like nicotinic agonists, 5-HT $_3$ agonists can produce analgesia (100). However, this is controversial and 5-HT_3 agonists also have been shown to potentiate nociception (101). Perhaps this is simply reflective of the variety of neurons on which 5-HT $_3$ receptors are located. For instance, 5-HT_3 receptors located on primary afferent terminals may, like nicotinic receptors, act to presynaptically inhibit nociception (as is more fully described for GABA receptors; see Gamma-Aminobutyric Acid, later in this chapter) (102). On the other hand, 5-HT_3 receptors on nociceptive neurons in dorsal horn could potentiate their nociceptive responses. We discuss further the role of serotonin in modulating nociceptive transmission when we discuss descending modulation later in this chapter (see Descending Systems that Modulate Nociception). For the purposes of this discussion, the fact that most, if not all, spinal 5-HT comes from supraspinal sites makes 5-HT_3 receptors more likely to modulate than mediate nociception.

Adenosine Triphosphate. ATP is probably the best nonglutamate candidate for mediating primary afferent and dorsal horn neurotransmission. ATP can both potentiate glutamatergic neurotransmission within the dorsal horn (103,104 and 105) and act directly at neuronal ligand-gated (ionotropic) P2X receptors (in contrast to the metabotropic P2Y ATP receptors) to produce *fast transmission* (104,105,106 and 107), relevant to nociception (108,109). The ATP P2X3 receptor subtype, specifically expressed in sensory neurons (110), has been implicated in nociception both by anatomic localization to small dorsal root ganglion neurons that project to the spinal cord via small-diameter C and A-d fibers (10) and by pharmacologic studies with available, rather nonselective, agonists and antagonists (104,108,111). Immunohistochemical co-localization studies suggest that primary afferents expressing P2X3 receptors project predominately to lamina II_i of the dorsal horn. This is one finding in an emerging literature suggesting that there may be important anatomic, neurochemical, and physiologic differences between nociceptive circuitry in laminae I and II_i of the spinal cord (10). For example, C-fiber primary afferents, which synapse in lamina I of the spinal cord and are likely to be involved in nociception, contain substance P and CGRP and are responsive to nerve growth factor via its trkA receptor (112). A separate subset of C-fiber primary afferents that synapse in the inner portion of lamina II_i, on the other hand, contains less substance P and CGRP and instead stains heavily for the enzymes fluoride-resistant acid phosphatase and thiamine monophosphatase and responds to glial cell-line derived neurotrophic factor (112) and presumably ATP via P2X receptors (107). Moreover, laminae I and II_i circuitry has been differentially implicated in inflammatory and neuropathic pain sensitization, respectively. We discuss more of the possible functional implications of this seeming anatomic and pharmacologic dichotomy in nociceptive processing in the section Modulatory Mechanisms: Increases in Synaptic Efficacy. We underscore here the changing understanding of spinal cord primary afferent and dorsal horn neurotransmission to introduce the important concept that nociceptive mechanisms differ across pain states.

Modulation of Dorsal Horn Neurotransmission

Until the late 1980s, virtually all small animal studies of nociceptive processes involved threshold changes in response to some nociceptive stimulus (usually heat).

This approach likely grew out of a preconception that the CNS, in general, and nociceptive transmission circuitry, in specific, normally underwent little change during an organism's adult life and was essentially hard-wired. Since that time, an explosion of neuroscience research has demonstrated the amazing plasticity of the adult brain and spinal cord. Correspondingly (and really since the Melzack-Wall Gate Control Theory in 1965), preclinical pain researchers have developed and investigated a number of innovative pain tests and animal models demonstrating that the basic nociceptive circuitry described thus far in this chapter is subject to complex modulatory influences. Much of this research has attempted to mimic clinically relevant pain states, such as inflammatory (e.g., formalin, capsaicin, complete Freund's adjuvant, or carrageenan injection responses) or nerve injury (e.g., Bennett, Chung, and Selzer models) pains. Studies of such models have shown that the mechanisms underlying inflammatory and neuropathic pain differ considerably and that both differ from more acute or *transient* [pains represented by threshold studies in the previously untreated animal (113)]. In particular, it has become clear that the pain responses elicited by noxious stimuli are integrally dependent on the prior nociceptive experiences of an animal.

Central Sensitization

The previous chapter thoroughly describes the mechanisms underlying inflammation and peripheral sensitization. A host of neurochemical changes takes place in primary afferents after inflammation, nerve damage, or both, which make them more responsive to nociceptive stimuli (hyperalgesia) or produce a nociceptive response to normally nonnociceptive stimuli (allodynia). Changes also take place in the spinal cord in primary afferent and spinal neurons that can produce such changes in nociceptive responses. These changes have collectively been termed *central sensitization*.

Although Hardy in 1950 suggested that hyperalgesia after tissue injury or inflammation was caused by changes in the spinal cord dorsal horn (secondary hyperalgesia), it was the work of Woolf and colleagues more than 30 years later that dramatically consolidated this concept. In 1966, Mendell noted a sequential increase in the number of dorsal horn action potentials elicited by a C-fiber stimulation given repeatedly at certain rates (at least 1 stimulation per second) (114). This effect was termed *wind- up* (Fig. 4-25). In 1983, Woolf reported (115) that tissue injury caused an increase in responses (measured by motor reflexes or motoneuron activity) that persisted even after local anesthetic blockade of the damaged tissue, suggesting central mediation of this sensitivity (Fig. 4-26). Despite their similarities, central sensitization is not simply wind-up (116) in that wind-up outlasts the initiating stimulus by only a few seconds (see Fig. 4-25), whereas other forms of sensitization may last many minutes to hours after a repeated afferent input ceases or is blocked (Fig. 4-26). Central sensitization has now been demonstrated in a number of laboratories using a variety of response end-points (threshold stimuli, response frequency, receptor field size) and eliciting stimuli (thermal, chemical, acute joint inflammation, and C-fiber electrical stimulation) (31).

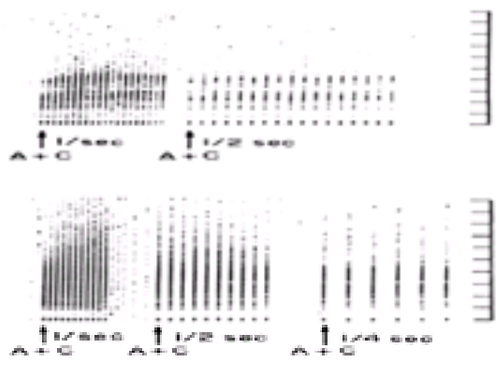

Figure 4-25. Wind-up responses of single units to repeated stimulation of sufficient intensity to activate A and C fibers (no wind-up seen with A- fiber stimulation by itself). The vertical time markers on the far right represent 100 msec. Each mark at the bottom of the time line represents the stimulation artifact, and the burst of activity immediately above each of these stimulations is the response to A-fiber stimulation (each dot represents an action potential). The more delayed responses to the more slowly conducting C-fiber stimulation are above that. *Top panel*: Response of dorsolateral column axon to stimulation of ipsilateral sural nerve at a stimulation rate of 1 per second (left) and 1 per 2 seconds (right). An increase in C-fiber responses is seen but only in response to the 1 per second stimulation rate. *Bottom panel*: Response of a separate dorsolateral axon to ipsilateral nerve again shows wind-up only to 1 per second stimulation. Here, wind-up lasts for several seconds, as seen by an increase in spontaneous activity and a more prolonged than normal response to the 1 per 2 seconds stimulation initially. This increased excitability resolves in spite of 1 per 2 seconds stimulation resulting in apparent *wind down* and normal responses to the 1 per 4 seconds stimulation. (From Mendell LM. Physiological properties of unmyelinated fiber projection to the spinal cord. *Exp Neurol* 1966;16:316–332, with permission.)

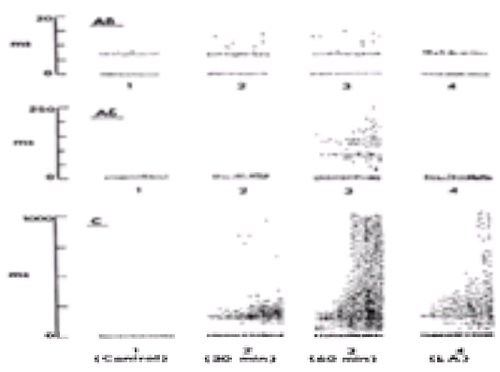

Figure 4-26. Rastor dot displays of a single biceps femoris unit activated by stimulation of the sural nerve 1 every 2 seconds before an ipsilateral thermal injury (control), 30 and 60 minutes postinjury, and 10 minutes after the injured foot has been completely anesthetized with local anesthetic. Each dot represents an action potential. The vertical scale is the latency of the responses after sural nerve stimulation, and the stimulus artifact can be seen at time 0. Stimulation strengths were given to activate A-b fibers (100 µA, 50 µs; top panel), A-b and A-d fibers (250 µA, 50 µs; middle panel), or A-b, A-d, and C fibers (5 µA, 500 µs; bottom panel). Note the different time scales used in the three panels to record the activity evoked by the three different fiber populations. In the preinjury state, only an A-b input was evoked. Thirty minutes after injury a C-fiber response begins to occur, whereas at 60 minutes both A-d and C-evoked responses are present. Note the development of wind-up of C responses. Ten minutes after the local anesthetic (administered 80 minutes postinjury) the sural C-evoked responses remain higher than before the injury, suggesting a central component of the sensitization. (From Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* 1983;306:687, with permission.)

Several chronic pain models have evolved with the goal of, or as a result of, studying central sensitization. Although a complete review of pain models is not possible here, they generally fall into two major categories: (a) inflammatory (some have suggested this category be labeled *tissue injury*) and (b) neuropathic (damage to nerves). The interaction between the immune and nervous systems makes this a somewhat arbitrary distinction in that immune cells can mediate nerve damage and nerve damage may activate immune cells. Nonetheless, the experimental manipulations that create these models tend to be one or the other.

Inflammatory agents, such as acetic acid, carrageenan, capsaicin, formalin, mustard oil, and Freund's adjuvant, have all been given on or in the skin or viscera to produce pain responses or facilitations in pain responses developing within seconds to days. On the other hand, animal models of neuropathy include cutting or ligating (tightly or loosely) nerves, or depriving nerves of blood flow. These manipulations increase pain responses localized to corresponding or adjacent dermatomes. Although important differences exist in the responses and mechanisms underlying these models, they are more similar to each other than they are to any of the threshold animal pain models that came before (e.g., paw or tail withdrawal from heat, pressure, or an electric shock) if only in their temporal dimension. Inflammatory and neuropathic pain models rely on mechanisms of central sensitization, although ongoing peripheral mechanisms also contribute to pain behaviors in many of these models (117).

A number of mechanisms can account for increased sensitivity of spinal nociceptive neurons to nociceptive stimulation: (a) an increase in activity at excitatory synapses, (b) an increase in excitatory synaptic connections (e.g., sprouting), and (c) a decrease in inhibitory tone in the spinal cord. Each of these mechanisms has been reported in the spinal cord, attesting to the remarkable plasticity of the adult CNS. Obviously, the rapid time course of certain models of central sensitization

cannot be explained by slower mechanisms such as sprouting of new axons. However, this may say more about the model than the mechanism in regard to the etiology of clinical pain states. Indeed, the primary weakness of most of the models of sensitization in trying to explain possible sensitization phenomena in humans is the short time course of most of the models and the sadly long time course of many neuropathic or inflammatory chronic pain states that the animal studies purportedly model. Nonetheless, it is only relatively recently that such models have been extensively used and despite their flaws they have already made important conceptual contributions to the study of pain mechanisms.

Modulatory Mechanisms: Increases in Synaptic Efficacy

Many of the studies of central sensitization have been patterned after the studies of long-term potentiation (LTP) in the hippocampus. This model of learning involves intense stimulation of afferent input to cells of the hippocampus and involves increases in synaptic efficacy of the synapses activated (118). This potentiation, which can last for several weeks after stimulation, has received extensive study, in part because of the intrinsic interest in studying learning at the molecular level and in part because the laminar cytoarchitecture of the hippocampus allows researchers easy access to the region for *in vivo* and *in vitro* electrophysiologic studies. As in the spinal cord, glutamate has proven to be a potent excitatory transmitter in the hippocampus, acting at AMPA (119), NMDA (120,121), and metabotropic (122) receptors to initiate a host of ionic, second messenger, and gene-expression processes, which with repeated stimulation mediate the induction, expression, and maintenance of LTP (Fig. 4-27 and Fig. 4-28). In particular, reports of presynaptic and postsynaptic changes in synaptic efficacy thought to underlie LTP provide a ready source for hypotheses concerning the mechanisms of nociceptive central sensitization.

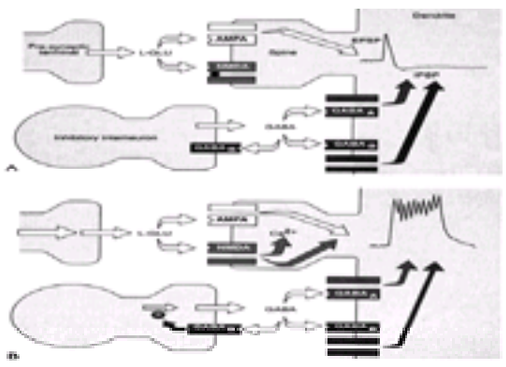

Figure 4-27. Excitatory amino acid–mediated induction of long-term potentiation. **A:** Low-frequency transmission: A single stimulus depolarizing an afferent terminal causes release of a neurotransmitter (e.g., l-glutamate or l-GLU), which binds to postsynaptic ionotropic receptors. In this example, the glutamate AMPA type receptor is activated, evoking an influx of sodium ions, a depolarization, and an excitatory postsynaptic potential (EPSP). Stimulation of afferent activity may also activate inhibitory interneurons in parallel or in series to release inhibitory neurotransmitters. In this example gamma-aminobutyric acid (GABA) is released and binds to postsynaptic $GABA_A$ receptors to activate chloride currents that produce an inhibitory postsynaptic potential (IPSP) and cause the delayed phase of the biphasic electrophysiologic response, which curtails excitation. Moreover, GABA is shown binding to presynaptic and postsynaptic $GABA_B$ receptors that can activate potassium channels via G-protein coupling to subsequently further limit excitation. *N*-methyl-d-aspartate (NMDA) receptors contribute little to the synaptic response, because by the time that the NMDA receptors become activated by depolarization (losing their shown magnesium block), IPSP-induced hyperpolarization has already begun. **B:** High-frequency transmission: The contribution of NMDA receptors to synaptic transmission alters radically to a high-frequency input. This is because a rapid rate of afferent glutamate release maintains the neuron in a more depolarized state (reducing magnesium block), while at the same time providing a more prolonged release of glutamate that activates the NMDA receptor. Several factors may contribute to sustained depolarization seen in this example. These include summation of AMPA receptor–mediated EPSPs and depolarizing shifts in the chloride or potassium reversal potentials because of buildup of intracellular chloride or extracellular potassium, which may interfere with the usual IPSP-producing mechanisms. The long duration of NMDA receptor–mediated EPSPs means that they summate effectively during high-frequency transmission, as shown. (From Bliss TVP, Collinridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 1993;361:35, with permission.)

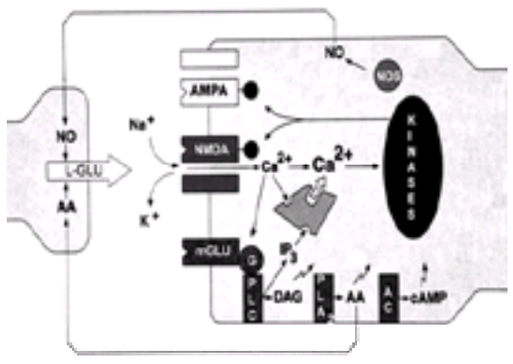

Figure 4-28. Schematic showing several ways in which glutamate can activate signal transduction mechanisms involved in long-term potentiation. Calcium influx through *N*-methyl-d-aspartate (NMDA) receptors can be supplemented by an additional calcium elevation via inositol trisphosphate (IP3) sensitive intracellular stores. A parallel pathway, perhaps important in certain forms of long-term potentiation is via activation of metabotropic glutamate receptors (mGLU). These receptors can couple through G proteins with a number of effectors, including phosphoinositide- specific phospholipase C (PLC), phospholipase A_2 (PLA_2), and adenylate cyclase (AC) to produce diacylglycerol (DAG) and arachidonic acid (AA) and to regulate the levels of cAMP, respectively. As shown, an intracellular calcium increase may be important for the activation of these mGLU signal transduction cascades. The amplified increase in calcium, in association with the other activators of a number of protein kinases (*zigzag arrows*), then leads to the phosphorylation of substrate proteins, including AMPA and NMDA receptors. Other enzymes, such as nitric oxide synthase (NOS), if present, also may be activated by the calcium transient. Biochemical changes in the presynaptic terminal also may be initiated by the action of retrograde messengers such as nitric oxide (NO), AA, and potassium (K), perhaps in conjunction with the action of glutamate on presynaptic mGLU or NMDA receptors (not shown). (From Bliss TVP, Collinridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 1993;361:36, with permission.)

Clinical observations suggesting that patients really do *learn to hurt* provided further support for mechanistic similarities between LTP and central sensitization. Anecdotes that phantom limb pain is more common in patients who have pain in the limb before amputation led to confirming studies: Patients with ischemic extremity pain scheduled for extremity amputation develop less phantom limb pain postamputation if they are made comfortable preoperatively with intraspinal analgesics (123). Moreover, reports that aggressive preoperative pain treatment significantly decreased pain and analgesic use for many days after the anesthetic or analgesic effects subsided (124,125,126 and 127) have led to the concept of *preemptive analgesia* and in some cases changes in anesthesiology practice as a strategy to avoid activity-dependent neuroplastic changes in nociception.

The true clinical significance of preemptive analgesia (i.e., whether preoperative analgesic therapy provides greater benefit than normal postoperative analgesic therapy independent of a simple increase in drug dosage) is controversial. The disparate results of these studies may stem from the varied quality of the investigators' normal (control) pain management practices. Unlike animal studies, even control patients in clinical studies receive some analgesics for their pain, including intraoperative analgesic use in almost all surgeries. It is not surprising, then, that additional analgesics given to the experimental group of patients before a 2- or 3-hour surgery might not significantly distinguish them from a group given normal analgesic intraoperative therapies, when both groups are given impeccable analgesic management beginning postoperatively for their 4- to 5-day hospital stay.

That aggressive pain management (e.g., with preoperative nerve blocks) can produce long-term benefits in pain control, compared with little (clinical studies) or no (animal studies) pain treatment, perhaps via an inhibition of central sensitization, is not controversial. Although this may seem a rather modest finding to many readers of this book and therefore of little clinical use, it is worth noting that the medical community in general is not so far removed from using muscle relaxants as the sole

“anesthetic” for heart surgery in neonates and b-blockade, rather than analgesics, to treat procedure-induced tachycardias in the operating room or intensive care unit.

N-*Methyl-d-Aspartate Glutamate Receptors.* Regardless of their current clinical application, animal studies of central sensitization have made important contributions to our understanding of nociception and its modulation. Returning to the LTP model of central sensitization, considerable evidence suggests that, like LTP in many brain regions, activity-dependent increases in excitation in the spinal cord depend on NMDA receptors. Numerous models of central sensitization are inhibited by NMDA antagonists. These include wind-up of dorsal horn neuronal activity (128), increases in dorsal horn neuron nociceptive responses or receptive field size by acute and chronic inflammation (129,130), increases in flexion responses from C-fiber stimulation or mustard oil irritation (131), hyperalgesia from thermal burn (132), peripheral nerve ligation (133) or chronic inflammation (134), autotomy behavior after nerve section (135), and pain behaviors in the second phase of the formalin test (136,137).

The clinically available weak NMDA antagonists, ketamine or dextromethorphan, can improve control of ischemic, postoperative or posttraumatic chronic pains in humans (138,139). However, side effects (particularly dysphoria) have limited their clinical use. The complicated structure of the NMDA receptor including its various modulatory binding sites (e.g., glycine's coactivating site) and subunits (e.g., the NR2B subunit) are probably the best hope for NMDA antagonists, playing an important role in clinical pain management. Possible nociceptor or spinal cord–specific NMDA receptor structures or functions (140) fuel the search for analgesic pharmacologic agents with NMDA antagonist activity and an improved therapeutic ratio.

The mechanism of NMDA's central sensitizing activity is less well studied in the spinal cord, but it probably resembles NMDA- dependent LTP in the hippocampus. Voltage-dependent magnesium blockade of the NMDA receptor, explains the lack of effect of antagonists on initial afferent activation (transient or acute pain thresholds). After initial depolarization of a cell (via glutamate's actions on AMPA or kainate receptors) unblocks the NMDA receptor, subsequent glutamate release also activates NMDA receptors, leading to a calcium influx and thereby modulation of a cascade of enzyme activities and genetic sequelae (see Fig. 4-27 and Fig. 4-28). Presumably, these latter effects make wind-up of a few seconds different from sensitization of many minutes, hours or days. Moreover, this difference, together with any ongoing primary afferent activity (117), probably defines the role of NMDA receptors in maintenance of sensitization, accounting for reports of efficacy of NMDA receptors in reversing, rather than simply preventing, sensitization (133).

In the hippocampus a number of second messengers facilitate postsynaptic responses, even after repolarization and presumed NMDA receptor magnesium blockade recurs. Phosphorylation of AMPA (141), NMDA (142), or both receptors potentiates subsequent responses, and a variety of calcium-modulated kinases have been implicated in mediating LTP (e.g., PKC, calcium/calmodulin kinase II, Trks). In dorsal horn neurons activation of PKC has been seen to increase NMDA currents (143,144) and nociceptive behaviors to subcutaneous formalin (145). Conversely, inhibition of PKC (145) or inhibition of PKC translocation from the cytoplasm to the cell membrane (146) blocks sensitization. Finally, and perhaps most interesting from a clinical perspective, mice lacking the PKC-g isoform, which is found exclusively in lamina II_i of the spinal cord, did not develop sensitization in a nerve injury model (147). Protein kinase A also has been implicated in the development of hyperalgesia although peripheral, rather than central, mechanisms have been shown to be primarily involved (148,149). The Trks, including those activated by neurotrophins such as nerve growth factor (Trk A) or brain-derived neurotrophic factor (Trk B), also may play a role in sensitization at peripheral and spinal levels. Indeed, new biologically relevant kinases are being identified, sequenced, and targeted pharmacologically or through transgenic technology at a rapid rate. Although many have wide-ranging functions making them unlikely for successful clinical inhibitory manipulations, some, or isoforms of some such as the PKC-g example, might conceivably be targeted therapeutically if found to be specific to nociceptive processes.

In addition to changes mediated by the second messengers mentioned previously, modulation of gene transcription, translation, or both as a result of movement of messages to the nucleus also may be an important consequence of NMDA activation and may mediate sensitization. Generally, only LTP observed 4 hours or longer after LTP induction relies on protein synthesis (150). Central sensitization has not been studied as carefully. Calcium-dependent increased expression of nitric oxide synthase has been associated with the development of thermal hyperalgesia (151). This enzyme produces nitric oxide, a gas that may mediate some forms of LTP by acting as a retrograde transmitter, diffusing from the postsynaptic to the presynaptic cell and potentiating presynaptic glutamate release (76). Similarly, inhibition of nitric oxide inhibits NMDA-mediated central sensitization in the spinal cord (152,153,154,155 and 156).

Another example of activity-dependent gene expression is the proto-oncogene c-*fos* or its protein product fos (31). Fos expression can be increased by a variety of noxious stimuli, many of which, though not all, can produce central sensitization. Moreover, fos expression can be inhibited by drugs that inhibit central sensitization including NMDA antagonists. Transcriptional activation of c-*fos* is calcium dependent, and thus it is not surprising that activation of NMDA receptors would be correlated with fos production. The function of fos or c-*fos* is largely unknown, but it may help regulate neuropeptide gene expression. Although c-*fos* immunohistochemistry has become a useful anatomic technique indicating cellular activity, it is quite sensitive to such activity and conclusions regarding sensitization induction or inhibition caused by c-*fos* activity merit caution.

Substance P. In 1931, von Euler and Gaddum discovered a potent vasodilator in extracts from horse intestine and named it substance P (the *P* perhaps indicating *precipitate*). In the mid-1970s, Leeman and colleagues sequenced this same compound in the hypothalamus (an 11 amino acid peptide that caused salivation in laboratory animals) and its ensuing mass production has led to many experiments detailing the anatomy, pharmacology, and physiology of this compound. Its subsequent localization in small primary afferents (see Chapter 3) synapsing on lamina I projection neurons (157) and other dorsal horn nociceptive cells (Fig. 4-29 and Fig. 4-30) linked substance P to the field of pain. The release of substance P with small-fiber stimulation and its potent depolarizing effects on dorsal horn neurons (200 times more potent than glutamate on a molar basis) have made substance P an obvious candidate as a nociceptive neurotransmitter. Nonetheless, the relatively slow onset and offset of its effects, relative to glutamate, for example, suggest that substance P functions as a modulator of nociception rather than a transmitter *per se*. The precise role of substance P in nociception has been difficult to define because of the absence of specific antagonists for the neurokinin 1 (NK1) G protein–coupled receptor to which it binds. Important advances have been made in this regard (158), and clinical trials are beginning to dissect the use of these antagonists in a variety of pain states. One such possible clinical use, the treatment of migraine (159), may take the study of substance P physiology back to its vasodilatory roots in hopes of alleviating this pain often linked to vascular pathogenesis. As yet, substance P antagonists, even when effective, have had only moderate efficacy in relieving pain in clinical trials (160). Perhaps no other area of pain research so clearly demonstrates the distinctions between differing types of nociception.

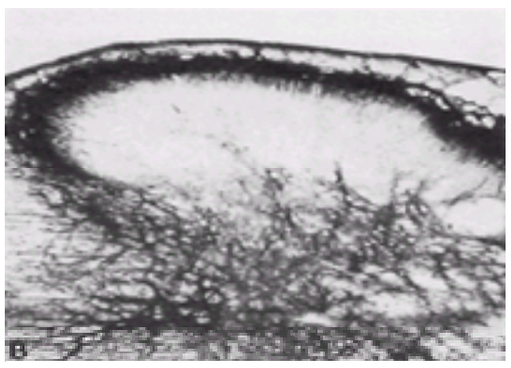

Figure 4-29. Immunocytochemical staining for substance P in the medullary dorsal horn of the cat. The substance P band is densest in laminae I and II_o; in lamina II_i there are few substance P axons; and in laminae V and VI the density of substance P is significant. Compare with Figure 4-35, which depicts the distribution of enkephalin in the same laminae. (From Ruda MA. The pattern of nociceptive modulation in the dorsal horn. In: Yaksh TL, ed. *Spinal afferent processing*. New York: Plenum, 1986:141–164, with permission.)

Figure 4-30. Camera lucida drawing of a lamina II stalked cell labeled with the intracellular horseradish peroxidase method. The tissue section was subsequently stained with substance P antisera. Arrows represent sites of substance P–like immunoreactivity contacts on dendritic shafts; asterisks denote sites of substance P–like immunoreactivity contacts on spines. Note the predominance of contacts on spines. Inset is an enlargement of the area outlined in dots and shows a substance P–like immunoreactivity axon with its varicosities contacting a spine and the dendritic shaft. *Dotted horizontal line* represents the border between laminae I and II. Scale bar represents 10 µm. (From Ruda MA, Bennett GJ, Dubner R. Neurochemistry and neurocircuitry in the dorsal horn. *Progr Brain Res* 1986;66:219–231, with permission.)

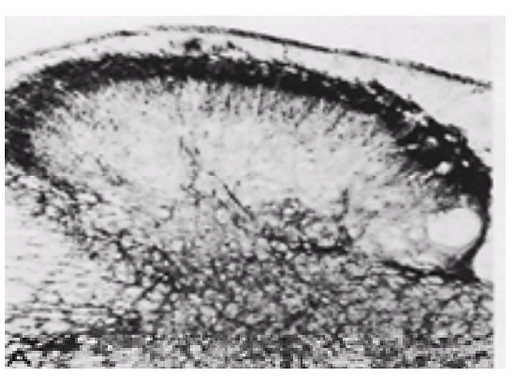

Figure 4-35. Immunocytochemical labeling of enkephalin in the medullary dorsal horn of the cat. Dense enkephalin-staining band is found in laminae I, II_o, and II_i, whereas laminae VI and VII have less staining. Compare with Figure 4-29, which depicts staining of substance P taken from a neighboring section of medullary dorsal horn of the same animal. (From Ruda MA. The pattern of nociceptive modulation in the dorsal horn. In: Yaksh TL, ed. *Spinal afferent processing*. New York: Plenum Press, 1986:141–164, with permission.)

Substance P antagonists have, in general, proven to have little analgesic efficacy in animal studies looking at tests of threshold pain responses (161). In contrast, animals lacking substance P or NK1 receptors, or given an NK1 antagonist, do differ from controls in their nociceptive responses to higher intensity or longer duration pain tests (e.g., high temperature stimuli, the second phase of the formalin test or writhing responses after intraperitoneal acetic acid) (162,163). Similarly, substance P is most reliably released from primary afferents by intense or prolonged stimuli (164). Indeed, substance P can not only be released in greater amounts, but by greater numbers of primary afferents during prolonged noxious conditions. After inflammation, for example, large (A-b) fibers, in addition to small (A-d and C) fibers, produce (165) and presumably release substance P, thereby contributing to inflammatory hyperalgesia.

Other important insights into the physiology of substance P have been provided by Mantyh and colleagues in a series of studies investigating the internalization of substance P receptors. Internalization of NK1 receptors and many other G protein–coupled receptors is common after agonist binding. Mantyh and colleagues used antibodies specific for the NK1 receptor and confocal microscopy to visualize internalized substance P receptors as a measure of substance P effects. They have seen that substance P receptor internalization takes place after repeated C-fiber stimulation (166), primarily in lamina I, but that after inflammation, internalization of substance P receptors becomes near maximal in lamina I and spreads to deeper laminae (III through IV) (167). This spread of agonist-induced activity is likely caused primarily by increases in substance P release and spread by diffusion to deeper laminae, called *volume transmission*. Large-fiber stimulation is still insufficient to induce internalization. This is true, even in allodynia models (produced by nerve injury), in which activation of large fibers by light touch produces pain behaviors (166).

Supplementary to these findings are the same group's use of intrathecal injections of the neurotoxin saporin bound to substance P. This compound, like substance P itself, is internalized and cleaved by intracellular enzymes to release the toxin and kill the cells into which it has been taken. Thus, this technique can be used to kill many of the cells expressing substance P receptors, particularly in lamina I, in which the compound diffuses most readily from the intrathecal space. Rats given this selective neurotoxin have unchanged pain thresholds but inflammation-induced hyperalgesia is attenuated (168). Substance P appears, then, to have an important role in central sensitization, at least during inflammation.

Wind-up from repeated C-fiber stimulation is correlated with a slow, long-lasting excitatory potential, which is partially reversed by NK1 antagonists and may represent a substance P–mediated central sensitization (89). However, given the importance of glutamate in nociceptive transmission, including central sensitization, we primarily focus on the synergistic interaction between NK1 and glutamate receptors in producing central sensitization (169,170). The majority of this work has been done in the spinal cord, although substance P can enhance LTP in other areas of the CNS (171). The interaction between glutamate and substance P is both presynaptic and postsynaptic. For instance, glutamate binding at presynaptic NMDA receptors has been reported to release additional substance P (172). Postsynaptically, the long-lasting (i.e., seconds) depolarizing effects of substance P may unblock NMDA receptors, thereby potentiating NMDA effects (173). Prior depolarization can also potentiate substance P effects (89), presumably by facilitating NK1 activation of voltage-dependent calcium channels or NK1-coupled inhibition of potassium channels.

Finally, NK1-activated second messengers interact with glutamate receptors in several important ways. Substance P binding to NK1 receptors as well as glutamate binding to metabotropic receptors stimulates the hydrolysis of polyphosphatidylinositol by phospholipase C into inositol trisphosphate and diacylglycerol. Inhibition of phospholipase C reduces sensitization in the formalin test (145). Inositol trisphosphate stimulates the release of calcium from intracellular stores, and this release is potentiated by high intracellular calcium levels as might occur with concurrent NMDA activity. In addition, diacylglycerol stimulates the cytosol to membrane translocation and resultant activation of PKC thought important in NMDA-mediated central sensitization.

Whatever the mechanism, the synergism between NMDA and NK1 receptors seen in the induction of central sensitization in the laboratory remains to be tested in the clinic. Important in this testing is the differentiation of effects on induction, expression, or maintenance of central sensitization only rarely addressed in laboratory and clinical studies. Induction, expression, and maintenance in clinical terms are analogous to preventative, symptomatic, and curative therapies, respectively. The finding that a drug can block central sensitization induction as most NMDA studies report may have little usefulness to the clinician treating a pain of 30 years' duration even if it is entirely mediated by sensitization mechanisms. Similarly, although reduction of the expression of nociceptive sensitization by high-dose opioids or local anesthetics is useful in the short term, blockade of maintenance mechanisms is clearly the goal. Unlike most hippocampal LTP, evidence suggests that NMDA antagonists given after induction of central sensitization can still decrease this altered nociception. This may result from an importance of continued peripheral input and corresponding NMDA receptor activity in at least a portion of central sensitization maintenance (117). The ideal analgesic would block maintenance of sensitization only, leaving other nociceptive processing (e.g., in other regions of the body) intact. In this regard, it is noteworthy that PKC-g knockout mice and rats lacking NK1-expressing lamina I neurons caused by saporin–substance P intrathecal injections both had normal nociceptive thresholds for transient noxious stimuli.

Modulatory Mechanisms: Other Pronociceptive Neurochemicals

As described in detail in Chapter 3 of this text, substance P and other peptides are produced in dorsal root ganglion cell bodies by ribosomal synthesis of large

precursor peptides. These precursors are then cleaved and transported to the peripheral and central terminals, in which they are stored in vesicles in a form amenable to release on appropriate stimulation (30). A number of peptides besides substance P have been implicated in nociceptive modulation by (a) their specific distribution in small primary afferents, (b) their quantity correlating with pain behaviors, or (c) their effects on nociception with intrathecal administration or antagonism.

Interpretation of behavioral effects of intrathecal drugs is complicated by possible nonspecific effects, caused, in large part, by an inability in such studies to definitively know the concentration of a compound reaching the receptor (174). For example, even oxygen and water, given at too high a concentration, can have toxic effects. Thus, some behavioral effects may be caused by toxicity of a drug. Moreover, even nontoxic agonists or antagonists at a specific peptide receptor may differ in their effects because of differences in drug distribution. Some compounds given intrathecally, for example, may be limited in their ability to reach receptors in deeper laminae and thus have concentration-dependent effects there, caused by rapid metabolism, poor diffusion, or both (175).

Clearly, the biggest problems in behavioral experiments examining peptide effects on nociception are the frequent lack of specific antagonists. Antisense studies, in which administration of specific oligonucleotides specifically disrupt a peptide's synthesis and thereby function, have been used to circumvent the lack of peptide antagonists. Such studies also experience issues of distribution as well as unknown mechanisms of cellular uptake of oligonucleotides. Knockout and other transgenic studies of animals genetically altered to have abnormal peptide levels also attempt to bypass pharmacologic limitations. These studies also are not a panacea, in that effects of a planned genetic manipulation may be confounded by unknown compensatory or accompanying (hitchhiking) genetic changes (161,176).

In our discussion, we try to focus primarily on compounds whose effects on nociception are antagonized by currently available receptor antagonists.

Neurokinins. Neurokinin A (NKA) and neurokinin B (NKB) are, like substance P, tachykinins and bind to NK2 and NK3 receptors, respectively. Little evidence exists for a role of NKB in nociception (although it is a weak agonist at the NK1 receptor normally associated with substance P effects). NKA (sometimes referred to as *substance K*) is produced by a gene closely associated with that producing substance P in mice (preprotachykinin), making the effects described previously from knockout experiments of substance P difficult to differentiate from an NKA knockout effect. Moreover, like substance P, NKA is found in fine primary afferents.

Studies of the nociceptive effects of NKA have been hampered by a lack of receptor antagonists. Nonetheless, several studies suggest an involvement of NKA in heat- (but not mechanically) induced nociceptive responses (177). Whether these selective NKA effects on noxious heat are specific to capsaicin receptor (vanilloid receptor or VR) expressing primary afferents, which also respond selectively to heat (see Chapter 3), is not yet known. However, NK2 antagonists at the spinal level inhibit peripheral capsaicin-induced STT neuronal responses in the primate (178). Such research also demonstrates an increase in capsaicin-induced sensitization of STT cells to mechanical stimuli after NK2 antagonism. This seeming difference between thermal and mechanical nociception and their respective sensitizations has been proposed by other investigators (88,152). However, difficulties in differentiating peripheral and central sensitization mechanisms have impeded progress in testing this hypothesis.

Calcitonin Gene-Related Peptide. CGRP is a prominent peptide in small primary afferents and thus has been of considerable interest for its possible role in nociceptive modulation. CGRP receptors are widely dispersed in the dorsal horn wherever primary afferent terminals are found. They appear to be predominantly postsynaptic, however. In laminae I, II, and V their number is unaffected or actually increased after dorsal rhizotomy. CGRP spinally administered exerts hyperalgesic effects, but the absence of an antagonist makes the interpretation of such data difficult. Indeed, knockout mice lacking a-CGRP do not differ from wild type in their heat nociceptive thresholds and paradoxically show reduced morphine analgesia in the tail-flick test (179). This latter finding contrasts with a study using CGRP antagonists that noted morphine potentiation (180). The role of CGRP, then, in nociceptive modulation awaits further investigation.

Bradykinin. Bradykinin is well known for its role in peripheral nociceptive mechanisms (Chapter 3). However, it may also play a part in modulating nociception in the spinal cord (181). Intrathecal bradykinin, binding at the B2 receptor, produces antagonist-reversible hyperalgesia. This effect probably takes place at the primary afferent terminals because two-thirds of bradykinin receptors disappear with rhizotomy (32). However, an effect on descending noradrenergic fibers cannot be ruled out because bradykinin receptors are also localized there. The source of endogenous bradykinin, which might mediate such hyperalgesia, physiologically is another matter. Bradykinin is primarily produced at sites of tissue damage from blood-borne precursors. Whether some peripherally produced bradykinin might make its way to the spinal cord or whether bradykinin might instead be produced within the spinal cord in the absence of gross spinal damage is unknown.

Pro-nociceptive Neuromedins. The amphibian peptide bombesin and its mammalian homologue gastrin-releasing peptide, as well as the structurally related neuromedin B and neuromedin C, have been most studied in the gastrointestinal tract but also produce CNS effects. Bombesin appears to bind to the neuromedin C receptor predominately, on presynaptic primary afferent terminals (32), and can facilitate nociceptive responses that are blocked by a neuromedin C antagonist (182,183). These facilitatory effects also can be blocked by an NMDA but not an AMPA receptor antagonist, suggesting an interaction of the neuromedin C receptor and glutamate NMDA receptors. The neuromedin C receptor in gut is coupled to a variety of second messenger systems that could facilitate NMDA receptors or their effects (184), but nothing is known of such mechanisms in the spinal cord as yet.

Vasoactive Intestinal Peptide. Another peptide initially isolated from the intestine, vasoactive intestinal peptide, in spinal cord is principally found in lamina I, with some sparse staining in the medial part of lamina V (185), and this is particularly evident in small primary afferents. In a spinal superfusion model (186), electrical stimulation of A-d/C, but not A-b primary afferents releases vasoactive intestinal polypeptide in addition to substance P and CCK *in vivo*. Postsynaptic excitatory effects of this peptide are clearly demonstrated by its iontophoretic administration onto dorsal horn cells (187). Nonetheless, vasoactive intestinal polypeptide is an important example of a peptide that, despite the anatomy and physiology, may have little role in normal or sensitized nociception in the spinal cord (188). Acceptable antagonists have been discovered, used experimentally, and found to have little effect. Naturally other receptor subtypes or related CNS peptides (e.g., pituitary adenylate cyclase–activating peptide) might still mediate pronociceptive effects of vasoactive intestinal polypeptide.

Cholecystokinin. CCK is an eight amino acid peptide that has been studied extensively for its effects on nociception. Although, we return to the effects of CCK when we talk about descending inhibition and facilitation of nociception, much spinal CCK is located in interneurons. CCK-like immunoreactivity is distributed in lamina IV and the central canal region, and its distribution is similar to that of substance P (185). CCK has been localized in axons descending from the brain stem and primary afferents in addition to the interneuronal pool. A coexistence of CCK and substance P is common, but a population of primary afferent somata contains either CCK or substance P without the other peptide (185). CCK receptors are divided into CCK-A and a CCK-B receptor subtypes. The former is the most common CCK receptor type in human and monkey spinal cord, and the latter is most common in the rodent (32). Rodents and primates show exclusively CCK-B receptors in dorsal root ganglion, however, so the CCK-A receptors in primate cord must be on cells intrinsic to the CNS.

Unlike the peptides discussed previously, CCK produces little potentiation of nociceptive responses in previously untreated animals when applied to the spinal cord. However, CCK attenuates several antinociceptive treatments, in particular opioid antinociception (189). Conversely, CCK antagonists in rodents and humans potentiate opiate analgesia and may slow the development of morphine tolerance. The mechanism for this inhibition has not been determined. In addition to its effects on morphine analgesia, CCK may be an important mediator of sensitization after nerve injury. After nerve section a dramatic increase occurs in CCK receptors and CCK in dorsal root ganglia (see Chapter 3). Autotomy behavior after nerve section can be significantly decreased by CCK antagonists, and this suggests a role for CCK in mediating this model of neuropathic pain. Indeed, the increase in CCK-mediated neurotransmission in neuropathic pains may be responsible for their relative insensitivity to opiate analgesics. The analgesia produced by CCK antagonists in neuropathic pain models, for example, is blocked by the opiate antagonist naloxone, as if endogenous opioids are being released to alleviate the neuropathic pain but that concurrently released CCK antagonizes these (189). Whether such rodent experiments will generalize to primates, and specifically humans, with their different CCK receptor subtype distributions awaits further investigation.

Thyrotropin-Releasing Hormone. The tripeptide thyrotropin-releasing hormone (TRH) binds to receptors in the superficial dorsal horn and like CCK also has been reported to inhibit opioid analgesia (190) and facilitate nociceptive responses. These effects may be caused by NMDA-facilitating effects of TRH (191). As we will discuss, TRH has effects on nociception via descending pathways as well. Nevertheless, the spinal nociceptive facilitatory effects have been shown to be independent of these descending effects by several investigators (191,192).

Prostanoids. The role of prostaglandins in modulating nociception has already been discussed in regard to the peripheral nervous system (see Chapter 3). Spinal prostaglandins and particularly prostaglandin E_2 (193) have been associated with the development of central sensitization as well, particularly in inflammatory pain states (194). Spinal administration of cyclo-oxygenase inhibitors can inhibit sensitized primary afferent increases in peptide release (195). Sensitization from spinal glutamate, substance P, or administration of both is also blocked by these drugs (196). The neurons and mechanism involved in this effect is not yet known, although an interaction with nitric oxide has been hypothesized and a presumably indirect inhibition of nitric oxide synthesis has been reported (197). Different mechanisms may be involved for different prostaglandins. Whereas prostaglandin E_2–produced hyperalgesia is absent in knockout mice missing an NMDA receptor subunit, prostaglandin D_2–produced hyperalgesia is not (198). In contrast, prostaglandin D_2, but not prostaglandin E_2, hyperalgesia is blocked by NK1 antagonists.

The clinical application of these findings awaits appropriate toxicology and dosing studies to determine whether the intrathecal versus the oral or intravenous routes of administering cyclooxygenase-inhibiting antiinflammatory drugs improves the therapeutic ratio. The development of cyclooxygenase II inhibitors specifically targeting the inducible isoform of cyclooxygenase is hoped to improve therapeutic ratios at least after systemic delivery. The cyclooxygenase II isoform predominates in dorsal horn; however, at least some CNS cyclooxygenase analgesic activity has been tied to the constituently active cyclooxygenase I isoform (199).

Cytokines. The role of CNS glial cells has classically been considered as primarily providing structural support to neurons, particularly within the gray matter. More recently, it has become clear that glia share several characteristics with neurons, including release and uptake of neuroactive chemicals (including glutamate, ATP, prostanoids, and nitric oxide). An example of possible neuromodulation by glia, which could play a role in nociception, is the finding that CNS glia synthesize, store, and presumably release d-serine, a coagonist at the glycine binding site on the NMDA receptor (200). At the very least, glia function to provide environmental homeostasis for CNS neurons, including those in the dorsal horn. Other homeostatic cells, including microglia and other immune-competent cells, contain a variety of neurochemicals important in mediating nociception. For instance, these cells contain and release chemicals called *cytokines*. Intrathecal interleukin-6 (IL-6), for example, produces hyperalgesia, whereas another IL, IL-1b, can enhance substance P release (201,202). Dorsal horn levels of these, as well as other cytokines (including leukemia inhibitory factor and tumor necrosis factor-a), all increase after nerve injury (201,202). Although research on the role of cytokines in the modulation of nociception in the spinal cord still lags behind that in the periphery (203), work is likely to continue as pharmacologic and genetic tools allow.

Modulatory Mechanisms: Inhibition and Disinhibition

In addition to the previously mentioned mechanisms of facilitated nociception, another hypothetical mechanism for central sensitization might be a loss of inhibitory tone. This could occur from a loss of inhibitory interneurons or depletion of, or tolerance to, antinociceptive neurochemicals. We briefly describe the major inhibitory systems in the spinal cord, including effects of their disruption, and then discuss the known peptidergic modulators usually classified as antinociceptive, including the opioid peptides.

Gamma-Aminobutyric Acid. GABA is the most prevalent inhibitory neurotransmitter system in the CNS. It has been known for many years that GABA exerts a presynaptic control of large primary afferent fibers, particularly Ia afferents from muscle (96,102). High concentrations of GABA are also found in laminae I and II of the superficial dorsal horn, in which there is dense input from small-diameter primary afferents. The pharmacology of the GABA system includes two receptor subtypes, the $GABA_A$ and $GABA_B$ receptors. $GABA_A$ and $GABA_B$ receptors are decreased, although not eliminated, in the spinal cord by dorsal rhizotomy, suggesting a presynaptic primary afferent locus for a significant portion of these receptors (32). The $GABA_A$ receptor is an ionotropic receptor complex composed of three subunits including barbiturate and benzodiazepine binding sites that modulate GABA-activated chloride currents. In adult CNS neurons, GABA-activated chloride currents flow into the neuron because of the low chloride concentration intracellularly. This current hyperpolarizes the neuron or inhibits depolarizing currents passing through other channels or receptors. On the other hand, $GABA_A$ effects on young hippocampal or primary afferent neurons differ in that intracellular chloride concentrations are kept high in these cells by active co-transport of chloride (along with sodium and potassium) into the neuron, and thus GABA-mediated chloride currents flow in an outward direction, depolarizing the cell. $GABA_A$-mediated primary afferent depolarization (PAD) is a mechanism of presynaptic inhibition associated with a decrease in excitatory transmitter release. Indeed, substance P release is under tonic inhibitory control by GABA, and GABA antagonists have been shown to produce allodynia. Interestingly, however, such PAD has an equilibrium potential (approximately –30 mv) more depolarized than the action potential threshold for primary afferents. In short, this means that excessive $GABA_A$-mediated depolarization could conceivably produce rather than inhibit excitatory transmitter release. Indeed, in one inflammatory pain model, $GABA_A$ antagonists inhibit hyperalgesia, suggesting that just such a potentiated PAD is responsible. Moreover, peripheral signs of inflammation (e.g., edema, flare) are reduced, suggesting that a PAD- initiated action potential can propagate antidromically from the spinal cord terminals to the periphery (dorsal root reflex) (102). In contrast, PAD has been found to be decreased in an axotomy model of neuropathic pain, implying that a loss of $GABA_A$ tone may facilitate pain behavior in this model.

$GABA_B$ receptor activation, although capable of causing presynaptic inhibition does not produce PAD. The $GABA_B$ receptor is a metabotropic receptor that inhibits depolarization via G protein–coupled effects on calcium or potassium currents. Much more information is available regarding the function of $GABA_A$ receptors in modulating nociception than $GABA_B$ receptors, primarily because of the better pharmacologic tools available for studying $GABA_A$ receptors. Indeed, much of the research on the spinal effects of $GABA_B$ agonists such as baclofen have focused on the inhibition of motor reflexes, particularly in laboratory animals or humans with spinal cord injuries. Nonetheless, a role for $GABA_B$ receptors is likely in the dorsal horn as well, if only because this region is virtually unique in the CNS for $GABA_B$ receptors outnumbering $GABA_A$ receptors.

In addition to the effects of GABA on presynaptic primary afferent inhibition, much evidence of postsynaptic inhibition in the spinal cord also exists. Some stalked cells contain GABA and inhibit the activity of STT neurons near their lamina I axonal arbors. GABA-containing layer II_i islet cells also have been identified. Based on their nonnociceptive inputs, some propose that these cells serve as the inhibitory interneurons of the inner SG, mediating nonnociceptive inhibition of second–order nociceptors (29,54).

Its inhibition of motor reflexes suggests that GABA's effects are unlikely to be selective to nociceptive processes. Even in the dorsal horn GABA (and particularly $GABA_B$) receptors densely populate laminae III and IV, as well as more superficial laminae. Nonetheless, $GABA_A$ (204) and particularly $GABA_B$ agonists inhibit sensitized responses to low-threshold mechanical stimulation (allodynia) in a number of neuropathic pain models (189). Such a model, the chronic constriction injury model, produces degenerated or *dark* neurons in laminae I and II of the dorsal horn. These dark neurons may be the result of excitotoxicity of inhibitory interneurons, and the mechanical sensitization may result from a loss of inhibitory, presumably GABAergic tone.

Initial clinical reports of $GABA_B$ agonists such as baclofen inhibiting allodynic pain have been hopeful (205). Such pain relief may prove short-lived because baclofen's inhibitory effects on muscle spasms have demonstrated rapid tolerance clinically. More than most receptors, $GABA_B$ receptors show dramatic increases and decreases in receptor number as a result of $GABA_B$ antagonist and agonist exposure, respectively (32). This is a possible mechanism for tolerance to these drugs.

Glycine. Like GABA, glycine is an important inhibitory neurotransmitter in the CNS. Glycine binding sites divide into two groups, strychnine-sensitive and strychnine-insensitive. We briefly discussed strychnine-insensitive glycine sites in discussing the NMDA glutamate receptor.

Glycine acts as a coagonist at the NMDA receptor. This action is not blocked by strychnine and is generally excitatory. In contrast, glycine's strychnine-sensitive effects are inhibitory, caused by anionic currents and the receptor itself is molecularly similar (35% to 40% sequence homology) to $GABA_A$ receptors. Glycine inhibition seems to be much more important in brain stem and spinal cord than at more rostral sites in the CNS. Like GABA receptors, strychnine-sensitive glycine receptors are definitely not restricted to the superficial laminae and, although common in lamina II, they are scattered from laminae II through VIII. Nonetheless, glycine does not seem to mediate PAD (102) and, indeed, dorsal rhizotomy has no significant effect on glycine binding. This suggests that glycine receptors are intrinsic to the CNS.

Strychnine given intrathecally causes impressive sensitization to light touch (allodynia) (206), implying that tonic glycine inhibition is important in normal somatosensation. Humans also show allodynia in strychnine toxicity. Central sensitization of STT cells in the deep dorsal horn has been associated with decreases in glycine and GABA inhibition. This takes place postsynaptically via effects of the nitric oxide/guanosine 3',5'-cyclic monophosphate pathway (154,207) activated by, in this case, capsaicin, presumably on the receptors themselves. Moreover, blockade of glycine facilitates dark neuron production after chronic constriction injury, suggesting that glycine is important in inhibiting excitotoxicity.

In summary, GABA and glycine appear important in modulating nociception in the spinal cord. These inhibitory transmitters appear particularly important in inhibiting allodynia in a variety of neuropathic pain models. Perhaps counterintuitively, increases in $GABA_A$ activity may potentiate inflammatory pain.

Adenosine. Adenosine administered intrathecally can produce potent analgesia in a variety of threshold, inflammatory, and neuropathic pain tests (208). Interestingly, adenosine is a metabolite of ATP, which we suggested previously might be pronociceptive. A1 and A2 adenosine receptors are implicated in producing analgesia, although the most convincing data implicate A1 receptors primarily. Adenosine receptors are present in the spinal dorsal cord and particularly in the SG. Postsynaptic adenosine inhibitory effects, including activating potassium currents, are probably most common because few adenosine receptors have been localized to primary afferent terminals. Nonetheless, adenosine inhibits substance P release from primary afferent electrical stimulation, presumably via a presynaptic effect.

Adenosine is a potent inhibitor of excitable cells throughout the body, including spinal motoneurons. Possible motor side effects confound several of the studies purporting to demonstrate adenosine analgesia. Dose-response studies, however, demonstrate a five- to tenfold increase in doses needed to inhibit motor responses over doses that inhibit pain. Human studies of the analgesic effects of adenosine are complicated by a $_2$-mediated algesic effects in the periphery. Nonetheless, intrathecal trials have been initially promising (209).

In animal models, no effect on nociception has been reported with adenosine antagonists, suggesting that endogenous adenosine does not tonically act to produce antinociception, at least not with its rapid metabolic pathways intact. Specific adenosine kinase inhibitors (210) may prove therapeutic by prolonging the actions of endogenous adenosine and by decreasing the side effects seen with administration of the drug. On the other hand, adenosine is an example of an agent that may have particular use in the sensitized pain state, particularly allodynia. Even when pain threshold tests demonstrate little analgesia, antihyperalgesic, or antiallodynic effects of adenosine (211), a_2-noradrenergic (212), cholinergic (212,213), and kappa opiate agonists (214) may have important clinical implications.

Inhibitory Synaptic Plasticity. We discussed previously the hypothesis that nociceptive sensitization may be caused by an LTP- like phenomenon strengthening or even unmasking previously silent (215) excitatory synapses in the spinal cord. Conversely, LTP of inhibitory synapses could counteract sensitization or inhibit nociception itself. Such inhibitory LTP has not been reported as yet in the nociceptive system, although it has been demonstrated in the hippocampus (216). In both the hippocampus and in the spinal cord the conceptually similar phenomenon of long-term depression has been reported. Long-term depression is similar to LTP in that it frequently depends on NMDA receptors and calcium influx through those receptors. In general, afferent stimulation just subthreshold for producing LTP (either because of the stimulus parameters used or partial pharmacologic blockade) results in long-term depression (217,218). Little work has been done in the spinal cord with this interesting phenomenon, which may well have therapeutic implications for reversing the maintenance of sensitization (219,220). This is likely caused by the need for single-cell analysis to rule out neural damage as the mechanism for a long-lasting inhibition of nociception after repeated excitation and the technical difficulties of such studies in the spinal cord. Indeed, in the hippocampus the most convincing studies are whole-cell voltage clamp studies in which induction of long-term depression is followed by induction of LTP at a single synapse or set of synapses. Whether long-term depression ultimately proves relevant to spinal cord nociception is unknown. However, if it does, the much-maligned NMDA receptor might prove an integral part of therapy for central sensitization.

Modulatory Mechanisms: Other Antinociceptive Neurochemicals

In addition to the mechanisms of inhibitory nociceptive modulation described above, several other neurochemicals inhibit nociceptive responses. As with the excitatory neuropeptides, research on inhibitory peptides has been hampered by a lack of selective receptor antagonists. Prominent exceptions to this are the opioid peptides or endorphins, whose receptor pharmacology is well worked out and exogenous agonists and antagonists abound.

Opioid Peptides and Their Receptors

Opiate Receptors. As previously mentioned, Martin (221) first subclassified opiate receptors into mu, kappa, and sigma groups using differing responses to the opiates morphine, ketocyclazacine, and SKF-10047, respectively (Table 4-1). Shortly thereafter, binding sites for these opiate agonists were identified pharmacologically and anatomically (222). With the discovery of the endogenous opioids by Hughes, Kosterlitz, and colleagues (223) new tools became available to identify specific targets. The delta opiate receptor was described as binding the two 5 amino acid opioid peptides methionine (met-) and leucine (leu-) enkephalin (ENK) with high affinity. Similarly, the 17 amino acid endogenous opioid dynorphin A was found to bind kappa receptors with relatively high affinity (224,225). Finally, two 4 amino acid peptides, the endomorphins, have been reported to have high affinity for the mu receptor (226), although ENKs and particularly dynorphin can also bind to these receptors. An epsilon receptor also has been hypothesized and is thought to bind the 31 amino acid b-endorphin. The sigma receptor proposed by Martin (see Table 4-1), although still a topic of interest to psychopharmacologists (227), is no longer thought to mediate opiate effects of endogenous or exogenous ligands.

	Receptor		
Organ/effect	Mu	Kappa	Sigma
Pupil	Miosis	Miosis	Mydriasis
Respiratory rate	Stimulation, then depression	No change	Stimulation
Heart rate	Bradycardia	No change	Tachycardia
Body temperature	Hypothermia	No change	No change
Affect	Indifference	Sedation	Delirium
Nociceptive flexor reflexes	Decrease	Decrease	Modest decrease

Modified from Iwamoto ET, Martin WR. Multiple opioid receptors. *Med Res Rev* 1981;1:411–440, as adapted from Martin WR, Eades CG, Thompson JA, et al. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther* 1976;197:517–532.

TABLE 4-1. Opiate receptor classification and action (studies in spinal dogs)

Pharmacologic agents have been developed to specifically act on or inhibit actions at mu, kappa, and delta receptors. Binding studies and behavioral pharmacology experiments suggested subtypes of these receptors and even more selective agonists and antagonists were developed to focus on the differential effects of these opiate receptor subtypes. The most highly cited example of such differential effects of receptor subtypes is the work of Pasternak's group on mu $_1$ and mu$_2$ receptor subtypes. Using an antagonist specific for the mu$_1$ receptor, the analgesic effects of morphine could be blocked without effect on the lethal dose of morphine (228). This finding gave great hope that the analgesic effects and the most serious side effect (respiratory depression) of mu agonists could be differentiated pharmacologically if a mu$_1$-specific agonist could be developed. Despite considerable effort, no one has produced such a drug.

Kappa and particularly delta opiate receptor subtypes also have been reported, based on binding affinities or behavioral studies using microinjections within the CNS. Several specific delta$_1$ and delta$_2$ agonists and antagonists have been produced, and the differential importance of these receptor subtypes in spinal (delta $_1$) and supraspinal (delta$_2$) antinociception has been reported.

With the cloning of the mu, delta, and kappa receptors in 1992 (Fig. 4-31), the biologic importance of opiate receptor subtypes became a topic of some controversy. At present, no generally accepted direct evidence exists for molecularly distinct subtypes of delta receptors or any other opiate receptor. Indeed, *in vitro*, specific delta$_1$ and delta$_2$ agonists act identically on delta receptors in cells from which the delta receptor amino acid sequence was cloned (229). Intrathecal antisense studies (230) suggest that, if a molecular difference exists between delta$_1$ and delta$_2$ receptors, it should lie in the amino, or extracellular, terminal of the seven transmembrane opiate receptor structure characteristic of G protein–linked receptors. Such an extracellular difference could explain a difference in binding affinities for various agonists and antagonists. Even if no molecular differences between delta $_1$ and delta$_2$ receptors are identified, differences in effects of specific delta $_1$ and delta$_2$ agonists could still result from different pharmacokinetic or pharmacodynamic influences on these drugs when centrally administered *in vivo*. For instance, differences in a drug's ability to penetrate the spinal cord to the receptor sites could produce differential effects, particularly if receptors at different depths had different functions. Moreover, differences in metabolism or activity at other opioid or nonopioid receptors might produce reliably different pharmacologic effects without molecularly different receptors. Another possible explanation for pharmacologically distinct opiate receptor subtypes has been reported. Devi and colleagues have shown that individual opiate receptors can bind to one another to produce a receptor dimer whose binding affinities and functions differ from those of monomeric mu, kappa, or delta receptors (231). The opiate receptor dimer made up of delta and kappa$_1$ receptor subunits, for example, acts *in vitro* (231) much like the kappa$_2$ receptor subtype described *in vivo* (232). This phenomenon, if it holds true *in vivo* for opiate receptors and is extended to other G protein–linked metabotropic receptors, will have important implications for mechanisms of synaptic plasticity in the field of pain and throughout neuroscience.

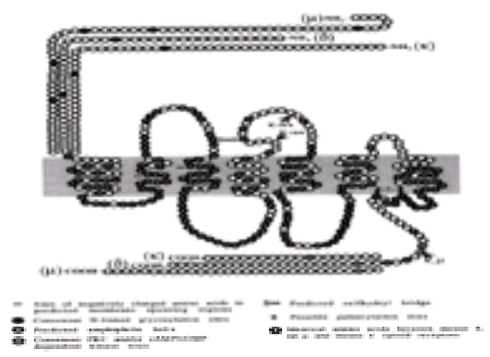

Figure 4-31. Structural homology among the delta, mu, and kappa opioid receptors. Amino acid sequences of opiate receptors show remarkable similarities to one another (approximately 60%) and across species (more than 95%). This homology is particularly evident in the transmembrane regions of the receptors. Arrows indicate where there are additional amino acids in the kappa or mu receptor. (From Miotto K, Magendzo K, Evans CJ. Molecular characterization of opioid receptors. In: Tseng LF, ed. *The pharmacology of opioid peptides*. Singapore: Harwood Academic, 1995:64, with permission.)

Clinically, opiate receptor *subtype* effects and agents may prove useful, regardless of the molecular events underlying their distinct pharmacologies. Subtype-specific effects might be limited to certain administration routes (e.g., intrathecal) or to combination therapy with other interacting drugs. Nonetheless, these effects would be of great use if tied to differential side effect profiles. For example, delta agonists have epileptogenic side effects and the kappa opiates are poorly tolerated because of dysphoric effects. If subtype-specific agonists could produce antinociception without the usual receptor-mediated side effects or analgesic tolerance, then the absence of receptor subtype clones would not reduce the importance of these results. Thus far, few such studies have been published, with the notable exception of the mu $_1$ and mu$_2$ investigations.

Spinal opiate receptors are 70% mu, 24% delta, and 6% kappa receptors. Antibodies to specific amino acid sequences of mu, kappa, and delta receptors permit study of the anatomic location of these receptors with much greater resolution than was possible previously with radiolabeled receptor autoradiography techniques. Presynaptic and postsynaptic mu and delta receptors have been identified with co-localization of these two receptor types, a common occurrence (74). Presynaptic receptors make up approximately 70% of all mu and delta receptors. Kappa receptors, although less studied, thus far appear to be more commonly located on postsynaptic structures in the dorsal horn (233). In accordance with the anatomy, both presynaptic and postsynaptic mu opioid effects inhibit primary afferent input to the spinal cord (234,235).

Another mechanism of opiate activity in other areas of the CNS (e.g., the hippocampus) is disinhibition: inhibition of inhibitory interneurons resulting in a net excitation of the system. Such excitatory effects of opiates in spinal cord nociception have not been demonstrated. Although suggestions of kappa opiate–mediated sensitization exist (236), this phenomenon is probably mediated by nonspecific NMDA receptor activation by dynorphin rather than a kappa-mediated disinhibition (237). Reports of opiate activation of SG cells have unclear significance to nociception (238). Presumably, opiate-induced disinhibition of SG inhibitory interneurons would be antinociceptive, whereas disinhibition of excitatory interneurons might potentiate nociceptive transmission. Regardless of their effects on any given neural circuit throughout the nervous system, opiates are inhibitory at the cellular level with few exceptions (239). The molecular mechanisms underlying this inhibition depend on the ion channels linked to the G protein–coupled opiate receptor. Opiates open potassium channels or close calcium channels. In either case, these actions cause less transmitter release presynaptically and make it more difficult for neurons to reach their action potential thresholds postsynaptically.

Mu receptors are predominately localized on small primary afferent terminals. This may account for mu agonist effects on nociception without affecting touch sensations carried by larger fibers. Indeed, it may be this selectivity that makes the allodynia (pain from light touch) experienced by some patients and laboratory animals after nerve injury less responsive to opioid therapy. Postsynaptically, second messengers can be inhibited (e.g., PKA and cAMP) or activated (e.g., inositol triphosphate, PKC, and Ca^{2+}) by opiates (240) (Fig. 4-32).

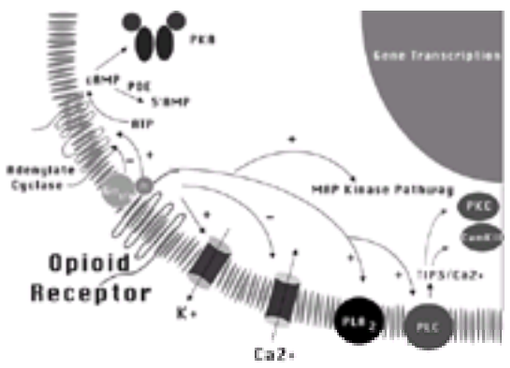

Figure 4-32. Opioid receptor effects on enzymes and second messengers. The opiate receptor is a G-protein–coupled receptor that can work via a number of effectors and second messengers to influence a variety of neuronal processes from resting membrane potential to gene transcription. Through G protein coupling, opiate receptors can activate potassium (K) channels, close calcium (Ca) channels, or both. Mu, delta, and kappa opiates have all been reported to have these effects. Opiate receptors can also act via i and o alpha G protein subunits (Ga $_{i/o}$) to inhibit adenylate cyclase and thus cAMP production from ATP. This in turn can inhibit cAMP-dependent protein kinase (PKA). Conversely, via s alpha subunits (Ga $_s$, not shown) or certain beta/gamma G protein subunits (bg) opiate receptors can activate cAMP production and PKA activity. Other kinases can also be activated by opiate receptors including G protein receptor kinases (not shown), mitogen activated protein kinases (MAP kinase), and via phospholipase C (PLC)- mediated increases in inositol triphosphate (IP3) and intracellular calcium, protein kinase C (PKC), and calmodulin-dependent kinase (CamK). Phosphorylation of the opiate receptor by these kinases can inhibit its function and may provide a mechanism for opiate tolerance. Opiate receptors can also activate phospholipase A $_2$ (PLA_2) and activate certain potassium channels via a 12-lipoxygenase–produced metabolite of arachidonic acid (see discussion in periaqueductal gray part of Descending Modulation section of this chapter). Phosphodiesterase (PDE) metabolizes cAMP to 5'AMP. (From Appleyard S. *Agonist dependent desensitization and opioid receptor phosphorylation: a potential role in the development of opioid tolerance*. Seattle: University of Washington Doctoral Thesis, 1998:14, with permission.)

Cross-talk by second messenger systems activated by other receptors may modulate opiate actions as well. One example of such cross-talk is the interaction of NMDA and opiate receptors. Calcium entering the cell via NMDA receptors can activate PKC. Phosphorylation of NMDA receptors can potentiate activity of these receptors, causing a positive feedback loop (241). In contrast, opiate receptors can also activate PKC, and phosphorylation of opiate receptors (by PKC or other kinases) can decrease the activity of those receptors causing opiate desensitization or tolerance (242). Mao and colleagues (243) have proposed that this cross-talk mediates morphine tolerance in cells with both activated NMDA receptors and opiate receptors. This explains why NMDA antagonists inhibit mu opiate tolerance in several animal models and why NMDA-mediated nociceptive phenomena are poorly responsive to opiates (Fig. 4-33 and Fig. 4-34). Whether enough dorsal horn cells with co-localized mu and NMDA receptors exist to allow this mechanism to mediate a significant portion of opiate tolerance is still under investigation. Nonetheless, NMDA antagonists are already being studied in humans for their ability to block or reverse opiate tolerance. Facilitated NMDA receptors may be responsible for the effects of opiate withdrawal. Fundytus and Coderre have implicated cross-talk between opiate receptors and metabotropic glutamate receptors in mediating opiate withdrawal excitability (87). In their model, desensitization of metabotropic receptors by opiate-induced kinase activity would increase excitability of the circuit (in the absence of opiate inhibition) via a loss of metabotropic glutamate autoreceptors presynaptically or via a postsynaptic increase in cAMP and subsequent activation of cation channels (see Fig. 4-34).

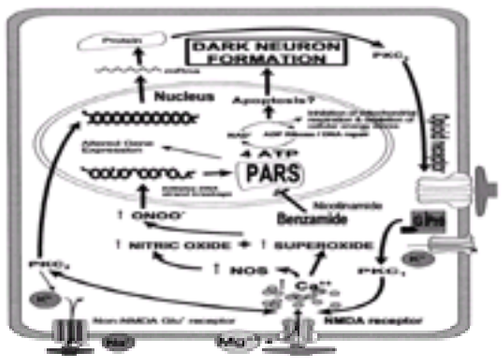

Figure 4-33. A model of the development of opioid tolerance in the dorsal horn of the spinal cord. Activation of the mu-opioid receptor initiates protein kinase C (PKC) activation (translocation to the membrane), which phosphorylates an *N*-methyl-d-aspartate (NMDA) receptor, activating it (by removal of the Mg^{2+} block) and allowing an increased influx of Ca^{2+}. The increased Ca^{2+} activates additional PKC [either the same pool (PKC_1) or a new pool (PKC_2), which can diffuse to the nucleus to alter gene transcription]. Increased Ca^{2+} also activates nitric oxide synthase (NOS), increasing nitric oxide, and the production of mitochondrial superoxide. The simultaneous generation of NO and superoxide produces peroxynitrite (ONOO–). ONOO– can initiate DNA damage and subsequent production of nuclear repair enzyme (PARS). PARS activation can deplete energy stores and lead to cell dysfunction and perhaps death (dark neuron formation?). (From Mayer DJ, Mao J. Mechanisms of opioid tolerance: a current view of cellular mechanisms. *Pain Forum* 1999;8:16, with permission.)

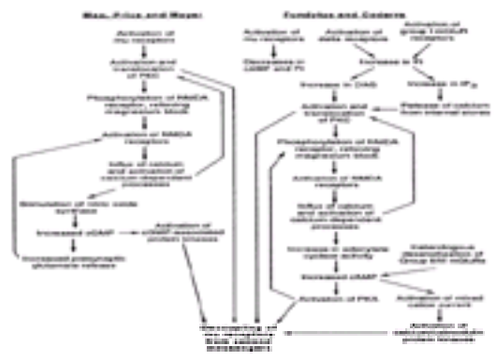

Figure 4-34. Flowchart diagram illustrating the key steps involved in the models by Mao and colleagues and Fundytus and Coderre of opioid tolerance and withdrawal. (cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; DAG, diacylglycerol; IP3, inositol-1,4,5-triphosphate; mGluR, metabotropic glutamate receptor; NMDA, *N*-methyl-d-aspartate; PI, phosphatidyl inositol; PKA, protein kinase A; PKC, protein kinase C.) (From Trujillo KA. Cellular and molecular mechanisms of opioid tolerance and dependence. *Pain Forum* 1999; 8:29–33, with permission.)

Endogenous Opioids (Endorphins). The discovery of leu-enkephalin and met-enkephalin, the two 5 amino acid peptides with opiate-like activity, suggested that these ligands, found in high concentration at the spinal and medullary dorsal horn and in various other parts of the CNS, might normally act on intrinsic opioid systems to inhibit nociception. That opiate antagonists such as naloxone generally have no effect on pain thresholds suggests that endogenous opioid systems are not tonically active (244). However, some studies, including one in postoperative patients, do report reduced pain thresholds after naloxone (245).

Three classes of endogenous opioids have been most thoroughly studied: the ENKs, dynorphins, and b-endorphin. These three distinct families of opioid peptides are cleaved from different precursors (Table 4-2), and each has a distinct anatomic distribution. The two 4-amino endomorphins described in 1997, have been less studied but also have a distinct anatomy and pharmacology (246,247,248 and 249).

Prohormone	Peptide	Sequence*		No. of amino acids
		L	M	
Proopiomelanocortin	β-Endorphin		X	31
	γ-Endorphin		X	17
Proenkephalin A	Leu-enkephalin	X		5
	Met-enkephalin		X	5
	Heptapeptide		X	7
	Methorphamide		X	7
Proenkephalin B	Dynorphin	X		17
	$Dynorphin_{1-8}$	X		8
	α-Neoendorphin	X		10
	Dynorphin B	X		13

*Indicates the end terminus is either identical to leu-enkephalin (L) or met-enkephalin (M).
Modified from Terenius L. Families of opioid peptides and classes of opioid receptors. In: Fields HL, Dubner R, Cervero F, eds. Advances in pain research and therapy. Vol. 9. New York: Raven, 1985:63–67.

TABLE 4-2. Amino acid sequences of major opioid peptides and their respective precursors (prohormones)

ENKEPHALIN. ENKs have a wide distribution throughout the CNS. However, their presence in several regions are consistent with their contribution to antinociceptive mechanisms (29,186). The most important and clinically relevant location is the dorsal horn, in which there are opiate-binding sites on central terminals of primary afferents and dorsal horn neurons. ENK also occurs in supraspinal regions implicated in nociceptive modulation, including the midbrain periaqueductal gray (PAG) and the medullary nucleus raphe magnus (NRM) and adjacent nucleus reticularis paragigantocellularis (250).

Although some spinal ENK immunoreactivity is from axons projecting to the spinal cord from the medulla (bulbospinal), the vast majority of ENK derives from intrinsic dorsal horn neurons (29). Immunohistochemical studies reveal that dense accumulation of ENK is in the superficial layers of laminae I and II and also in lamina V, most notably in the lateral part, as well as in laminae VII and X (29) (Fig. 4-35). Because these regions contain cells responsive to noxious input, the ENK axons and their terminals are strategically situated for direct postsynaptic inhibition of nociceptive neurons projecting rostrally toward the brain.

Combined immunochemical and retrograde HRP studies indicate that ENK immunoreactive endings make direct synaptic contact with the soma and proximal dendrites of approximately one-third of lamina I thalamic-projecting neurons (185). Lamina II_o stalked cells and some lamina II_i islet cells are ENK containing (185) (Fig. 4-36). Because the axons of stalked cells arborize in lamina I among dendrites of lamina I, ENK-containing stalked cells are a potential source of ENK input on thalamic projection neurons (185). Dubner and colleagues (54) suggested that, although some stalked cells that are not ENK-containing neurons may be excitatory local-circuit neurons as Gobel proposed, the ENK stalked cells are inhibitory local-circuit neurons that suppress the activity of lamina I thalamic projection neurons. Dubner and associates (185) further noted that, although lamina II_i cell axons and dendrites are confined to lamina II and therefore cannot directly influence output systems in lamina I, the islet cell dendrites are presynaptic to stalked cell dendrites. Thus, islet cells may indirectly modulate the activity of lamina I thalamic projecting neurons via the stalked cell–lamina I linkage. The most densely innervated lamina I neurons often are large Waldeyer's cells.

Figure 4-36. A composite from several sagittal sections of camera lucida drawings of lamina II enkephalin-immunoreactive stalked cells (a through d) and lamina IIb (II_i) islet cells (e through g) in cat lumbar spinal cord pretreated with colchicine. The dashed line at the top indicates that border between lamina I and the overlying white matter. The rapidly tapering processes (*arrowheads*) arising from the stalked cell somata resemble axon initial segments. *Arrow* beside (e) indicates a recurrent islet cell dendrite. (From Bennett GJ, Ruda MA, Gobel S, et al. Enkephalin immunoreactive stalked cells and lamina IIb islet cells in cat substantia gelatinosa. *Brain Res* 1982;240:162–166, with permission.)

ENK-containing local-circuit neurons are also present in deeper laminae of the dorsal horn (28). Lamina III contains small ENK-containing cells that have somata and dendritic patterns characteristic of intracellular HRP-filled lamina III neurons, which receive only low-threshold mechanoreceptor input. The ENK-containing lamina III neurons are ideally located to provide ENK input to the dorsal column postsynaptic neurons whose dendrites ramify throughout lamina III, and their axons project in the dorsal columns. Based on the importance of this pathway in visceral pain, one might hypothesize a role for these cells in modulating this visceral nociception.

ENK-containing neurons located in lamina V are situated well for providing ENK input to lamina V projecting neurons and, indeed, more than 50% of lamina V thalamic-projecting STT neurons receive ENK contacts (185). Evidence exists for a local negative feedback circuit that is turned on by arriving nociceptive impulses. Such impulses cause the local release of ENK, which modulates the output of ascending nociceptive neurons. In addition to these postsynaptic actions, the evidence for presynaptic opiate receptors points to possible opioid-mediated presynaptic control of primary afferents. Interestingly, this hypothesis for presynaptic control of primary afferents by ENK lacks support of ultrastructural evidence. Electron microscopic studies have generally revealed that the ENK terminals are primarily presynaptic to dendritic or somatic profiles, not primary afferent or other axons. Nonetheless, as previously mentioned, much electrophysiologic evidence suggests a pharmacologic presynaptic effect, if not a physiologic one.

DYNORPHIN. As noted in Table 4-2, dynorphin and a-neoendorphin are cleaved from proenkephalin B. Dynorphin-containing cell bodies are found in the PAG, mesencephalic reticular formation, and spinal and medullary dorsal horns (251). More than 80% of labeled medullary and spinal dorsal horn dynorphin cells are located in laminae I and V. After the discovery of dynorphin, evidence emerged that intrathecal, but not intracerebral, injections of the peptide produce profound and prolonged analgesia (252). Dynorphin's paralytic effects confound some of these studies. These effects are mediated via NMDA receptors, rather than opiate receptors, and they are a high-dose effect (253).

Cruz and Basbaum (251) suggested that because the axonal arborization of spinal dynorphin neurons is not in the immediate vicinity of the cell, some of the spinal dynorphin neurons project elsewhere. They also concluded that dynorphin neurons of the dorsal horn might provide a presynaptic opioid peptide input onto the primary afferent neurons. Again, studies showing considerable postsynaptic kappa opiate receptor immunoreactivity (233) appear to demonstrate a mismatch between peptide and receptor. Indeed, the role of dynorphin in nociception has been complicated by studies showing that inflammation and nerve injury produce a prominent increase in spinal dynorphin immunoreactivity with a time course associated (although slightly behind) hyperalgesia in these models (254). The elevation of dynorphin is localized in laminae I, II, V, and VI of the ipsilateral (but not the contralateral) dorsal horn. This suggests the involvement of dynorphin-containing neurons in nociceptive processing. Whether this correlation of dynorphin level and hyperalgesia implies a causative role for dynorphin (perhaps at NMDA receptors) or, in contrast, represents a negative feedback mechanism whereby dynorphin inhibits further hyperalgesia, is controversial. Indeed, dynorphin could do both in a dose-dependent way.

b-ENDORPHINS. Proopiomelanocortin is the precursor for b-endorphin, adrenocorticotropic hormone, and three forms of melanocyte-stimulating hormone. Unlike the ENKs and dynorphin, which are widely distributed in the neuraxis, proopiomelanocortin neurons are concentrated in the basal hypothalamus (infundibular nucleus) with their axons extending rostrally to the limbic system or caudally along the wall of the third ventricle toward the midbrain, PAG, and locus coeruleus. b-endorphins can produce analgesia and have been implicated in mediating certain forms of stress-induced analgesia (SIA) (255), although this is controversial. We discuss SIA later in this chapter (see Descending Systems that Modulate Nociception).

Opiate Inhibition of Sensitization. As mentioned, opiates can inhibit AMPA (234) and NMDA-receptor-mediated primary afferent neurotransmission (82) in the dorsal horn via presynaptic (82) and postsynaptic (235) mechanisms. This may explain their potent analgesic actions. Mu opiates can also inhibit induction of LTP in dorsal horn cells after repeated primary afferent activation (256), perhaps explaining their preemptive effects on sensitization in rodents (31) and humans (257). Mu opiates have proven less effective in providing antinociception in the sensitized state, particularly in neuropathic pain. Mu opiate receptors decrease in the spinal cord after nerve injury, perhaps providing a mechanism for this effect (240).

In contrast, kappa opioids seem particularly effective in inhibiting sensitized nociception after dorsal horn cell LTP (258), inflammation (259), surgery (260), or nerve injury (214), sometimes without effect on baseline nociception. This suggests that kappa agents interfere preferentially with maintenance, expression, or both, rather than induction of sensitized nociception. As previously mentioned, the therapy of most pain conditions would benefit from the targeting of sensitization without sacrificing normal nociception, by kappa opiate or other antinociceptive drugs.

Neuropeptide FF. The eight amino acid neuropeptide FF has complex effects on nociception, varying in its effects depending on the site of injection and prior nociceptive sensitization. Supraspinally administered neuropeptide FF lowers nociceptive thresholds and reverses morphine analgesia (261). After nerve injury, however, supraspinal neuropeptide FF inhibited mechanical (though not thermal) thresholds while still blocking morphine's antinociceptive effects (262). In contrast, intrathecal neuropeptide FF induces a long lasting, opioid-dependent analgesia and potentiates opioid analgesia (261), except after carrageenan-induced sensitization when neuropeptide FF had no effect on mechanical or thermal nociception (263). The mechanism for these differential effects of neuropeptide FF after sensitization is not known. Receptors for neuropeptide FF are present in laminae I and II of the dorsal horn and are unaffected by dorsal rhizotomy, suggesting that the peptide's spinal effects are on intrinsic, perhaps ENKergic, cells. Indeed, neuropeptide FF can potentiate delta opiate analgesia (264). Endogenous neuropeptide FF is present in the superficial dorsal horn and around the central canal. It increases after peripheral inflammation (263). Perhaps neuropeptide FF normally acts at the spinal cord to release ENK and produce analgesia, but tolerance develops to these effects after long-lasting noxious stimulation.

Neuropeptide Y. The 36 amino acid neuropeptide Y (NPY), and the structurally related avian pancreatic polypeptide, when administered intrathecally, also produces differential effects on sensitized and normal animals. NPY normally inhibits thermal nociception, although it has little effect on mechanical nociceptive thresholds. Presumably, this indicates that the NPY receptors located on small-caliber primary afferent terminals in laminae I and II (32) are located on thermal sensitive nociceptors specifically (e.g., capsaicin-sensitive afferents). There, NPY receptors produce presynaptic inhibition of these nociceptors (265), via G protein–dependent inhibition of calcium channels or activation of potassium channels. After nerve ligation (266) or inflammation (267), however, NPY potentiates nociceptive responses. As discussed in Chapter 3, primary afferent NPY and NPY receptors increase (147) after inflammation or nerve injury. Spinal cord laminae II and III NPY receptors also increase, at least after inflammation (32). These laminae are known to contain GABA interneurons that also contain NPY and synapse on cells expressing the NK1 (substance P) receptor (268). NPY inhibition of these presumably inhibitory interneurons, by way of newly expressed NPY receptors, might account for changes in NPY pronociceptive effects after sensitization. Moreover, five subtypes of NPY receptors have thus far been identified (269). NPY1 and NPY2 receptors are normally expressed in large and small dorsal root ganglion (DRG) cells, respectively, although changes with nerve injury and inflammation on receptor subtype distribution have not been well characterized. A change in NPY subtype phenotype could underlie the differences seen in NPY nociceptive modulation after sensitization.

Galanin. Galanin, a 29 amino acid peptide discovered from intestine in 1983, inhibits nociception. It is cleaved from a prepropeptide along with a 60 amino acid fragment called *galanin message-associated peptide*, which inhibits C-fiber wind-up (270). Galanin binds to specific receptors, three of which have been cloned,

Gal-R1, R2, and R3. Gal-R1 and R2 receptors have been identified in CGRP-containing DRG, in large and small neurons, respectively, as well as on central terminals of these cells (271). GAL-R1 receptors, the most prevalent receptor subtype on dorsal horn neurons, are located in lamina I and II. Galanin itself is also seen in laminae I and II, around the central canal, and is contained both in primary afferent terminals and in small second-order neurons coexisting with GABA, ENK, NPY, or all three.

Low doses of galanin given intrathecally facilitate nociceptive reflexes, whereas larger doses inhibit them (272). An antagonist to galanin blocks intrathecal morphine analgesia and potentiates wind-up, suggesting a normal role for galanin in modulating opioid action and sensitization. In this latter regard, galanin and galanin receptors are greatly affected by inflammation and nerve injury, as mentioned in Chapter 3. The effects are complex and we refer the reader to reviews on the topic (271) for detailed anatomic analyses. In short, intrathecal galanin inhibits allodynia after axotomy. This inhibition is probably postsynaptic because presynaptic (primary afferent nerve terminal) galanin receptors decrease after nerve injury.

Galanin antagonists potentiate pain behaviors after nerve injury, and increases in DRG galanin after nerve injury suggests this as the most important source of peptide mediating the effect (189). Galanin antagonists also can greatly increase nociceptive responses after inflammation, although increases in dorsal horn galanin suggest this as the predominant source of galanin for this effect. Whether presynaptic or postsynaptic galanin receptors are most important in this effect is unknown.

Neurotensin. Neurotensin, a 13 amino acid peptide, produces analgesia in certain pain tests after intrathecal injection (273). Neurotensin and its receptors are localized to spinal neurons intrinsic to the cord (29,32). Cell bodies containing neurotensin concentrate in laminae II and III of the dorsal horn, and their terminals extend through laminae I, II, and III (274). Like ENK, terminals containing neurotensin predominantly form axosomatic and axodendritic synapses with dorsal horn neurons, although some neurotensin terminals are located presynaptically to unidentified vesicle-containing structures (29). Neurotensin's effects are primarily excitatory at the cellular level, so its antinociceptive effects probably stem from excitation of inhibitory cells or presynaptic inhibition of excitatory interneurons (although neither mechanism has been demonstrated). Indeed, neurotensin's effects on nociception are much better characterized at supraspinal sites and a supraspinal site of action for its intrathecal effects has not been ruled out. Nonetheless, neurotensin-containing cells are heavily innervated by descending serotonergic input usually associated with antinociception (275) and thus its spinal action seems more likely to be facilitated by its supraspinal action than confounded by it.

Somatostatin. Like neurotensin, somatostatin (a tetradecapeptide) and its more metabolically stable analogues have been reported to mediate supraspinal and spinal analgesic effects (276). Moreover, several case reports suggest that both systemic and spinal administration of analogues of somatostatin can produce analgesia in humans; particularly for migraine (277) and cancer pain resistant to other forms of therapy (278). Somatostatin occurs predominantly in lamina II_o, but there is also some staining in lamina II_i and the dorsal part of lamina III. Sparse innervation is also seen in the rest of lamina III, lamina IV, the reticulated region of lamina V, and in the central canal region (185) (Fig. 4-37). Somatostatin receptors are located in laminae I and II and in the adult animal are not observed on primary afferents (279). Somatostatin derives from a population of small-diameter dorsal root ganglion cells and from somatostatin cell bodies within lamina II_i and exerts a predominantly inhibitory effect on nociceptors in electrophysiology studies (280). Somatostatin has also been found to have neurotoxic effects in some animal species (281) and perhaps humans (282). Whether these effects are caused specifically by somatostatin receptors is not known because of the absence of a selective somatostatin antagonist. Regardless, such effects underline the difficulty facing clinicians who attempt to alleviate their patients' pain without doing them harm. Clearly, a rat may stop flicking its tail away from a hot light for many reasons. The physician must be armed with toxicology and drug dosing information, not simply a new drug, before extrapolating preclinical results to his or her patient's pain complaints. At present, the jury is still out on somatostatin's role in the physiology and pharmacology of pain modulation.

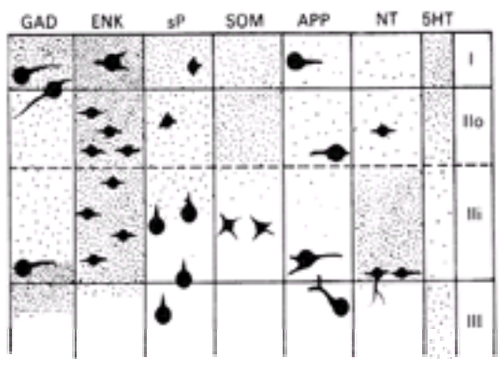

Figure 4-37. Diagram showing the location of neurons and of terminal zones in the upper three laminae of the dorsal horn that show immunoreactive staining for the following substances: glutamate decarboxylase (GAD), enkephalin (ENK), substance P (sP), somatostatin (SOM), avian pancreatic polypeptide (APP) (similar structurally to neuropeptide Y), neurotensin (NT), and 5-hydroxytryptamine (5-HT). (From Hunt SP, Kelly JS, Emson PC, et al. An immunohistochemical study of neuronal populations containing neuropeptides or gamma-aminobutyrate within the superficial layers of the rat dorsal horn. *Neuroscience* 1981;6:1883–1898, with permission.)

Ion Channel Blockers. A variety of ion channel blockers have neuronal effects and inhibit nociception. Sodium channel blockers, such as tetrodotoxin, for example, can be deadly, and local anesthetics (including analgesic oral antiarrythmic drugs such as mexiletene) share this characteristic as well as their sodium channel blocking properties. Other analgesic adjuvant drugs, such as phenytoin and carbamazepine (283), probably work by this mechanism. The small therapeutic ratios of these drugs, particularly with systemic administration, are quite reasonable, considering that sodium channels mediate all active neural transmission. However, the discovery of tetrodotoxin-resistant sodium channels (SNS/PN3), which are located predominately in small primary afferents and are increased coincident with neuropathic pain in some animal models (284,285), gives hope for the development of more selective antinociceptive sodium channel blocking agents, at least in the periphery.

Calcium channels are involved in all synaptic transmission by mediating exocytosis of neurotransmitter-containing vesicles. Thus, calcium channel blockers, of which there are many laboratory examples gathered from poisons throughout nature (e.g., conotoxins from cone snails), are dangerous drugs, at least systemically. Nonetheless, several subtypes of calcium channels have been identified and antagonists at several of these subtypes produce analgesia; these include *L*-type, *N*-type, *P*-type, and *Q*-type channel blockers (168,169,170,171,172,173 and 174). For example, in humans, analgesia from intrathecal SNX-111 (286) and, perhaps, gabapentin (287,288) is mediated via inhibition of calcium channels. Indeed, SNX-111 acts on the *N*-type calcium channel, and this is particularly important for vesicular release. If intrathecal doses of SNX-111 are identified that provide relatively specific antinociceptive effects, poor penetration into the spinal cord by peptides and the importance of lamina I in nociception may be responsible. Gabapentin appears to bind to a portion of the *L*-type calcium channel (289), thought less important in fast transmitter release. As discussed in Chapter 3, studies of inflammatory and nerve injury effects on calcium channel subtype expression may lead the way to better therapeutic options using calcium channel blockers for specific pain states. The tricyclic antidepressant adjuvant analgesic drugs have both sodium and calcium channel blocking properties (290,291), as well as monoaminergic reuptake blocking effects. They may be useful in certain pain states because of their mechanistic nonspecificity. Likewise, gabapentin, in addition to its channel blocking effects, also can potentiate GABA release (289). A myriad of ion channels exist that allow ions to flow down their electrical or concentration gradients to determine the electrical activity of a neuron. These may be ligand gated, voltage dependent, dependent on the concentration of a separate ion, and/or modulated by a host of G protein–coupled receptors or second messengers. Blockade or activation of any one of these channels or their modulators may be the key to pain management in the future. At present, however, our most useful antinociceptive pharmacologic tools have multiple mechanistic effects.

Nociceptive Modulation: Alternate Delivery Systems

The discovery of an increasing number of neurochemicals that modulate nociception at the spinal level in animals and in humans has led, not only to an increasing search for analogues with greater nociceptive specificity, but also to new methods of delivering these chemicals to their spinal targets. The studies by Yaksh and colleagues (174), demonstrating enhanced efficacy and potency of administering opiates directly to the spinal cord via intrathecal catheters in animals, have revolutionized clinical pain management through the routine use of intraspinal opiates. Other therapeutic agents also have been administered successfully via this route (Table 4-3) and a number of commercially available catheters and pumps are approved for spinal use in humans. Intrathecal drug administration allows targeting of the highest concentrations of drug at a site of high receptor number, thus theoretically increasing drug effect while minimizing drug side effects that might result

from actions in other areas of the brain or extranervous tissue (e.g., intestine). In addition, this technique allows drugs with minimal lipid solubility (e.g., peptides) to reach spinal sites by bypassing the blood–brain barrier and metabolism in liver or other peripheral sites. Investigators are now using other methods to achieve similar goals. Sagen and colleagues have shown that cells (such as adrenal medullary cells) that normally produce and excrete antinociceptive chemicals, when transplanted to the intrathecal space, can produce decreases in behavioral pain responses in rats (292,293) and humans (294). Other cells have been implanted intrathecally that have been genetically altered to excrete a number of antinociceptive neurochemicals (295,296). Carrying this reasoning one step further, genetically altered viral vectors have been used to induce opioid peptide production in primary afferent and meningeal cells and inhibit nociception in rodents (297,298). It remains to be seen whether such therapies using largely uncontrolled dosing and dosing regimens will be useful for treating clinical pain, whose intensity can fluctuate day to day and even hour to hour. However, molecular biology techniques exist to allow conditional changes in gene expression that might prove useful for overcoming these concerns.

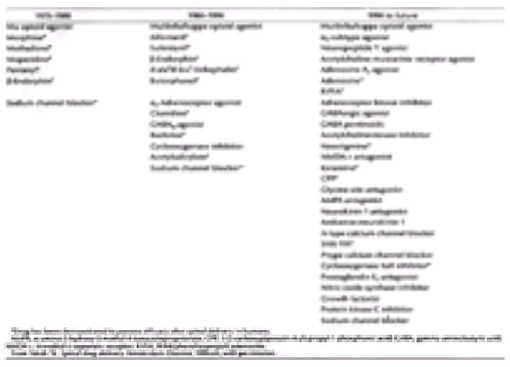

TABLE 4-3. Summary of drug classes that regulate nociceptive processing in preclinical and clinical models after spinal delivery

Overview of Neuropharmacologic Nociceptive Modulation

As is apparent from the preceding paragraphs, the pharmacologic modulation of spinal nociception is a complex topic. Many neurochemicals appear capable of inhibiting or facilitating nociception in animal and even human models (Fig. 4-38). Thus far, few of these compounds (or their antagonists) have been demonstrated to provide clinical benefit. A time lag always exists between basic science discoveries and clinical utilization, appropriately so, in order for toxicology and dose ranging studies to be done. Nonetheless, it is important to point out some of the possible incompatibilities between clinical pain studies and, for example, rodent pain studies that might lead to disparate results.

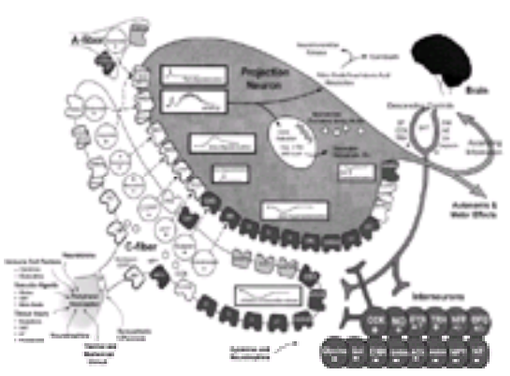

Figure 4-38. Pharmacologic systems thought to contribute to transmission and modulation of nociception in the dorsal horn of the spinal cord. The various neurochemicals and receptors depicted each has its own pharmacologic profile and may represent independent populations of individual neurons and fibers but more commonly interact with one another at any given synapse. Interactions can take place at presynaptic terminals, dendrites, and somata. Nonetheless, all of these neuromodulators are unlikely to be present at any one synapse. Not shown are interactions that can take place between interneurons [e.g., acetylcholine-induced gamma-aminobutyric acid (GABA) release]. Examples of A-fiber modulation are shown suggesting possible presynaptic antiallodynic mechanisms. Dark receptors (or –) indicate reported antinociceptive and white receptors (or +) pronociceptive effects. Gray receptors indicate presynaptic inhibitory effects. [Ach, acetylcholine (m and nAChR, muscarinic and nicotinic acetylcholine receptors); AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate; ATP, adenosine triphosphate; B2, bradykinin receptor subtype; CB1, cannabinoid receptor subtype; CCK, cholecystokinin; CGRP, calcitonin gene–related peptide; DA, dopamine; DYN, dynorphin; ENK, enkephalin; 5HT, serotonin; Gal, galanin (Gal1 and 2, galanin 1 and 2 receptor subtypes); GRP, gastrin-releasing peptide; mGlu, metabotropic receptor; NE, norepinephrine; NFF, neuropeptide FF; NK1 and 2, neurokinin 1 and 2 receptor subtypes; NM, neuromedin (bombesin) receptor; NO, nitric oxide; NPY, neuropeptide Y; NT, neurotensin; OFQ, orphanin FQ (nociceptin); ORL, orphanin receptor; SP, substance P; TRH, thyrotropin-releasing hormone; VR, vanilloid (capsaicin) receptor.] (Adapted from Dickenson A. Pharmacology of pain. In: *Receptor and ion channel nomenclature supplement*, 4th ed. Cambridge: Elsevier, 1993.)

Pain Assessment. Dubner (299) and Vierck and Cooper (300) specified that ideal pain assessment in laboratory animals should (a) distinguish responses to noxious and innocuous stimuli, (b) vary in response magnitude with changes in stimulus intensity from threshold to tolerance, (c) use multiple threshold and suprathreshold behavioral measures to infer pain, (d) be altered by manipulations (e.g., drugs) that alter perceived stimulus intensity, (e) distinguish modifications in responses caused by nonsensory variables (e.g., motor or motivational factors) from those caused by sensory variables, and (f) cause little or no tissue damage. The last of these ideals has been the most hotly debated in the field; swayed in one direction by important ethical considerations and in the other by the development of inflammatory and neuropathic pain models, many of which, like their human analogues, are the result of some degree of tissue damage.

To understand these ideals better, let us consider an animal or a population of animals (including humans) exposed to a stimulus of increasing intensity or severity (see Fig. 4-39A). As the stimulus gradually becomes more severe, the nociceptive response of the animal becomes more pronounced (e.g., faster, more likely to occur, and so forth). The shape of this stimulus to response curve is sigmoidal, with only few responses occurring with innocuous stimuli until a stimulus threshold is reached and a rapid increase in responses occurs with increasing noxious stimulation until an asymptote is reached, followed by a nearly maximal response (see Fig. 4-39A). The curve itself can be defined by four lines. One line represents a low frequency of *nociceptive responses* occurring in response to innocuous stimuli (e.g., incidental responses) and it intersects a line describing the stimulus severity at which responses begin to rapidly increase (nociceptive threshold) (see Fig. 4-39A). A third line defines the response frequency at which nociceptive responses normally asymptote, and it crosses a fourth line describing the stimulus at which asymptote is reached, *nociceptive tolerance* (Fig. 4-39A).

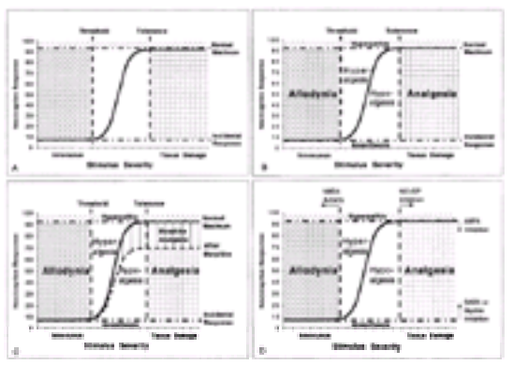

Figure 4-39. Stimulus/response curves for nociceptive responses and their modulation. **A:** A stimulus/response curve is sigmoidal and defined by four lines. One line

represents a low frequency of *nociceptive responses* occurring in response to innocuous stimuli (incidental responses). It intersects a line describing the stimulus severity where responses begin to rapidly increase (nociceptive threshold). A third line defines the response frequency where nociceptive responses normally asymptote (normal maximum), and it crosses a fourth line describing the stimulus intensity where asymptote is reached (nociceptive tolerance). **B:** An increased nociceptive response to normally innocuous stimuli is called *allodynia*. Increased responses to stimuli between nociceptive threshold and tolerance are hyperalgesic responses. Increases in responses over the normal maximum are called *hyperpathia* regardless of the intensity of the stimulus eliciting these responses. Response frequencies less than normal incidental responses (regardless of the stimulus severity) are seen primarily during anesthesia (or some motor impairment). Reduced responses to suprathreshold stimuli are best described as hypoalgesia. However, clinicians tend to describe reduced pain responses to stimuli beyond normal nociceptive tolerance as analgesia (even if some pain response is still present). **C:** Mu-opiate receptor agonists, such as morphine, seem to decrease maximum nociceptive responsiveness with much less effect on allodynia. **D:** An important mechanism by which mu opiates work is the inhibition of glutamate a-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) (or kainate, or both) receptor activity. Perhaps decreases in AMPA act to decrease the asymptote of normal or hyperpathic nociceptive responses. On the other hand, modulators that act to inhibit activity of the inhibitory neurotransmitters gamma-aminobutyric acid (GABA), glycine, or both frequently cause allodynia, as if shifting up the incidental responses to innocuous stimuli. *N*- methyl-d-aspartate (NMDA) agonists and antagonists also produce and inhibit allodynia, respectively, but are also effective in modulating responses at greater stimulus severities. NMDA receptors may set the *pain threshold*. As illustrated, a facilitator of NMDA receptor activity would cause both hyperalgesia and allodynia. Finally, the effects of inhibiting substance P (SP), or its neurokinin 1 (NK1) receptors, are illustrated here as producing a shift of pain tolerance to the right, resulting in primary efficacy for stimuli of moderate severity. [Based on Cervero F and Laird JMA. Mechanisms of touch-evoked pain (allodynia): a new model. *Pain* 1996;68:13–23.]

This stimulus to response function is useful for demonstrating the meaning of several clinical terms. For example, an increased nociceptive response to normally innocuous stimuli is called *allodynia* (Fig. 4-39B). On the other hand, increases in responses to stimuli between nociceptive threshold and tolerance are *hyperalgesic responses* (Fig. 4-39B). Increased response above the normal maximum is called *hyperpathia*, regardless of the intensity of the stimulus eliciting this response (Fig. 4-39B). Similarly, response frequencies less than chance (regardless of the stimulus severity) are seen primarily during anesthesia (or some motor impairment) (Fig. 4-39B). Reduced responses to suprathreshold stimuli are best described as *hypoalgesia* (Fig. 4-39B); however, clinicians tend to describe reduced pain responses to stimuli beyond normal nociceptive tolerance as *analgesia* (Fig. 4-39B). A majority of animal pain studies (including those in human volunteers) measure hyperalgesic or hypoalgesic responses to heat, cold, or electric shock. Many clinical pain problems arise from allodynia or, at the other end of the curve, from severe stimuli (above pain tolerance levels). Thus, the shrewd pain researcher reserves judgment on a pharmacologic agent that is reported to inhibit nociceptive responses in a heat threshold test, for example, because few patients would benefit from such an effect. As suggested at the beginning of this section, pain assessment should ideally be done at a number of different stimulus severities.

Having used this stimulus/response approach to illustrate nociceptive problems, it may also be useful in examining pharmacologic solutions. Mu opiate receptor agonists such as morphine, for example, are clinically useful in inhibiting pain responses to an array of suprathreshold noxious stimuli. These drugs have been found to be much less effective for allodynia (often a hallmark of neuropathic pain). If we examine a stimulus/ response curve (Fig. 4-39C), we might conclude that morphine decreases maximum nociceptive responsiveness. An important mechanism by which mu opiates work is the inhibition of glutamate release. Initially, this inhibition would decrease AMPA (or kainate or both) glutamate receptor activation. Given this mechanism, and the role of glutamate in nociceptive fast transmission, other neuromodulators that either release endogenous opioids or inhibit AMPA and kainate receptor activation might be expected to have analgesic effects, even at high stimulus severities. For ethical reasons, severe noxious stimuli are not normally given to the awake animal. Nonetheless, AMPA receptor inhibition has been found to inhibit acute nociceptive responses to noxious heat (81,301,302) and formalin injection (303,304).

As described previously, antagonists of the inhibitory neurotransmitters GABA and glycine (e.g., bicuculline and strychnine) produce allodynia in laboratory animals and humans. This effect can be conceptualized in the stimulus/response figure by an increase in the basal level of pain responses. Modulators that act to inhibit or facilitate release of these transmitters might be particularly active in this region of the stimulus/response curve (Fig. 4-39D).

NMDA agonists and antagonists also are reported to produce and inhibit allodynia, respectively, with much less effect on pain responses at greater stimulus severity. Such effects might result from a selective involvement of NMDA receptors in setting the *pain threshold* on the curve. Inhibitors or facilitators of NMDA receptor activity (such as depolarizing exogenous or endogenous agents or repeated stimulation from nerve injury) might modulate nociceptive effects near threshold (see Fig. 4-39D).

Finally, the finding that substance P knockout mice show decreased responsiveness in moderate severity pain tests is modeled on the stimulus/response curve as a shift to the right of the pain tolerance line. Agents affecting substance P release (including prostaglandins) might be particularly effective in modulating pain from moderately noxious stimuli (see Fig. 4-39D). Indeed, the World Health Organization recommends nonsteroidal antiinflammatory drugs for “pain of moderate severity.”

This approach of conceptualizing modulation of spinal nociception by the effects that neuroactive agents exert on stimulus/ response curves is not presented as a comprehensive model of spinal pharmacologic mechanisms. Indeed, mu opiates, by presynaptic primary afferent inhibition, would ultimately also decrease NMDA glutamate receptor activity over time (not just AMPA activity) and can certainly inhibit substance P release as well. Moreover, opiates work by other mechanisms including postsynaptic effects, perhaps explaining their synergistic, not simply additive, effects with AMPA antagonists (302). Nonetheless, such a simplified scheme does prove useful as (a) a reiteration of the importance of behavioral pain tests using several stimulus intensities, (b) an illustration of differences between experimental and clinical pains studied, perhaps, even at the spinal level, and (c) an impetus for a more integrative and, it is hoped, mechanistic (113) understanding of spinal cord nociceptive pharmacology and physiology. Findings that many of the neurochemicals discussed previously interact with each other when exerting their effects (e.g., nicotinic and muscarinic ACh analgesia is associated with increased GABA activity and a $_2$-noradrenergic analgesia is associated with increased ACh release) give hope that neurochemical modulation of nociception, although seemingly complex, may result from a few primary mechanisms.

Modulatory Mechanisms: Structural Reorganization

In addition to the pharmacologic or physiologic modulation of excitatory or inhibitory synaptic strength, nociceptive modulation can theoretically result from anatomic changes. Such synaptic reorganization would likely be slower in onset than other mechanisms modeled *in vitro*. However, many of the nerve injury and inflammatory models of central sensitization develop over many hours to days, more than enough time for anatomic changes to take place.

We have already discussed the possibility that dark neurons that appear in the spinal cord in a neuropathic pain model (the Bennett model) represent dead or dying inhibitory interneurons and lead to sensitization via this mechanism. Similarly, the inhibition of nociception produced by large-fiber activation referred to in the gate control theory led to the hypothesis that selective large- fiber damage may mediate heat hyperalgesia in a neuropathic pain model in rats (305) and postherpetic neuralgia in humans (306). This hypothesis was complicated by the fact that most models of rat and monkey neuropathic pain resolve spontaneously without corresponding neuronal repair, and that pain-free patients after herpetic infection have been found to share much of the nerve damage as neuralgic patients (307). In short, little conclusive evidence exists to support this hypothesis, and indeed, nerve injury appears more likely to damage small fibers than large fibers (308).

Sensitization via structural reorganization might also result from an increase in excitatory synapses. As mentioned for several peptides and their receptors (see Chapter 3), nerve ligation or axotomy can produce changes in potential synaptic activity through changes in peptide levels, receptor number, or both. Fast transmitter receptor number, location, and subtype also can be dramatically altered by nerve damage. AMPA receptors (particularly those most permeable to calcium) increase in laminae III, IV, and V after rhizotomy, possibly leading to sensitization of STT projection cells located there (309).

Probably the best documented example of structural reorganization playing a role in central sensitization is that, as a result of nerve injury, A-b low-threshold mechanosensitive primary afferent fibers that normally terminate exclusively in laminae III and IV, sprout into lamina II (310). Here, in SG, they are in excellent position to affect nociceptive processing and perhaps ultimately lead to pain from nonnoxious stimuli-allodynia (311). Several groups have replicated these findings and found that the loss of C fibers in SG is critical for prompting A-b sprouting (52). Conversely, agents that rescue C-fiber terminals from axotomy-induced damage, such as nerve growth factor, can inhibit nerve injury–induced A-b sprouting (312) and allodynia. Woolf and colleagues also have demonstrated that an increased A-b synaptic input to lamina II is present after 48 hours of inflammation (from complete Freund's adjuvant) as well, without direct nerve injury (313).

We have not fully discussed the roles of neurotrophins, including nerve growth factor, brain-derived growth factor, or neurotrophin-3 or their trk receptors (trkA, trkB, and trkC, respectively) in nociceptive modulation. Much of their reported activity has been in the periphery or on the dorsal root ganglion. Nonetheless, neurotrophins and their receptors can be demonstrated in the dorsal horn (314), neurotrophin-3 has been reported to produce naloxone-reversible mechanical hypoalgesia and inhibit substance P release (315), and neurotrophins are clearly active in other regions of the CNS (316). Thus, it is likely that these agents, in years to come, will be

found to have important spinal effects on both short- and long-term nociceptive processing.

ASCENDING SYSTEMS

In the mid-1800s, Schiff provided evidence that nociceptive messages in animals were transmitted from the dorsal horn to the brain via pathways located in the anterolateral quadrant, often referred to as the ventrolateral quadrant. In general, the terms *anterior* and *posterior* apply to human anatomy, whereas the terms *ventral* and *dorsal* apply to the anatomy of lower animals. The contributions made during the ensuing years by Gowers, Edinger, Spiller, Martin, and Walker have been detailed by others (2) including in the first edition of this book (317). By the early part of the twentieth century, it was widely accepted that the STT and trigeminothalamic tract were the pathways that predominantly transmitted the signals that produced pain and temperature sensation. However, studies during the past several decades have provided evidence that (a) both the STT and trigeminothalamic tract are composed of anatomically and physiologically heterogeneous axons, many of which transmit touch and other sensory information; (b) these tracts are composed of two parts that have somewhat different anatomic and functional characteristics; and (c) in addition to the STT and the trigeminothalamic tract, a number of other pathways with distinctive sites of origin, conduction velocities, areas of termination and function are involved in transmitting information about the threat of tissue injury or actual injury.

The following systems are known to transmit nociceptive information from spinal cord to brain: (a) the lateral (and perhaps the ventral) STT; (b) the spinoreticular tract; (c) the spinomesencephalic tract; (d) the dorsal column postsynaptic spinomedullary system, otherwise known as the second-order dorsal column pathway; and (e) the propriospinal multisynaptic ascending systems. The first two are located in the ventrolateral quadrant (anterolateral quadrant in humans), the third in the ventrolateral quadrant and in the dorsolateral funiculus, the fourth in the dorsal column, and the propriospinal multisynaptic ascending systems are composed of a web of short-chain neurons criss-crossing the spinal cord. The origin, course, and known physiology of each of these pathways are discussed separately.

Spinothalamic Tract

The STT is generally regarded as the most important pathway for transmission of nociceptive impulses in humans and subhuman primates. Evidence for this conclusion has come from clinical and behavioral effects of lesions that interrupt the anterolateral quadrant of the spinal cord. After such a lesion, humans cannot experience pain in areas below the segmental level of the lesion on the contralateral side of the body. Responses to noxious stimuli are diminished in the contralateral side of monkeys. In addition, surgical section of the anterolateral quadrant also interrupts the spinoreticular and most of the spinomesencephalic tracts (318). On this basis, these separate tracts are sometimes collectively known as the spinal lemniscus or anterolateral fasciculus.

Cells of Origin of the Spinothalamic Tract

The cells of origin of the STT have been localized by examining (a) the chromatolytic reaction after section of the anterolateral quadrant of the spinal cord, (b) retrograde labeling of spinal cells with HRP or other dyes injected into the thalamus (319), and (c) antidromic activation of spinal neurons by stimulating electrodes situated in the thalamus. These studies have unequivocally localized the cells of origin of the STT in the monkey, cat, and rat. Although comparably definitive experimental evidence for cells of origin of the human STT is lacking, available evidence is consistent with a pattern similar to that of the monkey. On the basis of HRP labeling of STT cells in the sacral segment of the monkey spinal cord, Willis and associates (38) estimated that there were as many as 2,500 STT cells on each side of the lumbar cord and presumably several thousand more at the rostral levels of the cord. The STT is more prominent in the human than in the monkey, because of the proportionately greater size of the neospinothalamic tract (nSTT) (Fig. 4-40); thus it is likely that there are more than 5,000 STT cells in the human (2).

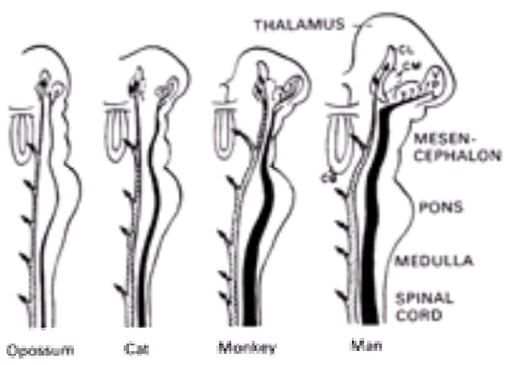

Figure 4-40. Schematic representation of the size, course, and distribution of the spinothalamic system in the opossum, cat, monkey, and humans. The neospinothalamic tract is shown in black, and the paleospinothalamic tract is shown stippled. (Modified from Mehler WR. Some observations on secondary ascending afferent systems in the central nervous system. In: Knighton RS, Dumke PR, eds. *Pain*. Boston: Little, Brown, 1966:11– 32.)

STT neurons exist throughout the entire gray matter except for the motoneuron pool (Fig. 4-41), but an obvious concentration occurs in laminae I, IV through VI, and, to a lesser extent, IX and X (6,38,41). Most of the STT cells project to the contralateral thalamus. Willis and associates (38) found in monkey that 95% of the STT cells labeled in the lumbosacral enlargement came from an injection in the region of the contralateral ventral basal complex, and 90% of the cells labeled from the region of the intralaminal complex were contralateral to the injection site. However, they also found that 26% of STT cells in the sacral cord were ipsilateral to the injection site and appeared to have a proprioceptive function. Moreover, STT cells in laminae VII and VIII of the upper cervical segments projected either ipsilaterally or contralaterally. Of the STT axons that project contralaterally, most cross within one or two segments and pass through the ventral white commissure to the opposite ventrolateral funiculus, at which they ascend rostrally as the lateral STT. This one- or two-segment delay in decussation explains the clinical finding that the uppermost level of analgesia after anterolateral cordotomy (section of the STT) is one or two levels caudal to the cordotomy site.

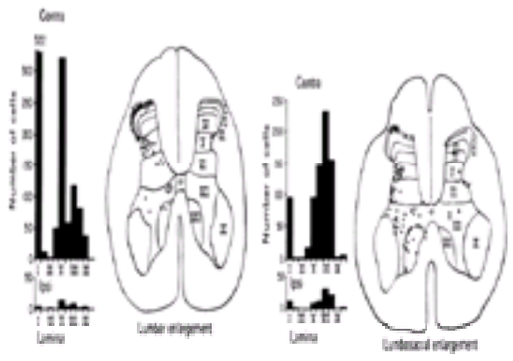

Figure 4-41. The locations of spinothalamic tract cells labeled with horseradish peroxidase transported retrogradely from the lateral thalamus **(A)** and from the medial thalamus **(B)** to the lumbosacral enlargement of the spinal cord in the monkey. On the left side of each diagram are histograms showing the number of spinothalamic tract cells in different laminae of the cord both contralateral (Contra) and ipsilateral (Ipsi) to the injection site. The diagrams are composite plots of all labeled cells found in 15 alternate serial sections. (Modified from Willis WD, Kenshalo DR, Leonard RB. The cells of origin of the primate spinothalamic tract. *J Comp Neurol* 1979;188:543–573.)

As mentioned previously, the axons of most STT cells in laminae I and V project directly to the ventrobasal and the posterior thalamus, where they synapse with cells that project to the somatosensory cortex (Fig. 4-42; see Chapter 5). This is often referred to as the nSTT (50,318,320,321,322 and 323). The cells in laminae IV through IX, as well as a subset of lamina I cells (324,325), project to nuclei of the reticular formation of the medulla, pons (spinoreticular tract), and the midbrain (spinomesencephalic tract), including the PAG, to the hypothalamus, or to the medial and intralaminar thalamic nuclei. These latter STT axons synapse with neurons

that connect with limbic forebrain structures via complex circuits and also with diffuse projections to other parts of the brain (see Fig. 4-42). This is often called the *paleospinothalamic tract* (pSTT) (65,326). Some STT cells form collaterals and project to both lateral and medial thalamus.

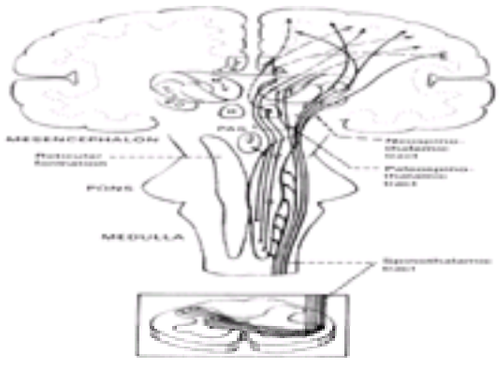

Figure 4-42. Simple diagram of the course and termination of the spinothalamic tract. Most of the fibers cross to the opposite side and ascend to the brain stem and brain, although some ascend ipsilaterally. The neospinothalamic part of the tract has cell bodies located primarily in laminae I and V of the dorsal horn, whereas the paleospinothalamic tract has its cell bodies in deeper laminae. The neospinothalamic fibers ascend in a more superficial part of the tract and project without interruption to the caudal part of the ventroposterolateral thalamic nucleus (VPLc), the oral part of this nucleus (VPLo), and the medial part of the posterior thalamus (POm). In these structures they synapse with a third relay of neurons, which project to the somatosensory cortex (SI, SII, and retroinsular cortex) (*solid lines*). Some of the fibers of the paleospinothalamic tract pass directly to the medial/intralaminar thalamic nuclei, and others project to the nuclei and the reticular formation of the brain stem and thence to the periaqueductal gray (PAG), hypothalamus (H), nucleus submedius, and medial/intralaminar thalamic nuclei. Once there, these axons synapse with neurons that connect with the limbic forebrain structure (LFS) via complex circuits and also send diffuse projections to various parts of the brain.

Axonal Distribution of the Spinothalamic Tract

Kerr (5) and Kerr and Lipman (318) examined the fiber composition of the lateral STT in the spinal cord of monkeys after midline myelotomy and found no unmyelinated axons. They concluded that C fiber nociceptive input from peripheral nerves must be transmitted onto the brain via myelinated fibers, although the presence of unmyelinated fibers could not be ruled out. When the larger fibers of the spinocerebellar tract (concentrated mainly in the periphery of the cord) were omitted, the fiber caliber spectrum ranged from 1 µm to 11 µm (318). However, most of the fibers had diameters between 3 µm and 6 µm with a peak concentration of 4 µm. These data confirmed those of an earlier study by Glees (321), who found that 60% of STT axons at the level of the superior colliculus had diameters between 2 µm and 4 µm, 35% had diameters between 4 µm and 6 µm, and only 5% had diameters between 8 µm and 10 µm. The spinoreticular and spinomesencephalic fibers are 1 µm to 5 µm in diameter (327). In the anterolateral quadrant, Bing (320) found that the thinner fibers are distributed more medially and the larger fibers more toward the periphery of the cord (318,322,328).

A number of studies of conduction velocity also have been carried out. One group found conduction velocities of 18 m per sec to 58 m per sec with an average of 36 m per sec; another reported conduction velocities of 7 m per sec to 74 m per sec with an average of 40.3 m per sec, and one reported an average rate of 37 m per sec (5). In monkeys, Albe-Fessard and associates (323) found that the conduction velocities of axons whose cell bodies are in lamina V range from 1 m per sec to 100 m per sec (with the majority at 50 m per sec to 60 m per sec, and they identified these neurons as part of the nSTT that projects without synapse to the ventroposterolateral nucleus of the thalamus. They further reported that the monkey nSTT is at least 20% composed of axons from lamina V cells. Mayer and Price (329) studied the physiologic properties of the anterolateral quadrant fibers in monkey and correlated these with studies in humans. They noted that lamina I nociceptive cells had a higher threshold, slower conduction velocity, and longer refractory period than cells in laminae IV through VI. They concluded that NS neurons in lamina I give rise to slow-conducting axons and the WDR neurons in laminae IV through VI give rise to faster conducting axons.

In the human (and monkey), as the STT ascends cephalad in the spinal cord, it continues to grow in size by the addition of fibers to its anteromedial borders. This results in a somatotopic layering or lamination: Axons arising from cells in the sacral region are outermost (dorsolaterally), those of cells in the lumbar and thoracic regions are more medial, and those from the cervical region are innermost. Some variation and significant overlap occur among the laminae from various levels. This lamination continues in the medulla, pons, and midbrain (Fig. 4-43). The course of the STTs (and the spinoreticular and spinomesencephalic tracts) through the spinal cord, brain stem, and their termination has been demonstrated in humans and monkey by anatomic studies using anterograde degeneration techniques (see Fig. 4-44, Fig. 4-45, Fig. 4-46, Fig. 4-47 and Fig. 4-48, including detailed descriptions in the legend) (318,328). In the spinal cord, white matter nociceptive ascending tracts are primarily intermingled in the anterolateral fasciculus and are situated medial to the anterior spinocerebellar tract (see Fig. 4-45). In its course through the brain stem, the STT gives off collaterals to nuclei and to the reticular formation, particularly to the nucleus cuneiformis and the PAG. At the rostral portion of the mesencephalic-diencephalic transition area, the STT separates into a medial component that projects to the medial thalamic region and a lateral component that projects to the ventrobasal and posterior thalamus (see Fig. 4-44, Fig. 4-46C, Fig. 4-47, and Fig. 4-48). Mehler and associates (106,107 and 108) pointed out that the medial portion is composed of fine fibers, and comparative studies on lower mammals indicate that these fibers represent a paleospinothalamic pathway distinct from the laterally deviating nSTT. In the thalamus (see Chapter 5), axons of neurons with cell bodies in lamina I project to both the caudal part of the ventroposterolateral nucleus (VPLc) (which also receives fibers from the medial lemniscus) and the oral part (2,5,41,322,330,331), as well as medial nuclei such as the ventral medial nucleus and nucleus submedius. The STT endings in the VPLc are in small patchlike zones, which Mehler (322) called *bursts* (see Fig. 4-46C). Neurons in laminae IV and V terminate in the medial part of the posterior complex and in the VPLc. Neurons in laminae VI through VIII terminate in the medial and the intralaminar thalamic nuclei (318,322,330,331 and 332) (see Fig. 4-46C). Spinothalamic terminations in the VPLc are somatotopically organized, whereas those in other thalamic nuclei are not (see Chapter 5 for more detailed discussion).

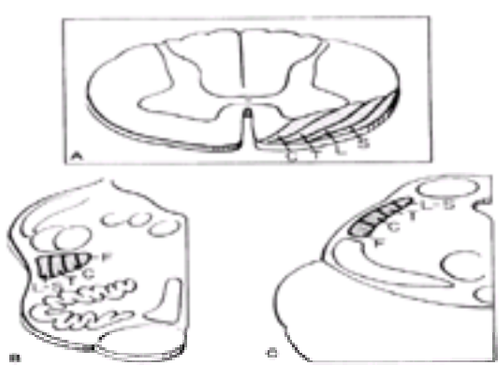

Figure 4-43. Schematic diagrams showing cross-section of the spinal cord, medulla, and midbrain, depicting the laminar arrangement of the ascending tracts in the anterolateral fasciculus in the upper part of the cervical spinal cord **(A)** and the anterolateral fasciculus and trigeminothalamic tract in the medulla **(B)** and midbrain **(C)**. **A:** In the cervical spinal cord the sacral segments (S) are most superficial, those from the cervical cord (C) are most medial and slightly anterior, and those from the thoracic (T) and lumbar (L) cord are in between. **B:** The section through the lower medulla shows that the fibers from the lower limb (L-S) are most superficial, followed by those of the trunk (T), arm (C), and finally the face (F), which is most medial. **C:** Diagram showing somatotopic pattern in the midbrain. (Modified from Brodal A. *Neurological anatomy in relation to clinical medicine*, 3rd ed. New York: Oxford University Press, 1981, and based on data by Walker, AE.)

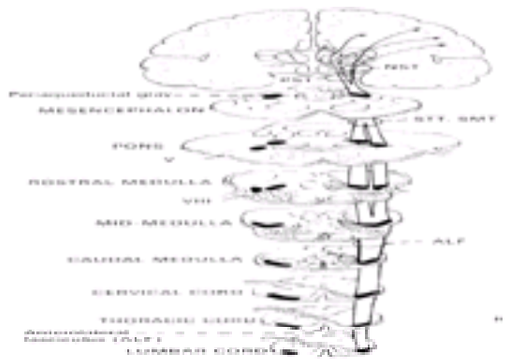

Figure 4-44. Diagram of the organization of the anterolateral fasciculus in the spinal cord, brain stem, thalamus, and brain. Note the separation into medial and lateral parts in the medulla and pons. This figure provides an overview of ascending nociceptive systems depicted in more detail in Figure 4-45 through Figure 4.48. (ALF, anterolateral fasciculus; NST, neospinothalamic tract; PST, paleospinothalamic tract; SMT, spinomesencephalic tract; STT, spinothalamic tract.)

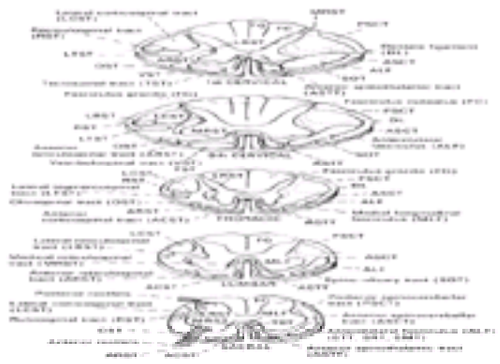

Figure 4-45. Diagram of the organization of the anterolateral fasciculus (ALF), composed of the spinothalamic (STT), spinoreticular (SRT), and spinomesencephalic (SMT) tracts in the spinal cord, and the relationship of the ALF to other important structures. The ascending tracts are emphasized on the right side and the descending tracts on the left side. As it ascends, the ALF becomes progressively larger, the largest part being in the upper cervical region. This is not only because the spinothalamic tract continues to add axons anteromedially, but also because there are more SRT cell bodies (and therefore axons) in the cervical enlargement than in the lumbosacral enlargement. Throughout the course of the ALF in the spinal cord the three nociceptive pathways are situated medial to the anterior (ventral) spinocerebellar tract, lateral to the anterolateral and anterior horns, and posterolateral to the spino-olivary tract. The anterior spinothalamic tract (ASTT), which may be an alternate nociceptive pathway, is separate from the three tracts in the ALF and is located deep in the ventral funiculus (not superficial, as sometimes written). Note the relation of various descending fibers to the ALF. Because a cordotomy lesion in the upper thoracic or cervical segments usually extends from the dentate ligament laterally to a few millimeters of the anterior sulcus medially (343), the ASTT and some of these descending tracts are likely to be interrupted with this operation. In the cervical region the ALF is shaped as a somewhat flat triangle with the apex medial and the base lateral. At successively higher cervical levels there is a gradual dorsolateral shift of the ALF.

Figure 4-46. Organization and course of the spinothalamic (STT), spinoreticular (SRT), and spinomesencephalic (SMT) tracts, collectively labeled the anterolateral fasciculus (ALF) in the medulla, pons, midbrain, and thalamus in humans (based on data in references 65, 157, and 322). On the right are emphasized the course of the ALF and its relationship to important structures and the termination of the tracts into the most important nuclei (shaded and named on the left). Large dots represent fibers of passage, and the thin lines depict projections to nuclei in which they terminate. The distribution and areas of terminations are not depicted on the left for the sake of clarity. **A:** Organization and course of the ALF in the medulla and caudal pons. 1. In the caudal medulla at the level of the pyramidal decussation, the dorsolateral shift of the ALF becomes progressively greater owing to withdrawal of the lateral corticospinal fibers into the pyramids. In this part of the medulla some SRT fibers course dorsomedially and terminate in nucleus medulla oblongata, nucleus supraspinalis, nucleus retroambiguus, and the commissural nucleus. 2. At midmedullary level, the inferior olivary nucleus causes a further dorsolateral displacement and flattening of the ALF triangle. At this level the more superficially placed STT fibers give collaterals, and a massive number of SRT fibers terminate medially in nucleus reticularis lateralis (NRL). The SRT fibers course medially and ascend between the NRL and the dorsal accessory olivary nucleus. Some of the medially coursing fibers terminate in nucleus gigantocellularis, nucleus Roller, nucleus interfascicularis hypoglossi, nucleus parvocellularis, nucleus raphe obscuruus, and nucleus paragigantocellularis lateralis and dorsalis (not shown in the diagram). 3. At the level of the rostral medulla and caudal pons the ALF in humans can be divided into a lateral superficial STT component and a medial SRT component more objectively than at any other level in the brain stem (322). This separation is caused by the intervention of the facial nucleus and superior olivary nucleus in the course of the ascending fibers. The fibers of the medial SRT lie ventral to the parvocellular reticular nucleus, and some terminate in the rostral pole of nucleus gigantocellularis, whereas others terminate in nucleus raphe magnus. **B:** Organization and course of the ALF in the pons and midbrain. 1. At the pontine level the medial SRT fibers lie ventral to the trigeminal motor nucleus, and its fibers course through the nucleus subcoeruleus. Many SRT fibers terminate in this nucleus and in nucleus pontis centralis caudalis and nucleus raphe pontis. The lateral component of the ALF (STT, SMT) lies ventral to the root of the trigeminal nerve, and its fibers pass through, and some terminate in, the processus tegmentosus lateralis of the pontine gray matter. More rostrally, the SRT fibers terminate in nucleus pontis centralis oralis and the subcoeruleus complex. 2. At the level of the isthmus, the ALF (composed of the SMT and STT) is dorsal to the medial lemniscus, ventrolateral to the lateral lemniscus, and lateral to the superior cerebellar peduncle. Fibers are given off to the nucleus pontis centralis oralis and nucleus raphe dorsalis. 3. In their course through the mesencephalon, the SMT fibers course medially and dorsally to reach their terminal zones, which include the subnucleus lateralis of the periaqueductal gray, nucleus intercollicularis, nucleus cuneiformis, the deep layer of the superior colliculus, nucleus Darkshevich, and nucleus Edinger-Westphal. **C:** Course and termination of the spinothalamic tract at the mesodiencephalic junction and in the thalamus. 1. As the STT continues rostrally through the mesodiencephalic junction (lower panel), it is surrounded by nucleus limitans on its dorsomedial side, the pulvinar dorsally, the medial geniculate body on its dorsolateral side, and the medial lemniscus ventrally. At this juncture some STT fibers end in the periaqueductal gray, in nucleus Darkshevich, the magnocellular part of nucleus medial geniculate body, and the superior geniculate nucleus (not shown). Just rostral to this level, at the caudal pole of the medial geniculate body, the STT fibers separate into a smaller medial component made up of thin fibers called the *paleospinothalamic tract*, and a much larger lateral component made up of thick fibers, the neospinothalamic tract. 2. The middle panel shows a frontal section of the caudal diencephalon and depicts the projection of STT fibers and medial lemniscus to the ventroposterolateral nucleus and the central lateral nucleus of the thalamus (not shown). Mehler includes in the central lateral nucleus the dorsolateral part of nucleus parafascicularis, the pars densocellularis, multiformis of the dorsomedial nucleus, and the entire central lateral nucleus (322). 3. The uppermost panel depicts terminal areas (fine stippling) and the fibers of passage (coarse stippling) of the STT in the ventroposterolateral nucleus and the other thalamic nuclei. Note the patchlike or burst pattern of the STT in the ventroposterolateral nucleus (see also Fig. 4-48 and Chapter 5). [The lower two panels were developed from data by Mehler WR, Feferman ME, Nauta WJN. Ascending axon degeneration following anterolateral cordotomy. An experimental study in the monkey. *Brain* 1960;83:718; and from Mehler WR: (a) The anatomy of the so-called “pain tract” in man: an analysis of the course and distribution of the ascending fibers of the fasciculus anterolateralis. In: French JD, Porter RW, eds. *Basic research in paraplegia*. Springfield, IL: Charles C Thomas, 1962:26–55; (b) Some observations on secondary ascending afferent systems in the central nervous system. In: Knighton RS, Dumke PR, eds. *Pain*. Boston: Little, Brown, 1966:11–32; (c) Some neurological species differences—a posteriori. *Ann NY Acad Sc*ı 1969;167:424. The uppermost panel was modified from Mehler (a) to show terminations

bilaterally.]

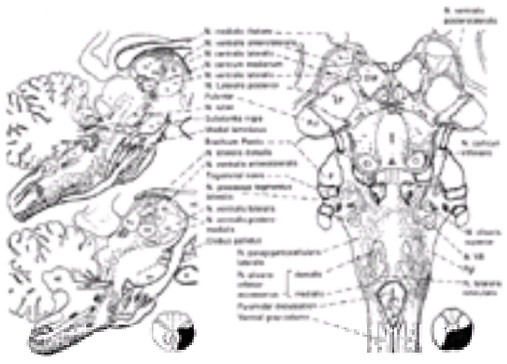

Figure 4-47. **A,B:** Sagittal sections of the brain stem and thalamus illustrating the course of ascending fibers and degeneration of the ALF after high cervical cordotomy (*inset*) in the monkey. Coarse stipple indicates degenerating fibers of passage, and fine stipple depicts areas of terminal degeneration. The most important structures related to the course of the neospinothalamic tract and paleospinothalamic tract are labeled, and their abbreviations are superimposed on the structures. **A:** Medial sagittal section depicting course and termination of the spinoreticular system. **B:** A more lateral section showing the more peripherally coursing spinothalamic tract. Terminal degeneration in the ventroposterolateral nucleus lies lateral to the plane shown in this figure. **C:** A horizontal composite diagram with a section through the dorsal thalamus and midbrain superimposed on a section through the pons and medulla, depicting the course and termination of the anterolateral fasciculus after thoracic (T6) cordotomy (*inset*) in the monkey. The superficial part of the anterolateral fasciculus passes out of the plane of section at the level of the lateral reticular nucleus (LR), but reappears at the level of the nucleus processus tegmentus lateralis (PTS). The spinothalamic component appears just lateral to the nucleus of the inferior colliculus (Ci) terminating in bursts in VPL and also in central lateral (CL) and parts of the dorsomedial (DM) and parafascicular (Pf) thalamic nuclei. (From Mehler WR, Feferman ME, Nauta WJN. Ascending axon degeneration following anterolateral cordotomy. An experimental study in the monkey. *Brain* 1960;83:718–750, with permission.)

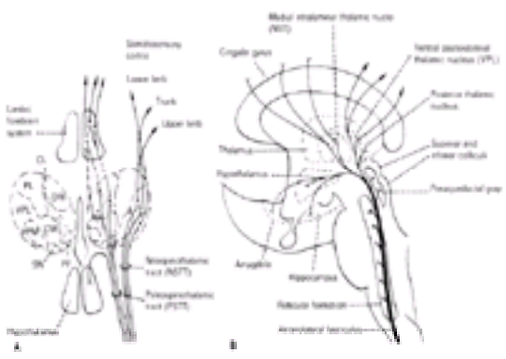

Figure 4-48. Schematic diagram showing the course and termination of the spinothalamic tract in the upper brain stem and thalamus. **A:** Coronal section showing the division of the system into the paleospinothalamic tract (pSTT) and neospinothalamic tract (nSTT). The nSTT terminates in the ventroposterolateral thalamic nucleus (VPLc), the oral part of this nucleus (VPLo), and the medial part of the posterior thalamus, where its fibers synapse with neurons that go to the somatosensory cortex in a somatotopically organized way. The pSTT projects to the reticular formation, the periaqueductal gray, the hypothalamus, nucleus submedius, and the medial and intralaminar thalamic nuclei [centromedial nucleus (CM), dorsomedial nucleus (DM), parafascicular nucleus (PF)]. There are also some spinothalamic terminals in parts of the paraventricular, paracentral, central medial, and reuniens thalamic nuclei. Some neurons, located primarily in lamina I, have a dense projection to the nucleus submedius. **B:** Sagittal section showing termination of nSTT and pSTT. (CL, central lateral; PL, pulvinar; SN, substantia nigra; VPM, ventral posteromedial nucleus.)

Physiology of the Spinothalamic Tract: Excitation

Spinothalamic projecting neurons are classified on the basis of their laminar location, response characteristics, and morphology. The response properties of these dorsal horn cells were discussed previously but are repeated here as specific to STT projecting neuron subtypes.

1. Neurons that respond uniquely to high-intensity stimuli, the NS neurons, are characterized by slowly adapting responses to either noxious pinch or heat and are located primarily in lamina I. Such cells have been found to have slower conduction velocities than other lamina I STT cells (1.8 m/sec in cats) (333) and as already mentioned in this chapter, Craig and colleagues have reported that such cells are often fusiform in shape (see Fig. 4-9) (44). The relatively recent use of noxious cold in animal pain studies (such studies, including the cold pressor test, had been used in human pain studies for years) has identified new categories of functionally discrete spinothalamic projecting cells that would otherwise have been labeled NS.
2. The so-called HPC lamina I STT projecting cells differ from the NS cells specifically in their activation by noxious cold. HPC cells also have been reported to have faster conduction velocities (approximately 4 m/sec) (333) than NS cells and have multipolar cell bodies (44). Like NS cells, HPC cells project to nucleus submedius and the ventral aspect of the ventrobasal complex of the thalamus (334) and their functional differences from NS cells in the awake behaving animal is unclear.
3. A third class of lamina I STT cell, the *cold* cell, is named for its activation by cooling (thermal stimuli less than body temperature) and is silent or inhibited by heat. These cells are primarily pyramidal in shape (see Fig. 4-9) (44), and although having conduction velocities similar to that of HPC cells (approximately 5 m/sec) (333), project to more dorsomedial locations in the thalamic ventrobasal complex (334). The importance of these cells in nociception seems minimal because they are most sensitive to innocuous or only mildly noxious cold temperatures. Nonetheless, these cells show increased responses to cold after morphine (335). Moreover, Craig and Bushnell (336) demonstrated a likely role for cold cells in mediating the thermal grill illusion described by Thunberg in 1896. In this illusion, simultaneous exposure to a grid composed of alternating cool and warm bars is perceived as hot. These investigators propose an inhibitory effect of cold cell activity on HPC-mediated thermal pain perception, presumably at a thalamic level (see Chapter 5). Their observations may explain not only the illusion but may underlie why cold pain is normally perceived as hot.
4. WDR (multireceptive) neurons respond in a frequency-dependent fashion to stimuli of increasing intensity and receive convergent input from cutaneous, visceral, and muscle afferents. They display a sustained discharge to pressure, a rapid adaptation to light tactile input, and they also respond to thermal and chemical stimuli in the noxious range. These WDR neurons are located primarily in lamina V, but also in lamina I and constitute one-third of STT cells (28).
5. Laminae IV and V contain STT neurons that respond only to innocuous tactile and thermal stimuli (low-threshold mechanoreceptors and low-threshold thermoreceptors). These constitute approximately 20% of the neurons in the STT (28).
6. Neurons situated in laminae IV and V are responsive to proprioceptive input.

In addition to transmission of nociception and temperature, the STT clearly carries information pertinent to tactile pressure and proprioception. Moreover, STT projecting cells are obviously classified somewhat arbitrarily as a function of whatever stimuli an investigator decides to use in studying a given cell or group of cells in a study. For example, the noxious stimuli that activate the STT include not only mechanical pinch and noxious heat but also the rarely studied noxious cold. Furthermore, few experiments thus far have systematically looked at STT cell responses to chemical noxious stimulation. Such experiments will likely result in still more functional classifications of STT projecting cells based on, for example, capsaicin, neurokinin, or cytokine differential responsiveness (see Chapter 3). In addition, apart from these cutaneous stimuli, muscle and visceral noxious stimuli also can activate STT cells (41). Finally, STT cells are well known to demonstrate synaptic modulation described previously for dorsal horn neurons in general. Whether all STT cell types show the same degree and neuropharmacology of such modulation is entirely speculative at present, but seems doubtful.

STT neurons that project to the VPLc are, in general, somatotopically organized and have small receptive fields. STT neurons that project to the medial thalamus, on the other hand, do not show this same somatotopic organization and have large receptive fields on much or all of the surface of the body and face (332). The receptive fields, apart from that on the ipsilateral limb, depend on a supraspinal loop believed (2) to exist in the reticular formation because stimulation in the reticular formation produces a powerful excitation of these, primarily WDR, cells. Giesler and colleagues (330) reported that nearly two-thirds of STT neurons projecting exclusively to the medial thalamus are excited only by noxious stimuli and are therefore NS neurons. In contrast to other NS neurons, however, these have large receptive fields, often including the skin of more than one limb, or the entire surface of the body. STT cells that branch and supply the VPL and the medial thalamic central lateral nucleus have receptive fields like those of cells that project only to the VPL (2). STT cells with small nociceptive fields may be involved in sensory-discriminative aspects of pain perception, whereas larger nociceptive fields are more suited for a role in the motivational-affective aspects of pain (41).

Physiology of the Spinothalamic Tract: Inhibition

In addition to excitatory receptive fields, STT cells often have inhibitory receptive fields. Inhibition is sometimes caused by activation of sensitive mechanoreceptors in the same region, but, more commonly, it is produced only by noxious stimuli delivered to areas remote from the excitatory field (2). Such inhibitory fields are more readily identified for WDR than for NS neurons. Although these effects may appear to be similar to those described as diffuse noxious inhibitory controls (337) (see Environmental Influences Modulating Nociception , later in this chapter), they differ in that the inhibition does not usually outlast stimulation and much of the inhibition remains after the spinal cord is transected. Nonetheless, such segmental mechanisms of STT neuronal inhibition have been proposed as mediating several clinical pain therapies, including transcutaneous electrical nerve stimulation (TENS), acupuncture, and dorsal column stimulation. The practice of stimulating or irritating the skin to provide relief of pain dates back to prehistoric times. Rubbing, massage, vibration, cupping, and even painful electrical stimulation of the skin as a means of relieving pain have stood the test of time. The mechanism of their efficacy has been more difficult to explain than their time-honored efficacy itself. Neither presumed peripheral mechanisms (e.g., increases in blood flow leading to enhancements in tissue repair) nor the proposed spinal gate of Melzack and Wall (see Chapter 1) has thus far collected much experimental evidence to support them. These mechanistic shortcomings may point to the limitations of such methods in acute pain models and highlight the complexity of counterirritation phenomena.

One such phenomenon, TENS, is an excellent example of a therapy that works well for certain patients and certain pains (see other chapters for fuller clinical detail). TENS produces analgesia that is not reversible by naloxone (thus, presumably does not involve endogenous opioids) when stimulation is given at high-frequency and low-intensity parameters. In contrast, stimulation using high intensity and low frequency (as used in acupuncture) produces analgesia that is partly reversible by naloxone and thus may involve these opioids. In monkeys, however, Willis' group (41) found that high-intensity, low-frequency TENS produced prolonged inhibition of STT neurons that was not affected by naloxone. They also demonstrated that the inhibition was not caused by peripheral nerve conduction failure. They concluded that inhibition of STT cells may mediate TENS analgesia but that the naloxone-reversible analgesia seen in humans is at another level of the nervous system than the STT. On the other hand, the same group did observe naloxone-reversible STT inhibition from repetitive stimulation of a peripheral nerve in a monkey (41,338). Because the inhibition occurred and was prolonged in animals with transected spinal cords, the mechanism is segmental. This inhibition was most effectively evoked by stimulation of A-d fibers, although there was also a contribution from A-b fibers. In short, although mechanisms of TENS' nociceptive inhibition can be demonstrated in animal models, and specifically on STT cells, whether these mechanisms are identical to those activated by TENS in the clinic is not clear.

Dorsal column stimulation has been suggested in some studies to inhibit nociception, primarily by activating dorsal roots rather than the dorsal columns (339). In either event, this therapeutic modality may also *close the pain gate* by tapping into intrinsic spinal inhibitory circuitry, activating large-diameter primary afferents terminating in the dorsal horn either orthodromically or antidromically. Because inhibitory effects by dorsal column stimulation on WDR neurons have been reported in animals with transected spinal cords, segmental spinal mechanisms appear to be sufficient for such inhibition (338). The neuropharmacology of dorsal column stimulation analgesia appears independent of endogenous opioids. It is not sensitive to naloxone. On the other hand, inhibition of nerve injury–induced allodynia by dorsal column stimulation relies on GABA release, consistent with other antiallodynic effects of GABA. The segmental analgesic effects seen on STT cells in animal models of therapies such as dorsal column stimulation or TENS should not be interpreted as ruling out a role for supraspinal, descending, or both modulatory roles in mediating these phenomena in the clinic (see Chapter 93).

Ventral Spinothalamic Tract

Most of the studies discussed previously refer to the lateral STT, although this distinction is rarely demonstrated experimentally. Kerr (340), believing that, like the lateral STT, the ventral or anterior STT might also be involved in transmission of nociceptive information, transected the ventral funiculus in the cervical area of macaque monkeys. By using an anterior transvertebral approach he was able to avoid damage to the fibers of the anterolateral quadrant and, in particular, to those of the lateral STT whose most medial axons lie among and slightly medial to the intra-axial ventral roots. On the basis of the pattern of degeneration, he concluded that the ventral STT is considerably smaller than the lateral STT, and its fibers appear to be distributed throughout the ventral funiculus, as determined by comparison of complete with superficial and deep lesions (see Fig. 4-45). Subsequent work suggests that the cells of origin of the ventral STT are located in laminae I, IV, V, VI, and VII (341). Although it was formerly believed that the ventral STT mediated only touch and pressure, evidence suggests that ventral STT axons of cells activated by tactile stimulation are intermingled with axons of cells that respond only to high-threshold stimulation (342).

Kerr (5,340) pointed out that although the ventral STT shares some of the structural features of the lateral STT, including a significant projection to nucleus cuneiformis in the mesencephalon, its connection to the brain stem and its course in the pons are different, and it should therefore be considered a separate tract. Kerr emphasized that the evidence that the ventral STT has a role in nociception is indirect, derived from its projection to cell groups that are known to be involved in pain mechanisms, including the ventrolateral PAG and the intralaminar nuclei of the thalamus. In carrying out cordotomy it is usually necessary to extend the incision from the dentate ligament to within 2 mm of the anterior sulcus (343), likely interrupting most, if not all, of the ventral STT in addition to the lateral STT.

Spinoreticular Tract

The reticular formation almost certainly plays an important role in pain mechanisms. The primary function of this loose collection of medullary, pontine, and mesencephalic nuclei triggers arousal to appropriate stimuli. Thus, it is probable that reticular activity accompanies pain, perhaps triggering motivational and affective responses to nociception as well as influencing somatic and particularly autonomic nociceptive reflexes. The spinoreticular tract is the most direct input from the spinal cord to the medullary and pontine reticular formation and indeed many spinoreticular tract neurons identified by antidromic activation are nociceptive (2).

The location of the cells of origin of the spinoreticular tract in the human is unknown. Monkey HRP studies indicate that spinoreticular tract projection cells are located predominantly in laminae VII and VIII, with some cells also scattered in other laminae, including I, V, and X (2,344,345) (Fig. 4-49). More spinoreticular cell bodies exist in the cervical than in the lumbosacral enlargement, the highest concentration being in the uppermost cervical segments. In monkey the number of spinoreticular tract cells is similar to the number of STT neurons (51,344), and the axons of spinoreticular tract are 1 µm to 5 µm in diameter (327), and thus are the same size as the thinner fibers of the STT. Approximately one-half of the spinoreticular tract neurons in the cervical enlargement project ipsilaterally and the other half project contralaterally (344,345), whereas in the lumbosacral enlargement more cells project contralaterally than ipsilaterally (318). Giok (327) estimated that the spinoreticular tract constitutes approximately 20% of all the fibers in the anterolateral quadrant and these axons are also likely damaged by cordotomy.

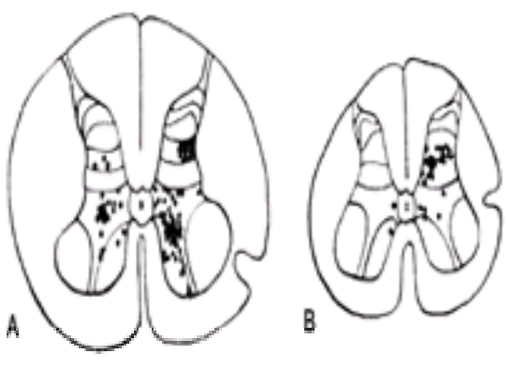

Figure 4-49. Location of spinoreticular tract cells labeled with horseradish peroxidase transported retrogradely from the medial reticular formation in the pontomedullary region of the monkey. **A:** Cross-section of the cervical enlargement. **B:** Cross-section of the lumbar enlargement. In the cervical enlargement slightly more cells are located contralaterally than ipsilaterally, but in the lumbar cord virtually all of the cells are located contralaterally (see Fig. 4-50). (Modified from

Kevetter GA, Haber LH, Yezierski RP, et al. Cells of origin of the spinoreticular tract in the monkey. *J Comp Neurol* 1982;207:61–74.)

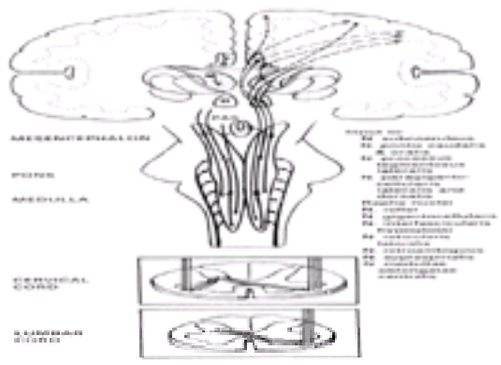

Figure 4-50. Schematic illustration showing the origin, course, and termination of the spinoreticular tract. Note its projection to the numerous nuclei and reticular formation of the medulla and pons (also see Fig. 4-46A for a description of the course and termination of the spinoreticular tract). (H, hypothalamus; LFS, limbic forebrain structure; MIT, medial/intralaminar nuclei; PAG, periaqueductal gray.)

In the spinal cord and brain stem the spinoreticular tract accompanies the STT and spinomesencephalic tract, taking a medial position to the other two tracts in the medulla and pons (346). Indeed some STT cells send collaterals to reticular nuclei. Figure 4-50 is a schematic depiction of the origin, course, and termination of the spinoreticular tract. No somatotopic organization has been reported for the spinoreticular tract. Spinoreticular projections terminate in nuclei of the caudal medulla, including nucleus superspinalis and the more rostral lateral reticularis, gigantocellularis, paragigantocellularis, parabrachial region, and nuclei pontis caudalis and oralis. Many of these nuclei play an important role in descending nociception modulatory pathways. Of particular importance in this regard are spinoreticular tract fibers from lamina I that ascend rather diffusely in the lateral funiculus of the spinal cord to synapse with a number of noradrenergic cell groups in the medulla and pons. Thus, the spinoreticular tract's role in nociception modulation is not only in its connections to more rostral brain regions stimulating arousal, but in its connections to cells thought important in mediating descending modulation.

Spinomesencephalic Tract

The spinomesencephalic tract is sometimes classified with the spinoreticular tract. Certainly, many of the aforementioned comments regarding the possible role of the medullary and pontine reticular formation in pain may also apply to the midbrain reticular formation.

Most of the spinomesencephalic tract cell bodies are in laminae I and V, but some are scattered in other laminae (2,51). Hylden and colleagues (347), in the cat, found that the majority of cell bodies of spinomesencephalic tract neurons were concentrated in lamina I and most were NS neurons (Fig. 4-51). Approximately 60% to 75% of these cells are contralateral to the side of the midbrain to which they project, and the rest are ipsilateral (347). Like the spinoreticular tract, the spinomesencephalic tract consists of relatively thin fibers (1 µm to 5 µm) (340) with conduction velocities of approximately 7 m per sec (2,347). Although human and monkey studies indicate that spinomesencephalic tract axons ascend in the anterolateral spinal cord and accompany the STT as far as the isthmus (328), McMahon and Wall and others found in rat, and Hylden and colleagues found in cat, that lamina I spinomesencephalic tract cells ascend in the contralateral dorsolateral funiculi (347). The spinomesencephalic tract cells in lamina V and in deeper laminae are scattered, and their axons ascend in the ventral and ventrolateral funiculi (347).

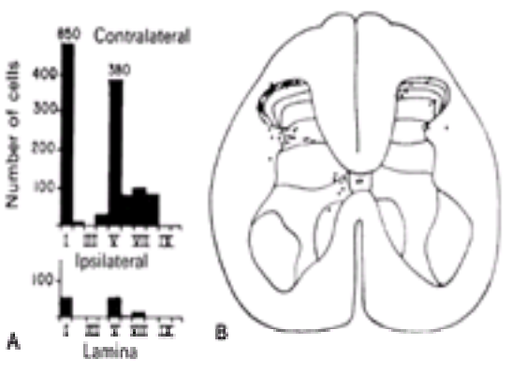

Figure 4-51. The location of spinomesencephalic tract cells in the various laminae of the lumbosacral enlargement after an injection of horseradish peroxidase into the midbrain. **A:** Histograms showing the number of cells in various laminae of the cord both contralateral and ipsilateral to the injection. **B:** Composite plot showing distribution of all labeled cells found in 15 alternate serial sections. (Modified from Willis WD, Kenshalo DR, Leonard RB. The cells of origin of the primate spinothalamic tract. *J Comp Neurol* 1979;188:543–573.)

The spinomesencephalic tract courses through the medulla and pons with the STT and spinoreticular tract. At the level of the mesencephalon, spinomesencephalic tract fibers course dorsomedially and terminate in the subnucleus lateralis of the PAG, in the nucleus intercolliculus (between the inferior and superior colliculi), nucleus cuneiformis, the superior colliculus, the nucleus Darkshevich, anterior and posterior pretectal nuclei, red nucleus, interstitial nucleus of Cajal, and the nucleus Edinger-Westphal (6,322,331,347) (Fig. 4-52). Spinomesencephalic projections are somatotopically organized with projections from more caudal parts of the body terminating more caudally in the midbrain (41).

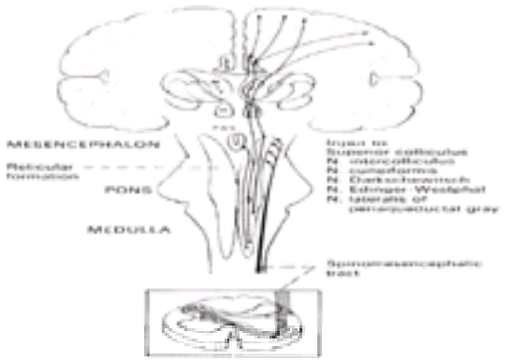

Figure 4-52. Diagram of the origin, course, and termination of the spinomesencephalic tract in primates. Note its projections to the nuclei and reticular formation of the midbrain (see Fig. 4-46B for detailed description of the course and termination of the SMT). (H, hypothalamus; LFS, limbic forebrain structure; MIT, medial/intralaminar nuclei; PAG, periaqueductal gray.)

Electrophysiologic and HRP studies in rat and cat suggest that spinomesencephalic tract neurons are largely nociceptive (347). In humans, electrical stimulation near

the PAG often causes the sensation of diffuse pain referred to the central part of the body or a feeling of fear (348). Comparable stimulation in animals often elicits rage reactions and vocalizations. Moreover, surgical lesions in humans at midbrain level made just medial to the location of the STT results in relief of chronic pain (343). Because ascending pathways from the midbrain project to the ventrobasal and medial thalamus and limbic system, it is likely that some spinomesencephalic tract neurons are involved in processing nociceptive impulses that have discriminative function and others provoke autonomic reflexes and motivational and affective responses. Termination of spinomesencephalic tract fibers in the PAG may be the course by which ascending impulses activate midbrain descending inhibitory systems that result in analgesia. Finally, projections to the collicular and cuneiformis nuclei may suggest a role for the spinomesencephalic tract in orienting and motor responses, respectively.

Other Ascending Pathways

Pain often returns several months after an initially successful cordotomy (at 1 year, 50% of subjects have neither pain relief nor analgesia). Moreover, subsequent cordotomy (including bilateral section) does not necessarily restore analgesia (343). This suggests that the renewed pain depends on pathways other than those in the anterolateral quadrant that have been discussed. The alternative pathways presumably have the potential to carry nociceptive signals but are not normally relied on for this function. Known pathways that might assume such an alternative role include the dorsal column postsynaptic system, the spinocervical tract (and portions of the spinomesencephalic tract and spinoreticular tract already mentioned) in the dorsolateral funiculi, and the propriospinal multisynaptic ascending system.

Dorsal Column Postsynaptic System

According to tradition, the dorsal column carries only fibers activated by innocuous stimuli such as touch and proprioception. However, several investigators have shown that cells in the dorsal column nuclei respond to noxious stimulation. Some of these responses are mediated by unmyelinated primary afferents that travel in the dorsal columns. However, second- or third-order neurons in the spinal cord also send axons into the dorsal columns and up to the dorsal column nuclei making up the dorsal column postsynaptic system, also called the *postsynaptic dorsal column pathway* (41). These dorsal column postsynaptic neurons constitute nearly 10% of the dorsal column. Approximately one-half of the dorsal column postsynaptic neurons respond differentially to both innocuous and noxious stimuli (349). Approximately 7% of dorsal column postsynaptic neurons respond only to noxious stimuli (350).

The cells of origin of the dorsal column postsynaptic neurons in the monkey are cells in laminae III and IV, including cells just lateral to or within lamina X (41,50,349,351). Most of the axons of the dorsal column postsynaptic neurons are deep within the dorsal column, but a few are found in the dorsolateral funiculus (41,50,351). The destinations of the dorsal column postsynaptic fibers, as already mentioned, are primarily the dorsal column nuclei, and the fibers are somatotopically organized: Those originating from cells in the lumbar cord project to the nucleus gracilis, and those from cells in the cervical cord project to the nucleus cuneatus (352). From the dorsal column nuclei they ascend to higher levels in the medial lemniscus and terminate principally in the VPL, but also in the zona inserta, the posterior thalamus, the superior and inferior colliculi, and the midbrain reticular formation (352). A few of the cells that project to the dorsal column nuclei also project to the contralateral thalamus, so that they are both postsynaptic dorsal column cells and STT cells (2) (Fig. 4-53).

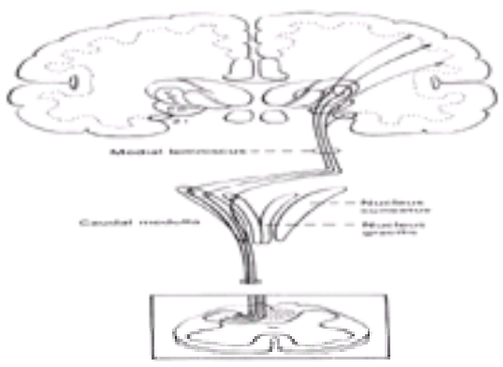

Figure 4-53. Diagram of the origin, course, and termination of the dorsal column postsynaptic system (also called the *postsynaptic dorsal column pathway*). The stippled area indicates the location of axons in the dorsal column. (PO, posterior thalmus; VPL, ventroposterolateral nucleus; ZI, zona inserta.)

The postulated role this system plays in nociception has expanded in response to demonstration of its importance in visceral pain, referred to previously in this chapter. Findings in rats and monkeys that dorsal column lesions block visceral pain behaviors and that noxious stimulation of visceral organs activates cells in the dorsal column nuclei reemphasize the importance of this pathway, and at the same time explain why previous researchers were unable to find effects of dorsal column lesions on standard nociceptive tests. Finally, these studies may give mechanistic explanations for the use of dorsal column lesions on visceral pain in humans.

Spinocervical Tract

The spinocervical tract comprises axons from dorsal horn neurons that travel in the dorsolateral funiculus to the lateral cervical nuclei at the first and second cervical levels, which in turn project to the contralateral thalamus (hence the alternate name, spinocervicothalamic tract) (352). The spinocervical tract is an important nociceptive pathway in the cat; it is much reduced in the lower primates and is considered absent or vestigial in humans (2,50,352). However, Truex and associates (353) carried out autopsies of 16 people and found the lateral cervical nucleus in nine, giving some evidence for the existence of a spinocervical tract in humans. One subject's lateral cervical nucleus contained nearly as many cells as that of the cat.

In the cat, the cells of origin are found chiefly in laminae I, III, V, and, particularly, IV (50) and have dendrites that project dorsally. At the border of III and IV they turn longitudinally (50). As mentioned, the axons ascend in the ipsilateral dorsolateral funiculus and terminate in the lateral cervical nucleus located in spinal segments C-1 and C-2. Second-order neurons in the lateral cervical nucleus send their axons to the contralateral ventral funiculus, wherein they run rostrally to reach the brain stem. At this level they join the medial lemniscus and ascend to terminate in the midbrain, VPL, and medial part of the posterior complex (Fig. 4-54).

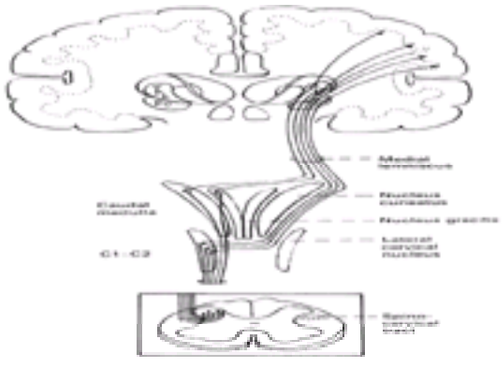

Figure 4-54. Diagram of the origin, course, and termination of the spinocervical tract. The stippled area indicates the location of axons in the dorsolateral funiculus. (PO, posterior thalmus; VPL, ventroposterolateral nucleus.)

Most of the spinocervical tract cells respond exclusively to tactile stimulation, but some cells respond to stimulation of C cutaneous nociceptors and fine muscle afferents. The paucity of spinocervical tract cells in humans argues against a significant role of this system in transmitting nociceptive information—at least in most humans.

Propriospinal Multisynaptic Ascending Systems

A concept first proposed by Goldscheider in 1898 (354) is that transmission of nerve impulses in humans takes place to a great extent via long chains of short neurons. Soon thereafter, a number of authorities attached great importance to the spinal-spinal fibers in the afferent conduction of sensory impulses. In 1914 Karplus and Kreidl (354) carried out simultaneous crossed hemisections at different levels of the spinal cord of the cat and noted that reaction times to “painful stimuli” were not decreased. They concluded that these impulses were conducted along multisynaptic pathways that crossed and recrossed the spinal cord and, furthermore, that in humans, in whom crossed pathways predominate, such an arrangement might still be present. Since the 1950s, a number of physiologists and neurosurgeons have repeated these types of experiments (354) and have restated the importance of such a system. The writings of Noordenbos (354) strongly support the notion that a multisynaptic ascending system plays a critical role in chronic pain states (Fig. 4-55). Basbaum (355) sectioned all of the long fiber tracts in rats, thereby isolating the short fiber system. He achieved this objective by hemisecting the thoracic spinal cord on one side, and later, at a slightly lower level, hemisecting the spinal cord on the other side. This operation did not abolish a learned response consisting of the rat turning its head to stop an electric shock. Moreover, he was able to train a rat to learn this response after the two hemisections. It was only when the cord was transected at a single level that the learned response was abolished (355). These findings may have important implications for the refractory nature of residual pain after bilateral cordotomies.

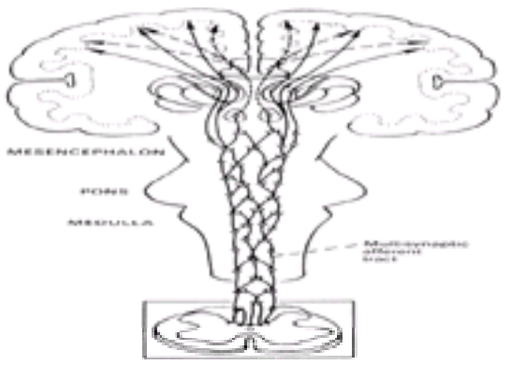

Figure 4-55. Schema of the multisynaptic ascending system, composed of neurons that have very short axons and have multiple synaptic contacts with other similar neurons. The cell bodies of this system are located in the medial aspect of the deeper laminae of the dorsal horn and in lamina X, which receives a prominent input from deep nociceptors and the viscera. This multisynaptic pathway, which has been called the *cornu commissural tract*, projects rostrally to the brain stem reticular formation and from there to the medial/intralaminar thalamic nuclei.

Ascending Trigeminal Pathways Mediating Head Pain

Nerve impulses contributing to head pain originate primarily in the peripheral sensory distribution of four cranial nerves, cranial nerve V (trigeminal), and, to a lesser extent, cranial nerve VII (facial), cranial nerve IX (glossopharyngeal), and cranial nerve X (vagus), and also in terminations of the upper three cervical nerves. These nociceptive impulses activate neurons in the trigeminal brain stem nuclei and spinal dorsal horn. Signals are then relayed to other CNS sites including brain stem reticular nuclei, the thalamus, and the cerebral cortex.

The ascending tracts that convey sensory information from the head divide into several functional types. One type is similar to the dorsal column pathways and receives input from large myelinated fibers that mediate touch, pressure, and proprioceptive information. Cell bodies of such neurons are located in the main sensory nucleus and the rostral (oralis) part of the spinal nucleus, and some proprioceptive fibers originate in the mesencephalic nucleus. The axons of most of these cells cross the midline at the level of the pons and become a defined fiber tract called the ventral (secondary) trigeminothalamic tract, also known as the ventral trigeminal lemniscus (65,356) (Fig. 4-56). It ascends in close relationship to the medial lemniscus and more rostrally also comes into close relationship with the spinal lemniscus. Some fibers from the main sensory nucleus do not cross but ascend ipsilaterally as the dorsal (secondary) trigeminothalamic tract or dorsal trigeminal lemniscus, which is associated also with the medial lemniscus of the same side. These lemniscal tracts terminate in the ventroposteromedial thalamic nucleus, in which a precise somatotopic organization is maintained (Fig. 4-57). After they synapse in the ventroposteromedial thalamic nucleus, a third relay of fibers passes to the extensive face area of the main sensory neocortex (S-1 and S-2). In addition to somatotopic organization, this system throughout has small receptive fields and modality specificity, which are consistent with its participation in fine sensory discrimination (57).

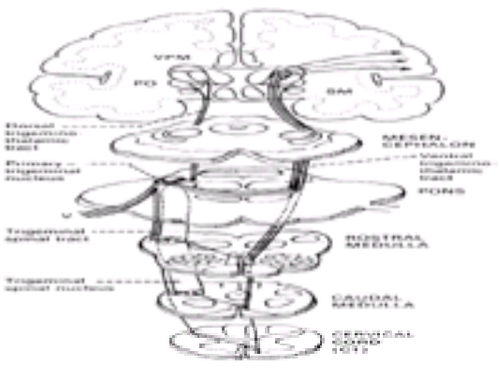

Figure 4-56. The *lemniscal* trigeminothalamic pathways transmitting tactile, thermal, and some proprioceptive and nociceptive information. The cell bodies are located in the main sensory nucleus and subnucleus oralis (some proprioceptive fibers originate in the mesencephalic nucleus). The axons of most of these cells cross the midline at the level of the pons and ascend rostrally as the ventral trigeminothalamic tract, but some ascend ipsilaterally as the dorsal trigeminothalamic tract. Second-order neurons from the subnucleus caudalis, which transmit touch, pressure, and thermal and noxious impulses also cross to the opposite side to join the ventral trigeminothalamic tract and project rostrally in company with the medial lemniscus to synapse in the ventroposteromedial nucleus (VPM) of the thalamus. (PO, posterior thalmus; SM, nucleus submedius.)

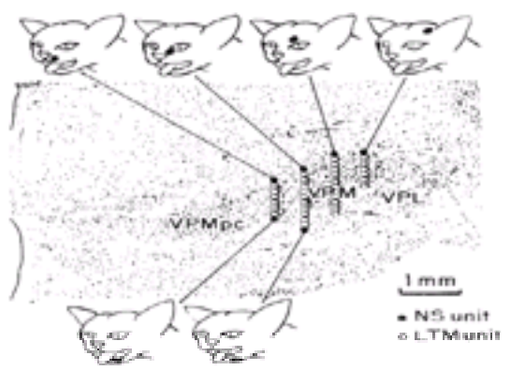

Figure 4-57. Somatotopic distribution of trigeminal nociceptive-specific (NS) neurons within the shell region of the ventroposteromedial nucleus (VPM) in the cat. Note that in the rostral part of the caudal third of the VPM, NS neurons having receptive fields in the ophthalmic division are found dorsolaterally, maxillary NS neurons are found dorsomedially, and mandibular NS neurons are encountered ventromedially along the border between the VPM proper and the parvocellular part of the ventroposteromedial nucleus (VPMpc). A similar somatotopic distribution of trigeminal wide dynamic range neurons is found in the shell region of the VPM proper. (VPL, ventroposterolateral thalamic nucleus.) (From Yokota T. Neural mechanism of trigeminal pain. In: Fields HL, Dubner R, Cervero F, eds. *Advances in pain*

research and therapy. Vol 9. New York: Raven, 1985:211–232, with permission.)

Neurons in the subnucleus caudalis, which, as previously noted, receive input from A-d and C fibers that carry touch, pressure, thermal, and noxious impulses, also project to the thalamus and ultimately the cortex via the ventral trigeminothalamic tract. One group of long fibers projects directly to the ventroposteromedial thalamic nucleus and medial part of the posterior complex and is analogous to the nSTT; hence it is the neotrigeminothalamic tract. Like the lemniscal tract, the neotrigeminothalamic tract is somatotopically organized and transmits discriminative information about tissue injury and temperature. The neotrigeminothalamic tract joins the trigeminal lemniscus and medial lemniscus to terminate in the ventroposteromedial thalamic nucleus (57).

Other neurons in the subnucleus caudalis send axons that project ipsilaterally and contralaterally and send terminals to the reticular formation, hypothalamus, PAG, and medial thalamic nuclei including nucleus submedius (Fig. 4-58). Neurons from these structures connect with limbic forebrain structures and with diffuse projections to many other parts of the brain. This system, like much of the paleospinothalamic tract, is not somatotopically organized and is considered a part of the nonlemniscal or paleotrigeminothalamic system (for summary see Fig. 4-59).

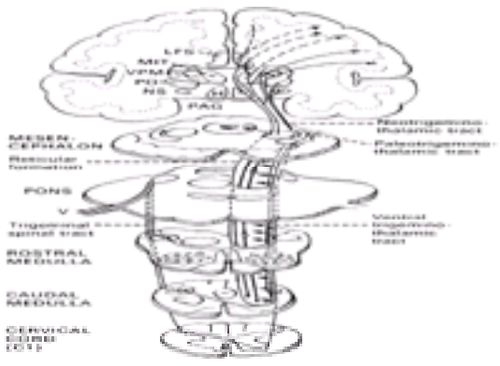

Figure 4-58. Schema of the ventral trigeminothalamic pathways, composed of neotrigeminothalamic and paleotrigeminothalamic axons. The cell bodies of these axons reside in the subnucleus caudalis, cross to the opposite side, and ascend rostrally. The lateral part of the tract comprises long axons that synapse in the ventroposteromedial nucleus (VPM) and medial part of the posterior thalamus (POm). The paleospinothalamic pathway consists of axons that pass into the reticular formation in the medulla, pons, and midbrain and there synapse with reticulothalamic fibers that project to the periaqueductal gray (PAG), hypothalamus (H), nucleus submedius, and medial and intralaminar thalamic nuclei (MIT). Within these structures they synapse with neurons that project to the limbic forebrain structures and with diffuse projection systems via complex circuits in the limbic system. (LFS, limbic forebrain structure; NS, nucleus submedius.)

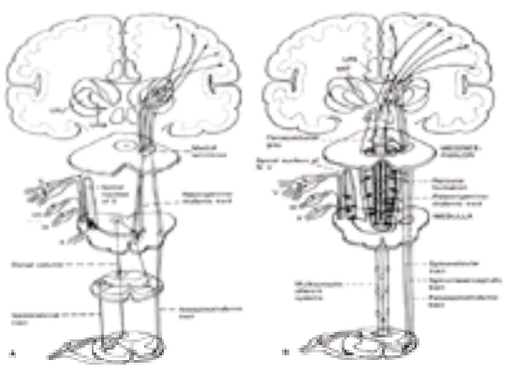

Figure 4-59. Diagrams illustrating the origin, course, and projection of the **(A)** lateral (lemniscal) and **(B)** medial (nonlemniscal) ascending systems. **A:** The lateral system includes the neospinothalamic tract, neotrigeminothalamic tract, dorsal column postsynaptic system, and spinocervical tract. These tracts are composed of long, relatively thick fibers that conduct rapidly, have a discrete somatotopic organization, and connect with the ventrobasal thalamus and thence with the somatosensory cortex. The evidence suggests that the lateral system is concerned with rapid transmission of phasic discriminative information about the onset of injury, its precise location, and its intensity and duration and can quickly bring about a response that prevents further damage. It has been suggested that these fast nociceptive pathways represent different sensory channels that are individually inhibited or facilitated, depending on the ongoing behavior or behavioral state of the organism (352). **B:** The medial system is composed of the phylogenetically older pathways, the paleospinothalamic tract, spinoreticular tract, spinomesencephalic tract, and multisynaptic ascending system, which transmit nociception from the body, and the neotrigeminothalamic tract and paleotrigeminothalamic tract for the head. Because of the thinness of these fibers, their multisynaptic nature, and the lack of somatotopic organization, impulses passing through the medial system are much slower in reaching the brain than those in the lateral system and are said to transmit tonic information about the state of the organism (352). Thus, an important although perhaps not exclusive role of these medial tracts may be to signal the actual presence of peripheral damage and to continue to send messages as long as the wound is susceptible to reinjury. In this way, the slow nociceptive pathways may, in part, determine the level of arousal or the general behavior state necessary to prevent further damage and to foster rest, protection, and care of the damaged area, thereby promoting healing and recuperative processes.

DESCENDING SYSTEMS THAT MODULATE NOCICEPTION

[Editor's note: The last edition of this book contained this section in a separate chapter cowritten by the late John C. Liebeskind, the father of this field of pain research. We have reproduced much of Liebeskind's work here, updating it with more recent findings as appropriate.]

Thus far we have discussed the multiple neuroanatomic, neurophysiologic, and neuropharmacologic pathways activated by a nociceptive stimulus. These pathways transmit information from the periphery to the brain, in which perception of the stimulus can take place. Activation of these pathways is neither necessary (e.g., in the case of thalamic pain syndromes) nor sufficient to produce pain perception. The modulation of these multiple transmission systems by inhibitory and excitatory neurochemicals as well as by their genetic and environmental (including prior activity) determinants offers a mechanism by which a certain stimulus may have remarkably disparate effects on pain perception. The previous discussion does not address why a biologic system would put so much energy into seemingly redundant nociceptive and pain modulatory circuitry. Indeed, *why* questions are difficult to answer scientifically, but pain is an adaptive warning signal and all animals have at least rudimentary nociceptive systems. The modulation of these systems must similarly provide some adaptive advantage. Mechanisms of central sensitization, for example, are unlikely to fully explain the development of chronic pain states after tissue injury (if they explain them at all) but more likely represent normally useful processes that can, on occasion, go wrong. A likely selective advantage to an animal in modulating pain perception is in ensuring that an organism's attention is directed to more biologically relevant sensation that is often, but not always, nociception. Such prioritization of incoming stimuli must be done at the highest levels of the neuraxis and communicated caudally to blunt or amplify the responses to noxious stimuli as a function of the appropriateness of the response for the organism as a whole. Perhaps it is less surprising, then, that there exist endogenous pain inhibitory and facilitatory systems descending from brain to spinal cord, whose normal function is the modulation of nociception as early as the first spinal synapse and perhaps, via autonomic outflow, at the nociceptors themselves.

The concept of descending pain modulation was proposed during the early part of the twentieth century by Sherrington (357), who emphasized that the interaction between excitatory and inhibitory systems was critical in the processing of sensory information from the body structures to the brain. In 1954 Hagbarth and Kerr (358) were the first to provide clear-cut evidence that corticospinal fibers influence afferent transmission and conduction at spinal levels. During the ensuing decade, others confirmed these observations and provided additional evidence that supraspinal mechanisms influence sensory input to ascending pathways in the spinal cord.

Nonetheless, the existence of specific nociceptive modulatory systems was first clearly proposed in 1965 by Melzack and Wall (359) as part of their gate-control

theory of pain. As discussed in Chapter 1, it included a proposal that modulation of dorsal horn cells could be affected by input coming from the periphery and also from supraspinal descending systems. At the time, the proposal for such a system was speculative, but this hypothesis received strong support from the report by Reynolds in 1969 (360) that electrical stimulation of the PAG (Fig. 4-60) resulted in sufficient analgesia to perform laparotomy in rats. These observations were soon confirmed and extended by Liebeskind and his students (361) in the early 1970s, who labeled the phenomenon *stimulation-produced analgesia* (SPA). Conversely, a number of laboratories have also reported descending pathways from brain to spinal cord that facilitate transmission of nociceptive information. We describe what is known about the neuroanatomy and neuropharmacology of these facilitatory and inhibitory descending systems and how they may normally function to modulate nociception in the spinal cord. It is likely that similar modulation, although perhaps by very different mechanisms, takes place at every rostral stop of the tissue trauma message on its way to consciousness.

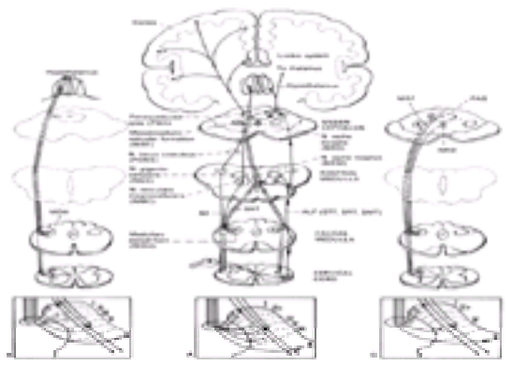

Figure 4-60. Descending endogenous pain inhibitory systems. **A:** The most extensively studied and probably the most important descending system, composed of four tiered parts, described in the text. The ascending anterolateral fasciculus (ALF), composed of the spinothalamic, spinoreticular, and spinomesencephalic tracts, has important inputs into the nucleus raphe magnus (NRM), nucleus magnocellularis (NMC), nucleus reticularis gigantocellularis (NGC), and the periaqueductal gray (PAG) via the nucleus cuneiformis. The ALF also has input to the medullary/pontine reticular formation, the nucleus raphe dorsalis (NRD), and the mesencephalic reticular formation (MRF). The PAG receives input from such rostral structures as the frontal and insular cortex and other parts of the cerebrum involved in cognition, and from the limbic system, thalamus, and hypothalamus, which sends b-endorphin axons to the PAG. The locus coeruleus in the pons is a major source of noradrenergic input to the PAG and dorsal horn (tract labeled NE). These mesencephalic structures (PAG, NRD, MRF) contain enkephalin (ENK), dynorphin (DYN), serotonin (5HT), and neurotensin (NT) neurons, but only the latter two send axons that project to NRM and NGC. Here, they synapse with neurons that are primarily serotonergic, whose axons project to the medullary dorsal horn and descend in the dorsolateral funiculus to send terminals to all laminae of the spinal gray (the densest populations are found in laminae I, II_o, and V of the dorsal horn and the motor neuron pools of lamina IX). The projection from NRM is bilateral, whereas the projection from NGC is ipsilateral. Noradrenergic fibers descend and project to the medullary dorsal horn and then descend in the dorsolateral funiculus of the spinal cord to send terminals to laminae I, II_o, IV through VI, and X. **B:** A simplistic schema to show the direct hypothalamospinal descending control system, which originates in the medial and paraventricular hypothalamic nuclei. This descending system consists of vasopressin and oxytocin neurons (and perhaps some enkephalinergic neurons), which send terminals predominantly to laminae I and X, but also provide sparse input into laminae II and III and the lateral part of lamina V, as well as the homologous area in the medullary dorsal horn. **C:** Direct PAG-spinal projection system, which bypasses the medullary nuclei and projects directly to the medullary dorsal horn and then descends in the dorsolateral funiculus to send terminals to laminae I, II_o, V, and X. Most of the axons are serotonergic and noradrenergic.

Stimulation-Produced Analgesia

The early studies by Liebeskind and associates (361) found SPA to be specifically antinociceptive, producing no generalized sensory, attentional, emotional, or motor deficits. They showed also that SPA could outlast the period of brain stimulation and that it occurred in a restricted peripheral field such that noxious stimuli applied outside that field elicited normal defensive reactions. They reported that during stimulation the sensation of light touch was intact, there was no indication of seizure activity, and animals were still capable of eating. Furthermore, rats could be trained to self-administer brain stimulation in the presence of noxious stimuli, and this self-administration did not recur when the noxious stimuli were terminated. These findings demonstrated the existence of a potent natural pain-inhibitory substrate in the PAG matter and were replicated by many other investigators (see 362 for comprehensive review of the early history of SPA). Subsequent demonstrations that stimulation of homologous brain regions in humans could relieve chronic pain provided even greater interest in this phenomenon (see Chapter 101).

In the rat, the analgesia produced by electrical stimulation of the PAG can be equipotent to that induced by high doses of morphine, and SPA completely inhibits withdrawal responses to noxious stimuli at even the severest intensities. These analgesic effects extend to spinal nociceptive reflexes, such as the tail-flick, clearly indicating a descending inhibition rather than a primarily supraspinal effect on ascending pathways. The observation, made somewhat later, that responses of spinal cord dorsal horn nociceptive cells to nociceptive stimuli were also inhibited by SPA validated this concept. SPA eliminates behavioral responses to such varied noxious somatic and visceral stimuli as electric shocks applied to the tooth pulp and limbs, heating of the skin, and injection of irritants into the skin and abdominal cavity (363). The analgesia elicited by brain stimulation can be observed within seconds after stimulation is begun and may last for minutes or even hours after stimulation is terminated. In human beings, relief from chronic pain outlasts the period of stimulation by up to 24 hours (see Chapter 101).

Another important characteristic of SPA found during these early studies was that analgesia induced by brain stimulation shared several characteristics with analgesia from opiate drugs (361,362). Concomitant with the first reports of SPA were the initial studies demonstrating the existence of specific opiate receptors in the neuraxis. Reports of these receptors in turn triggered an intense search to isolate endogenous ligands for them, ultimately culminating in the discovery of the ENKs in 1975 by Hughes, Kosterlitz, and associates (223). This search was reinforced by the emerging literature on SPA, demonstrating the existence of endogenous pain inhibitory systems. In turn, the discovery of ENKs greatly increased interest in the anatomic, physiologic, and pharmacologic bases of SPA and opiate analgesia. Areas of the brain from which SPA can be elicited are rich in opioid peptides and opiate receptors (364). Microinjection of morphine into these same brain regions produces analgesia (365), indicating that common brain sites support both SPA and opiate analgesia (see, however, 366). Systemically and centrally administered morphine increase the activity of some neurons in the PAG region, suggesting that opiate analgesia, like SPA, involves an active rather than a passive process of nociceptive inhibition. Like opiate analgesia, tolerance develops to the analgesic effects of repeated brain stimulation. Moreover, cross-tolerance is observed between opiate analgesia and SPA (367), suggesting a common underlying mechanism. Finally, opiate antagonists such as naloxone antagonize SPA (368), a crucial finding in encouraging the search for the “endorphins.” Ironically, the naloxone-sensitivity of SPA has proven controversial, and it is now clear that not all SPA is mediated by opioid peptides. Indeed, differential production of opioid and nonopioid forms of SPA result from stimulation of anatomically distinct sites within the PAG (363).

Early in the study of SPA, it became evident that if endogenous opioids play a role in this phenomenon, it is at the local level in brain stem and spinal cord rather than via long descending, opioid-containing pathways. ENK-containing cell bodies, fibers, and terminals and a high concentration of opiate receptors in the superficial dorsal horn (185,362) make this a probable site for stimulation-produced opioid activity. Moreover, anatomic and physiologic evidence of opiate inhibition of STT cells helped lead to the development of intraspinal opiate therapy in routine clinical use today. In addition to endogenous opioids, 5-HT proved important in mediating SPA. Even in the initial studies (28,252) inhibitors of serotonin synthesis and serotonin antagonists were found to antagonize SPA (369).

The serotonergic-rich raphe nuclei, particularly the NRM, were implicated in mediating SPA (Fig. 4-60). Stimulation of the NRM produced analgesia, whereas lesions of this structure inhibited SPA from PAG (252,370). Consequently, the NRM appeared to be a relay station that received descending input from the PAG and modulated spinal and medullary dorsal horn nociception via 5-HT–containing descending fibers. Basbaum and associates (371) went on to produce lesions of various quadrants of the spinal cord to determine the spinal locus of the brain stem to spinal cord descending inhibitory system. They found that lesions of the dorsal part of the lateral funiculus markedly reduced or abolished SPA (see Fig. 4-60). Once again, an analogous series of studies on opiate analgesia determined that lesions of the dorsal part of the lateral funiculus also interfered with morphine analgesia and that bilateral lesions were much more effective in this regard than unilateral lesions.

By the mid-1970s, sufficient knowledge had accumulated so that Mayer and Price (362) and Basbaum and Fields (370,372) could publish reviews of nearly 150 reports of stimulation-produced analgesia, including schematic diagrams of the anatomic and biochemical substrates of SPA and opiate analgesia.

Descending Nociceptive Modulation: Circuitry

Circuitry models of descending inhibitory systems consist of four tiers of CNS processing (see Fig. 4-60): (a) cortical and diencephalic systems; (b) mesencephalic

PAG sites, which are rich in ENKs and opiate receptors and when activated by opiates or electrical stimulation produce analgesia; (c) the rostroventral medulla, and especially the NRM, which receives excitatory input from the PAG and in turn sends serotonergic projections via the dorsolateral funiculus to the spinal and medullary dorsal horn; and (d) the spinal and medullary dorsal horn, which receives terminals of axons from the NRM and adjacent nuclei. Descending serotonergic fibers terminate among nociceptive transmission cells in laminae I, II_o, and V and can selectively inhibit nociceptive neurons, including interneurons and the rostrally projecting STT, spinoreticular tract, and spinomesencephalic tract cells. Evidence also suggests that norepinephrine-containing neurons originating in the locus coeruleus and other reticular brain stem sites contribute to endogenous pain inhibitory systems.

Cortical and Diencephalic Descending Systems

Stimulation of S-1 and S-2 and various other cortical and diencephalic structures inhibits afferent transmission in the spinal cord and medullary dorsal horn. We discuss these only briefly, in keeping with this chapter's focus on spinal mechanisms. Stimulation of S-1 cortex inhibits spontaneous activity of WDR STT neurons, as well as responses to C-fiber volleys in sural nerve and to noxious thermal and mechanical stimuli (373). Moreover, stimulation of S-1 and S-2 in the somatosensory cortex inhibits responses of WDR neurons of the trigeminal subnucleus caudalis to noxious and nonnoxious stimuli, although the effect on the latter is greater than that on the former. The corticospinal tract and extrapyramidal pathways mediate these effects. The axons of corticospinal neurons from S-1 and S-2 follow the major corticospinal tracts, which pass ipsilaterally in the brain stem and send collaterals to the trigeminal spinal nucleus. Most of these corticospinal fibers cross at the pyramidal structures and descend in the dorsolateral funiculus, whereas a smaller portion descend ipsilaterally as the anterior corticospinal tract (Fig. 4-61). Corticospinal afferents from the somatosensory cortex terminate in laminae I through VII, and axons from the motor control areas terminate in laminae VI through IX (Fig. 4-62). Corticospinal fibers in laminae I and II exert direct postsynaptic control on dorsal horn neurons, but the neurotransmitters involved are unknown (185). Because neurons of S-1 and S-2 cortex also project to the striatum, to the reticular ventrobasal posterior and intralaminar thalamic nuclei, and to the mesencephalon and reticular formation, descending fibers from these locations may mediate the analgesic effects of somatosensory cortical stimulation not involving the pyramidal tracts (373). The descending influence of cognitive and motivational processes on nociception are more difficult to study systematically because of the complex brain circuitry involved in these processes, but they are of equal importance. Limbic structures including amygdala and cingulate cortex are implicated in pain modulation and may be involved in analgesia resulting from hypnosis, learned helplessness, and uncontrollable stress.

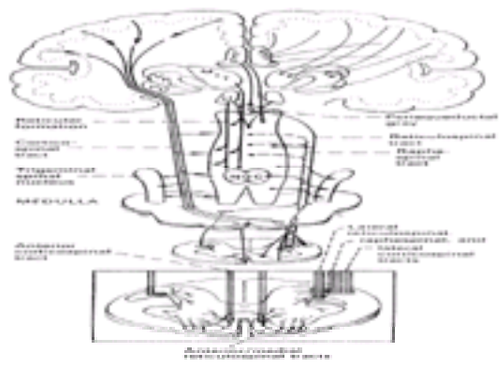

Figure 4-61. A simple diagram to depict descending pain-inhibitory systems. Note that the thalamus and the limbic system (LFS) receive afferents from the cerebral cortex, and they, in turn, send descending fibers to the brain stem and spinal cord. The corticospinal tracts modulate (excite or inhibit) various structures in the brain stem, trigeminal spinal nucleus, and dorsal and ventral horns. The raphespinal and the medullary reticulospinal tracts from each side project bilaterally, descend in the dorsolateral funiculus, and send terminals to laminae I, II_o, and V through VII. An exception to this is the reticulospinal fibers originating in the nucleus gigantocellularis (NGC) that terminate in laminae VII through VIII. The pontine reticulospinal tracts project ipsilaterally and descend in association with the medial longitudinal fasciculus in the anterior funiculus and terminate in laminae VII and VIII. See Figure 4-62 for a more detailed description of the termination of these descending fibers. (H, hypothalamus; MIT, medial/intralaminar nuclei; PO, posterior thalamus; VPL, ventroposterolateral thalamic nucleus.)

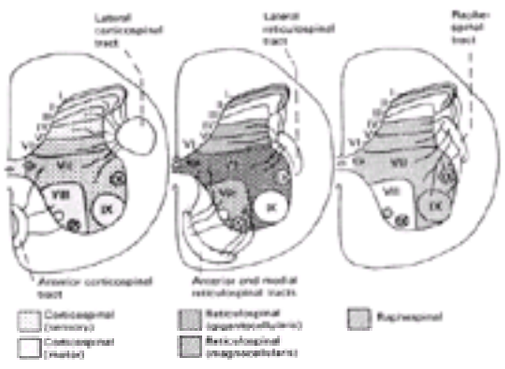

Figure 4-62. Schematic diagrams depicting the terminations of various descending systems in the gray matter of the spinal cord (and the spinal nucleus of the trigeminal complex). The corticospinal tract from the sensory cortex sends terminals to laminae I through VII, and the corticospinal tract from the motor cortex sends terminals to laminae VI through IX. The reticulospinal tract, which originates in the nucleus gigantocellularis, sends terminals to laminae VII and VIII, whereas the reticulospinal tract, which originates in nucleus magnocellularis, sends terminals to laminae I, II_o, and V through VIII. The raphespinal tract sends terminals to all laminae except III, IV, and VIII.

Diencephalic structures that participate in the centrifugal control of nociceptive information in the spinal cord and the trigeminal subnucleus caudalis include the periventricular gray, medial and lateral hypothalamus, medial preoptic/basal forebrain region, and somatosensory nuclei of the thalamus. Stimulation of the ventroposterolateral and medial nuclei of the thalamus inhibits evoked responses of identified WDR and high-threshold STT neurons (374). Although stimulation of these nuclei does not preferentially inhibit the responses to nonnoxious or noxious natural stimuli, the response to C-fiber volleys in the sural nerve is reduced to a greater extent than is the response to A-fiber volleys (374). Little evidence exists to suggest a direct projection of thalamic neurons to the spinal cord, and it has been suggested that stimulation of the ventrobasal thalamus produces antidromic activation of STT collaterals, synapsing in medullary reticular formation and PAG, which, in turn, activates neurons in these structures, which do project to the spinal cord (373).

A direct, predominantly ipsilateral projection to the spinal cord of the medial nuclei, and to a lesser extent, the lateral nuclei of the hypothalamus (373,374), travels principally in the dorsolateral funiculus and may mediate the antinociceptive effect of hypothalamic stimulation (see Fig. 4-60B). Although the spinal laminae in which these projections terminate have not been identified, it is known that oxytocin- and vasopressin-containing neurons of the hypothalamus terminate predominantly in laminae I and X, and that there are sparse inputs in laminae II, III, and V (185). Oxytocin (375,376) and vasopressin (377) have been reported to produce analgesia at the level of the spinal cord, although the effects of the latter, at least, may be confounded by paralytic motor effects (378). Another neurochemical possibly involved in such hypothalamic stimulation–induced analgesia is dopamine. Dopaminergic innervation terminates in lamina I and particularly laminae III and IV (379) of the spinal cord and dopamine has been found to reduce nociceptive responses in lamina I neurons (380) and behaviorally (381). Because both the medial and lateral hypothalamic nuclei project to the periventricular gray and medullary reticular formation, including the NRM, indirect pathways to the spinal cord may also mediate inhibition of nociceptive transmission by hypothalamic stimulation.

The experimental results cited previously are complemented by numerous clinical reports that electrical stimulation of the thalamus, septal area, caudate nucleus, medial forebrain bundle/lateral hypothalamic region, or internal capsule can produce analgesia in humans (382). The invasive nature of such SPA and the resultant risks involved in such therapy may make such reports of more scientific than therapeutic value. They show the mechanistic similarities between humans and laboratory animals without implying that such stimulation is recommended for either.

Mesencephalic Descending Systems

As mentioned previously, stimulating many areas of the CNS does not produce any direct or indirect SPA. On the other hand, the areas most sensitive to such stimulation appear to be concentrated in the periaqueductal and periventricular gray matter of the brain stem extending from the diencephalon to the medullary raphe nuclei (see Fig. 4-60 and Fig. 4-61). The nucleus raphe dorsalis in the midbrain and the mesencephalic reticular formation are also sensitive sites for electrical activation of descending inhibitory mechanisms.

Anatomy. The PAG is well positioned to relay messages from the forebrain to the hind brain. It receives inputs from such rostral structures as the frontal and insular cortex, limbic system, septum, amygdala, and hypothalamus (373,374,383) (see Fig. 4-60A; also see Fig. 5-10 and Fig. 5-11). Input from caudal structures includes those from nucleus cuneiformis, pontomedullary reticular formation, locus coeruleus, and spinal cord (see Fig. 5-2 and Fig. 5-3 for more detailed anatomy of brain stem nuclei). The locus coeruleus projection may contribute to norepinephrine's antagonism of opiate analgesia and SPA in this region. The PAG has descending connections to the rostral medulla, particularly its ventromedial part—the medullary reticular nuclei—and the NRM (383,384). These sites in the rostral medulla are a major source of axons projecting to the medullary and spinal dorsal horn, principally via the raphespinal and reticulospinal tracts that send fibers to the subnucleus caudalis or via the dorsolateral funiculus to laminae I, II, and V of the spinal cord. In addition to these descending relay systems, there are direct projections of the PAG and nucleus raphe dorsalis to the medullary and spinal dorsal horn via the dorsolateral funiculus (see Fig. 4-60C). Moreover, a direct projection of the mesencephalic reticular formation descends in the ventral and ventrolateral funiculi. Thus, at least a portion of the inhibitory effects of PAG stimulation is likely to depend on these direct projections from midbrain to the spinal and medullary dorsal horn. The PAG also sends ascending projections to the intralaminar nuclei of the thalamus in a pattern similar to that known for the paleospinothalamic tract (see Chapter 5).

As might be expected from its many inputs and outputs, the PAG is functionally not a unitary brain region. This area, apart from its role in pain modulation, has been implicated in controlling fear, anxiety, cardiovascular tone, lordosis, and vocalization (385). Indeed, even regarding its role in pain modulation, different subregions of the PAG differ markedly. For example, Liebeskind and colleagues reported that SPA was differentially sensitive to naloxone as a function of the stimulation site, with stimulation of much of the PAG producing naloxone-insensitive analgesia, but stimulation of the most ventral regions of the PAG, dorsal raphe, and subjacent tegmentum evoking analgesia blocked by naloxone (386).

Neurochemistry. The PAG contains ENKergic cells and terminals, dynorphin-containing cells, and b-endorphin–containing axon terminals. Like opiate actions elsewhere in the CNS, opiate actions in the PAG are largely inhibitory (or more accurately here, disinhibitory). Excitation of PAG output neurons, which initiates descending inhibitory controls, is thought to be caused by the endogenous opioids (ENK, dynorphin, b-endorphin, or all three) inhibiting a tonically active inhibitory interneuron (i.e., disinhibition) (Fig. 4-63).

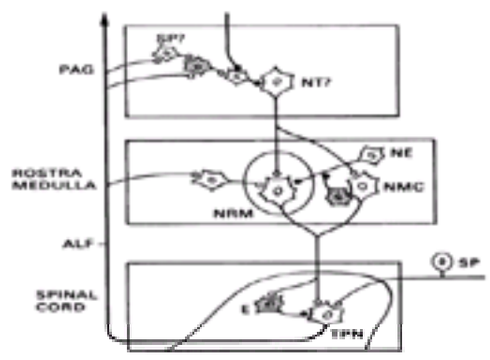

Figure 4-63. Schema modified from one by Basbaum and Fields (252) to depict the circuits in the periaqueductal gray (PAG), rostral medulla, and spinal cord. Unfilled boutons indicate release of excitatory transmitter, and shaded boutons indicate an inhibitory input. Stimulation from primary afferents activates thalamic projecting neurons (TPN), which transmit nociceptive impulses to the rostral medulla and PAG. The PAG receives input from cortical, thalamic, hypothalamic, or limbic sites. In the PAG, the output neuron is depicted as an excitatory neurotensinergic (NT) neuron that activates cells of nucleus raphe magnus (NRM) and nucleus magnocellularis (NMC) in the rostral medulla, although AMPA glutamate and nicotinic acetylcholine ionotropic receptors are also excitatory to rostral ventral medulla and perhaps more likely to mediate fast transmission (see text). An endogenous opioid peptide neuron (*shaded*) in the PAG presumably inhibits an inhibitory interneuron that in turn controls the PAG neuron. Input to the opioid interneuron may derive from ascending nociceptive pathways via substance P (SP) or histamine-containing local neurons. PAG output neurons also may be excited by neurotensin and nicotinic acetylcholine receptor activation. At the level of the rostral ventral medulla there is an inhibitory norepinephrine (NE) input to raphe bulbospinal neurons, although the importance of this inhibition for nociception is complicated by the functionally heterogeneous nature of rostral ventral medulla neurons. Included also is the possibility that local neurons presynaptically control the NE input to raphespinal axons. The bulbospinal 5-HT axons are shown to inhibit the projection neurons via two circuits: One is a direct postsynaptic inhibition, and the other involves an inhibitory opioid containing interneuron (E) (see further discussion in text). (ALF, anterolateral fasciculus.) (Modified from Basbaum AI, Fields HL. Endogenous pain control systems: brain stem spinal pathways and endorphin circuitry. *Ann Rev Neurosci* 1984;7:309–338.)

The $GABA_A$ antagonists bicuculline or picrotoxin can produce reliable antinociception when microinjected into the PAG, presumably via blocking the effects of such tonically active interneurons (387). The injection of glutamate or its analogues into the PAG, on the other hand, produces a much more complex behavioral response (e.g., antinociception, aversion behaviors, and so forth) depending on the dose and site injected (388). As in electrical stimulation experiments, results of such studies are likely to represent the sum of activating various ascending PAG inputs, inhibitory and excitatory interneurons, and descending and ascending PAG outputs because of the ubiquity of excitatory amino acid effects in the CNS.

The ionotropic and metabotropic effects of glutamate are implicated in PAG-mediated antinociception (389). Vaughan and Christie (390) reported that opiates (particularly ENKs), *in vitro* at least, have inhibitory effects on NMDA and non-NMDA glutamatergic excitation by both presynaptic and postsynaptic mechanisms. Disinhibitory effects of presynaptic mu receptors on GABA-releasing terminals were also reported in these studies, however.

Specifically, this inhibition appears to be mediated by a particular subtype of voltage-gated potassium channel (391). The function of this channel after mu receptor activation depends on arachidonic acid and its metabolites. Arachidonic acid (produced via phospholipases from cell membrane phospholipids) is metabolized via cyclooxygenases to prostaglandins and thromboxanes, via 5-lipoxygenase to leukotrienes or via 12-lipoxygenase to 12-HETE or 12-HPETE. Vaughan and colleagues (391) found the 12-lipoxygenase pathway to be critical in mediating the opiate inhibitory effects (disinhibition is blocked by a 12-lipoxygenase inhibitor). This finding is of obvious interest to cell biologists in understanding second-messenger effects of opiates (see Fig. 4-32). However, it also has clinical significance in that nonsteroidal antiinflammatory drugs may potentiate opiate analgesia, at least in part by this mechanism. Any inhibition of one metabolic pathway may shunt metabolism of arachidonic acid down alternate paths, producing more 12-lipoxygenase products and potentiated mu opiate effects. Whether this mechanism generalizes to sites other than the PAG is not known.

In addition to morphine and the endorphins, other putative neurotransmitters can produce analgesia when injected into the PAG including histamine (at the H_2 and perhaps H_1 receptors) (392) and substance P (at NK1 receptors) (252), although naloxone blocks these effects, pointing to an interaction with endogenous opioids. Nicotinic ACh agonists and the tridecapeptide neurotensin also produce analgesia in the PAG, but these effects are not blocked by naloxone. Carbachol-induced analgesia from dorsal PAG, but not ventral PAG, sites is blocked by systemic adrenergic antagonists, however. As mentioned previously, these are the sites that support nonopioid SPA. Ventral PAG SPA, in contrast, is naloxone sensitive and inhibited by NRM lesions (393), suggesting a serotonergic rather than a noradrenergic mechanism.

Neurotensin is a neural excitant in many areas of the CNS, and the PAG is no exception (394). PAG neurotensin-induced analgesia has also been reported to be blocked by NRM lesions (395) and opiates release neurotensin in the PAG (396). Investigation of neurotensin's role in pain modulation has been slowed by the paucity of selective antagonists and information regarding neurotensin receptor subtypes (397). TRH (398) and somatostatin (399) also produce antinociception when microinjected into the PAG. But again, the lack of specific antagonists has constrained research on these effects.

Another neurochemical of interest in this region is the peptide orphanin FQ (sometimes called *nociceptin*). Possibly the most interesting aspect of this chemical thus far is in the history of its discovery (400). Shortly after the opiate receptors were cloned, a receptor similar in its amino acid sequence, opiate receptor-like 1 (ORL1) was discovered that then led to the discovery of the endogenous ligand for that receptor, orphanin FQ. Despite its pedigree, the orphanin receptor is clearly not an opiate receptor in the usual sense (e.g., blockade by naloxone, binding of other opiates). Indeed, functionally, orphanin was originally labeled *nociceptin* by one group that first (401) described it because it blocked analgesia, and some have since proposed that it is an endogenous antiopiate (402). Orphanin has been studied electrophysiologically and is able to potently inhibit neural activity both by activating potassium channels (403) and by inhibiting calcium channels (404), and thus it is almost universally inhibitory. Its function primarily depends on the function of the cells it inhibits. In the PAG, it can inhibit analgesia from kainate or morphine injection, presumably by inhibiting descending pain inhibitory neurons. In the spinal cord it has nociception inhibitory effects (405), although its mechanism suggests that it has little nociceptive specificity. In the medulla, orphanin is both analgesic and hyperalgesic, depending on what population of cells it inhibits (406).

Pontine and Medullary Descending Systems

Anatomy. Since the earliest studies of descending modulatory circuitry, much anatomic, physiologic, and behavioral evidence has been published concerning the NRM (252). Raphe spinal neurons are excited by PAG opiate microinjection or PAG electrical stimulation, as well as by direct electrical stimulation of, or opiate microinjection into, the NRM. All produce inhibition of dorsal horn neurons. Subsequent findings suggest other important alternative descending paths activated by opiates and electrical stimulation. Raphe lesions have little effect on behavioral analgesia induced by morphine or PAG stimulation, unless the lesions are extended into the magnocellular reticular field (407). Electrical stimulation or lesions in the medullary reticular core activate or interfere with multiple descending pathways. These include rubrospinal, tectospinal, and pontine reticulospinal fibers of passage, including fibers originating from noradrenergic cell groups in the pons, all of which can influence dorsal horn activity (28) (Fig. 4-64).

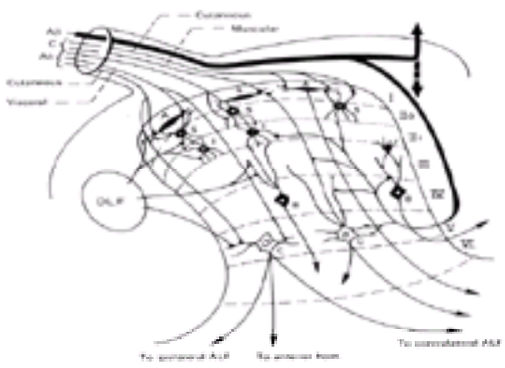

Figure 4-64. Simplified schematic cross-section diagram of input and output of the dorsal horn of the spinal cord, as well as interneurons and axonal terminals of descending control systems. A-d and C fibers transmit innocuous and nociceptive impulses. They synapse primarily in laminae I, II $_o$, and V, although they make synaptic contact through interneurons with cells in other laminae. Cutaneous nociceptive afferents project to laminae I, II $_o$, and V, whereas visceral and muscle nociceptive afferents project to laminae I and V but not to lamina II. Note the convergence of cutaneous and visceral afferents on viscerosomatic neurons in laminae I and V (C cells, which are wide dynamic range neurons), the axons of which pass to the anterolateral fasciculus (ALF) of the opposite side and project to the brain. Similarly, A-d and C muscle nociceptive afferents and cutaneous afferents also converge on neurons in laminae I and V, including some with long ascending axons that make part of the ALF. Although most of the axons ascend in the contralateral ALF, some ascend ipsilaterally. The collaterals from A-b fibers, which course along the medial side of the dorsal horn, take a retroflex course at the level of lamina V, ascend dorsally, and then branch out to make contact with interneurons and output neurons. In this way they modulate dorsal horn output. Note the interneurons in laminae II and III and an *antenna* cell in lamina IV (cells B) that may project rostrally as dorsal column postsynaptic fibers or as spinocervical fibers. Raphe spinal and reticulospinal fibers (from nucleus reticularis magnocellularis) descend in the lateral fasciculus to make contact with cells in laminae I, II, and V, and deeper laminae to exert modulating influences on dorsal horn function (see Fig. 4-61 and Fig. 4-62). The dorsolateral funiculus (DLF) contains descending axons of cells in the brain stem that are inhibitory (off-cells) and, perhaps, facilitatory (on-cells) to nociception. (S, stalk cell; I, islet cell.)

Clearly, the largest population of brain stem cells projecting to the spinal cord via the dorsal part of the lateral funiculus is located in the ventral tegmentum of the rostral medulla and caudal pons (408). In addition to the NRM, other nuclei in the adjacent reticular formation, all of which are located ventral to the nucleus reticularis gigantocellularis, are important in the modulation of nociception. These include the nucleus reticularis magnocellularis (in cat) and the nucleus reticularis paragigantocellularis lateralis (in rat). Fields (408) gives the label of rostral ventromedial medulla to the combination of NRM, reticularis paragigantocellularis lateralis, and nucleus reticularis gigantocellularis in the rat. All of these regions receive projections from the PAG, contain cells that can be activated by PAG stimulation (409), send axons to the spinal cord, and can produce antinociception (*analgesia*) when electrically stimulated (252) (see Fig. 4-60A). To completely block the effect of midbrain stimulation, NRM, nucleus reticularis magnocellularis, and reticularis paragigantocellularis lateralis must be simultaneously interrupted, either by lesion or by injection of local anesthetic (252,407). Thus, most researchers refer to the rostral ventromedial medulla as a unit rather than a collection of disparate nuclei. No one has suggested that these areas are functionally identical, however. To the contrary, these regions are probably grouped together primarily because even one such nucleus has cells within it that appear to have markedly differing effects.

The work of Fields and his colleagues best represents this diversity (410). Studying rostral ventromedial medulla cells in lightly anesthetized rats, they subclassified cells specifically by their response to a hot light during the tail-flick test. Among the cells that change their firing rates in temporal relation to the heat stimulus, two groups are evident. Some cells stop firing just before the animal flicks its tail away from the stimulus and are called *off-cells* in that they are thought to normally inhibit spinal nociceptive transmission. The other group of cells shows a burst of activity just before the tail-flick and these *on-cells* are hypothesized to facilitate spinal nociceptive transmission (Fig. 4-65). Thus, in addition to the descending inhibitory systems from this area, facilitatory descending systems may also exist.

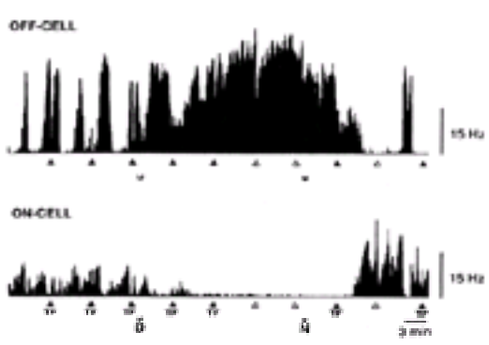

Figure 4-65. Examples of on- and off-cells in the rostral ventromedial medulla and their sensitivity to mu opioids. Rate meter recordings of the firing of an on-cell and an off-cell in rostral ventromedial medulla, recorded simultaneously from a single electrode in an experiment also accessing tail-flick in lightly anesthetized rats. Tail heat trials are indicated by triangles below the rate meter trace. Filled triangles (and TF) indicate that a tail-flick reflex occurred on that trial, whereas open triangles indicate no tail-flick response. Off-cells show a pause in their activity with tail flick, whereas on-cells show a burst of activity with tail flick. Administration of the mu opiate DAMGO [Tyr-D-Ala-Gly-(NMe)Phe-Gly-ol] (D) into the rostral ventromedial medulla produced a naloxone- (N) reversible change in the firing rate of both on and off-cells during the tail-flick stimulus preceding and then concurrent with the inhibition of the tail flick. Off-cell pause and on-cell burst were eliminated by DAMGO. (From Heinricher MM, Morgan MM, Tortorici V, et al. Disinhibition of off-cells and antinociception produced by an opioid action within the rostral ventromedial medulla. *Neuroscience* 1994;63:283, with permission.)

Several studies (410,411,412 and 413) have reported excitation, rather than inhibition, of WDR cells from electrical stimulation in the rostral ventromedial medulla. Indeed, neurochemical activation of cells in the rostral ventromedial medulla by neurotensin (414) and glutamate (413) also produces facilitatory and inhibitory effects on nociception, presumably depending on the particular subclass of cells primarily activated. In contrast, lidocaine injected into the rostral ventromedial medulla blocks allodynia from nerve ligation (415), suggesting a role of descending facilitatory pathways in sensitization phenomena.

Although nociceptive facilitatory and inhibitory descending systems project to the spinal cord from the rostral ventromedial medulla, inhibitory systems course primarily in the dorsolateral funiculus as described previously, whereas facilitatory systems project primarily in the ventrolateral funiculus (413,416).

Descending Inhibitory Neurochemistry. Descending axons that originate in raphe nuclei and reticular nuclei of the medulla or pons are primarily monoaminergic and release 5-HT or norepinephrine and, less commonly, ENK and other peptides as is discussed in the following section. As for rostral ventromedial medulla cells themselves, both excitatory amino acids (Fig. 4-66) and neurotensin (see Fig. 4-63) have excitatory effects and orphanin inhibitory effects, regardless of the on-cell or off-cell classification of any particular rostral ventromedial medulla cell. The nicotinic ACh agonist ABT-594 has analgesic effects when microinjected into NRM (94,417), presumably activating descending inhibitory pathways preferentially (perhaps via specific effects of on- and off-cells).

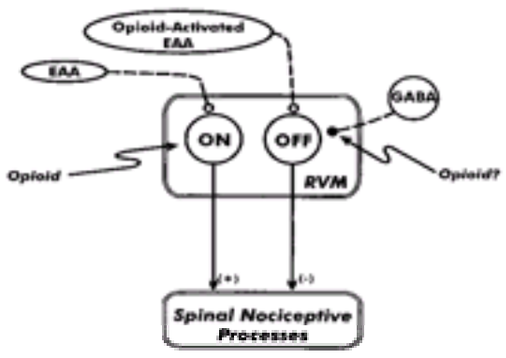

Figure 4-66. Circuitry diagram of the rostral ventromedial medulla (RVM). *Open circles* indicate excitatory and closed circles inhibitory connections. *Dashed lines* indicate possible multisynaptic pathways. The tail flick related on-cell burst is mediated by glutamate (or other excitatory amino acids) and is blocked by local application of mu opioids, which can inhibit on-cells directly. The glutamatergic input could be from spinal or periaqueductal gray projecting cells, both known to be inhibited by mu opioids at those sites as well. Glutamate-mediated inputs do not contribute to ongoing activity of off-cells (neurotensin also has excitatory effects in this region). Systemic morphine, however, does activate glutamate-mediated excitation of off-cells, perhaps via disinhibition of periaqueductal gray glutamatergic projecting cells. Mu opioids do disinhibit off-cells in the RVM, presumably by inhibiting gamma-aminobutyric acid (GABA) input on the off-cells. These GABA inhibitory inputs may be driven directly or indirectly by on-cell activity (not shown). Kappa opioids also have been reported to inhibit off-cells directly, thus providing a kappa physiologic antagonism of mu opioid effects (not shown). In contrast, cannabinoids have been found to increase off-cell activity, although the circuitry of this effect is unknown (see text for further discussion and references). (Adapted from Heinricher MM, McGaraughty S, Farr DA. The role of excitatory amino acids transmission within the rostral ventromedial medulla in the antinociceptive actions of systemically administered morphine. *Pain* 1999;81:63.)

Fields, Heinricher, Morgan, and others have intensively investigated the effects of opiates in this area. As previously mentioned, mu opiates microinjected into rostral ventromedial medulla produce inhibition of antinociceptive spinal reflexes. A correlation has been demonstrated between this analgesia and (a) inhibition of on or nociceptive facilitatory cells and (b) disinhibition (activation) of off or nociceptive inhibitory cells (418). Their model (see Fig. 4-66) (419,420) also includes an indirect or direct GABA-inhibitory influence on the off-cells that is caused by on-cell activation, mu receptor inhibition of both the on-cell and the GABA inhibition of the off-cell, and a kappa inhibition of off-cells. This last point suggests a physiologic antagonism between kappa and mu opiate activity in the rostral ventromedial medulla (419), although this antianalgesic effect is greater in male rats. Women are more sensitive to kappa opiate analgesia than men (421), although the mechanisms for this effect are still unknown.

Like mu opiate analgesia, cannabinoid analgesia (including that from endogenous cannabinoids such as anandamide) has been correlated in rostral ventromedial medulla with activation of descending inhibitory neural activity (off-cells) (422), although the cannabinoid effects are not blocked by opiate antagonists. Cannabinoid receptor antagonists, which do block the analgesia, also decrease pain thresholds, implicating endogenous cannabinoids in tonic pain inhibitory mechanisms at either spinal cord (423) or brain stem sites (422).

The brain-stem-to-spinal-cord connections and the neurochemistry underlying descending nociceptive modulation are much studied and have primarily focused on monoaminergic systems.

Serotonin. Cell bodies containing 5-HT are located in the NRM, nucleus raphe obscurus, nucleus raphe pallidus, nucleus raphe dorsalis, and other nuclei in the medulla and pons (B1 through B3, B7, and B9 cell groups) (Fig. 4-67). Indeed, almost all 5-HT–containing neurons in the dorsal horn must originate from descending brain stem neurons because chronic spinal cord transection results in complete depletion of 5-HT below the lesion (29,185,424) (Fig. 4-68). Most NRM 5-HT neurons project to spinal cord via the dorsolateral funiculus to terminate predominantly in laminae I, II $_o$, IV, and V of the spinal dorsal horn and near the central canal (185) (see Fig. 4-67). A similar termination is seen in the medullary dorsal horn. In contrast, the axons of 5-HT neurons located in nucleus raphe obscurus and nucleus raphe pallidus project near the ventral funiculus to the ventral horn. The 5-HT neurons of the NRM and other nuclei thus are presumed to provide the serotonergic link in the controls exerted by most rostral sites in the diencephalon and forebrain. Early studies of SPA from a number of brain stem sites, as well as systemic opiate analgesia, inhibited analgesia by inhibiting 5-HT synthesis (with parachlorophenylalanine) or by neurotoxic destruction of spinal 5-HT terminals (with 5-7-dihydroxytryptamine) or by lesions of the medullary 5-HT cells (407). Moreover, intrathecal methysergide, a serotonin antagonist, blocked analgesia produced by microinjection of morphine into the raphe nuclei (407). Iontophoresis of 5-HT was largely reported to inhibit the response of dorsal horn neurons to noxious stimulation, and when 5-HT is applied directly to the spinal cord it produces analgesia. Moreover, drugs that block 5-HT reuptake are effective analgesics in animals and humans (408). Microdialysis studies, in which the release of 5-HT into spinal cord or CSF has been measured, show that 5-HT levels increase after injection of morphine into the PAG, stimulation of the spinal dorsolateral funiculus, and intense sciatic nerve stimulation (407).

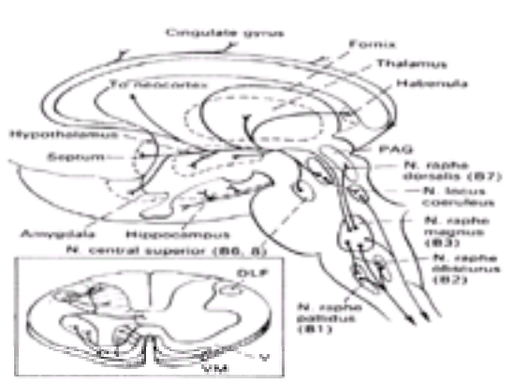

Figure 4-67. Diagram of the origin and projection of the serotonergic system. Serotonergic neurons are distributed within the midline raphe nuclei in medulla, pons, and mesencephalon. Rostrally projecting neurons are located in nucleus raphe dorsalis and nucleus centralis superior, and their axons project to various diencephalic structures as well as the cortex as depicted in the figure. From nucleus raphe magnus, rostrally projecting fibers pass to the periaqueductal gray (PAG) and the hypothalamus. The primary sources of raphespinal descending serotonergic neurons are in B1 through B3 nuclei and in B7 and B9 (not shown). The axons of these neurons project to the trigeminal spinal nucleus as well as to the spinal cord. 5-HT axons are found at the lumbar level throughout the white matter, with two areas of dense concentration: A well-defined wedge-shaped bundle occurs in the dorsolateral fasciculus (DLF), which sends terminals to laminae I, II $_o$, V, and X and a dense concentration is found in the ventral (V) and ventromedial (VM) white matter, and these send terminals to the motoneuron pools of lamina IX. At the thoracic level of the spinal cord the densest 5-HT concentrations are found in the intermediolateral cell column, which contains preganglionic sympathetic neurons. (Modified from

Nieuwenhuys R, Voogd J, van Huijzen C. *The human central nervous system*, 2nd ed. New York: Springer-Verlag, 1981.)

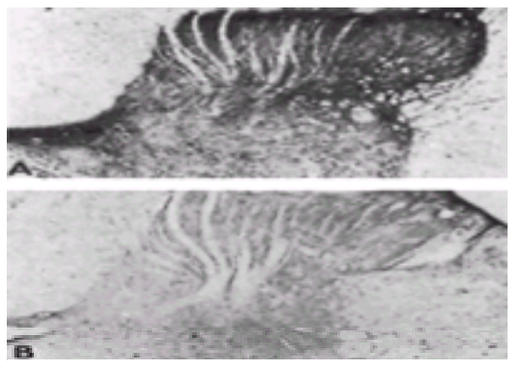

Figure 4-68. The contribution of descending 5-HT to the cat lumbar spinal cord evaluated immunocytochemically 8 weeks after transection of the spinal cord. **A:** View of the spinal cord processed for 5-HT. **B:** The 5-HT staining of the same cat after transection. All 5-HT-LI had disappeared 8 weeks after transection, indicating that all 5-HT axons are derived from the brain stem. (From Ruda MA, Bennett GJ, Dubner R. Neurochemistry and neural circuitry in the dorsal horn. *Progr Brain Res* 1986;66:219–268, with permission.)

Dubner, Ruda, and associates (54,185) examined sites of interaction between descending 5-HT axons and laminae I and II neurons in a series of experiments (Fig. 4-69). The majority of spinal 5-HT terminals form axosomatic and axodendritic synapses with neurons of the dorsal horn including STT neurons (54,185). In primates, evidence exists for a possible presynaptic 5-HT control of primary afferents (29). Stimulation of NRM inhibited all NS or WDR neurons identified, including STT cells, and all of these lamina I neurons exhibited many 5-HT immunoreactive contacts. As previously described, stalked cells (54,185) are either NS or WDR nociceptive neurons, and all stalked cells exhibit numerous 5-HT immunoreactive contacts. Stimulation of NRM inhibits all stalked cell neurons. These results suggest that direct descending 5-HT postsynaptic inhibition modifies the output of both lamina I projection neurons and stalked cells, which can directly modulate the output of lamina I projection neurons. In contrast, stimulation of NRM has no effect on lamina II_0 or II_i islet cells and has few or no 5-HT contacts (185).

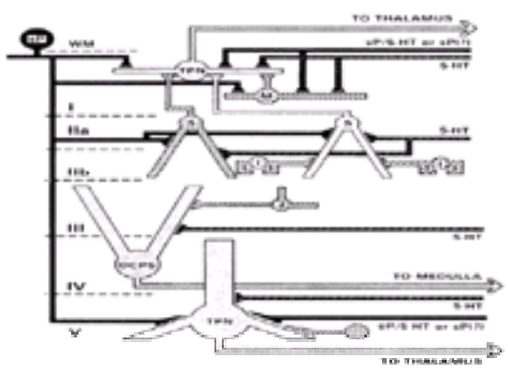

Figure 4-69. Diagram of dorsal horn circuitry, proposed by Dubner, Ruda, and coworkers. Laminae borders and white matter (WM) are represented at the left. Primary afferent axons enter at the left, and descending extrinsic axons enter at the right. (5-HT, serotonin; I, islet cell; M, lamina I local circuit neuron; S, stalked cell; sP, substance P; 3, lamina III local-circuit neuron; TPN, thalamic projection neuron; sP/5-HT or sP, descending axon that coexists in 5- HT and sP or sP only.) Striped cells are enkephalin-containing local-circuit neurons; cross-hatched cell is a gamma-aminobutyric acid–containing local- circuit neuron. (From Ruda MA, Bennett GJ, Dubner R. Neurochemistry and neural circuitry in the dorsal horn. *Progr Brain Res* 1986;66:219–268, with permission.)

Similar retrograde HRP and 5-HT immunocytochemical double-labeling studies have demonstrated 5-HT contacts on dorsal column postsynaptic neurons in lamina IV in both cat and monkey (54). All of the dorsal column postsynaptic system neurons in cat and 97% of those in monkey had 5-HT immunoreactive varicosities in contact with their somata and proximal dendrites. With the emerging importance of this pathway in visceral pain, the functional implications of such contacts might benefit from reevaluation, and 5- HT has already been implicated for some time in human visceral pain states (425,426) although primarily pronociceptive, rather than antinociceptive. Indeed, exceptions to the 5-HT antinociception story have been common over the years. Although most studies indicated that 5-HT iontophoresis inhibited laminae I and V dorsal horn neurons, excitatory effects were reported in deeper (lamina VI) neurons (29).

Descending serotonergic influences are now clearly implicated in nociceptive facilitation, not just in deeper laminae but in superficial dorsal horn as well. This difference from the antinociceptive role of 5-HT discussed previously may be primarily caused by differential effects of different serotonergic receptor subtypes (of which there are more than 10 cloned) or, instead, from differences in circuitry in the spinal cord.

Serotonin acting at 5-HT_{1A} receptors generally inhibits nociceptive activity in the spinal cord (427,428,429 and 430). 5-HT_2 (428) receptor effects, in contrast, have been reported to facilitate spinal nociception [see, however, (100)], and 5-HT_{1B} (431) and 5-HT_3 (100,101) receptors may have dual effects.

In terms of circuitry, serotonin has been seen *in vitro* to have fast synaptic effects on dorsal horn cells (432) and potentiates glutamate transmission (215). However, whether these effects are on excitatory or inhibitory neurons is unknown. For instance, 5-HT has been shown to release adenosine (433) presumably via an excitation of inhibitory interneurons. In addition, PAG stimulation-induced inhibition of STT cells also has been linked to excitation of spinal glycine and GABA-inhibitory interneurons (434). Finally, 5-HT_3 receptors located on primary afferent terminals should be able to mediate primary afferent presynaptic inhibition and thereby inhibit nociception, although pronociceptive 5-HT_3 effects are also seen (101). Zhuo and Gebhart (413) have found that NRM stimulation has excitatory or inhibitory effects on dorsal horn nociception at virtually overlapping stimulation sites dependent on the glutamate dose or electrical stimulation intensity administered (lower doses or intensities producing facilitation). Such findings emphasize the intermingling of nociceptive inhibitory and facilitatory cells in serotonin-rich rostral ventromedial medulla as described by Fields.

Norepinephrine. A second neurochemically distinct monoamine descending system involves noradrenergic neurons whose cell bodies are in A5, A6, and A7 cell groups and whose axons descend in dorsolateral, ventrolateral, and ventral funiculi to end in all of the laminae of the spinal cord (Fig. 4-70) (185). The A6 and A7 subgroups project most densely to the ventral horn to motor neurons but also to laminae I, II_0, IV through VI, and X. Neurons within A6 (nucleus locus coeruleus) have dense projections to the parasympathetic preganglionic cell column in the sacral cord, whereas the neurons in A7 (nucleus subcoeruleus) and medial parabrachial nucleus contribute axons to sympathetic preganglionic neurons in the intermediolateral cell column in T-1 to L-2 spinal cord (185,435).

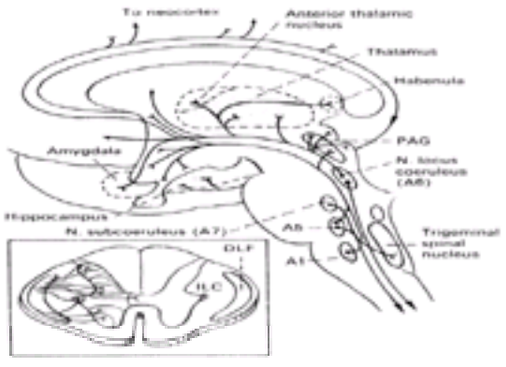

Figure 4-70. Schematic diagram of the noradrenergic system. The neurons that synthesize norepinephrine are located in the pontine and medullary tegmental regions; seven cell groups designated A-1 through A-7 have been described. Neurons that project rostrally to various parts of the diencephalon and the neocortex are found primarily in nucleus locus coeruleus (A-6) and in cell groups A-5, A-2, and A-7 (nucleus subcoeruleus). Dysfunction of the rostrally projecting norepinephrine system may play a role in pathologic anxiety, affective disorders, and schizophrenia. Neurons that have descending axons that project to the trigeminal spinal nucleus, especially the medullary dorsal horn and to the spinal cord, are found in A-5, A-6, and A-7 cell groups. In the spinal cord norepinephrine axons descend in the dorsal and ventral part of the lateral funiculus (DLF). A-6 and A-7 cell groups contribute afferents to laminae I, II $_o$, IV through VI, and X, and to motoneuron groups in the ventral horn. In addition, neurons in A-7 contribute axons to the intermediolateral cell column (ILC) of the thoracic and upper two lumbar segments of the spinal cord, whereas neurons in A-6 send a dense projection to the parasympathetic preganglionic cell column in the sacral spinal cord. (PAG, periaqueductal gray.) (Modified from Nieuwenhuys R, Voogd J, van Huijzen C. *The human central nervous system*, 2nd ed. New York: Springer-Verlag, 1981.)

Several studies indicate that a descending norepinephrine system can mediate analgesia and dorsal horn inhibition and that the norepinephrine descending system is critical for opiate-induced analgesia (28,407). Intrathecal phentolamine, an adrenergic blocker, attenuates the analgesia produced by systemic morphine administration or microinjection of morphine into the PAG. Intrathecal phenoxybenzamine, another adrenergic antagonist, blocks behavioral analgesia produced by morphine injected into the magnocellular tegmental field, and intrathecal phentolamine attenuates analgesia induced by electrical stimulation of the same region (373). Moreover, norepinephrine is released from the spinal cord after morphine microinjection or electrical stimulation in the magnocellular tegmental field, a procedure that does not release 5-HT (373). Norepinephrine is also released after electrical stimulation of the spinal cord dorsal part of the lateral funiculus or of the sciatic nerve. Anatomic evidence suggests that PAG stimulation may activate descending noradrenergic projections via the A-7 cell group (436).

Blockade of PAG SPA by intrathecal a_2-adrenergic antagonists underlines the importance of noradrenergic systems in descending nociceptive modulation (434). Intrathecal a_2-adrenergic agonists, of which clonidine is the prototype, produce analgesia in laboratory animals and humans, although such analgesia is associated with hemodynamic and sedative side effects. Much ongoing work attempts to identify a_2-adrenergic receptor subtypes that might mediate analgesia without inducing undesirable side effects. Studies in a_{2A}-receptor subtype knockout mice suggest that these receptors are primarily responsible for the spinal analgesic effects of a_2-agonists and for the synergism between spinal a_2-agonists and spinal morphine (437). Sedative and hemodynamic side effects also seem to be mediated by this receptor subtype.

The mechanism by which a_2-receptors inhibit nociception in the spinal cord is unclear. a_{2A}-Subtype receptors have been localized to substance P, presumably primary afferent, terminals in spinal cord (438). On the other hand, a number of anatomic studies have failed to show axoaxonic noradrenergic connections in spinal cord (379,439,440 and 441), making direct presynaptic primary afferent inhibitory effects unlikely. Instead, most of the anatomic evidence suggests that descending noradrenergic systems act postsynaptically on STT, trigeminothalamic tract, or dorsal horn local-circuit neurons (185). Indeed, analgesia from intrathecal injections of norepinephrine can be blocked by naloxone (442), suggesting a release of endogenous opioids, perhaps from local-circuit neurons, mediates this effect. Nonetheless, presynaptic inhibition may still take place on primary afferents, as a large number of *nonsynaptic* noradrenergic nerve terminals have been noted in the dorsal horn (379). Perhaps norepinephrine released from these terminals acts by volume transmission to inhibit primary afferent nociceptive activity (particularly with intense activation of descending fibers).

Microinjection of a_2-adrenergic agonists into the rostral ventromedial medulla also inhibits the tail-flick response, producing a long- lasting decrease in on-cell firing rate (443,444). Noradrenergic input to rostral ventromedial medulla is from A-1 to A-5 catecholamine cell groups (445) (and includes cells that also contain neurotensin). Interestingly, in contrast to the a_2 effects, rostral ventromedial medulla on- cells were excited by a_1-noradrenergic receptors (443). Thus, a_1 compounds might be expected to be facilitatory to nociception and therefore like serotonin, norepinephrine may have opposite effects on nociception depending on the specific receptor subtypes and the neural circuitry activated (412). Indeed, lesions of various noradrenergic cell groups (e.g., A5 and A7) have been found to both potentiate morphine analgesia and inhibit sensitization in the second phase of the formalin test (446), suggesting pronociceptive effects of norepinephrine in certain paradigms.

Enkephalin. Studies have demonstrated several brain stem sources of ENK-like immunoreactivity in or adjacent to NRM, including the midbrain nucleus cuneiformis, the nucleus of the solitary tract, and the dorsal parabrachial nucleus of the pons (252). Moreover, in some rostral ventromedial medulla neurons ENK and 5-HT coexist. Dynorphin-containing cells also project to the rostral ventromedial medulla (252), making the previously discussed physiologic inhibition of mu and kappa opiate receptors of more physiologic relevance. Despite the ENKergic cells projecting to and intrinsic to the spinal cord, little evidence has emerged to demonstrate the importance of spinal opioids in descending inhibition of nociception. Budai and Fields (387) find that descending inhibition of heat responses in dorsal horn cells from PAG is antagonized by iontophoresed mu antagonists. Their finding that descending dorsal horn antinociception had no effect on-cell responses to iontophoresed glutamate suggests a presynaptic antinociceptive effect, consistent with other *in vivo* and *in vitro* studies, suggesting presynaptic mu effects in the spinal cord (235) (Fig. 4-71).

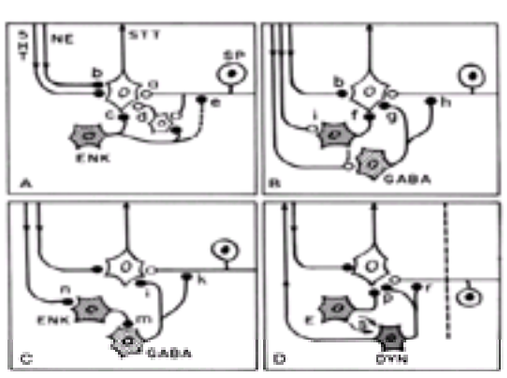

Figure 4-71. Cytochemical circuitry in the dorsal horn. Excitatory and inhibitory connections are represented by open circles and filled circles, respectively. **A:** Three major inputs to dorsal horn nociceptive neurons, some of which are at the origin of spinothalamic tract (STT) axons. Excitatory primary afferent inputs (a) are shown as originating from a substance P (SP)–containing primary afferent fiber. Descending inputs are by bulbospinal serotonin (5HT) and norepinephrine (NE) axons that postsynaptically inhibit an STT neuron (b). Local interneurons also converge onto the thalamic projection neurons, including enkephalinergic (ENK) interneurons that postsynaptically inhibit the STT neuron indicated by (c). The SP excitatory and ENK inhibitory controls may also be exerted through other excitatory interneurons of the dorsal horn (d). **B:** An example of interactions that may occur between bulbospinal axons and interneurons of the dorsal horn. Two inhibitory interneurons are shown: ENK (*cross-hatched*) and gamma- aminobutyric acid (GABA) (*dotted*) neurons postsynaptically inhibit the STT neuron (f, g, respectively). GABAergic neurons also presynaptically control the primary afferent input (h). Descending inhibitory control (from 5HT or NE axons) may be exerted either by direct postsynaptic inhibition of the STT neuron (b) or by excitation of the inhibitory interneurons (i, j). The bulbospinal inhibition and excitation derive from different populations of descending axons. Presynaptic inhibition of the primary afferent terminals also might be used by descending systems to inhibit nociception (as pictured for GABA interneurons). However, little anatomic evidence supports this mechanism, suggesting that if such effects take place (as is likely) they involve volume transmission rather than direct synaptic connections. **C:** A circuit demonstrating disinhibition by bulbospinal axons. GABAergic interneurons that presynaptically (k) or postsynaptically (i) inhibit STT projecting neurons are shown to be under tonic inhibitory control by ENK-containing interneurons (m). Activation of bulbospinal inhibition of these ENK neurons would disinhibit GABAergic cells with a net inhibition of the projection neurons. In this circuit, enkephalin would be hypothesized to cause a net excitation of spinal neurons, an action that has been reported, although not for identified STT cells. **D:** The effects of dynorphin (DYN) (fine stipple) on nociception. The action of the DYN-positive

neurons in the dorsal horn is complicated by the dual pharmacologic effects of DYN on kappa opiate and NMDA glutamate receptors. DYN, released from spinal interneurons, may inhibit primary afferent fibers (r) and projection neurons (p) via kappa opiate receptors. However, DYN also can excite nociceptive cells and increase SP release, probably via effects at the *N*-methyl-d-aspartate receptor (not shown). The interaction between dynorphinergic and enkephalinergic cells (s) is unknown. DYN-containing cells, although largely interneuronal, have also been reported to project rostrally (523). (Modified from Basbaum AI. Functional analysis of the cytochemistry of the spinal dorsal horn. In: Fields HL, Dubner R, Cervero F, eds. *Advances in pain research and therapy*. Vol 9. New York: Raven, 1985:149–175.)

Several studies report inhibitory effects of mu opioids (particularly with low doses) on descending pain inhibitory modulation produced by heterosynaptic noxious stimulation (so-called diffuse noxious inhibitory control). These findings may represent opioid inhibition of the noxious signaling that normally activates such inhibitory systems. We discuss more about the natural activation of such systems in the following sections.

Descending Facilitatory Neurochemistry. In addition to reports of monoaminergic nociceptive facilitatory effects, several other neurochemicals are implicated in mediating descending nociceptive facilitation. For example, substance P has been demonstrated in PAG and NRM somata, some of whose axons project to the superficial dorsal horn (447). Most substance P inputs to the spinal cord are still from primary afferents, however.

Descending release of TRH facilitates nociception, although, as mentioned previously, the absence of specific antagonists and the nonspecific effects of this compound (191,448) make interpretation of these findings difficult.

In contrast, several authors (100,449) have reported spinal release of CCK as underlying the nociceptive facilitatory effects of rostral ventromedial medulla stimulation, and the CCKB receptor antagonists block these effects in rodents. Moreover, spinal CCK inhibits opiate, intrathecal 5-HT_3 agonist and $GABA_B$ agonist (though not $GABA_A$ agonist) analgesia (100). Descending nociception facilitatory systems may also work by potentiating or disinhibiting spinal cord facilitatory mechanisms (e.g., glutamate or nitric oxide). Indeed, CCKB receptors are coupled to the production of arachidonic acid and presumably its cyclooxygenase and lipoxygenase metabolites, which modulate nociception. Glial activation and cytokine release also have been implicated in descending nociceptive facilitation (450).

Descending Nociceptive Modulation: Function and Physiologic Triggers

As already noted, the intricate modulation of nociception at the spinal level described thus far in this chapter must be adaptive for the animal despite the energy expended and the importance of nociception for survival. Why should an intrinsic nociception control system exist if the perception of pain is such an important life-preserving warning signal? The fact that injurious stimuli are generally perceived as hurting indicates that such a nociception-suppressive system is neither easily nor often fully activated. Little evidence suggests a tonic activity of these systems. Yet under some circumstances it might be more adaptive to inhibit pain than to perceive it. During sexual arousal, aggression, or fear, for example, perceiving pain could interfere with behaviors associated with these states, and pain suppression might have greater survival value to the organism and species than pain itself.

Teleologic speculation aside, what factors normally activate a pain-inhibitory system? A painful stimulus itself is one candidate. The firing of raphe neurons is augmented by noxious peripheral stimuli, and activation of raphe neurons by electrical stimulation can generate analgesia. David Livingstone, the Scottish missionary and explorer of Africa, reported a personal example of nociception-induced pain suppression when he was attacked by a lion during an early journey to find the source of the Nile:

> . . . I heard a shout. Starting, and looking half round, I saw the lion just in the act of springing upon me. I was upon a little height; he caught my shoulder as he sprang, and we both came to the ground below together. Growling horribly close to my ear, he shook me as a terrier does a rat. The shock produced a stupor similar to that which seems to be felt by a mouse after the first shake of the cat. It caused a sort of dreaminess in which there was no sense of pain nor feeling of terror, though quite conscious of all that was happening. It was like what patients partially under the influence of chloroform describe, who see all the operation, but feel not the knife . . . . The shake annihilated fear, and allowed no sense of horror in looking round at the beast. This peculiar state is probably produced in all animals killed by the carnivora; and if so, is a merciful provision by our benevolent creator for lessening the pain of death. [David Livingstone, *Missionary Travels*, 1857, as cited in (451).]

Much less dramatic environmental stimuli, not usually associated with pain, have been found to produce analgesia. Restraint, rotation, forced swim, and threat can all produce analgesia in laboratory animals. In humans, athletic competition, sexual stimulation, and battlefield exposure all produce substantial increases in pain thresholds. Many such situations are stressful, and stress may be a natural or physiologic trigger of intrinsic pain inhibitory systems. This phenomenon has been termed *stress-induced analgesia*.

Stress-Induced Analgesia

The first demonstrations of SIA were made in rats by Akil and collaborators (452) and Hayes and associates (453). Their results differed in one major respect, the sensitivity of SIA to antagonism by opiate antagonists. The analgesia observed by the Akil group was blocked by pretreatment with naloxone, suggesting that opioid peptides are involved in SIA as they are in SPA. The analgesia seen by the Hayes group, on the other hand, was not blocked by naloxone pretreatment, indicating a different, nonopioid, mechanism. Subsequently, SIA was studied in response to many varied stressors, but the question of the involvement of endogenous opioid peptides remained unclear. Some investigators reported naloxone blockade, and others did not see this effect. In addition, the Hayes group (453) noted that not all stressors, as defined by corticosterone release, elicit analgesia. Thus, what specific characteristics cause one type of stressor to elicit analgesia, whereas others do not, remained a mystery and is still not completely known.

Multiple Neural Mechanisms Mediating Stress-Induced Analgesia. A major problem in comparing the early studies of SIA was the variety of types of stressors used. Liebeskind's group (454) studying a single stressor, inescapable foot shock of constant intensity, found that they could elicit either naloxone-sensitive or naloxone-insensitive analgesia by varying the temporal pattern of the shock. Thus, like SPA, SIA has both an opioid form engaging endogenous opioid peptides and a nonopioid form, seemingly independent of opioid peptides. The naloxone-sensitive analgesic response met two other important criteria for inferring the involvement of opioid peptides: It showed development of tolerance with repeated administration of foot shock, and it was reduced in morphine-tolerant rats, indicating the presence of cross-tolerance (455). The nonopioid form of foot shock induced analgesia, in addition to revealing no inhibition by naloxone, and failed to show either tolerance or cross-tolerance with morphine. Further supporting the independence of these two forms of SIA is the lack of cross-tolerance between them (456).

Concurrent with the studies by Liebeskind and associates, Watkins and Mayer (457) observed that naloxone sensitivity of SIA has markedly different effects depending on the body region shocked. Low doses (0.1 mg/kg) of naloxone antagonized analgesia induced by shock to the front paw, indicating activation of an opiate system, whereas even high doses (20 mg/kg) did not reduce analgesia induced by shock to the hind paw, indicating that a nonopiate system was involved. The greater duration of stress analgesia from hind paw shock suggested that the two regionally discrete stimuli might not be equipotent stressors (458). Nonetheless, Watkins and Mayer, in a series of studies (457,459), carefully documented the anatomic and neurochemical pathways involved in SIA, finding important similarities between SIA and the SPA mechanisms supposedly activated by stress. Descending rostral ventromedial medulla to spinal cord projections in the dorsal part of the lateral funiculus proved important for mediating both opioid and nonopioid analgesia (460), and intrathecal naloxone reversal of opioid SIA suggested a spinal opioid receptor site of action. Supraspinal opiate receptors also have been found to be important in opioid SIA (461), and spinal and supraspinal opiate mechanisms may interact in a multiplicative way, just as spinal and supraspinal exogenous opiate analgesia mechanisms have been reported to do (462). A nonsegmental intraspinal inhibitory circuit is involved in nonopioid SIA; this is called a *propriospinal antinociceptive system* (409,463).

Hormonal and Autonomic Influences on Stress-Induced Analgesia. Even the opioid form of SIA has proven not to be a unitary phenomenon (464). Opioid SIA produced by numerous intermittent foot or tail shocks depends on higher brain functions: It is blocked by decerebration, muscarinic antagonists, amygdala lesions (465), and pentobarbital anesthesia, and it is correlated with the development of learned helplessness behavior. On the other hand, shorter duration shock produced opioid-mediated descending inhibition of spinal reflexes, even in the anesthetized animal. This shock-induced antinociception further muddies the use of the term *stress* in SIA, although no anesthesiologist would argue that even surgical levels of barbiturate anesthesia blocks stress.

The term *stress* as proposed by Selye (466) involved the body's response to increased physical or psychological demands by activation of the pituitary-adrenal-cortical and sympathetic-adrenal medullary axes. The hormonal products of these activations contribute to the adaptive responses of the organism to

stress by affecting energy production and the cardiovascular and immune systems (467). Because pain suppression can be viewed as an adaptive response to stress, it seems logical that these hormonal systems also play a role in SIA, and several lines of evidence support this hypothesis. b-Endorphin is highly concentrated in the pituitary, and stress causes the corelease of pituitary opioids (b-endorphin) and adrenocorticotropic hormone. In addition, the adrenal medulla contains opioid peptides that are released under the same circumstances of sympathetic activation that elicit the release of catecholamines (468). Stimuli that activate the pituitary-adrenal axis as well as the adrenal medulla cause the release of endogenous opioids from the pituitary and adrenal medulla. As might be expected, the form of opiate SIA insensitive to barbiturate anesthesia is also independent of the pituitary adrenal axis, being unaffected by adrenalectomy or hypophysectomy. Learned helplessness–linked opioid SIA, on the other hand, is blocked by hypophysectomy and adrenalectomy (454) and is mediated through adrenal medullary release of ENKs via sympathetic outflow (468). Activation of other autonomic pathways is also associated with descending nociceptive inhibition. Stimulation of vagal afferents via volume changes in the heart (469,470) or direct vagal stimulation (463,471,472,473 and 474) can activate descending inhibitory pathways, which are reported to involve opioid peptides (470,474) but that probably do not require rostral ventromedial medulla (470,471). In contrast, stimulation of sympathetic afferents has been reported to inhibit lumbar nociception without supraspinal involvement (463).

Whether various opiate SIA phenomena constitute completely independent analgesia substrates or, instead, represent different paths of access to a common neural core remains unknown. Evidence for the latter is that both opioid SIA linked to learned helplessness and opioid SIA insensitive to barbiturate anesthesia demonstrate mutual cross-tolerance. This suggests that they share a common receptor (464). Moreover, cross-tolerance develops between opioid forms of SPA and SIA (464). The effects of intrathecal naloxone in blocking opioid SIA points to a spinal opiate site of action; however, naloxone in the ventral tegmentum of the midbrain also inhibits SIA (475).

Nonopioid Stress-Induced Analgesia. The neurochemistry of nonopioid SIA is still poorly understood despite considerable study. It would be useful to activate pharmacologically the form (or forms) of SIA that shows less or no tolerance or cross-tolerance to morphine in the clinic. Although reserpine blocks nonopioid SIA (464), more specific dopamine, norepinephrine, and serotonin antagonists have proven inconsistent in inhibiting nonopioid SIA. Histamine, acting at the H_2 receptor, has been implicated in mediating nonopioid SIA (476,477). This effect most likely occurs in the PAG. Another line of evidence suggests that nonopioid analgesia may not really be nonopiate at all, but is really mediated by parallel opiate systems and, in particular, kappa opiate receptors and the kappa agonist dynorphin (478,479). Although kappa opiate–mediated analgesia has indeed been reported after or during stress (479,480,481 and 482), the large doses of naloxone normally given to define nonopiate analgesia should theoretically have been sufficient to block kappa opiate receptors as well.

$GABA_A$ (483) and $GABA_B$ (484) receptors have also been implicated in mediating SIA. Little is known of the spinal or supraspinal site of such an action.

Liebeskind and colleagues reported that nonopioid SIA, in particular that produced by swim stress, was blocked by NMDA antagonists (485). This NMDA-dependent SIA was sex specific, in that female mice demonstrated similarly potent *nonopioid* SIA not blocked by NMDA antagonists in an estrogen-dependent way (486). Kappa opiate analgesia also shows a sex difference, and endogenous kappa analgesia depends on female sex hormones (487). One wonders whether NMDA antagonist–resistant SIA in female mice might be kappa mediated. This speculation raises the issue of how various forms of SIA interact to produce nociceptive modulation.

Environmental Influences Modulating Nociception. Many stressors can produce SIA. Electric shock has been the first choice for most of the pharmacologic, anatomic, and hormonal investigations of SIA because of the ease of reproducible stress parameter manipulation without causing tissue damage. Forced swim stress has been intensively studied for similar reasons. Although neither stimulus is particularly relevant to the animal in the wild, these studies still reveal how natural stimuli might affect the organism and its nociceptive processing.

Continuous afferent stimulation via foot shock or swim stress produces opioid or nonopioid SIA differentially as a function of stress severity (464,488). The more severe the stress, the more likely that naloxone will not block the analgesia significantly.

The question of whether opioid and nonopioid mechanisms act independently has been posed, and the hypothesis put forward that they are mutually inhibitory (489,490), largely because of the potentiation of nonopiate SIA by naloxone in some studies. However, many nociceptive modulatory influences exist. Blocking opiate SIA might potentiate residual SIA simply by disinhibiting nociceptive circuitry, thereby increasing descending inhibitory influences by increasing ascending nociception.

Conversely, opiates might inhibit SIA by decreasing the nociceptive triggers for descending inhibition. Le Bars and colleagues, in a series of electrophysiologic studies of the anesthetized rat, find just such a phenomenon (337). Dorsal horn neuronal nociceptive responses are inhibited by noxious stimulation applied outside the neuron's receptive field. This phenomenon, termed *diffuse noxious inhibitory controls*, is blocked by low doses of morphine, perhaps because morphine inhibits the very nociceptive input that elicits diffuse noxious inhibitory controls. Similarly, SIA produced by severe afferent input may be sensitive to NMDA antagonists because NMDA receptors are especially likely to participate in the signaling of repeated nociceptive transmission. In addition, substance P knockout mice also have been reported to have reduced SIA (491). Thus, discriminating between a drug's effects on ascending and descending mechanisms underlying SIA is important; particularly if one hopes to activate descending nociception-inhibitory pathways without activating ascending nociceptive pathways, as would be clinically desirable. The NMDA sensitivity of SIA, then, may indicate the activation of descending feedback mechanisms when spinal NMDA receptors are activated, perhaps to keep NMDA sensitization at the spinal level to a minimum. Indeed, descending antinociceptive pathways block sensitization phenomena (492) and thresholds for sensitization are lower in spinalized (493) or animals with lesions on the dorsal part of the lateral funiculus (494).

Thus, forms of SIA elicited by continuous afferent input probably diminish nociceptive input in the behaving animal, allowing efficient escape behavior in the midst of ongoing nociception. Counterirritation analgesic therapies (including TENS, acupuncture, moxibustion, cupping, and so forth) in humans probably tap into these mechanisms to cause their pain-relieving effects. However, these forms of SIA are also important in decreasing inappropriate development of nociceptive sensitization at the spinal level.

In addition to the direct effects of noxious stimuli in producing analgesia, a large literature points to the importance of fear of such stimuli in activating pain inhibitory substrates (495,496). For example, the scent of an animal's natural predator can induce analgesia (497). One adaptive response to stress is learning to associate neutral environmental cues accompanying or preceding stress with its aversive qualities. Placing rats in a cage in which foot shock was previously received, but is not currently administered, elicits many of the responses formerly seen during shock presentation. One of these responses is analgesia, and this phenomenon has been termed *conditioned analgesia*. Evidently, animals can not only activate their intrinsic pain inhibitory systems in the presence of stress, but they can learn to activate them in anticipation of such stimuli (498) (Fig. 4-72).

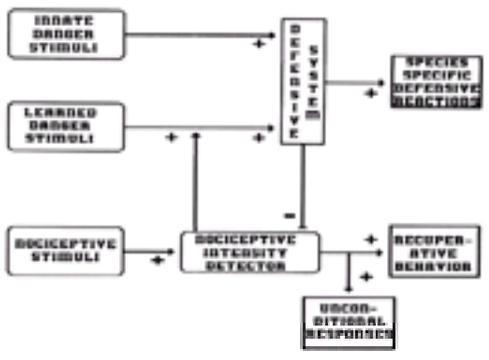

Figure 4-72. Illustration of the perceptual-defensive-recuperative model underlying descending nociceptive modulation. All links are excitatory (+) except for the link between the defensive system and the nociceptive intensity detector (–). This inhibitory link corresponds to an analgesic process. Presumably opposite processes (e.g., learned safety signal instead of learned danger) would produce opposite effects on nociception (i.e., facilitation instead of inhibition). (From Fanselow MS. Conditioned fear-induced opiate analgesia: a competing motivational state theory of stress analgesia. In: Kelly DD, ed. *Stress-induced analgesia*. New York: The New York Academy of Sciences, 1986:41, with permission.)

Most reports of conditioned analgesia have suggested that this phenomenon is mediated by endogenous opiates. The studies by Watkins and colleagues (459) have demonstrated a descending pathway mediating conditioned analgesia coursing from amygdala through PAG to lateral rostral ventromedial medulla (reticularis paragigantocellularis lateralis) and down the dorsal part of the lateral funiculus to the spinal cord. Much has been made of possible similarities between conditioned analgesia and the clinical phenomenon of placebo analgesia (499). Both, for instance, can be blocked by naloxone and CCK. Clearly, it is hard to draw comparisons between such different paradigms. In most studies of placebo, careful controls are used to avoid either SIA or conditioned analgesia (500) and unlike fear-elicited conditioned analgesia, hope is seemingly the expectation that elicits placebo analgesia. Nonetheless, conditioning greatly potentiates placebo analgesia, even when the placebo is described to the subject as being of no analgesic benefit (500).

In contrast to fear eliciting analgesia, Watkins and colleagues (416) have demonstrated that signals associated with safety after shock can block analgesia from opiate or $GABA_B$ receptor agonists. This phenomenon disappears with lesions of the midbrain dorsal raphe, NRM, and the dorsal part of the lateral funiculus (in contrast to other pain facilitatory spinal pathways suggested to lie in the ventral cord), and it is mediated by CCK. This is an antianalgesic phenomenon, rather than a nociceptive sensitization *per se* (Fig. 4-73). On the other hand, illness (450,483) activates a true descending pain facilitatory phenomenon (as anyone who has ever had a viral illness can attest) that shares many of the anatomic and neurochemical mechanisms of the antianalgesia system but over time also appears to activate spinal mechanisms of central sensitization (including NMDA and nitric oxide mechanisms). Indeed, descending facilitatory pathways have been implicated in mediating, at least partially, sensitization from mustard oil, subcutaneous formalin, carrageenan monoarthritis, and certain neuropathies (450).

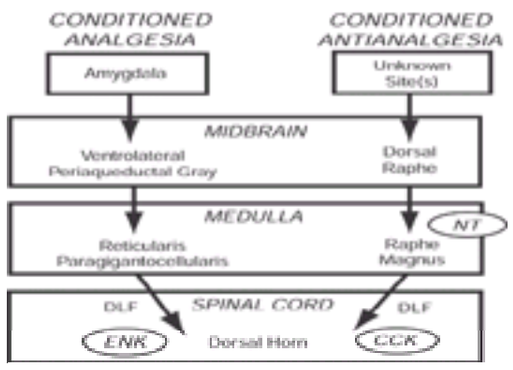

Figure 4-73. Neurocircuitry of conditioned analgesia and conditioned antianalgesia relies on distinct neural substrates that lie in close proximity throughout the neuraxis. Conditioned analgesia results from activation of the amygdala, leading to activation of the ventrolateral periaqueductal gray in the midbrain, to activation of the nucleus reticularis paragigantocellularis in the medulla through the dorsal lateral funiculus (DLF) to the spinal cord dorsal horn, where enkephalin (ENK) is released. Conditioned antianalgesia results from activation of unknown rostral brain sites that activate dorsal raphe in the midbrain, which, in turn, activates nucleus raphe magnus in the medulla, perhaps by the release of neurotensin (NT). The activated raphe magnus sends axons via the DLF to the dorsal horn where conditioned antianalgesia is produced, at least in part, by the release of cholecystokinin (CCK). (From Watkins LR, Wiertelak EP, McGorry M, et al. Neurocircuitry of conditioned inhibition of analgesia: effects of amygdala, dorsal raphe, ventral medullary and spinal cord lesions on antianalgesia in the rat. *Behav Neurosci* 1998;112:371, with permission of the American Psychological Association.)

Finally, after injury on the battlefield (or, in Livingstone's case, in the jungle), following prolonged electric shock or certain other SIA paradigms, all mechanisms of escape behavior may be exhausted. Maier and colleagues have demonstrated that animals learn to stop attempting escape from a shock: This is termed *learned helplessness*. These investigators also report a correlation of this behavior with activation of endogenous pain inhibitory mechanisms (501,502). This opioid SIA is dependent on pituitary and adrenal mechanisms and may be similarly activated by other intense forms of physical activity. Some hypothesize that this form of opioid SIA may occur in long-distance runners world-wide (503,504), who continue running even after the lions have quit chasing them.

Descending Nociceptive Modulation: Clinical Significance

Do studies of SIA have human applications? Demonstrations exist of opioid and nonopioid analgesia in humans provoked by various procedures that might be considered stressful, including acupuncture (505,506), TENS (507), and exercise (508). Perhaps such procedures activate areas of the human brain homologous to those activated by SPA and SIA in rats. Regardless, elucidating the neural basis of SIA might one day lead to the development of new approaches to pain management. Perhaps the greatest promise for such an advance lies in determining the neurochemistry of nonopioid analgesia. The similar efficacy of opioid and nonopioid SIA bode well for a nonopioid analgesic that shows no tolerance or cross-tolerance to mu opiates. A number of spinal and supraspinal nonopioid antinociceptive agents have been identified. However, in the past decade, the pharmacologic emphasis has swung subtly from investigating antinociceptive agonists to developing antagonists of certain forms of nociception.

In general, naloxone has no effect on pain thresholds, suggesting that opioid intrinsic pain inhibitory systems are not tonically active (244). Opiate antagonists can produce hyperalgesia in patients having postoperative pain, however, indicating that stress or nociception from surgery activates opioid intrinsic pain inhibitory systems (252). In this regard, to the extent that our intrinsic pain- inhibitory systems are mediated by endogenous opioid action, a consequence of prolonged opiate therapy might be a blunting of natural analgesic mechanisms through cross-tolerance. Just as opioid-mediated forms of SPA and SIA diminish in morphine-tolerant rats, so too might an opiate-tolerant pain patient's intrinsic capacity to modulate his or her own pain be reduced. Moreover, as research further defines the neurochemistry of pain and pain modulatory pathways, clinicians need to keep in mind that even nonopiate drugs appropriately prescribed for an ailment unrelated to pain might have a cost to the patient in terms of lessened pain tolerance by blocking some aspect of the intrinsic pain-inhibitory system.

Finally, the pain patient's knowledge of descending pain modulation provides a psychological double-edged sword. The existence of inhibitory systems can provide hope for overcoming debilitating nociception. Descending facilitatory systems, however, provide fodder for fears of patients (or their doctors) that their pain is “all in their heads.” Such psychological dilemmas (and their treatment) are well outside the scope of this chapter on spinal mechanisms of nociception but are integral to a full understanding of pain.

GENETIC AND DEVELOPMENTAL ASPECTS OF NOCICEPTIVE MODULATION

To this point in this chapter, we have discussed the modulation of nociception in terms of environmental influences on an organism producing a physiologic response. It is important to note, however, that modulation of nociceptive circuitry also may be under genetic preprogrammed control. We have mentioned the use of knockout mice and other genetic techniques, primarily as tools for investigating the molecular mechanisms that might be involved in producing certain nociceptive phenomena (e.g., sensitization or SIA). Investigators are also studying the genetics of nociception *per se*, however, in hopes of determining the heritability of nociception (i.e., how much of a mouse's, or human's, response to a noxious stimulus is caused by its genotype and, similarly, how much are response differences from its neighbor genetically determined). Mogil, for example, has shown that various inbred strains of mice differ dramatically in their responses to standard pain tests and their development of sensitization (509,510). Elmer (511) has, likewise, noted strain differences in opiate analgesia in mice. Although such genetic differences will be difficult to tease apart clinically from cultural and other environmental determinants, genetic risk for sensitization, for example, might one day alter pain management strategies in an individual.

Indeed, it is now clear that genetically defined modulation of nociception takes place in all of us as a function of ontogeny. For example, a decreased number of primary afferent nociceptors are found in the elderly (512). Nonetheless, an increase in pain complaints with age has been consistently reported in the clinical literature (513). Moreover, the aged appear particularly susceptible to sensitization phenomena such as postherpetic neuralgia. Two possible mechanisms for such an effect have emerged from animal models. In contrast to younger rats, aged rats have decreased neurogenesis and thus fewer cells in the dorsal root ganglia, as mentioned. Moreover, cells that remain may have increased ectopic discharges and potentiated cross-excitation of neighboring primary afferents (512). Such ectopic electrical activity is a well-studied peripheral mechanism for neuropathic pain after nerve injury decreases in DRG cell number (i.e., involution). Aged rats also contain decreased levels of spinal monoamines (serotonin and norepinephrine), possibly indicating a decrease in descending antinociceptive pathways (514). Such a decrease may also increase sensitization at the spinal level. Either or both of these hypotheses may ultimately prove correct in explaining the susceptibility of the elderly to neuropathic pain. In the meantime, research suggests that responses to therapy, including opiate pharmacodynamics (515), are not different in aged

patients.

The nociceptive processing of young animals is also quite different from animals of other ages. In general, the neonatal cord is more excitable than that of the adult, with larger reflexes and lower thresholds to noxious, particularly mechanical, stimuli (516). The A-b low-threshold mechanoreceptors, which in the adult terminate superficial to lamina III except in pathologic states associated with allodynia, normally synapse in lamina I and II of the rat until 3 weeks of age (517). Moreover, C fibers appear to facilitate their withdrawal at 3 weeks, just as in the adult, C-fiber damage appears to allow A-b return to lamina II through sprouting. Descending pain inhibitory pathways (and presumably descending facilitatory pathways as well) are absent or incomplete until 18 to 21 days of age (518).

Pharmacologically, the neonate spinal cord also differs considerably from that of the adult until 2 to 3 weeks of age. NMDA receptor responses are common in the neonatal spinal cord even without prior depolarization, and glycine and particularly GABA inhibition are greatly diminished during the first week (519). Substance P binding is nearly six times that of the adult, although normal primary afferent substance P levels are not present until day 14.

In short, the neonatal spinal cord is primed for central sensitization (519). Indeed, a number of inflammatory and neuropathic sensitization models have been described and some evidence suggests that early nociceptive experience can have long-lasting sensitizing effects in rats (520). With all of these data on the rat in hand, and similar data evident in the human neonate (521), it is tragic that there is, nevertheless, continued controversy over the importance of even minimal pain management for the child too young or too sick to complain (522).

GENERAL SUMMARY

The material presented in this chapter illustrates the concept that nociception at the spinal level, provoked by injury or disease, is the net effect of many interacting physiologic, biochemical, and even psychological mechanisms.

It is obvious that the concept of pain being transmitted via labeled line communications from body tissues to the brain is simplistic, and worse, it is wrong. A great variety of mechanisms modulate the transmission of information about tissue damage at virtually every synaptic relay station throughout the neuraxis. At the level of the STT cell (the gate-control theory's T-cell in Fig. 4-74), this is achieved through dynamic interactions between numerous neurotransmitters, their receptors, and the neural circuitry inputs from the periphery, spinal interneurons, and descending control systems from the brain. Through this process of modulation, the character of the nociceptive information received by the highest brain structures is determined. It is this low-fidelity signal that reaches the thalamus and contributes to autonomic reflexive, sensory-discriminative, motivational and affective, cognitive, and motor responses characteristic of pain behavior.

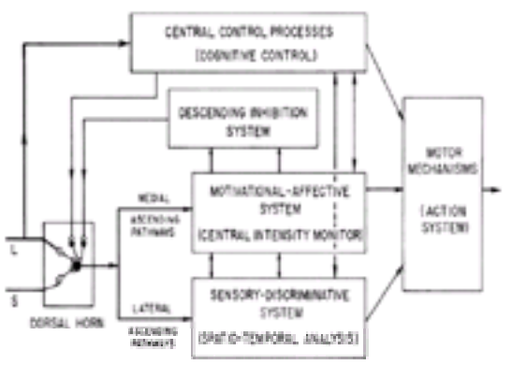

Figure 4-74. Model of the sensory, motivational, and central control of pain by Melzack and Casey. The output of the T cell in the dorsal horn projects to the sensory-discriminative system via the lateral ascending system and to the motivational-affective system via the medial ascending system. These systems interact supraspinally and eventually activate projections back to the spinal cord, modulating nociception via brain stem inhibitory and facilitatory systems as well as motor and autonomic efferent pathways. (Modified from Melzack R, Casey KL. Sensory, motivational and central control determinants of pain. In: Kenshalo DR Jr, ed. *The skin senses*. Springfield, IL: Charles C Thomas Publisher, 1968:423–443.)

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CHAPTER 5

Supraspinal Mechanisms of Pain and Nociception

Eric H. Chudler and John J. Bonica

The two preceding chapters have discussed processing of nociceptive information at the peripheral and spinal levels of the nervous system. Electrophysiologic, neuropharmacologic, behavioral, and clinical data have suggested that numerous supraspinal structures process nociceptive information and may have varied roles in pain sensation and perception. Despite advancements in brain imaging methodologies that have provided new information about supraspinal pain mechanisms, a relative paucity of these data exist compared to the large body of literature pertaining to peripheral and spinal nociceptive mechanisms. This lack of data most likely is because of technical and ethical issues related to performing appropriate experiments. For example, supraspinal neuronal responses to noxious stimuli are affected by anesthetics requiring the use of awake animal preparations. This requires careful experimental planning to protect the animal from unnecessary exposure to painful stimuli.

Pain is a multidimensional experience that includes identification of somatic sensory events in terms of space, time, intensity, and submodality (mechanical, thermal, and chemical). It is associated with aversive motivational-emotional mechanisms leading to escape and other forms of aversive behavior. This complex multidimensional aspect of pain was implied by Melzack and Wall (1) and elaborated by Melzack and Casey (2), who took into account knowledge derived from physiologic and behavioral studies. Melzack and Casey (2) (Fig. 5-1) suggested three major psychological dimensions of pain: sensory-discriminative, motivational-affective, and cognitive-evaluative. Each influences motoric behavior in response to painful events. Physiologically specialized systems within the neuraxis are hypothesized to subserve these dimensions of pain. Although the Melzack-Casey conceptual model does not explain all questions regarding pain, it does provide a framework for investigating supraspinal pain processes.

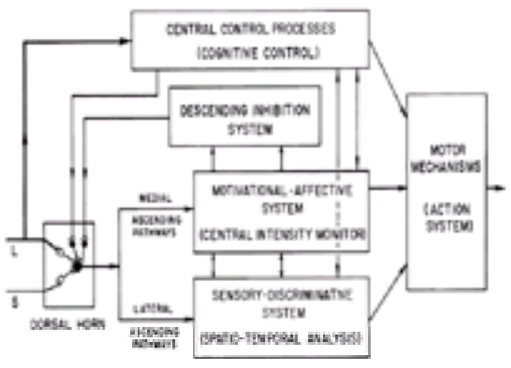

Figure 5-1. Conceptual model of the sensory, motivational, and central control determinants of pain, according to Melzack and Casey (2). The output of the T cell in the dorsal horn projects to the sensory-discriminative system via the lateral ascending system and to the dorsolateral projection systems and is represented by a heavy line running from the large fiber system of the central control processes that take place in the brain. These, in turn, project back to the dorsal horn and to the sensory-discriminative and motivational-affective systems. Added to the scheme of Melzack and Casey is the brainstem inhibitory control system activated by impulses in the medial descending system. It provides descending control on the dorsal horn. Much interaction occurs between the motivational-affective and the sensory-discriminative system, as indicated by the arrows. The net effect of all of these interacting systems is activation of the motor (action) system. (Modified from Melzack R, Casey KL. Sensory, motivational and central control determinants of pain. In: Kenshalo DR, ed. *The skin senses*. Springfield, IL: Charles C Thomas, 1968:423–443.)

RETICULAR FORMATION

The reticular formation has an important role in mediating motor, autonomic, and sensory functions. It also is involved with aversive drive and the motivational-affective dimensions of pain.

Anatomy

The reticular formation is composed of several nuclear groups each with cell bodies of distinctive sizes and shapes (Fig. 5-2, Fig. 5-3). However, as Casey (3,4) pointed out, silver stain studies reveal some common and unifying structural features superimposed on this morphologic heterogeneity. The reticular formation consists of core isodendritic neurons extending through the medulla, pons, and mesencephalon. The axonal projections of these cells are typically long, extending substantial distances along the rostral-caudal axis of the brainstem and brain. The number of short reticular formation neurons is small. Along their course, the axons send collaterals to (a) the spinal cord, (b) other reticular neurons, (c) various sensory and motor nuclei of the brainstem, (d) the diencephalon, and (e) the cerebral cortex (Fig. 5-4).

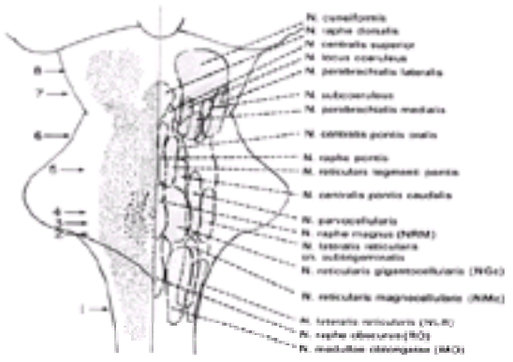

Figure 5-2. Semidiagrammatic representation of the dorsal view of the human brainstem depicts the cytoarchitecture of the reticular formation on the left and the most important subdivision of the right. The numbers to the left of the diagram indicate the sites of the cross sections shown in Figure 5-3. The abbreviations, derived from Mehler et al. (36,66), are used in Figure 5-3. (Modified from Nieuwenhuys R. *The human central nervous system: a synopsis and atlas*. New York: Springer-Verlag, 1981.)

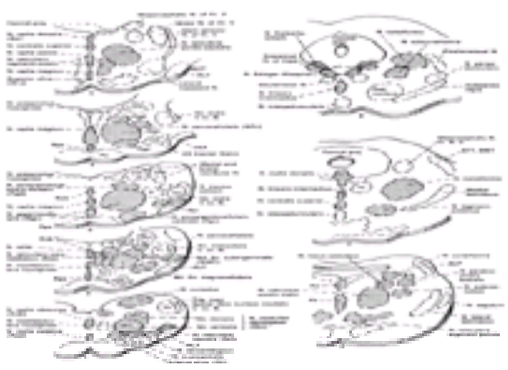

Figure 5-3. Right hemisections of eight different levels of the brainstem, indicated by the numbers on the left side of Figure 5-2, show the locations of the most important nuclei of the reticular formation and other important structures in the cat. The abbreviations in Figure 5-2 and in levels 1 to 5 are used in other levels to avoid overcrowding of the names of nuclei. (N., nucleus; Sn., subnucleus.) (Modified from Brodal A. *The reticular formation of the brain stem: anatomical aspects and functional correlations*. Springfield, IL: Charles C Thomas, 1957; and Taber J. The cytoarchitecture of the brain stem of the cat. *J Comp Neurol* 1961;116:27–52.)

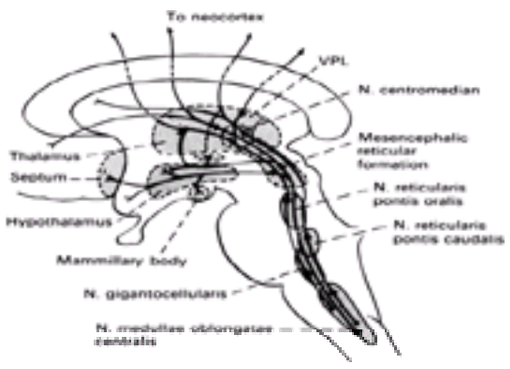

Figure 5-4. Sagittal section of the brainstem and the diencephalon shows the most important nuclei of the reticular formation and their projections to the thalamus, hypothalamus, septum, and mammillary body. (N., nucleus; VPL, ventroposterolateral nucleus.) (Modified from Nieuwenhuys R. *The human central nervous system: a synopsis and atlas*. New York: Springer-Verlag, 1981.)

Bulboreticular neurons with ascending axons send projections in the medial thalamic region, particularly in the nucleus parafascicularis, the nucleus centrum medianum, and to the more rostral mesencephalic reticular formation. Cells within the medial brainstem reticular formation of the caudal pons and the gigantocellular medial reticular area in the medulla send long ascending projections to the medial mesencephalic reticular formation and to the medial and intralaminar thalamic nuclei. Moreover, a direct relay exists from the nucleus gigantocellularis (NGC), in the medullary reticular formation, to posterior and medial thalamic nuclei. An especially massive projection exists from the mesencephalic tegmentum, particularly the central gray substance to the thalamus, subthalamus, and hypothalamus.

The periaqueductal central gray in the midbrain, a recipient of spinomesencephalic fibers, sends projections in the surrounding mesencephalic reticular formation and via the dorsal longitudinal fasciculus, in the dorsal and posterior hypothalamus, and in the midline and intralaminar thalamic nuclei and zona incerta of the subthalamus. A direct reticulocortical projection exists, and such fibers may be the longest axons in what is mainly a relay system. Therefore, at least five routes exist by which the midbrain reticular formation has access to the cerebral cortex: (a) direct, (b) via the medial forebrain bundle and hypothalamus, (c) through the thalamocortical pathway, (d) from the posterior thalamic group to the second somatosensory cortex (SII), and (e) through the ventral tier of thalamic nuclei. These ascending projections have important significance in pain-related behavior and responses. It is obvious that the reticular formation is not a diffuse network of short-axon neurons forming a multisynaptic chain, but rather a group of neurons that appears organized to distribute information quickly to multiple foci throughout a substantial portion of the neuraxis, extending from the spinal cord to the diencephalon and cerebral cortex.

Physiology and Behavior

Physiologic studies show that reticular formation neurons can mediate motor, autonomic, and sensory functions. Although circumscribed regions with specialized functions exist within the reticular formation, impressive evidence exists for substantial interaction that would provide the basis for unified operations of the reticular core (4). The reticular formation is essential for the coordination of motor behavior in animals experimentally deprived of forebrain function. Medullary and pontine reticular neurons also regulate various aspects of spinal motor activity and respiratory and other autonomic functions, including those carried out in the spinal cord. The reticular formation also has important sensory functions and is capable of modulating somatic, auditory, and visual sensory systems (4).

Electrophysiologic findings have clearly demonstrated that nociceptive afferents are among the most effective inputs that influence the discharge of a subpopulation of reticular formation neurons (3,4,5,6 and 7). Mechanical, thermal, electrical, and chemical stimuli are all capable of activating medullary and mesencephalic reticular formation neurons (3,4,5 and 6) in an exclusive or preferential manner. The receptive fields of nociceptive reticular formation neurons can be ipsilateral or bilateral. Often, the receptive fields are large and may include the entire body.

Within the medullary reticular formation, NGC neurons are most effectively activated by electrical stimulation of peripheral nerves sufficient to evoke A-d and C-nerve fibers (8). It also has been demonstrated that intraarterial injection of algogenic agents, such as bradykinin, or intense stimulation of the splanchnic nerve evokes discharge of neurons in the NGC. Neurons in the rat subnucleus reticularis dorsalis (SRD) of the reticular formation (caudal medulla) also respond to cutaneous and visceral nociceptive stimuli in the rat (9). Neurons in the monkey medullary reticular formation appear to have many of the same response properties as those in the rat SRD (10) (Fig. 5-5). Within the SRD, nociceptive neurons respond exclusively or preferentially to noxious mechanical, electrical, and thermal stimulation of the skin (11,12). Moreover, these neurons are capable of encoding the intensity of noxious stimulation in a linear fashion (12). However, the large whole body receptive fields of SRD nociceptive neurons suggest that this area may not be involved in localizing noxious stimulation. Rather, the electrophysiologic response properties and anatomic connectivity of neurons in the SRD have led Villaneuva and co-workers to hypothesize that the SRD is involved in a feedback loop that modulates spinal

outflow (9).

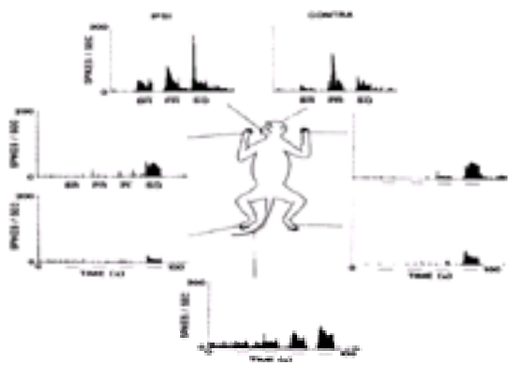

Figure 5-5. Responses of a medullary reticular formation neuron to graded mechanical stimulation of the skin on the indicated areas of the body (dorsal view). Stimuli included brushing with a soft-bristled brush (BR), pressure from a large arterial clip (PR), pinch from a small arterial clip (PI), and squeezing with forceps (SQ). Each stimulus lasted 10 seconds (*bars*). (IPSI, ipsilateral; CONTRA, contralateral.) [Reprinted from Villanueva L, Cliffer KD, Sorkin LS, et al. Convergence of heterotopic nociceptive information onto neurons of caudal medullary reticular formation in monkey (*Macaca fascicularis*). *J Neurophysiol* 1990;63:1118–1127, with permission.]

Casey and co-workers (7,8) correlated escape behavior of a cat with the neuronal activity of NGC neurons. As the intensity of electrical stimulation of radial nerve was increased, the discharge of NGC neurons increased and reached maximum levels when the cat performed a learned response that terminated the stimulus. Direct electrical stimulation of the NGC also elicited escape behaviors that were often accompanied by vocalization (13). Electrical stimulation of the mesencephalic reticular formation and central gray also have elicited aversive behavioral responses (13,14). Lesions within the medullary and mesencephalic reticular formation can produce marked decreases in the response to noxious stimuli. Melzack et al. (15) reported that medial mesencephalic lesions reduced pain behavior in cats immediately after the lesion but resulted in increased responsiveness to noxious stimuli at later postlesion periods.

Casey and associates (3,4,14) provide impressive evidence that the reticular formation is strongly influenced by nociceptive input. It also is an important determinant of pain behavior and, presumably, some aspects of the pain experience. Melzack and Casey (2) have suggested repeatedly that reticular formation neurons with ascending projections may mediate the affective-motivational dimension of the pain experience. With input from the reticular formation, the medial thalamus and hypothalamus project to limbic system forebrain structures, such as the cingulate gyrus and hippocampal formation. Both are known to play important roles in motivational and affective mechanisms. Casey (4) points out that selective lesions within limbic forebrain structures of humans and animals markedly attenuate the aversive quality of noxious stimuli without interfering with the discriminative aspects of somesthesia.

The effects of opioid analgesics on reticular formation neurons also may account in part for the reduction of suffering of clinical pain while preserving much of the discriminative ability to recognize noxious stimuli (4). Finally, the neural system mediating motivational and affective mechanisms is not simply a specialized pain pathway. Other inputs are important determinants of the affective state and can motivate behavior. Because pain is an especially compelling experience, however, nociceptive input has a major influence on the function of the reticular formation, which appears to be organized to play a critical integrating role in pain experience and behavior.

MIDBRAIN (SUPERIOR COLLICULUS)

The role of the superior colliculus (SC) in vision and sensory-motor behaviors is well established (16). Neurons in the SC receive multisensory (auditory, visual, and somatosensory) input (17,18,19 and 20) and form descending projections to the brainstem and spinal cord to influence facial, head, and neck movement (21,22 and 23). Data also suggest that the SC may be important in coordinating movements elicited by noxious stimuli (22,24).

Anatomy

Located in the mesencephalon, the superior colliculi are organized in a laminar fashion. The superficial (upper) layers of the SC receive direct input primarily from the retina and visual cortex. Neurons in the intermediate and deeper layers of the colliculi receive input from a variety of structures, including the spinal cord, basal ganglia, medullary nuclei, and cerebral cortex. Extensive crossed and uncrossed descending projections from the SC to areas in the pons, reticular formation, and spinal cord and ascending projections to the thalamus (25,26) suggest an important role of this midbrain structure in the control of sensorimotor behaviors (24).

Physiology and Behavior

Direct physiologic evidence for a role of the SC in pain comes from several laboratories. Stein and Dixon (27) first showed that neurons in the intermediate and deep layers of the SC were preferentially or exclusively activated by noxious mechanical and thermal stimulation. Moreover, intraperitoneal administration of etorphine suppressed the activity of 67% of these nociceptive neurons, and this inhibition was reversed by naloxone (27). Nociceptive SC neurons appear to be distributed in a somatotopic fashion and are found more often in the rostral SC (28). Telford et al. (29) demonstrated that noxious mechanical and chemical stimulation result in an even distribution of c-*fos* immunoreactivity along the rostrocaudal axis of the intermediate and deep layers of the SC. Nociceptive SC neurons [wide-dynamic-range (WDR)– and nociceptive-specific (NS)–type neurons] are capable of encoding mechanical and thermal stimulation intensity (23,28,30) (Fig. 5-6). The mechanical receptive field sizes of these SC neurons are often large. Within the receptive field area, a smaller, more sensitive region is usually found. It is possible that such a receptive field organization provides for location encoding of noxious stimuli.

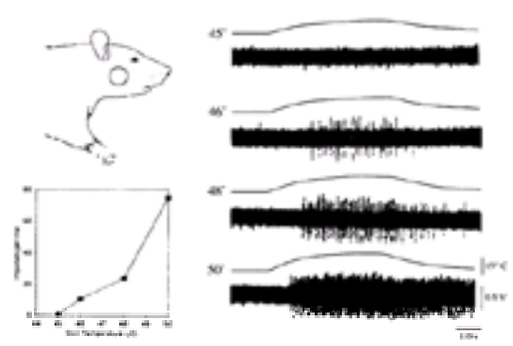

Figure 5-6. Example of the response of a nociceptive neuron in the superior colliculus. The number of impulses evoked by noxious stimuli was related to stimulus intensity. This nociceptive-specific neuron, which had a whole-body receptive field with no obvious best area, was responsive to the heat thermode placed on the face **(A)**. It showed a series of responses **(B)**, which were graded according to the intensity of the thermal stimulus. The baseline thermode temperature was matched with the ambient skin temperature (35°C). The values plotted in **C** show the number of impulses recorded during the 5- second duration of the heat pulse in each trial. (Reprinted from Redgrave P, McHaffie JG, Stein BE. Nociceptive neurones in rat superior colliculus. I. Antidromic activation from the contralateral predorsal bundle. *Exp Brain Res* 1996; 109:185–196, with permission.)

The existence of a nociceptive tectothalamic pathway has been demonstrated using electrophysiologic methods. Almost half of the SC neurons that are antidromically activated by stimulation of the intralaminar nuclei of the thalamus have been classified as nociceptive (25,26). Grunwerg and Krauthamer (26,31) found that 58% of the intralaminar thalamic neurons orthodromically activated by electrical stimulation of the intermediate and deep layers of SC were responsive to noxious mechanical

stimulation. Chemical lesions of this same region of the SC resulted in a significant reduction in the number of nociceptive intralaminar thalamic neurons (26). Redgrave and co-workers (23,32) also provided convincing evidence that chemical disruption of the SC and lesions of the descending pathway from the SC result in deficits to localize and respond to noxious mechanical and chemical stimuli while leaving general motor behavior unaffected.

The tectothalamic pathway and its extension to the striatum as well as tectofugal pathways may mediate withdrawal, orientation, and avoidance of noxious stimuli (28,33,34). The high incidence of neurons with trigeminal receptive fields within the SC, intralaminar nuclei of the thalamus, and striatum suggests that these neurons may play a role in controlling or coordinating head movement, orientation, and positioning during escape behavior (34).

THALAMUS

As a gateway and relay center for afferent input transmitted to the cerebral cortex, the thalamus makes refined cutaneous awareness of pain possible. It is subdivided into several anatomically or functionally distinct nuclei, most of which are linked to the cerebral cortex and limbic areas by ascending and descending tracts. Jones (35) defines the three major subdivisions of the thalamus as the (a) epithalamus (anterior and posterior paraventricular nuclei, habenular nuclei); (b) dorsal thalamus [ventrobasal (VB) nuclei and intralaminar nuclei]; and (c) ventral thalamus [reticular nucleus, ventral lateral (VL) geniculate nucleus, and zona incerta]. The majority of pain-related experiments in the diencephalon have focused on the role of the dorsal thalamus (Fig. 5-7).

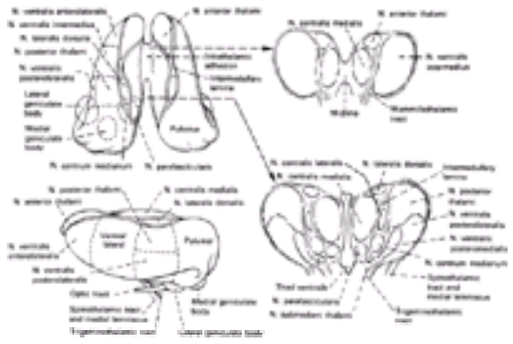

Figure 5-7. Schematic diagram of the human thalamus. **A:** Superior view. **B:** Lateral view shows the locations of the most important nuclei. **C:** Frontal section of the anterior part of the thalamus depicts the relationships of various nuclei. **D:** Frontal section of the middle part of the thalamus. Note that the spinothalamic tract and medial lemniscus terminate in nucleus (N.) ventralis posterolateralis, whereas the trigeminothalamic tract terminates in N. ventralis posteromedialis.

Ventrobasal Nuclei of the Thalamus

Anatomy

The VB nuclei comprise the ventral and posterior thalamic nuclei. These nuclei are subdivided into lateral and medial divisions called the *ventral posterior lateral* (VPL) (or *ventroposterolateral*) nucleus and the *ventral posterior medial* (VPM) (or *ventroposteromedial*) nucleus.

Ventroposterolateral Nucleus

The VPL nucleus receives fibers principally from the medial lemniscus formed, in part, by the second-order neurons of the dorsal column nuclei of the opposite site, which terminate on the VPL nucleus in basketlike clusters of terminal endings (see Fig. 5-7). Spinothalamic tract (STT) neurons that originate in laminae I and V terminate in the caudal and oral portions of the VPL nucleus in patchlike clusters that Mehler (36) called *bursts* in transverse sections or rod-like zones in three dimensions. The STT and medial lemniscal (dorsal column nuclei) projections to the VPL nucleus are organized somatotopically, with fibers from the lumbosacral cord (lower extremity) distributed laterally and fibers from the cervical cord (upper extremity) ending medially in the nucleus (Fig. 5-8). The VB nuclei also receive projections from the periaqueductal gray. The VPL nucleus projects to the first somatosensory (SI) cortex, the posterior parietal cortex, and may have a small projection to the SII cortex (37), and receives corticothalamic projections from these areas (38).

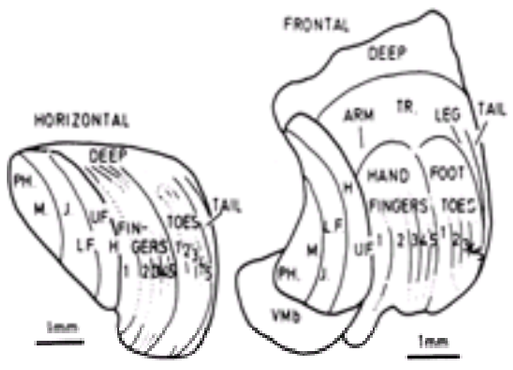

Figure 5-8. Schematic diagram of the left half of the thalamus shows on horizontal and frontal planes the overall lamellar pattern of representation in the cutaneous core of VPLc (the caudal division of the VPL) and ventroposteromedial nucleus and the anterodorsal deep shell of the ventrobasal complex in monkeys. The diagrams indicate a nearly complete separation of zones for cutaneous and deep modalities. The caudal body parts are represented laterally and the rostral body parts medially. The axial body parts are represented dorsally with the limbs represented progressively more ventrally. (H, head; J, jaws; LF, lower face; M, mouth; PH, pharynx; UF, upper face.) (Reprinted from Jones EG, Friedman DP. Projection pattern of functional components of the thalamic ventrobasal complex in monkey somatosensory cortex. *J Neurophysiol* 1982;48:521–544, with permission.)

Within the SI cortex, separate thalamic termination zones exist in areas 3a, 3b, 1, and 2 (38,39). Figure 5-9 illustrates the projection scheme by Jones and Friedman (39). The central core of the VPLc (the caudal division of the VPL), with neurons responsive to cutaneous stimuli, projects to areas 3b and 1 and the thinner anterodorsal shell of the VPLc, with neurons responsive to deep-tissue stimulation, projects to areas 2 and 3a. Penny et al. (40) presented evidence for a separate population of thalamic neurons that project to different cortical laminae in the SI cortex. Small VPL neurons project to lamina I, whereas large VPL neurons terminate in layers (40). Penny et al. suggest that large and small VPL neurons have separate functions based on inputs from large and small neurons in dorsal column nuclei. This may also apply to STT projections to the VPL nucleus.

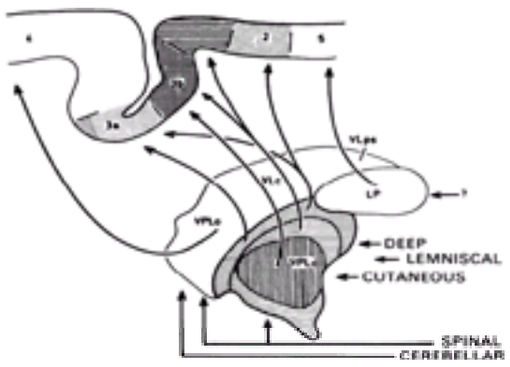

Figure 5-9. Schematic diagram shows on sagittal sections the pattern of input-output connections of the ventrobasal complex and adjacent thalamic nuclei in monkeys. Note the projection from the medial lemniscus to two components of the central cutaneous core of VPLc (the caudal division of the VPL), which projects to area 3b and 1 or area 3b only; projection of the anterodorsal deep shell is to area 3a and 2. The spinothalamic tract ends in the cutaneous core region that projects to area 3b and 1 and in the VPLo (the oral division of the VPL) nucleus, which is connected with the motor cortex (area 4). The cerebellar projections to VPLo are to separate neurons from those receiving spinothalamic projections. (Reprinted from Jones EG, Friedman DP. Projection pattern of functional components of the thalamic ventrobasal complex in monkey somatosensory cortex. *J Neurophysiol* 1982;48:521–544, with permission.)

Ventroposteromedial Nucleus

The VPM nucleus receives input from the main sensory trigeminal nucleus, from the pars interpolaris, and from the subnucleus caudalis via the trigeminothalamic tracts. VPM nucleus input from the main sensory nucleus and the subnucleus interpolaris is roughly analogous to the lemniscal input to the VPL nucleus, whereas the input from the subnucleus caudalis is roughly analogous to input from the neospinothalamic projection. VPM neurons project to the somatosensory cortex on the lateral part of the cerebral convexity in the postcentral gyrus. Corticofugal fibers descend from this region into the VPM nucleus.

Physiology and Behavior

Ventroposterolateral Nucleus

It is well established that the majority of neurons in the VB nuclei respond exclusively to somatic stimuli delivered to discrete regions of the contralateral body surface. Many investigators have emphasized that neurons respond to mechanoreceptive input either from tactile receptors, proprioceptors, or other deep receptors. A small percentage of VPL neurons in anesthetized and unanesthetized monkeys have either NS- or WDR-receptive field characteristics (41,42 and 43). Morrow and Casey (41) reported that only 13.1% of the recorded VPL neurons in awake monkeys were WDR-type neurons and none were NS-type neurons. Nociceptive VPL neurons have small receptive fields on the body and are arranged somatotopically within the VPL nucleus. More recently, in human subjects, thalamic neurons within the ventrocaudal nucleus (Vc), the human equivalent of the VPLc and VPM nucleus, have been identified that are preferentially or exclusively activated by noxious mechanical or thermal stimulation (44,45). This same area of the thalamus evokes pain sensations when stimulated (44,46,47). Moreover, abnormal spontaneous and evoked discharge patterns in some Vc neurons have been observed in patients with central pain during neurosurgical procedures (48,49).

In addition to receiving cutaneous input, the VPL nucleus receives visceral input. Colorectal distension and chemical irritation, urinary bladder distension, and electrical stimulation of the renal nerve all activate neurons in the VPL nucleus (50,51,52 and 53). Most neurons responsive to visceral stimuli have convergent somatic receptive fields. Lesions of the dorsal column reduce the neuronal response to visceral and cutaneous stimulation, but lesions of the ventrolateral column reduce only the response to cutaneous stimuli (52,53). These observations suggest that the dorsal columns play a critical role in the transmission of visceral nociceptive information to supraspinal structures.

Ventroposteromedial Nucleus

Like neurons in the VPL nucleus, VPM neurons are somatotopically organized and respond to innocuous and noxious input, but the majority of cells are classified as low-threshold mechanoreceptive neurons. These neurons are place specific: Each neuron responds only to stimulation of a restricted area of the contralateral side of the orofacial region. In awake monkeys trained on a thermal discrimination task, VPM neurons respond in a graded fashion to noxious cutaneous stimuli between 46°C and 49°C (54). Most VPM neurons in awake monkeys are multimodal because they respond to thermal and mechanical stimulation.

The role of the VPM nucleus in the sensory-discriminative aspect of pain is strengthened further by the observation that lidocaine microinjections in the VPM nucleus reduce the ability of monkeys to discriminate noxious cutaneous heat stimuli (55). Although inactivation of the VPM nucleus with lidocaine disrupted the monkey's ability to discriminate innocuous cooling and mechanical stimuli, the greatest effect was on noxious heat discrimination. Early attempts in humans to alleviate pain by surgical lesions focused on ventrocaudal nuclei of the thalamus (56). Neurosurgeons have abandoned this procedure because of the inconsistent results and a high complication rate (e.g., sensory loss, ataxia, and dysesthesia).

Summary

It is clear that the VPL and VPM nuclei play important roles in discriminative functions of pain. Electrophysiologic experiments have demonstrated that nociceptive neurons in these regions of the thalamus have small, somatotopically organized receptive fields. Furthermore, disruption of neural activity within the VB thalamus affects sensory discriminative abilities.

Posterior Group of Thalamic Nuclei

Anatomy

The posterolateral thalamus contains a cytoarchitecturally heterogeneous group of cells medial to the medial geniculate nucleus, extending rostrally to the nucleus ventralis posterior. This thalamic region, called the *posterior group* (PO) of thalamic nuclei, receives spinal somatic sensory input. This is contributed primarily by the spinothalamic system (57). It also receives lemniscal input from the dorsal column nuclei and from the spinocervical tract. Several projections arise from the posterior complex, but of principal interest is the projection of the medial portion of the posterior nuclear complex to the retroinsular cortex. This cortical zone is adjacent to the SII cortex and forms an additional somatosensory receiving area independent of SI and SII (see the section Cerebral Cortex). Cortical projections from the PO thalamic region include far fewer ascending axons than the extensive corticofugal input into the PO from the somatosensory cortical areas.

Physiology and Behavior

In lightly anesthetized cats, Poggio and Mountcastle (58) found a substantial proportion of PO neurons responded to noxious mechanical stimulation of the skin. They proposed that this region of the thalamus was a major relay center for neural activity subserving pain sensation. Subsequent studies failed to reveal a significant number of nociceptive neurons (59). This discrepancy may be because of the use of deeply anesthetized animals. Subsequent experiments have studied the response properties of PO neurons in lightly anesthetized and unanesthetized monkeys. Dong and Wagman (60), using lightly anesthetized cats, found a significant population of PO neurons that responded to noxious stimulation. Out of 258 somatosensory neurons studied, 16% were classified as NS and 14% were WDR. Guilbaud and co-workers (61), who worked with unanesthetized cats, found that 76 of 135 neurons (56.3%) were nociceptive. Furthermore, of these 76 nociceptive neurons, 41 neurons (53.9%) responded exclusively to noxious stimuli and 35 neurons (46.1%) were preferentially responsive to noxious stimuli.

In humans, Hassler (62) reported that stimulation of a region similar to the PO elicited reports of pain. Whether this effect was caused by excitation of PO neurons or ascending spinal fibers passing through the PO region toward other thalamic cells is uncertain. Destruction of the PO-like region in patients provides pain relief if the lesion is extensive enough to also involve some medial thalamic structures (63,64 and 65) (see Chapter 108). All authors agree that this region lacks somatotopic

organization and that receptive fields of neurons are often large and bilateral (5,59).

Medial and Intralaminar Thalamic Nuclei

Anatomy

The medial and intralaminar thalamic nuclei belong to the so-called diffuse or nonspecific thalamic system. This is so designated because electrophysiologic evidence suggests that these thalamic structures have widespread cortical influence in contrast to other thalamic nuclei, such as the VPL nucleus, which project directly to circumscribed cortical areas. (For a detailed discussion of the anatomic and physiologic properties of these nuclei, see reference 57.)

The intralaminar nuclei form a shell around the lateral aspect of the nucleus medialis dorsalis and are composed of five nuclear groups: the nucleus paracentralis, nucleus centralis medialis, nucleus centrum medianum, nucleus centralis later–alis, and nucleus parafascicularis (see Fig. 5-7). According to Mehler and associates (36,66), direct spinothalamic fibers from the ventrolateral spinal cord sweep over but do not terminate with the centrum medianum. They send terminals to the nucleus centralis lateralis and lateral portion of the dorsal medial nucleus, called *subnuclei multiformis* and *densocellularis*. Although endings of the STT in nucleus parafascicularis and nucleus centrum medianum are sparse (66), noxious inputs from the STT can gain access to these nuclei by way of the reticular formation (67,68). As mentioned previously, this part of the spinothalamic system originates from the deeper layers of the spinal gray and does not have somatotopic organization.

In addition to the direct spinothalamic input to the intralaminar complex, direct projections from the reticular formation relay impulses initiated by the spinoreticular projection from the ventrolateral spinal cord. Anatomic and electrophysiologic evidence exists for projections from the NGC to the centrum medianum and parafascicular region. Mancia et al. (69) have provided evidence that stimulation of the NGC excites intralaminar thalamic neurons directly. Finally, the intralaminar nuclei receive input from the mesencephalic reticular formation and central gray. Therefore, the posterior midline and intralaminar nuclei of the “diffuse projecting thalamic system” receive somatic input either directly from ascending spinal and trigeminal pathways or indirectly via reticular neurons that receive spinoreticular and trigeminoreticular input. The intralaminar thalamic nuclei also receive projections from the cerebral cortex, principally from areas rostral to the central sulcus.

Projections from the intralaminar thalamic nuclei are quite heterogeneous and diffuse. A major projection links the centrum medianum-parafascicular complex to the basal ganglia (caudate nucleus and putamen). This suggests that the role of this thalamic complex in pain is related to motor and emotional reactions and aversive drive (70). Although most of these thalamic nuclei are thought to have few direct projections to the cerebral cortex, electrophysiologic evidence leaves little doubt that electrical stimulation of the intralaminar area has widespread cortical effects. It appears to function as part of the “diffuse reticular activating system” studied extensively by Magoun (71). Neurons of this region project diffusely to wide areas of the cerebral cortex, including the frontal, parietal, and limbic regions (see the section Cerebral Cortex).

Physiology

In the unanesthetized monkey, Casey (72) noted that cells in the lateral part of the medialis dorsalis and in other medial and intralaminar nuclei responded to innocuous stimuli but responded much more vigorously to stimuli defined as noxious on the basis of the behavioral response of the animal. Other findings also show that neurons in this region of the rat respond to noxious visceral stimulation (73).

Dong et al. (60) found that a large proportion of neurons in these regions responded exclusively to noxious stimuli or to noxious and innocuous (tap) mechanical stimuli. Several investigations have made observations consistent with those of Dong et al.: Electrical stimulation of peripheral nerves at intensities necessary to recruit A-d and C nerve fibers evoke activity in medial and intralaminar nuclei neurons (59). The receptive fields of these thalamic neurons are large and often bilateral. Little evidence exists for somatotopic organization of input. This nuclear complex receives convergent input from skin, joint, and muscle (74).

Recordings from neurons in the intralaminar nuclei in humans are similar to those in animals. Thus, Ishijima et al. (75) demonstrated the existence of nociceptive neurons in the centrum medianum-parafascicular complex. These neurons possessed large receptive fields that occasionally included the contralateral half and ipsilateral upper part of the body. They observed two classes of neurons: Those with a short latency responses were found predominantly in the basomedial portion of the parafascicular nucleus; those with long latencies were located in the dorsal centromedian and parafascicular regions. They proposed that neurons responding with short latencies were activated by A-d nerve fiber input whereas those that respond with long latencies were activated by C nerve fibers.

Tasker et al. (76) reported that stimulation of the medial-intralaminar thalamus in normal individuals did not elicit pain, but in patients with deafferentation pain, stimulation of the mesencephalon and medial thalamus produced burning pain in the area of peripheral deafferentation. Sano et al. have reported similar observations (77). They also found that lesions within the medial and intralaminar system could relieve intractable pain caused by neoplastic disease. The centrum medianum-parafascicular-medialis dorsalis complex appears to be a critical determinant of the efficacy of the operation. These lesions appear to diminish the affective dimension of pain, while preserving somatosensory discriminative capacity. The effects of such lesions resemble those produced by frontal lobotomy on responses to painful stimulation, but they do not produce the same effects on cognition or social behaviors.

Nucleus Submedius

Anatomy

Craig and Burton (78) detailed the anatomic connections of a ventromedial thalamic area called the *nucleus submedius* (Sm), also called the *nucleus gelatinosus*. In the cat, lamina I neurons in the medullary and dorsal horn project directly to Sm (78,79,80 and 81). In contrast to these findings, the Sm in the rat receives projections from deep and superficial layers of the medullary and spinal dorsal horn (82,83 and 84). A reciprocal connection between Sm and the ventrolateral orbital (VLO) cortex has been demonstrated using anterograde and retrograde tracing methods (85,86) and electrophysiologic techniques (87).

Physiology and Behavior

The Sm contains a substantial number of neurons driven exclusively or preferentially by noxious cutaneous and visceral stimuli (79,87,88,89,90 and 91). The majority of nociceptive neurons in this region respond to noxious stimuli, but some are inhibited by noxious cutaneous stimuli. Many nociceptive Sm neurons respond to noxious stimulation with activity that outlasts the duration of the stimulus, and most nociceptive Sm neurons have large, bilateral receptive fields. Although spinal and trigeminal input terminate in the dorsal portion of Sm, nociceptive neurons extend throughout the dorsal-ventral extremes of the nucleus. These findings suggest that nociceptive neurons in the ventral portion of the Sm have dendrites in the dorsal portion of the nucleus or receive axons or axon collaterals from neurons in the dorsal region (88).

Two behavioral experiments have provided additional evidence regarding a possible role of Sm in pain modulation. Using an anesthetized rat preparation, Zhang et al. (92) demonstrated that bilateral, but not unilateral, destruction of the Sm facilitated the tail-flick reflex and reduced the analgesic effects of hindlimb stimulation as measured with the tail-flick test. Roberts and Dong (93), however, were unable to show any effect of bilateral Sm lesions on tail-flick latency 7 days after surgery. They did report significant decreases in the intensity of electrical shock necessary to evoke vocalization. Additional behavioral experiments are necessary to clarify the role of Sm in pain.

Ventral Medial Nucleus

Anatomic (94) and electrophysiologic studies (95) have demonstrated a projection from lamina I of the dorsal horn to the posterior part of the ventral medial (VMpo) nucleus of the thalamus. Anterograde tracing studies have revealed that the VMpo nucleus projects to the insular cortex (94). Unlike the majority of neurons in the VPL and VPM nuclei, most (97%) neurons in the VMpo nucleus responded to noxious or thermal (cold) stimuli (96). Thermally responsive VMpo neurons had small receptive fields and increased activity with increasing stimulus intensity. These data suggest an additional supraspinal pathway for nociceptive information that may function in the sensory-discriminative and affective-motivational dimensions of pain.

HYPOTHALAMUS AND LIMBIC SYSTEM (AMYGDALA, CINGULATE CORTEX)

Noxious stimuli that elicit pain often are highly motivating and tend to provoke strong autonomic arousal and emotional responses mediated by the hypothalamus and limbic system structures (97,98,99 and 100). The hypothalamus integrates and regulates the autonomic nervous system and the neuroendocrine response and helps to organize and coordinate visceral and somatic reaction patterns caused by tissue damage and pain.

As Jänig (97) described in a simplified view, the cerebrum consists of the neocortex and the limbic system (paleocortex). Goal- directed human behavior is generated by the cerebrum by integrating limbic and neocortical activity. In this process, the neocortex, which is clearly involved in sensory processing and integration, tends to regulate the precise spatiotemporal communication with the environment and formal intellectual and stereognostic capabilities. The reciprocal connection between the neocortex and many parts of the limbic system makes possible the interplay between these two systems that constitutes a functional anatomic substrate for behavior expression and regulation. The limbic system is concerned with mood and incentives to action, such as a person's motivational interaction and emotions (97). The limbic system endows the information derived from internal and external events with its particular significance to humans, and thus it determines each person's characteristic purposeful behavior.

The limbic system comprises the phylogenetic old parts of the telencephalon and the subcortical structures derived from them (99), as well as parts of the diencephalon and mesencephalon (Fig. 5-10). The telencephalic components of the limbic system include the amygdala, hippocampus, septal nuclei, nucleus accubens and diagonal band of Broca, bed nucleus of the stria terminalis, and the preoptic region. In addition, several transitional cortical areas also are involved in limbic circuitry: the parahippocampal, periamygdaloid, entorhinal and cingulate gyrus, insular and temporal cortex, and the orbitofrontal part of the neocortex. In the diencephalon, limbic structures include the hypothalamus and parts of the thalamus and “epithalamus,” or habenula. Limbic brain areas that occupy a paramedian position include the ventral tegmental area, dorsal tegmental nucleus, and parts of the periaqueductal gray and midbrain raphe nuclei.

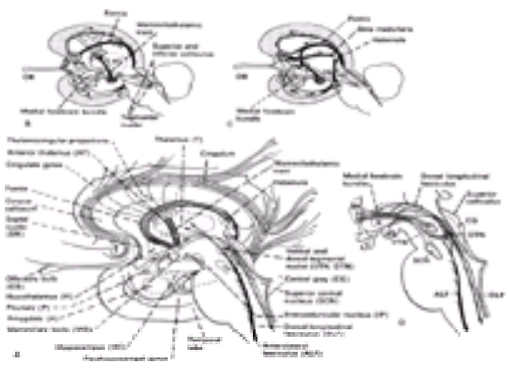

Figure 5-10. The limbic system. **A:** Sagittal section depicts the most important structures and connecting pathways. Note the projection of the anterolateral fasciculus containing the spinothalamic tract to the central gray of the mesencephalon and to the thalamus and the connections of the latter structure with other parts of the limbic system. The nucleus submedius also receives spinothalamic tract input and projects to the orbitofrontal cortex (not shown in this figure). **B, C:** Modifications of MacLean's schematic drawing, which placed emphasis on the medial forebrain bundle (MFB) as a major line of communication between the limbic cortex of the hypothalamus and the midbrain (262). Note the relationship between the fornix and cingulum, which become separated through the growth of the corpus callosum. **B** shows ascending pathways to the limbic cortex with emphasis on divergence of fibers from the MFB to the amygdala and septum and **C** shows descending pathways from the limbic cortex. (MT, medial thalamus; other abbreviations in **B** and **C** are listed in **A**.) **D:** Diagram to show connections made between the central gray (CG), the dorsal tegmental nucleus (DTN), the superior central nucleus (SCN), and the ventral tegmental nucleus (VTN) on the one hand, and the septal nuclei (SN) and mammillary body (MB) via the MFB on the other. The diagram also depicts the projection from the dorsal longitudinal fasciculus (DLF) from the hypothalamus to the brainstem and spinal cord, mediating sympathetic and parasympathetic and other autonomic information to these structures. (Developed from material in Isaacson RL. *The limbic system*. New York: Plenum Press, 1974; and MacLean PD. Contrasting functions of limbic and neocortical systems of the brain and their relevance to psychophysiological aspects of medicine. *Am J Med* 1958;25:611–626; Netter FH. Nervous system: anatomy and physiology. In: *CIBA collection of medical illustrations*. Vol. 1. CIBA, West Caldwell, NJ: 1983; and MacLean PD. The limbic system with respect to self- preservation and the preservation of the species. *J Nerv Ment Dis* 1958;127:1–11.)

Hypothalamus

Anatomy

The hypothalamus is a phylogenetically old part of the brain, considered essential in regulating the internal milieu. It is the diencephalic center of a group of structures forming a ring or “limbus” (border) of the medial forebrain structures around the rostral pole of the brainstem. As the ventral part of the diencephalon, the hypothalamus bounds the ventral half of the third ventricle, lying ventral to the thalamus and bounded caudally by the mesencephalon and rostrally by the laminae terminalis, the anterior commissure, and the optic chiasm. Lateral to the hypothalamus lie the optic tract, the internal capsule, and the subthalamic structures. Figure 5-11 depicts the anatomy and connectivity of the hypothalamus.

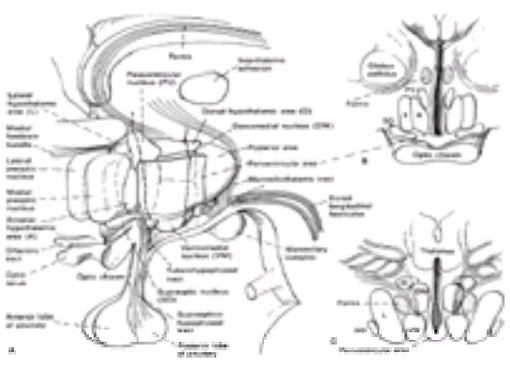

Figure 5-11. Schematic diagram of the hypothalamus. **A:** Sagittal view shows the most important nuclei and the pathways connecting the hypothalamus with the pituitary gland, fornix, brainstem, and spinal cord (dorsal longitudinal fasciculus). **B, C:** Frontal sections at sites 1 and 2 in **A** show the relationship of the various nuclei, named with abbreviations indicated in **A**. (Modified from Netter FH. Nervous system: anatomy and physiology. In: *CIBA collection of medical illustrations*. Vol. 1. West Caldwell, NJ: CIBA, 1983.)

Within the hypothalamus are three mediolaterally arranged parts: the periventricular zone, the medial hypothalamus, and the lateral hypothalamus. The periventricular zone is a thin sheet adjacent to the third ventricle. The medial hypothalamus contains various nuclear regions that control sympathetic and parasympathetic function. The ventromedial part of the hypothalamus gives rise to the hypophyseal stalk (infundibulum with the adenohypophysis and neurohypophysis). The lateral hypothalamus does not contain distinct nuclear regions. Instead, neurons disperse throughout it and surround the medial forebrain bundle (97,98).

The circuits that involve the hypothalamus include major pathways, such as the mammillothalamic tract and medial forebrain bundle in the lateral hypothalamic region, the fornix, and the stria terminalis (see Fig. 5-10). These fiber pathways interconnect the hypothalamus with limbic forebrain structures, such as the cingulate cortex, hippocampus and hippocampal gyrus, the amygdala, and the septal region. The hypothalamic region receives ascending input through the dorsal longitudinal fasciculus formed by fibers connecting the hypothalamus with the periaqueductal central gray and the dorsal tegmental nucleus of the midbrain, as well as visceral, sensory, and somatic motor autonomic centers in the caudal medulla (e.g., nucleus tractus solitarius and the dorsal motor nucleus of the vagus). The hypothalamic distribution of this pathway is mainly to the supramammillary, premammillary, and posterior hypothalamic group of cells, and the caudal end of the lateral

hypothalamus. The mammillary peduncle also carries ascending fibers from the caudal mesencephalic area via the medial forebrain bundle of the hypothalamus. In addition, more diffuse reticulohypothalamic connections exist by which activity of the brainstem reticular formation can influence hypothalamic and limbic forebrain function.

Neuroanatomic (101,102,103,104 and 105) and physiologic (106,107,108,109,110 and 111) tract tracing experiments have demonstrated a direct bilateral pathway from the spinal cord to the medial and lateral divisions of the hypothalamus (112,113). In rats, this spinohypothalamic tract (SHT) is almost the same size as the STT (102). The existence of the SHT in cats (114) and monkeys (115) also has been demonstrated. Within the spinal cord, the majority of cell bodies that give rise to the SHT are located in the marginal zone (lamina I), the lateral reticular area (lamina V), and the area around of the central canal (lamina X). Many SHT neurons provide collateral axons to structures in the brainstem and thalamus (92,109). A direct pathway from the medullary dorsal horn (nucleus caudalis) to the hypothalamus also has been demonstrated (113,116,117). Giesler et al. (112) have reviewed convincing evidence for a role of each of these spinal cord areas in nociception. Because of the anatomic connectivity and physiologic characteristics of SHT neurons, these authors suggest that the SHT has a role in emotional, autonomic, and neuroendocrine responses to nociceptive stimuli.

Physiology

Most SHT neurons in the cervical, lumbar, and sacral spinal cord respond preferentially or exclusively to noxious mechanical and thermal stimulation (107). SHT neurons in the sacral segments of the spinal cord also may respond to visceral stimulation (110,111). Approximately one-half of the SHT neurons recorded in the cervical spinal cord of rats have large or complex (e.g., discontinuous) receptive fields (106,107). In the lumbar spinal cord, however, all SHT neurons have small receptive fields incorporating only the ipsilateral hindpaw (118). SHT neurons encode the intensity of visceral stimulation (colorectal distension and vaginal distension) best described by a power function (111). Within the hypothalamus, some neurons respond to visceral and somatosensory (noxious and nonnoxious) stimuli (98). These neurons have bilateral receptive fields and may respond to multisensory input. Thus, it appears that the hypothalamus is not organized to provide spatial, temporal, or modality-specific information. The short- and long-latency hypothalamic responses to somatic stimulation suggest a rapidly conducting input (perhaps via the SHT) as well as a presumably polysynaptic input (119).

A few studies have shown that some hypothalamic neurons respond to nociceptive stimulation of the teeth and skin. Electrical tooth pulp stimulation activates some neurons in the lateral (120,121), anterior, posterior, and tuberal hypothalamus (122,123). Noxious mechanical stimulation of the skin also can activate some neurons in the paraventricular nucleus (124), lateral area (121,125), supraoptic area (126), preoptic area, and anterior hypothalamus (127). Sidar and Oomura (128) demonstrated that noxious radiant heat applied to the scrotum of rats was capable of inhibiting 69% of those lateral hypothalamic neurons that also were sensitive to glucose. These glucose-sensitive, nociceptive neurons were inhibited in a stimulus-dependent manner. Because all of these experiments have used anesthetized preparations, how the responsiveness of nociceptive hypothalamic neurons relates to nocifensive behavior remains unknown. Further quantitative investigations that study the response properties of hypothalamic neurons to nociceptive stimuli and that correlate these responses to behavioral indices of pain are warranted.

Lesion Studies

Electrolytic lesions of the hypothalamic periventricular nucleus (129) and posteromedial nucleus (130,131) have provided some relief for patients with cancer pain (see Chapter 108).

Amygdala

In primates, the amygdala occupies a large portion of the medial temporal lobe. The amygdala is subdivided into several distinct groups of nuclei, each having its own unique cytoarchitecture, afferent and efferent patterns, and histochemistry. The central nucleus of the amygdala (CEA) has received the most attention with regard to pain and nociception and is discussed in detail here.

Anatomy

The CEA is located in the caudal portion of the amygdala. It extends laterally to the external capsule and medially to the medial nucleus of the amygdala. The CEA can be separated into two divisions: the medial division, with small to medium-sized neurons; and the lateral division. In addition to receiving many intrinsic afferent projections from other nuclei of the amygdala, the CEA receives afferent input from the hypothalamus and thalamus. Anatomic studies have demonstrated that neurons in the lateral parabrachial area that receive spinal input project directly to the CEA (132,133,134,135 and 136).

Physiology and Behavior

Electrophysiologic studies have shown that some nociceptive neurons in the lateral parabrachial region can be antidromically activated by electrical stimulation of the CEA (137). In anesthetized rats, the activity of a large proportion (77%) of neurons in the CEA is altered by noxious mechanical and thermal stimulation of the skin (Fig. 5-12) (137). Many neurons in the lateral nucleus of the amygdala also can be activated by noxious electrical stimulation (138). CEA neurons have large cutaneous receptive fields, which suggests that the amygdala is not involved with the precise localization of noxious stimuli (137). On the other hand, the ability of CEA neurons to encode noxious stimulus intensity suggests that the amygdala may be involved in the intensive aspect of the sensory-discriminative dimension of pain.

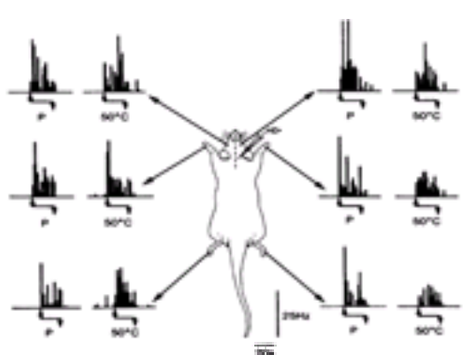

Figure 5-12. Response of a nociceptive-specific neuron located in the rostral lateral capsular subdivision of the nucleus centralis of the amygdala, with a very low spontaneous discharge (<0.1 Hz) and large receptive field. Thermal (50°C) and mechanical stimuli (P, pinch) were applied (duration between the two arrows) to the four paws and the face. (Reprinted from Bernard JF, Huang GF, Besson JM. Nucleus centralis of the amygdala and the globus pallidus ventralis: electrophysiological evidence for an involvement in pain processes. *J Neurophysiol* 1992;68:551–569, with permission.)

Although endogenous opioids play many roles in the central nervous system, the abundance of opiate receptors in the amygdala (139) suggests a role for the amygdala in pain. However, the reported effects of opiate injection in the amygdala on pain reactivity are equivocal. The injection of morphine or an enkephalinase inhibitor in the CEA has no effect on pain behavior when measured by the tail-flick and hot-plate tests (140,141 and 142). But supraspinal pain tests indicate that the amygdala may have a role in pain behavior. After bilateral amygdalar lesions, several behavioral effects occur, including (a) increased vocalization and jump thresholds, (b) apparent decreased pain sensation caused by trigeminal neuralgia, (c) reduced localization of painful electrical stimuli, (d) decreased aggressive behavior directed toward a noxious stimulus, and (e) reduced morphine- and stress-induced analgesia (140,143,144,145,146,147,148 and 149). Microinjection of neurotensin or an enkephalinase inhibitor in the CEA also results in analgesia as measured by the latency to paw lick and jump in response to a thermal stimulus (142,150).

Cingulate Cortex

Anatomy

The anterior cingulate cortex participates in motor, autonomic, and affective behaviors. It has attracted attention for its possible role in pain and nociception. This area of the limbic system is characterized by a high concentration of opioid receptors (151). Moreover, the anterior cingulate cortex receives direct input from several thalamic nuclei (e.g., nucleus parafasicularis, centrolateral nucleus, ventromedial nucleus, and Sm) known to process nociceptive information (152).

Physiology and Behavior

In the anterior cingulate cortex (area 24) of the rabbit, approximately 28%, 42%, and 19% of the tested neurons responded to noxious electrical, mechanical, and thermal stimuli, respectively (Fig. 5-13) (153). Many area 24 neurons that are responsive to noxious thermal stimuli also are activated by noxious mechanical stimuli. Nociceptive neurons in this area of the brain have bilateral, broad, mechanical receptive fields: In 12 of 15 tested neurons, noxious mechanical stimuli anywhere on the dorsal surface of the body elicited a response. These neurons apparently do not provide information pertaining to stimulus localization. In addition to noxious cutaneous stimuli, visceral stimulation delivered by colorectal distension can activate neurons in the anterior cingulate cortex of rats (154). In human subjects undergoing surgery for epilepsy, laser-evoked potentials are maximal in amplitude over area 24 (155).

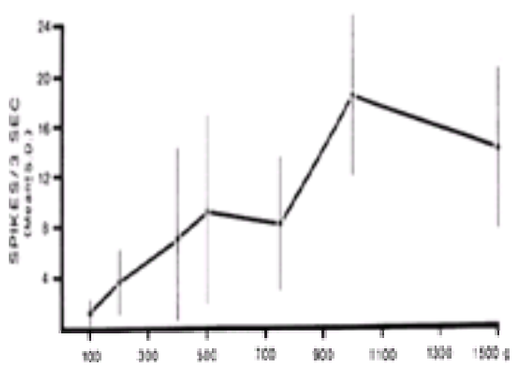

Figure 5-13. Responses to a graded series of mechanical stimuli for five units. The response was calculated by subtracting the average baseline activity previous to the stimulus from 3 seconds of the response. The mean value for each stimulus amplitude was calculated for each unit and the mean plus or minus the standard deviation (SD) calculated for all units. (Reprinted from Sikes RW, Vogt BA. Nociceptive neurons in area 24 of rabbit cingulate cortex. *J Neurophysiol* 1992; 68:1720–1732, with permission.)

Numerous studies show that lesions of the cingulate gyrus can decrease pain sensitivity. In the cat, bilateral destruction of the cingulate gyrus raised the escape threshold to electrical stimulation of the teeth (156). In the rat, an injection of local anesthetic in the cingulum bundle resulted in analgesia as measured by the formalin test (157) and reduced autotomy caused by a sciatic-saphenous nerve ligation (158). Pain arising from intractable cancer and reflex sympathetic dystrophy has diminished in human subjects after lesions of the cingulate gyrus (159,160), and electrical stimulation of the cingulate gyrus has resulted in a contralateral pain sensation in one patient (161). Devinsky et al. (152) hypothesize that the anterior cingulate cortex may participate in several aspects of pain, including the (a) affective nature of noxious stimuli, (b) motor response to noxious stimuli, and (c) learning associated with predicting and avoiding noxious stimuli.

Blood flow to the anterior cingulate cortex is increased by nonnoxious and noxious stimulation. However, numerous brain imaging studies have shown that the anterior cingulate area is one of the few supraspinal structures that consistently exhibits a significant increase in blood flow in response to noxious stimulation compared to that evoked by nonnoxious stimulation (Table 5-1). Noxious cutaneous thermal stimulation and intradermal chemical (capsaicin) administration result in a significant increase in blood flow to the anterior cingulate gyrus (162). Although it is possible that the alterations in anterior cingulate cortical blood flow evoked by noxious stimuli may be because of nonspecific attentional mechanisms, Derbyshire et al. (163) have shown a minimal overlap in the cingulate cortical area activated during an attentional-cognitive task (Stroop interference task) and noxious thermal stimuli.

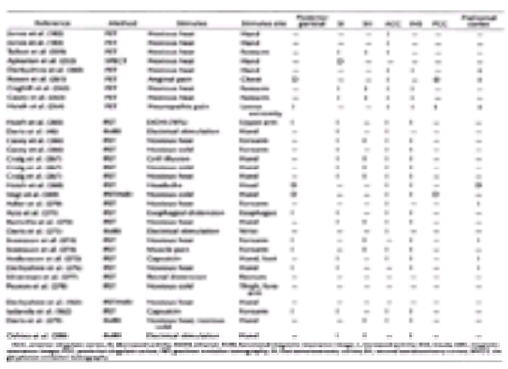

TABLE 5-1. Cortical areas activated by noxious cutaneous and visceral stimulation

Basal Ganglia

The role of the basal ganglia in movement has been studied for several decades. The functional organization and results from clinical studies suggest additional roles for the basal ganglia in higher order cognitive behaviors and sensory processes. Although it has been known since the 1950s that neurons within the basal ganglia may respond to visual, auditory, and somatosensory stimuli, some electrophysiologic, pharmacologic, behavioral, and clinical studies have implicated the basal ganglia in various dimensions of the pain experience (34).

Anatomy

The basal ganglia include a number of interconnected subcortical nuclei, including the caudate nucleus, putamen, globus pallidus (GP), substantia nigra, and subthalamic nucleus. The caudate nucleus and putamen collectively are known as the *neostriatum* or *striatum*. The striatum receives input primarily from the cerebral cortex, intralaminar nuclei of the thalamus, and substantia nigra pars compacta and projects to the GP. Efferents from the GP include those to the substantia nigra pars reticulata and thalamus (ventral anterior and VL nuclei). The substantia nigra pars reticulata also projects to ventral anterior and VL nuclei and has additional descending projections to the SC and pedunculopontine tegmental nucleus. The subthalamic nucleus receives input primarily from the cerebral cortex and GP and projects to the substantia nigra and back to the GP. Parent and Hazrati (164,165) provide an extensive review of the afferent and efferent pathways of the basal ganglia. Nociceptive information may reach the basal ganglia through several convergent pathways, including the cerebral cortex, medial and posterior thalamus, amygdala, parabrachial nucleus, and dorsal raphe nucleus (34). Direct spinostriatal and spinopallidal pathways may provide an additional source of nociceptive input to basal ganglia structures (105,115).

Physiology and Behavior

Although many neurons in the basal ganglia respond to low-intensity, nonnoxious, cutaneous stimulation, some neurons within the caudate nucleus, putamen, GP, and substantia nigra respond preferentially or exclusively to noxious thermal or mechanical stimulation (34). In rats and cats, a high proportion (44% to 97%) of the caudate-putamen (CPu) and GP neurons have been classified as nociceptive (33,166,167 and 168). Many of these nociceptive neurons are capable of encoding

noxious mechanical and thermal stimulus intensity (Fig. 5-14). The majority of nociceptive neurons in all basal ganglia structures have large receptive fields that may include the whole body (33,138,166,168,169,170 and 171), but orofacial structures appear to predominate within the receptive fields of CPu and GP nociceptive neurons (33,172,173,174 and 175).

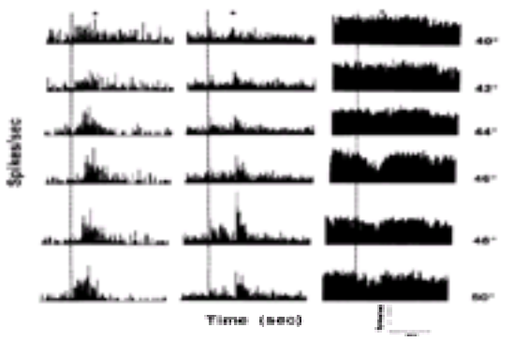

Figure 5-14. Thermal stimulus response functions of caudate-putamen (CPu) and globus pallidus (GP) neurons. The discharge frequency of some thermoreceptive CPu and GP neurons increased during the plateau stimulus temperature **(A)** while that of other neurons increased during the phasic rise, plateau, and phasic decrease in stimulus temperature **(B)**. Other neurons responded with a decrease in discharge frequency during the plateau stimulus phase **(C)**. The vertical dashes indicate the start of the stimulus increase. The down arrow indicates the start of the return of the stimulus to the baseline temperature of 38°C. The vertical scale bar represents 8, 40, and 32 spikes per sec in **A**, **B**, and **C**, respectively; horizontal scale bar represents 5 seconds in all figures. (Reprinted from Chudler EH. Response properties of neurons in the caudate-putamen and globus pallidus to noxious and non-noxious thermal stimulation in anesthetized rats. *Brain Res* 1998;812:283–288, with permission.)

Microinjection of opioid and dopaminergic agents in the CPu, GP, and SN have mixed effects on nociceptive behaviors (34). Administration of morphine in the GP and SN may produce dose-dependent, naloxone-reversible analgesia in rats as measured using the tail-flick test (176,177). On the other hand, intrastriatal morphine and beta-endorphin injections do not raise reflexive pain thresholds consistently. In primates, electrical stimulation of the caudate nucleus alters escape force without affecting escape latency or the number of escapes to electrical stimulation of the skin (178). In humans, electrical stimulation of the caudate nucleus can reduce chronic pain (179). Systemic administration of levodopa, the precursor of dopamine, has proven effective in relieving pain caused by diabetic polyneuropathy (180) and Parkinsonism (181), but the mechanisms responsible for the pain relief are unknown.

Brain imaging methodologies show that blood flow within several basal ganglia structures changes after experimentally induced pain and during several clinical pain states. Positron emission tomography studies have shown that noxious thermal stimulation of the skin (182,183) and an intradermal injection of capsaicin (162) increase blood flow to the putamen or GP, or both. Patients with pain caused by fibromyalgia and headache also show changes in blood flow to the caudate nucleus and putamen (184,185 and 186). In rats, neuropathic pain produced by a chronic constriction injury of the sciatic nerve produces an increase in glucose utilization within the CPu (187).

Several groups of patients with clinical conditions that affect the basal ganglia have been studied with regard to alterations in somatosensory function. A large proportion of patients with Parkinson's disease has sensory abnormalities, including pain. This pain may be contralateral to the side affected by motor tremor and may appear before the onset of motor symptoms. Although clinical pain testing of patients with Parkinson's disease may fail to uncover deficits in pain sensibility, careful psychophysical experimentation has revealed deficits in pain threshold and tolerance (188,189). Other neurologic conditions that affect the basal ganglia (i.e., neuroleptic-induced extrapyramidal syndrome, Huntington's disease, inherited peripheral neuropathy with extrapyramidal symptoms, torticollis, and “restless legs and pain toes”) also may present with alterations in pain perception (34,190,191).

These clinical and experimental data led Chudler and Dong (34) to hypothesize that the basal ganglia may play a role in the cognitive, motivational-affective, and sensory-discriminative dimensions of pain and participate in the motor response evoked by noxious stimuli and modulation of pain. Further experimentation with animal models of basal ganglia disease and human subjects afflicted with basal ganglia disease will help clarify the role of these areas in pain and nociception.

Cerebral Cortex

Anatomy

The VB thalamus and parts of the paleothalamus connect to the cerebral cortex by ascending (corticopetal) and descending (corticofugal) projections. The thalamus sends sensory input to the SI and SII cortices. The SI is located on the postcentral gyrus and extends from the longitudinal cerebral fissure superiorly to the lateral sulcus below (Fig. 5-15). The SII cortex is located on the superior bank of the lateral sulcus. Two other areas of the parietal lobe implicated in the processing of nociceptive information are the retroinsular cortex (Ri) and area 7b. Some electrophysiologic and brain imaging studies provide strong evidence that areas of the frontal and cingulate cortices play a role in the emotional dimension of pain. The thalamic Sm projects to the orbitofrontal cortex, which sends afferents to the cingulate gyrus. Gingold (192) used combined anterograde and retrograde tracing methods to show that the SI receives nociceptive information via a spinothalamocortical pathway through the VPL, VPI, and CL nuclei of the thalamus. Other work with these anatomic techniques indicates that nociceptive information from the spinal cord is relayed to the SII via the VPI, VPL, PO, and CL nuclei (193). Corticofugal afferents from these areas terminate in various thalamic nuclei and contribute to corticobulbar and corticospinal descending systems. Friedman et al. (37) have proposed that tactile learning and memory are mediated by serial processing of information from the SI to SII cortexes to the temporal lobe. Moreover, Pons et al. (194,195) have provided physiologic evidence for serial processing of somatosensory information in the SI and SII cortices. Stevens et al. (193) postulate that the STT may reach the SII directly through the VPI, VPL, and PO nuclei of the thalamus. Although it has not been demonstrated that learning and memory of painful events follow these pathways, Lenz et al. (196) hypothesize that a thalamic-parasylvian cortical-limbic pathway may be involved in some affective component of painful memories.

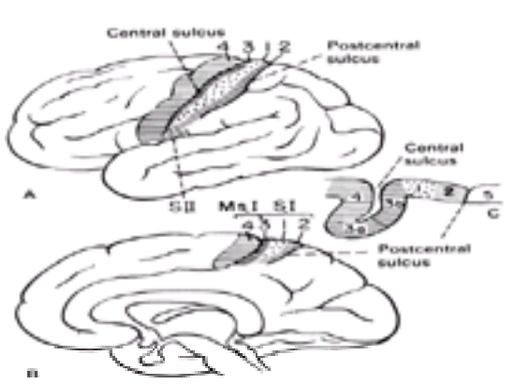

Figure 5-15. Diagrams of superolateral **(A)** and medial **(B)** surfaces of the human cerebral hemisphere to depict the cytoarchitectonic areas of the first (SI) and second (SII) somatosensory areas of the cerebral cortex. **C:** Sagittal section to show the relationship of the four areas of SI. Area 3 of SI extends through the floor of the central sulcus, where it becomes continuous with the primary motor cortex (area 4). This transitional zone is called *3a*, and the main part of area 3 is called *3b*. Area 2 extends along the posterior wall of the postcentral gyrus to the postcentral sulcus, which separates SI anteriorly from areas 5 and 7 in the superior parietal lobule posteriorly. (MsI, primary motor cortex.) (Modified from Jones EG, Friedman DP. Projection pattern of functional components of the thalamic ventrobasal complex in monkey somatosensory cortex. *J Neurophysiol* 1982;48:521–544; and Brodmann K. Dergleichende lokaliastionstehre der grosshirnde. In: *Ihren prinzipien dargestellt auf grund des zellendaues*. Leipzig: Barth, 1909.)

First Somatosensory Cortex (SI)

The SI consists of three distinct cytoarchitectonic subdivisions: areas 3, 1, and 2 (see Fig. 5-15). Area 3 is further subdivided into area 3a that is adjacent to the motor cortex (area 4) and area 3b. Posterior to 3b and oriented longitudinally along the crest of the postcentral gyrus is area 1, and behind this is area 2, which extends along the posterior wall of the postcentral gyrus to the postcentral sulcus. Neurons in SI are organized somatotopically: Each area of the body is represented in distinct, well-defined loci within the SI (197) (Fig. 5-16). Figure 5-16 illustrates that certain areas of the body have larger cortical surface area representation than other body parts. For example, the face and hands occupy more cortical area than the trunk and legs. This seemingly distorted map of the body on the cortical surface correlates with the peripheral density of somatosensory receptors in various body parts. Correlations between peripheral nociceptor density and cortical surface area have not been demonstrated.

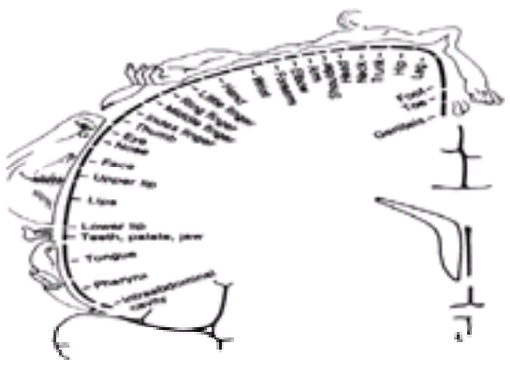

Figure 5-16. Somatotopic pattern of representation in the human first somatosensory (SI) cortex. Differences in relative size of body parts were determined by electrical stimulation of the SI cortex. (Reprinted from Penfield W, Rasmussen T. *The cerebral cortex of man*. New York: Macmillan, 1950, with permission.)

Lesion Studies

In the early 1900s, Head and Holmes (198) and Head (199) examined patients with cortical injury, disease, or tumors. The persistence in the ability to appreciate pain in this population of patients led these authors to conclude that the cerebral cortex has a minimal role in pain perception. Nevertheless, many lesions of the SI do alter the ability to detect and discriminate painful stimuli and also may alleviate phantom limb pain and central pain syndromes (200,201). Sweet (65) cites studies in which patients underwent resection of the postcentral gyrus related to the painful site. Nearly 80% of the patients derived early relief, but the relief persisted in fewer than 25% of the cases. A widely cited report in support of the role of the SI in pain was published by Marshall in 1951 (202). Using rigid criteria, he selected patients who had penetrating brain wounds with permanent severe sensory loss. He examined these patients meticulously 5 years after their injuries, at which time the sensory findings were constant. All 11 patients had superficial wounds of the parietal cortex that produced contralateral, highly localized loss of superficial pain. Loss of deep pain was observed in some patients. Tactile sensation was markedly or moderately reduced.

Experimental lesions in nonhuman primates provide additional support for a role of the SI in the detection and discrimination of noxious stimuli. Impairments in the ability to localize or discriminate noxious mechanical and thermal stimuli have been demonstrated in monkeys with lesions of the SI (200,203,204). Kenshalo and Willis (200) (Fig. 5-17) have demonstrated that bilateral lesions of the SI produce deficits in the ability of trained monkeys to detect and discriminate noxious thermal stimuli. Because the monkeys' ability to detect cold and visual stimuli was unimpaired, the effects of the lesion were probably not the result of alterations in motor, attentional, or motivational factors. Recovery in the ability to detect and discriminate noxious stimuli occurred after approximately 24 weeks.

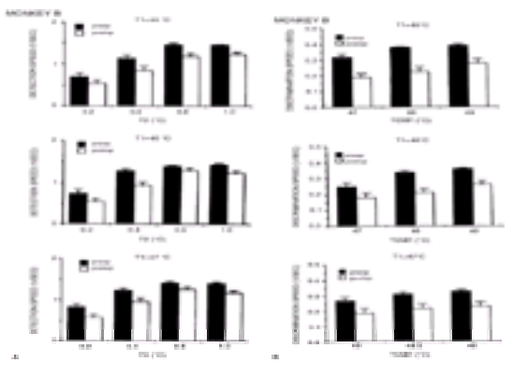

Figure 5-17. **A:** Effect of bilateral first somatosensory cortex (SI) lesions on the speed of the second temperature shift (T2) detection of noxious thermal stimuli is depicted for the first temperature change from a baseline of 38°C (T1) intensities of 45°C, 46°C, and 47°C. **B:** Effect of bilateral SI cortex lesions on discrimination of noxious thermal stimuli. The monkey's preoperative (preop) performance for 3 weeks is shown by the filled bars and postoperative (postop) performance for 3 weeks by the open bars. Error bars represent the standard error of the mean. (Reprinted from Kenshalo DR Jr, Willis WD Jr. The role of the cerebral cortex in pain sensation. In: Peters A, ed. *Cerebral cortex*. New York: Plenum Publishing 1991;9:153–212, with permission.)

Electrical Stimulation

Early experiments in which electrical stimulation was used to stimulate the exposed cerebral cortex of awake patients undergoing brain surgery failed to produce reports of pain (205,206). Although sensations, such as tingling and numbness, were reported, pain was rarely evoked by electrical stimuli. Sweet (65) has summarized this work, which led to the view that thalamic circuits, rather than the cerebral cortex, subserved pain sensation. Careful review of the literature, however, indicates that electrical stimulation of the SI can elicit pain (59,63,200). Moreover, excitation of the SI during epileptic seizure may result in an aura of pain (200). Young and Blume (207) reported that approximately 3% of those patients with an epileptic focus over the SI have painful seizures. Patients report such events as burning, tingling, shooting, cramping, and throbbing.

Electrophysiology

Evoked potential methodologies have been used since the 1960s in attempts to provide an objective measure of the cortical response to pain (208,209). The somatosensory evoked potential represents a time-locked alteration in the electroencephalogram produced by cutaneous stimulation. Technologies to detect magnetic fields originating from the brain also have afforded the opportunity to study pain-evoked responses from the cerebral cortex. In most cases, an averaged response evoked by multiple trials is used in the final analysis. Noxious thermal, mechanical, electrical, and chemical stimuli all have been used to generate evoked potentials in human subjects. Most studies have attempted to correlate the amplitude or latency of near-field components of the evoked potential with noxious stimulus intensity and pain report.

The tooth pulp, a structure comprised almost entirely of unmyelinated C and small myelinated A-d nerve fibers, was one of the first structures used to elicit pain-evoked potentials. Electrical stimulation of the tooth pulp in humans results in pain and a highly reliable series of positive and negative waveforms (208). Increases in stimulus intensity applied to the tooth result in increases in the pain report and in the amplitude of the evoked potential. Tooth pulp–evoked potentials also have been recorded over the SI of nonhuman primates (70,210,211).

Despite the positive correlation of evoked potential amplitude with pain report, several methodologic problems cloud the interpretation of the pain-evoked potential

studies. First, increases in stimulus intensity may result in the recruitment of additional nonnociceptive afferents in the nerve volley. This is especially true in studies using mechanical and electrical stimulation. Therefore, increases in evoked potential amplitude may reflect the recruitment of additional nonnociceptive neural activity rather than nociceptive activity. Second, the generator site of the evoked potentials elicited by noxious stimuli is not well understood. Often, only an electrode located at the vertex is used to record changes in the activity. Because the neural generator of the vertex potential is unclear, the origin of this waveform remains unknown. Magnetoencephalographic studies have indicated that painful electrical stimulation causes bilateral activation of the SI and SII cortices that may result in a maximal, electrically recorded, evoked potential at vertex (212). Other reports have attempted to map laser heat-evoked potentials in attempts to isolate the generator of pain-evoked potentials (213,214). Third, it is possible to dissociate the pain report and evoked potential amplitude. Chapman et al. (215) and Jacobson et al. (216) reported that increases in stimulus rate resulted in a reduction in the amplitude of the tooth pulp–evoked potential, but no change in pain report. Pain perception and evoked potential amplitude also are differentially affected by benzodiazepines (217). Small doses of benzodiazepine, which reduce anxiety without changing pain report, significantly reduce the amplitude of carbon dioxide laser–evoked potentials. Furthermore, hypnosis that reduces pain report has no effect on the amplitude of evoked potentials elicited by electrical stimulation (218). A dissociation between laser stimulus intensity, pain report, and the vertex response to noxious thermal stimulation has also been reported (219). These considerations indicate that evoked potentials elicited by noxious stimuli may reflect emotional or motivational components of pain, not just the sensory-discrimination aspects of pain.

Extracellular single-unit recording from the SI in rats, cats, and monkeys has provided convincing evidence that the SI plays a role in the sensory-discriminative aspect of pain. Noxious electrical and chemical tooth pulp stimulation (211,220,221) and noxious mechanical and thermal stimuli all are capable of preferentially or exclusively activating SI neurons (33,222,223). These nociceptive SI neurons have receptive fields that follow the same somatotopic organization of nonnociceptive neurons. Many nociceptive SI neurons in awake monkeys are capable of encoding the intensity of noxious tooth pulp stimuli (221) and noxious thermal stimuli applied to the face (Fig. 5-18) (223). Moreover, the discharge frequency of some nociceptive SI neurons is correlated to the perceived intensity of noxious stimuli (221,223). Chudler et al. (224) found that alterations in the interstimulus interval, which produced changes in the intensity of pain sensation, also affected the discharge rate of nociceptive SI neurons (Fig. 5-19). SI neurons in the primate (225) and rat (226) also can be activated by noxious stimulation of the viscera (bladder, colon, and esophagus).

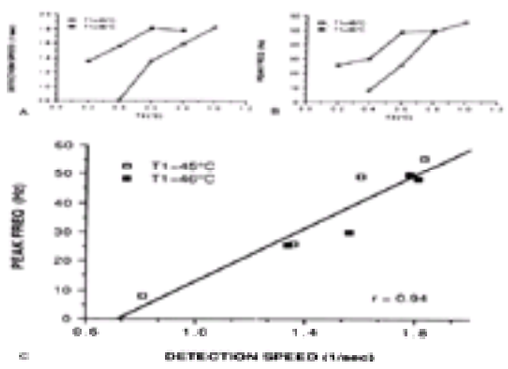

Figure 5-18. **A:** Average detection speed plotted as a function of the second temperature shift (T2) stimulus intensity from a first temperature change from a baseline of 38°C (T1) of either 45°C or 46°C. **B:** Peak frequency of neuronal discharge of a first somatosensory cortex neuron plotted as a function of T2 intensity for either a 45°C or 46°C T1. The peak frequency was determined from peristimulus time histograms (200-millisecond bin width) after the onset of T2 and before the monkey released the button. Each point represents the average of four trials. **C:** Peak frequency plotted as a function of detection speed for all T2 stimuli. The solid line represents the linear regression of the equation fit to the scatter plot. (r, regression coefficient.) (Reprinted from Kenshalo DR Jr, Chudler EH, Anton F, et al. SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. *Brain Res* 1988; 454:378–382, with permission.)

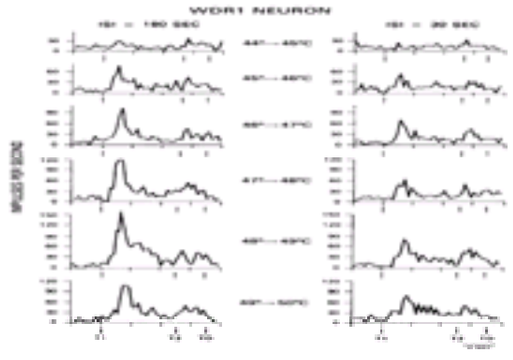

Figure 5-19. Averaged peristimulus time histograms of wide-dynamic-range type 1 (WDR1) neurons in first somatosensory cortex obtained when the interstimulus interval (ISI) was 180 seconds and 30 seconds. Each histogram was constructed by averaging two trials for each first temperature change from a baseline of 38°C (T1) and second temperature shift (T2) temperature for all neurons. Therefore, 28 pairs of T1 and T2 stimuli comprise each histogram. Numbers in the middle of the figure refer to the initial T1 and final T2 temperatures presented. Significant suppression of the T1 neuronal response observed within activity elicited with ISIs of 30 seconds is compared with that evoked when ISIs were 180 seconds (bin width, 100 milliseconds). (TD, temperature begins to return to baseline.) (Reprinted from Chudler EH, Anton F, Dubner R, et al. Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval. *J Neurophysiol* 1990;63:559–569, with permission.)

A few studies have examined the laminar distribution of nociceptive SI neurons. Kenshalo et al. (227) and Chudler et al. (224) reported that the majority of SI neurons that respond to noxious thermal stimulation of the face were located in cortical layers III and IV. In rats, however, cutaneous nociceptive neurons are located primarily in cortical layers V and VI (228,229), and visceral noxious neurons are located in layers IV and V (226).

Brain Imaging

Introduction of noninvasive brain-imaging methods has provided investigators with an additional tool to study cortical pain mechanisms (230). Several laboratories have demonstrated that activity in the SI is altered after noxious thermal, electrical, and chemical stimulation (see Table 5-1). Porro et al. (231) demonstrated that activity within the SI (and other areas) is positively correlated to the perceived intensity of noxious chemical stimulation. However, the SI is not activated consistently by noxious stimuli, and one study described a decrease in blood flow to the SI (232). Differences in stimulation procedures may partially account for the inconsistent observations that brain-imaging methods produce. It also is possible that the relatively low number and distribution of nociceptive neurons within the SI may contribute to the variable changes in cerebral blood flow after noxious stimulation. For example, SI nociceptive neurons appear to be distributed in discrete clusters scattered among nonnociceptive neurons (208,223). This arrangement of responsive neurons may impair the observation of change in blood flow using current brain-imaging methods.

A novel approach to understanding the role of the SI in nociception uses intrinsic optical signal imaging in nonhuman primates (233,234). Differences in the reflectance patterns over the anterior parietal cortex provide evidence that area 3a of the SI, not areas 3b or 1, are most important in the perceived intensity of noxious thermal stimulation. However, alterations in reflectance patterns over areas 3b and 1 after noxious thermal stimulation also suggest some interactions within SI subareas that may influence the processing of nociceptive information.

Second Somatosensory Cortex (SII)

The SII represents another complete somatotopic representation of the body within the parietal lobe. Located lateral and slightly posterior to the representation of the face in the SI cortex, the SII cortex is located on the superior bank of the Sylvian (lateral) fissure. Extracellular single-unit and evoked potential recordings from the

primate SII cortex have shown that this area of the parietal lobe is activated by noxious stimuli (210,235,236 and 237). Although the number of neurons responsive to nociceptive stimuli is small, the SII cortex participates in the encoding of noxious mechanical, thermal, and electrical stimuli. Dong et al. (237) reported that 4% of the neurons recorded from the SII/area 7b region responded exclusively to noxious mechanical stimulation and that one-half of these nociceptive neurons had bilateral receptive fields. These data agree favorably with those of Whitsel et al. (238) and Robinson and Burton (236), who also found a high percentage of SII neurons with bilateral receptive fields.

Acute Painful Stimuli

Acute painful stimuli activate the SII cortex in human subjects. Noxious electrical stimulation of the tooth pulp and painful stimulation of the nasal mucosa with humidified carbon dioxide evoke magnetic field changes that appear to originate in the SII cortex (239,240).

Electrical Stimulation

Few studies have examined sensory phenomena associated with electrical stimulation of the SII cortex. Sensations reported as quivering and unpleasant may be evoked by electrical stimulation (241), but reports of pain are rare (242). As with epileptic seizures involving the SI, abnormal electrical activity generated posterior to the SI in the SII may evoke painful sensations. Young et al. (243) and Balkan (244) described patients with painful epileptic seizures involving the SII. Salanova et al. (245) reexamined the records of 82 patients with parietal lobe epilepsy who were treated between 1929 and 1988. They reported that the most common aura produced was one of tingling or numbness. In 13 of 82 (16%) cases, however, the aura involved pain sensations. These aurae could be reproduced by electrical stimulation posterior to the SI.

Insula and Surrounding Regions

Several other regions of the parietal lobe in and around the lateral sulcus participate in the processing of nociceptive input: the insular cortex (Ri) and area 7b. The primate insula lies buried with the sylvian fissure in monkeys and humans. Ri also is found within the Sylvian fissure and is located immediately posterior to the insula. Area 7b (also known as *PF*) is located on the rostral inferior parietal lobe. These cortical areas each receive distinct thalamocortical projections and maintain extensive reciprocal corticocortical connections.

Area 7b

As indicated under Second Somatosensory Cortex, Dong et al. (237) identified a small number of neurons in the SII, area 7b region that responded to noxious mechanical stimulation. Later experiments by Dong et al. (246) extended these observations by demonstrating that some primate area 7b neurons can encode noxious thermal stimulation intensity, and that the neuronal discharge of these neurons is correlated to the perceived intensity of noxious stimulation (Fig. 5-20). Approximately 9% of the recorded neurons responded either exclusively or preferentially to noxious thermal stimuli. Of those neurons responsive to thermal stimulation, approximately 45% also were responsive to mechanical stimulation. Bilateral mechanical receptive fields were found in 40% of those neurons responsive to thermal and mechanical stimulation.

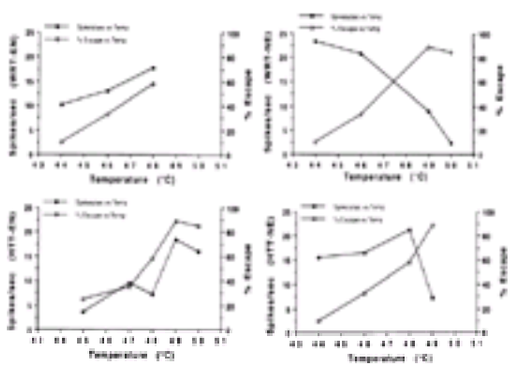

Figure 5-20. Relationships of noxious thermal stimulus intensity to the discharge frequency of wide-range thermoreceptive (WRT) and high- threshold thermoreceptive (HTT) neurons in area 7b and to escape frequency. All electrophysiologic and behavioral data illustrated were obtained from the same monkey. The mean discharge frequencies evoked during noxious plateau temperature are plotted for individual WRT and HTT neurons that did grade noxious thermal intensities (WRT-EN and HTT-EN) and that did not grade noxious thermal intensities (WRT-NE and HTT- NE). For each type of neuron, the mean discharge frequencies and mean escape frequencies (percentages) that were associated with the same thermal shifts are plotted. In these examples, note that the slopes of the stimulus intensity-discharge frequency function and stimulus intensity-percent escape function for WRT-EN and HTT-EN neurons are more alike than the slopes of the same functions for WRT-NE and HTT-NE neurons. (Temp, temperature; EN, encoding; NE, not encoding.) [Reprinted from Dong WK, Chudler EH, Sugiyama K, et al. Somatosensory multisensory and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *J Neurophysiol* 1994;72:542–564, with permission.]

Of particular interest is the response of many nociceptive area 7b neurons to multisensory stimuli (246). One-third of the thermal nociceptive area 7b neurons also were responsive to visual stimulation. The most effective visual stimuli included the approach and withdrawal of novel or threatening objects in line with the most sensitive portion of the cutaneous receptive field.

Clinical and experimental lesions of area 7b provide additional evidence for the role of area 7b in pain and nociception. Greenspan and Winfield (247) reported changes in pain perception in one patient after a tumor compressed the posterior insula and parietal operculum, but spared the postcentral gyrus (Fig. 5-21). The patient had higher mechanical and heat pain thresholds and higher cold pain tolerance levels on the side contralateral to the tumor. No changes were observed in innocuous temperature perception in this patient. Removal of the tumor and alleviation of the cortical compression resulted in improvement of the sensory phenomena. Dong et al. (248) reported similar findings in a monkey who sustained compression of posterior parietal cortex, including area 7b, the SII cortex, and insula (Fig. 5-22). This monkey showed a dramatic increase in the pain tolerance as indicated by the absence of escape to noxious thermal stimuli. However, the ability of the monkey to detect changes in thermal stimulation intensity remained unchanged.

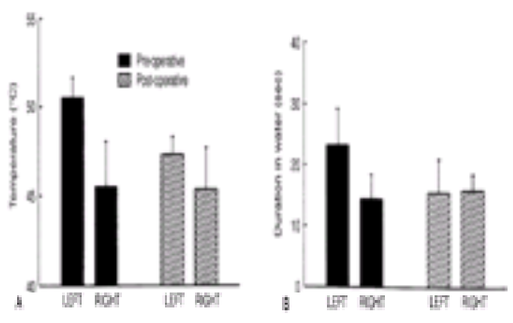

Figure 5-21. Means and standard deviations of thermal pain assessments. **A:** Heat pain thresholds based on 4 days of testing preoperatively and 4 days of testing postoperatively. **B:** Cold pain tolerance based on 4 days of testing preoperatively and 3 days of testing postoperatively. (Reprinted from Greenspan JD, Winfield JA. Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* 1992;50:29–39, with permission.)

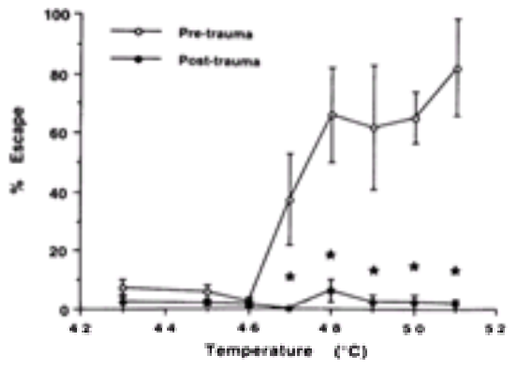

Figure 5-22. Escape frequencies to thermal stimulation of the face before and after cortical injury. Thermal shifts from an adapting temperature of 38°C were applied to the skin on the contralateral maxillary face region. The value at each thermal shift represents the mean percent escape (± SE) determined over several testing sessions. After cortical trauma, note the significant loss of sensitivity (*, $p < .05$) to noxious temperatures (47°C to 51°C) applied to the contralateral maxilla. (Reprinted from Dong WK, Hayashi T, Roberts VJ, et al. Behavioral outcome of posterior parietal cortex injury in the monkey. *Pain* 1996;64:579–587, with permission.)

Ventrolateral Orbital Cortex

Anatomy

The VLO, an area thought to be homologous with the inferomedial orbital cortex in humans (249), has interested investigators in its role in pain and nociception based on the reciprocal connections it maintains with the thalamic Sm (85,86 and 87,250,251). In addition to these thalamic connections, the VLO is reciprocally connected with the somatosensory cortex.

Physiology and Behavior

Noxious electrical stimulation of the skin and bradykinin injection significantly increase blood flow to the frontal cortex in cats (252). VLO neurons in the rat and cat respond exclusively or preferentially to noxious mechanical, visceral, and cold stimuli (253,254) (Fig. 5-23). Nociceptive VLO neurons are activated in a graded fashion to cutaneous stimuli, and all have large, whole body receptive fields. Backonja et al. (255) found that compared to sham-operated rats, rats with a loose chronic constrictive nerve injury had a greater (80% vs. 61%) proportion of VLO neurons responsive to noxious cold stimuli. Although the magnitude of the VLO neuronal response was not significantly different in these two groups of rats, VLO neurons recorded from animals with nerve ligations exhibited a longer afterdischarge after cold stimulation. VLO neurons responsive to noxious colorectal distension in rats (256) and gallbladder distension in cats have large, bilateral cutaneous receptive fields (254).

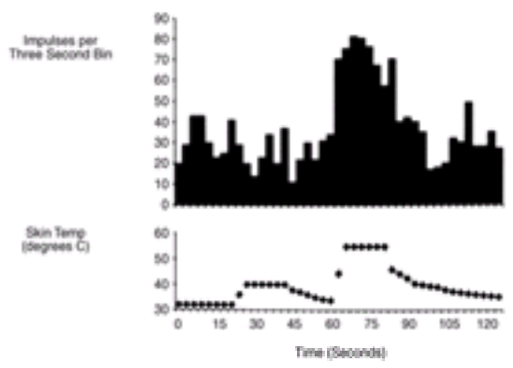

Figure 5-23. Response of a ventrolateral orbital cortex-alpha neuron to application of innocuous and noxious radiant heat pulses (40°C and 55°C) to the glabrous skin of the contralateral hind paw. (Reprinted from Snow PJ, Lumb BM, Cervero F. The representation of prolonged and intense, noxious somatic and visceral stimuli in the ventrolateral orbital cortex of the rat. *Pain* 1992;48:89–99, with permission.)

Clinical and experimental evidence suggests that the VLO may play a role in the modulation of pain. Prefrontal cortical lesions have relieved intractable pain in some cancer patients (257). More recently, Zhang et al. (258) reported that glutamate microinjections in the VLO significantly increased the rat tail-flick latency.

CONCLUSIONS

Pain is a subjective experience resulting from activity in many distinct areas of the brain. Complex patterns of activation are the reason why pain is multidimensional, including heightened emotions, increased motivational drive to reduce pain, cognitive and motoric strategies to reduce or prevent tissue damage, and memory of the sensory-discriminative and affective qualities of the painful event. Each supraspinal area plays an important role in the pain experience. The complex central processing that produces pain poses challenges to the study of supraspinal nociceptive processes and makes the treatment of chronic and acute pain difficult.

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CHAPTER 6

Psychological Aspects of Pain

C. Richard Chapman and Judith A. Turner

Pain is a complex aversive experience normally associated with tissue trauma, inflammation, or a disease process. Because it is subjective and personal, pain is inherently psychological in nature. Bonica emphasized in the 1950s that psychology is important in the study of pain, and that psychological factors exert major causal influences in a person's experience and expression of pain. In the first edition of this book (1), he wrote,

> The crucial role of psychological and environmental factors in causing pain in a significant number of patients only recently received attention. As a consequence, there has emerged a sketch plan of pain apparatus with its receptors, conducting fibers, and its standard function, which is to be applicable to all circumstances. But . . . in so doing, medicine has overlooked the fact that the activity of this apparatus is subject to a constantly changing influence of the mind.

In other words, we could not then (and cannot today) reconcile a sensory neurophysiology model of pain with the typical patient's complex presentation of pain, which is often loosely related or unrelated to tissue damage. Nearly half a century ago, Bonica had identified a problem that then bedeviled the emerging field of pain management and continues to impede our understanding of pain and its control, even now.

Today, we understand the mind to which Bonica referred is an emergent property of the higher order, self-organizing processes of the brain (1). Protection of biological integrity is normally the mind's highest priority. As Chapter 24 indicates, injury-instigated physiologic processes involving the autonomic nervous system, the hypothalamo-pituitary-adrenocortical axis, and the immune system feed into the ongoing construction of somatic consciousness. Emotional responses to and cognitive appraisals of bodily changes that such processes create thread into the fabric of pain, along with sensory awareness. Severe pain typically involves shifting one's attention away from all else to one's body, experiencing strong negative emotion, having an urge to escape injury, and mental preoccupation with the meaning of the injury or disease. Pain is both a major mechanism for biological protection and a powerful psychological experience. Severe pain takes over the mind by dominating the higher order processes of the brain and the behavior that the brain directs.

This chapter addresses the psychological nature of pain, and it offers a perspective designed to help the practicing physician better understand the psychology of pain. Its purposes are to clarify the complex, subjective nature of pain and the importance of cognitive factors in the pain experience and to lay a groundwork for understanding subsequent chapters on psychological interventions. Because the history of neuroscience has shaped the thinking of many physicians about the brain and mental functions, we begin by reviewing some of the fundamental ideas about pain that come from past thinking in neuroscience and contrast them to the perspective of cognitive-behavioral psychology.

HISTORY AND CURRENT UNDERSTANDING OF PAIN

Although all physicians feel pain, many find the diagnosis and treatment of pain states perplexing and frustrating. In some cases, the root of the difficulty is the physician's fundamental understanding of pain. Medical education and the culture of medicine impose fundamental implicit beliefs and assumptions on young health care professionals in formative stages of career development, and these beliefs become the foundation for later clinical understanding and reasoning. Sometimes, the implicit beliefs are out of date, inappropriate for the situation at hand, or just plain wrong. Most have roots in the thinking of bygone eras. This section reviews some fundamental assumptions about pain from the past and emerging assumptions in contemporary thinking, particularly those that Freeman (2) has emphasized. Its purpose is to help the physician clarify his or her reasoning about pain and its psychological aspects.

Sensory Mechanisms: Energy or Information?

Our current understanding of pain reflects the influence of two dominating metaphors, each with deep roots in history: energy and information. A metaphor is a way of describing an unknown or complex process in familiar terms. We tend to think of metaphors in terms of language, but metaphors pervade our thinking and actions as well as our language (3). They do this by governing our concepts and shaping how we view the world. Metaphors in science often play key roles in the paradigms that guide inquiry.

Metaphors, as conceptual conveniences, provide approximations rather than perfect descriptions. Sometimes in science, knowledge outgrows an instantiated metaphor, and yet the metaphor remains in the language. When this happens, the metaphor can become an impediment rather than a facilitator of learning. We suggest that this has happened in the pain field with two metaphors in particular: the energy and information metaphors.

Energy Metaphor

Because of pain's sensory qualities, many neurophysiologists and physicians think of pain as a strong sensation that forms at the point of tissue damage, makes its way to the central nervous system (CNS), and elicits higher level psychological responses. This view has roots in historical concepts of the nervous system that used an energy metaphor. Energy is a force that flows from a source or reservoir, like water under pressure, running through conduits to some end point, where its release exerts some effect. Using this metaphor, we might reason that tissue injury via heat, for example, is a stimulus in the form of energy. Transduction at the nociceptor converts the heat to neural energy (electrochemical activity), and this neural energy moves from the periphery to the first cells of spinal transmission, and from there to the CNS, where it triggers higher levels of activity.

Descartes (1596–1650) initiated these ideas in his description of the nervous system (4,5). In *Traité de l'Homme*, he indicated that sensory messages ascended to the ventricles of the brain via little strings (petit filets). He described their actions using a mechanical metaphor: Pulling at one end of a rope rings a bell at the other. A control center housing the soul (the pineal body) acted as a pump for efferent fluids that Descartes called *animal spirits*. These, he said, flowed from the ventricles through the spinal cord and out into the muscles via the nerves in response to the tugging of the little strings. He envisioned the nerves as hollow conduits.

This notion implies that some sort of efferent life force moves along neural pathways in a feed-forward manner to activate muscles, an idea that resembles the ancient Chinese notion of vital life force flowing through meridians. Descartes thought that, in humans, the soul exerted control over this flow, but in animals, which lack souls, this process must be purely mechanical. Descartes was a good enough scientist to offer a testable hypothesis. Muscles, he proposed, should shorten and thicken during contraction, increasing in volume as they fill with animal spirits. Croone (1633–1684) extended and modified this idea, asserting that two types of spirit materials had to flow together for muscle swelling to occur. A spirituous liquid from the nerve had to interact with the nourishing juice of the muscle for the muscle to swell. Swammerdam (1637–1680) demonstrated the nonviability of this hypothesis in studies of frog muscle: Contracting muscles changed shape but not size (5). Willis (1621–1675) criticized the Cartesian principles that the pineal gland is the seat of the soul and that the cerebral ventricles are the origin of animal spirits and the loci of voluntary acts. Instead, he attributed acts of will to the brain. He also rejected the idea of muscles swelling as they filled with spirit substance, and he identified

fibers that ended in muscles (6). Willis retained the notion that animal spirits flow through tubules in nerves (albeit as heat or light), but he denied that they could perpetually inflate the fibers that end in the muscles. As the seventeenth century drew to a close, the question of how the soul could activate the body remained, and so did the notion of a force flowing through nerves.

The focus shifted to electrical energy in the eighteenth century after Galvani (1737–1798) demonstrated the intrinsic electricity of nerve and muscle. He believed that an electrical fluid flowed through nerves, and eventually he came to speak of animal electricity instead of animal spirits. Galvani postulated that the brain secreted animal electricity and the nerves distributed it (5). Thus, animal spirits gave way to electrical currents, but the notion of flow remained.

Matteuchi, Du Bois-Reymond, Mueller, von Helmholtz, and others further refined the concept of electricity in the nervous system in the nineteenth century (7). Despite his careful work on the electrical properties of nerves in frog muscle and electrical fish, Matteuchi continued to argue for a mysterious nerve force that was a specific form of energy. Du Bois-Reymond rejected this notion and tried to explain neurophysiology on purely chemical and physical grounds. He discovered the injury current and the action current of muscle. Mueller introduced the idea that a given kind of stimulus in a particular sensory pathway provokes only one sensation in a given sensory modality (*Doctrine of Specific Nerve Energies*), but others quickly disproved it. Mueller's thinking led to the notion of pain as a specific modality, an assumption that survives today in the thinking of many pain researchers, even though Mueller's short-lived theory of specific nerve energies long ago fell into disrepute. von Helmholtz measured the rate of conduction in a nerve and introduced the concept of conservation of energy. Observable conduction velocities seemed to support the idea that energy moves from the periphery to the brain: But what is the source of such energy? It seemed to the nineteenth century mind that centripetal energy flow is possible only if peripheral nerves pick up energy from an external source via transduction.

Freeman (2) described the understanding that emerged at this time in this way: Nerve energies enter the body from the environment via transduction at sensory receptors, flow to the brain, and then flow back out again to the muscles. He offered this quote from Spencer (8), which seems to echo von Helmholtz's notion of conservation of energy:

> [It is] . . . an unquestionable truth that, at any moment, the existing quantity of liberated nerve-force, which in an inscrutable way produces in us the state we call feeling, must expend itself in some direction—must generate an equivalent manifestation of force somewhere . . . [A]n overflow of nerve-force, undirected by any motive, will manifestly take the most habitual routes; and, if these do not suffice, will next overflow into the less habitual ones.

Researchers were equating energy with electricity. Energy flowed from some peripheral source via neural pathways to a central reservoir in the brain and then back again to muscle.

The energy metaphor led neurophysiologists to look toward physics as a model neuroscience. It generated various hypotheses about excesses and deficiencies in energy and models of energy discharge that applied at all levels of the nervous system, from the neuron to the brain. Freud's ideas of repressed energy probably originated in this intellectual climate. Neurologists saw epileptic fits as problems of energy discharge. Eventually, as Freeman (2) has explained, the energy flow paradigm failed to account for the phenomena at hand and fell into discredit. It became clear that the synapse was not a resistance barrier and that the nervous system was not an electrical circuit. Science outgrew the energy metaphor. Like a snake shedding its old skin, it should have dropped it and moved on. But new knowledge tends to build on old, even when the old knowledge is imperfect.

It is easy to find evidence of the energy metaphor in contemporary thinking. Duthie (9), for example, offered an energy flow model for pain:

> The appreciation of pain requires that the energy of a painful stimulus be transformed by peripheral receptors into impulses which are conducted along sensory neurones to the CNS. Onward transmission to higher centres triggers the appreciation of pain. Pain may be alleviated either by impeding the transmission of impulses or by enhancing the mechanisms which modulate onward transmission.

Duthie further noted that “pain appreciation has never been localized to a particular region of the brain. The post-central gyrus and parietal operculum are both possibilities.” An intriguing aspect of the energy flow model is the implication that the energy that is pain must somehow flow to a specific region in the brain. Because of nineteenth century preoccupations with localization of brain functions, many workers assumed that pain must flow to a specific brain region. As Chapter 24 notes, this assumption (which Duthie echoes) is inconsistent with the broad base of current evidence about pain, particularly brain imaging studies of persons in pain.

The energy metaphor itself is still with us in other, more subtle ways as well. It survives in contemporary science in studies of CNS activity, for example. Electroencephalography research associates brain activity with energy fields. Evoked-potential researchers try to identify dipole sources that create specific stimulus-related energy fields. Electroencephalography researchers examine spectral power densities of various electroencephalographic frequency bands (10,11). These sorts of pursuits are wholly concerned with changes in brain energy fields. However, they place less emphasis on flow of energy than do earlier paradigms.

Information Metaphor

In 1948, Shannon, an unassuming young mathematician at Bell Labs, introduced new ideas in a technical report that many would later call the *Magna Carta of the information age* (12). His notions of information began to affect many areas of science, including the life sciences. The formal introduction of information theory (13) greatly changed thinking about neural activity. It largely replaced energy flow concepts with the notion of information moving via signal transmission through the nervous system, limited by channel capacities and degraded by entropy. Bits combine to form words, and words combine to form symbols. Early thinkers contended that individual cells could act as binary switches that make possible Boolean algebra within neural networks. Memory processes, they contended, must store and retrieve information in mathematically specifiable ways. Information theory allowed for the conceptualization of higher order entities in the form of networks. This framework gave birth to a bold new vision of computer science, beginning with von Neumann's work (14) and moving forward into artificial intelligence and the neural network modeling of today. In the biological realm, investigators have defined DNA as the basis for the transmission of genetic information, and currently some investigators are pursuing the informational codes that control memory (15).

The neural network concept grew out of Hebb's (16) notion of cell assembly. Networks are simply higher order assemblies of cell assemblies. One could think of the spinal reflex as a neural network. Imagine a boy touching a hot stove accidentally and quickly withdrawing his hand. This spinal reflex requires neither higher order levels of processing nor conscious reflection. It is an assembly of sensory neurons, spinal cord intermediary neurons, and motor neurons (and each of these groups is itself an assembly). The highly efficient neural network serves an important protective function. Of course, current thinkers postulate the existence of far more complex neural networks in the brain (17,18). Neural networks perform computations, and consequently the neural network researcher delights in the computational modeling of brain functions.

The notion of information parallels that of energy in many ways, and some writers describe information flow. However, the information metaphor is far more powerful than the concept of energy flow. The transducer of the energy metaphor becomes a feature detector in the information model. The external or somatic environment contains information, not energy. Sensory end organs detect and gather information, sending it to the CNS for processing. A collection of feature detectors can fire in synchrony, thereby defining a cell assembly that feeds forward information that provides a basis for higher order computation. The notion of synchrony reemerges at higher levels of processing under the label of *resonance* (a term that remains popular despite the lack of biological evidence for resonating circuits in the brain).

By postulating neural networks as higher level organizational entities, information theorists can extend the metaphor to account for the complexity and nonlinearity of information transmission. The information metaphor has taken root in many areas of contemporary neurophysiology, ranging from the neurochemistry of synaptic transmission to studies of sensory coding and feature extraction. It still vies with the energy metaphor on some levels, but, by and large, it dominates thinking in neurophysiology and neuropharmacology. The energy metaphor still exists in our language and often becomes entangled, quite inappropriately, with that of neural information processing. The energy assumption still dominates receptor physiology, which concerns itself with stimulus transduction. This situation demonstrates that two competing metaphors can coexist in a single field, confounding reasoning.

The contemporary neural information metaphor represents nociception as information that originates with tissue trauma (recall that feature detection and coding correspond to transduction), follows various connections, undergoes redefinition by computation at many levels, and through resonant circuits in the brain generates the awareness called *pain*. The simplest information models (which resemble the energy metaphor) hold that information must exist in the periphery as a specific code, be transmitted from point to point, and, finally, undergo interpretation in the cortex. Emmers (19), for example, contended that pain was a spike-interval coded sensory message. In his framework, which carries forward Mueller's sensory specificity ideas, the nonuniform spacing of spikes leads to the decoding of highly specific messages.

Today, many writers mix the energy and information metaphors, referring to pain as a *specific sensory modality*. Some use the term *pain* as a synonym for tissue trauma, thus implying that pain is either a specific form of energy that exists in the periphery and is relayed to the brain or a specific message code that, when interpreted within the brain, invariably results in the sensation of pain. The concept of specificity tends to constrain thinking about pain to the realm of sensory neurophysiology.

Classical Metaphors and the Psychology of Pain

It is difficult to understand the psychology of pain from a historical neuroscience perspective. The notion of something, whether energy or information, flowing from one source to another is limiting for the description of behavior. One can build a cognitive psychology on the basis of information theory, but contemporary psychology contains many different paradigms and perspectives. It is difficult to address pain behavior in the framework of classical thinking, in large part because early thinkers such as Descartes attributed willful actions to the soul, a concept often equated with the mind. As described in the following section, the Cartesian dualism of mind and body still survives in neuroscience, and this dualism is incompatible with most frameworks in contemporary psychology.

Cartesian Thinking and the Mind

The easiest way for energy flow thinkers to account for the vagaries and complexity of pain, or any other complex human experience, was to postulate that the mind exists. Through the nineteenth century, neurophysiology implicitly accepted the ideas of René Descartes and others, who in the seventeenth century construed bodily processes within the metaphor of clockwork mechanics (4,20). Descartes proclaimed that body and mind were separate entities. He saw pain as a specific modality, a straight-through sensory projection system that moved injury messages from damaged tissue to the pineal body where the mind could appreciate them. Descartes held that the awareness of pain, like awareness of other bodily sensations, must occur in a special location where the mind observes the mechanistic body, namely the pineal gland. Dennett (21) and others concerned with the nature of conscious experience have characterized this concept as the *Cartesian theater*. The mind, like a small person watching a television in the control tower of the brain, observes and interprets the array of multimodality sensory input that the body produces, and decides how to respond.

Although the notions of neural activity evolved from the flow of animal spirit energy to the transmission of information, Cartesian dualism itself went unchallenged for two centuries. Sir John Eccles, probably the last formal dualist, died near the end of the twentieth century (22), but dualistic thinking has become endemic in our culture. Descartes left as his legacy the seemingly intransigent concept of dualism: The mind and body are separate entities.

Cartesian notions have deep roots in medicine and, although almost no one now formally accepts Cartesian dualism, it still exerts a strong, albeit subtle, influence. It does so, not because people still teach it explicitly, but because it has shaped our past in subtle ways. Consider, for example, the words of nineteenth-century neurologist J. Hughlings Jackson, “The doctrine I hold is: first, that states of consciousness . . . are utterly different from nervous states; second that the two things occur together—that for every mental state there is a correlative nervous state; third, that, although things occur in parallelism, there is no interference of one with the other” (23). Jackson refused to face the challenge of bridging the mental and physical. He chose the Cartesian way out.

Jackson's generation separated the disciplines of psychiatry and neurology, a contrived distinction that profoundly affects how patients are evaluated and treated today. Thinking in this period also laid the groundwork for the assumption that the psychological aspects of pain are separate from the neurology of pain (i.e., although they may confound medical diagnosis, psychological factors cannot alter the fidelity of the sensory message itself). Thus, our heritage predisposes us to separate mind and body and to see pain as either neurologic and therefore real or psychological and therefore mental. Like a conceptual boomerang thrown away whenever found, Cartesian dualism keeps coming back.

Do alternatives to Cartesian thinking exist? Today, some advocates of the neural-activity-as-information model argue for a functionalist concept based on a computer metaphor. Put simply and in its extreme form, computer hardware is to the brain as software is to the mind. The nervous system can never be the mind, because it is only the hardware. The software, programmed by environment and culture, constitutes the mind. The computer metaphor nicely evades the assumption of a separate mind or spirit operating a mechanical brain, and yet it preserves the limiting notion of dualism. As demonstrated in the following discussion, this metaphor is fatally flawed because it cannot account for neuroplasticity and self-organization in the nervous system.

Learning and Self-Organization

New information-based frameworks are evolving that recognize and emphasize neuroplasticity: Experience can alter synaptic connections and the presumed resonant processes at higher levels. Black (24), for example, offered a cogent and elegant argument for this position. In such models, information does not simply move through a passive and mechanical nervous system, it alters the structures and functions that its processing involves. Sensory input changes the neurotransmitter signals that neurons send, the nature and number of synapses, the structures of neurons, and the neural circuits themselves. In other words, the nervous system adapts to information and changes with it. In psychological language, we say that the organism learns from experience. This perspective contends that the nervous system is the mind: Mental phenomena are not somehow disembodied or separated from the underlying physiology.

The perspective that Black (24) provided is powerful: It accounts for learning and adaptation, it allows for cognition, and it dismisses the restricting Cartesian notions of dualism and a passive (clockwork mechanics) nervous system. However, it is locked to the idea that informational messages move from sources in the environment or the body into the brain. More important, perhaps, it stops short of accounting for an important feature of the brain: self-organization.

Self-organization is the tendency for highly complex, dynamic systems (in biology and nature as a whole) to form metastable states and to accommodate new information or disturbance by adjusting those states (25). Biology offers thousands of examples for how organisms, ranging from colonies of bacteria to herds of caribou, adapt to the environment by organizing themselves as a leaderless collective. The orderly assembly of a flock of geese illustrates the idea. One can argue that crowd behavior, traffic jams, and culture itself are human aspects of this process. Nonlinear systems dynamics, as a field, lends itself nicely as a descriptive framework for this process (26,27). Researchers can characterize seemingly chaotic phenomena as complex, self-organizing systems. The amount of information one needs to describe the behavior of such a system is a measure of the system's complexity.

Several variations of this notion exist. The autopoiesis (literally, self-forming) model that Varela et al. (28) introduced described systems that (a) maintain their defining organization over time despite environmental perturbation and structural change, and (b) regenerate their components in the course of their operation. All living systems, therefore, qualify as autopoietic systems. Every system has as one of its features an observer that distinguishes between itself and others and between itself and objects in the environment. The realm or sphere in which a system exists (its environment) is its domain. Systems constantly engage in self-regulation and self-reference, within the constraints of their domains.

Nervous systems are organs of physiologic self-organization. Chapter 24 describes the participation of the autonomic nervous system in physiologic self-organization, for example. At higher levels of CNS function, other forms of self-organization occur. These include cognitive functions, such as memory, attention, thinking, and affective functions. At a still higher level, the brain produces meaning, a sense of self, and suffering. These mental components are far from mechanical functions of a passive or mechanistic nervous system; they are the constructions of an active and self-organizing brain.

It seems reasonable to assume that pain, as a complex experience, is also a component of a self-organizing organism that detects damage to its biological integrity. Put another way, each person uniquely assembles the perception of pain from his or her complex and chaotic stimulus array of sensory input, emotional arousal, awareness of the present situation, memory, prior learning history, immediate goals, and social relationships (29). This is why pain varies markedly across persons with identical tissue damage, and the same tissue damage may affect a person differently depending on immediate circumstances.

If pain is the product of self-organization processes, then the brain must actively construct the experience of pain; it does not passively register it as a preformed sensory event. The psychology of pain is, in part, about how the process of construction happens.

Summary

This brief review of metaphors for neural function reminds us that science does not hold absolute truth but rather an approximation of the truth, often framed as a familiar metaphor. A good descriptive framework for explaining how the nervous system works is still lacking. This insight has important implications for understanding the psychology of pain. Evolving concepts of the nervous system and Cartesian dualism have hampered the integration of psychology into medicine. Physicians have

tended, and still tend, to see psychological factors as concepts that belong to a mental, nonneurologic realm. It is now clear that all pain is “in the mind,” inasmuch as all pain is the complex product of brain activity. It is equally clear that the mind is a product of the brain and not a separate entity. The psychological aspects of pain are highly complex patterns of neurophysiologic phenomena, best described in language different from that used in neurophysiology.

PLACE OF PSYCHOLOGY IN SCIENCE

Psychology offers a broader language for the description of experience and behavior than neurology and neurophysiology can provide, and thus it is better suited to account for complex CNS functions and behavior. The psychological aspects of pain refer to those higher CNS levels of processing that produce the perception of pain, including the emotional and cognitive aspects of pain, and the behaviors and expressions associated with the experience of pain. The language that psychology provides allows description of higher order processes and their reciprocal interactions with the environment and development of models and theories in this more abstract framework.

Science functions according to a hierarchy of knowledge organized by levels of inquiry (30). Figure 6-1 illustrates this point. The laws of science, language, and frames of reference differ at each level. Normally, little interchange exists among scientists across levels, apart from fields like pain research that emphasize cross-disciplinary cooperation. Scientists who attempt to work on more than one level typically find that they can reason linearly within levels but not across levels. This is because, at each lower level, new entities and complexities emerge that provide the basis for the next higher level.

Figure 6-1. Levels of inquiry in science. The bold topics and the associated bidirectional arrow represent some of the topic areas that psychology as a discipline covers. The longer area, indicated at the left margin, represents the levels at which one might investigate pain.

The concept of emergence simply means that combining certain elements produces a complex system that possesses properties lacking in the individual elements and unpredictable from knowledge of the individual elements (31,32). To express this as a familiar cliché, one can say that the whole is greater than the sum of the parts. Atoms of hydrogen and atoms of oxygen at room temperature are gases, but when one combines them, the curious property of liquidity emerges. Emergent properties are just this, the spontaneous emergence of hitherto nonexistent features. The apparent intelligence of an ant hill is an emergent property of the collective. No individual ant is intelligent, and nothing known about individual ants allows prediction of the astonishing intelligence that the colony displays. The concept of emergent property helps one escape the constrained thinking of Cartesian clockwork mechanics.

The emergent properties at one level of scientific inquiry become the focus of inquiry at the next highest level (30). Interesting, unprecedented properties emerge as one goes from lower to higher levels in the hierarchy portrayed in Figure 6-1. Emergent properties often define domains of study by specifying the boundaries of a given paradigm. The researcher who attempts to explain subjective reality from the activity of neurons and circuits in the brain simply arrives at the edge of the territory. To work with subjective reality, one needs the paradigms of psychology. Curiously, workers engaged at one level of scientific inquiry tend to ignore the efforts of colleagues working at higher or lower levels and sometimes consider them misguided or busy wasting time and effort. The ultimate goal of reductionist science, of course, is to build knowledge bases at each level and then extend explanatory bridges across levels. Ideally, pain researchers recognize the importance of building knowledge and bridges at all levels.

One of the important features of psychology as a field is that it concerns itself with more than one level of scientific inquiry, as Figure 6-1 shows. For this reason alone, any attempt to stereotype what psychologists think or do misrepresents the field. Psychologists contribute to pain research at basic science levels, through the study of perceptual and motor processes, with studies of cognition and emotion, via studies of drug effects, and in clinical research studies of many kinds.

What is the nature of contemporary psychology as a field? Robins et al. (33) described the current field of psychology as the product of competition across four competing schools of thought: psychoanalytic, behavioral, neuroscientific, and cognitive. To determine the relative influence of these four schools of thought at the close of the twentieth century, Robins and colleagues looked at the subject matter of articles published in the most influential (flagship) psychology journals, the subject matter of doctoral dissertations, and the degree to which flagship publications cite articles from the major journals of each school. Their inquiry indicated that psychoanalysis has slipped from prominence and now lies outside of the mainstream of contemporary psychology. It produces few, if any, scientific papers, and workers in other areas of psychology essentially ignore it. The Robins study suggested that behaviorists, too, are on the decline. Studies of a purely behavioral nature are becoming infrequent, and behavioral principles survive because of their integration into other perspectives rather than through the momentum of purely behavioral research. This area has largely succumbed to the cognitive revolution, and much of what was once behavioral has become cognitive-behavioral. To their surprise, Robins and coworkers (33) found little evidence that the rest of psychology was paying close attention to the strong neuroscience within its midst. Although neuroscience as a whole is rising in prominence, it does so outside of the ranks of mainstream psychology, and it would seem that psychologists engaging in neuroscience are beginning to see themselves as neuroscientists rather than psychologists. The area of greatest growth in the literature, and current prominence, is cognitive psychology. To provide a snapshot of the influence of psychological factors on pain, the following sections introduce the area of cognitive psychology and describe pain within this complex framework.

COGNITIVE PSYCHOLOGY AND PAIN

The field of cognitive psychology is complex and resists straightforward definition. In the broadest sense, cognition involves the construction of reality from moment to moment. The brain seeks and processes information from the external environment and the internal environment, attempting to define and meet the needs that arise in both. Unlike lower animals, humans possess the resource of a frontal lobe, and this makes possible planning, forecasting, abstract thinking, complex judgment, and a multidimensional sense of self. Cognition, overall, is a self-organizing process that gives coherence to life and one's sense of self across external settings and across long periods.

Figure 6-2 provides a rough overview of the content of the field, dividing it into two groups of processes: perception and ratiocination. The former class comprises processes that are normally transparent (i.e., processes that are used without awareness or deliberation). The latter group contains more complex processes that are normally used intentionally. Other subdivisions of cognitive science exist, such as computer modeling of intelligent processes, knowledge engineering, and decision process research. Indeed, some areas of cognitive science lie outside of psychology (engineering, computer science). For immediate purposes, however, the field consists of processes concerned with the perception of events in the internal (bodily) and external environments, along with higher order rational processes that involve reasoning and decision making.

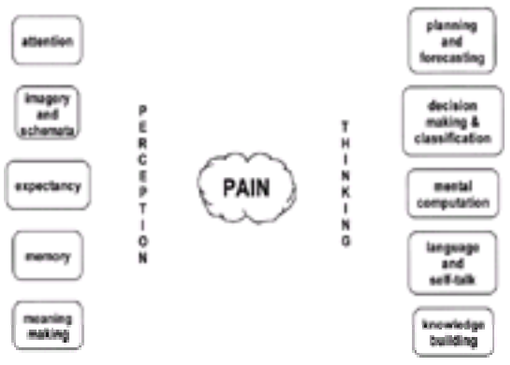

Figure 6-2. Cognitive factors influencing pain.

Classical views of cognition have held that cognition always entails conscious mental effort. Thinking, reasoning, and memory recall always occur within awareness and as a consequence of intentions that can be explained. More recent perspectives, however, emphasize the limitations of conscious processes (34,35). Rational thought, reasoning, purposeful memory recall, and the like are slow and singular processes. Much of what we do well in mental and physical performance seems to occur automatically in the service of conscious effort rather than from conscious effort itself. Greenwald (36) breaks such phenomena into two classes: (a) cognition outside of attention and (b) verbally unreportable cognition. Examples include balancing while riding a bicycle, estimating the passage of time, guessing distances, adjusting speed in a motor vehicle, keeping appointments, using rules of grammar, obeying laws, and exercising ethics. In general, unconscious cognition has severely limited analytic capability. Nonetheless, many people find that creative effort, problem solving, complex reasoning, and many other processes work best when attempted consciously and then relegated to unconscious levels. Solutions to difficult problems can then emerge as insights or “Aha!” experiences (37). Cognitive scientists now understand that mastery of knowledge, problem solving, and skilled performance always require rapid and powerful computational routines that occur at unconscious levels in the service of consciously maintained goals. These considerations indicate that cognition and conscious thinking are not one and the same. Some cognition depends on extensive unconscious, background processes.

Overview of Cognitive Processes in Pain

Attention

As Figure 6-2 shows, many cognitive factors affect the perception of pain. *Attention* refers to the selective filtering of relevant information from the internal and external environments, to the exclusion of other information. It relates closely to distraction, the blocking of certain sources of information from processing by narrowly focusing attention elsewhere. Some writers favor the spotlight metaphor for attention. Unable to process all of the information in the internal and external environments at a given moment, the brain spotlights certain things for processing and excludes others. Like someone sitting in a darkened theater, the brain only *sees* the lighted performers on the stage.

One of pain's cognitive features is that it captures and holds attention. A nonmedical writer described the qualities of severe pain as including extreme aversiveness, an ability to annihilate complex thoughts and other feelings, an ability to destroy language, and a strong resistance to objectification (38). The evolutionary purpose of this is clear: Injury threatens survival and requires adjustments in awareness and ongoing behavior. In contemporary human life, chronic pain normally provides no new information, and its domination of attention is more counterproductive than adaptive. Persons experiencing pain find it difficult to concentrate on normal work, recreation, social activities, or creative expression because the pain constantly intrudes on awareness.

Imagery

Awareness of pain is one of many types of somatic imagery. In everyday life, we think of an image as a visual experience, such as recalling a visual impression of the Mona Lisa painting. Clearly, however, we also have auditory images, such as a familiar tune or the sound of a train passing. Similarly, many can recall the feeling of a familiar low-grade pain localized in some part of their bodies. The feeling qualities of a pain, its personal and subjective nature, constitute a somatic image. Hebb (39) described the image associated with a pain as a mental representation of the actual sensory activity associated with an injurious external event. He emphasized that an image does not always correspond faithfully to an external stimulus. Visual afterimages associated with bright lights, for example, are poor representations of the lights that evoked them. Similarly, pains need not correspond accurately to features of an injurious stimulus.

Strange though it may seem, the brain does not deal with reality *per se* because it has no direct access to it. Rather, it deals with sensory images and creates models of the internal and external environments from patterns of sensory information. Ellis (40) contended that images can occur at a low level of consciousness and that they are the basic building material of concepts. To this we would add that complex images are multidimensional. When a friend's face is seen, the brain creates a visual image. Interacting with that friend involves multidimensional imagery that has an auditory dimension, sometimes an olfactory dimension, and, if we shake hands or otherwise touch the friend, a somatic dimension.

Pain, too, is an image, and it is no less complex. We construct somatic images, drawing not only on the sensory information provided via the spotlight of attention but also from memory. Autonomic nervous system arousal produces strong somatic images that contribute to emotion and feed the development of elaborate somatosensory schemata, which are complex patterns of images and associations (these are described in greater detail under Schemata).

Expectation

Because the brain constructs its reality, imagination sometimes enters into the process. Imagination often builds on expectations. Knowing, for example, that one's mother had breast cancer or that one's father died prematurely from a myocardial infarction may make a person hypervigilant for certain symptoms. The female patient who feels soreness in one breast and imagines a tumor has embellished the somatic image of the pain substantially and attached additional expectations and meanings. The hyperventilating middle-aged male patient who appears in the emergency room with severe chest pain and the conviction that he is experiencing a heart attack may have constructed a personal reality that does not fit objective reality. Physicians should keep in mind that their interactions with patients shape and embellish patients' thinking by shaping understanding and expectations.

Schemata

A schema is a normally nonconscious pattern of concepts, assumptions, images, affects, and associations that reflects a person's past experience as well as expectations for the present and future (41,42). Thinking of baseball, for example, brings a host of associations forward for most Americans: stadiums, game rules, famous players, umpires, balls, bats, and so forth. Note that thinking of baseball does not bring to mind the focused image of a particular player in a specific game engaging in a specific play. Rather, the baseball schema is a nonspecific frame of reference that assists the brain in dealing with a complex area by activating a learned network of associations. In a similar way, the patient with chronic pain, when thinking about the pain, activates a complex schema that involves past medical history, present fears, social consequences, and more. Rumelhart and colleagues (42) described the highly abstract nature of the schema concept as follows:

> Schemata are not single things. There is no representational object which is a schema. Rather schemata emerge at the moment they are needed from the interaction of large numbers of much simpler elements, all working in concert with one another. Schemata are not explicit entities, but rather are implicit in our knowledge and are created by the very environment that they are trying to interpret as it is interpreting them. . . .

Thus, a schema is the basis for screening out and organizing the stimuli surrounding an individual. It directs attention, brings images forward from memory, and organizes expectations. People categorize and evaluate their experiences through their schemata.

Some schemata are partially preformed patterns of multidimensional imagery that emerge from memory and adapt to fit the immediate environment. They are never simple memory traces. A schema can include a postural and motor pattern formed from learning processes that involved extensive repetition (e.g., riding a bicycle).

Beck and colleagues have emphasized the role of schemata in psychological dysfunction (43). A schema may be inactive for long periods, then activated by specific situations. The schemata activated in a particular situation determine the person's responses. In states of psychological dysfunction (e.g., depression), dysfunctional and idiosyncratic schemata distort patients' interpretations of specific events. In cases of severe psychopathology, patients cannot recognize that their thinking is erroneous or illogical, and their thinking may become dominated by idiosyncratic schemata. Such individuals may find it extremely difficult to concentrate on external stimuli or engage in voluntary mental activities (e.g., problem solving). A person's cognitive organization may become increasingly independent of external stimulation so that he or she is unresponsive to changes in the immediate environment.

Schemata depend heavily on memory of past experience. Presumably, the brain stores certain images and motor patterns associated with visual, auditory, proprioceptive, somatosensory, and visceral sensory awareness. As it periodically retrieves, uses, and restores this information, the brain alters and refines schemata. In other words, retrieving and using memory contents (which are more akin to networks of association than stored computer records) change those contents and associations to some degree. This idea is consistent with those of Black (24).

Repeatedly accessing and using a schema expands that schema and makes it readily available. The practice of medicine, for example, requires the formation of multiple schemata that continue to expand and develop with repeated use and degrade with disuse. Airway management for anesthesiologists is but one of many possible examples. An anesthesiologist doing airway management on a daily basis has every detail and maneuver readily available, but one who long ago left the operating room and shifted to a pain practice has to stop and recall principles and actions before managing an airway. In the same way, having a chronic disease, such as cancer or arthritis, leads patients to many repeated experiences that generate and revise schemata. Patients think, feel, and act as they do because of past experience, current appraisals and expectations, goals, and other cognitive factors.

Some schemata become learned (i.e., they survive indefinitely in memory as relatively stable working perceptual hypotheses). Learned schemata are readily available for recall. Importantly, certain sensory events or other schemata can act as triggers for a particular schema. The appearance of a trigger in the environment (any conditioned stimulus) can bring a schema to the foreground of a person's immediate awareness and experience.

The schema concept helps explain a painful, trigger-sensitive condition known as *phantom limb pain* that exists across individuals and cultures. Phantom body parts tend to appear in consciousness after a person has lost a limb. They are kinesthetically vivid realizations of a body part that is physically absent. Sometimes a phantom limb hurts, and treatment directed at the stump or administered systemically may not relieve it (44).

In a study of 68 patients with phantom limb pain, Katz and Melzack (45) found that patients had experienced various postamputation pains, all localized to the missing limbs. The patients described these pains as immediate and real, quite unlike recollection of a past pain state. The patients seemed to be reproducing or recreating the pain and not simply recalling a past event. Some of the phantom experiences involved painless experience (e.g., feeling a shoe on a missing foot) and some had multimodal sensory qualities. Katz and Melzack (45) speculated that a higher order somatosensory memory component, once formed, can be activated when only some of its elements are present in the sensory input. Their description captures the concept of schema trigger. This concept may help explain the experience of some chronic pain patients.

The schema concept underscores the fact that the human brain can generate its own patterns of awareness and imagery in the absence of extrinsic signaling. Moreover, it can store these patterns in memory, retrieve them selectively, modify them, and put them back into storage. This means that perception is more an act of constantly building and remodeling one's view of the world than it is of passively receiving and registering information. Pain, therefore, is rarely a passive experience of tissue trauma, but rather a complex construction that involves multiple cognitive dimensions.

Meaning

Meaning making is an important feature of pain schema formation. Meaning involves causal attribution and the fitting of an experience or circumstance in to a greater framework of purpose and global coherence. One way to assess meaning is through measuring sense of coherence (whether life seems to hold together, make sense). Buchi and colleagues, for example, found that low sense of coherence was associated with depression in rheumatoid arthritis patients (46).

Most people find it difficult to experience pain without attributing it to some physical cause. In cases in which patients experience severe debilitating disease, such as rheumatoid arthritis, or life-threatening disease, such as cancer, patients often need to create a framework that gives meaning to their condition. Sometimes, the schema of self (“who I am”) becomes a part of the search for meaning. Attributing pain to a physical cause sometimes proves difficult or impossible when pain is chronic and medical evaluation fails to identify pathology.

Because meaning and emotion are closely related, the search for meaning typically involves strong feelings. In dealing with physicians, some patients seek information about the cause of the painful condition or the disease, and some raise the “Why me?” question. It is important to identify and address patient questions and concerns, but the physician must recognize that he or she cannot dispense meaning. The patient must construct it. Ordinarily, the physician can only recognize and affirm the value of the process of meaning making.

In some cases, patients engage in inappropriate or maladaptive meaning making. Some tend to fit the pain into a larger life schema in which they define themselves as innocent victims in a cruel world. Sometimes, the pain is linked to rage against a spouse or parent. Negative schemata of this sort impede the patient's ability to respond to intervention or rehabilitation. In cases in which the patient appears to have created a maladaptive meaning framework for the pain, psychotherapy can sometimes help. Schemata are powerful factors in the treatment and rehabilitation of the patient with chronic pain. They are dynamic in nature, and motivated patients can change maladaptive schemata to more adaptive schemata.

Multiple Drafts

How does the brain handle variation in subjective experience across time? Dennett and Kinsborne (47) asserted that one's mental representation of reality changes constantly in a nonlinear way, relatively independent of time (i.e., instead of generating conscious representation of stimulus events in a chronologically serial fashion, the brain constantly produces revised drafts of awareness, mixing old and newer sensory, affective, and cognitive representations without particular regard for time). Put another way, elements of memory and expectation compete for, and eventually integrate with, recent sensory messages from the environment in constructing a representation of reality.

Because this is the case, schemata emerging from unconscious processing into immediate awareness need not carry the most recent information that the brain has processed. A part of the immediate representation of reality comes from memory. Some anesthesiologists have performed diagnostic nerve blocks on patients with chronic pain and found, in frustration, that the patient cannot say whether the pain has disappeared as a function of the nerve block. This is a genuine and reasonable response on the patient's part, because the awareness of pain depends on a complex cognitive process that constructs a model of reality and not simply on a sensory signal from the periphery.

The multiple drafts concept of consciousness suggests that the most remarkable feature of consciousness formation is its extraordinary plasticity. The brain creates a representation of immediate reality by interweaving records of the past with sensory input from the immediate present, and it forecasts images of the future. Far from being a passive entity that merely registers information that arrives from various sensory channels, the brain is an active, complex adaptive system that constantly simulates the world and the body in which it dwells. Nociceptive signals may trigger complex responses and schemata, leading to elaborate experiences of pain with sensory, affective, cognitive, and motor dimensions.

Patients with chronic pain sometimes develop elaborate presentations of pain that involve abnormal body postures and movements. The patient's immediate social environment can shape such behaviors, and this process may occur outside of the patient's awareness. For example, pain behaviors may increase in the presence of a physician or a spouse just as blood pressure sometimes increases when measured in a physician's office. Most physicians view a patient's description of pain as directly reflecting a sensory experience that has potentially important diagnostic value. In the case of acute pain, this view is usually appropriate. In the case of chronic pain, it is more useful to view pain as a cognitive schema that involves multiple determinants and complex patterns of association.

For a subset of patients with chronic pain, certain schemata may lead to persistent doctor shopping and an obsession with finding and eliminating the organic cause of pain. On the face of it, such patients seek help for a relentless, unpleasant sensory experience that seems to have no adequately defined origin. A complex history of suffering, discouragement, physical exhaustion, and emotional upheaval that may include mood problems or anger is often integrally associated with this

experience, as are limitations in social, role, and vocational functioning. Many such patients fail to recognize or acknowledge the other stressors and problem areas in their lives, and they focus solely on their pain as the reason for their limitations and problems. In such cases, when patient and physician alike look only to biomedical explanations and treatments for the pain, long-term pain relief from any treatment is unlikely.

Physicians have difficulties in treating patients whose pain problems are influenced in important ways by environmental factors. Today, many physicians refer difficult cases to multidisciplinary pain centers, but some still prefer to think of such pain problems as psychogenic. Historically, this means that the pain stems from deep-seated, unconscious conflicts, such as one might see with Briquet's syndrome (48,49). Labeling as psychogenic patients whose pains reflect environmental factors serves little purpose beyond protecting patients from risky intervention, and it wrongly denies the genuineness of the patients' suffering. Psychological assessment and intervention can help alleviate suffering and disability in many such patients (see Chapter 89).

How Pain Impairs Normal Cognition

In day-to-day practice, most physicians think of pain as a simple aversive sensation that a patient feels. Cognitively, as already indicated, it is much more. At the perceptual level, pain is a somatic image that captures or narrows attention (i.e., pain is felt as a focus of distress in a bodily area). The person trying to work while experiencing the pain of a kidney stone has major problems with concentration. Because pain represents a threat to biological integrity in the most fundamental emotional sense (see Chapter 24), it normally involves thinking about the origin of the tissue trauma and the meaning that this has for the immediate and long- range well-being of the person. These complex processes draw on memory, may involve forecasting and planning, and often entail decisions about activity, medication use, or self-care.

Because of pain's cognitive complexity, most patients who seek medical help for pain want more than simple pain relief. They typically wish to achieve some or all of the following goals: (a) understand the cause of the pain, (b) obtain a diagnosis for it, (c) gain a forecast for the pain (how long it will last, whether it will worsen), (d) acquire information about how to control or relieve the pain, (e) learn how to treat or eliminate the cause of the pain, and (f) obtain information about whether certain activities will cause damage or harm. Identifying and addressing such needs is a part of optimal pain medicine. It is important to provide realistic information, when available, about the natural history of the patient's pain problems. For example, current knowledge on back pain reveals that an acute episode of low back pain persists longer than what was once thought and that low back pain is a recurrent condition for most patients. Knowing this can reassure patients whose pain does not resolve within 1 or 2 weeks. The timely offering of such information may motivate patients to engage in behaviors that reduce the chances of future back pain episodes, and it may reduce unnecessary health care use. Some patients worry that persistent or recurrent pain means physical examination has failed to detect a serious cause of the pain.

At sensory and emotional levels, pain feels unpleasant, causes fatigue, and impairs sleep (see Chapter 24), and it probably interferes with cognitive memory (50). Sleep disturbance degrades normal cognitive ability, impairing concentration, and at times pain can interfere with productive mental effort by dominating immediate awareness and causing somatic preoccupation. What is the nature of pain's deleterious effect on the patient's cognitive well-being and functional capability?

Mandler (51), while ostensibly describing stress in cognitive terms, essentially identified the mechanism by which pain impairs cognitive function. Pain captures or narrows attention and thereby disrupts organized action and thought. In other words, it disturbs and eventually controls self-organization and self-reference. When it is chronic, pain becomes the theme around which the patient organizes thinking and action. Pain biases memory, and it may cause the patient to preferentially recall negative ideas and feelings (52,53,54,55 and 56). Pain can sometimes bias perception of the external environment such that everyone and everything in the environment are selected and evaluated for their relevance to pain relief. Moreover, it creates a preoccupation with somatic well-being, causing the patient to dwell on signs and symptoms. Often, patients seek information about pain and its relief, information about other patients like themselves, and information that suggests overlooked or withheld cures. Naturally, the experience of pain in the absence of cancer or another serious disease is incomprehensible to patients and families alike, and most patients engage in a search for meaning and personal dignity. In all of these respects, pain becomes a dominant influence on the patient's cognition. The cognitive and emotional associations that surround the experience of pain are major features of most patients' presentations.

Because pain can interfere with a person's ability to see his or her own situation and life stressors clearly, it tends to create vicious circle situations. The development of a painful condition causes a host of life problems and depletes the person's normal coping resources. The person with chronic pain forms elaborate and negative schemata related to the pain and the search for relief. Often, people with unrelieved pain become preoccupied with the pain and somatic processes. Pain may disrupt sleep; cause depression, irritability, and social withdrawal; sap energy; and limit the sufferer's ability to engage in customary recreational, social, household, and vocational activities. These changes further deplete the person's coping resources and increase his or her focus on pain and its relief, sometimes to the exclusion of all else. Such cases require a multidisciplinary rehabilitation approach that facilitates the patient's return to normal activities, the formation of more adaptive beliefs about the pain, and the application of adaptive pain and stress coping skills (see Chapter 11).

Cognition and Coping with Pain

Persons with pain problems vary widely in the beliefs they hold about their pain and in the ways they cope with or manage their pain. Beliefs and coping strategies are associated importantly with their physical and psychosocial adjustment. Among the beliefs particularly important in adjustment to chronic pain problems are one's perceived ability to control one's pain and one's tendency to think catastrophically (i.e., to expect or worry about major negative consequences from a situation, even one of minor importance). For example, patients who believe they have little control over their pain and who think catastrophically frequently are more likely to exhibit physical and psychosocial dysfunction (57,58 and 59). Close associations exist between thinking catastrophically, fear of pain and of reinjury, and attention (hypervigilance) to pain and other unpleasant somatic sensations (60). People who think catastrophically frequently may attend excessively to pain and have difficulty using coping strategies that involve distraction or attention diversion (60).

Coping refers to “constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person” (61). Coping involves two fundamental tasks: the management of affect or emotional states, and planning and problem solving (62). Pain-coping strategies can include cognitive strategies (e.g., self-statements such as “I can deal with this”), and behavioral strategies such as increasing or decreasing specific activities (e.g., resting, exercising, and using heat or ice).

Numerous studies have shown that patients' beliefs about their pain (such as perceived ability to control the pain) and the strategies they use to cope with their pain are associated with their pain intensity ratings and psychosocial and physical functioning (57,63,64,65,66,67,68,69,70,71,72 and 73). Most of this work addresses chronic pain problems, but the principles also apply to acute pain, as Ulmer's study of coping in burn trauma patients shows (74). She measured pain, coping, and depressed mood in patients with moderate to severe burn injuries. Patients' tendency to think the worst or to think catastrophically was positively associated with pain intensity and pain distress. Conversely, personal belief in one's ability to control and decrease pain correlated negatively with depressed mood.

Awareness of the importance of patients' cognitions and coping strategies in their physical and psychosocial adjustment to chronic pain has led to the widespread application of cognitive-behavioral therapy approaches in multidisciplinary pain centers (see Chapter 89). However, such approaches have yet to find their way into most primary care settings.

Chapter 89 discusses and provides examples of negative cognitions that patients frequently have about their pain and how a therapist might work with a patient to identify such negative cognitions and generate alternative, more adaptive cognitions. Most physicians do not have the time necessary to use such an approach with their patients. However, physician awareness of the importance of these cognitive and behavioral factors may result in improved treatment of patients with chronic persistent or recurrent pain problems in a variety of health care settings. For example, identifying and addressing patient concerns about the pain problem; providing accurate information concerning the likely course of the pain problem; encouraging patient use of self-management strategies rather than continued pursuit of a medical cure; and assisting the patient in return to normal functional, vocational, and social and recreational activities that the pain has interfered with may help reverse and prevent the negative effect of pain on patient psychological and physical functioning.

CONCLUSIONS

The psychology of pain is a rapidly growing field with roots in behavioral and cognitive psychology. This field's fundamental assumptions differ markedly from those of neurology, psychiatry, and anesthesiology because these medical disciplines build on the field of neurophysiology. Classical lines of thinking in neurophysiology, particularly the energy metaphor and Cartesian dualism, are conceptually incompatible with much of the work in current psychology, although information theory provides some potential for interaction. Achieving a full integration of pain medicine and pain psychology requires reconsideration of fundamental assumptions on

both sides and intensive dialogue. The possibilities that such integration would offer for multidisciplinary care are exciting and unprecedented.

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CHAPTER 7

Gender, Cultural, and Environmental Aspects of Pain

Linda LeResche

This chapter focuses on several socially related aspects of pain—specifically, gender, culture, and the social environment. Gender and ethnicity are aspects of personal identity that are rooted in biology, but develop over the course of the lifetime within the context of the individual's social milieu. For example, an individual may be born female and of Japanese heritage, but how she responds to pain as an adult depends not only on those biologic characteristics bestowed by virtue of having two X chromosomes and certain genes associated with racial origin, but also on whether she grows up in Tokyo or Toronto, behavioral expectations for women and girls within the context of her family and culture, and even how persons with her cultural background are viewed by persons in other cultures. Gender, the proximate social environment of family and friends, and social role within the context of the larger culture all have the potential to influence the individual's perception and appraisal of a pain problem and his or her behavior in response to pain experiences. At an even more basic level, because different social and occupational roles expose people to different risk factors for disease and injury, a person's gender, culture, and social environment also influence the very probability of developing any specific clinical pain problem.

GENDER

Gender differences in pain have been the focus of a number of review articles (1,2 and 3) and a major conference (4). In attempting to understand how gender can affect pain, one must consider that biological differences may exist in the nociceptive and perceptual systems of males and females. Work with rodents suggests differences in the pain modulation systems of males and females in some species (5,6) that appear to be related to hormonal factors, specifically estrogen. Moreover, Mogil (7) and colleagues have shown that gender differences in pain responsiveness vary for different strains of mice.

In humans, laboratory studies of gender differences in pain perception are usually designed to compare pain threshold and tolerance measures in men and women. The bulk of these studies seems to indicate slightly higher pain sensitivity in women than in men (2). However, gender differences in pain threshold and tolerance measures appear to vary with the type of experimental pain stimulus applied (e.g., larger and more consistent differences are found for pressure than for thermal stimuli) (2). In addition, different study designs can yield differing results, and even those studies that show statistically significant differences by gender find overlapping distributions of pain sensitivity for men and women (1). A further complicating factor in these studies is that phase of the menstrual cycle in reproductive-aged women is rarely taken into account (8). Although numerous studies have attempted to determine how pain sensitivity might vary with menstrual cycle phase (9,10,11,12,13,14 and 15), they have reached somewhat contradictory conclusions about when sensitivity is highest, perhaps because of different study designs, use of different pain stimuli, and different definitions of phase. Furthermore, sample sizes for most of these studies are quite small, and few studies have provided corroborative evidence of hormonal state.

Despite the difficulties with human laboratory experiments on pain sensitivity, many investigators are willing to draw the inference from these studies that women are, in general, more sensitive to painful stimuli than men, and that this difference is biologically based (1,2). Although this conclusion is plausible, it may be premature, not only for the methodologic reasons just mentioned, but, perhaps more important, also because information on pain sensitivity in these human experimental studies is gathered via self-report or behavior (e.g., terminating exposure to the stimulus). Thus, the findings could reflect willingness or propensity to report pain, rather than biological differences. In addition, nearly all of the experimental studies have been conducted on European or North American subjects, and the majority of them have investigated only pain responses of young adult men and women, not those of the elderly or of children (16). Thus, as yet, little evidence exists to indicate the extent to which the (usually small) gender differences observed in these studies are a product of human biology, and the extent to which they reflect social and cultural influences on pain report.

For many common pain conditions, including migraine and tension-type headache, facial pain, and abdominal pain, population-based studies indicate higher prevalence rates in adult women than in men (17). However, higher pain prevalence in women is not a universal finding. For example, epidemiologic research on back pain is contradictory, with some studies finding higher rates of pain report in men and other studies showing higher rates in women of the same age (18,19 and 20). For some pain conditions, women show a higher prevalence at some points in the life cycle, but not at others. Migraine and temporomandibular pain, for example, tend to show a female predominance only after puberty (21,22), and joint pain shows a female predominance only after approximately age 50 years (23).

Higher prevalence rates for pain in women could be related to a number of factors. First, as has been mentioned, socialization of children in European societies may be such that less stigma is associated with reporting pain for women than for men. Because most of the epidemiologic research, like the experimental research, has been conducted in Europe and in persons of European origin in North America, there have been few opportunities to test whether different socialization patterns could influence gender- specific prevalence patterns. However, at least one cross-national study of primary care patients (24) found that the higher prevalence of persistent pain among women was not confined to Western societies. Second, men and women may have different benchmarks for reporting pain related to their prior pain experience. For example, boys, at least in earlier generations, were more likely to experience pain from sports injuries than girls. On the other hand, after puberty, women's monthly menstrual cycles provide them with a set of physiologic signals from their bodies that are not experienced by men. These sometimes painful physiologic signals could have a sensitizing effect on pain perception (1) or result in behavioral and social role responses (e.g., taking medication, staying in bed) that can generalize to other types of pain. Finally, the prevalence of a pain condition (i.e., the number of cases in the population at a given point in time) is a product of the rate of onset of the pain condition, as well as its duration. If pain prevalence rates for women are higher than for men, this could occur either because women are more likely to experience pain in the first place, or because pain, once present, tends to last longer for women. Few data are available on differential rates of onset and duration for chronic and recurrent pain conditions in men and women.

Whatever the pain prevalence differences for men and women, most studies show that women seek health care for pain at a higher rate than men (3). The predominance of women in treatment settings is not surprising, given that women are more likely than men to seek care for most medical conditions (25). Although there has been little research concerning the factors associated with seeking care among persons with pain in the population, one study found that the major predictors of health care in both genders were pain severity and persistence (26) (i.e., persons with more severe, persistent pain were more likely to seek care). For some pain conditions, such as temporomandibular pain, women experience pain of higher average severity than do men. If it is true that pain severity drives treatment seeking and that women, on average, experience pain of higher severity than men, we would expect that the levels of pain and pain-related symptoms among men and women seeking pain treatment would be fairly comparable, although women could outnumber men in treatment settings. The few studies that have examined this question have, in fact, found that levels of pain, pain-related signs and symptoms, and psychosocial profiles are roughly comparable for men and women seen in the same treatment setting (27,28).

Some research suggests that women and men with pain problems differ in their patterns of coping with pain. For example, in a sample of patients from a pain management center, Buckelew and colleagues (29) found women more likely than men to report the use of cognitive restructuring and information seeking. A daily diary study (30) found that women with arthritis reported greater pain, but also used more pain-coping strategies on a daily basis than men. Furthermore, men showed a greater carryover effect of intensifying pain on the presence of negative mood the next day. Thus, although women may experience more intense pain, they may also be better able to limit its negative emotional consequences.

Only a few studies have explored possible differences in how men and women respond to pain treatment. Clinical experiments have found differential response to some pain medications among men and women (31), with some drugs, notably kappa opioids, being more effective in women than in men. Although little reported research exists on the effectiveness of nonpharmacologic therapies by sex, one study found that women were more likely than men to be successful in a cognitive-behavioral program of the type frequently used in multidisciplinary pain centers (32). Finally, in a study of injured workers with musculoskeletal pain, Crook and Moldofsky (33) found that patterns of return to work after injury differed for men and women. Although men returned to work sooner than women, they were more likely to experience recurrent disability. Women, possibly because of additional duties at home, took more time than men to return to employment, but were more

likely to stay on the job once back in the work force.

Thus, it appears that gender affects not only pain perception, pain coping, and pain report, but also pain-related behaviors, including use of health care and the social welfare system. It is also probable that men and women differ systematically in their responses to pain treatments, although further research is needed in this area.

CULTURE

The influence of culture and ethnicity on pain perception and expression has been a focus of research attention since the pioneering work of Zborowski in the 1950s and 1960s (34). However, summarizing the body of research in this area systematically is difficult, because a wide variety of research approaches have been used, including direct observation; in-depth, open-ended interviews with a small number of informants; the administration of structured questionnaires; and experimental studies of responses to painful stimuli. Furthermore, although a wide variety of cultures have been examined across the various studies, little replication has occurred in the cultural groups investigated from study to study, so it is difficult to know whether findings about a given culture reported in one study are generalizable to other research settings. Some research investigates persons of a given culture living in their native land, where they are usually the predominant culture, and other studies focus on persons of specific ethnic backgrounds living in a multicultural society such as the United States, where they are frequently cultural minorities. Although some studies carefully control for factors such as socioeconomic status, degree of acculturation to the predominant culture, and age and gender of the subjects, and report intracultural as well as intercultural variation, others fail to do so. Given these concerns, a comprehensive review of the literature on culture and pain is beyond the scope of this chapter. Instead, I highlight some of the more important issues in this area by reviewing selected studies that have taken a variety of approaches to studying culture and pain.

Moore and colleagues have used qualitative and quantitative methods to examine the words used by persons in Anglo-American and Chinese cultures to describe specific pains (35,36 and 37). These studies of pain language reveal that different concepts are applied to the same types of pain in different cultures. For example, muscle pain was viewed as *deep* by nearly all Anglo-Americans, but only approximately one-half of Mandarin Chinese. Eighty-two percent of Chinese described the pain of tooth drilling as *sourish*, whereas only 8% of Americans agreed that this was an accurate descriptor (37). In the same study, dentists' views of the appropriate words to describe various kinds of pains did not differ from those of laypeople in their respective culture, indicating that professional socialization may not have a strong influence on basic concepts of the qualities of pain. In contrast, earlier studies of coping with pain among ethnic Chinese, Anglo-Americans, and Scandinavians in a U.S. city found that although pain remedies endorsed by patients showed ethnic differences, dentists in all three cultures seemed to have similar views of appropriate remedies, suggesting that professional socialization had a larger influence in this domain than did ethnicity (38).

In 1990, Zatzick and Dimsdale (39) systematically reviewed the literature on cultural differences in responses to experimentally induced pain and located 13 studies published between 1943 and 1989. The studies were diverse with regard to the racial and ethnic groups studied, as well as the pain stimuli applied and the outcomes measured (i.e., pain threshold and/or pain tolerance). The authors concluded that although there appear to be no racial or ethnic differences in the ability to differentiate painful stimuli, the experimental evidence is not consistent with regard to cultural differences in pain response. They suggested that future laboratory investigations focus on behavioral pain tolerance measures, rather than pain threshold measures (which are likely to be influenced by language), and stressed the importance of assessing intragroup as well as intergroup differences. Perhaps because some have questioned the relevance of such laboratory studies for understanding how culture influences pain in clinical contexts, I was not able to locate additional human experimental studies published since 1990.

In contrast, a number of studies have been published investigating the perception of acute and chronic pain in daily life and clinical contexts. For example, menstrual and premenstrual symptoms were assessed using daily symptom diaries in Afro-Caribbean, white, and Chinese women recruited through a community center in London (40). Relative to the Afro-Caribbean subjects, white women reported more pain in both the premenstrual and menstrual periods. Similar results were found in analysis of retrospective report of menstrual distress. Another study investigated ratings of the pain of ear piercing in 84 young women and men, aged 15 years to 25 years. Again, the study was carried out in London and investigated Afro–Caribbean, Anglo-Saxon, and Asian subjects. One-half the subjects of each gender in each ethnic group were told that they were participating in a study of pain, and one-half were told the study involved sensory experience. Significant effects were found for ethnicity, and for pain versus sensory experience conditions, but no significant sex differences were found. Afro–Caribbean subjects reported significantly lower pain levels than the Anglo-Saxon and Asian subjects; although Asians reported the highest pain levels, no significant difference was found between the Asians and Anglo-Saxons.

A few studies have examined differences in the levels of chronic pain reported by patients of different cultures in pain treatment centers. In a well-controlled study in a single multidisciplinary pain management center, Bates and colleagues (41) examined variability in pain report on the total Pain Rating Index of the McGill Pain Questionnaire among “Old American” (at least third-generation United States–born non-Hispanic whites), Hispanic, Irish, Italian, French Canadian, and Polish subjects. The majority of subjects in all groups had chronic low back pain, and no significant differences existed in diagnosis, mean number of medications, or types of medications by ethnic group. Hispanics reported the highest pain levels and were also more likely than the other groups to have an *external* locus of control. In multiple regression analyses, both ethnic group identity and perceived locus of control were significantly associated with pain intensity after controlling for the influence of age. The significant ethnic group differences were between Hispanics and Old Americans, Hispanics and French Canadians, and Hispanics and Polish subjects. Intraethnic group variation in pain intensity was also investigated and found to be related, albeit in a complex way, to locus of control and to the degree to which the individual identified with his or her ethnic group. Although this study provides a wealth of interesting information regarding ethnic group differences, it represents findings from only a single health facility. Caution should also be taken in attributing differences between Hispanics and other ethnic groups solely to cultural factors, as the level of education of the Hispanic sample was significantly lower than that of other groups in the study.

A few investigators have examined the prevalence of specific pain conditions in different ethnic groups in large, well-controlled epidemiologic studies. Using International Headache Society criteria for migraine, Stewart and colleagues (42) examined migraine prevalence in more than 12,000 residents of Baltimore County, Maryland, aged 18 years to 65 years. In women, migraine prevalence was significantly higher among whites than among African-Americans or Asian-Americans (prevalence rates of 20.4%, 16.2%, and 9.2%, respectively). A similar pattern was shown for men (rates of 8.6% for whites, 7.2% for African-Americans, and 4.2% for Asian-Americans), although absolute rates were lower than for women. In models adjusting for age and education, African-American and Asian women showed significantly lower prevalence ratios when compared with white women. African-American men also displayed significantly lower adjusted prevalence than white men. Although the adjusted prevalence for Asian men was only 60% of that of white men, this difference was not statistically significant, because of the very small number of Asian men with migraine. These findings are particularly interesting in light of the fact that meta-analyses of studies of migraine prevalence using International Headache Society criteria indicate lower migraine prevalence rates in Asia and Africa than in Europe or the Americas (43). The authors speculate that genetic differences between races are likely to account for the observed variability, although other factors, such as dietary and symptom-reporting differences, cannot be ruled out.

Skovron and colleagues (44) assessed the prevalence of back pain among Flemish and French speakers in Belgium, a bicultural, economically diverse society that has a national social security system and single-payer health care reimbursement. In multivariate analyses controlling for several variables (social class, rural-urban location, occupation, and work status), increasing age, female gender, and French language were associated with reporting a history of back pain (i.e., ever having had back pain). Only female gender and French language predicted being in a first episode of back pain, with language being the stronger predictor. However, when predictors of daily back pain were examined, the factors that emerged as predictors, other than age and sex, were largely social, rather than cultural (i.e., social class, living in a large city, and being an unskilled worker). Thus, it appears that cultural factors may have influenced rates of reporting a history or a first episode of back pain in this study; however, pain persistence was unrelated to culture.

Finally, a few large multinational studies have examined the effects of pain across cultures. One set of studies (45,46) examined the consequences of pain in more than 1,800 patients with metastatic cancer and pain in four countries, the United States, France, the Philippines, and China. Patients rated their worst pain on a 1 to 10 numeric rating scale and the degree to which pain interfered with enjoyment of life, activity, walking, mood, sleep, work, and relations with others on 0 to 10 scales. It was found that, based on the degree of interference with function, pain ratings of 1 to 4 corresponded with mild pain, 5 to 6 with moderate pain, and 7 to 10 with severe pain. These cut points were the same for each of the national samples, although the specific interference items affected by pain differed from country to country.

Gureje and colleagues (24) examined measures of well-being for more than 5,400 persons with persistent pain in primary care settings in 15 countries in Asia, Africa, Europe, and the Americas, compared with persons in the same settings who did not experience persistent pain. Across all the centers, the prevalence of persistent pain was 22%, but there was wide variation in prevalence from center to center, with a range of 5.5% to 33.0%. No cultural reasons for the variability in prevalence were apparent. Relative to patients without persistent pain, patients with persistent pain were more likely to experience an anxiety or depressive disorder, to experience significant activity limitations, and to rate their general health status as fair or poor. For all 15 centers, the difference in rates of depressive and anxiety disorders for those with versus without pain was statistically significant. However, statistical differences in self-rated health status, self-rated interference, and interviewer-rated work-related interference did not emerge in all centers, and there was no straightforward interpretation of the pattern of results that emerged across

cultures. This lack of consistency across settings in a well-controlled study with substantial sample sizes at each center suggests that caution should be used in drawing conclusions about cultural differences in the effects of persistent pain when samples are drawn from a limited number of health care settings in each culture.

ENVIRONMENT

Two classic experimental studies illustrate the role that the environment theoretically can play in the perception of pain. Dworkin and Chen (47) tested young women's sensation threshold, pain threshold, and pain tolerance levels in a laboratory situation using tooth pulp stimulation and then retested one-half of the subjects in a dental operatory setting and one-half in the original laboratory setting. The salience of the dental environment was enhanced by the experimenter's introducing himself as a dentist and telling the subject that information on her pain responses was relevant to her risk of dental health problems. Those subjects tested in the dental environment had significantly increased anxiety and not only had significantly reduced pain threshold and pain tolerance levels, but also had significantly reduced thresholds for reporting the presence of any sensation compared with their original measures and with the levels of those subjects retested in the original laboratory environment. Craig and Best (48) exposed young female subjects to electrical stimulation in the presence of a confederate who modeled either tolerance or intolerance to pain (i.e., systematically gave ratings either lower or higher than those of the subject) or was inactive. Subjects exposed to tolerant models exhibited significantly higher pain tolerance than those exposed to the intolerant model, whereas the tolerance levels of subjects in the inactive control condition were intermediate. When the model was removed and subjects were informed of the model's role, they continued to respond in the same manner as when the model was present. Thus, it appears that, at least in some circumstances, the social environment in which a pain response is learned may have a lasting effect on pain behavior.

Does the social environment influence the tendency to report clinical, as well as experimental, pain? Because the family is the primary agent of socialization about health and illness, if there are social environmental influences on pain perception and pain reporting, it seems logical to look for these influences within the family. Turk and colleagues (49) reviewed a fair amount of empirical evidence supporting the view that children and adults with chronic pain are likely to have individuals in their families with chronic pain (i.e., models for chronic pain). However, these authors also point out that most of the reported studies of chronic pain in families suffer from one or more significant methodologic problems, including reliance on retrospective self- report of patients and families, lack of control groups, and potential for recall bias among persons with pain. Thus, although a strong role for the family, as well as the larger social and cultural environment, in shaping an individual's perception and appraisal of pain is highly plausible, detailed longitudinal research is necessary to confirm or refute the suspected relationships. Until such research findings are available, it may be best for the clinician to be aware that the behavior of individual patients presenting with pain is likely to be influenced by a range of social factors, including their gender, culture, and family upbringing; yet, none of these factors is sufficient to determine the individual's experience of pain.

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CHAPTER 8

Applied Anatomy Relevant to Pain

John J. Bonica and John D. Loeser

This chapter contains information about those aspects of the gross anatomy and neuroanatomy relevant to painful disorders and is intended to complement the information contained in Chapter 3 and Chapter 4. The material is presented in two parts. The first section contains a description of the segmental and peripheral nerve supply to the skin, muscles, and bones and the segmental sensory and autonomic nerve supply to viscera. The second section is devoted to a general discussion of the autonomic nervous system (ANS) as relevant to its role in pain. The sensory supply of each region is discussed in more detail in the introductory chapter of each section of Part IV of the book and is also considered briefly in the introduction to some of the chapters. For example, Chapter 46, the first chapter of the section on pain in the head, contains a detailed discussion of the nerve supply to the head and precedes the chapters in which the various head pain syndromes are discussed. Some of the information is also repeated in the sections on neurologic and orthopedic examination of Part II and in connection with those chapters in Part V dealing with therapeutic modalities that require full knowledge of the relevant anatomy and physiology. The material is derived in part from updated reviews and other reliable sources (1,2,3 and 4).

SEGMENTAL AND PERIPHERAL NERVE DISTRIBUTION

Figure 8-1 and Figure 8-2 are included as reference points with regard to the derivation of peripheral nerves from the spinal cord and brainstem. Figure 8-1 depicts the gross anatomy of the spinal cord and the attachment of rootlets of the posterior (dorsal) roots and anterior (ventral) roots. Figure 8-2 depicts the relationship of the segments of the spinal cord to the vertebral canal and column. The anatomy of the cranial nerves involved in nociception and their derivation from the brainstem are discussed in Chapter 46.

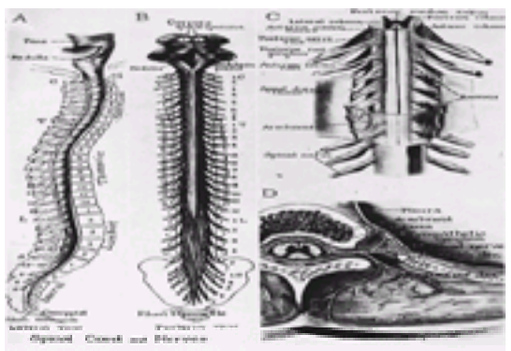

Figure 8-1. The spinal cord and the proximal portions of the spinal nerves. **A:** Lateral view of the spinal cord showing attachment of the nerves to the cord by their anterior and posterior roots. **B:** Posterior view of the spinal cord made possible by removal of the spinous processes and laminae. Note the relationship of the spinal cord segments and nerves to the vertebrae. In most individuals, the conus medullaris terminates at the lower border of the first lumbar vertebra. Caudal to the conus medullaris is the cauda equina, made up of rootlets that join together to form the anterior and posterior roots, near the point at which the latter join to create the formed nerve within the intervertebral foramina. **C:** Anterior view of the spinal cord with the dura-arachnoid removed from the upper portion of the specimen. The smaller anterior root fans out and divides into four to six rootlets, which form irregular rows attached to the cord in the anterolateral sulcus. The larger posterior root is composed of 6 to 10 rootlets attached to the spinal cord in a linear series along the posterolateral sulcus. These rootlets (fila radicularia) converge peripherally into two bundles, the fasciculi radiculi, which in turn unite near the dorsal root ganglion to form the posterior root. Within the intervertebral foramen the anterior and posterior roots join to make the formed spinal nerve. **D:** Cross section of the thoracic region showing the course and relation of a typical spinal nerve. Note its connection with the sympathetic ganglion. (div., division.)

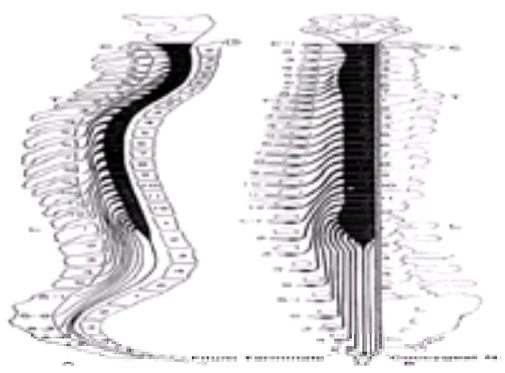

Figure 8-2. Schematic representation to show the relation of spinal column and the spinal cord, nerve roots, and the formed nerves. **A:** Lateral view. **B:** Posterior view. Note the direction of the spinal rootlets/roots in the various segments. The size of the spinal cord in relation to the spinal canal is exaggerated in **B** for the sake of clarity of the numbers of spinal cord segments and their relationship to the vertebrae. (C, cervical; L, lumbar; N, nerve; S, sacral; T, thoracic.)

Segmental Distribution of Sensory Nerves

The distribution of sensory fibers, which, of course, contain nociceptive axons, is more or less segmental throughout the body. This is the result of the preservation by the sensory levels of the nervous system of the original embryologic division of the body into metameres. The spinal segments that provide sensory and motor innervation to one embryologic division constitute a *metamere.* The cutaneous area supplied by a single pair of sensory roots and their ganglia is known as a *dermatome,* and the area of bones supplied by a similar unit is known as a *sclerotome.* The ventral roots also innervate the dermatomes and sclerotomes, supplying them with sudomotor, pilomotor, and vasomotor fibers, but the distributions of the two classes of fibers, the sensory (afferent) and the motor (efferent), never exactly coincide. Furthermore, the ventral root supplies motor fibers to skeletal muscles, and the area supplied by each segment is often referred to as the *myotome.*

This distribution is particularly segmental for the ectodermal structures—the skin and subcutaneous tissue. The nerves supplying the viscera are also segmentally distributed; as mentioned in Chapter 3, however, visceral afferent fibers are few in number in comparison with the number of somatic primary afferents. It has been estimated that visceral afferents constitute only 10% of the total number of afferents in dorsal roots. This paucity of visceral afferents is compensated in part by the

much larger area supplied by the visceral fibers in one root, the peripheral processes of which ramify widely. This is discussed later in this chapter in the section on segmental innervation of the viscera. Knowledge of the segmental distribution of sensory fibers is of critical importance in managing patients with acute and chronic pain.

Dermatomes

There are as many dermatomes as there are spinal segments, with the single exception of the first cervical segment, which in most individuals has no cutaneous distribution. Many investigators using various methods have mapped out the boundaries of the dermatomes. Although there were several investigations of the areas of skin supplied by dorsal roots during the nineteenth century, the first satisfactory delineation of the dermatomes came from the work of Sherrington in the 1890s (5,6). Sherrington's technique, known as the method of *residual sensibility*, was carried out in monkeys and consisted of sectioning several (usually three) dorsal (sensory) roots rostrad and three roots caudad to the root under consideration, which was allowed to remain intact. The area of sensation that remained in the otherwise unanesthetized area that resulted was the dermatome. Maps were drawn of the different dermatomes, and it was assumed that each dermatome resulted from the sensory axons that remain in the intact root.

Subsequently, the method of remaining sensibility was used extensively in humans by Foerster (7), who in the course of long experience with posterior root section (rhizotomy) for the management of intractable pain had the opportunity of determining every dermatome in the lower limbs and one dermatome in the upper limbs in humans. To fill the gap and to define other cervical and the thoracic dermatomes, he used what he called the *constructive method*, which consisted of dividing a series of contiguous posterior roots and testing sensitivity in the areas they supplied. Thus the superior border of the resulting anesthesia represented the inferior border of the dermatome supplied by the next higher intact root, and the inferior border of anesthesia marked the upper border of the next lower dermatome. The third method Foerster used was based on the antidromic response, in which the vasodilation that followed stimulation of the distal cut end of a dorsal root was mapped out. Foerster reported not only that great overlap existed among contiguous dermatomes, but also that significant variations existed in the cutaneous distribution of specific sensory roots, especially in the limbs, of different patients he studied. Figure 8-3 is based on reconstructions of Foerster's data by Haymaker and Woodhall (3) and by Lewis (8).

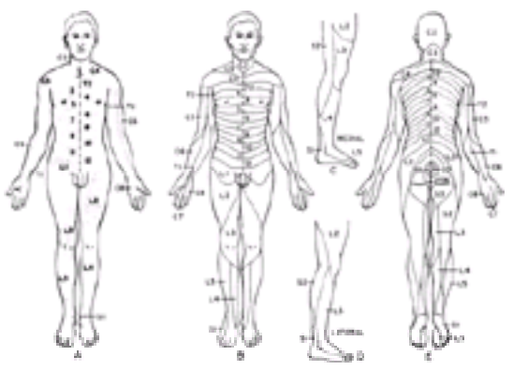

Figure 8-3. The dermatomes in humans according to the studies of Foerster. **A:** Overlap of the dermatomes in the upper and lower limbs not depicted in **B** to **E**. (**A** modified from Lewis T. *Pain*. New York: Macmillan, 1946; **B** to **E** from Haymaker W, Woodhall B. *Peripheral nerve injuries: principles of diagnosis*. Philadelphia: WB Saunders, 1945.)

At the same time as Sherrington's studies, Head (9), believing that herpes zoster was a disease of the posterior roots, closely observed and recorded the cutaneous eruptions of this affliction in the hope that it might accurately disclose the distribution of the posterior roots to the skin. Maps provided by a large number of cases of herpes zoster were examined and correlated with the borders of sensory loss arising from cord lesions at certain levels. Figure 8-4 is based on Head's preliminary data on cutaneous areas published in 1893 (9) and additional observations published in 1900 (10). It is important to note that there is little overlap in the trunk but some overlap in the lower limb. The patterns of Head's dermatomes in the lower limbs are similar to those reported by Foerster, but there are significant differences between the two patterns in the distribution of the upper limbs.

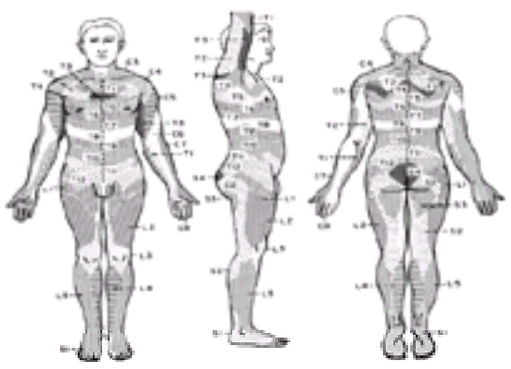

Figure 8-4. The dermatomes developed by Head, from observation of patients with herpes zoster lesions. There is no overlap of the dermatomes in the trunk, but there is some overlap of the dermatomes in the lower limbs. (Modified from Head H. On disturbance of sensation with special reference to the pain of visceral disease. *Brain* 1893;16:1; and Head H, Campbell AW. The pathology of herpes zoster and its bearing on sensory localization. *Brain* 1900;23:353.)

Many other investigators used Sherrington's technique of residual sensibility to produce dermatomal maps for many species. The major conclusions of these studies were that (a) the dermatomes overlap, and thus the area of the body wall supplied by the axons of a single dorsal root is greater than one segment; (b) because of this overlap, it is usually not possible to render an area of the body anesthetic by cutting only one dorsal root; (c) although the dermatomes overlap, the threshold for various stimuli is lowest in the central part of the dermatomal field; and (d) most of the dermatomes for the limbs do not extend to the midline of the body, so that dorsal and ventral axial lines are found in the extremities and result when the dermatomes from continuous spinal levels abut. Thus, the C-4 dermatome lies next to the T-2 dermatome and L-2 is next to S-2. This nonsegmental pattern of dermatomes in the limbs, published by Sherrington and Foerster, was based on the concept of dermatomic development proposed by Sherrington (5) and refined by others during the early part of the twentieth century. This concept suggests that whereas during embryonic life the spinal portion of the embryo is divided into metameres, this arrangement loses its uniformity when certain groups of metameres migrate into the limb buds, and as these extend more and more distally, the corresponding dermatomes also migrate. The dermatomes that have migrated become grouped parallel to the long axis of the future limb except at the distal part of the limb, at which they are arranged in loops over the expanding limb buds. Consequently, the dermatomes of the higher (rostral) segments are grouped along the preaxial border of the limb, and those of the lower (caudal) segments along the postaxial border, the two divided by ventral and dorsal axial lines.

In the 1940s, Keegan (11) carried out a series of studies of the dermatomes using three different techniques. One detailed careful charting of the area of pain and hypalgesia associated with compression of a single nerve root due to herniation of an intervertebral disk. By careful preoperative examinations, with particular emphasis on the distribution of the pain (obtained by asking the patient to indicate precisely where the pain was located) and skin testing by a light scratch method with a safety pin, he was able to map out the dermatomes in a large group of patients. The diagnosis of single root compression by a posterolateral (unilateral) disk was verified at surgery. He also studied hypalgesia produced by (a) paravertebral injection of procaine on individual cervical nerves that supply the upper extremity, carried out under radiographic control in 10 human volunteers, and (b) posterior rhizotomy of a single nerve root in the lower extremity. Figure 8-5 shows dermatomal charts of the upper and lower limbs, and Figure 8-6 is a complete dermatomal chart, published by Keegan. As shown in these figures, the dermatomes to the limbs consist of a series of continuous bands extending from the distal part of the limb to the midline, and there is no dorsal axial line. Moreover, these dermatomal areas do not overlap, but Keegan pointed out that his outlines were areas of detectable hypalgesia from loss of a single nerve root and represent the *primary* innervation, not the entire distribution of each nerve root. He agreed there must be considerable secondary overlap innervation for each nerve root, otherwise analgesia (rather than

hypalgesia) in the primary area would be found with loss of a single nerve root. He mentioned that at times he found a faint parallel strip of hypalgesia on each side of the primary dermatome that was half the width of the primary zone.

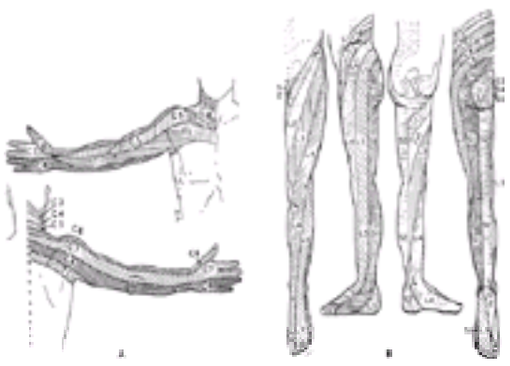

Figure 8-5. **A:** Dermatome chart of the upper extremity. **B:** Dermatome chart of the lower extremity. Dermatomes determined by pattern of hypalgesia from loss of a single nerve root. (**A** from Keegan JJ. Dermatome hypalgesia with posterolateral herniation of lower cervical intervertebral disc. *J Neurosurg* 1947;4:115; **B** from Keegan JJ. Neurosurgical interpretation of dermatome hypalgesia with herniation of the lumbar intervertebral disc. *J Bone Joint Surg* 1944;26:238.)

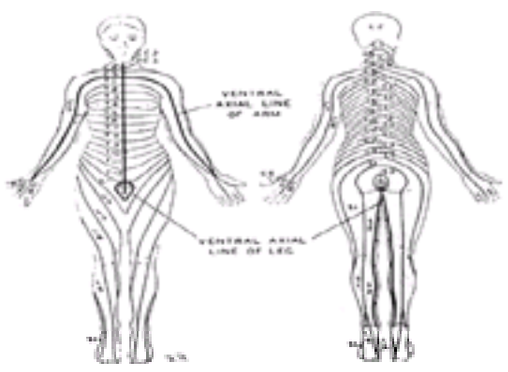

Figure 8-6. Composite dermatome chart of the human body developed by Keegan, from studies of the dermatomes in the upper and lower limbs and from a classical pattern of the dermatomes in the trunk. (From Keegan JJ. Dermatome hypalgesia with posterolateral herniation of lower cervical intervertebral disc. *J Neurosurg* 1947;4:115.)

Keegan, in collaboration with Garrett (12), suggested that the primary zone, containing more dense distribution of fibers from the dorsal root, represented the true primitive dermatome and that the secondary zone, containing fewer fibers, represented the area of overlap. In support of Keegan's finding and their explanation, they presented a different conception of the development of the dermatome in the limb bud. They postulated that the sensory branches of the limb nerve grew with the development of the limb bud along its dorsal surface and wound themselves around the preaxial and postaxial borders to the ventral surface, meeting along the axial line. Figure 8-7 depicts the concept they proposed and the one proposed earlier.

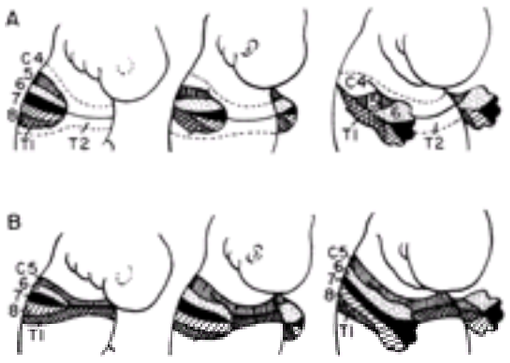

Figure 8-7. **A:** The classic concept of the development of the dermatomes in the limb bud at three stages of development, following the scheme suggested by Sherrington and refined by Bolk. **B:** The concept proposed by Keegan and Garrett. In **A**, certain groups of metameres migrate into the limb buds, and as they extend distally the corresponding dermatomes also migrate and become grouped parallel to the long axis of the future limb bud, except at the distal part of the limb, where they are arranged in a semicircle. As a result, the rostral segments are grouped along the preaxial border of the limb and the caudal segments along the postaxial border, with the two divided by the ventral and dorsal axial line. In **B**, the sensory branches of limb nerve grow with development of the limb bud along its dorsal surface and wind around the preaxial and postaxial borders of the ventral surface, meeting along the axial line. As a result, neighboring dermatomes across this line are noncontiguous with respect to number and overlap across the axial line is minimal.

More recently, studies of the dermatomes have been carried out by a number of other clinical investigators, including Hansen and Schliack (13), who, like Head, used the distributions of herpetic lesions and the zone of hyperalgesia associated with visceral disease and also used the pattern of hyperalgesia produced by a herniated intervertebral disk. Patterns published by these investigators are similar to those of Head for the trunk and somewhat similar to those of Keegan and Garrett (11,12) and Inman and Saunders (14) for the limbs. Bonica made observations of the pattern of dermatomes after paravertebral somatic nerve blocks, identifying the nerve by (a) the distribution of paresthesia upon contact with the needle point, (b) radiographic control of the precise location of the vertebral level of the bevel of the needle, and (c) injection of 2 mL of contrast medium and again verifying the location of the needle point. The nerve was then injected with a small volume (2 mL) of a local anesthetic (to avoid diffusion to adjacent segments), and the pattern of hypalgesia that developed was carefully ascertained. In the course of four decades, he used this technique experimentally in a group of human volunteers and as a diagnostic/prognostic procedure in evaluating more than 400 patients with segmental pain that was suspected to be due to herniation of an intervertebral disk, osteophyte, or other pathologic process that was subsequently proven at surgery. Bonica also used the technique to study the dermatomal pattern in surgical patients requiring an operation to a limited part of the trunk or the upper or lower limb. In these cases, each segment was injected with small amounts of fast-acting local anesthetic, observations were made as soon as hypalgesia developed, and the next segment was then injected. The procedure was also used to study the nociceptive pathways to the uterus in parturients (see Chapter 71).

Figure 8-8 has been developed on the basis of the dermatomal pattern published by Hansen and Schliack (13) and modified according to Bonica's observations. The dermatomal distribution to the anterior part of the lower limb is somewhat similar to that of Keegan, except that the first toe is predominantly supplied by L-5 and not L-4. It is difficult to rationalize the discrepant findings between Keegan and others with regard to the dermatomal pattern in the upper limb, particularly in regard to distribution of the dermatome to the midline anteriorly and posteriorly. Bonica was not able to demonstrate these patterns. Regional analgesia for operation on the neck, carried out with paravertebral block of C-2, C-3, and C-4 (deep cervical plexus block), invariably produces analgesia that extends anteriorly to the second, and often the third, thoracic dermatome on the trunk. In such patients, intense, noxious stimulation of the skin overlying the clavicle and just below that structure, which according to Keegan are supplied by C-5 and T-1, produced no sensation of pain. Similarly, deep cervical plexus block has been used to produce analgesia of the skin overlying the spinous process of the first, second, and third thoracic vertebrae and the skin of the adjacent paravertebral region. Perhaps the most important part of Keegan's pattern to rationalize is the difference in the distribution of the dermatomes in the back, discussed in the next paragraph.

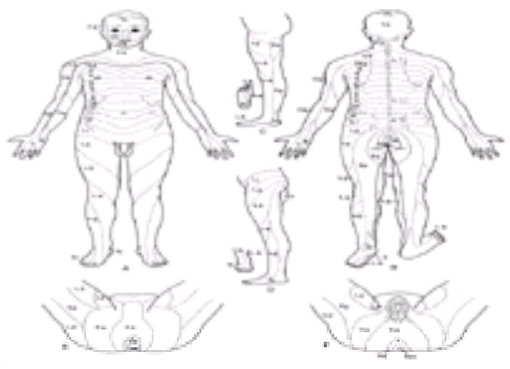

Figure 8-8. The dermatomes developed by Bonica on basis of personal observation and data published by others. See text for description.

Two clinically important features of the posterior part of the dermatomes need comment in relation to the distribution of the posterior primary divisions of the spinal nerves. One is the fact that the first cervical nerve does not supply any area of the skin, but the posterior primary division of the second and third cervical nerves not only compensates for this but also innervates the back of the scalp as far forward as the vertex and abut the first division of the trigeminal nerve. Moreover, the posterior primary rami of the sixth, seventh, and eighth cervical nerves, and of the fourth and fifth lumbar nerves, do not supply the skin. The second extremely important point is that beginning at approximately T-4 or T-5, the posterior division of each spinal nerve migrates within muscles caudally for a progressively greater distance before emerging from the muscles to supply the skin and subcutaneous tissue overlying the spinous processes, vertebrae, and the adjacent paravertebral region (Fig. 8-9, Table 8-1). These points are critically important when evaluating patients with back pain and attempting to identify the cutaneous nerve supply.

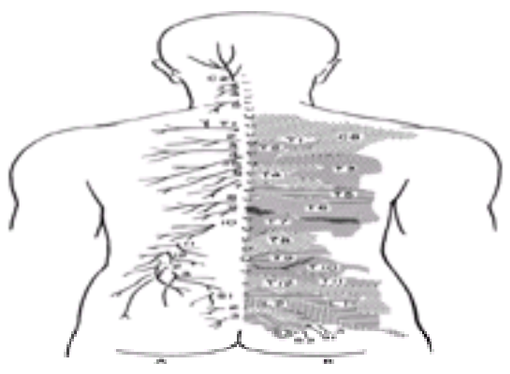

Figure 8-9. **A:** Caudad migration of the posterior primary division of the thoracic and lumbar spinal nerves. **B:** Distribution of these cutaneous nerves to the skin of the back.

Nerve of origin of cutaneous branch	Area of distribution*
T-2	T-4-5
T-3	T-5-6
T-4	T-6-7
T-5	T-8-9
T-6	T-9-10
T-7	T-10–12
T-8	T-12–L-1
T-9	L-1–2
T-10	L-2-3
T-11	L-3–4
T-12	L-5–S-1
L-1	S-1–2
L-2	S-2–3
L-3–5	Lower one-third of sacrum

*Skin overlying spinous process and paravertebral region.

TABLE 8-1. Distribution of cutaneous branches of posterior division of spinal nerves

The differences of pattern of dermatomes suggest that these are not simple sensory patterns that are the result of anatomic distribution of sensory axons of each particular dorsal root. Instead, the interaction of primary afferent fibers from various segments with neurons whose axons are in Lissauer's tract probably determine not only the size of the dermatome but the quality of the sensation as well (15). This is suggested by the monkey study carried out by Denny-Brown and associates (15,16) with section of roots distal to the dorsal root ganglion rather than proximal (as all other investigators before them had done). These studies showed that the size of each dermatome was enlarged. Strychnine also greatly enlarged the size of each dermatome, as did section of the lateral part of Lissauer's tract. The size of the dermatome was decreased by cutting the medial part of the tract of Lissauer or by cutting six roots on each side of the intact isolated root. This form of neuronal plasticity was also described in patients who had had dorsal rhizotomies for the relief of pain; the area of sensory loss and pain relief was modified by orally administered drugs (17).

Notwithstanding these issues, careful mapping of the dermatome to help pinpoint the site of a lesion that involves the formed nerve (or nerves) before it divides as it makes its exit through the intervertebral foramen is an important clinical tool. Similarly, as will be noted, elicitation of the area of segmental hyperalgesia present in patients with painful diseases involving various thoracic and abdominal viscera helps in differential diagnosis.

Sclerotomes

The segmental nerve roots that supply bones (sclerotomes) are illustrated in Figure 8-10. Comparison of this figure with those showing the dermatomes makes it obvious that they do not agree in spatial relationship, particularly in the limbs. It is only occasionally that a dermatome overlies a portion of the corresponding sclerotome. Whereas dermatomes are arranged along preaxial and postaxial borders of the limb, sclerotomes extend distally for almost the entire length of a limb. In some instances, the sclerotome is continuous, and in others it is interrupted. The skull is innervated by the trigeminal nerve in its anterior two-thirds and by the second and third cervical nerves in its posterior third. Each vertebra is supplied by the recurrent nerve derived from the posterior division of spinal nerves, whereas the ribs are supplied by the posterior and anterior primary divisions of their respective spinal nerves.

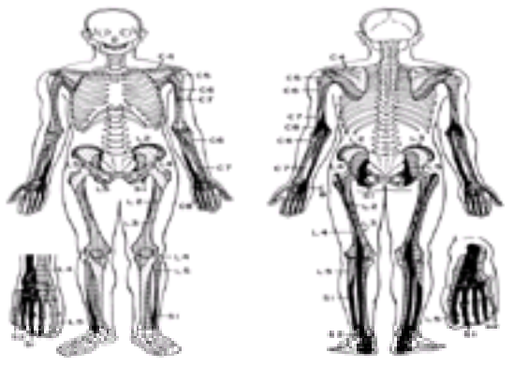

Figure 8-10. The sclerotomes in humans. Various patterns indicate the field of supply of each spinal segment. The skull is innervated by the trigeminal nerve in the anterior two-thirds and by C-2 and C-3 in the posterior third; the vertebrae are supplied by the posterior divisions of the spinal nerves, whereas the ribs are supplied by both posterior and anterior primary divisions of the spinal nerves. The inserts show the sclerotomes of the bones of the feet. (Modified from Déjerine J. *Sémiologie du système nerveux*. Paris: Masson, 1914.)

Myotomes

The segmental nerve supply of various muscles in the body is listed in Table 8-2 and is discussed in Chapter 13 in the section on evaluation of painful conditions by the use of electromyography.

TABLE 8-2. Nerve supply of muscles

Segmental Innervation of the Viscera

The viscera are supplied by sensory fibers, which are constituent fibers of the spinal and cranial nerves because they have their cell bodies in the posterior root ganglia of spinal nerves or the sensory ganglia of cranial nerves. The sensory fibers' central processes pass via the dorsal (and occasionally ventral) roots, whereas their distal processes accompany the sympathetic or parasympathetic nerves to end in the viscera. Usually, each viscus is supplied by dorsal roots of a number of spinal nerves.

Study of the segments that supply various thoracic and abdominal viscera was also initiated in the latter part of the nineteenth century when physiologists used the visceromotor reflex in animals. This method involves applying noxious stimuli to the stomach, for example, then determining the segmental reflex response of the abdominal muscles by systematically carrying out surgical dorsal rhizotomy until response is eliminated. At approximately the same time Head (9) also studied the segments supplying each viscus by carefully determining the extent of cutaneous hyperalgesia in patients with various visceral diseases. As is discussed in Chapter 9, nociceptive stimulation produces reflex responses, which include cutaneous hyperalgesia in the same segments that supply the viscera. After a long and very comprehensive study, Head developed the map of cutaneous hyperalgesia. In the 1920s, the knowledge he acquired in humans (10) and by experimental work in animals was confirmed in humans by various clinical investigators who used paravertebral somatic nerve block, discussed in Chapter 102 in patients with pain caused by disease of various viscera (18, 19). Subsequently, the data were also confirmed by using rhizotomy or sympathectomy for permanent relief of various painful conditions such as cardiac pain (20).

Because the segmental sensory supply of the various viscera is via the sympathetic and parasympathetic nerves, it is presented after discussion of the ANS. It is also repeated in each chapter containing discussion of pain due to each specific type of visceral disease, together with depiction of the gross anatomy of the nerve supply to the particular viscus.

Peripheral Nerve Supply

With a few exceptions, each peripheral nerve contains fibers from two or more adjacent dorsal roots, as depicted in Figure 8-11. As with dermatomes, some overlap exists among peripheral nerves, but less than with dorsal roots: Interruption of the nerve produces an area of complete sensory loss surrounded by a field of altered or diminished sensibility. Both of these zones are smaller than the area of skin that the nerve supplies. Such an area is revealed only if the nerve is left intact and all of the adjacent nerves are cut. Figure 8-12 shows the peripheral nerve supply of the skin, and Figure 8-13 depicts the peripheral nerve supply of bones. It is important to note that the peripheral nerve supply of the skeleton is closely linked with the muscle innervation. Most of the bones receive their innervation from nerve twigs that have penetrated from the attached muscles. For example, the nerve to the quadratus femoris muscle sends twigs to that part of the bony pelvis to which this muscle is attached. Moreover, joints are usually supplied by two types of nerves: articular branches derived directly from major nerves that supply the joint exclusively, and “accessory” nerves that are short branches derived from nerves supplying the muscles near or surrounding the joint.

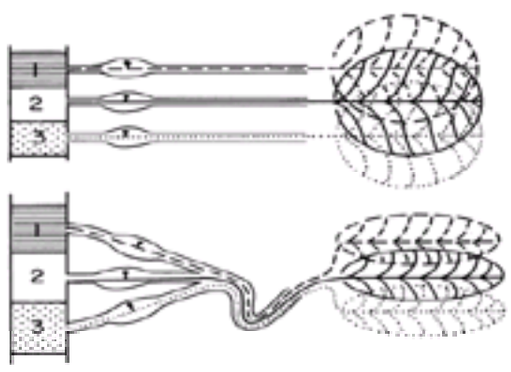

Figure 8-11. Simple diagrams to illustrate the overlap of cutaneous fields of segmental and peripheral nerves. In the upper figure three intercostal (segmental) nerves extending from the periphery to the spinal cord are represented. The lower figure illustrates a somewhat analogous but less extensive overlap in the peripheral nerves.

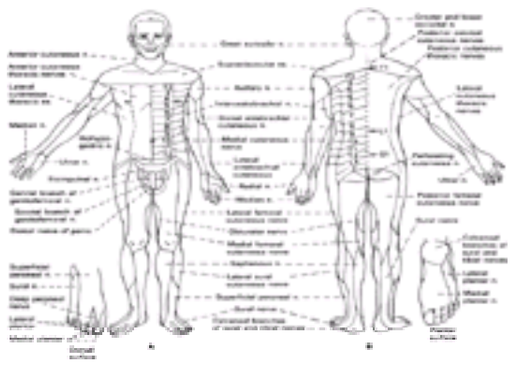

Figure 8-12. The cutaneous fields of peripheral nerves (n.). **A:** Anterior view. **B:** Posterior view. In both figures, the numbers on the trunk refer to the intercostal nerves. (Modified from Haymaker W, Woodhall B. *Peripheral nerve injuries: principles of diagnosis*. Philadelphia: WB Saunders, 1945.)

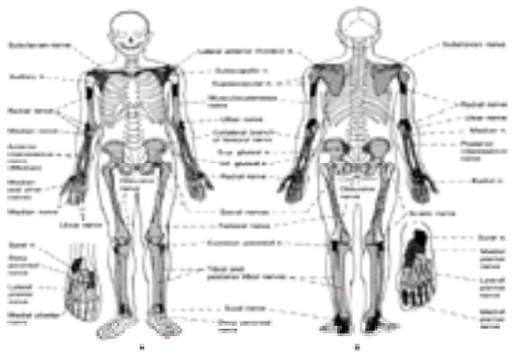

Figure 8-13. Peripheral nerve supply of the skeleton. **A:**Anterior view. **B:** Posterior view. The various peripheral nerve fields are indicated by different patterns. (Modified from Déjerine J. *Sémiologie du système nerveux*. Paris: Masson, 1914.)

Pain Sensibility of Tissues and Structures

This section contains a brief summary of the pain sensibilities of various body tissues and organs. Although mention of these is made throughout Chapter 3, here they are presented in a unified fashion to obviate the need for the reader to search for the information in various parts of that chapter.

Skin and Other Ectodermal Structures. The skin and mucous membranes in their entirety are pain sensitive to mechanical, thermal, or chemical injury, or a combination of these, and the pain is sharp, well localized, and often composed of two temporal parts: first pain and second pain. Other tissues of ectodermal origin, such as the *cornea* and the *dentin*, and the deeper structures of the *teeth* are also sensitive to noxious stimuli. The *conjunctivae* and the *glans penis,* like other mucous surfaces, are extremely sensitive to noxious mechanical and thermal stimuli. The subcutaneous tissues such as areolar tissue and fat are less pain sensitive because of the lesser number of nociceptive nerve endings. In contrast, deep fascia is very pain sensitive, mechanical or thermal injury causing moderately severe pain.

Musculoskeletal Structures. Skeletal muscles are sensitive to a variety of noxious stimuli, including injection of hypertonic saline or other algogenic substances, strong pressure, stretching, ischemia, and unduly forceful or sustained contraction during exercise. The severe pain and intermittent claudication caused by peripheral vascular disease are undoubtedly due to ischemia of the exercising muscle. Backaches, myalgias, and certain types of headaches are probably due to unduly prolonged contraction of the involved muscles. The tendons of muscles are sensitive to noxious stimuli, so strong pressure, injection of hypertonic saline, or squeezing causes pain.

Most *joints* are heavily supplied by nociceptors, including group IV and some group III afferents, which are markedly sensitized by chemical substances that are products of acute or chronic inflammation (see Chapter 3).

The *periosteum* is very sensitive to mechanical stimulation. Scraping with a periosteal elevator or stimulation of any kind results in moderately sharp pain. The cancellous portion of the bone is also pain sensitive, but the cortex is not.

Cranial Structures. Much of the *dura mater* can be incised, scratched, or cauterized painlessly in many patients. However, parts of the dura at the base of the brain and the dural arteries (particularly the middle meningeal and the great venous sinuses and their various tributaries from the surface of the brain) are uniformly pain sensitive. When these structures are pinched or stimulated electrically or stretched, pain is produced. The *cortex* of the brain and its pia-rachnoid covering can be stimulated electrically, burned, or incised without producing pain, but the *cerebral arteries* at the base of the brain, particularly the middle cerebral, vertebral, basilar, and posterior cerebral arteries, are sensitive, and noxious stimulation such as pinching, cutting, or electrical stimulation produces pain. Stimulation of the fifth, ninth, and tenth cranial nerves also produces pain. The *inner portion* of the brain, including its white matter, the ependymal lining of the ventricles, and the choroid plexus, is not sensitive to nociceptive stimuli. The *meninges* of the spinal cord have the same relative sensitivity as those that cover the brain.

Thoracic Viscera. The *visceral pleura* and the lung parenchyma are insensitive to nociceptive stimuli, but the *parietal pleura*, being richly supplied with somatic nerve endings derived from the intercostal and phrenic nerves, is very sensitive to painful stimuli. The *pericardium*, with the exception of its lower portion, which is supplied with nociceptive fibers from the phrenic nerve, is insensitive to noxious stimuli but produces pain in the presence of inflammation. The *heart* is insensitive to touching or manipulation of the ventricular walls or aortic ring or any other mechanical stimulation, but myocardial ischemia, endocarditis, vascular insufficiency, and certain other pathologic processes give rise to pain.

The *esophagus* is pain sensitive to chemicals applied to its mucosa, and abnormal motor function produces pain.

Abdominal Viscera. The *parietal peritoneum* is richly supplied with nerve endings derived from the intercostals and other spinal nerves and is sensitive to stretch and to chemicals. The visceral peritoneum and mesentery are insensitive to cut, burn, or scratch, but traction on the mesentery or rapid distension of the visceral peritoneum covering the spleen and liver results in pain.

The *stomach* and the rest of the *gastrointestinal tract* are also insensitive to cut, crush, or burns, but traction, rapid distention, and strong contraction under isometric conditions produce pain. Similarly, the normal mucosa is relatively insensitive to touch or pressure, but when inflamed, it is extremely sensitive to touch and chemical stimuli.

The *parenchyma* of the liver is insensitive to ordinary stimuli because it can be cut, burned, or torn without pain, but rapid enlargement of this organ, such as occurs in cases of cardiac decompensation or rapidly growing tumors, gives rise to pain, probably due to stretching of the hepatic capsule. The *gallbladder* is insensitive to cutting or clamping, but traction or distension causes pain that is especially severe when the gallbladder is inflamed. The *pancreas* is insensitive to stimuli that produce pain when applied to the skin, but inflammatory lesions or necrosis of this organ gives rise to excruciating pain. The *spleen* is also insensitive to cutting or mechanical stimuli, but inflammation of its serosa can give rise to pain, probably due to involvement of the parietal peritoneum. Rapid enlargement of the spleen is usually accompanied by pain caused by distension of its covering.

The *renal parenchyma*, like other solid viscera, can be cut, torn, or cauterized without pain, but traction on the kidney gives rise to pain due to the pull on the renal

blood vessels and the parietal peritoneum. Rapid distension of the *kidney, pelvis, ureters, bladder*, and *urethra* causes pain, especially in the presence of inflammation. *Kidney stones* are the most common cause of ureteral colic, one of the most painful disorders that can be experienced by humans.

The *body* of the uterus is insensitive to such mechanical stimuli as incision or gentle manipulation, but, as is well known, uterine contractions are invariably associated with pain. Stimulation of the *fallopian tubes* and *ovaries* gives rise to no sensations unless there is traction on the parietal peritoneum and the ligaments of the uterus. Faradic stimulation or rapid distension of the cervix causes pain referred to the lower abdominal wall, although this structure can be pinched with a forceps in conscious patients without invoking pain. The normal *vaginal mucosa* is insensitive to mechanical noxious stimuli. The *female external genitalia* have been found to be moderately pain sensitive to faradic stimulation; pain is felt at the site of stimulation. Pressure on the *testicle* causes excruciating pain, as does noxious heat.

AUTONOMIC NERVOUS SYSTEM

Because the ANS, especially sympathetic afferents and efferents, is frequently involved in various painful states, this is one of the most important portions of the nervous system to the physician involved in managing patients with acute and chronic pain. To properly manage the pain of angina pectoris, complex regional pain syndromes types I and II, pancreatitis, various peripheral vascular diseases, and other conditions, it is essential for the clinician to have thorough knowledge of the anatomy, physiology, and pharmacology of this system. For the anesthesiologist or other physician using nerve block therapy, it is also essential to have thorough knowledge and experience in techniques of blocking various portions of this system. These are discussed in Chapter 102. In this chapter, we discuss the general anatomic arrangement of the ANS and summarize the physiologic and pharmacologic considerations. As previously mentioned in Part IV, the sympathetic or parasympathetic nerves and the associated afferent nerves supplying various parts of the body are discussed in detail at the beginning of each section and also mentioned in some of the chapters contained in each section.

Anatomic Considerations

The ANS is composed of central and peripheral portions, as shown in Figure 8-14. The central portion consists of centers located in the cortex, hypothalamus, midbrain, and medulla and pathways located in the brainstem and spinal cord. The peripheral portion consists of afferent and efferent neurons, the axons of which are located outside of the central nervous system. The autonomic centers are discussed first, and then the peripheral parts of the system are considered. More detailed description can be found in the books by Hovelacque (21), Kuntz (22), Mitchell (23), and Pick (24) and the more recent paper by Janes et al. (25).

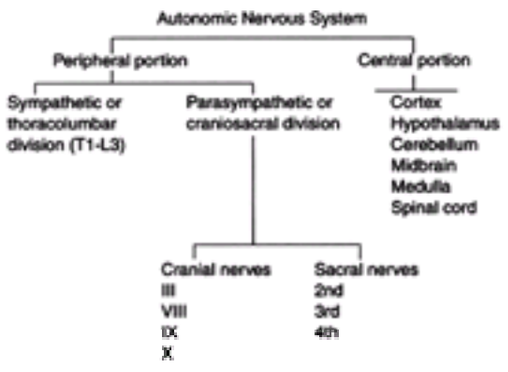

Figure 8-14. Autonomic nervous system.

Autonomic Centers

In the central nervous system, aggregates of neurons are functionally connected with the ANS by extensive ramifications that influence and coordinate all autonomic functions and, among other things, particularly integrate the control of respiration, blood pressure, body temperature, carbohydrate and fat metabolism, water balance, and sexual behavior.

The *cortex* provides integration of somatic and vegetative functions, including the correlation of conditioned reflexes, visceral processes, and pain with mental states. Experimental and clinical data (26) indicate that the major portion of the cortical influence on autonomic function emanates from the motor, premotor, and orbital regions of the frontal lobes. The cortical regulation of a given visceral function emanates from areas that are closely related to the cortical areas that influence the corresponding somatic function. In addition, fibers originating in the cortex pass to the autonomic centers in the hypothalamus and brainstem.

In the *hypothalamus* the anatomic centers of the ANS are most distinct and consist of 16 nuclei, depicted in Figure 5-11 and Figure 8-15. These include the supraoptic, paraventricular, suprachiasmatic, ventromedial hypothalamic, and dorsomedial hypothalamic nuclei, which are concerned with sympathetic function; the preoptic nucleus, which is concerned with parasympathetic function; and the mammillary nuclei, the actions of which are uncertain. In addition to these nuclei, autonomic nerve tracts in the hypothalamus integrate autonomic function among the various hypothalamic nuclei and between these and the limbic system, cerebral cortex, thalamus, and the reticular formation. A detailed discussion of the anatomy and physiology of the hypothalamus is given in Chapter 5.

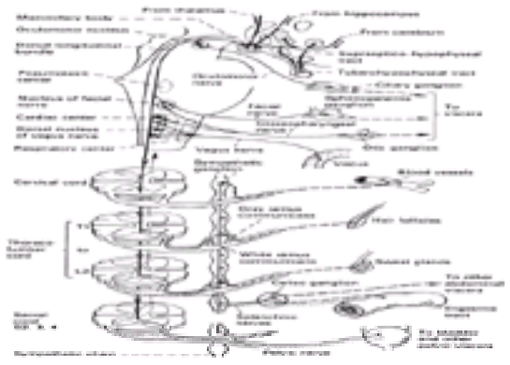

Figure 8-15. Schematic representation of autonomic pathways in the neuraxis and the efferent peripheral pathways. Note the connection among the various hypothalamic nuclei and between these structures and the nuclei and important autonomic centers in the brainstem and spinal cord. The dorsal longitudinal fasciculus (DLF) passes from the hypothalamus caudad through the central and tegmental portion of the mesencephalon and the tegmental portion of the pons to terminate in the reticular formation, the autonomic centers and cranial nerve nuclei in the brainstem, and in the intermediolateral cell column of the spinal cord. The DLF is composed of both crossed and uncrossed fibers, including some long ones and an extensive system of short fibers, which are arranged in the gray matter in frequent relays. Note also that the cell bodies of preganglionic sympathetic neurons are located only in spinal cord segments T-1 through L-2, whereas the parasympathetic neurons are located in cranial nerves and in S-2, S-3, and S-4. The solid lines represent preganglionic fibers, the dashed lines represent postganglionic fibers, and the dotted lines are afferent (sensory) fibers. Not shown are the sensory fibers contained in the facial, glossopharyngeal, and vagus nerves, which transmit nociceptive and other somatosensory information from the head.

The *cerebellum* plays a part in certain autonomic regulation, the anterior lobe being involved in the functions of respiration, circulation, and thermal regulation (27).

In the *midbrain*, *pons*, and *medulla* are located distinct autonomic centers that have been physiologically delineated. These include the nuclei, which give rise to the parasympathetic visceral efferent fibers of the cranial nerves, and special centers that regulate respiration and circulation.

The *thoracic* and *upper lumbar segments* of the spinal cord contain autonomic centers that regulate vasomotor activity, piloerection, and perspiration of the entire body as well as sympathetic and parasympathetic function of the viscera. The locations of the cell bodies of preganglionic sympathetic and parasympathetic neurons, which mediate their function in various parts of the body, are listed in Table 8-3. Some autonomic functions, such as vasomotor control, are bilaterally represented, whereas others, such as pupillary dilation, are unilateral. With bilateral representation, visceral nerve conduction takes place more effectively on the ipsilateral than on the contralateral side. Figure 8-15 depicts the autonomic pathways that connect the preganglionic neurons in the intermediolateral horn of the spinal cord with the hypothalamus and other brainstem structures.

Structure	Location of AC in spinal cord
Head and neck	T-1–4
Upper limb	T-2–8/9
Upper trunk	T-2–8
Lower trunk	T-9–L-2
Lower limb	T-10–L-2
Viscera	
Thoracic (sympathetic)	T-1–5 (8)
Abdominal (sympathetic)	T-5–L-2
Pelvic (parasympathetic)	S-2–4

TABLE 8-3. Autonomic centers (AC) in spinal cord

Peripheral Autonomic Nervous System

The peripheral portion of the ANS consists of pre- and postganglionic efferent fibers and afferent fibers from various body structures (22,23,28). These fibers are concerned with transmission of visceral sensation such as nociception, nausea, and fullness; with circulatory, respiratory, and visceral motor reflexes; and with the integration of visceral activities. Although many writers have followed the suggestion by Gaskell (29) and Langley (30) to restrict the term “autonomic nervous system” to efferent (motor) pathways, Mitchell (23), among others (28,31), points out the irrationality of this concept. If the role of the ANS is to regulate visceral function through reflex activity, it cannot do so without afferent and intercalary (connector) neurons as well as efferent (motor) neurons. In this book, the afferents associated with the ANS are referred to as “sympathetic afferents” and “parasympathetic afferents.”

The peripheral efferent pathways consist of a two-neuron chain, a primary presynaptic or preganglionic neuron, and a secondary postsynaptic or postganglionic neuron. The cell bodies of the primary preganglionic neurons are located in the central nervous system, either in the intermediolateral cell column of the spinal cord or in the visceral efferent nuclei in the brainstem. The axons of these cell bodies travel toward the periphery either by way of the anterior roots of the spinal nerves or through the cranial nerves, to reach outlying autonomic ganglia, in which they affect synaptic connection with the postganglionic neurons. The cell bodies of the postganglionic neurons are located within these outlying autonomic ganglia, and their axons pass to their terminal distribution in the wall of the viscera or in the wall of the blood vessels and to sweat glands and other target organs. On the basis of anatomic, physiologic, and pharmacologic characteristics, the peripheral portion of the ANS is divided into two parts: the parasympathetic or craniosacral division and the sympathetic or thoracolumbar division.

The cell bodies of the postganglionic neurons are arranged in aggregates known as *ganglia*, wherein the synapses between pre- and postganglionic neurons take place. As shown in Figure 8-16, there are four general groups of these ganglia, two with the sympathetic division and two with the parasympathetic division.

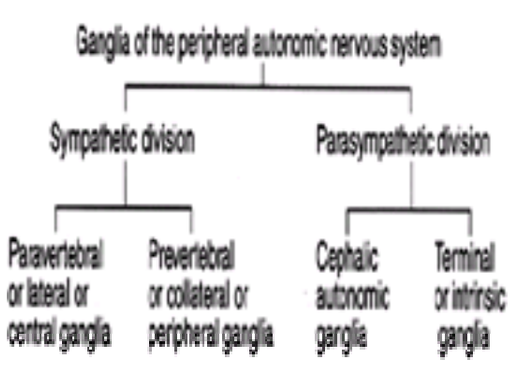

Figure 8-16. Ganglia of the peripheral autonomic nervous system.

Parasympathetic Division

Cranial Parasympathetics. The central portion of the parasympathetic division of the ANS consists of preganglionic fibers, which have their cell bodies in the gray matter of the brainstem, and their axons, which pass as component parts of the oculomotor, facial, glossopharyngeal, and vagus nerves (see Fig. 8-15). Those in the first three nerves synapse with short postganglionic fibers in the ciliary, sphenopalatine, otic, and submaxillary ganglia. The very long preganglionic parasympathetic fibers in the vagus terminate in intramural ganglia contained in the walls of the gastrointestinal tract, heart, and lungs, wherein they synapse with short postganglionic fibers that innervate the smooth muscles and glands in these organs.

Somatic afferent fibers are component parts of the facial, glossopharyngeal, and vagus nerves and transmit nociceptive and other somatosensory information from the ear, throat, back of the tongue, larynx, and tracheobronchial tree. Visceral afferents associated with the vagus nerve supply viscera in the chest and abdomen; transmit sensation of distension, fullness, and nausea; and constitute the afferent limb of reflex control of these structures.

Sacral Parasympathetics. The sacral portion of the parasympathetic division consists of preganglionic neurons, which have their cell bodies in the intermediolateral column of the gray matter of the second, third, and fourth sacral segments (see Fig. 8-15 and Fig 8-17). Their axons leave the spinal cord via the anterior roots of the nerves and run directly as the pelvic splanchnic nerves (nervi erigentes) to the pelvic plexuses. They pass through the plexus without interruption and finally reach and terminate in the terminal ganglia in the pelvic plexus and vesical plexus, and some in intramural ganglia of the urinary bladder, the descending colon, the sigmoid colon and rectum, and the genital organs. Afferent fibers associated with sacral parasympathetics transmit nociceptive information from the urinary bladder, lower part of the ureter, the descending colon, and the sigmoid colon and rectum. Other afferent fibers are involved in autonomic reflexes relevant to the functions of these structures.

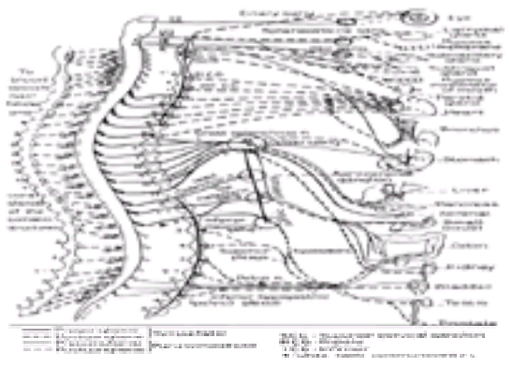

Figure 8-17. Distribution of peripheral autonomic nervous system to various structures of the body. On the reader's right are shown (from above downward) the four cranial nerves, which contain preganglionic parasympathetic fibers, the axons of preganglionic sympathetic fibers (which pass from the anterior root to the paravertebral sympathetic chain), and the parasympathetic preganglionic axons in S-2, S-3, and S-4. Note that the axons of all of the preganglionic sympathetic neurons pass via the white rami communicantes into the paravertebral chain, in which some synapse with postganglionic neurons, whereas others pass to the prevertebral sympathetic ganglia, in which they synapse with postganglionic fibers. On the reader's left are depicted the gray rami communicantes, containing postganglionic sympathetic fibers, which originate in the paravertebral chain and then pass to each of the spinal nerves to innervate blood vessels, hair follicles, and sweat glands in various parts of the body.

Sympathetic (Thoracolumbar) Division

The efferent portion of the sympathetic division of the ANS consists of preganglionic neurons, the two paravertebral (lateral) sympathetic chains, prevertebral and terminal ganglia, and postganglionic neurons (21,22,23 and 24) (see Fig. 8-15 and Fig 8-17).

Preganglionic Neurons. The cell bodies of the preganglionic neurons are located primarily in the first thoracic to second lumbar spinal cord segments, inclusive. Most of the cell bodies of preganglionic neurons are located in the intermediolateral (lateral) column of the spinal cord, but some become aggregated and form a second, less definite column on the medial side of the intermediolateral gray matter, which has been termed the *intermediomedial (medial) column* (22,23). Evidence also exists that some cell bodies of preganglionic neurons exist in the eighth cervical and third lumbar segments, and in some instances the seventh cervical and fourth lumbar spinal segments (32,33). In some instances, the axons of preganglionic neurons in the cervical cord descend, whereas those in the third and fourth lumbar segments ascend within the spinal cord and emerge through the first thoracic and second lumbar segments, respectively. Others pass via the eighth cervical or third (and perhaps fourth) lumbar anterior root and the homologous white rami communicantes.

The axons of these preganglionic neurons are carried in the anterior nerve root of the spinal nerve of the same segments and then via the white rami communicantes to synapse with postganglionic neurons in the sympathetic ganglia outside the neuraxis (see Fig. 8-17). The paravertebral ganglia and interganglionic fibers make up the lateral sympathetic chain, to which axons of preganglionic neurons first pass. On entering the sympathetic chain or trunk, some preganglionic axons end in the first ganglion they reach; some pass cephalad or caudad for varying distances within the sympathetic trunk before they synapse in the trunk; others pass through the chain without interruption to terminate and synapse within one of the prevertebral ganglia. Preganglionic fibers pass to and through the adrenal medulla and synapse within chromaffin cells, which are homologous to postganglionic neurons.

Preganglionic fibers from the upper five thoracic segments either terminate in the first sympathetic ganglion they reach or turn upward within the sympathetic trunk to synapse in a ganglion at a higher level, particularly the inferior or stellate ganglion and the intermediate, middle, and superior cervical ganglia. Some preganglionic fibers from the fifth to the tenth thoracic segments terminate in the first ganglion they reach; some ascend or descend; others pass through the paravertebral ganglia without interruption to become the superior thoracic (greater) splanchnic nerves, which terminate within the celiac ganglia (see Fig. 8-17). Some of the preganglionic fibers from the tenth to the twelfth thoracic segments and first and second lumbar segments terminate in the first ganglion they reach; some pass caudad; and others pass through the ganglia uninterrupted to become the middle thoracic (lesser) splanchnic nerves and the inferior thoracic (least) splanchnic nerves. The middle thoracic splanchnic nerves enter the celiac plexus and synapse in the aorticorenal ganglion, and the inferior thoracic splanchnic nerves pass directly to the renal ganglion, in which each synapses with postganglionic fibers.

Many preganglionic axons converge on each postganglionic neuron, whereas the collaterals of each preganglionic axon diverge into many postganglionic neurons. An extraordinary variability exists among ganglia and the quantitative degree of convergence and divergence. The number of postganglionic neurons in a ganglion is usually considerably higher than the number of preganglionic axons innervating it. The divergent and convergent synaptic connections guarantee a high safety factor for the transmission of excitation in the ganglia.

Postganglionic Neurons. The axons of some of the postganglionic neurons, which have their cell bodies in the paravertebral chain, become gray rami communicantes and join the spinal nerves and thus are distributed to the skin and various other somatic structures. The axons of other postganglionic neurons, which have their cell bodies in the paravertebral chain, pass to the thoracic and pelvic viscera, whereas the postganglionic neurons, which have their cell bodies in the prevertebral ganglia, become part of the prevertebral plexuses and thus are distributed to various viscera in the abdomen.

In addition to this classic distribution, some synapses take place in spinal nerves and thus bypass the sympathetic trunks (22,23) (Fig. 8-18). Moreover, some intermediary ganglia are located on the white rami communicantes or anterior spinal nerve roots and are thus located outside of the lateral sympathetic trunk (22,23). These anomalous sympathetic pathways are most frequent in the lower cervical and upper thoracic sympathetic trunk and in the lower thoracic and upper lumbar sympathetic trunk. As a result of these anomalies, the usual technique of surgical sympathectomy does not include them and may be responsible for incomplete sympathectomy of the limbs. In contrast, these anomalous pathways are invariably involved by sympathetic blocks because the local anesthetic solution diffuses to these various anomalous structures. The clinical implication of this is important: Even though a prognostic sympathetic block with local anesthetic produces complete sympathetic interruption (and pain relief), the sympathectomy might not. In such cases, the incomplete resection can be proven by a postsurgical sympathetic block, which invariably produces evidence of complete interruption and pain relief in sympathetically dependent pain syndromes.

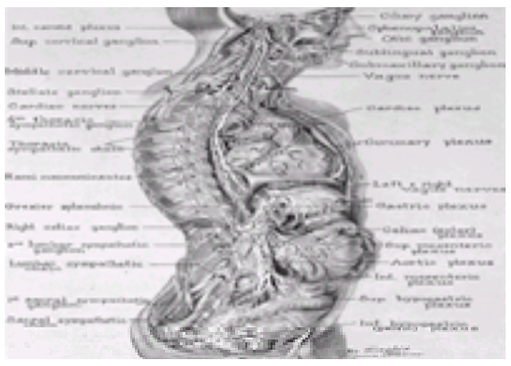

Figure 8-18. Gross anatomy of the peripheral autonomic nervous system. (After Hirschfeld L. *Traite et iconographie du système nerveux*, 2nd ed. Paris: Masson, 1865.)

Lateral Sympathetic Trunk. The paravertebral ganglia are segmentally arranged in two vertical rows, each ganglion being connected to the adjacent ganglia by longitudinal ascending and descending nerve fibers, thus forming what are commonly called the *two sympathetic trunks* (Fig. 8-19). These two trunks extend along the ventrolateral aspect of the vertebral column from the second cervical vertebra to the coccyx. The cervical ganglia lie ventral to the base of the transverse processes;

the thoracic ganglia lie over the heads of the ribs; the lumbar ganglia lie on the anterolateral surface of the lumbar vertebrae; and the sacral ganglia lie on the anterior surface of the sacrum medial to the anterior sacral foramina (see Chapter 102 for illustrations). The cephalic end of each of the two trunks is continued upward as the internal carotid nerve, branches of which eventually become distributed to the head. The caudal end of the trunks converges and terminates in front of the coccyx as the ganglion impar.

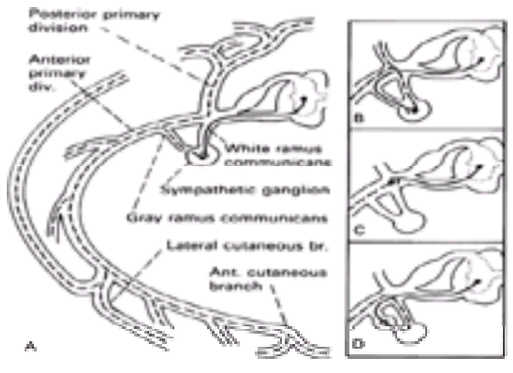

Figure 8-19. **A:** The course of sympathetic fibers in thoracic spinal nerves. Note particularly the course of the preganglionic fibers in the rami communicantes. Preganglionic fibers are shown as solid lines and postganglionic fibers as dashed lines. **B**, **C**, and **D** show unusual sites of synapse between preganglionic and postganglionic fibers. Section of the sympathetic ganglion in **C** would not produce interruption of the sympathetic pathways. (Ant., anterior; br., branch; div., division.)

In the cervical region, a condensation of the segmental ganglia has occurred, there being only four: the superior, middle, intermediate, and inferior ganglia. In 80% of subjects, the inferior cervical ganglion is fused with the first thoracic ganglion, forming the stellate ganglion (21,23). Below this level the paravertebral ganglia are segmentally arranged, there being 10 to 12 thoracic, three to five lumbar, four or five sacral, and one coccygeal.

Macroscopically, the lumbar sympathetic chain is the most variable portion of the peripheral sympathetic system, particularly with regard to the number of ganglia and the general forms of the two chains, which are extremely inconstant not only among different individuals but also on each side of the same person. According to Hovelacque (21), it is almost exceptional to find five ganglia, as classically described in most textbooks; it is more common to find only four or three, and not uncommonly a fusion of the first lumbar and twelfth thoracic ganglia. In addition, one rarely finds a chain on one side that is the same shape and size and in a similar position as the one on the other side. The location of the lumbar ganglia is also inconstant. In some instances they are segmentally located, whereas in other cases they are closely grouped and lie over particular segments, the most common location being between the second and fourth lumbar vertebrae. The ganglia may be situated on the body of the vertebra immediately in front of the aponeurotic arcades giving origin to the psoas muscles, or they may lie anterolateral to an intervertebral disk, the upper portion of the ganglion being in front of the vertebra above and the lower portion in front of the vertebra below.

Connections between Sympathetic Trunks and Spinal Nerves. The sympathetic trunks are connected to the spinal cord and spinal nerves by one or more rami communicantes and with visceral and somatic afferent fibers.

White Rami Communicantes. The white rami communicantes consist of myelinated preganglionic neurons and visceral afferent fibers. These are limited in their distribution and are present only in the thoracic and upper two or three lumbar segments, but usually not in the cervical, lower lumbar, or sacrococcygeal segments (see Fig. 8-17). These 14 or 15 pairs of white rami communicantes carry the only preganglionic fibers of the sympathetic outflow and are therefore the only connections between the central nervous system and the peripheral sympathetic system. All sympathetic motor impulses to the body and visceral sensory impulses to the central nervous system are conveyed through these anatomic bridges.

Gray Rami Communicantes. The gray rami communicantes consist of unmyelinated postganglionic sympathetic fibers, which pass from the sympathetic trunks to each of the spinal nerves to become distributed as vasomotor, sudomotor, and pilomotor fibers in the somatic areas. The vasoconstrictor fibers consist of unmyelinated postganglionic neurons, the cells of which arise in the ganglia of the sympathetic trunk, and the axons of which pass by way of the gray rami communicantes to all spinal nerves. By coursing peripherally through these nerves, they finally reach the blood vessels of the trunk and limbs. The pilomotor and sudomotor fibers have a similar course.

In addition to the gray rami communicantes, the sympathetic trunks give off rami that supply the viscera. The most important of these are the carotid nerve; the superior, middle, and inferior cardiac nerves; the superior, middle, and inferior thoracic splanchnic nerves; and the lumbar and sacral splanchnic nerves. They supply sympathetic fibers to the viscera of the head, chest, and abdomen. These are discussed in greater detail in various chapters of Part IV.

Sympathetic Afferents. Many sympathetic afferents mediate visceral pain from the heart and from the abdominal viscera, except some pelvic organs that are supplied by parasympathetic afferents. Although these fibers do not establish direct connections with the peripheral autonomic neurons, they pass through the ganglia of the sympathetic trunk, at which point they can be surgically or chemically interrupted. As previously mentioned, the cell bodies of visceral (and somatic) afferent fibers are located in the dorsal root ganglia of spinal nerves. Their short central processes pass to the spinal dorsal horn, where they make synaptic connection with dorsal horn interneurons and also with the cell bodies of neurons, the axons of which make up ascending pathways. Some dorsal horn neurons onto which primary afferents synapse pass anteriorly to connect with somatic motor neurons, and some make synaptic connection with preganglionic neurons in the intermediolateral cell column. Through these spinal segmental circuits, visceral afferents affect reflex connections, which are involved in increased skeletal muscle tension and increased sympathetic activity, and which in turn alter the function of the viscera (see Fig. 8-16).

The long peripheral processes of sympathetic afferents pass through the distal part of the posterior root, the formed spinal nerve, the white rami communicantes, and then through the ganglia of the sympathetic trunk without interruption to reach the viscera by one of two ways. One is by passing through one of the cardiac or splanchnic nerves and through the corresponding prevertebral plexus. The other is by passing through one of the nerves that passes from the sympathetic trunk directly to the viscera without traversing any of the prevertebral plexuses.

Ganglia and Plexuses of the Peripheral Autonomic Nervous System

Cephalic Ganglia. Autonomic ganglia include the ciliary, sphenopalatine, otic, and submaxillary ganglia, which are situated in relation to the third, fifth, and ninth cranial nerves. Each of these ganglia receives sympathetic postganglionic fibers, parasympathetic preganglionic fibers, and sensory fibers. The anatomy of these ganglia, as well as the sympathetic plexuses to the head, are discussed in Chapter 46, concerned with the anatomic and physiologic bases of pain in the head.

Autonomic Plexuses in the Chest. Three great prevertebral plexuses exist, consisting of aggregates of ganglia and interconnecting sympathetic, parasympathetic, and afferent fibers. These include the cardiac plexuses, the pulmonary plexuses, and the esophageal plexuses and are discussed in Chapter 60 in connection with the anatomic and physiologic bases of pain in the chest.

Abdominal Prevertebral Ganglia/Plexuses. As in the chest, three large prevertebral plexuses exist, which include prevertebral sympathetic ganglia as well as parasympathetic fibers from the vagus or the sacral parasympathetics and afferent fibers. These include (a) the celiac (solar) plexus, which breaks into approximately 10 important subsidiary plexuses that supply the abdominal viscera above the pelvis; (b) the superior hypogastric plexus; and (c) the inferior hypogastric or pelvic plexus, which supplies the pelvic viscera. These are discussed in Chapter 65, concerned with the anatomic and physiologic bases of abdominal pain, and Chapter 70, concerned with the anatomic and physiologic bases of pelvic pain.

Sympathetics to the Limbs and Trunk. The sympathetic nerve supply to the limbs is discussed in Chapter 54, dealing with the anatomic and physiologic bases of pain in the upper limb, and in Chapter 75, concerned with the anatomic and physiologic bases of pain in the lower limbs.

Summary of Sympathetic and Nociceptive Supply to Body Structures

Table 8-4 summarizes the sympathetic and nociceptive pathways to various body structures. It is based on information contained in the first edition of this book and subsequent comprehensive reviews (28,34) and information published by Mitchell (23), Pick (24), Pick and Sheehan (35), Netter (4), and Meyer (36). The parasympathetic supply to these various structures is not included for the sake of clarity and also because the origins of preganglionic parasympathetic fibers, their routes, and the locations of postganglionic fibers have previously been mentioned and are discussed in detail in Chapter 46, Chapter 54, Chapter 60, Chapter 65, Chapter 70, and Chapter 75.

TABLE 8-4. Summary of sympathetic and nociceptive nerve supply to more important body structures

Pharmacology and Physiology of the Autonomic Nervous System

This section on the pharmacology and physiology of the ANS is included for the sake of completeness and is *not* intended to be all inclusive. A few pharmacologic principles and the physiologic action of sympathetic and parasympathetic nervous systems are considered. Detailed discussions can be found elsewhere (21,23,29,35).

Pharmacology

Neurohumeral transmission in the peripheral ANS occurs in principle by the same mechanism as that at the neuromuscular endplate and at central synapses (Fig. 8-20). In contrast to the endplate, however, the pre- and postsynaptic structures in the ANS are extremely variable (myocardial cells, smooth muscle cells, gland cells, and neurons). Moreover, the density of innervation varies greatly among different smooth muscles.

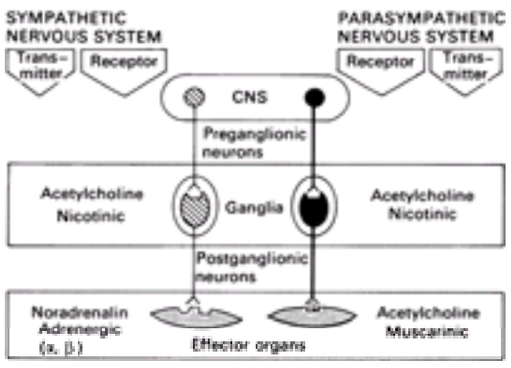

Figure 8-20. Transmitter substances in the peripheral autonomic nervous system. (Modified from Jänig W. The autonomic nervous system. In: Schmidt RF, Thews G, eds. *Human physiology*. Berlin: Springer-Verlag, 1983:111.)

Acetylcholine. Acetylcholine is released at all preganglionic autonomic nerve endings, both sympathetic and parasympathetic, and also by most postganglionic parasympathetic neurons—so-called cholinergic neurotransmitters. Some sympathetic postganglionic neurons are also cholinergic—those to the sweat glands and perhaps the vasodilator neurons to the resistance vessels in the skeletal muscles. The action of acetylcholine on the postsynaptic membranes of the postganglionic neurons can be simulated by nicotine and its action on the effector cells by muscarine. This suggests there are two kinds of receptors to which acetylcholine reacts: nicotinic and muscarinic, respectively (37,38). It has long been known that there are drugs that selectively block one or the other action. The nicotinic action of acetylcholine on the postganglionic neurons can be blocked by quaternary ammonium bases, which are thus called *ganglionic blocking agents*. The muscarinic action of acetylcholine can be selectively blocked by atropine (see Fig. 8-20).

Norepinephrine. Norepinephrine (noradrenalin) is the transmitter substance in sympathetic postganglionic nerve endings, and these cells are called *adrenergic neurons*. The cells in the adrenal medulla, which are homologues of the postganglionic neurons, mainly release epinephrine (adrenaline) into the bloodstream (80% adrenaline and 20% noradrenaline). The response of organs to catecholamines is mediated by two types of receptors: a-adrenergic and b-adrenergic receptors. As is well known, a variety of pharmacologic agents can either enhance or block the a-adrenergic and b-adrenergic action of the catecholamines.

Physiology

The ANS regulates activities that are normally not under voluntary or conscious control, including such important physiologic processes as metabolism, circulation, respiration, body temperature, digestion, sweating, and endocrine secretion. The integrating action that is exerted over these and other physiologic processes helps to maintain the constancy of the internal environment. This integration of function, termed *homeostasis* by Cannon (39), frees the individual from having to pay constant attention to the management of bare existence. It thus obviates the necessity of always being alert to the constant danger to which a changing environment subjects the individual.

All portions of the ANS take part in homeostasis, and the function of some of these parts is relevant to pain. The part played by the central portions has been alluded to in connection with the anatomy. The functions of the hypothalamus and the limbic system in pain are discussed in some detail in Chapter 5. The part played by the peripheral portion of the ANS in the regulation of autonomic function and homeostasis deserves emphasis because of the significant role its dysfunction plays in some painful states.

The sympathetic and parasympathetic divisions of the ANS have mutually coordinated actions that are often antagonistic, thus maintaining a functional balance. This balance is made possible by the dual autonomic supply of almost all of the viscera and of the other parts of the body. The effects of stimulating either portion of the ANS and its impact on various organs, visceral structures, and effector cells are summarized in Table 8-5. It deserves strong emphasis that in most situations the two systems act in an exquisitely synergistic fashion. For example, a reduction in arterial blood pressure produces a reflex response on the part of the cardiovascular system that consists of an increase in the rate and contractility of the heart and an increase in peripheral vascular resistance. This increase in heart and peripheral vascular resistance is brought about by an increase in the activity of the sympathetic nervous system and a concomitant and exquisitely coordinated decrease in the activity of the parasympathetic system (functional synergy).

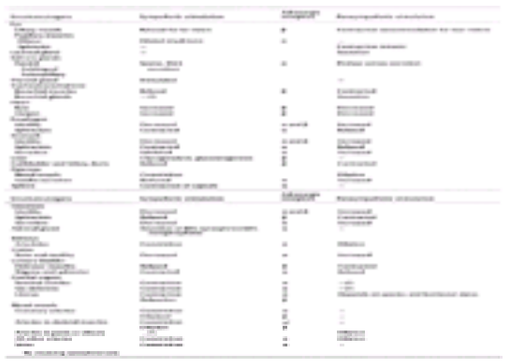

TABLE 8-5. Physiologic responses to autonomic stimulation

Close study of Table 8-5 makes it obvious that the sympathetic outflow is catabolic in function, a fact that is duly emphasized in discussing the pathophysiology of acute pain in Chapter 9. Although the sympathetic system is considered not absolutely essential to life, because in its absence one can survive in a very sheltered existence, it does have the important function of protecting the organism against adverse conditions by immediately and simultaneously activating all organs through rapid diffuse action. This prepares the individual for “fight” or “flight” by increasing cardiac output, through chronotropic and inotropic action and increase in peripheral resistance with consequent rise in blood pressure; an increase in blood sugar; contraction of the spleen with an increase in circulating red blood cells; constriction of all blood vessels (except those of the brain, heart, and skeletal muscles), resulting in redistribution of the blood to where it is needed most (the high-priority organs); and dilation of the bronchi and inhibition of the gastrointestinal and urinary functions. This rapid and diffuse action is made possible by the aforementioned vast synaptic connection of pre- and postganglionic fibers, a characteristic that is not common to the parasympathetic division, in which there is a one-to-one relationship between pre- and postganglionic neurons.

In contrast to the catabolic function of the sympathetic system, stimulation of which often gives rise to an extraordinary liberation of energy, the parasympathetic function is anabolic and most essential for life. It is concerned with conserving and storing energy, by slowing the heart rate, by enhancing digestion and absorption of food through stimulating the gastrointestinal tract, and by emptying the hollow organs, including the lower colon and urinary bladder, thus aiding in the elimination of waste products.

The functional balance that is normally maintained by the two systems is disturbed in certain disease states, either by the hyperactivity of one or hypoactivity of the other, or a combination of these. The resultant disturbance in autonomic function, if persistent, can prove deleterious to the entire organism. Linkages exist between the autonomic and immune systems that may be important in the production of disease states and the response to neoplasia and other chronic disease that may lead to pain (40). Pain itself may alter the immune response and thereby alter the progression of a disease (41). Animal and human physiologic and pharmacologic studies of visceral as well as somatic pain have demonstrated both plasticity and functional characteristics that are far more complex than the basic anatomy described in this chapter; entire books have been written, for example, on visceral pain (42). Some of these issues are discussed in Chapter 3, Chapter 4 and Chapter 5.

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CHAPTER 9

General Considerations of Acute Pain

Barbara A. Coda and John J. Bonica

Acute pain consists of a complex constellation of unpleasant sensory, perceptual, and emotional experiences and certain associated autonomic, cognitive, emotional, and behavioral responses. Invariably, acute pain and these associated responses are provoked by noxious stimulation produced by injury or disease of skin, deep somatic structures, or viscera or abnormal function of muscle or viscera. The pathophysiology of acute pain is fairly well understood; its diagnosis is usually not difficult, and with important notable exceptions mentioned in the following chapter, therapy is effective. As a result of effective treatment, the self-limiting nature of the disease or injury, or both, and the pain and associated responses usually disappear within days or weeks. Improper therapy, however, can cause the acute pain to persist and the pathophysiology to progress to a chronic condition.

The purpose of this chapter is to give a historical perspective and to discuss fundamental aspects of acute pain that are applicable to various painful conditions considered in detail in other parts of the book. These include general characteristics, mechanisms, and the autonomic reflex responses associated with the various types of acute pain. The chapter is presented in six sections: Basic Considerations, including classification and general comments on etiology and epidemiology; Superficial (Cutaneous) Pain; Deep Somatic Pain; Visceral Pain; Referred Pain; and Biology and Pathophysiology of Acute Pain.

BASIC CONSIDERATIONS

That acute pain of peripheral origin is usually caused by injury or disease of the skin, subcutaneous tissue, or deep somatic structures, spasm of skeletal muscles or smooth muscles of the hollow viscera, or disease or abnormal function of the viscera is well known. Acute pain involving peripheral-central mechanisms is caused by injury, disease, or inflammation of the peripheral nervous system, whereas acute pain of central origin is caused by disease of the neuraxis. Because acute pain caused by diseases of the nervous system presents specific issues, it is omitted from this chapter but is considered in Parts III and IV.

The division of pain of peripheral origin into superficial and deep pain is based on the quality of pain and the structure from which nociception is initiated. In his classic book, Lewis (1) emphasized the importance of distinguishing superficial and deep types of pain by stating that “the difference in the qualities of skin pain and of deep pain is so clear and each belongs so exclusively to the corresponding structures that it would perhaps seem unsafe to class both together under the one unqualified term 'pain.'” He suggested that the differences might be caused not only by the involvement of “two corresponding systems of peripheral nerves,” but also by the embryologic origin of each structure: Skin pain arises from ectodermal structures and deep pain is derived from mesodermal structures, whereas “the endodermal structures are either devoid of pain fibers or contain very few.” Lewis insisted that no differences exist between deep somatic pain and visceral pain. Cervero (2,3) also used an embryologic approach to classify pain within the perspective of current knowledge, but supported the differentiation between pain from visceral structures and pain from somatic structures. He noted that pain of ectodermal origin (skin and mucous membrane) is characterized by its good localization and *brightness*; a pain of mesodermal origin corresponds to the present concept of deep pain, and pain of endodermal origin is represented by visceral pain: “The degree of ill-localization and dullness would be greater in pain of endodermal origin than that of mesodermal origin.” Peripheral mechanisms that contribute to these differences have been reviewed previously (4) and are considered in detail in Chapter 3.

Magnitude of the Problem

Acute pain problems are the most frequent reasons why patients seek the help of family practitioners and various other specialists; they are routinely encountered in emergency room care, the postoperative setting, obstetric practice, sports medicine, and the care of trauma and burn patients. In family practice, acute headache, minor injuries, and many other disorders routinely result in patients' requests for pain relief. This is also true in the practice of orthopedic surgery, dermatology, and virtually all other specialties of medicine and in dentistry and osteopathy as well as other, less orthodox, types of practices, such as chiropractic and acupuncture. Nurses spend a significant portion of their professional time providing relief of acute pain.

The incidence of acute pain problems for which health care is sought or for which medication is taken is vast, but precise data derived from comprehensive national epidemiologic surveys are not available. The following are general comments on the incidence of acute pain in various injuries, diseases, and disorders. Results of a national survey published in 1984 indicate that in a 1- year time period, more than 40 million visits were made to office-based physicians in the United States because of new pain (5). These were self-referred visits in which pain was the chief complaint, and the physician had not previously seen the patient for the condition associated with the pain. The pain complaints were diverse and included earache, headache, chest pain, back pain, gastrointestinal pain, and pain in other parts of the body. The largest proportion (41%) presented with musculoskeletal pain, particularly that localized to the lower and upper back. This figure represents the initial visit for the condition; the cumulative number was probably significantly higher because many of these patients made return visits. Although more recent data regarding physician visits for a chief complaint of new pain are not available, information about the number of physician visits for painful conditions suggests that the problem is not decreasing. In 1995 and 1996, musculoskeletal problems remained one of the most frequent principal reasons for visits and accounted for approximately 90 million visits each year (6,7). In addition, large numbers of visits were estimated for the following pain-related visits: ear and throat symptoms, 35 million; stomach and abdominal pain, spasms or cramps, 18 million; chest pain, 13 million; and headache, 11 million. In 6 of 10 visits, medication was prescribed, and the most common type of medication was for pain relief (approximately 14% of all medications in 1995 and 1996) (6,7).

Data published by the National Center for Health Statistics suggest that, in 1996, 129 million visits were related to acute injuries. Americans sustained 9.8 million fractures and dislocations, 19.4 million sprains and strains, 12.7 million open lacerations and wounds, 12.1 million contusions and other superficial injuries, and approximately 8.6 million “other concurrent injuries” (7). Because most of these injuries involved skin, subcutaneous tissue, bone, and other pain-sensitive structures, more than 80% of these persons experienced acute pain either at the time of injury or a few hours later (see Chapter 41 and Chapter 43). In addition, each year more than 1.5 million burns are experienced; burns and associated surgeries cause pain that may last for a few days to weeks and months, and many patients require prolonged hospitalization (see Chapter 42).

In 1996, nearly 25 million “surgical procedures” were performed on ambulatory patients and inpatients (8). Included in this total are nearly 1 million cardiac, thoracic, and major vascular surgeries; more than 7 million musculoskeletal surgeries; approximately 3 million abdominal surgeries; 1 million nose, throat, and dental surgeries; 3 million obstetric and gynecologic surgeries; more than one-half million debridements, skin grafts, and mastectomies; and 1 million renal and genitourinary tract surgeries. These totals do not include minor procedures and those expected to cause minimal pain, such as biopsies, lens and cataract surgeries, and nonorthopedic laparoscopic procedures. Based on available information, a large proportion of these surgical patients is likely to have experienced moderate to severe pain, lasting from 1 to 7 days (see Chapter 41). Moreover, a majority of the nearly 3 million women who experience labor and vaginal delivery each year are likely to have suffered

moderate to severe pain during childbirth (see Chapter 71).

A comprehensive and most revealing source of information on the incidence and prevalence of various types of pain is the Nuprin Pain Report (9). This publication contains data derived from the first nationwide survey on the prevalence of pain, which was carried out in 1985 by Lou Harris Associates under the sponsorship of Bristol-Myers Company. The survey was limited to adults and provided detailed information on the demographic characteristics of pain sufferers; the effect of pain on the work and lives of Americans; how people cope with pain; the relationship between pain, stress, and a number of environmental factors; use of physicians and other health professionals in the treatment of pain; and the relationship between pain and different lifestyles and behavior patterns. An abbreviated summary is given in Table 9-1. Most of the data have a sampling error of approximately 3% to 6% and therefore are likely to be representative of the pain experienced by adult Americans. The survey indicated that most Americans experience three or four different types of pain every year. Approximately one-half of those with pain have only an occasional problem 1 day to 5 days in duration, and in the majority the pain is mild to moderate. On the other hand, pain duration was 31 days or more in 32% of those with joint pain, in 27% of those with bacand in 7% to 10% of those with other types of pain. Moreover, the pain was severe or excruciating in more than one-third of the persons with pain in six of the seven categories.

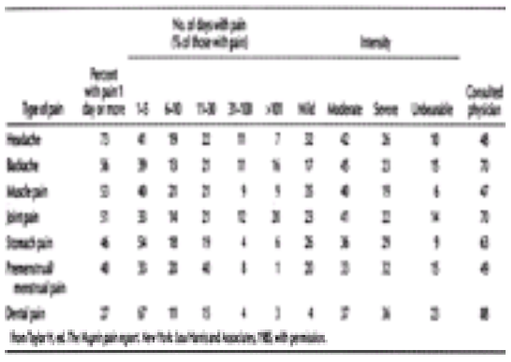

TABLE 9-1. Prevalence of pain

The Nuprin report also showed that physicians were consulted by 39% of those with mild pain, 51% with moderate pain, 74% with severe pain, and 82% with unbearable pain. Dentists were consulted by 12% of those with headache and 88% of those with dental pain; among the latter, 12% had mild pain, 18% moderate pain, 31% severe pain, and 48% excruciating pain. Clinical pain specialists were consulted by only 4% of those with headache, 7% of those with backache, and 5% of those with stomach pain, and, as expected, most of these were patients with severe or excruciating pain. These data suggest that surveys based on visits to physicians and other health professionals seriously understate the prevalence of pain. The survey also revealed that more than 4 billion workdays were lost by all adults, including 550 million by those employed full-time. Adding workdays lost by teenagers 17 years or younger and adults employed part-time gives a total loss of more than 650 million workdays by Americans in 1985. Using the mean income per day for that year, the data suggest that pain cost the American people more than $65 billion per year in loss of work productivity.

SUPERFICIAL (CUTANEOUS) PAIN

Superficial pain includes pain derived from the skin, subcutaneous tissue, and mucous membrane (see Chapter 3, Chapter 4 and Chapter 5). Noxious stimuli that are moderate and brief do not produce significant tissue damage and consequently have the purpose of alerting the individual and protecting him or her from external threat of injury. Throughout this text such stimuli are labeled *transient pain*. They rarely lead to health care consumption. Actual tissue damage that produces acute pain is caused by external or iatrogenic trauma, by burns or chemical agents applied to the skin, or by dermatologic disorders. The noxious stimuli associated with these conditions activate nociceptors that transduce the stimuli into nociceptive impulses that are transmitted to the neuraxis via A- d and C fibers. In addition, the tissue injury causes liberation of intracellular substances that produce sensitization characterized by (a) decrease in threshold; (b) increase in responsiveness to suprathreshold stimuli, manifested by decreased latency or greater number of impulses, or both; (c) the development of low-frequency spontaneous discharges; and (d) afterdischarge. These mechanisms are responsible for the pain, tenderness, certain associated sensations, and segmental and suprasegmental reflex responses.

Characteristics of Superficial Pain

The characteristics of superficial pain that distinguish it from deep somatic and deep visceral pain are its quality and localization. In 1937, Lewis described the two-phase response evoked by a single noxious stimulus applied to the skin, superficial tissue, or mucous membrane (10). These phases, called *first* and *second pain*, have been studied by Price and colleagues (11,12). Nociceptive mechanisms subserving these sensations, as well as their modulation, are described in Chapter 3 and Chapter 4. First pain, which is mediated by A-d nociceptors, is brief and localized, and has a sharp, pricking, or stabbing quality. This is followed 1.0 to 1.5 seconds later by a second burning, throbbing, or aching sensation of longer duration, which is mediated by C-nociceptive afferents (12). These qualities of pain are influenced by the extent of the injury and the time required for healing. In approximately one-third of the patients with acute injuries, an initial phase of no pain also exists. This phenomenon is discussed in the last section of this chapter, because it also applies to injuries to the deep somatic structures.

Sensation Associated with Cutaneous Pain

Superficial pain is usually associated with cutaneous tenderness, hyperalgesia, and hyperesthesia; in certain conditions, allodynia also occurs.

Cutaneous Tenderness

Cutaneous tenderness is said to be present when pain and discomfort are elicited by moderate pressure on the skin. This is related to, but is somewhat different from, hyperalgesia and allodynia. Pain may or may not be present concomitantly. The tenderness may occur with inflammation of the skin or after trauma to the skin, subcutaneous tissue, or deeper muscular tissue, and is likely caused by sensitization of nociceptors. Cutaneous tenderness can be elicited by pinching or pressing on the skin, and any area with cutaneous tenderness should always be compared with the symmetrically identical area on the opposite side.

Hyperalgesia and Allodynia

As noted in Chapter 2, *hyperalgesia* is increased sensitivity to noxious stimulation, whereas *allodynia* is pain caused by a stimulus that does not normally provoke pain. Among his early observations, Lewis (13) identified two distinct types of hyperalgesia: primary and secondary hyperalgesia. Sensitization at the site of injury to the skin, subcutaneous tissue, or mucous membrane is called *primary hyperalgesia*. Cutaneous hyperalgesia occurs after sustained exposure to ultraviolet radiation (sunburn), thermal or chemical burns, and laceration, contusions, or cuts of the skin. Primary hyperalgesia is characterized by a lowered pain threshold, increased response to suprathreshold stimuli, and spontaneous pain. *Secondary hyperalgesia* refers to changes that occur in a much larger area that surrounds the site of injury. It is characterized by hyperalgesia as well as allodynia. Within this diffuse region of secondary hyperalgesia, a smaller erythemic area of vasodilatation occurs called the *flare*, presumably caused by increased blood flow, and some edema caused by increased vascular permeability (14).

Cutaneous hyperalgesia also may occur with acute diseases of the peripheral nerves such as herpes zoster, and cutaneous hyperalgesia and allodynia also frequently develop after peripheral nerve injuries (complex regional pain syndrome type II) and central pain states. As discussed later in this chapter (see Cutaneous Hyperalgesia, Hyperesthesia, and Tenderness), cutaneous hyperalgesia also can be associated with deep somatic pain and can be a referred phenomenon of visceral pain.

Mechanisms of Cutaneous Hyperalgesia and Allodynia

The mechanisms of hyperalgesia and allodynia have been the subject of intense study for three-fourths of the twentieth century, and many speculations and hypotheses have been proposed to explain these phenomena. An extensive review of the older literature can be found on pages 94 through 101 of the first edition of this book. The most accepted hypotheses regarding the mechanism of cutaneous hyperalgesia include (a) sensitization of nociceptors by the endogenous chemicals

liberated from damaged tissue, (b) the axon reflex, and (c) increased sensitivity of dorsal horn neurons. Studies reviewed in the following sections suggest that sensitization of nociceptors is the basis for primary hyperalgesia, whereas secondary hyperalgesia involves neural elements, with axon reflex, changes in dorsal horn neurons, or both.

Sensitization of Nociceptors. LaMotte and associates (15) and Meyer and Campbell (16), among others, have studied the sensitization of different types of nociceptors in primary hyperalgesia by comparing the altered response of monkey nociceptors with human psychophysical responses to tissue injury caused by noxious heat. The results of these studies have been summarized by Meyer and colleagues (17). The marked primary hyperalgesia to heat after a burn to the glabrous skin is the result of sensitization of high-threshold mechanical nociceptors [Meyer and colleagues (17) labeled these *AMHs* (A-d nociceptors sensitive to intense mechanical and heat stimuli)]. Glabrous skin C-fiber polymodal nociceptors (CPNs) do not sensitize regardless of the intensity of the heat injury. However, sensitization appears to vary with skin type. Thus, in contrast to CPNs in glabrous skin, the hyperalgesia to heat after a minor burn to the hairy skin appears to be signaled by sensitization of CPNs [Meyer and colleagues (17) labeled these *CMHs* (C nociceptors sensitive to intense mechanical and heat stimuli)]. More substantial injuries to hairy skin lead to sensitization of high-threshold mechanical nociceptors and CPNs. Meyer and colleagues (14,17) emphasized that the characteristics of primary hyperalgesia differ from those of secondary hyperalgesia: Whereas in primary hyperalgesia an increased sensitivity to both mechanical and heat stimuli occurs, in the secondary region hyperalgesia only occurs with mechanical stimuli. Thus, light touch and light brushing cause considerable pain in the areas of secondary hyperalgesia and primary hyperalgesia. The mechanism of secondary hyperalgesia appears to involve changes in the peripheral and central nervous systems. Experimental evidence suggests that it may be caused by an axon reflex mechanism and central sensitization of dorsal horn neurons.

Axon Reflex. Some studies have suggested that the axon reflex is the basis for production of secondary hyperalgesia (18). This hypothesis is a modification of Lewis' conceptualization, which he first published in 1936 (13). Lewis proposed that secondary hyperalgesia was caused by spread of sensitization to adjoining pain receptors by activity of a distinct nervous channel, which he called *nocifensor nerves*, composed of a finely branching and rich end plexus in the skin, independent of sensory afferents and sympathetic fibers. Activation of nociceptors triggered a response reflexively (the axon reflex) in the nocifensor system that branched into adjoining tissue. Activation of these nocifensor branches led to release from their terminals of substances that in turn (a) increased blood flow and thereby produced a flare; (b) caused vascular permeability and thus produced edema; and (c) caused sensitization and activation of nociceptors that innervated the adjoining area, thus leading to secondary hyperalgesia. An important observation in Lewis' proposal was that electrical stimulation of a nerve trunk led to hyperalgesia to mechanical stimuli in the distribution of that nerve, even if the proximal end of the nerve was blocked with a local anesthetic during the stimulation period. Although the existence of a nocifensor system has been disproved, the axon reflex is now well established.

Fitzgerald (19) reported similar observations. She noted that antidromic stimulation of a population of CPNs in the hairy skin of rabbits resulted in heat thresholds that were significantly lower than those of CPNs of a control population. She showed that if a local anesthetic was injected into the injured area, there was no sensitization of C-polymodal nociceptors. Moreover, a population of CPNs that had a cut beside the receptive field before heat testing had a lower heat threshold than that of the control population. Fitzgerald did not report on the effects of antidromic stimulation or the cut on mechanical sensitivity. On the basis of these observations, it has been concluded that the effects are local (i.e., nerve impulses are involved locally in the spread of sensitivity from the damaged area to the undamaged part; secondary hyperalgesia). Others have been unable to replicate these results in other species.

Thalhammer and LaMotte (20) sought to determine whether an injury to one-half of the receptive field of a nociceptor might lead to spread of sensitization to the other half by applying a 56°C 7-second burn to one-half of the receptive fields of high-threshold mechanical nociceptors and CPNs located in the hairy skin. Sensitization to heat resulted in the half of the receptive field that was burned, but not in the other half, and no significant change in mechanical threshold was observed in either half. Similar results were reported by Meyer and colleagues (17) with a more substantial injury: 53°C 30-second burn. Meyer and colleagues also found that the response to heat of CPNs before and after scalpel cuts surrounding the three sides of its receptive field (no cut on proximal side) did not differ. Scalpel cuts on the volar forearm of human subjects resulted in hyperalgesia to heat stimuli within, but not adjacent to, the area of injury (17).

Cervero and Laird (21) demonstrated central interactions between low-threshold mechanoreceptors and nociceptors in human volunteers with experimentally induced secondary hyperalgesia. They found that tactile stimulation in an area of allodynia evoked axon reflexes (measured as increased cutaneous blood flow) concomitant with touch-evoked pain, whereas stimulation of normal skin did not. Furthermore, they showed that cooling the area of primary hyperalgesia or A-fiber blockade in the distribution of the area of allodynia abolished axon reflexes and allodynia. Thus, their studies suggest that pain sensations of allodynia and axon reflexes are produced by the same mechanism.

Sensitivity of Dorsal Horn Neurons. Meyer and colleagues (17) hypothesized that secondary hyperalgesia is caused either by a decrease in central inhibition of the mechanically induced nociceptive input or by excitation of low-threshold mechanoreceptors by central nociceptors. A similar concept had been proposed by Hardy and associates (22) three decades earlier, in 1952. After extensive experiments, they concluded that secondary hyperalgesia associated with deep or superficial injury caused increased excitability in the network of *internuncial neurons*, which received convergent noxious impulses from cutaneous and deep somatic tissue or cutaneous and visceral structures. They postulated that injury to the skin produced primary hyperalgesia and that as a result, the nerve endings became hyperexcitable, consequently barraging the dorsal horn with noxious impulses that sensitized the dorsal horn neurons to such an extent that they would be excited by *subliminal stimuli*. Evidence suggests that secondary hyperalgesia (more properly called *allodynia*, pain caused by nonnoxious stimulus to normal skin) is caused by sensitization of wide dynamic range neurons in dorsal horn. This has been discussed in Chapter 4.

DEEP SOMATIC PAIN

Previous chapters have included descriptions of the ample supply of nociceptors to muscles, tendons, joints, and bones. Under normal conditions, the order of sensitivity of these structures is as follows: The periosteum has the lowest threshold, followed by the ligaments, fibrous structures of joints, tendons, fasciae, and muscles (23). Inflammation causes significant lowering of pain threshold in these structures, especially joints and bones, including not only the periosteum but also the cancellous portion. Acute ischemia of muscle does not produce pain while the muscle is at rest, but pain becomes progressively more intense during exercise.

Clinical Characteristics

Deep somatic pain has a dull, aching quality, and although it is less localizable than cutaneous pain, it is sufficiently well circumscribed for avoidance of further damage to joint, muscle, bones, or all three. This is typically accomplished by immobilization of the involved structure, rather than escape. The extent and distribution of pain are significantly influenced by the intensity and duration of the noxious stimuli and the depth of the structure stimulated. Injury or disease of these deep somatic structures produces the same reflex responses as does injury to skin or viscera.

Pain in deep somatic structures has been experimentally induced in humans by pain-producing substances and by methods intended to reproduce spontaneous painful conditions: ischemia of a limb, experimental inflammation, injection of hypertonic saline, and other techniques (23). Measurements of deep somatic pain have been performed to determine the threshold of the sensation. Other studies have investigated phenomena frequently accompanying deep pain: radiation of pain, cutaneous hyperalgesia, and provocation of autonomic reflexes. The study of these phenomena in experimentally provoked deep somatic pain is fundamental for the interpretation of similar phenomena associated with spontaneous clinical pain. These studies have demonstrated the influence of the intensity and duration of the stimulus and the depth of the structure subjected to noxious stimuli on the spread of the pain and other characteristics.

Among the earliest human studies of the characteristics of deep somatic pain and the associated responses were those carried out by Kellgren and Lewis, who did most of the studies on themselves and their colleagues (24,25 and 26). They passed a needle through skin that had been locally anesthetized and then injected 0.1 to 0.3 mL of 6% saline as a form of noxious stimulus of deeper tissues. Kellgren (24,24) systematically studied the distribution of pain from stimulation of various skeletal muscles, interspinous ligaments, periosteum, deep fasciae, and tendon sheaths. Using these techniques, Kellgren (25) noted that stimulation of deeply situated periosteum with the point of a needle caused brief pain that the subject could localize at one, two, or three points, whereas prolonged stimulus from injected saline produced a more diffuse pain. Moreover, he noted that the intensity of the stimulus also affected the spread of the pain (Fig. 9-1).

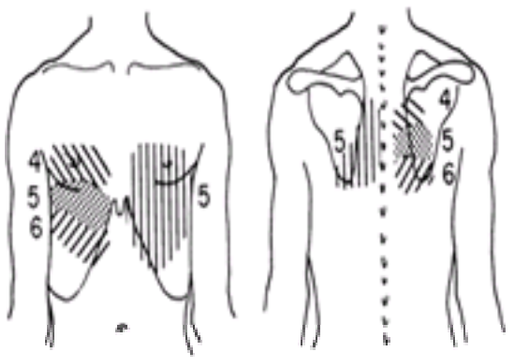

Figure 9-1. Distribution of pain caused by injection of intercostal muscles that shows effect of intensity of the stimulus on the spread of the pain. The right side of the figure shows pain produced by mild stimulation of the fourth (*cross-hatched*), fifth (*stippled*), and sixth (*cross-hatched*) intercostal spaces, depicting a segmental distribution. Following this, a more intense stimulus was provoked by injection of the left fifth intercostal muscle, which provoked pain that spread over the three segments, probably because of spread within the dorsal horn. (Modified from Kellgren JH. On the distribution of pain arising from muscle. *Clin Sci* 1937–1938;3:175–190.)

The influence of the duration of stimulus on the spread of pain was observed by Wolff (27). These investigators noted that brief stimulation of the mucosa about the ostium of the maxillary sinus produced a localizable intranasal sensation of pain, whereas prolonged stimulation of the same area caused the pain to spread over the homolateral portion of the nose, cheek, along the zygoma, into the temporal region, and into the upper teeth (Fig. 9-2). When the noxious stimulation was continued for 10 minutes, the area of pain spread over most of the area of the distribution of the second division of the fifth cranial nerve and ultimately spread to involve adjacent portions supplied by the first and third divisions. As noted in a later section (see Visceral Pain), a similar spread occurs with prolonged stimulation of viscera.

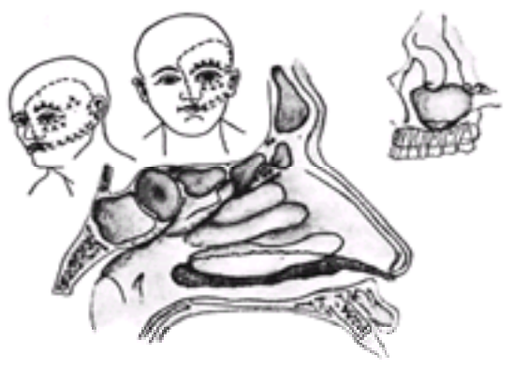

Figure 9-2. The influence of stimulation duration on the spread of pain. Brief repeated stimulations of the ostium of the maxillary sinus produced pain in the areas marked with an *X*, whereas when the stimulation was continued for 10 minutes, the area of pain spread over most of the area of the distribution of the maxillary nerve and ultimately spread to involve adjacent portions supplied by the ophthalmic and mandibular nerves (disorder indicated by *dashed line*). (From Dalessio DJ, Silberstein SD, eds. *Wolff's headache and other head pain*, 6th ed. New York: Oxford University Press, 1993:299, with permission.)

This phenomenon of spread caused by a prolonged stimulus is also seen clinically. If a localized pain caused by a minor injury is unrelieved, it can become diffuse, poorly localizable, and referred to a part that is remote from the original site of injury. Thus, the duration factor affecting spread of pain is of great clinical importance and must be seriously considered; early relief of clinical pain can preclude its spread.

Another important factor that affects the localization and spread of deep somatic pain is the depth at which the involved tissue is situated. Kellgren (24) found that pain elicited by stimulation of such subcutaneous tissue as superficial fascia; superficial tendons; superficial joints, ligaments, or periosteum; or superficial bone could be fairly well localized by the subject. Pain from the same structures, when deeply situated or from the belly of the muscle, was diffuse and was often referred to a distant area of the skin surface (Fig. 9-3).

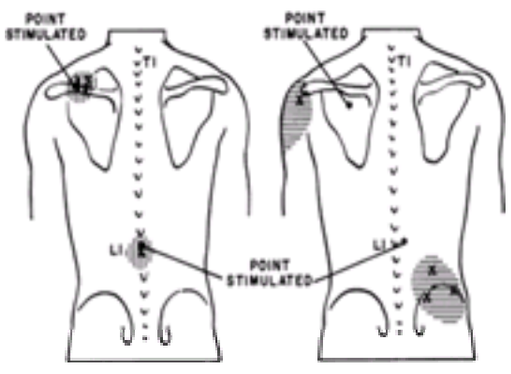

Figure 9-3. Diagram showing distribution of pain produced by injecting saline into subcutaneous periosteum (*vertical hatching*) and deeply situated periosteum (*horizontal hatching*). Points stimulated are top of spine and lamina of first lumbar vertebra and the spine and infraspinatus fossa of the scapula. The crosses indicate where the pain was experienced when the periosteum at the site of injection was scratched with a needle point. (Redrawn from Kellgren JH. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clin Sci* 1939;4:35–46.)

Kellgren (24) also noted that the deep portion of the interspinous ligaments produced pain that followed a segmental pattern. Although the segmental pattern is best noted in the trunk (Fig. 9-4), it also is found in the limbs (Fig. 9-5 and Fig. 9-6).

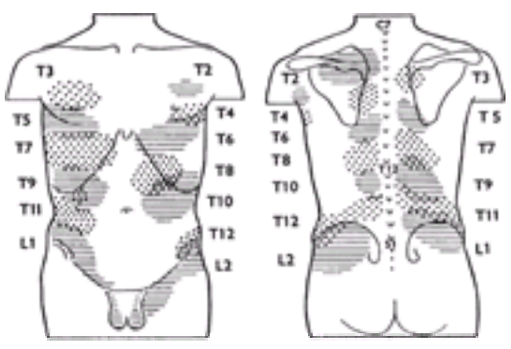

Figure 9-4. The areas of referred pain provoked by injection of saline into the interspinous ligaments of T-2–L-2 inclusive. Alternate areas have been hatched and

stippled for the sake of clarity. **A:** Anterior view. **B:** Posterior view. Note the overlap between areas of references, which, in the anterior part of the trunk **(A)**, are located in the skin supplied by the intercostal nerves and appear to follow a somewhat dermatomal pattern, depicted in Figure 8-8. In contrast, in the posterior paravertebral region the areas of referred pain are situated significantly more caudally than the vertebral levels and the intravertebral foramina through which the spinal nerves exit. Thus, it is noted that the area of referred pain from stimulation of the fourth thoracic interspinal ligament (i.e., ligament between T-4 and T-5) produces pain in the paravertebral region, which is opposite the spinous processes of T-6 and T-7; the area of referred pain from stimulation of the tenth thoracic interspinous ligament is opposite T-12 and L-2, and from stimulation of the first lumbar interspinous ligament the area of referred pain is opposite the spinous processes of L-4, L-5, and S-1. This is because of the progressively greater caudad migration of the posterior division of each spinal nerve. (From Kellgren JH. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clin Sci* 1939;4:35–46. Copyright Biochemical Society and the Medical Research Society, with permission.)

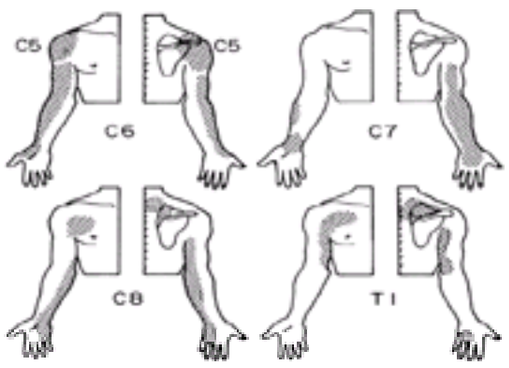

Figure 9-5. The area of referred pain provoked by injection of hypertonic saline into the interspinous ligaments C-5–T-1 inclusive on the anterior half of the body (on the reader's left in each of the four figures) and on the posterior part of the body. Note the segmental pattern of the area of referred pain similar to the dermatomes. (Modified from Kellgren JH. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clin Sci* 1939;4:35–46.)

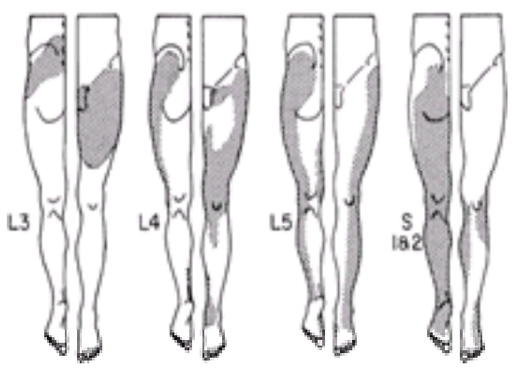

Figure 9-6. Diagram depicting the area of referred pain from injecting hypertonic saline into the interspinous ligaments L-3–S-2 inclusive. (Modified from Kellgren JH. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clin Sci* 1939; 4:35– 46.)

Kellgren (25) also studied the reference of pain from injection of hypertonic saline into various muscles. Figure 9-7 shows the segmental distribution of pain produced by injection of various muscles in the upper limb and the first intercostal space, and Figure 9-8 shows distribution of pain from injection of muscles in the lower limbs. These observations also led Kellgren to observe that the injection of a given muscle is felt over a definitive area, seemingly following a segmental pattern, and that distribution for a given muscle is similar in different individuals. He concluded that the segmental areas displayed were determined by the nerve roots involved in supplying the corresponding muscles, so that different muscles supplied from a common root source yielded a common general field of pain distribution (Fig. 9-9) (25). Figure 9-10 is a map showing the reference of pain resulting from stimulation of various muscles by injecting hypertonic saline, which was developed from the data published by Kellgren (25).

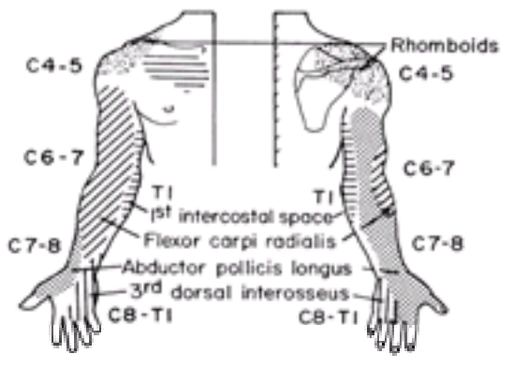

Figure 9-7. Distribution of pain provoked by injection of hypertonic saline into various muscles of the upper limb. (Modified from Kellgren JH. Observations on referred pain arising from muscle. *Clin Sci* 1937–1938;3:175–190.)

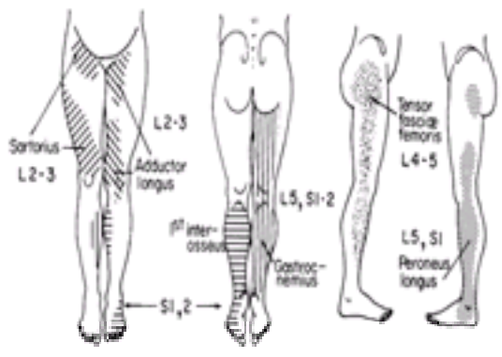

Figure 9-8. Distribution of pain provoked by injection of hypertonic saline into various muscles of the lower limbs. **A:** Anterior view showing pain (*oblique hatching*) from injection of the sartorius on the right side of the subject and injection of the adductor longus on the left side. **B:** Posterior view showing pain reference from injection of the first interosseous on the left side of the subject and gastrocnemius on the right side. **C:** Pain distribution from injection of the tensor fasciae femoris (*fine stipple*) and injection of the peroneus longus (*coarse stipple*). The numbers indicate the segmental nerve supply. (Modified from Kellgren JH. Observations on referred pain arising from muscle. *Clin Sci* 1937–1938;3:175–190.)

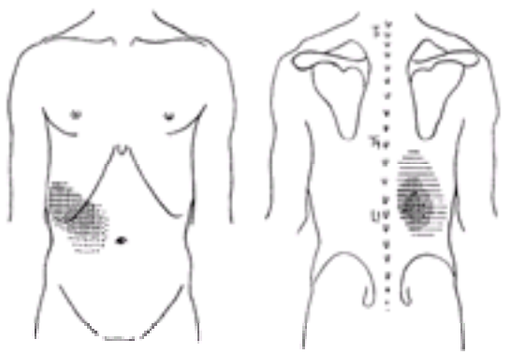

Figure 9-9. Distribution of the referred pain provoked by injecting hypertonic saline into different muscles supplied by the ninth thoracic nerve. Horizontal hatching shows areas of pain provoked by injection of multifidus muscle opposite the ninth spinous process; vertical hatching shows pain caused by injection of the ninth intercostal nerve in the midaxillary line; and stippled area shows area of pain caused by injection of rectus abdominus 3 cm above the umbilicus. (From Kellgren JH. Observations on referred pain arising from muscle. *Clin Sci* 1937–1938;3:175–190. Copyright Biochemical Society and the Medical Research Society, with permission.)

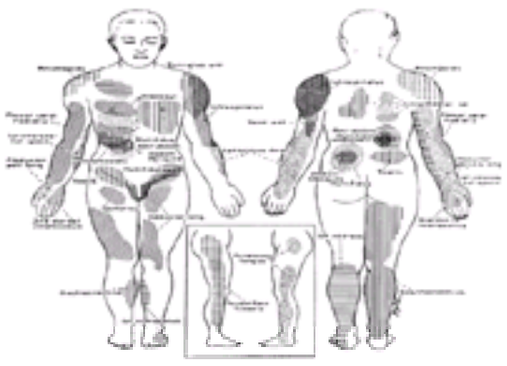

Figure 9-10. Composite map showing the reference of pain resulting from noxious stimulation of various muscles by injecting hypertonic saline. (From data by Kellgren JH. Observations on referred pain arising from muscle. *Clin Sc*ı 1937–1938;3:175–190.)

After his extensive investigations, Kellgren concluded that beneath the skin a second sensitive layer exists in which pain is localized with fair accuracy. This layer consists of the deep fascia encasing the limbs and trunk and any periosteum, ligament, or tendon sheath that is situated subcutaneously. On the other hand, all the structures deep to this layer give rise to diffuse pain of more or less segmental distribution. The pain is fully segmental in distribution when arising from the interspinous ligaments, intercostal spaces, and other structures situated deeply in the trunk and limbs, whereas the pain is more localized when arising from less deeply placed structures.

The work of Kellgren has been confirmed by several groups of investigators. The experimental human studies of Inman and Saunders (28) demonstrated the segmental pattern of deep somatic pain and noted that this pattern did not correspond to the dermatomes, but rather to the segmental distribution of muscles (myotomes) and bones (sclerotomes). They concluded that a deep somatic lesion, such as injury to muscle tendon or periosteum, can give rise to pain that radiates along the pathway corresponding to the approximate segmental innervation of the deep somatic tissues. Similar data derived from noxious stimulation of various skeletal structures were obtained by Travell and Simons (29). These investigators also found that the referred pain was experienced either within the reference area attributed to one segment, within a different portion of one segment, or within different fragments of several segments. These patterns were especially clear in myofascial pain syndromes with trigger areas in which the pattern of the referred pain and the associated phenomena are relatively constant and predictable. These findings suggest that impulses concerned in the unfamiliar reference of somatic pain, like those of visceral pain and cutaneous pain, follow fixed neural pathways.

Other Manifestations of Deep Somatic Pain

Like visceral and superficial pain, deep somatic pain is associated with cutaneous hyperalgesia, tenderness, reflex muscle spasm, and, not infrequently, sympathetic hyperactivity. Although these associated responses have long been known to occur with the pain of visceral disease, it was not until Lewis and Kellgren (26) demonstrated that these responses also occur with stimulation of deep somatic structures that they were fully appreciated. In one of these studies, they stimulated the first lumbar interspinous ligament because of the known likeness of the pain distribution to that of renal colic (Fig. 9-11). After injecting this ligament, they looked for retraction of the testicle on the same side because this is a phenomenon associated with attacks of renal colic. They noted that the retraction occurred unmistakably and repeatedly, became maximal as the pain increased to its maximum, and gradually disappeared as the pain subsided during the next 3 to 5 minutes. They also noted palpable rigidity and deep tenderness of the lower part of the abdominal wall of the corresponding side, which also disappeared with the passing of the pain.

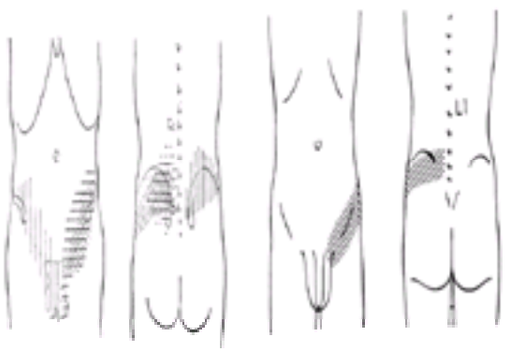

Figure 9-11. **A:** Distribution of pain in the first lumbar segment when provoked from stimulation of the testes (*vertical hatching*); from abdominal oblique (*horizontal hatching*); and from multifidus (*stippling*). **B:** Distribution of pain from stimulation of the first lumbar interspinous ligament. Note similarity in distributions of pain from stimulation of visceral and somatic structures. (Modified from Lewis T, Kellgren JH. Observations relating to referred pain, visceromotor reflexes and other associated phenomena. *Clin Sci* 1939;4:47–71.)

Similar observations have been made by many others. Procacci and colleagues (23) noted that on inducing pain in different muscles of the upper limb or chest with hypertonic saline injection, they were able to produce pain, hyperalgesia, alteration of cutaneous impedance, and an abnormal dermographic response (white dermographia) that had a segmental distribution corresponding to the injected muscle. They noted that injection of the somatic nerves with local anesthetic eliminated the cutaneous hyperalgesia and the variation of skin impedance and dermographia.

VISCERAL PAIN

Two main types of pain are associated with visceral disease, particularly disease of the abdominal organs: pain arising from the diseased viscus itself and thus called true visceral pain, and pain arising from the parietal peritoneum or pleura. Each of these may be felt in or near the diseased structure or in a remote area. On the basis of these considerations, Lewis (1) suggested four types of pain associated with disease of the viscera: true or localized visceral pain, referred visceral pain, localized parietal pain, and referred parietal pain.

True visceral pain occurs early in the disease and is characterized by a vague, diffuse, dull, aching pain, which is poorly localized and tends to radiate. It can be accompanied by a feeling of malaise, and, when severe, it induces strong autonomic phenomena such as sweating, vasomotor responses, bradycardia, nausea and vomiting, and sometimes an alarm reaction. It is usually felt in the midline and deep in the body. Thus, visceral pain caused by disease of the stomach and duodenum early on is felt around the midline area above the umbilicus, pain from appendicitis is felt in the periumbilical region, and pain caused by disease of the colon is felt in the lower abdomen (30) (Fig. 9-12). Some authorities call this type of pain *true visceral pain*, and others call it *splanchnic pain* [see Lewis (1) for references]. Another example of true visceral pain is the first manifestation of myocardial infarction; the pain is usually deep and poorly localized, and most often in the midline substernal or epigastric region (sometimes also in the interscapular region). Rather than pain, other unpleasant sensations such as gastric fullness, heaviness, pressure, squeezing, or choking may be experienced. As the intensity and duration of visceral pain increase, the pain may radiate and seem to originate from a wider area. For example, substernal pain or pressure, the sensations typically associated with early myocardial infarction, may spread to include diffuse chest pain as well as radiate down the arm or up into the neck and jaw. In some instances, the pain arising from viscera is referred to the skin and other somatic structures at considerable distance from the diseased viscus and has a segmental dermatomal pattern. One example of this type of referred pain is that felt in the inguinal region and testicle caused by ureteral stones.

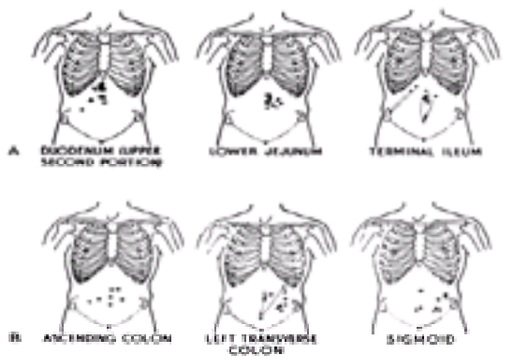

Figure 9-12. Areas of referred pain provoked by distension of various parts of the small intestine **(A)** and large intestine **(B)** by inflating a balloon sufficiently to provoke pain. (Modified from Jones CM. *Digestive tract pain*. New York: Macmillan, 1939.)

Parietal pain occurring with a disease process involves the parietal pleura or parietal peritoneum. This type of pain, which is usually described as sharp and occasionally stabbing, may be localized or referred to a distant site. When the disease process comes to involve the anterior abdominal wall or the parietal pleura in the chest, the pain is felt close to the diseased viscus. Parietal pain associated with the diaphragm presents a complex pattern. If the disease process involves the parietal pleura or parietal peritoneum covering the peripheral portion of the diaphragm, the pain is referred to the lower chest and abdominal wall on the ipsilateral side, reflecting the nerve supply to this region by the lower six intercostal nerves. On the other hand, if the disease process involves the central part of the diaphragm, whether the thoracic surface, as in diaphragmatic pleurisy or pericarditis, or the inferior peritoneal surface, as in subdiaphragmatic abscess, the pain is felt in the neck. It is usually sharp, lancinating, accurately localized, and referred to the skin and superficial structures overlying the trapezius muscles. This area of reference is explained by the embryonic origin of the organ. The diaphragm has its origin as a cervical muscle that has migrated caudally, carrying with it a cervical nerve supply (i.e., the phrenic nerves).

In a manner analogous to cutaneous dermatomes, which are arranged according to the embryologic anatomy of these tissues, viscerotomes are arranged according to the embryologic location of the viscera and involve both mesodermal and endodermal tissues. Ness and Gebhart (31) published an extensive review of the clinical and experimental studies that have led to our current understanding of the anatomy and physiology of visceral pain (Fig. 9-13). Figure 9-13A illustrates how the human viscerotomes correspond to the embryologic origins of the viscera. Because of the migration and rotation of viscera during embryologic development, somatotopic progress of the viscerotomes is not always obvious. One example is the complex formation of the diaphragm as described previously. Another example is the development of the gut, which forms loops and rotates in such a way that structures originally in the lower abdomen are finally located in the upper abdomen.

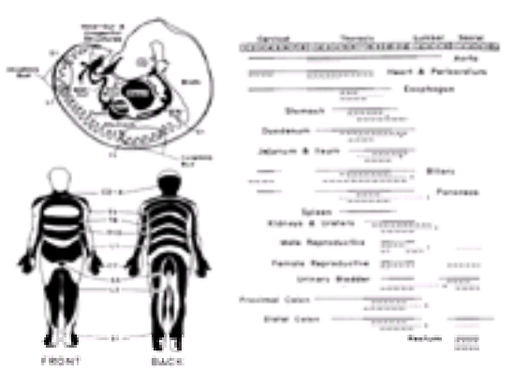

Figure 9-13. Human viscerotomes. **A:** Cross-sectional illustration of human embryo shows the original relation between location of the viscera and developing spinal nerves. **B:** Examples of dermatomes with corresponding spinal segments. **C:** Schematic representation of human viscerotomes (*solid, dashed,* and *dotted lines*) and their relation to dermatomes (segments indicated in grid above). The type of line indicates how the viscerotomes were determined, and the thickness of each line relates to the frequency of occurrence of referral site. Solid lines indicate sites of referred pathologic pain, dashed lines indicate sites of cutaneous hyperalgesia associated with visceral disease, and dotted lines indicate sites where nerve blocks or ablation of dorsal roots relieve pain related to visceral pathology. (From Ness TJ, Gebhart GF. Visceral pain: a review of experimental studies. *Pain* 1990;41:167–234, with permission.)

Visceral pain and parietal pain are usually associated with reflex skeletal muscle spasm, tenderness, hyperalgesia, and sympathetic hyperactivity and may evoke stronger emotional responses than superficial pains. These phenomena are discussed in connection with Referred Pain, later in this chapter.

Mechanisms of Visceral Pain

Effective (Adequate) Stimuli

Visceral pain cannot be provoked by stimuli that usually provoke cutaneous or deep somatic pain, such as pressure, cutting, or burning. In the early 1900s, Lewis (1) summarized work done by Lennander in 1900, a series of extensive observations of patients being operated on for intraabdominal surgery under local anesthesia and demonstrated that the intestine could be cut, crushed, burned, or stretched without causing sensation. These findings led him to advance the hypothesis that all of the internal organs that are innervated solely through autonomic nerves are devoid of pain sensation. Similar findings by Mackenzie (32) led many investigators to deny the possibility of painful sensations arising from stimulation of the viscera unless the stimulation is such that it will spread beyond the area innervated solely by visceral nerves and affect afferent components of spinal nerves (33). In 1911, Hurst showed that stretching of the intestine gave rise to considerable pain, and many subsequent studies (1) have established that pain does arise from viscera, but that cutting, burning, and crushing as described in early reports may not have been adequate stimuli.* Subsequently, Holmes (34) expressed his views on this matter thus: “This insensitivity of viscera to such somatic stimuli as burning and cutting is

not surprising, for as the viscera are not normally exposed to such traumas, it cannot be expected that they would be endowed with a nervous apparatus to respond to them."

Adequate stimuli that provoke visceral pain include (a) spasm of smooth muscles of hollow viscera; (b) contraction of gastrointestinal or genitourinary tracts under isometric conditions (i.e., contraction against obstruction); (c) sudden abnormal distension, stretching, or tearing of these structures; (d) rapid abnormal stretching of the capsule of solid viscera such as liver and spleen; (e) rapidly developing ischemia; (f) inflammation of the lining of the hollow viscera; (g) chemical or mechanical stimuli applied to the inflamed mucous membrane of these structures; (h) traction, compression, or twisting of the mesentery, ligaments, or blood vessels; and (i) necrosis of such viscera as the pancreas or myocardium (35). In clinical conditions, two or more of these causative factors may be concomitant and interact with each other. For example, a stone in the ureter or biliary tract usually provokes intense contraction and spasm of the smooth muscles and produces excruciating pain, which is promptly relieved by passage of the stone without causing tissue injury.

Visceral Nociceptors

Not all afferent innervation of the viscera is sensory. Stimulation of receptors such as the arterial baroreceptors and carotid body chemoreceptors activate autonomic functions that are not perceived, and thus are part of the afferent, but not sensory, innervation of the internal organs. Activation of other visceral receptors evokes sensations of fullness, discomfort, and even pain and are thus part of the sensory innervation of the viscera. The encoding mechanism for visceral nociceptive events remains a topic of controversy. One possible mechanism is that a single population of visceral receptors responds at an increased frequency to noxious stimuli. The other possible mechanism is that visceral pain is mediated by a population of specific nociceptors that responds only to noxious stimuli. Cervero (36) has presented experimental evidence for both specific nociceptors and nonspecific sensory receptors in the viscera. For example, some colonic receptors respond with increasing frequency to increasing magnitude of distension of the colon; this is paralleled by subjective feelings that progress from fullness to discomfort to pain. In other viscera, such as the ureter and biliary duct, pain seems to be the only sensation evoked, mediated by specific nociceptors (36,37).

Peripheral and Central Sensitization

Conscious perception of visceral pain, like cutaneous and deep somatic pain, depends on how afferent inflow is integrated in the central nervous system. Visceral input is subject to both peripheral and central modulation (37), but these processes differ in some ways from those observed in sensitization of cutaneous receptors (38).

One possible trigger for the sensation of visceral pain is peripheral sensitization of visceral nociceptors. Several investigators have demonstrated that ischemia lowers the response threshold for nociceptors in the colon and ureter (36). McMahon and colleagues (38) have described *silent* nociceptors, which are only activated in pathophysiologic states, such as inflammation. McMahon and colleagues have also presented evidence that this process may be mediated by nerve growth factor (38).

Unlike cutaneous nociception, spatial summation may reduce the effective threshold for pain in viscera (38). Spatial summation of visceral input may also help to explain the inability of localized mechanical stimuli to produce pain. Prolonged noxious visceral stimulation also increases the excitability of viscerosomatic neurons in the spinal cord. Cervero (37) has suggested that the increase in excitability may be mediated by positive feedback loops between spinal and supraspinal structures; these feedback loops may be responsible for enhanced motor and autonomic reflexes that frequently accompany visceral pain states. However, the postsynaptic actions of peptides such as *N*-methyl-d-aspartate can also contribute to enhanced visceral nociceptive neuronal activity (37). Nerve growth factor may also act indirectly to increase central nervous system excitability (38).

REFERRED PAIN

The term *referred pain* is generally used for pain localized not to the site of its cause but to an area that may be adjacent to or at a distance from such a site. Although Henry Head (39) is usually given the credit for first using the term in 1864, the phenomenon of referred pain had also been recognized by Sturge (40), Ross (41), and others. The mechanism of referred visceral pain has caused greater controversy than perhaps any other aspect of the general problem of visceral pain. As mentioned earlier in this chapter, referred pain is usually accompanied by hyperalgesia, reflex muscle spasm, deep tenderness, and autonomic hyperactivity.

Associated Clinical Manifestations

Cutaneous Hyperalgesia, Hyperesthesia, and Tenderness

Deep somatic, visceral, or both somatic and visceral diseases are frequently manifested by secondary hyperalgesia in the dermatomes supplied by the same spinal segments that supply the deep structure or viscera. Head (39) used cutaneous hyperalgesia to map out the dermatomes and thus study the nerve supply for various viscera. The hyperalgesia may involve the entire dermatome(s) or only part of a specific dermatome.

The presence of cutaneous hyperalgesia associated with deep somatic disorders or visceral disease had been recognized by Sturge (40) in 1883 and Ross (41) 4 years later. Since Head's classic publication (39), many investigators have studied various aspects of deep somatic or visceral pain (1,22,26,27). Properly carried out, the examination for hyperalgesia and hyperesthesia is used by the clinician to help in the diagnosis of the source of the pain.

Reflex Muscle Contraction

Muscular rigidity and contraction are important clinical manifestations of deep somatic or visceral disease. The muscles involved depend on the segments supplying the deep somatic structure or viscera as well as the intensity of the noxious stimuli. In diseases or disorders that produce mild referred pain, the reflex muscle spasm may be mild and limited to the spinal cord segments that supply the structure involved in the disease or the injured somatic tissue. An example of the correlation between the segments involved in the muscle spasm and the nerve supply is seen in the location of spasm in cholecystitis and appendicitis: In cholecystitis the spasm is in the upper abdominal muscle, and in appendicitis it is in the lower abdominal muscle. In renal colic, the contraction involves the cremasteric muscle, which is supplied by the first and second lumbar segments (which also supply much of the ureter).

Intense and prolonged noxious stimuli not only influence the extent of the referred pain, but also the extent and duration of muscle contraction. This point was well demonstrated by the experimental studies on genitourinary pain carried out by McLellan and Goodell (42). They noted that brief low-intensity electrical stimulation or overinflation of a balloon placed in the ureter caused localized pain and little or no muscle contraction, whereas prolonged or intense stimulation evoked a more complex phenomenon. The muscles of the abdominal wall on the stimulated side remained contracted, and after approximately half an hour the side began to ache. This ache became quite severe and lasted 6 hours, after which the pain subsided, but deep tenderness in the muscle continued until the following day (Fig. 9-14).

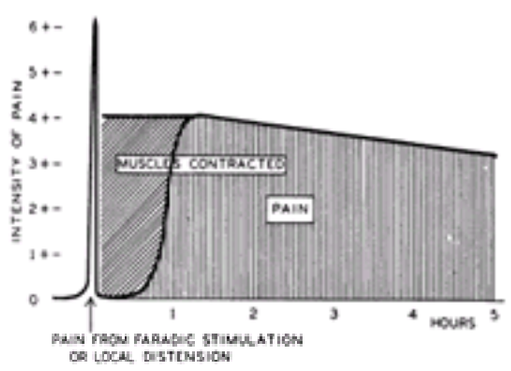

Figure 9-14. Schematic representation of a sudden pain arising from either faradic stimulation or local distension in the ureter or kidney pelvis. The severe transient pain was followed by contraction of skeletal muscles (erector spinae transversalis and internal and external oblique), which later developed an aching pain that lasted for several hours. (From MacLellan AM, Goodell H. Pain from the bladder, ureter and kidney pelvis. *Proc Assoc Res Nerv Ment Dis Am* 1943;23: 252–262, with permission.)

Clinically, muscular contraction associated with referred visceral pain may also be maintained for a long period of time and may even continue after the pain disappears. Moreover, in clinical conditions it is noted that extremely intense and prolonged noxious stimuli such as occur with acute pancreatitis not only produce more intense visceral and referred pain, but also may cause contraction of muscles above and below those spinal segments that supply the pancreas. In such circumstances there may be contraction of all of the thoracic muscles.

In addition, prolonged and sustained skeletal muscle spasm caused by intense noxious stimuli from the deeper structures can initiate new nociceptive impulses from the muscles, and thus sustain and aggravate the initial pain and discomfort. If the skeletal muscle spasm is not eliminated, it may lead to a vicious circle that tends to perpetuate the condition. The concept of intense contraction of skeletal muscles as a cause of new nociceptive impulses had been proposed by Lewis (1), Lewis and Kellgren (26), and Hardy and associates (22), and Bonica emphasized it repeatedly over three decades. This thesis was adopted by Zimmermann (43), who hypothesized that the positive feedback loop provokes new nociceptive impulses that not only aggravate acute pain, but also may contribute to the development of chronic pain.

Deep Hyperalgesia and Tenderness

In addition to cutaneous hyperalgesia, hyperesthesia, and tenderness, visceral disease and deep somatic disorders are frequently associated with deep hyperalgesia and tenderness. The tenderness is often felt by the patient deep to the skin and, in most instances, is closely associated with muscular contractions. It is felt in the affected muscles and usually outlasts the contractions and even the pain. The deep tenderness is not always of muscular origin, because the viscera themselves may be the site of the soreness. Thus, it is seen that patients with renal colic complain of deep tenderness in the testicle of the same side, which is presumably elicited from the deep tissues of the scrotal wall or from the tunics vaginalis.

Still other mechanisms can produce deep tenderness. In one study, Wolff (27) produced headache, deep tenderness, cutaneous hyperalgesia, and hyperesthesia in the temporal region of the head by prolonged stimulation of a tooth. Intracutaneous infiltration with procaine at the site of the most intense temporal headache, tenderness, and surface hyperalgesia resulted in reduction of the intensity of the headache, but the temporal muscles beneath the analgesic skin remained tender to palpation. When the local anesthetic was injected into the temporal muscle as well as intracutaneously, pain persisted although local tenderness was eliminated. It was only after infiltration of the tooth with procaine that there was complete relief of pain. They concluded that such tenderness resulted from a central (within the neuraxis) spread of hyperexcitatory effects induced by the sustained noxious stimulation.

Autonomic Manifestation

As mentioned previously, true visceral pain and referred pain associated with visceral disease or deep somatic disorders are often accompanied by sympathetic or parasympathetic hyperactivity. In most instances it is sympathetic hyperactivity manifested by increase in blood pressure, tachycardia, sweating, piloerection, and vasoconstriction associated with a neuroendocrine response (see Biology and Pathophysiology of Acute Pain, later in this chapter). In some patients, sudden intense noxious stimuli of the abdominal viscera produce parasympathetic hyperactivity, manifested by bradycardia, hypotension, and a feeling of severe general malaise.

Effects on Referred Pain of Anesthetizing the Area of Reference

One controversial and confusing problem of referred pain is the effect produced by infiltrating the area of reference with a local anesthetic. In 1928 Weiss and Davis (44) reported that local anesthesia of the abdominal wall in 25 patients with visceral disease produced pain relief. Subsequently, similar results were reported by Morley (45) on 13 patients with referred pain caused by visceral disease. Morley (45) also reported that the pain and hyperalgesia referred to the shoulder as a consequence of diaphragmatic irritation could be eliminated or diminished by infiltration of local anesthetic in that region.

Rose (46) noted that the pain of the first stage of labor could be relieved by anesthetization of the skin of the lower abdomen, an observation subsequently substantiated by others [see Bonica (47) for references]. Theobald (48) also reported the relief of pain in the reference zone resulting from dysmenorrhea or from electrical stimulation of the uterus. In his experimental studies of pain from the gastrointestinal tract using an inflatable balloon, Jones (49) reported that “it was possible to infiltrate with Novocain the skin area at which pain was experienced, for example, in the midepigastrium after distension of the first portion of the duodenum with resulting abolition of the local reference of pain.”

Notwithstanding these and other early reports on the efficacy of superficial analgesia in relieving the referred pain and hyperalgesia, negative results have also been reported. Woollard and colleagues (50) attempted to confirm Morley's findings by stimulating the phrenic nerve, which was exposed before avulsion. They noted that although stimulation produced pain in the distribution of the fourth cervical segment, it was not reduced by anesthetization of the skin of this area. Similar negative reports were made by Lewis (1), McLellan and Goodell (42), and many others [see Hardy (22) and Bonica (51) for references].

The obvious discrepancies reported have prompted several explanations. Theobald (52) suggested that the divergence between the results obtained by Morley (45) and those by Woollard and colleagues (50) could be attributed to the difference in the intensity of the stimulus they applied. In support of this hypothesis, he demonstrated that mild referred pain elicited by weak electrical stimulation of the cervix could be relieved by needling the affected cutaneous area. A further increase in the current caused pain that could not be relieved by needling, but frequently could be relieved by injecting 5 mL of saline solution intradermally. A still further increase in the current caused pain that could not be relieved by saline but could be eliminated by injection of 1% procaine. In nearly every patient studied, by raising the stimulus intensity, a point was ultimately reached when the pain persisted despite the injection of large amounts of local anesthetic and was usually referred to the same cutaneous area in which the latter was completely anesthetic. Bonica (47) observed that mild labor pain of the early first stage can be virtually eliminated by infiltrating the skin of the lower abdominal wall, whereas the severe pain of the late first stage is not affected appreciably. Wolff and coworkers (27) also reported that when the cutaneous hyperalgesia was more marked, the effect of procaine injection into the zone of hyperalgesia was more dramatic.

Hardy, Wolff, and colleagues have also explained the discrepancies and contradiction on the basis of whether the referred pain is associated with hyperalgesia (22,27). If hyperalgesia is not present, the referred pain depends only on the central effects of the spread of excitation of the original noxious impulses to the same and adjacent segments, and anesthetization of the region of referred pain does not reduce the intensity of pain. If hyperalgesia is present, injection of local anesthetic should abolish the element of the referred pain complex that depends on impulses from the zone of reference.

Hypotheses on the Mechanism of Referred Pain

In the 1880s and 1890s, Sturge (40), Ross (41), and Head (39) proposed similar concepts regarding the mechanism of referred pain. Sturge (40) suggested, in physiologic terms, that the pain in the left arm and fingers of patients with heart disease must be a conscious recognition of an “abnormal commotion” in the gray matter of the spinal cord. Four years after Sturge's hypothesis, Ross (41) proposed that in visceral disease two types of pain exist, a true splanchnic pain and a somatic pain, and that the somatic pain is caused by an irritable focus in the spinal cord. Head (39) seems to have accepted and somewhat elaborated the Sturge-Ross hypothesis. He did not deny the existence of pain of visceral origin and localization, but divided visceral pain into that localized vaguely inside the body (dull visceral pain) and that referred to the skin surface (aching referred pain). Head assumed that the reference was caused by convergence of visceral and skin nerves into the same spinal cord structures and a subsequent “physical error” of localization.

Mackenzie (32,53) incorporated Ross' concept of referred pain into his own theory of visceral pain, but he denied the existence of true splanchnic pain. For Mackenzie, only somaticlike structures (e.g., the skin, muscles, and peritoneum) were sources of painful stimulation. He believed that although sensory impulses can and do arise from viscera, none of these produces pain. He suggested that such impulses would, on entering the spinal cord, set up an *irritable focus* by constant bombardment of the same segments in which they entered (Fig. 9-15). In this way, they would diminish the threshold for somatic sensory impulses and produce cutaneous hyperalgesia and referred pain in the corresponding segments. Mackenzie labeled these phenomena, which he believed accounted for referred pain, as *viscerosensory reflexes*. Furthermore, he suggested that visceral afferent impulses activated the anterior horn cells in the same manner to produce skeletal muscle spasm and also activated anterolateral autonomic (sympathetic) cells, which produced piloerection, vasoconstriction, and other sympathetic phenomena. He referred to these somatic and autonomic motor reactions as *visceral motor reflexes*. Morley explained referred pain by using a modification of the *irritable focus* theory (45). He suggested that irritation of the spinal nerve endings in the mesentery or parietal peritoneum produced peritoneocutaneous and peritoneomuscular reflexes, provoked by inflammation of the disease. Shortcomings of this theory include, for example, its inability to explain the referred pain associated with conditions such as angina

pectoris, in which no inflammatory process exists and usually no direct contact with the overlying intercostal nerves exists.

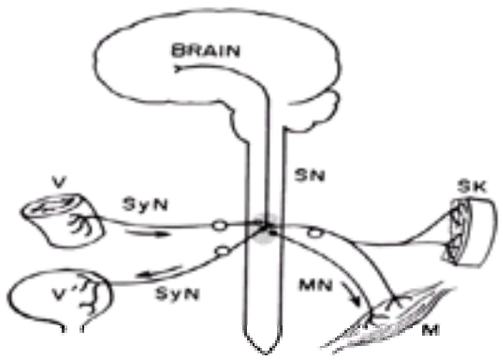

Figure 9-15. Diagram to depict Mackenzie's theory of mechanism of visceral referral of pain and related reflexes. An adequate stimulus from viscus (V) is conveyed to the spinal cord by afferents associated with sympathetic nerves (SyN) and stimulates spinal cord cells. If this stimulus produces activation of a pain pathway (SN), it results in pain being referred to the peripheral distribution of the somatic nerve from the skin (SK). The visceral stimulus also activates other neurons, which cause a reflex contraction of the skeletal muscle (M), supplied by motor nerves (MN), and also provokes a viscerovisceral reflex (V'). If the visceral stimulus is of sufficient intensity it may leave an *irritable focus* in the spinal cord (*stippled area*), resulting in cutaneous hyperalgesia, vasomotor and sudomotor changes in the skin, and persistent muscle contraction. (Modified from Mackenzie J. *Symptoms and their interpretation*. London: Shaw and Sons, 1912.)

Ruch (54) pointed out that Mackenzie's irritable focus theory, which is an extension of Sturge's and Ross' hypotheses, amounts to the suggestion that visceral impulses facilitate cutaneous impulses that originate in the skin, but that are insufficient in quantity to excite the spinothalamic tract fibers. Ruch (54) called this the *convergence-facilitation theory* to distinguish it from his own *convergence-projection theory*, which he first proposed in the early 1940s. Ruch's convergent-projection theory suggests that referred pain is brought about by the convergence of visceral afferent fibers with cutaneous nociceptive fibers on the same neuron at some point in the sensory pathways, at spinal, thalamic, and cortical levels, and that the system of fibers is organized topographically to provide the dermatomal reference (54). The first opportunity for this convergence is on the same spinothalamic tract neurons (Fig. 9-16). The resulting impulses, on reaching the brain, are misinterpreted as originating from somatic structures (such as the skin), because this had been the interpretation learned from previous experience in which the same tract fiber was stimulated by cutaneous afferents. The same explanation serves equally well for referred parietal pain, for example, as for that obtained by stimulation of the diaphragm. Although this theory accounts for the localization of referred pain, it does not address the issue of referred hyperalgesia.

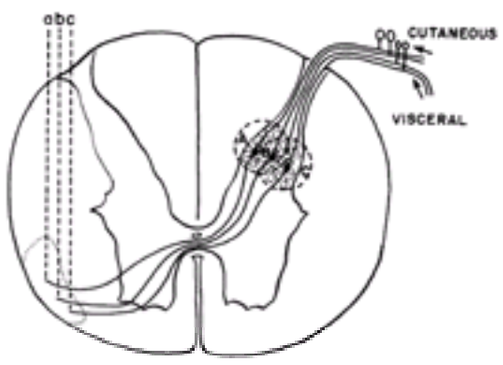

Figure 9-16. Diagram illustrating Ruch's theory on the mechanism of referred visceral and somatic pain. This theory is based on Sherrington's neuron pool concept. Because there are many more primary afferent fibers in the posterior roots than there are spinothalamic tract neurons, several primary afferent fibers converge on one spinothalamic tract neuron. *A*, *B*, and *C* represent a neuron pool consisting of all the spinothalamic tract neurons in one segment of the spinal cord. *A* is the field of neurons having connections only with afferent fibers from cutaneous sense organs. *B* is the field of overlap constituted by spinothalamic tract neurons that receive impulses from both visceral and cutaneous afferents, and impulses in *B* give rise to pain referred to the skin. *C* indicates those neurons of the pool that connect only with afferent fibers from the visceral cavities and give rise to unreferred or true splanchnic pain. Only one neuron in each category is represented; others are indicated by *ghost cells*. *a*, *b*, and *c* are fibers in the spinothalamic tract having cell bodies in fields *A*, *B*, and *C*, respectively. (From Ruch TC. Pathophysiology of pain. In: Ruch TC, Fulton JF, eds. *Medical physiology and biophysics*, 18th ed. Philadelphia: Saunders, 1960:350–368, with permission.)

In 1937, Morley (55) published an alternative explanation for referred pain based on the concept of the presence of efferent collaterals associated with afferent nerves. Stimulation of one of the afferent fibers could result in impulses that are conveyed antidromically by one or more of its efferent collaterals, and this causes liberation of chemical metabolites in the skin that stimulate nociceptive fibers. In 1948, Sinclair, Weddell, and Feindel (56) extended the hypothesis and proposed that “an essential factor in the production of referred pain is the existence of branching among the sensory pathways conveying the sensation of pain.” This theory suggests that the branched neurons innervate both somatic and visceral sites such that the source of afferent activity is obscured. Figure 9-17 summarizes the theories of referred pain. In the last three decades of the twentieth century, experimental evidence has been acquired to support both the visceral-somatic convergence theory and the peripheral nerve-branching theory.

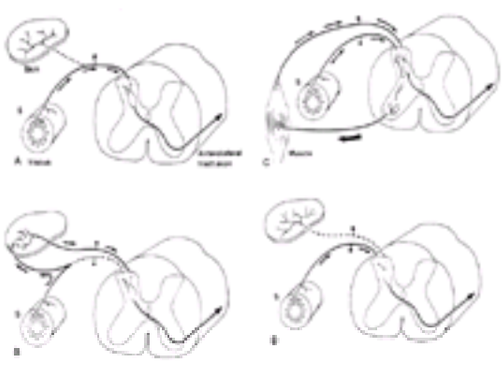

Figure 9-17. Summary of the most important theories of referred pain. **A:** A single primary afferent fiber, which branches to supply two structures, a viscus and the skin. Disease of the viscus causes stimulation (S) of the afferent fiber and thus produces impulses that reach the dorsal horn, where they are transmitted to cell bodies whose ascending axons transmit the message to the brain. Because the brain receives *pain* messages from the skin much more frequently than from the viscus, it misinterprets the location of the pain as being in the skin. **B:** Referred pain caused by antidromic activation of receptors at a distant secondary site. Disease of the viscus causes stimulation, which provokes impulses. Instead of passing to the dorsal horn, the impulses pass antidromically to the skin, where pain-producing substances are released and sensitize the terminals of cutaneous nociceptors so that innocuous stimuli can cause pain. In this case the brain correctly localizes the site of origin of the nociceptive messages, but not the site of the original pathologic process. **C:** Referred pain resulting from reflex phenomena. Stimulation of the diseased viscus provokes impulses that pass to the dorsal horn and then to the anterior horn. These cause powerful and sustained reflex muscle contractions and activation of muscle nociceptors. Impulses from these nociceptors are transmitted to the dorsal horn and thence to cells whose axons pass cranially via the anterolateral quadrant to the brain. As in the process described in **B**, the brain correctly localizes active muscle nociceptors but not the site of the original pathology. **D:** The convergence-projection hypothesis of referred pain, which suggests that visceral afferent nociceptors (S) converge on the same pain projection neurons as the afferents from the skin in which the pain is mistakenly perceived. (From Fields HL. *Pain*. New York: McGraw-Hill, 1987:90–91, with permission.)

Visceral-Somatic Convergence

Experimental data for the existence of convergence of visceral and cutaneous afferent fibers were first demonstrated in 1968 by Pomeranz and associates (57) in the thoracic spinal cord of cat, and a year later by Selzer and Spencer (58) in the lumbar cord of the same species. Both groups showed that many neurons within the gray matter of the spinal cord responded to electrical stimulation of skin nerves, and, in addition, could be driven by stimulation of the splanchnic nerves. Analysis of the visceral afferent fibers involved in the convergence showed that only small myelinated and unmyelinated fibers converged onto spinal cord neurons. These findings were confirmed by Fields and associates (59), and several years later they were confirmed by Guilbaud and associates (60). The latter group reported that only those spinal cord neurons that had a cutaneous noxious input could also be excited by injection of algogenic substances into the mesenteric artery. These and other older studies were cited in the report by Foreman and colleagues in 1981 (61), and Cervero (62) showed that visceral noxious input converged mainly onto those neurons having a noxious cutaneous input. Neurons in the spinal cord driven exclusively by innocuous stimulation of the skin were rarely driven by visceral input.

More recent work also has demonstrated that the neurons that have visceral and somatic convergence and that respond to visceral nociceptor stimulation have superficial receptive fields in the area expected for that viscus [see Foreman (63) and Willis (64) for references]. Thus, Foreman and Ohata (65) found that those neurons in the thoracic spinal cord of cat that had responded vigorously to coronary artery occlusion had superficial receptive fields in the left forelimb and shoulder of the animal. In his study of nociceptors of the gallbladder, Cervero (66) noted that those neurons activated by noxious intensities of biliary pressure had cutaneous receptive fields in the flank of the animal at the thoracoabdominal junction. These neurons could be activated by noxious and innocuous cutaneous stimulation of the receptive field as well as by stimulation of the muscle layers beneath the skin. Cervero (2,3) has pointed out that these types of cutaneous superficial inputs originate from the area to which the pain of biliary origin is usually referred in humans.

Finally, others have shown that nearly one-half of the neurons in the thalamic nuclei in which the spinothalamic tract terminates respond to noxious cutaneous inputs and to noxious stimulation of the abdominal viscera, and that visceral and somatic convergence has also been found in neurons in the somatosensory cortex of cat (3,64). Thus, findings in the experimental animal support Ruch's prediction.

Branching of Peripheral Nerves

Several investigators have found evidence of bifurcation in central and peripheral axons of dorsal ganglion cells (31). Perl and colleagues (67) have observed collateral projection of some mechanical nociceptors to receptive fields in skin and muscle. Bahr and associates (68) were able to activate dorsal root ganglion cells antidromically from the sympathetic chain (which contains visceral afferents) and a cutaneous nerve. Pierau and colleagues (69) have demonstrated that individual dorsal root ganglion cells can sometimes be activated by stimulation of two different peripheral nerves. Because these responses could be shown even after dorsal rhizotomy, they could not depend on spinal cord mechanisms. Double fluorescent dye transport studies (69,70 and 71) have provided additional evidence for branching of peripheral fibers, which supply both visceral and peripheral structures. Although it is possible that they may play a role in referred pain, the function of these dichotomizing fibers has not been conclusively demonstrated.

BIOLOGY AND PATHOPHYSIOLOGY OF ACUTE PAIN

The first edition of this book contains a detailed discussion on the long-standing controversy as to whether pain is a physiologic sensation with a protective function or a pathophysiologic phenomenon that is not protective but destructive. Biologists, physiologists, and other scientists have long adhered to the thesis that pain has the important biological function of signaling to the organism that it is in danger or of the existence of a noxious stimulus or agent, and that it is associated with immediate protective reflexes that tend to maintain homeostasis. Sherrington defined pain as “the psychological adjunct to an imperative protective reflex (72).” Other writers, especially clinicians who frequently treat patients with persistent or chronic pain, have opposed the biological protective concept. Leriche (73) wrote that “physicians too readily claim that pain is a reaction of defense, a fortunate warning which puts us on our guard against the risks of disease . . . I would oppose this extraordinary error, whose persistence I fail to understand, which has no shadow of justification.” These opposing views reflect a major difference between acute and chronic pain. With certain acute injuries or visceral disease, the pain and the associated reflexes have an important biological function that prevents further tissue damage. On the other hand, Leriche (73) and others, in taking the antiprotective function position, were speaking of the “pain associated with cancer, causalgia and neuralgia, which has become pathologic because of its mental and physical effects,” thus pointing out differences between acute and chronic pain. However, acute pain does not always have a beneficial biological function. The pathophysiologic effects of severe acute pain in the postoperative period, as well as with certain injuries, can be detrimental. Bonica (74,75) repeatedly emphasized these points, and they are reexamined here under the following headings: Biological Function, Relation of Pain and Injury, and Pathophysiology of Acute Pain.

Biological Function

Transient acute pain, as occurs when a person touches a hot stove or steps on a sharp object, promptly alerts the individual and causes him or her to immediately withdraw the limb and thus avoid further damage. Acute pain associated with more severe injuries involving deep somatic structures, such as fractures or sprains, imposes limitation of action and therefore tends to prevent further damage or aggravation of pathophysiology. The protective biological function of acute pain under these circumstances is widely accepted and appreciated. Similarly, acute pain of visceral disease has the biological function of warning the individual that something is wrong, it prompts him or her to consult a physician, and it is used by the physician as an aid in making the diagnosis. Moreover, as previously mentioned, acute pain associated with injury or disease is often associated with certain segmental and supersegmental reflex responses that help the organs maintain homeostasis. These autonomic reflex responses permit a person to *fight or run* and later enhance the healing process. In all of these and other circumstances, the pain and the associated reflex responses have an important biological function.

In some instances, the warning signal (pain) comes too late to avoid injury. Sunburn is a good example: We do not feel the pain until after the too-lengthy exposure to the sun has occurred. Similarly, in most visceral diseases, the pain is produced long after the beginning of the pathology, and therefore it is of no value as a protective reflex. Moreover, in many instances, injury to somatic structures occurs so rapidly that the associated pain does not help to prevent the injury. Indeed, some individuals who sustain an accidental injury experience no pain for minutes or even hours after the injury.

Relation of Pain and Injury

The phenomenon of a painless period after an injury has been reported by many writers. The most famous and widely quoted report was that of Beecher (76), who surveyed wounded soldiers admitted to the U.S. field hospital on the Anzio beachhead and noted that only one-third had sufficient pain to ask for medication. Similar findings of an initial painless period were reported by Carlen and associates (77), who studied Israeli soldiers who had suffered traumatic amputation during the Yom Kippur War. During World War II, Bonica also encountered wounded patients who, on questioning, stated they had felt no pain at the time of, and for some minutes after, an injury that subsequently required amputation of a limb. Although the incidence of a painless period after injury was significantly less than that reported by Beecher (76), it nevertheless was most impressive.

Injuries including fractures, severe sprain, and severe laceration that occur during contact sports are frequently painless for varying periods of time. Thus, the football player who sustains an injury may continue to play until he returns to the bench, or the boxer who sustains severe damage to his nose or face does not feel pain until the end of the contest. Such painless periods can be explained on the basis of stress-induced analgesia. However, painless periods are also experienced among persons who have incurred injuries in the home, at work, or in connection with vehicular accidents. This phenomenon was impressively demonstrated by Melzack and colleagues (78), who examined 138 consecutive accident victims admitted to the emergency department of a large city hospital. The injuries consisted of fractures (19%), sprains (18%), lacerations (17%), severe bruises (18%), and smaller percentages of amputations, stab wounds, burns, or crush injuries. Approximately 60% of the injuries were sustained at work or in the home, and the remainder occurred in the street or were sports related. Among this group, 37% of the patients reported a pain- free period, which varied in duration: 53% with injuries limited to the skin had a pain-free period, as had 28% of patients with deep tissue injury. The analgesia was specifically spatially limited to the region of injury, and all patients eventually developed pain.

On the basis of some of the aforementioned reports, his own experience of a painless period after a severe laceration of the scalp, and his observation of the behavior of two animals that had been injured, Wall (79) developed an innovative conceptualization of the relation between acute injury and pain. He proposed that after acute injury there are three periods of response: the immediate phase, a secondary phase, and a tertiary phase. He attributed the painless period to circumstances in which treatment of the injury does not have the highest biological priority: the three obvious high-priority behaviors are fighting, escaping, and obtaining aid. In humans,

escape includes calling for help or organizing help. In discussing the results of their study, Melzack and associates (78) state that the painless period “may have survival value.” They suggest that a limit on pain after injury prevents the organism from being overwhelmed by pain and therefore allows it to carry out adaptive behavior such as escape, hiding, “playing possum,” and other maneuvers that might prevent further injury in a dangerous situation. The secondary phase is characterized by the combination of tissue damage, pain, and anxiety and represents a transition period between coping with the cause of injury and preparing for recovery. During this phase, most individuals who incur tissue injury have moderate to severe pain. The tertiary phase is characterized by limited activity, prolonged sleep, poor appetite, limited attention span, and sometimes depression. Wall (79) suggested that these characteristics are “the optimal tactic to encourage cure and recovery of the damaged tissue.”

Pathophysiology of Acute Pain

Although it is universally accepted that acute pain has a biological function under certain circumstances, it is not generally realized or appreciated, even by some physicians, that persistent severe acute pain may prove deleterious to the organism. Thus, severe postoperative pain not only has no biological function but, if not adequately relieved, can also produce abnormal physiologic and psychological reactions that often cause complications. Similar deleterious effects result if the severe pain of injury or of such diseases as myocardial infarction and acute pancreatitis is not effectively relieved after it has served its biological function. Indeed, even severe pain associated with certain physiologic processes such as parturition, if allowed to persist, produce deleterious effects. These detrimental effects are consequent to progression of the segmental and suprasegmental reflex responses and cortical responses to an abnormal state. Because of the potential deleterious effects of severe postoperative and postinjury pain, clinicians have focused increasing effort on preemptive analgesia. Aggressive attention to prevention and treatment of postoperative pain, including the use of multimodal therapies, has been a topic of several reviews (37,80,81 and 82).

Responses to Tissue Injury

Tissue destruction, whether from crush injury, fracture, operation, or internal disease, results in local biochemical changes and autonomic reflex responses that are intended to maintain body integrity (see Chapter 3). The local biochemical changes produced by liberation of intracellular chemical substances into the extracellular fluids surrounding nerve endings to induce local pain, tenderness, and hyperalgesia have been discussed earlier. In addition to sensitizing the nerve endings, these algogenic substances also act indirectly by altering the microenvironment consisting of smooth muscles, capillaries, and efferent sympathetic fibers (43). The nociceptors, thus activated, transduce the noxious stimuli into impulses that are transmitted to the neuraxis. On reaching the spinal or medullary dorsal horn, these impulses are promptly subjected to peripheral, local, segmental, and supraspinal descending modulating influences, which, together with other factors, determine their further transmission. Some of the nociceptive impulses pass to the anterior and anterolateral horn of the same and adjacent segments of the spinal cord to stimulate somatomotor and sympathetic preganglion neurons, respectively, and thus provoke segmental autonomic (nocifensive) reflex responses. Other nociceptive impulses coming from the periphery stimulate dorsal horn neurons, the axons of which make up ascending afferent systems in the spinal cord and higher parts of the neuraxis, and transmit the nociceptive information to various parts of the brainstem and brain. Some of the impulses that reach the brainstem provoke suprasegmental reflex responses; others may activate the supraspinal descending modulating system, and still others reach the brain to provoke cortical responses.

Segmental (Spinal) Reflexes and Responses. Segmental (spinal) reflexes may enhance nociception and produce alteration of ventilation, circulation, and gastrointestinal and urinary function. Thus, stimulation of somatomotor cells may result in increased skeletal muscle tension or spasm, which initiates positive feedback loops that generate nociceptive impulses from the muscle (43) (Fig. 9-18). In their classic studies, Lewis and Kellgren (26) noted that when the pain provoked by injection of the ninth thoracic interspinous ligament was severe, the upper belly of the rectus abdominus muscle developed severe spasm, which stood out as an obvious *phantom tumor*. This usually caused the subject to “cease breathing owing to a sense of fixation of the chest,” and there was flattening of the lower ribs and diminished movement on the affected side. Although the reflex spasm and pain disappeared within minutes after the injection of the hypertonic saline, the skin tenderness remained for a considerable period.

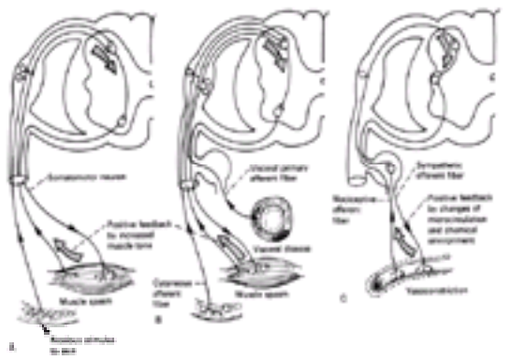

Figure 9-18. Diagram indicating possible mechanisms of self-excitation nociceptors by spinal reflexes. **A:** A somatomotor reflex induced by stimulation of cutaneous or muscle nociceptors causes skeletal muscle contraction, which in turn acts as a positive feedback to excite dorsal and ventral horn neurons (*arrows*) and produces an abnormal reflex mechanism, resulting in still further increase in muscle tension. **B:** A similar mechanism producing skeletal muscle spasm, initiated by a convergence of cutaneous and visceral primary afferents on viscerosomatic spinothalamic tract neurons. Stimulation of somatomotor neurons in the anterior horn produces reflex skeletal muscle spasm, which acts as positive feedback to produce and maintain a vicious cycle. **C:** Noxious stimulation of primary afferent fibers produces nociceptive input, some of which is transmitted to spinothalamic tract neurons. Other impulses travel to the anterolateral horn to stimulate sympathetic preganglionic (efferent) fibers, causing vasoconstriction, increased smooth muscle tone, and change in the chemical environment. The latter, in turn, acts as positive feedback to further increase nociceptive input.

Stimulation of sympathetic preganglionic neurons in the anterolateral horn of the spinal cord causes an increase in heart rate, stroke volume, and, consequently, cardiac work and myocardial oxygen consumption (38). In addition, sympathetic hyperactivity can decrease gastrointestinal tone that may progress to ileus and a decrease in urinary function that reduces urinary output. Because these responses to noxious stimuli occur in animals who have had vagotomy and C-1 spinal section, they are produced by truly spinal segmental reflexes.

It deserves emphasis that massive nociceptive stimulation not only sensitizes peripheral nociceptor afferents, but also can produce a nociceptive barrage that sensitizes dorsal horn neurons, interneurons, and anterior motor neurons. This is most likely to occur when C fibers from muscles, joints, and periosteum are stimulated and produce long-latency, long-duration facilitation that affects cells in lamina I and in deeper laminae and thus triggers prolonged increase in excitability of cells in lamina I and in deeper laminae (83). It produces a large expansion of receptive fields and can convert nociceptive-specific cells to cells that respond to light as well as intense stimulation (83). It also affects cells with receptive fields distant from the area served by the stimulated nerve. Although the facilitation is triggered by the arrival of impulses in C fibers from deep tissue, it is sustained by intrinsic spinal cord processes (84). This prolonged increase of excitability of central cells is probably the basis for widespread prolonged tenderness, hyperalgesia, that can persist for days or weeks after the injury (see Chapter 4).

Suprasegmental Reflex Responses. Suprasegmental reflex responses result from nociceptive-induced stimulation of medullary centers of ventilation and circulation, of hypothalamic (predominantly sympathetic) centers of neuroendocrine function, and of some limbic structures. These responses consist of hyperventilation, increased hypothalamic neural sympathetic tone, and increased secretion of catecholamines and other hormones. In 1929, it was shown that increased neural sympathetic tone and catecholamine secretion add to the effects of spinal reflexes and further increase cardiac output, peripheral resistance, blood pressure, cardiac workload, and myocardial oxygen consumption (85). In addition to catecholamine release, an increased secretion of cortisol, adrenocorticotropic hormone, glucagon, cyclic adenosine monophosphate, antidiuretic hormone, growth hormone, renin, and other catabolically acting hormones occurs, with a concomitant decrease in the anabolically acting hormones insulin and testosterone (85,86,87 and 88) (Table 9-2). This type of endocrine secretion, characteristic of the stress response, produces widespread metabolic effects, including increased blood glucose, free fatty acids, blood lactate, and ketones, as well as a generalized increased metabolism and oxygen consumption. The endocrine and metabolic changes result in substrate use from storage to central organs and injured tissue and lead to a catabolic state with a negative nitrogen balance. The degree and duration of these endocrine and metabolic changes are related to degree and duration of tissue damage, and many of these biochemical changes last for days (89). These and other findings have led to the development of the concept that inhibition of the stress response may improve outcome after surgery and trauma. To date, however, this hypothesis has not been adequately addressed in clinical studies (81).

TABLE 9-2. Neurophysiologic, endocrine, and metabolic response to injury

Psychophysiologic Responses

The intense anxiety and fear that develop in patients who experience severe acute pain consequent to an unexpected severe injury or acute myocardial infarction greatly enhance the hypothalamic responses characteristic of stress through cortical stimulation. Indeed, cortisol and catecholamine responses to anxiety may exceed the hypothalamic responses provoked directly by nociceptive impulses reaching the hypothalamus (90,91) (see Chapter 24). Moreover, anxiety and the related stress response can cause increased blood viscosity (92), clotting time (93), fibrinolysis (94), and platelet aggregation (95).

The deleterious effects of such reflex responses consequent to tissue injury and acute pain in producing complications have been reviewed (81) and are discussed in detail later in this book, but the following two examples illustrate some potential detrimental effects of acute pain. First, severe postoperative pain and the associated reflex responses are responsible for such pulmonary complications as hypoxemia, atelectasis, and even pneumonia. Moreover, as a result of powerful cutaneovisceral and viscerovisceral reflexes, patients develop ileus and decreased urinary output, as well as impairment of muscle metabolism, and are at increased risk of thrombus formation. That pain plays an important role is indicated by the fact that the excellent pain relief achieved with regional analgesic techniques can reduce complications (81) (see Chapter 41).

Studies of unpremedicated primaparas and multiparas have shown that the pain of uterine contractions causes a 5- to 20-fold increase in ventilation, with consequent severe respiratory alkalosis during contraction and alkalosis-induced hypoventilation between contractions (47). Moreover, the pain and anxiety produce a marked increase in sympathetic activity, resulting in increases of 50% to 200% in secretion of catecholamines and cortisol. These cause a significant increase in cardiac output and work of the heart and a marked increase in oxygen consumption, which is added to that inherent in the work of labor. This, together with loss of bicarbonate from the kidney (as compensation for pain-induced respiratory alkalosis and often reduced carbohydrate intake), can result in a progressive metabolic acidosis that is transferred to the fetus. The critical role of pain in these abnormal responses, which affect not only the mother but also the fetus and newborn, have been amply demonstrated by the use of regional analgesia, which eliminates the hyperventilation and markedly decreases the increase in cardiac output and other deleterious effects. These are discussed further in Chapter 71.

In conclusion, acute pain is commonly associated with injury or disease involving superficial and deep structures. Persisting acute pain stresses the injured or ill patient and can lead to deleterious physiologic and psychological effects. The relief of acute pain is an imperative for modern physicians.

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*According to Sheehan (33), this concept was first suggested by Whyt in 1751, but his writing went unnoticed for 150 years until Hurst's investigations.

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CHAPTER 10

General Considerations of Chronic Pain

Louis Jacobson and Anthony J. Mariano

> The world we have made as a result of the level of thinking we have done thus far creates problems we cannot solve at the same level of thinking at which we created them.
>
> —Albert Einstein

Chronic pain has customarily been defined as pain that persists for a specified time that is arbitrarily determined (e.g., 3 months or 6 months, or beyond the expected period of healing). A problem exists with this way of distinguishing chronic from acute pain. How would syndromes such as osteoarthritis be classified? Are they characterized by acute or chronic pain? In these cases, the syndromes may cause both acute and chronic pain. Acute pain may be initiated by ongoing stimulation of nociceptors, abnormal activity in inflamed tissue, or abnormal activity of sensitized neurons within the central nervous system (CNS), indicating tissue damage, but the pain extends over long periods. The fact that the pain may persist for years increases the likelihood that psychosocial and environmental factors will contribute to emotional distress and physical disability that are commonly observed with pain syndromes for which there is no ongoing physical pathology. Thus, two dimensions must be considered simultaneously, a time dimension and a pathology dimension. Pain that extends beyond the period of healing, in the absence of ongoing pathology, should be viewed as chronic pain. Pain of relatively short duration elicited by injury of body tissues and activation of nociceptive transducers at the site of local tissue damage should be viewed as acute pain. Pain, however, that extends over periods for which there is ongoing pathology might best be viewed as acute and chronic pain (see Chapter 2).

There has been a tradition within the literature to distinguish between chronic pain associated with cancer—"malignant pain"—and "nonmalignant pain," as from other syndromes unrelated to cancer. Little evidence exists to suggest that different neuronal elements are involved to warrant such a distinction. Moreover, given the discussion of acute and chronic pain, it is apparent that pain associated with a malignant disease may share features of both acute and chronic pain.

The term *chronic pain* as used in this chapter specifically excludes persistent pain that is associated with cancer. Although frequently confused in the literature, pain associated with malignant disease differs in several significant ways from the problems addressed in this chapter. First, pain associated with terminal cancer states is by definition time-limited. The problems and strategies outlined in this chapter are more appropriate for patients who are faced with the challenge of living with pain for many years. Second, pain associated with a malignant disease typically does not involve the conflict with the medical system and enmeshment in the legal-disability system that is characteristic of the population of chronic pain patients with pain not associated with neoplastic disease. Finally, pain associated with cancer is a symptom of a disease bearing a direct relationship predominantly with tissue pathology. In contrast, there is only a weak association between reported pain and objective findings of disease in chronic pain not associated with cancer (1,2,3 and 4). Of course, the treatment of pain associated with cancer can lead to new pain syndromes that are not directly owing to the neoplastic disease, such as radiation plexitis or painful neuropathy caused by chemotherapeutic agents. These pain syndromes are related to pathology in this case, iatrogenic and not neoplastic.

Thus, this chapter focuses on the large fraction of chronic pain patients for whom the cause of pain remains a mystery to biomedicine, because no associated lesion can be found or similar lesions exist in people who do not complain of pain. It should be noted, however, that many of the psychosocial and behavioral factor and related issues that we cover with regard to chronic pain not associated with cancer are relevant for consideration in treating patients with pain associated with cancer and for pain syndromes that share features of both chronic and acute pain.

Despite significant advances in medicine and the treatment of disease, chronic pain remains an enigma that health care professionals often manage poorly (5). Conventional understandings of disease fail to explain why some people are disabled by pain in the absence of an organic process that adequately accounts for the severity of their symptoms (1). Pharmacologic and somatic treatments fail to provide enduring pain relief. Patients who are overwhelmed by chronic pain fail to improve and are frequently intensely disliked by physicians (6,7). These patients are among the most debilitated, demanding, and dissatisfied of health care consumers (8,9).

The practitioners' challenge is how to help patients who attribute pervasive disability and dysfunction to persistent pain in spite of repeated failed treatment efforts and the absence of physical etiology. For the patient, intractable nonmalignant chronic pain is an overwhelming and all-consuming life experience. In a futile search for biomedical solutions, the patient develops a lifestyle that is centered around seeking diagnoses or treatment for pain, avoiding activities that are thought to cause pain, and attaining financial compensation for putative injuries or the inability to remain employed.

Recognition of the complexity of the problem is the initial challenge for the health care provider who wishes to help chronic pain patients. The report of the Commission on the Evaluation of Pain encourages an awareness by practitioners that chronic pain is best understood as a process that evolves over time (1). The chronic pain experience results from the entire progression of the patient's illness, the sociocultural context in which it occurs, and the interactions between health care professionals and patients (1). Iatrogenesis is a significant problem, and the health care professional who offers only biomedical "solutions" inadvertently risks becoming a large part of the problem. The challenge facing health care professionals is to learn new ways of thinking about chronic pain and disability.

The goals of this chapter are to provide an overview of chronic pain, outline key conceptual issues, and furnish broad clinical recommendations for the management of disabling chronic pain. Biological mechanisms of pain are reviewed briefly as a background for subsequent chapters in this book. More attention is focused on psychological and social factors that influence a patient's experience of pain, regardless of the presence or absence of a specific etiology.

The fundamental difficulties in treating disabling chronic pain lie in the philosophical and structural underpinnings of biomedicine. Cartesian dualism and notions of the "body as machine" permeate the culture of contemporary medicine and the medical-legal system of disability. Modern thinking about chronic pain emphasizes a more holistic approach that incorporates psychological, social, and cultural influences on pain and suffering (10,11). A general biopsychosocial systems approach to chronic pain is advocated (12,13), with special attention to the important role of the patient-provider interaction and self-care rehabilitation (14). From this perspective, practitioners frequently rely less on technical skills and more on interpersonal skills.

SIZE AND SCOPE OF THE PROBLEM

Disabling chronic pain is a major health care and social problem of epidemic proportions (15,16,17 and 18). Pain is the second most frequent complaint brought to the offices of providers in North America, after upper respiratory tract infections (1,18). Pain is also a common reason for hospital admissions (19). It is the most frequent cause of suffering and disability that seriously impairs quality of life (20).

A review of published information on chronic pain reveals both the magnitude and scope of the problem:

- Seventy million Americans report chronic pain, and many are permanently disabled (1).
- Approximately 10% of people in the United States have pain on more than 100 days per year (1).
- Chronic pain conditions, such as arthritis and migraine headaches, affect tens of millions of people.
- Low back pain (LBP) is the most common cause of workdays missed because of disability related to pain (14) and the condition that leads most often to workers' compensation claims (21).
- The annual incidence of LBP in the United States is estimated as 5% of the adult population (22), with a lifetime incidence or risk of 60% to 85% (23,24).
- The average sufferer has a long history of multiple episodes.
- Chronic, continuous back pain accounts for approximately one-fourth of the total prevalence (25,26). Seven million individuals experience LBP at any one time (1).
- Fourteen percent of the adult population in the United States have serious chronic back conditions, and approximately the same percentage experiences less severe back pain that is still significant enough to interfere with daily work or routine (27).

These findings also represent the experience of other Western countries, such as Sweden and Denmark (1).

The financial burden of chronic pain in the United States is astronomic. In 1987, the National Center for Health Statistics documented 70 million physician visits over a 3-year period in which pain was the primary complaint. These staggering numbers translate into more than 4 billion lost workdays for pain conditions (1). LBP alone costs at least $16 billion per year, with one-third allocated for medical costs and the remaining two-thirds for compensation (27).

Pathology alone does not account for the continued increase in disability and health care consumption related to chronic pain. The huge impact on the health care and social support systems of the inordinate amount of medical care expended on chronic pain is an important public health issue. Therefore, in addition to the suffering of individual patients, enormous medical and social resources are expended, and pain is costly in terms of compensation and loss of work (23).

Pain is especially challenging, because the more subjective the complaint, the more difficult and expensive it becomes to establish its relation to the inability to work (1). The award of disability for pain is growing rapidly (25). Conditions of the workplace are a better predictor of return to work than biomedical tests and measurements. Workers who do not recover from a back injury within several months have a high likelihood of progressing to long-term disability. Even among those who return to work after their injuries, the return to work is often unstable (28). Industrial injuries often have sequelae that persist beyond the time of the first return to work and may lead to recurring difficulties in the workplace. Therefore the recommendation is that the unit of analysis for the study of industrial LBP ought to be the individual who has the pain rather than an episode of back pain, and follow-up should continue for several years rather than for several months (29).

BIOLOGICAL MECHANISMS OF CHRONIC PAIN

The biological factors that contribute to chronic pain are considered under the following categories: peripheral, peripheral-central, and central. The following comments are intended to provide background material to chapters in Parts III and IV of this volume, in which detailed discussion of some of these hypotheses can be found. Chapter 6 discusses psychological aspects of pain in greater detail. Diagnostic issues are presented in Chapter 18, and treatment strategies are covered in Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92, Chapter 93 and Chapter 94. Aspects of chronic pain are also covered in the chapters on regional pain in Part IV.

Peripheral Mechanisms

Peripheral mechanisms contribute to pain associated with chronic musculoskeletal, visceral, and vascular disorders. Peripheral pain conditions include arthritis, myofascial syndromes, chronic tendinitis, chronic ostalgia, headache, some forms of neoplasms, chronic pancreatitis, chronic peptic ulcer, coronary artery disease, and peripheral vascular disease. The pain may result from persistent noxious stimulation of nociceptors and their sensitizations (30). Alternatively, various reflex mechanisms and other factors may operate. These chronic pain syndromes are referred to as *nociceptive pain* because the pain is provoked by prolonged excitation of nociceptors. In addition, chronic pain produced by pathology limited to peripheral nerves without major irreversible change in the CNS is attributed to “peripheral mechanisms.”

The tissue damage of disease or injury causes liberation of endogenous chemicals, such as serotonin, histamine, bradykinin, and prostaglandins, which have excitatory effects on nociceptors. Many of these algogenic substances are both neuroactive and vasoactive. Excitation of nociceptors occurs either by direct action on the membrane of nociceptors or indirectly by altering their microenvironment. Depending on which substance predominates, there is impairment of the microcirculation with vasoconstriction or vasodilation. These agents promote a vicious cycle of nociception by increasing capillary permeability, enhancing the extravasation of additional algogenic substances, and perpetuating disturbances in the physiologic and biochemical microenvironment of nociceptors. Thereby, nociceptor excitation is increased.

Liberation of substance P from the peripheral nerve endings of nerve fibers, excited either orthodromically or antidromically, may exacerbate the peripheral nerve irritation. The role of algogenic substances in increasing the sensitivity of nociceptors to both noxious and nonnoxious stimuli is also discussed in detail in Chapter 4. Nociceptors are sensitized to nonnoxious stimuli, thus explaining the allodynia, hyperalgesia, and hyperpathia associated with chronic inflammatory disease.

Experimental studies show that chronic inflammation of the joint lowers the threshold to mechanical stimuli (30). A-d and C- nociceptor afferents are usually excited only by noxious stimuli. Nociceptive-specific neurons in lamina I of the spinal dorsal horn and neurons in the ventrobasal complex of the thalamus are also sensitized and are activated by light mechanical stimulation of the inflamed joint (31,32). The important role of peripheral mechanisms in chronic pain syndromes associated with chronic inflammation is suggested by the efficacy of aspirin and nonsteroidal antiinflammatory agents, whose action is predominantly peripheral (33).

Sensitization of nociceptors may occur after the administration of certain therapeutic agents and in various types of peripheral nerve injuries. The pain associated with peripheral neuropathies with no discernible nerve damage is also peripheral pain. Patients with neuritis (i.e., inflammatory reaction of the nerve without major permanent damage) experience relief with regression of the neuritis. The deep aching pain of brachial neuritis is alleviated by keeping the arm and shoulder motionless in the preferred position. The acute neuropathic disorders associated with leprosy are possibly caused by humoral antibody responses to systemically released antigen of *Mycobacterium leprae*. The nerve trunks are turgid with accumulated fluid, thereby resulting in tenderness and deep aching pain. That the symptoms may disappear with systemic corticosteroids strongly suggests peripheral mechanisms.

Persistent stimulation and consequent sensitization of nociceptors probably account for the pain of rapidly growing cancers of solid viscera associated with rapid distension of the investing fascia. A similar peripheral mechanism operates in tumor obstruction of large veins with consequent severe edema of the head or one of the limbs. Chronic obstruction of blood flow in arteries produces ischemia and consequent excitation or sensitization of nociceptors. Experimental data to support these speculations are meager, but clinical observation and experience suggest a peripheral mechanism.

Influence of Spinal Reflexes

Segmental spinal reflexes contribute to homeostasis. Acute disease or injury excites and sensitizes nociceptive afferents. This sensitization produces positive spinal reflex feedback loops that enhance nociceptor responses, induce excessive skeletal muscle tension, and increase sympathetic activity. Experimental studies suggest that tissue and nerve injury can cause prolonged increase in the excitability of cells in lamina I and deeper laminae of the spinal cord that can result in persistence of abnormal reflex muscle spasm and other reflex responses (34,35). These exaggerated responses may persist and contribute to the development and maintenance of

chronic pain states.

Clinical Implications

Pain due to ischemia from coronary artery disease recedes with bypass surgery and improved blood flow. Chronic pain due to persistent inflammation, such as arthritis, is relieved by drugs that decrease inflammation and prevent the synthesis of prostaglandins. Examples include aspirin and indomethacin. Local anesthetic injections into muscles (myofascial syndromes), tendons (tendinitis), and joints may relieve peripheral nociceptive pain. Pain attributable to joint degeneration is often relieved by removal of the affected joint and replacement with a prosthesis. These examples demonstrate the role of peripheral mechanisms in certain kinds of pain. Effective therapy may mitigate the long-term effects of persistent nociception on the CNS.

Peripheral-Central Mechanisms

Peripheral-central mechanisms are possibly relevant in chronic pain associated with partial or complete lesions of the peripheral nerves, dorsal roots, or dorsal ganglion cells that produce dysfunction in the neuraxis. Causalgia (complex regional pain, type 2), phantom limb pain, postherpetic neuralgia, and tumor invasion of peripheral nerves are clinical examples. The dysfunction involves both the central and peripheral nervous systems and is referred to as *deafferentation pain* (36).

A number of hypotheses, none fully inclusive, are proposed to account for these chronic pain states. These include the vicious circle mechanism, central summation theory (37), decreased peripheral inhibition theory (nerve dissociation theory, sensory interaction theory) (38,39), ectopic impulse generation or chronic nerve compression (40,41,42 and 43), deafferentation hypersensitivity (40,44,45,46,47 and 48), and the central biasing mechanism (49). They attempt to explain various clinical and experimental observations.

Patients with recent injury to a peripheral nerve may respond to targeted peripheral therapy. If early therapy is not available, the condition becomes refractory to treatment. It is as if the pathophysiologic process initially confined to the periphery becomes embedded in the neuraxis and is thereafter irreversible. Then, like central pain, it is intractable to therapy.

Central Pain Mechanisms

Disease or injury of the CNS may produce “central pain,” characterized by burning, aching, hyperalgesia, dysesthesia, hyperpathia, and other abnormal sensations. Central pain is associated with thalamic lesions (thalamic pain), spinal cord injury, surgical interruption of pain pathways, tabes dorsalis, syringomyelia, and multiple sclerosis. Integral to the genesis of central pain of spinal cord injury is the abnormal burst activity of deafferented neuron pools referred to as *pattern-generating mechanisms* (50). Diminished descending inhibition allows recruitment of extra neurons into the abnormally firing neuron pools, which intensify the pain and promote its spread. A detailed discussion of the mechanisms of central pain is presented by Tasker in Chapter 23.

CONCEPTUAL CONSIDERATIONS

Enigma of Chronic Pain

Patients present with the hope of a pain cure or a significant immediate symptom relief. Chronic pain puzzles patients because they are unable to comprehend why modern medicine cannot find a solution for their problem. Chronic pain frustrates providers because the etiology is usually unclear and satisfactory treatments are elusive (51,52,53,54 and 55). Complaints of incapacitating pain are reported either in a context of undiagnosable pathology or are grossly exaggerated in light of established physical findings. Little correlation exists between reported pain levels, physical findings, results of diagnostic tests, and observed disability (2,3 and 4). Carron's declaration that “minimal pathology with maximum dysfunction remains the enigma of chronic pain” epitomizes the challenge facing health care practitioners (56).

Over time, the course for many chronic pain patients is characterized by increasing disability in spite of multiple interventions. Brief periods of improvement often occur as new treatments are implemented, but these successes are typically short-lived, and the patient continues to decline functionally. Objective data suggest that the disease process is stable (or nonexistent) at a level that cannot account for the progression of subjective reports of distress and disability. The providers' enigma is that the patient's functioning is discrepant with the objective findings of pathology.

In the presence of this ambiguity, the relationship between the patient and the provider becomes strained and conflicted over time. To explain the discrepancy, the biomedically based provider, who relies solely on physical status to account for disability, typically concludes that the problems are psychological and either uninteresting or beyond his or her skills. Consequently, the patient is referred to a mental health practitioner, with either the explicit or implicit communication that his or her pain problems are “not real,” “in the head,” or psychogenic (57). Mutual frustration characterizes the relationship between “enigmatic” chronic pain patients and their providers. These emotions are fueled by failure of multiple treatments, distrust concerning the inadequacy of diagnoses, suspicion around the implications for disability determinations, tension over compliance with treatment recommendations, friction surrounding the voluntary control of symptoms, and conflict over rational surgical or pharmacologic treatment options.

“Overwhelming” Chronic Pain Syndrome

Despite the pain syndromes described earlier, many chronic pain patients do not present with a coherent, clearly defined constellation of symptoms and signs that denote a medical diagnosis. No common etiology, predictable natural history, defined course, or specific treatment exists for the multitude of painful conditions that suggests a basis for positing a single chronic pain condition (1). This void spawns a profusion of painful conditions with labels that masquerade as diagnoses but without a unifying rubric (10). Although the generic term *chronic pain syndrome* is widely used, it remains without official sanction. Like beauty, this syndrome is difficult to define, but one knows it when one sees it.

Much of the patients' and providers' frustration is traceable to this uncertain status of chronic pain within the scientific, clinical, and medical-legal communities. This lack of consensus among professionals and the conceptual tensions that emerge from different interpretations of related variables engender confusion and contradiction (1). What emerges is the designation of a “chronic pain syndrome” distinguished by behaviors and psychological characteristics that supersede the specific physical aspects of the painful condition (14). These characteristics are listed in Table 10-1.

An "enigmatic" presentation of pain to medical providers characterized by conflict and mutual dissatisfaction.
A lifestyle centered on seeking immediate relief from pain via repeated attempts to obtain medical or surgical treatment.
Repeated attempts to obtain pain-related financial compensation from social agencies such as Social Security, workers' compensation, and the Veterans Administration.
Significant disease conviction and excessive focus on somatic functioning.
Development of a variety of symptoms of psychosocial dysfunction that the patient maintains are secondary to pain. These include depression, alcohol abuse, illicit substance abuse for "pain relief," dependence on opioids or other medications with high potential for abuse, sleep disruption, excessive physical deactivation, severe family dysfunction, and significant disruption of vocational and familial roles.

TABLE 10-1. Characteristics of a patient with an overwhelmingly “chronic pain syndrome”

Even though the designation “chronic pain syndrome” implies a generic classification for an undefined ailment, it leads to confusion. We think it is a label born of desperation and used in the absence of anything more worthwhile. Chronic pain is common in the general population, but the full-blown chronic pain syndrome is relatively rare. With regard to chronic LBP, for example, only a small proportion of all individuals (5%) develop disabling chronic pain. They account, however, for a

disproportionately large proportion of the costs (85%) in terms of compensation and loss of work (22). The practitioner unaware of the distinction typically uses the same methods to address persistent pain in these qualitatively different problems. The iatrogenic process that begins as a well-meaning attempt to provide pain relief ends with the mutual frustration and conflict between provider and patient that is characteristic of chronic pain syndrome.

The term *chronic pain syndrome* causes misunderstanding relating to duration of illness and its implied benign nature, although one could argue that no pain is truly benign. The primary distinction for assigning pain as chronic is temporal. Chronic pain typically is defined as pain of longer than 3 months' duration. Patients with pain associated with a neoplastic disease, however, often have persistent pain for longer than 3 months and yet few manifest the chronic pain syndrome. The confusion between chronic pain associated with cancer and chronic pain not associated with neoplastic disease results in serious misunderstandings about their clinical management with regard to the long-term use of opioids (58,59). Providers inappropriately extrapolate management strategies for cancer patients to other types of chronic pain patients and advocate escalating opioid doses (60,61 and 62) without an appreciation for the differences in these populations (63,64). The chronic intractable benign pain syndrome (65,66) was proposed to differentiate these patients from those with malignant pain. The condition is, however, not benign and therefore it inaccurately represents the pain experience. Objections are raised about the use of terms such as *nonmalignant chronic pain syndrome*, with calls for more etiologically meaningful diagnosis (67). When specific, effective, targeted therapies are available, specific diagnoses are helpful because they profoundly influence the choice of treatment(s). With chronic pain, however, the presence or absence of an identifiable abnormality has little bearing on how a patient experiences pain, suffering, or disability (68).

Overwhelming chronic pain syndrome is a useful term because it accomplishes the hitherto elusive goals of creating a unifying rubric and overcoming the diagnostic conundrum. Regardless of the etiology of the painful condition and the presence or absence of a disease, enigmatic patients are universally both overwhelmed by pain and overwhelming to the medical and disability systems. Their distinguishing feature is that they repeatedly present to biomedical providers with pervasive disability and severe emotional distress that they attribute to pains that do not respond to conventional treatments.

Understanding overwhelming chronic pain syndrome begins with an examination of the process of help seeking. It is important to recognize that patienthood is a psychosocial, not a biological state (69). Many people with serious disease do not seek medical help. Conversely, in the case of chronic pain, many people without serious disease make use of medical services extensively. Rather than a disease, it is an experience in which psychosocial factors are better predictors of health care utilization than the number or severity of physical symptoms (70,71). Overwhelming chronic pain syndrome is fundamentally a psychosocial problem that is all too often managed in a biomedical culture and setting. It is a psychosocial condition with medical aspects, rather than a medical condition with psychosocial aspects (72).

Biomedicine underestimates the complexity of the pain experience. Understanding the process of medical help seeking by patients overwhelmed by chronic pain requires an appreciation of the distinction between disease and illness (73,74). Disease is a physical condition resulting from an organic process. Illness is the subjective experience and observed behaviors of an individual who believes that he or she is not well. Physicians diagnose and treat diseases and patients experience illnesses. It is pivotal to recognize that disease and illness do not stand in a one-to-one relationship and that the course of disease is distinct from the trajectory of the accompanying illness (69). Disease alone is neither necessary nor sufficient to account for the pain experience, and becoming well is not simply a matter of cure or pain relief.

Many contemporary health problems, of which chronic pain is a prime example, relate to illness rather than disease. Overwhelming chronic pain syndrome is an illness that has either no disease determinant or is discrepant with that accountable by disease alone (74). The incidence and prevalence of disease(s) are declining due to prevention and advances in early detection, elimination, and control of disease processes (75). Paradoxically, illness behavior, disability, health care utilization, and costs continue to increase. Chronic pain patients are overwhelmed by their subjective experience of illness, not by disease. It is this experience of illness, not the presence of disease, that motivates them to seek repeated medical treatment. The gap between disease as conceptualized by physicians and illness as experienced by patients requires bridging (69).

Social factors play a major role in the pain experience. The provider is an important source of social support through the medium of a healthy patient-provider partnership (76,77,78,79 and 80). However, the typical biomedical practitioner has neither the training nor the interest to address the many nonmedical issues that require consideration in treating people overwhelmed by subjective distress. Patients who stridently maintain that they have real physical disease in the absence of objective findings are difficult to manage because they do not respond positively to reassurances about their physical status. They vehemently object to suggestions that they have psychosocial problems other than those caused by pain. For the biomedical practitioner, such patients are overwhelming, both interpersonally and in terms of their demands for more and more service.

It is the mutual frustration and conflict among the patient, providers, and the medical-legal systems that distinguish the patient with overwhelming chronic pain syndrome from the more typical patient who has chronic pain but is easier to help. The addition of the designation “overwhelming” succinctly demarcates this distinction by identifying a unifying theme across many pain diagnoses. How practitioners attempt to help these patients is determined by their pain model.

MODELS OF CHRONIC PAIN

The chronic pain domain is inundated by a plethora of models. Eight prominent theoretical perspectives, categorized as either restrictive or comprehensive, have been posited to account for chronic pain (81). Restrictive models (mind-body dualism, psychological, radical operant-behavioral, and radical cognitive) ignore certain plausible facets of pain or potential interactions among them as either irrelevant or clearly secondary to the central facet of interest. Comprehensive models (International Association for the Study of Pain, gate control, nonradical operant-behavioral, cognitive-behavioral) take into account multiple facets and their reciprocal interactions. Colinearity among multiple and diverse facets of pain is clearly identifiable. The restrictive models are inconsistent with the empiric evidence. The evolution of thinking about chronic pain is characterized by progression from unicausal linear models to multicausal interactive models (82,83). It is repeatedly stressed in this textbook that only a comprehensive approach to chronic pain is plausible and capable of broad-based utility (81).

The choice of a particular model of pain is of paramount importance in determining the goals, methods, and desired outcomes of chronic pain treatment. Models are important because they determine the questions asked, the methods chosen, and the phenomena of interest to pain researchers. Models also dictate the behavior of health care practitioners in choosing diagnostic procedures, making therapeutic interventions, and making judgments about efficacy. Models determine how social institutions and agencies address the problem of pain (14). Therefore, the models profoundly influence the choice of which issues are relevant, the interpretation of clinical information, and the manner in which clinical and research questions are framed (84). In addition, the model has important implications for the expected behavior of both the provider and the patient during the therapeutic interaction. It virtually determines both the patients' and the providers' every clinical action and reaction.

One restrictive model, mind-body dualism (biomedical), requires further consideration because it has been the dominant perspective in Western medicine since the time of Descartes. It is also the ascendant lay model of chronic pain and the basis for the social health care structures that address the problem of chronic pain and disability. The biomedical restrictive model can be sharply contrasted with a comprehensive model, the biopsychosocial systems model, and both perspectives are examined in relation to the enigma of intractable chronic pain.

Biomedicine and Mind-Body Dualism

The biomedical model is enticing to providers trained in Western medicine because it offers the intricacies of diagnosis, therapeutic regimens that require sophisticated management, and the promise of exciting cures through the application of high technology. The clinical encounter is analytic, rationalistic, and scientifically oriented, with the putative painful disease process, and not the patient, as the main object of analysis. Pain is considered to be a sensory event, and the emphasis is on identifying the cause of nociception. Cure or pain relief is the desired outcome. It is assumed that once the pain is reduced, the observed disability will resolve.

Human beings are perceived in terms of their component parts and are fractionated into molecules, cells, organ systems, and body parts. Practitioners use sophisticated technical skills and resources in search of a diagnosis and a solution. They rely heavily on technology in the search for objective evidence of disease. Once the source of nociception is identified, treatments are initiated to fix the problem through surgical, physical, or pharmacologic interventions. Cure is contingent on precise diagnosis and rational treatment that is derived from pathophysiology and empiric research on clinical outcomes. Treatment is directed toward the underlying cause of the pain rather than its outward manifestations (the effects of the pain). Treatments considered most effective are those that eliminate or decrease the pain. It is usually assumed that the health care provider has the necessary expertise. The patient adopts a passive role while submitting to the expert recommendations of the physician (14). The patient's role is to follow the directions of the provider.

Reverence for objective information encourages a view of patients as repositories of disease rather than whole persons (85). The pain is separated from the person, who serves as its host. Cure-oriented physicians have no need to get to know pain patients, understand their individual values, or explore how illness affects their lives. When the goals are cure and pain relief, facts become differentiated from feelings, and the body becomes dissociated from the mind (85). Pain provides clues to diagnosis rather than existing as a phenomenon worthy of treatment in its own right. Patients are categorized as either diseased persons or as persons who erroneously believe themselves diseased. Becoming well involves either proper treatment or reassurance that “there is nothing wrong.” Patienthood is equated with pathology and interest is focused on the agents, the mechanisms, and the treatments of chronic pain (69).

Despite claims of biomedicine to a scientific basis that is both neutral and universal, social scientists point out the “hidden cultural scaffolding and social processes that shape practice and knowledge” (11). Some of these tenacious assumptions are so fundamentally linked to dominant Western philosophical traditions that they are taken for granted without awareness by the practitioner. Such background assumptions of Western biomedicine are exemplified by the belief that disease resides in the individual, independent of psychological and social influences, and the higher value placed on objective information rather than subjective patient reports. The result of such a world view is that the biomedical health care provider's attention is focused not on the patient but on the “it” of disease.

Chronic pain, however, challenges the central tenet of biomedical epistemology that there is objective knowledge, knowable apart from subjective experience (10). Pain is inseparable from psychological and social experiences, and there is no purely objective measure such as a “pain thermometer” (1,10). Without an objective measure of pathology that correlates with observed dysfunction, the biomedical practitioner is unable to form a rational treatment plan.

Despite growing dissatisfaction with health care, dualism is so entwined with the Western concept of the person that it remains the dominant model of health and disease in Western society. Most chronic pain patients adhere to this model as they cling tenaciously to their conviction that they have a “real, physical” disease. Patients respond poorly to traditional mental health services because they steadfastly insist that their primary problem is “physical, not mental pain.” The care of patients seeking medical treatment for symptoms related to psychosocial factors is difficult and costly. Multiple providers often treat one patient's pain from different perspectives with different goals. They exhaust all medical options, perform extensive diagnostic tests, and refer to numerous specialists for anesthetic and surgical procedures.

Rejected by biomedical practitioners who are no longer interested in their condition, patients search for other opinions, tests, and interventions. The health care system reinforces this notion and is unable to integrate the myriad of factors that influence a person's experience of pain and his or her search for pain relief. This often culminates in fragmented care, expensive and repetitive cycles of diagnostic tests, treatment failure, and a frustrating experience for both patients and providers. The medical-disability system insists on objective evidence of pathology before concluding that the patient is legitimately ill. Throughout this process, psychological and social factors are considered to be irrelevant in this restrictive model of pain.

The curative model fosters the clinical sciences that divide the care of patients among various subspecialties. The “soft” social sciences that examine intact human beings and their complex relationships are deemphasized. Subjective, immeasurable, unverifiable, and nonspecific phenomena that are not explicable by biological sciences are devalued. Psychological factors are ascribed a secondary role and regarded as trivial or spurious. Pain not conforming to current understanding of pathophysiology is disparagingly described as “all in the head.” The emphasis is on biological information as opposed to psychological or social data that are considered irrelevant to the disease process that is causing the pain. Biomedicine promotes the modernist belief that all things are potentially knowable (86). The implicit promise of modern medicine, based on the belief in inexorable progress, is that some day all disease will be conquered and, presumably, chronic pain, too. Although the concept of progress may be suitably applied to pure science, it creates problems for those in the health care professions because people are complex systems of whom complete understanding is unrealistic (86).

Biopsychosocial Systems Model of Pain

The enigma becomes decipherable with a shift from a biomedical to a biopsychosocial model, which views pain as an illness and an experience. The chronic pain experience is more comprehensible if viewed from a biopsychosocial perspective. This requires, however, that practitioners expand their skills beyond traditional biomedical methods, learn new conceptual models of chronic pain, acquire nontraditional skills, and become comfortable in different professional roles. The challenge is to create roles that use providers' expertise and skills while simultaneously providing services within a model that recognizes the complexity of chronic pain.

The biopsychosocial model is an alternative model for understanding health and disease that subsumes biomedical concerns and incorporates psychological and social dimensions (12). It provides a template for managing an individual person's suffering that is central to the chronic pain experience and compatible with current conceptualizations. Hanson and Gerber (14) have elegantly applied this perspective to chronic pain by building on cognitive-behavioral (75) and systems models (13) to develop a self- management approach.

From this perspective, responsibility for the daily management of pain and quality of life resides with the patient. Greater attention is given to the person with the disease than to biological processes. The provider's task is not to become more expert in the newest medication, intervention, and high technology, but instead to acquire the skills necessary to function effectively in the role of educator, motivator, and physician-healer (10,87,88,89 and 90). The provider is not a caretaker responsible for providing immediate pain relief to a passive patient. The role is one of an educator who assists an active patient in developing life-management skills and learning new ways to think about pain and coping.

In contrast to the reductionism of a biomedical approach, a systems model maintains that the whole is more than the sum of its parts. People, as living systems, are viewed from multiple levels of analysis ranging from the cellular to the social (13). Phenomena are best understood by studying interactions among the levels. From the biopsychosocial systems perspective, with regard to chronic pain, all three dimensions (biological, psychological, social) are considered as equally important determinants of the person's experience. Rather than positing simple cause-effect relationships, all aspects of the pain experience are in a continuous reciprocal determinism. Because the fundamental process is interactive, it is fruitless to attempt to identify any one dimension of the pain experience as more important than any other.

The enigma is not solved but rather dissolved. A cure does not exist for the multidimensional experience that is the overwhelming chronic pain syndrome. Therefore, questions of whether pain is real—that is, associated with pathology—are irrelevant. Pain is defined as simultaneously a physical and psychological experience (91). Rather than fractionating pain into separate parts, the biopsychosocial systems perspective regards nociception as inextricably embedded within a complex web of physical, psychological (cognitive, emotional, behavioral), social, and cultural factors (12,14,92,93). The person experiences pain and related disability in a wholeness inseparable from subjective states and social influence. Pain is lived as a whole, with perception, experience, and coping blending into each other as a unified experience (10).

A major focus of therapy initially is to assist the patient in moving from a biomedical perspective to a biopsychosocial model of chronic pain. Such a shift is critical in redefining the goals, methods, and expected outcomes of treatment. The provider adopts the role of a teacher or guide as opposed to a medical expert skilled in surgery, nerve blocks, or medication management. The patient is an active participant in the treatment process rather than a passive recipient of medical expertise. Therapeutic goals are rehabilitative and restorative rather than curative. The aim is to assist patients to develop pain management skills, identify targets for change in various areas of their lives, and accept more responsibility for the outcomes of treatment (see Chapter 109).

It is important to recognize, however, that a biopsychosocial systems perspective uses most treatments offered in traditional biomedicine, such as medications, physical, and psychological treatments. Rather than being diametrically opposed to a biomedical perspective, this model subsumes it (84). The biopsychosocial model is inclusive and fully accommodates all biomedical aspects, placing them in a broad context and providing guidance in the advisability and timing of their use. The major difference is that pain relief *per se* is neither the major goal of treatment nor the predominant focus of the clinical encounter. The biopsychosocial approach offers a wider scope of inquiry and intervention because biological factors are only one of many complex influences on pain. Efforts are made to shift the focus away from symptoms and to concentrate on strategies that increase functional activity and wellness despite the persistence of pain. The primary methods are educational, motivational, and interpersonal rather than medical, pharmacologic, or technological.

The biopsychosocial systems approach is tolerant of incomplete medical knowledge and accommodates medicine's limitations. When complete understanding is abandoned as a goal, the traditional tasks of the health care provider—listening, witnessing, educating, motivating, and relieving suffering—are no longer relegated to the small corner of medicine, the “art of medicine,” but return to its core (86). The biopsychosocial systems approach to chronic pain accommodates efficient, effective, and low-technology chronic care for a population of patients whose complexities outstrip the resources of a single provider. It effectively manages patients

who make inappropriate or excessive demands for services within organizations striving for cost-effective management.

CLINICAL CONSIDERATIONS

Patient-Provider Interactions and Chronic Pain: The Treatment Imperative

In 1974, Sternbach drew attention to the central role of the patient-provider interaction in the treatment of patients with overwhelming chronic pain (94). Many chronic pain practitioners and their patients participate in the mutually frustrating interaction termed the *pain game*. Reduced to its simplest form, the initial interaction between patient and professional proceeds as follows:

Patient (in obvious distress): I hurt. Please fix me.
Provider (with obvious confidence): I'll fix you.

When, however, neither a cause is identified nor adequate pain relief provided, the provider has little choice but to invoke one of the three Rs of biomedical chronic pain management: repetition, rejection, or referral. The diagnostic-treatment ritual can be repeated, the patient can be referred to yet another specialist, or the caregiver or health care system can simply reject the patient as having mental health problems, not physical problems. Over time, a variety of treatments are tried that ultimately fail, multiple investigations are offered, and referrals are eventually made to specialists. This cycle of defeat and frustration continues, the conflict escalates, and the relationship is terminated. The final meeting concludes:

Patient (indignantly): Another incompetent quack.
Provider (defensively): Another crock.

At this point, the patient transfers to another provider, and the process is repeated. The provider concludes that the reason the patient failed to respond favorably to treatment was because the pain was not real and there was “something wrong with the patient who did not respond to my perfectly good treatments.” He or she therefore repeats the process with the next patient who presents with similar initial problems because this patient has real pain and is a “good patient.”

The basic problem lies in the nature of the traditional patient-provider relationship (94,95). Both patients and providers share a biomedical model of chronic pain that regards the patient as a helpless victim of a disease. The fundamental challenge is to modify this process, in which the patient is assumed to present with clearly defined disease, the provider is expected to diagnose and treat a single cause, and cure or significant symptom reduction is the only meaningful outcome. It is further assumed that the provider is responsible for treatment outcomes and that any hope for improvement lies in the medical expertise of the professional. It is the responsibility of the provider to respond with some change in treatment until the patient reports satisfactory reduction of symptoms.

Use of the term *pain game*, although appropriate in the language system of transactional analysis, suggests that the patient is engaged in some sort of factitious effort to get well. For the vast majority of patients this is not true. The complaint of pain is virtually always real; malingering is rare. Similarly, providers unfamiliar with this terminology do not describe the process of being overwhelmed by such patients as any form of entertainment.

We prefer the term *treatment imperative* to describe this process because it emphasizes the tremendous professional, social, and interpersonal pressures that health care providers experience in their efforts to help patients (84). Chronic pain treatment is fundamentally a psychosocial process, not a scientific or technical endeavor. Patients are active participants in the treatment process, not passive objects of study. Overwhelmed providers are not dispassionate scientists who remain objective in their efforts to help patients. Regardless of the specific intervention, pain treatment always occurs in a psychological and social context in which the mutual expectations of the patient and provider interact to determine the exchange that occurs in the office (96).

A major impediment to treating chronic pain patients is the lack of awareness on the part of professionals of the importance of their own behavior on the patient's experience of chronic pain. The patient-provider relationship (76,77,78,79 and 80,95,97) is critically important for patients with overwhelming chronic pain and chronic illness. It is through their relationship with health care providers that patients seek validation of their problems for themselves, family members, and the various legal and social agencies involved in disability payments. Patients define the appropriate methods, goals, and desired outcomes of treatment through their interactions with helping professionals. It is difficult for patients to change their behaviors outside the office unless providers first change their own behaviors toward patients.

Role of the Health Care Professional in Chronic Pain Treatment

The behavior of the professional toward a patient who is overwhelmed by chronic pain depends on the model of pain used. A biomedical provider who values objective information and is most comfortable examining data minimizes interpersonal aspects of care. The clinical interaction is primarily one of gathering a report of symptoms, assessing the efficacy of current treatment, prescribing new treatments, and ordering further evaluations if the symptoms have not resolved. Practitioners work through an algorithm (list) of plausible treatments directed at pain relief. Both patient and provider share a biomedical view that maintains that social and psychological information is irrelevant, and a premium is placed on diagnostic and therapeutic procedures that can identify and eliminate “real” pain. The goals of treatment are curative, and the expectations are that treatment will attempt to provide maximal pain relief in the minimum amount of time.

In contrast, the biopsychosocially oriented professional functions as an educator-healer (84). In the context of stable chronic illness, a provider working from a biopsychosocial perspective feels little pressure to order additional high-technology investigations. Just as important as it is to know how to treat, it is important to know when to stop because there is no end to the number of potential treatments and procedures. No need to identify a single physical cause of pain exists because pain is assumed to represent a complex interaction across multiple systems of influence. Psychological information and social information are equally relevant to the patient's experience of pain and distress and are considered legitimate areas of clinical inquiry. Because the purpose of the clinical interaction is not to treat disease but to provide care (98,99 and 100), successful management involves the formation of a cooperative partnership in which there is clear communication, mutual respect, and trust (76,77,78,79 and 80,95,101,102). It is explicitly recognized that there can be healing without cure when one is attempting to help patients change their lives and not just their pain. The appropriate goals for such treatment are rehabilitative and long-term changes in function rather than immediate pain relief. Care is oriented toward patients taking responsibility for their own well-being, health, and functioning.

The key therapeutic challenge is to assist the patient in reconceptualizing chronic pain (the fourth *R* of pain management). The most fundamental goal is to change the nature of the patient-provider interaction by redefining the goals, methods, and outcomes of treatment (84). The focus of care is not to reduce pain but to redefine the problem. Decreased disability (14,103), increased ability (improved overall quality of life, increased function, decreased suffering), and decreased health care utilization (14,84,104) are considered meaningful goals of treatment.

The purpose of treatment is not to solve the problem of chronic pain but rather to dissolve it (84). Immediate pain relief is not the goal in the life-long management of chronic pain (84). By relinquishing pain relief as a primary goal and placing responsibility for rehabilitation with the patient (self-care), physicians are liberated from the shackles of the treatment imperative. Biopsychosocial care proceeds unimpeded by the specter of pain relief and the enigma is decipherable. Biomedical treatments are placed in a broad context and used as adjuncts to facilitate achieving a better life (84).

The fundamental assumptions in managing chronic pain are that it is a life-long condition not amenable to cure, patient-provider relations are pivotal, and beliefs and expectations determine outcome (84,105,106 and 107). A self-care, rehabilitation approach is advocated, healthy patient-provider partnerships are encouraged, and education and motivation are the primary tools (84). The most powerful therapy is the provider's attention, concern, interest, and careful listening. The practitioner who ignores the person and focuses on the disease, especially in cases in which there is no straightforward relationship between physiology and dysfunction, is part of the problem rather than the solution. Sir William Osler (108) provided the pivotal clue to deciphering the enigma with his statement: “It is more important to know what sort of person has a disease than to know what disease a person has.”

Patient and provider beliefs (105,106), expectations, and the quality of their interactions are more important than specific treatments in determining treatment outcome (107). Physicians should establish meaningful, long-term relationships with chronic pain patients that include social and interpersonal interactions. The common idiom “compliance with treatment” is pejorative because it carries connotations of fault with the patient, stigmatizes the patient, and ignores the role of the provider or medical system in the problem. *Cooperation* is a preferable term because medical consultation is a process of negotiation between the perspectives of the provider and the patient to elicit mutual cooperation in working toward common objectives.

Effective management requires an educational approach, a wise presentation of choices, and motivation based on mutual respect and trust. The processes of

relationship formation, education, and motivation enable patients to improve by adjustment of their beliefs and expectations. Effective communication and relationship building are optimally nurtured in an environment that values humanistic qualities and interpersonal skills. Getting to know a patient takes time. Transient encounters are inappropriate in long-term chronic pain management. Therefore, chronic pain care is best delivered in circumstances that allow for lengthy encounters over a long period. Efficiency-driven and time-limited settings typical of many outpatient treatment settings and acute care hospitals are incompatible with a biopsychosocial, self-care rehabilitation approach and instead reinforce the curative model.

Demedicalization of Overwhelming Chronic Pain

Demedicalization (74) refers to the efforts by health care professionals to reeducate patients that their disability and life problems are influenced by many other factors in addition to pain. Demedicalization is not an effort to convince patients that their pain is caused by psychological factors. Demedicalization does not preclude the use of active medical interventions. Rather, demedicalization is a process of challenging the belief that pain is the patient's primary problem and that medical interventions are the only solution. The full range of medical interventions are used but in a context that emphasizes the far greater importance of the efforts the patient makes in his or her own rehabilitation.

Chronic pain patients are stuck in an unhealthy equilibrium that is self-perpetuating and self-restrictive (109). They are overwhelmed by life and seek medical solutions for psychosocial problems. The more the traditional medical system rejects them, the more vigorously they pursue additional medical treatment and confirmation that their pain is real. Patients have elaborate, convoluted explanations for why they are helpless to change their lives. They lament that doctors victimize them and social agencies refuse to recognize the extent of their disability. They believe that they require further evaluations. They continue to stridently advocate for interventions that their providers believe are not indicated. A major goal of treatment is to engage these patients in a manner that supports them as people but challenges their dysfunctional beliefs about pain, its treatment, and the nature of their multiple problems.

Health care providers in general and physicians in particular ought to assume roles radically different from the Western tradition. The physician plays a pivotal role in demedicalization that transcends token “white coat credibility” (74,84). It is an active and crucial role because the physician has the skills, credibility, and authority to deliver the pivotal initial messages that patients can be better and hurt does not mean harm. He or she does this either alone or, preferably, in the context of the “team as the provider” (84). It is important that psychosocial providers understand, facilitate, and augment demedicalization to avoid couching their more holistically oriented treatments in a biomedical context. In the early stages of management, demedicalization prepares the way for full patient participation in their rehabilitation. In established patients, demedicalization is important in responding appropriately to somatic concerns, maintaining the biopsychosocial focus, and effectively managing lapse and relapse.

The process of demedicalization begins with the first clinical encounter. Despite numerous failures, the patient comes to the health care professional looking for pain relief. Most patients with overwhelming chronic pain are firm adherents of a biomedical model and have experienced many negative interactions with previous providers. They are highly sensitized to suggestions that their pain is “in their head.” It is very important that providers address this issue openly with patients and give reassurances that endorse the pain as real. It is helpful during the evaluation process to explain the detailed inquiry into psychosocial information as an attempt to get to know the patient as a person. Pain is a “family affair” and therefore spouses or other family members should be invited to clinical sessions and actively participate in the formal group education, individual evaluation, and long-term management process. Patients usually respond favorably to these approaches and are reassured after experiencing many previous negative “treated-like-an-object” encounters with providers.

Demedicalization requires that greater attention be paid to the person than to somatic processes and symptoms. Evaluation is directed toward understanding factors other than chronic pain that contribute to the person's experience of being overwhelmed. It is important to inquire directly about patients' beliefs concerning their own problems, what they want the providers to do, and what they are willing to do for themselves. Clear statements of the practitioner's own model of pain, clinic policies, and expectations about the process of working together are also helpful in identifying potential areas of conflict early in the treatment relationship. The interpersonal aspects of clinical care involve a continual process of negotiation and consensus building with regard to the nature of the problems and the appropriate treatments. The worst outcome is when the provider assumes the role of expert, neglects to ascertain the patient's beliefs, recommends treatment that is disregarded, and then manipulates drugs and doses in a futile effort to arrest the symptoms.

It is essential that patients are provided initially with a multidimensional formulation of their problems and the impact pain has on their lives. Previous biomedical providers have focused primarily on diagnosis and treatment of disease. A formulation, by contrast, is a set of working hypotheses about the patient's experience of pain, including past frustrations with medical care. An effort is made to communicate to the patient an understanding of the widespread impact pain has on his or her life. Rather than focusing exclusively on causes of pain, attention is paid to psychosocial factors that exacerbate and maintain disability. Special attention is given to identifying psychosocial factors that independently contribute to the patient's sense of being overwhelmed. The stage is set for subsequent long-term management by identifying pain as only one of numerous problems that a patient has in his or her life. The patient's belief that the only avenue leading to a better life is less pain is diplomatically but directly challenged. Patients are taught that only after they learn how to live better lives will they be less overwhelmed by pain.

This self-management perspective is not a grim alternative to failed medical interventions. A biopsychosocial self-care rehabilitation approach is recommended for the management of overwhelming chronic pain (11). It represents a positive option and an opportunity to develop a personal sense of control over pain and its effects. It matches the contemporary emphasis on social values of fitness, contentment, autonomy, individualism, self-control, and responsibility for one's own health and lifestyle. Patients who acknowledge that some pain is inevitable and that pain does not always lead to disability and who give up unproductive efforts to control pain are less disabled physically and psychosocially (105,110,111). Patients respond favorably to the message that they can be better, they may heal even if they are not cured, hurt does not mean harm, and they can do most things they want to do whether they hurt. Therefore, in the context of a supportive relationship, patients acknowledge and expect that cure is not possible. After many failures, most patients recognize the limitations of medicine (86). They become embroiled, however, in a new series of well-meaning but impossible promises as they continue the cycle of “doctor shopping.” Patients who are overwhelmed by chronic pain are desperately seeking help. The social-cultural-medical cure imperative drives them to follow the mirage of miracle treatments. Reformulation of the problem provides patients with the insight to switch their search to better care, not better treatment.

Patients should be offered a full range of medical, pharmacologic, and somatic interventions in the context of a self-management approach. Rather than promising pain relief, patients are informed at the outset that immediate and total pain relief is not an appropriate goal of treatment (84,111). Meaningful and prolonged change depends far more on patients' efforts in addressing their other problems. Patients who are physically deconditioned and lacking in essential social skills can expect to experience increased pain as they make efforts to change their lifestyle. In addition to somatic treatments, patients should be offered psychiatric or psychological care, counseling, family therapy, and drug and alcohol treatment, depending on the nature of their concomitant problems. It is important to realize that such treatment is not offered in place of medical treatment but rather as part of a treatment package for a “total person.”

Medications are offered as a means to “take the edge off pain” to facilitate physical, social, recreational, and vocational reactivation. Opioids are used rationally and are viewed as neither a panacea nor an ogre (medication to be avoided at all costs). The goal with opioids is to establish a stable, reasonable dose that does not escalate over time (58,59,63,64). The response to exacerbations in chronic pain is not to increase the medications. Rather, factors that potentially accentuate the patient's level of distress are explored. Exacerbations are more typically associated with life changes rather than biological changes.

Return visits emphasize the shift in focus away from pain symptoms to an emphasis on strategies that increase functional activity and wellness despite the persistence of pain (109). Emphasis in treatment is on helping the patient identify specific actions and facilitating the process of committing to change. In the context of patients making the cognitive reappraisal that they can get better and be well, they are asked to set specific behavioral goals for reactivation in areas such as recreation, socialization, and exercise. As long as cure is no longer promised, the emphasis is on what the patients are doing to help themselves have a better life. Failure to reach realistic goals that patients establish for themselves are recast as choices they make rather than treatment crises that demand changes in strategy and additional biomedical investigations and interventions.

From the provider's perspective, the actions of patients with overwhelming chronic pain seem self-defeating. They are, however, a way, albeit dysfunctional, for patients to maintain stability within their lives. Patients act in accord with their total experience of pain and any other way of behaving involves risk (109). Life in the “sick role” of a chronic pain patient may be safer, securer, and more predictable than life as a healthy, independently functioning adult (95,112). Although overt malingering is rare, the issue of secondary gain must be directly addressed. In addition to the frequently cited payoffs associated with disability compensation, access to opioids, or attention from spouses, the practitioner must be aware of the subtler reinforcement of the sick role. As long as the patient perceives himself or herself to be a “victim” of a disease (or an unfair medical or legal system), the patient is not responsible for the unsatisfactory circumstances of his or her life. A medical diagnosis endorses his or her disability. It enables the patient to reconcile personal failure and garner the privileges of the sick role. Overwhelming chronic pain legitimizes this role for overwhelmed patients unable to manage the demands placed on them. Demedicalization involves challenging this victim role and providing patients with access to the mental health or other services that enable them to learn more effective coping methods. The fundamental problem of these patients is not

that they cannot cope with pain but rather that they cannot cope without it. In these enigmatic patients, pain is often the solution, not the problem.

STRUCTURAL CONSIDERATIONS

The unsatisfactory results of treatment from both the patients' and providers' perspectives fomented demand for effective therapy. The complexity of overwhelming chronic pain requires an integrated multidisciplinary approach. Multidisciplinary treatment is essential in helping these patients (113,114). The structure of multidisciplinary care varies from inpatient programs affiliated with large teaching hospitals to time-limited day treatment programs, through to small outpatient clinics of cooperating professionals. Knowledge of the methods used by multidisciplinary programs is largely limited to the few that contribute to the published literature (115). Irrespective of the “local recipe” all formulae for multidisciplinary care require that the patient have access to medical and mental health providers who have a cooperative working relationship. Several broad issues are particularly relevant to the delivery of pain services by multidisciplinary teams operating from a biopsychosocial model of pain.

No single discipline has all of the skills and training necessary to address this multifaceted problem without consultation and participation from other professionals. Nevertheless, in the current health care environment, multidisciplinary programs struggle to survive. Fundamental systems-level changes are needed in the structure of pain programs, the models of service delivery, and the reimbursement for pain services (116,117). Several broad issues are relevant to the delivery of pain services by multidisciplinary teams using a biopsychosocial approach.

Beyond the identification of chronic pain as a clinical problem of interest, the term *pain clinic* implies nothing that is specific about the methods, models, or policies of a given program. Factors such as the reimbursement practices of insurance companies and the structure of the local health care delivery systems are important determinants of the types of services provided. Many “multidisciplinary” programs rely on invasive procedures and offer only lip service to a biopsychosocial approach (118). A multidisciplinary team working from a biopsychosocial perspective is more than a collection of specialists working independently. The defining characteristic of a multidisciplinary team is the integration and coordination among different disciplines in working toward shared goals. Effective teams do not simply treat the same patients, but rather work from a common biopsychosocial model of pain treatment. It is possible for a multidisciplinary team to inadvertently work within a biomedical model of pain if all participants simply treat the patient in parallel. A team composed of an anesthesiologist performing nerve blocks and a psychologist independently doing relaxation training foster the biomedical myth that immediate pain relief is the primary goal of treatment.

Multidisciplinary care is nurtured by interactive approaches to pain and disability. Traditional medicine is characterized by a hierarchical structuring of relationships among health care professionals. Physicians possess the most biomedical knowledge and consequently command the most authority. The hierarchy of rank determines to what degree other staff members can question decisions. Interdisciplinary teamwork, not an authoritarian hierarchy, best accommodates the needs of chronic pain patients. Effective teams recognize that biological, psychological, and social factors interact in determining the patient's experience. No single dimension is given primacy because it is explicitly recognized that it is impossible to separate out the various components of chronic pain. This recognition that “real” pain is not the sole province of physicians has important implications for the structure of the team. Traditional multidisciplinary structures, in which physicians are the team leaders by virtue of the primacy of their skills in a curative treatment model, are less relevant.

In addition to the prototypic multidisciplinary pain clinic described in Chapter 11, Chapter 18, and Chapter 109, other less complex approaches may be successfully used. Models of collaboration that emphasize an equal partnership between biomedical and psychosocial providers have been described (119). The codisciplinary approach (84,96,120,121) introduces the notion of the “provider as a team” (119,122,123) to those with overwhelming chronic pain. Patients and their families are seen jointly by a medical and a psychosocial provider for all clinic visits. This change in structure effectively communicates a biopsychosocial model to patients, facilitates the resolution of difficult patient interactions, changes patient expectations of physician behavior, and legitimizes the role of a mental health practitioner in chronic pain treatment. Codisciplinary care blends participating disciplines, incorporates the biopsychosocial system's ideal, and accommodates generic health care and ecosystemic approaches (74,119,122,123).

A biopsychosocial model requires that all involved providers, irrespective of discipline, function primarily as educators and motivators. Education and motivation are integral aspects of all clinical encounters, not the sole responsibility of nurses or psychologists in time-limited classes that teach coping skills. Initial extensive formal group education around key beliefs and expectations facilitates the initiation of cognitive reappraisal required for patients to shift the goals, methods, and outcomes of treatment (84). Although initial group education is helpful before individual treatment, the education process is ongoing. Patients may learn as much from their providers' own behavior (questions asked, treatments offered, explanations provided) in clinics as they do from more formal classes about pain.

Ultimately, it is all too often the structure of reimbursement systems and not the preponderance of scientific evidence that determines the nature of chronic pain services (124). Changes in health care delivery and reimbursement shifted the emphasis from inpatient to outpatient services (125). Attention has turned to managed care organizations (117,126). The cost-containment emphasis and the predominance of the biomedical model in reimbursement decisions has created tension between pain programs and the payers. In the interest of greater efficiency and improved outcomes, more effective screening procedures for pain programs have been suggested to select only “motivated” patients for treatment. The implementation of screening policies is understandable for structured pain programs to ensure “optimal return on their investment.” They do, however, beg a much more fundamental issue. What is the primary care provider to do with the vast majority of patients who do not meet such stringent eligibility criteria? Rejected by pain programs, such “unmotivated” patients return to their health care system and once more resume the process of searching for biomedical miracles.

Radical structural changes in reimbursement are needed to address the long-term care and management of difficult, high-utilizing patients. In pain programs that service capitated integrated network systems, such as the Veterans Administration medical system, health maintenance organizations, and national health care programs, patients rejected for pain treatment do not simply disappear but continue to demand more services. In fee-for-service settings, they simply fall by the wayside. Outside of a few specialized rehabilitation programs, screening criteria weed out those most in need of care. Consequently, we recommend no routine screening criteria despite many patients' active engagement in the pursuit of compensation for pain, significant psychiatric disorders, and many referrals because of provider discomfort with patient demands for escalating opioids (84,96,120). The key to success with such “unmotivated” patients lies in a focus on the patient-provider interaction and the formation of long-term relationships (see Chapter 94). Integrated network systems permit the formation of long-term treatment relationships rather than time-limited pain services. The Veterans Administration, in contrast to many health maintenance organizations, provides access to mental health service that patients receive concurrently with pain treatment. It also allows close coordination between pain specialists and primary care providers in long-term care.

Reimbursement practices based on biomedical curative models have not supported the delivery of systems-oriented biopsychosocial services. Acceptance of the biopsychosocial model seems impossible in a biomedically oriented reimbursement system. Changes in compensation are necessary before widespread access to integrated multidisciplinary care becomes routinely available. Ultimately, for wide acceptance, the structure of health care and the attitudes of caregivers need to change. Although change is slow, the reality of the exponentially escalating costs of treatment has led to the consideration of alternatives and experimentation (74,84,119,122,123). As the failure of models based on a no-cost denial of services becomes apparent, health care systems may consider low-cost alternatives (124).

CONCLUSIONS

Overwhelming chronic pain is a complex experience and not simply a biological event. Difficulties in pain management arise from the dominance of a dualistic model in medical training and clinical practice, the structure of health care and disability systems, and in lay knowledge. However, a biomedical model of pain dominates the delivery of services to chronic pain patients despite recommendations to the contrary by experts in the field (124).

Health care providers, insurance companies, and attorneys contribute to the problems of overwhelming chronic pain (109). To address the issues of overwhelming chronic pain, health care providers are required to scrutinize themselves and their own contributions to the problem. Patients who are overwhelmed by chronic pain are stuck in a “pain rut,” in which short-term strategies that reduce pain create long-term problems. Well-intentioned providers participate in this process by focusing on immediate pain relief as the primary goal of treatment. The inevitable failure of such efforts and the rejection of patients as not having real pain further intensify their search for biomedical solutions and documentation of disease. No villains exist in this mutually frustrating experience of the patient and provider. Pain patients are victims of providers trying their best to help them.

An important purpose of this chapter is to outline different ways of thinking about how to be helpful. The focus on interpersonal processes within a self-management model is not merely a poor alternative to biomedical treatment. It is the indicated treatment for those patients overwhelmed by problems of living, for which there are no rational medical options available. If one wants to help such people one has to learn new ways to think about the problem.

A major challenge to the health care system is the issue of severe disability that does not correlate with objective physical findings (see Chapter 17). In these enigmatic patients, pain is often the solution, not the problem (84). A medical diagnosis endorses their disability. It enables them to reconcile personal failure and garner the privileges of the sick role. Chronic pain legitimizes this role for overwhelmed patients unable to manage the demands placed on them. If patients are required to constantly prove that they are ill, it is impossible for them to get well. Acceptance of the complexity of chronic pain implies a rejection of the need to have objective evidence of pain to validate the patient's report of distress. The enigma of overwhelming pain is best understood and dissolved by never asking the initial inappropriate question(s). Chronic pain is a common idiom for communication, personal, and interpersonal problems (10). Patients with overwhelming chronic pain need better care, not more effective treatment. Care is an interpersonal process that occurs between a provider and a patient (98,99 and 100). Treatment is a technological process that occurs between a provider and a disease.

The chronic pain experience is a psychosocial problem with medical aspects rather than a medical problem with psychosocial aspects (72). Overwhelming chronic pain syndrome results from well-intentioned providers and health care systems trying to help patients but instead inadvertently reinforcing their illness conviction and more deeply entrenching their pain problem. No pill can cure and no surgery can excise the need to be sick (127). Patients' symptoms arise from cognitive, situational, psychological, social, and cultural factors that biomedical interventions fuel by their failure to abate. Pain patients are victims of a system that augments their need to be sick.

Disabling chronic pain is conceptualized as a marker of overwhelming distress, a dysfunction engendered by failure to cope with the demands of industrialized society. Chronic pain patients have a vulnerability to being overwhelmed by problems of living. Western medicine fuels the “chronic pain epidemic” by assigning medical diagnostic labels to ambiguous conditions (128,129). The process of medicalization is pervasive in biomedicine. Is degenerative disc disease, a natural continuous aging process observed in most people, best viewed as a disease process? What distinguishes it from graying of the hair, wearing of the teeth, and changes in the skin? The aging process, a natural continuous phenomenon, is viewed in disease terms as though it is a dysfunction (74). The health care system is an accomplice in the chronic pain epidemic, which is fueled by the processes of medicalization, somatization, and iatrogenesis (5,127,128,129,130,131 and 132). From the lifelong perspective of reducing disability, efforts directed at immediate pain relief are iatrogenic. The fruitless search for medical diagnosis, cure, and symptom relief fosters excessive health care use, iatrogenesis, somatization, medicalization, invalidism, and disability.

The understanding of the pain experience and the discipline of pain medicine have evolved greatly from meager beginnings. In the 1950s, enlightened and visionary providers questioned the value of somatic treatments (133,134 and 135), epitomized by nerve blocks performed in pain relief clinics (136,137 and 138). This healthy skepticism spawned the intellectual effort, inquiry, and experimentation that led to the progress that supplanted nerve blocks with more enlightened treatments. Pivotal contributions and milestones include multidisciplinary clinics (139), the gate control theory (140), behavioral techniques (141), the International Association for the Study of Pain and its journal *Pain* (139), analysis of interpersonal interactions (94), the biopsychosocial model (12), systems theory (13), the role of cognition, (75) and pain as a multidimensional experience (10,142).

The pioneering spirit and innovation that advanced the specialty of pain management ought to provide the impetus for the conceptual leap necessary to jump to the next level: a shift from coordinated to integrated care for chronic pain patients. To accomplish this change, it is essential that providers recognize the importance of relinquishing pain relief as a primary goal (84,106,111) and placing responsibility for rehabilitation with the patient (self-care) (14). It liberates patients from the stifling effects of the treatment imperative and enables biopsychosocial care to proceed unimpeded by the specter of pain relief. Another prerequisite for the shift is that multidisciplinary clinics and health care systems recognize the inextricable reciprocal relationships between the many facets that comprise the chronic pain experience (13). This serves as the springboard for the jump from coordinated to integrated care models. The integrated application of biological, psychological, social, and cultural factors in chronic pain management is essential to deciphering the enigma. A holistic view that unites mind and body and espouses an ecosystemic approach that blends the individual with his or her social contexts is crucial (74,84,122,123,142). An equal partnership between biomedical and psychosocial providers in generic health care teams is advocated (74,84,119,122,123). Thereby, the enigma is dissolved, and hitherto difficult and dissatisfied patients are managed satisfactorily. The major obstacle and challenge are that ecosystemic biopsychosocial care cannot be provided in a system that reimburses according to biomedical tenets.

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CHAPTER 11

Multidisciplinary Pain Programs

John D. Loeser

In the introductory chapter, emphasis was placed on the need for a multidisciplinary/interdisciplinary (M/I) team approach to study the mechanisms of pain in general and many chronic pain syndromes in particular. Moreover, as mentioned there and emphasized in Chapter 10, the complex nature of these syndromes requires an M/I approach for evaluating patients and for developing and carrying out the most effective therapeutic strategies. Related to both issues are the needs of education and training in pain management. This chapter deals with all of these issues. The material is presented in three sections: evolution and current status of pain programs; description of the University of Washington (UW) Pain Center as one example of such a facility; and comments and conclusions regarding the development of such programs. More detailed discussion of the M/I approach to evaluation of patients with chronic pain syndromes is provided in Chapter 18. The implementation and results of this therapy are described in Chapter 109. This chapter is included at this juncture to serve as a bridge between the basic information contained in preceding chapters and the clinical aspects of the chapters that follow.

EVOLUTION OF MULTIDISCIPLINARY/INTERDISCIPLINARY PAIN PROGRAMS

Bonica first began to appreciate the need for a multidisciplinary approach to chronic pain during World War II after several months' experience in treating military personnel with a variety of pain problems at Madigan Army Hospital, Tacoma, WA. The writings of Leriche (1), Livingston (2), Mandl (3), and others (4,5 and 6) made neurologists, surgeons, and other physicians aware that blocking nerve pathways with local anesthetic was useful in managing patients with certain types of pain. As an anesthesiologist, he was referred many patients with major causalgia and reflex sympathetic dystrophy (now labeled *complex regional pain syndromes, types I and II*), painful phantom limb and other postamputation pain syndromes, myofascial pain syndromes, and obscure neurologic and musculoskeletal disorders. Not having had any experience with these procedures during his anesthesia training, Bonica read the available literature and proceeded with his assigned task.

In applying nerve blocks, he noted that patients with causalgia and other straightforward painful conditions responded to therapy, but patients with other complex chronic pain problems did not. Bonica realized that as a result of these factors, and because of lack of education in medical school and postgraduate training for specialization, he, like most other clinicians of his era, did not know the basic principles of managing patients with chronic pain. This realization prompted him to search the literature to acquire the necessary knowledge about the broad field of pain, especially chronic pain problems. He found that there was little information about the treatment of chronic pain, primarily because little research had been done, and that, other than the books by Leriche (1), Livingston (2), and Mandl (3), the available knowledge was scattered in numerous basic and clinical science journals and books, and thus inaccessible to the average physician.

Despite consulting the textbooks on medicine, neurology, and various other disciplines, Bonica continued to experience great frustration in trying to manage patients with complex pain problems by himself. Consequently, he sought the consultation of colleagues in neurology, neurosurgery, orthopedics, psychiatry, and other specialties in the usual manner inherent in traditional medical practice. Thus, if he wished to have a patient with a complex pain problem seen by an orthopedist, neurologist, and psychiatrist, each of these individuals would evaluate the patient in his or her office or in the patient's ward and then report the findings to Bonica by telephone, in writing on the patient's chart, or both. After the patient had been seen by all consultants, Bonica attempted to read the evaluation of each consultant and formulate a correct diagnosis and develop the best therapy. If questions arose he again contacted the consultant(s). It soon became apparent to him that to read and integrate the information of several consultations was slow and inefficient. This prompted Bonica to have frequent (two or three per week) face-to–face meetings in a conference room with all the specialists who had seen the patient, during which they reviewed each other's findings and discussed the case until they reached a consensus on the diagnosis and therapy. As far as is known from the literature and other sources of information, this was the first time that the M/I approach to pain was conceived and practiced.

These early experiences convinced Bonica that complex pain problems could be more effectively treated by an M/I team, each member of which would contribute his or her specialized knowledge and skills to the common goal of making a correct diagnosis and developing the most effective therapeutic strategy. These early experiences also led to the firm belief that much more research needed to be done on the basic mechanisms and pathophysiology of pain and that this also would require M/I efforts by groups of scientists and clinicians who could contribute their individualized expertise and skills to such studies.

By the end of his military duty in late 1946, Bonica had developed deep convictions about the need for (a) the widespread application of this multidisciplinary concept of pain management, (b) a better classification of pain syndromes, and (c) a textbook on the role, efficacy, and limitations of diagnostic, prognostic, and therapeutic nerve blocks.

First Multidisciplinary Pain Clinic

Immediately after World War II, Bonica put the concept of a multidisciplinary facility for the diagnosis and therapy of complex chronic pain problems into practice at Tacoma General Hospital, Tacoma, WA. The group consisted of an anesthesiologist, neurosurgeon, orthopedist, psychiatrist, internist, and radiation therapist, all of whom had special interest and some expertise in pain management. The group met every week or every 2 weeks and discussed complex problems. In addition to the members of the group, the conferences were attended by the patient's referring physician and others interested in the field, as well as by physicians in training (interns and residents).

At the beginning, a number of problems were encountered that were inherent in individual private practice. These included (a) the resistance by many physicians to accept the team approach and their reluctance to refer patients to the group, especially if the physician was in the same specialty as one of the members of the group; (b) difficulty in coordinating the time of conferences so that all of the key persons and the referring physician could attend; (c) difficulty in discussing the problem frankly, especially failure(s) of the referring physician and other specialists to make a correct diagnosis or to carry out effective therapy; and (d) the cost of the comprehensive evaluation, which was then considered too high. Despite these problems, for 13 years the group was modestly successful in its objectives and goals, and Bonica's conviction of the value of the multidisciplinary approach grew stronger.

Other Early Pain Clinics

After the war, Bonica had personal discussions with Dr. W. K. Livingston, who several years earlier had published his excellent book (2) and whose clinical research on pain and conceptualization of pain mechanisms made him one of this century's giants in this field. Bonica also communicated with a number of other anesthesiologists who were using diagnostic and therapeutic nerve blocks. In 1949, he met Dr. F. A. D. Alexander, who, unlike many other anesthesiologists, had a broad view of pain and its management (7). Alexander had independently developed the same concept, and in 1947 initiated a multidisciplinary pain diagnostic and therapeutic program at the Veterans Administration Hospital in McKinney, TX (8). During this early postwar period, a number of other anesthesiologists organized and ran *pain clinics*. Although some of these programs also involved other physicians as ad hoc consultants, the primary method of diagnosis and therapy consisted of various nerve block procedures, which at the time were the only nonsurgical treatment method besides drugs for pain control. These included programs in the United States developed by Woodbridge (4), Ruth (5), Rovenstine and Wertheim (6), Dittrick (9), Stubbs (9), Papper (10), Ruben (11), and Moore (12). In the United Kingdom, the first nerve block clinic was initiated in 1947 at the University College Hospital, London, by Dr. B. G. B. Lucas (13). The first multidisciplinary clinic was established in Oxford in 1964 by R. Richie Russell, who was a neurologist. Over the next decade, several other nerve block clinics were developed. The Intractable Pain Society was founded in Manchester in 1967 by Swerdlow; initially it had 17 members, but a decade later there were 59 members, 54 of whom were anesthesiologists. There were then 43 clinics, of which 23 had more than anesthesiologists on the active staff. From 1950 through 1970, similar clinics, usually based on anesthesiologic procedures, were started in most European countries, Canada, and Israel (14,15,16,17 and 18).

In New Zealand, the first nerve block clinic was started by Dr. Robert Boas in Auckland in 1971; it became multidisciplinary in 1972. Boas had received a year of training in Seattle and was strongly influenced by Dr. Bonica. The first pain clinic in Australia was founded by a multidisciplinary group of physicians at St. Vincent's Hospital in Sydney in 1962. This group published an article describing its early experiences in 1965 (19).

The first pain clinic in Japan was established in 1962 by Dr. H. Yamamura in Tokyo. Many other clinics developed in the subsequent decade throughout that country. Pain clinics did not develop in other Asian countries until the 1970s. Reviewing what is written about these earliest clinics suggests that there were physicians scattered throughout the world who recognized the failure of modern medicine to deal effectively with patients who suffered from chronic pain. Bonica's influence on the formation of multidisciplinary clinics and pain societies throughout the world started in the early 1970s when there were pain treatment facilities in most of the developed countries. The impetus for these clinics was clearly from individual health care providers, for little evidence exists that either governments or organized medicine had an interest in pain management.

Further Developments

By 1950, Bonica had records of more than 2,000 military and civilian patients he had treated alone and in collaboration with others, and he began to write a book on diagnostic and therapeutic nerve blocks. After formulating an outline, he undertook an exhaustive review of the literature and communicated with or visited many individuals working in nerve block clinics. From these various sources and personal observations he noted that (a) many anesthesiologists working in the field believed that nerve blocks were the primary diagnostic and therapeutic tools for most patients with pain; (b) many did not have the knowledge then available on pain mechanisms and had only a vague idea of the symptoms and signs of various pain syndromes and therapeutic methods available at the time; and (c) many were satisfied to act as mere technicians from whom the referring physician expected nothing more than a technical procedure. These experiences prompted Bonica to drastically alter the original format of the book and include large sections containing information about the anatomic, physiologic, pathophysiologic, and psychological bases of pain, general principles and guidelines for pain management, a classification and comprehensive discussion of the most important pain syndromes, and, of course, descriptions of the nerve block techniques as well as other therapeutic methods.

In this classic textbook, published in 1953 (18), Bonica emphasized the need for more research on pain, described the multidisciplinary approach to pain diagnosis and therapy, and emphasized the difference between acute pain and chronic pain. He proposed a new physician specialist, a *dolorologist*, as the leader of such a team. Although he realized that this was a hybrid term of Latin (*dolor*) and Greek (*logos*), he thought that the term would be more widely used than the term *algologist*, because at the time the term *dolorimeter* was widely used in pain research. In the late 1960s, Bonica began to use the term *algologist*. By the 1990s, the terms *pain management specialist* and *pain physician* were most commonly used, and neither *dolorologist* nor *algologist* had been widely accepted.

Although, as previously mentioned, during the early 1950s there were many pain clinics, only three were really multidisciplinary facilities. In addition to the one in Tacoma and the one directed by Alexander in Texas, there was one at the University of Oregon in Portland, directed by W. K. Livingston, who was then Chairman of Surgery. That program, which included the collaboration of Dr. Frederick Haugen, Chairman of Anesthesiology, and a number of other clinicians and researchers, was not only concerned with pain diagnosis and therapy, but was the first multidisciplinary pain research program supported by the National Institutes of Health of the United States.

His favorable experiences with these types of programs prompted Bonica, in the early 1950s, to begin espousing the multidisciplinary concept in numerous lectures and published papers, first in various parts of the United States and, beginning in 1954, in other parts of the world (20,21 and 22). During this period, Alexander also promulgated the multidisciplinary concept, but because of personal illness, he discontinued these efforts by the mid–1950s.

Start of University of Washington Pain Clinic

Promptly after his appointment as Chairman of the then new Department of Anesthesiology at the UW in 1960, Bonica enlisted the help of Dr. Lowell White, a neurosurgeon, and Dr. Dorothy Crowley, a member of the faculty of the School of Nursing, to develop a multidisciplinary pain clinic at the University. Because of his conviction about the multidimensional character of pain and of the importance of an M/I program, other specialists were recruited soon thereafter. Over the course of the next few years, the chairmen of the Departments of Psychiatry and Orthopedics and senior faculty in Rehabilitation Medicine, Clinical Psychology, Oral Surgery, General Surgery, and Radiation Therapy joined the pain clinic group. The program that Bonica started gradually evolved in complexity and the acquisition of support staff and space. By the late 1960s, he delegated leadership responsibility to other anesthesiology faculty.

Emergence of Pain Research and Therapy

Despite several hundred lectures and the publication of numerous articles in various parts of the world, the M/I concept was largely ignored by the medical profession for two decades. In the late 1960s and early 1970s, a number of factors converged to cause an increasing number of clinicians to put the concept into practice. These included the gradual development of additional M/ I clinics (23,24), the publication of the Melzack–Wall gate hypothesis (25), and the immense worldwide curiosity about the mechanism and efficacy of acupuncture as a method of pain therapy and for surgical anesthesia (26,27). Bonica planned and obtained funding from governmental and commercial sources for the First International Pain Meeting in Issaquah, WA, in June 1974. This gathering of scientists and clinicians led directly to the founding of the International Association for the Study of Pain (IASP) in 1974, and the publication of its journal, *Pain*, a year later. The willingness, indeed even eagerness, of the members of this multidisciplinary group to devote a significant amount of their time to the launching of IASP fulfilled Bonica's dream of making pain research and patient care an important scientific and medical activity throughout the world. The development of IASP, an international and truly interdisciplinary organization, was Bonica's most enduring contribution and the primary mechanism for the dissemination of the pain movement throughout the world. That organization has been extremely fortunate to have had Louisa Jones, who was originally a secretary for Dr. Bonica, as its Executive Director since its founding.

As also discussed in Chapter 1, these developments provoked an impressive surge in pain research, not only by neuroscientists, but also by behavioral scientists, and this work has added new dimension to the understanding of chronic pain and its M/I treatment. Other factors that nurtured this trend included (a) the training in the UW pain programs of a significant number of physicians from various parts of North America, Europe, Latin America, and Asia who subsequently returned to their homes and developed similar programs; (b) worldwide publicity given the UW facility in the lay press, several national television documentaries, and numerous articles in medical news media and scientific journals; and (c) during the period between 1969 and 1975, Bonica was invited by the ministers of health of a number of European and Latin American countries and Japan as a consultant to provide advice and direction for the organization and function of such pain management facilities. Key members of the UW Pain Center faculty also traveled through the United States and foreign countries carrying Bonica's message. Furthermore, those clinicians who had received training at the UW Multidisciplinary Pain Center returned to their home countries carrying both information and motivation inspired by Dr. Bonica and his UW colleagues.

Period of Growth of Pain Programs

From 1970 through 1990, the number of pain management facilities continued to increase. The proliferation of such facilities was so rapid as to prompt one medical

writer to refer to it as "medicine's new growth industry" (28). Because most of these facilities were directed by anesthesiologists, the American Society of Anesthesiologists, through its Committee on Pain Therapy, chaired by J. Modell, carried out a survey on such facilities in collaboration with the IASP and subsequently published the *Directory of Pain Clinics* in 1977 (29). Soon after it was published, as members of the committee, Bonica and Butler undertook the task of analyzing the report, which listed a total of 327 pain clinics. After studying the characteristics of each clinic, including the different number of specialties involved, the number and varieties of diagnostic and therapeutic methods used, and the number of pain syndromes treated, they arbitrarily classified them into the following categories: major comprehensive pain centers, comprehensive pain centers, monodisciplinary pain clinics, syndrome–oriented pain programs, and single–modality pain clinics. Of the entire group, 60% were located in the United States, 20% in Europe, 7% in Asia, an equal percentage in Canada, and the remainder in Australia and New Zealand. They also analyzed the distribution of these various categories in different countries and the specialty of the person in charge of each program.

Subsequently, Bonica recommended to the American Society of Anesthesiologists Committee on Pain Therapy that they adopt the aforementioned classifications and also suggested that the term *clinic* be used for outpatient facilities and the term *center* for programs with inpatient and outpatient facilities and educational programs. In 1979, the American Society of Anesthesiologists Committee, chaired by H. Carron, carried out a second survey and subsequently published the *International Directory of Pain Centers/Clinics* (30), which included the following classifications.

Major Comprehensive Pain Center. A major comprehensive pain center is an organized facility with space and personnel committed to the evaluation of the interaction of the physical, emotional, and sociological aspects of chronic pain problems, possessing the capability of developing a multidisciplinary approach to pain management. The following prerequisites are necessary to be identified as a major comprehensive pain center: space and beds assigned solely to the pain center; a professional staff representing five or more disciplines; full–time support staff (secretaries, nurses, therapists, and so forth); organized evaluative process for screening and selecting of patients; review and maintenance of records; participation of consultants of multiple disciplines; routine psychological assessment; ongoing research activities; organized training programs; availability of therapy appropriate for the physical and psychosocial problems found; and periodic evaluation of treatment results.

Comprehensive Pain Center. A comprehensive pain center is an organized facility with individuals or groups managing a great variety of chronic pain syndromes but unable to fulfill all the prerequisites for a major comprehensive pain center. The center should have the personnel and facilities for evaluation of the psychosocial as well as the physical aspects of chronic pain behavior and for administration of therapy appropriate to the problem found. To be identified as a comprehensive pain center, at least two– thirds of the criteria listed under major comprehensive pain center should be met.

Syndrome–Oriented Pain Center. A syndrome–oriented pain center is an organized facility that provides an in–depth study of all aspects of a particular pain syndrome and offers an acceptable treatment program for that syndrome. Examples of syndrome–oriented pain centers are low–back pain clinics and centers, headache or facial pain clinics and centers, cancer pain centers, and spinal cord injury centers.

Modality–Oriented Pain Center. The modality–oriented pain center is a facility that offers the chronic pain patient the appropriate therapy as defined by the specialty of the center. Other therapies may be used as adjuncts on a referral basis. Such a center may or may not provide extensive evaluative processes. Examples of such a center include nerve block clinics, transcutaneous electrical nerve stimulation clinics, acupuncture clinics, biofeedback clinics, and mental health centers.

Brena (31) analyzed the data in the 1979 directory and noted that of the 428 facilities, 278 (65%) were in the United States, 27 (6%) in Canada, 20 (5%) in Japan, 18 (4%) in Britain, between 8 and 12 facilities in each of the following countries: France, West Germany, Israel, Italy and Sweden; and the 21 other countries had one to five facilities. He also analyzed the density of pain clinics per 1 million population, and this ranged from 1.28 in the United States to 0.01 for Brazil. He also analyzed the distribution of clinical models among the pain control facilities and was also able to determine the medical specialty that directed the program in 335 of the facilities. The data presented in Table 11-1 are similar to those developed by Bonica and Butler from the 1977 directory (i.e., type of program and specialty primarily responsible for its direction).

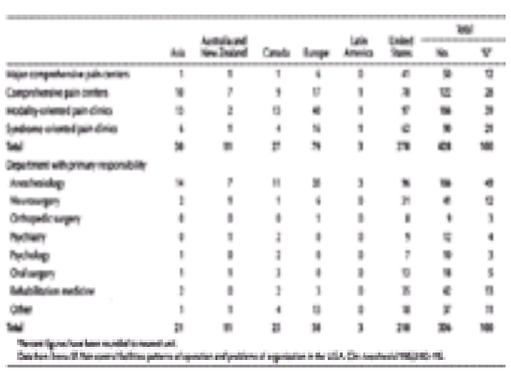

TABLE 11-1. Distribution of clinical models and medical specialties in pain control facilities

On the basis of various sources of information, it is estimated that in 1988 there were between 1,800 and 2,000 pain facilities in some 36 countries. Of these, 1,000 to 1,200 were in the United States, 200 to 225 in Britain, an equal number in Western Europe, 75 in Canada, 80 in Asia and Australasia, and the remaining countries had between 2 and 20 facilities. Making the uncertain assumption that the evolution of these centers has been similar to that before 1979, it could be roughly estimated that there were 150 to 200 major comprehensive pain centers, 500 to 550 comprehensive pain centers, 800 to 850 modality–oriented pain programs, and 350 to 400 syndrome-oriented programs. It is likely that these numbers will have doubled by the year 2000. Multidisciplinary pain centers have become a mature, recognized method of providing care to those who suffer from chronic pain. Texts have been written describing all aspects of their operation and discussing their efficacy (32,33,34 and 35). Diagnosis in a multidisciplinary pain center is discussed in Chapter 18, and treatment strategies and outcomes in Chapter 109.

Current Status of Pain Programs

Pain treatment facilities have now been created in almost every academic medical center and in hospitals of large and small size throughout the United States and Canada. Programs exist in most of the major cities of Central and South America and in every European country and most of its large cities. Pain treatment facilities are common in Japan and most of the Asian countries and are rapidly developing in China and India. New Zealand and Australia are also well supplied in the major cities. The only pain programs in Africa can be found in Egypt and South Africa; all of the Middle Eastern countries have some pain treatment facilities, led by Israel and Turkey. The qualifications of the personnel who staff these treatment facilities are variable, and no uniform standards for training or determination of competence exist. Only in the United States are there certifying organizations for individual providers and pain treatment facilities.

Sources of Concern

The impressive increase in the number of individuals who devote their time and effort to pain diagnosis and therapy and the large number of pain centers and clinics are gratifying, but they are also a source of serious concern. First, some of these facilities have been staffed by physicians and other health professionals who have had little or no training or experience in managing patients with chronic pain. Some of these well–intentioned clinicians have been attracted to the field because it is the fashionable thing to do; in other words, pain is the *in thing* of modern medicine. Of even greater concern is that some of these facilities are run by unscrupulous physicians and nonphysicians who use the current surge of interest in pain to exploit patients, as occurred with acupuncture clinics during the height of the public's interest in acupuncture during the early 1970s. These facilities run by dilettantes will surely be detrimental to the general cause of pain research and treatment and to the current international movement in the field, and, most important, will do more harm than good to individual patients.

Another concern is the implication that chronic pain is purely a psychological phenomenon. This has resulted from the involvement of psychologists and psychiatrists in the study of chronic pain, which has shown that the medical model is not sufficient to explain the abnormal illness behavior manifested by some patients and that the behavioral model of pain is required. This emphasis on chronic pain behavior resulting primarily from reinforcing environmental influences or so–called operant mechanisms is long overdue and has had a favorable effect on the management of many patients with chronic pain. Because these investigators have studied mostly patients with intractable pain caused by behavioral, psychological, and sociologic factors, they have come to believe that most, if not all, patients' chronic pain has

developed as a result of operant mechanisms or psychological factors. In view of the fact that in the United States only approximately 3% to 4% of all patients with pain are seen in pain centers and clinics (36), this is obviously a skewed view and does not include the more than 70 million Americans with chronic arthritis, cancer, complex regional pain syndrome, neuropathic pain, myofascial syndromes, and a host of other chronic pain syndromes in which the chronic pain is not caused primarily by affective and environmental factors, but rather to persistent dysfunction of the nociceptive system (tissue pathology, nervous system dysfunction, or both). Obviously, many of these patients are effectively managed by rheumatologists, orthopedists, neurologists, anesthesiologists, neurosurgeons, physiatrists, dentists, and other health professionals and need not be referred to a multidisciplinary pain program. On the other hand, as emphasized in Chapter 10, many other chronic pain patients are not effectively managed because of improper application of available knowledge and therapies. Such patients frequently develop physiologic, psychological, behavioral, and emotional problems and could benefit from a comprehensive M/I evaluation and rehabilitation program (see Chapter 18 and Chapter 109).

Another concern is the exploitation of a single modality to treat all patients, ignoring the unique needs of each. This is commonly seen in the pursuit of anesthesiologic procedures to treat chronic pain: Patients may have multiple blocks (until funding ceases) that do not lead to long–term improvement in the patient's functional status. Another example could be excessive physical therapy treatments, especially those that are *passive*, in the absence of functional gains. Finally, the fascination with alternative therapies is likely to deprive some patients who need comprehensive evaluation and treatment of an opportunity to obtain optimal outcomes.

Accreditation of Pain Programs and Certification of Specialists

Bonica repeatedly expressed concern for the proper training of clinicians involved in pain clinics, and soon after the founding of IASP he suggested that this organization, through its national chapters and perhaps with other professional societies, develop guidelines or criteria that could be used by facilities organized for the treatment of patients with chronic pain problems. It is now clearly recognized that accreditation of treatment facilities and certification of individuals must be a national or regional activity because of differing training and health care delivery systems. Within the United States, efforts were initiated in the late 1970s to establish guidelines and criteria for pain programs through the American Pain Society. During the course of several years, a committee of the American Pain Society, under the chairmanship of G. Aronoff, developed the criteria that were eventually accepted by the Board of Directors of the Commission on Accreditation of Rehabilitation Facilities (CARF). CARF, a nonprofit organization supported by the Joint Commission on Accreditation of Hospitals and a number of other national sponsoring organizations, has been surveying and accrediting rehabilitation facilities since the late 1960s. In 1981 the Board of Directors of CARF accepted the tasks of setting up criteria and surveying pain clinics and centers in the United States and in 1982 convened 13 regionally distributed full–time pain center directors to form the National Advisory Committee on Chronic Pain Management Programs. This group developed criteria and guidelines that were subsequently approved by the American Pain Society and CARF, and surveying of pain management facilities was begun in July 1983. Within 5 years, approximately 100 pain centers and clinics had been certified. By 1998, 204 programs had achieved certification. A summary of the evolution and function of CARF in evaluating pain programs has been published by Morse (37). CARF accredits pain treatment facilities, not individuals .

In the early 1980s, a group of physicians in the American Pain Society embarked on a program to establish certification for individual medical providers. They established an organization, initially called the American Academy of Algology, whose name was soon changed to the American Academy of Pain Medicine. The primary purpose of this group was to obtain recognition from the American Medical Association as a bona fide specialty and to offer a certifying examination for physicians. In 1998, the Academy had 1,200 physician members. It had been partially successful in obtaining AMA recognition and had established the American Board of Pain Medicine that had 827 diplomates who had passed their certifying examination. Pain medicine was still not a recognized specialty by the American Board of Medical Specialties. Similar programs both to certify individuals and accredit pain treatment facilities were being considered in many countries.

The American Society of Anesthesiology began to encourage training in pain management as part of anesthesiology residency training in the late 1980s. Fellowship training in pain management for anesthesiologists was not an official part of anesthesiology, however, and many individuals, as a response to community demand, claimed to be pain specialists with limited training. The American Board of Anesthesiology and the Accreditation Council for Graduate Medical Education held a series of meetings that led to approval of guidelines for pain education both in the anesthesiology residencies and in anesthesiology–sponsored pain fellowships. Training programs for pain fellowships were certified and a written examination was established to provide Advanced Qualification in Pain Medicine for anesthesiologists only. The first examination was offered in 1993 and it has been available in alternate years since that date; 1,541 anesthesiologists have been certified by 1998. There are 97 accredited pain management training programs as of this date. Only anesthesiology board–certified or board–eligible physicians may sit for this examination; those who have not trained in the United States are ineligible. The qualification is now known as Fellowship in Pain Medicine. No other specialty of American medicine offers a similar training program.

UNIVERSITY OF WASHINGTON PAIN CENTER

In the first decade after its founding, the multidisciplinary pain clinic program at the UW evolved into a group of 20 persons from 14 different medical specialties and other health care disciplines who participated in the activities of the program to varying degrees and devoted variable time and effort (20,21). Initially, the collaborative efforts of the pain clinic group were devoted exclusively to patient care and teaching, although certain members were doing independent research in their own laboratories. In 1971, Bonica recruited C. R. Chapman, an experimental psychologist who later became qualified in clinical psychology. Soon thereafter, a clinical and experimental pharmacologist joined the program, and we have subsequently recruited other basic scientists and clinical investigators with interests in pain research. The interaction, conceptual cross–fertilization, and scientific interchange made possible by these individuals and their efforts culminated in extensive collaborative research programs. As a result of the progressive growth of the program, especially research, in 1980 the Board of Regents of the UW designated the organization as the UW Multidisciplinary Pain Center. In 1983, Bonica resigned as Director of the Center and a major reorganization occurred under the leadership of J. D. Loeser. At that time, the Behavioral Medicine Division of the Department of Rehabilitation Medicine, led by Wilbert Fordyce, merged with the Anesthesiology Pain Service to create a unified patient care organization for those who suffered from either acute or chronic pain. This organization had inpatient and outpatient resources at the University of Washington Medical Center (UWMC). Faculty who worked at the affiliated hospitals (Seattle Veterans Administration Medical Center, Harborview Medical Center, Fred Hutchinson Cancer Research Center, and Children's Hospital and Medical Center) developed pain management services that were conceptually similar but totally independent of the Multidisciplinary Pain Center. Shortly thereafter, L. B. Ready began the relatively autonomous Acute Pain Service at the UWMC. This was designed to provide for the pain management of postoperative and posttrauma patients.

The separate inpatient and outpatient facilities were merged onto one ward of the UWMC in 1989, creating a wonderfully efficient base of operations for all of our pain management services. This also facilitated research and teaching programs. This ideal facility was dismantled in 1994, when the Multidisciplinary Pain Center was transferred to a primary care satellite clinic approximately 1 mile from the UWMC. At that time, a separate, hospital–based anesthesiology pain service was created to provide pain management services to all inpatients; only outpatients were to be cared for by the Multidisciplinary Pain Center. The fractionation of the Multidisciplinary Pain Center into separate sites and programs created many issues that interfered with the goals, finances, and training programs of the Multidisciplinary Pain Center.

Objectives and Goals

The primary objective of the Center has been to develop and maintain a broad M/I program for research, education, training, and patient care in pain and related areas. The specific missions of the Center are listed here:

- To enhance the quality of the care of patients with chronic pain referred to the UWMC and affiliated hospitals and to have the Clinical Pain Service serve as a model of an M/I facility for the diagnosis and therapy of complex pain problems
- To contribute to the education in pain management of graduate students of medicine, dentistry, clinical psychology, and other health professions
- To encourage the study of the basic mechanisms and the anatomic, physiologic, psychological, behavioral, and psychosocial aspects of acute and chronic pain, through individual research projects, program projects, and demonstration projects
- To encourage the development of research teams composed of critical masses of scientists and clinical specialists from appropriate disciplines to study some of the most important clinical pain syndromes, to evaluate current therapeutic modalities, and to develop new and better procedures for diagnosis and treatment of such syndromes
- To enhance interaction and communication among all pain investigators at the UW and to encourage cross–fertilization of ideas on pain research and therapy
- To educate and train biomedical scientists who will pursue careers in pain research
- To enhance the transmission of new knowledge about the diagnosis and therapy of pain to all practitioners of the health professions

The ultimate goal of these efforts is to contribute to the improvement of the quality of life for millions of persons who currently suffer needlessly from acute or chronic pain.

General Organization

To achieve its objectives, the Center was organized into two sections, the Clinical Pain Service and the Pain Research Center. The Center includes a staff of more than 50 scientists, physicians, and other health professionals who are members of or are affiliated with the following disciplines (in alphabetical order): anesthesiology, biological structure (anatomy), general dentistry, internal medicine, neurology, neurophysiology, neurosurgery, nursing, oncology, oral medicine, oral and maxillofacial surgery, orthodontics, orthopedics, clinical and experimental pharmacology, psychiatry and behavioral sciences, clinical and experimental psychology, rehabilitation medicine, sociology, and social work. Although some of the basic scientists' activities are limited to research and teaching, most of the persons are also involved in patient care. Their efforts are supported by more than 30 technical and clinical personnel and administrative and secretarial staff. The keys to such complex multidisciplinary efforts are effective organization of personnel and ample physical facilities, equipment, and financial resources.

Clinical Pain Service

The Clinical Pain Service includes outpatient and inpatient facilities for the diagnosis and therapy of all types of pain patients and for providing effective teaching and training programs for students of medicine, dentistry, and other health professions, for physicians in specialty training, for pain management fellows, and for practicing health professionals. The clinical pain services exist at each of the hospitals affiliated with the UW Medical School, as mentioned previously. At each hospital, clinical and support personnel are allocated to provide acute and chronic pain management services. At the UWMC, the Multidisciplinary Pain Center currently is located in a free– standing primary care clinic that manages outpatients and a separate service provides acute pain services as well as consultation and management for inpatients with chronic pain and for cancer patients who attend the Cancer Center at the UWMC.

Multidisciplinary Pain Center Personnel

Personnel include faculty and staff; almost all are full–time employees of the UW; many of the faculty spend only a portion of their professional time within the Pain Center. The following staff are required to operate the clinic:

Patient care coordinator: The patient care coordinator is responsible for (a) the initial review of referral letters and making telephone contact with the referring physician, patient, and sponsoring agency; (b) coordinating and processing all inpatient and outpatient admissions and patient consultations; and (c) obtaining authorization for care from the sponsoring agencies.

Patient services representatives: Patient services representatives answer and triage telephone calls, staff the reception desk, schedule patients, and process paperwork as needed.

Medical assistants: Medical assistants assist with patient flow in the clinic, process medical records, assist in procedures, and process billing records.

Nurses: Nurses assist in patient care and procedures, answer telephone calls, process prescription refills, educate patients, and process paperwork.

Physical therapists: Physical therapists participate in the assessment and treatment of patients.

Occupational therapists: Occupational therapists assist in the evaluation of new patients and provide patient care services.

Vocational counselors: Vocational counselors participate in patient assessment and the placement of patients into a job or job simulation activities.

Administrative assistani: The administrative assistant supports the programs of the Pain Service and works with the director to implement and maintain programs.

Secretaries: Secretaries provide direct support to the director and to the faculty who work on the Pain Services.

The faculty who work on the Clinical Pain Service are drawn from departments of the School of Medicine including Anesthesiology, Family Medicine, Physical Medicine and Rehabilitation, Psychiatry and Behavioral Sciences, Neurology, and Neurological Surgery. They include physicians and psychologists. A few private practitioners who are on the Clinical Faculty also regularly attend the Pain Center and assist in patient care. Faculty may participate in the structured program and its associated screening process or may see consultations and manage individual patients, or may do both.

Trainees: Resident physicians who rotate through the pain clinic, the pain fellows, and other health professionals assigned to the Clinical Pain Service as part of their training, constitute an important group of personnel who help with the evaluation and day– to–day care of patients.

Physical Facilities

The physical facilities of the Clinical Pain Service have changed dramatically in the 37 years since the Pain Clinic was established. At present, the Multidisciplinary Pain Center has superb clinical space in a new outpatient clinic approximately 1 mile from the UWMC. The clinic has a large waiting area, eight patient examination rooms, three counseling rooms, three conference areas, a patient lunch room area, a nerve block room equipped with an operating room table, an anesthesia machine and a C–arm fluoroscope, and three monitored recovery room beds. It is adjacent to a physical therapy/occupational therapy area known as the *exercise training center*. The clinic has underground parking and in–house laboratory and radiology facilities. The director and some faculty and staff have offices.

Patient Care

The operation of the Clinical Pain Service in evaluating and providing care for patients is discussed in Chapter 18 and Chapter 109. In general, (a) only patients referred by physicians or other health professionals are considered for treatment, and preference is given to patients with complex pain problems requiring M/I evaluation and those having such emergency pain problems as cancer or complex regional pain syndromes; (b) once the decision is made to accept the patient, the referring physician and the patient are requested to provide all available medical information, including a comprehensive summary of the pain problem and therapies used, imaging studies, and laboratory data; (c) patients are triaged to either an initial consultation with one physician or to a screening evaluation by a physician, psychologist, and vocational counselor (see Chapter 18).

An important aspect of patient care has been the development of an Acute Pain Service under the direction of Dr. Brian Ready. This was prompted by Bonica's personal experience and observation of patients as well as numerous reports (cited in Chapter 41) of the past and current inadequacy of providing effective relief to patients with acute postoperative and posttraumatic pain. Pain management anesthesiology specialists rotate through the service and provide relief using epidural analgesia achieved with narcotics, local anesthetics, or both and with patient–controlled analgesia, as well as regional anesthesia and analgesia. This service has been highly successful and has demonstrated the superiority of these techniques over the standard method of intramuscularly administering narcotics in relieving moderate to severe acute pain. This topic is discussed further in Chapter 41, Chapter 102, and Chapter 103. Loeser and Egan (35) have published a book on the Clinical Pain Service, describing its patient care activities in detail as they were in 1990.

When the Multidisciplinary Pain Center moved to the primary care clinic building in 1994, a new chronic pain service was created to provide services to inpatients at the UWMC. This was closely linked to the Acute Pain Service and was directed by Dr. Ready. Its faculty worked closely with the members of the Cancer Center to develop appropriate pain management services for this group of patients who were cared for at the UWMC. In 1997, new hospice care activities were under development at the UWMC that will also change the need for pain management services.

Educational Programs

The Clinical Pain Service provides teaching programs for medical students, residents (registrars) from various medical specialties and disciplines who are interested in pain, pain management fellows, and practicing physicians and psychologists who have special interest in pain.

Medical Students

The medical student teaching program includes (a) a preceptorship that provides first– and second–year students the opportunity to observe patient care activities; (b) a 4–week clerkship for students who have completed their basic clerkships and are in their third or fourth year of medical school; and (c) programs for students to work with Pain Center faculty in fulfilling the independent study requirements of the medical sciences program, which include the completion of a research project and a thesis. In addition, the faculty of the Pain Center participates in conjoint medical student lectures related to the anatomic, physiologic, and psychological substrates of nociception and pain.

Residents (Registrars)

In the past, residents from the Departments of Anesthesiology, Rehabilitation Medicine, Neurosurgery, Neurology, Psychiatry, Dentistry, and Oral Medicine have rotated through the Clinical Pain Service. Anesthesiology residents currently are required to have a 2– month rotation covering both acute and chronic pain; they may elect additional exposure in their final year of training.

Psychology Interns

The UW sponsors a psychology internship program, which allows its clinical psychology trainees to elect a rotation on the pain service for a period of 4 months. In addition, clinical psychology fellows from the geriatric training program have spent 3 to 6 months on the Clinical Pain Service.

Pain Management Fellows

The Pain Center has four 1–year fellowships available only to anesthesiologists. Fellows rotate through the Multidisciplinary Pain Center, the UWMC, Harborview Medical Center, and the Seattle Veterans Administration Medical Center. They may also elect to spend a month at Children's Hospital and Medical Center or in a private practice environment. This program is accredited by the American Board of Anesthesiology. The goal of this training program is to present the fellows with the broadest possible array of pain patients and to have them learn all aspects of the treatment of chronic and acute pain.

Other Health Professionals

During the 1990s, 20 to 25 physicians, called *short–term visitors*, have attended the Clinical Pain Service annually for periods ranging from a few days to a week. During this period they are given a formal presentation that describes the activities of the Clinical Pain Service and the Pain Center as a whole, and they are permitted to observe the management of patients with a variety of chronic pain problems.

In addition, during each year 7 to 10 physicians visit the Clinical Pain Service for periods of 1 to 12 months, and these are called *long–term visitors*. Most of these individuals are from countries in Western Europe, Latin America, and Asia. Whenever possible, these individuals are encouraged to obtain a temporary license so that they can participate in the care of patients and have a more extensive learning experience. Those who are not eligible for a Washington State license can only observe the clinical activities. Although these long-term visitors are an increased teaching and administrative burden on the resources of the Center, they represent a worthwhile expenditure of the energies of the Pain Center staff.

Pain Research Center

The Pain Research Center is intended to achieve its mission by (a) encouraging the integration of existing and new research projects into major areas of pain research; (b) developing a milieu that will attract young scientists to undertake pain research training and established pain scientists to contribute to the UW Pain Research Center as funds, space, and other resources become available; (c) encouraging collaboration with other research and clinical programs related to pain within the UW, and with other pain research programs in other institutions; (d) developing an active schedule of informal and formal research meetings of scientists and clinicians at appropriate intervals; (e) organizing and sponsoring or cosponsoring visits of outstanding pain scientists and clinicians to the Pain Research Center and the Clinical Pain Service; and (f) organizing and sponsoring an annual regional or national symposium on various aspects of pain research.

The scientific staff of the Pain Research Center carries out a large number of individual research projects on various aspects of pain and also has several program projects that include two or more research projects focused on such special problems as orofacial pain, cancer-related pain, spinal opioids, and nonmalignant chronic pain. Links to many other research and training programs exist within the UW and its affiliated institutions.

Research Training

The Pain Research Center provides laboratory, clinical research training, or both at the postdoctoral level for Ph.D. scientists and physicians, dentists, and other health science professionals who have a long–range interest in, and commitment to, the field of pain research. This effort has been supported by a research training grant awarded to the Pain Center with C. R. Chapman as program director. Since this program was initiated, a total of 17 research trainees have completed 1 to 3 years of training in pain research. These included Ph.D. and M.D. trainees from the United States and eight other countries. Although most of these trainees have returned to their home universities, several have accepted faculty posts at the UW and continue to remain as members of the Pain Research Center. The Pain Research Center also has had a successful predoctorate training program that has accommodated a number of individuals who have obtained their doctorates in the center. The program has also attracted qualified basic and clinical scientists who spent varying periods of time collaborating with Pain Research Center investigators.

Emma and John Bonica Endowed Chair for Research on Pain and Analgesia/Anesthesia

At the time of Dr. Bonica's retirement from the faculty of the Department of Anesthesiology in 1983, his colleagues, trainees, and friends embarked on a fund–raising campaign to create an endowed chair in pain research. Capably led by Dr. Thomas Hornbein, Dr. Bonica's successor as Chair, this group raised sufficient funds to create the first endowed chair in pain research. The initial occupant of this unique faculty position, Dr. Dennis C. Turk, assumed his duties in 1996. The existence of this key faculty position should lead to continued strength of the research activities of the Pain Center and helps to keep pain research alive within the Department of Anesthesiology.

COMMENTS AND CONCLUSIONS

With progressively greater experience with the multidisciplinary team approach in treating patients with complex chronic pain problems acquired since the late 1940s, we have become increasingly more convinced that the concept is sound and is one of the most efficient, if not the best, method of managing such patients. The same opinion was expressed by all of the participants of the symposium and workshop on multidisciplinary pain clinics sponsored by the National Institutes of Health (38). The IASP endorsed these concepts when it published, in 1989, its “Guidelines for Desirable Characteristics for Pain Treatment Facilities” (39). Review of our data at intervals has revealed the following conclusions.

1. Development of such a comprehensive facility was a slow process, especially at the beginning, when the American medical profession tended to discourage group efforts. One internationally known orthopedic surgeon (who knew nothing about our facility) referred to this concept as “treatment by committee.”
2. The emphasis of the group has changed from time to time as new members, representing disciplines previously not represented in the group, joined the team.
3. Unfortunately, patients are usually referred to the facility after too many ineffective therapies have been applied and failed and the patient has been subjected to prolonged needless suffering. Unrelieved chronic pain is a personally devastating experience that wreaks havoc with the patient and his or her family and work.
4. Many physicians believe that *pain clinic* is a synonym for *garbage pail* and demand that all their treatment failures be immediately transferred to pain clinic specialists. The treatment strategies used in a pain clinic are not universally applicable; patients must be selected for treatment just as they are for any other type of health care.
5. The success rate in the pain center varies with each of the different pain syndromes. The team does *not* make a correct diagnosis 100% of the time, nor do we always eliminate pain permanently. Nevertheless, the rate of success is better than that obtained by practitioners working alone, by members of a specialty group, or by members of general medical or surgical clinics. Although many of the physicians who have treated patients that were eventually referred to our facility have the same expertise in their particular fields as their counterparts in the pain center, they were unsuccessful because they worked in the isolation of

their offices with their available therapeutic facilities and did not have the benefit of an M/I input. Because most of the patients seen in our facility have not responded to traditional health care, the pain center would have to be considered successful even if only a small percentage were enabled to return to productive lives. Indeed, of the treated patients for whom return to work was a practical option, 65% were working at time of follow–up 6 to 12 months or longer after completion of treatment. Detailed data on this type of program are presented in Chapter 109.

6. One of the most important benefits from the M/I team effort is the *esprit de corps* generated among and enhanced by its members. Equally important is the continuous exchange of information. This broadens the knowledge and perspective of each member so that he or she can better use his or her professional talents during diagnostic workups or consultations as well as in teaching and research.
7. The facility has gradually attracted more and more scientists interested in pain research and has been highly effective in integrating clinical efforts and scientific investigation. These individuals have come to appreciate the problems encountered by the clinician in dealing with patients with chronic pain, which are quite different from the problems encountered in the experimental laboratory. By the same token, the presence of scientific research allows clinicians to appreciate the problems of the investigator, improves the quality of patient care, and helps keep clinicians abreast of recent progress in relevant fields. As a result, the pain center has developed several critical masses of basic scientists, clinical scientists, and practitioners who are doing individual and collaborative research, most of which has direct clinical relevance and that, one hopes, will eventually have therapeutic applications.

Problems and Disadvantages

During the evolution of the Pain Center we have encountered a number of problems. We have noted certain disadvantages of such a broad–based M/I effort.

1. During the early years, the hospital administration and health agencies provided a level of support that did not permit expansion of the program to meet the progressively increasing needs in patient care, education, and training. In recent years, financial issues have also retarded the development of the Pain Center. Furthermore, the unique aspects of M/I care are still not understood by many physicians and medical administrators.
2. An inadequate amount of time has been devoted in the curriculum of medical and dental students to permit an effective teaching program on pain. Moreover, funds have not been available to train pain management specialists. As indicated in the section Educational Programs, in more recent years we have been able to get more time for some students and to generate funds to train a number of clinical and research pain specialists.
3. Solving and treating complex problems requires a great amount of time and effort, and the team approach is costly, a fact that has created a number of problems. Thus, the cost of a comprehensive evaluation and the 3–week behavioral/medical/rehabilitation program totals approximately $17,000, a figure that uninformed insurance carriers, who refuse to reimburse for the services of the psychologist and other nonphysician personnel, find difficult to accept. On the other hand, the benefits of such programs outweigh even these costs. Low back pain patients at the UW Pain Center, for example, have not worked for an average of 3.4 years and have had an average of 2.6 major surgical operations for their pain (one had 42 operations for low back pain). On the basis of compensation payments for lost work days paid by the State of Washington and the cost of major operations, it can be conservatively estimated that the total cost for the average patient has been in excess of $75,000. Because, as previously mentioned, 65% of our patients are able to return to work after treatment, it is obvious that the program is cost–effective. The cost of efforts of numerous multidisciplinary teams is worth it, and in the long run will save society billions of dollars. This issue is discussed in Chapter 109.
4. Another disadvantage of the team approach is the risk of fragmenting the care of the patient among several people. In such a situation, if no single person is responsible for overall care, the patient is deprived of the important patient–physician relationship. This result can and must be obviated by having one member of the team serve as managing physician.

Advantages

Our experience has convinced us that these disadvantages are more than offset by the advantages of the team approach used for patient care, teaching, and research. The advantages are presented here.

1. The team approach provides a broad–based source of knowledge and expertise for the care of patients. Long experience has confirmed the deep conviction that the close interaction among various members of the team and the face–to–face group discussions during the conferences are much more effective and productive in making a correct diagnosis and formulating the most appropriate therapeutic strategy than communication by letter or telephone or through fragmented independent efforts inherent in traditional medical practice. In addition to providing a highly specialized consultant service to the referring physician and the patient, these conferences serve as an excellent forum for the exchange of ideas and information and thus constitute an effective teaching mechanism.
2. The M/I collaborative research efforts are likely to generate more information and more comprehensive perspectives on the problems of pain than could be generated by individual investigators working alone. The grouping of investigators fosters interaction among basic scientists and a variety of clinicians, and it helps to encourage other basic and clinical scientists to devote their efforts to pain research. Equally important, this interaction creates stronger bridges among the basic sciences and clinical disciplines of the institution. These bridges help to eliminate the chasm between basic scientists and clinicians that has heretofore precluded this type of collaborative research program and has unduly delayed the application of new knowledge to the scientific care of patients. All of the previously mentioned factors should result in a much more productive program of research, teaching, and patient care.
3. The multidisciplinary pain center is an ideal method of applying the biopsychosocial model of illness to patient care. This concept is particularly important for patients who suffer from chronic pain, as the more common biomedical model does not suffice to lead to optimal outcomes.

Requisites for Optimal Results

To achieve these objectives and accrue the aforementioned benefits, it is necessary to fulfill the following requisites and conditions:

1. The director of the program should have the capability of providing vigorous medical, scientific, and administrative leadership to the entire group. Because the team is composed of individuals who have appointments (and consequently allegiance) to their parent departments, it is essential that the director possess those qualities necessary to bring a heterogeneous group together and have it function as a single, efficient unit. He or she must possess a superior knowledge and skills in a special area of pain, and his or her performance in patient care, teaching, and research must be such as to win the respect of all his or her colleagues. In large programs of the type developed at the UW, the director must have an associate director for research and one for the clinical pain service. These associates must have the knowledge, expertise, and skills to provide the same type of vigorous leadership in their respective areas.
2. Each other member of the group must have special interest in pain and must be willing and able to devote sufficient time to the activities of the program. Moreover, each member must have the ability to interact frequently and productively with other members of the program and be willing to respect the opinions of others—in other words, each must be a real team player. Moreover, each member must possess thorough knowledge, experience, and skills in a particular area to contribute to a vigorous collective team effort and also must acquire broad knowledge of the basic and clinical aspects of pain beyond that of his or her specific discipline.
3. Each member of the team dealing with patient care, teaching, or research must work in an exquisitely coordinated manner, and all members of the team must meet frequently to discuss their findings on each patient and on specific research projects.
4. The program must have sufficient space and equipment as well as personnel and other resources, including a strong financial base, to carry out its program efficiently and effectively.
5. An M/I pain center must have highly effective teaching programs for students and practitioners and must develop a productive research program on various aspects of pain.
6. The multidisciplinary pain center must develop an intensive program to inform and educate the public and the staff of various governmental agencies to recognize and appreciate the importance and magnitude of pain as a serious national and world health problem that requires and deserves ample financial support.

SUMMARY

Pain has long been, and continues to be, an important subject for study by scientists and a phenomenon that still taxes the diagnostic acumen and therapeutic skills of physicians and other health professionals. In this chapter, the evolution of the various types of pain clinics and centers in the United States and other parts of the world has been summarized. It is apparent that the marked increase in pain research has not only greatly enhanced our knowledge of sensory coding and sensory modulation, but also has brought about a significant change in our conceptualization of clinical pain and pain therapy, particularly with regard to chronic pain syndromes. This, in turn, has encouraged many physicians and other health professionals to become involved in managing patients with pain within the context of multidisciplinary pain diagnostic and therapeutic facilities. The UW Multidisciplinary Pain Center has been described as an example of a university–based facility that has productive programs for the management of patients with complex chronic pain problems and for education and training and for research on pain. The problems, disadvantages, advantages, and requisites for success have been summarized.

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CHAPTER 12

Medical Evaluation of the Patient with Pain

John D. Loeser

The general principles of the medical evaluation of patients with pain with special emphasis on patients with complex pain problems are discussed in this chapter. This chapter describes the initial medical evaluation in the physician's office, in which the patient with pain is seen for the first time. It also includes discussion of the objectives of the medical evaluation, general method of approach, characteristics of the pain, eliciting a detailed history, performing a comprehensive physical examination, including neurologic and musculoskeletal studies, and a presentation of the types of laboratory, radiographic, and other data that assist in the establishment of a correct diagnosis and developing the most appropriate and effective therapeutic strategies. This section is intended for physicians working either individually or within multidisciplinary programs.

The medical evaluation of patients with complex chronic pain problems is time consuming and often psychologically and physiologically taxing to the physician and patient. In addition to the medical evaluation, a psychological evaluation, preferably by a clinical psychologist, is often essential for the establishment of a diagnosis and the development of a therapeutically beneficial treatment plan. These tasks may be most efficiently achieved within the setting of a multidisciplinary/interdisciplinary pain program, particularly for the patient who has already consumed large amounts of health care resources.

The diagnostic processes carried out for specific pain syndromes are presented in Parts III and IV of this book. The reader is referred to the text by Weiner on the differential diagnosis of acute pain syndromes (1).

PRELIMINARY CONSIDERATIONS

Objective of the Medical Evaluation

Medical evaluation of the patient's pain involves making a correct diagnosis that permits the development of optimal therapeutic strategies. A primary objective is determination of whether the patient is having acute or chronic pain and, if the pain is chronic, whether it is a result of cancer or of a nonmalignant disease process. As emphasized frequently in this book, management strategies for acute pain and cancer pain often are dramatically different from those used for nonmalignant chronic pain. It is also important to determine whether organic disease was actually overlooked or arose during the course of the patient's pain complaint.

Another objective of the evaluation and treatment process is avoiding the fragmentation of care. Because patients with chronic pain have already had multiple interactions with health care systems through various, often simultaneous, physician contacts, it could be erroneously assumed that the patient has been and is receiving coordinated and monitored comprehensive care, thorough physical examination, coordinated medication management, and the necessary psychological assessment and treatment. This is often not the case, not only among pain patients but also among patients with other disorders who receive fragmented care from multiple physicians.

Another important objective of the medical evaluation is development of sufficient rapport with patients to be able to convince them that a psychological and psychosocial evaluation is essential. Without adequate information and psychological preparation, many patients reject the recommendation that they be evaluated by a clinical psychologist, social worker, vocational counselor, or other health professionals.

Initial Interview

During the initial visit between the patient with pain and the physician, several things should be accomplished, the most important of which is the physician's obtaining the confidence of the patient. The necessity of establishing a rapport between the physician and patient to gain full cooperation of the patient and to achieve optimal results cannot be overemphasized. As a result of previous therapy failures, many patients with chronic pain come to the consulting physician discouraged and pessimistic. Others are angry, bitter, and resentful. Many have been told that “your pain is in the head” and that “nothing can be done for the pain.” The difficult task of cultivating the confidence and faith of the patient can be accomplished in several ways. First, the referring physician should convince the patient that the consultant is a specialist in the management of pain and has special attributes that can help to solve the pain problem. During the initial visit, the pain specialist should strengthen the patient's belief in this by using and exploiting to the fullest extent those intangible attributes called the *art of medicine*. The physician should bring to the pain patient a quiet, considerate humanity and a confidence and security based on the conviction that all that can be done will be done to help. All patients must be made to feel that their individuality is recognized and that their problem is not meaningful only to them but is the most important phase of the physician's practice. A sympathetic attitude, consideration, affectionate care, and a deep interest in the patient's problem greatly enhance the cooperation of the patient during the evaluation procedure and also help to convince the patient that he or she can be helped with this pain problem.

The next objective is to inform the patient about the various steps and procedures to be followed during the evaluation process. Even if this has been done by others, the physician should describe the entire plan of assessment and management. The evaluation process and treatment could require a great deal of time and either repeated visits or a stay in the hospital. The patient's cooperation is essential; without it, favorable results cannot be guaranteed. The patient should agree to follow through either verbally or, as Sternbach (2) suggested, by signing a *management contract*. As mentioned, such cooperation is usually obtained without difficulty, provided that the physician discusses the problem fully with the patient, explaining the entire management plan in language that can be understood. At least 2 hours should be reserved for the initial visit to achieve all these objectives and to take the history and perform a comprehensive physical examination. It might take less time, but generally it takes longer. In the current health care environment, several visits may need to be scheduled to obtain adequate information.

Several points should be made in regard to the diagnosis. First, it is necessary to confirm or reject the diagnosis if one has already been made by the referring physician. In some cases the prior diagnosis, when critically examined, is found to be inappropriate or outdated, or to be a mere description of an initiating disease entity that might have little or no relation to the patient's present chronic pain problem. Even if the diagnosis was made correctly by a respected physician who has referred the patient to the clinical pain specialist for management, it is essential to investigate the problem fully. Often, additional information can be obtained that aids in the treatment plan. A detailed history and a comprehensive physical examination are therefore essential. Generally, the medical evaluation of the patient's chronic pain is based to a major degree on the history and to a lesser degree on the physical examination, and least on the laboratory data and imaging studies. Indeed, in many patients with chronic pain, it is essential to await the results of the psychological and psychosocial evaluation as well as those of consultation with other specialists and diagnostic studies before a definitive diagnosis can be reached.

Taking the History

Taking a detailed history is the most important part of the evaluation of the pain patient. Experienced clinicians rely heavily on a history in arriving at a diagnosis, because, when it is carefully and meticulously elicited, skillfully interpreted, and carefully analyzed, it provides important information not only about the possible mechanisms and pathophysiology of the chronic pain syndrome, but also about the emotional and psychological status of the patient (3). The history often affords the physician such a clear picture that diagnosis can be largely established from the symptoms alone, even before physical, neurologic, and laboratory examinations have been carried out. In other cases, the history might not be so decisive but can so limit the diagnostic possibilities that a logical program of investigation is suggested.

Finally, and equally important, the history affords the physician an unequaled opportunity to establish rapport with the patient by being friendly, understanding, and courteous; by being visibly interested in the problem and anxious to help; and by centering all attention on the patient. These actions are the cornerstone for a successful patient–physician relationship.

Guidelines

A comprehensive history consists of a history of the pain problem, a past medical history, a general psychological and psychosocial history, and a family history. These are elicited as for any other medical condition and need no elaboration here except in regard to matters that are of special concern in patients with chronic pain syndromes. The patient with chronic pain is frequently fatigued, irritable, and nervous, so the history is best taken in privacy with the patient as comfortable as possible. (The issue of having the spouse or some other involved family member or significant other present as part of the psychosocial evaluation is mentioned later and discussed in detail in Chapter 16 by Turner and Romano.)

During the process of history taking, the physician should avoid appearing hasty and should meet the patient on a common ground of language and vocabulary, resorting to the vernacular if necessary. Although a regular sequence is valuable in obtaining and recording the history, both for ensuring completeness and facilitating future reference, the history should never be obtained by following a stereotyped form or repeating a memorized list of questions. Patients may become resentful of losing their individuality when coerced into the physician's evaluation format.

The history should be recorded clearly and concisely in a logical, well–organized manner. Each statement must be considered in its relationship to the whole. It is important to stress the more significant manifestations and to keep irrelevancies to a minimum; essential factual material must be separated from extraneous information. Diagnosis involves the careful sifting of evidence and the art of selecting and emphasizing relevant data to enable a correct conclusion to be reached. It might be advantageous to record negative as well as positive statements, so that later examiners understand that the historian inquired into and did not overlook certain aspects of the disease.

The initial step of the history is to let patients tell their stories in their own words. The importance of this part of the examination of patients with pain was stressed by Leriche (4), who stated that the physician “who really wishes to investigate pain and find some means of abolishing it, ought to give great attention to his patient's complaints. He ought to listen to the story of their sufferings, however long and tedious it may be.” Although some patients do appear to exaggerate subjective sensations, they should be given an opportunity to express their feelings, because this can reveal important information. While the patient is talking, the physician should intervene as little as possible, and only to lead the story into directions in which useful information can be obtained, to exclude obviously irrelevant material, or to obtain amplification of statements that seem to be vague or incomplete. The use of open–ended questions is essential; closed questions might distort the patient's history and obscure diagnosis.

Whereas the patient's spontaneous narrative affords the examiner valuable information that aids in orientation to the patient's problem, rarely is it complete. Only exceptional patients recall all particulars of their illness and repeat them in accurate and chronologic order without confusing symptoms and their interpretation of symptoms (3). Furthermore, if the patient's mind is focused on a particular manifestation, he or she might not mention others of equal importance. Thus, it is usually necessary to augment the patient's account by asking leading questions that are tactfully presented. It is often necessary to go into detail regarding specific factors, many of which patients might not relate to their present condition, but whose presence or absence could be significant. The importance of an accurate, detailed record of events in cases that involve compensation for medical or legal problems deserves special emphasis.

Patients should be allowed to use their own words, and any suggestion of symptoms or diagnosis should be avoided. This is particularly important in obtaining the history from overly suggestive and somatically preoccupied patients (3). Special consideration must be given in taking the history of certain types of individuals. The garrulous person might have to be stopped from getting lost in a mass of irrelevant detail, whereas the timid, inarticulate, or worried patient might have to be helped by sympathetic questions or reassuring comments. The fearful, antagonistic, or paranoid patient should be questioned carefully so as not to arouse fears or suspicions; the patient with multiple vague complaints must be kept to specifics, and the evasive or undependable patient should be questioned more searchingly. This wide range of individual variations is important to consider in taking the history of any illness, but it is especially important when appraising the pain patient's complaints.

During the taking of the history, the physician has an unequaled opportunity to study the patient as a whole (i.e., manner, attitude, behavior, and emotional reactions). The tone of voice, bearing, facial expressions, any gesticulations, restlessness, delay or hesitancy of speech, and emotional responses to description of certain events or facts about marital or work history constitute important information in evaluating the character, personality, and emotional state of the patient and should be recorded in detail.

With these considerations regarding the taking of the history, we can now consider the general outline of the history and the specific aspects that must be elicited to make a correct diagnosis. Before doing so, however, the characteristics of pain on which taking the history of the pain and the physical examination are based are briefly reviewed.

Characteristics of the Pain

In eliciting the history of the pain and in examining the painful part, it is essential to obtain a detailed description of the location and distribution of the pain, quality of the pain, severity or intensity of the pain, and periodicity and duration of the pain and the affective concomitants of pain, best labeled as *suffering*.

Location and Distribution. The value of localizing the site and distribution of the pain in diagnosing its cause is universally recognized, but it should be remembered that the accuracy for such localization begins to diminish from the moment the pain ceases, and it is therefore best to obtain this information while the pain is actually present. Moreover, as elaborated in Chapter 9, pain arising from the skin or mucous membranes, and from the nervous apparatus that supplies these structures, is localized with almost negligible error, but pain arising from deep somatic or visceral structures can be referred remotely or localized with difficulty. Such referred pain might be accompanied by hyperalgesia, hyperesthesia, and deep tenderness. Pain with a segmental distribution can arise from dysfunction of the nerve roots or formed spinal nerves. Pain can be classified as localized, projected (transmitted or transferred), referred, or of reflex (sympathetic) distribution and as what some call *psychogenic pain* (see Chapter 26). Pain of any etiology also may be influenced by environmental and affective factors.

Localized Pain. Localized pain remains confined to its site of origin without radiation. Cutaneous hyperalgesia and hyperesthesia and deep tenderness can be present, but are also confined to the site of the disease. Examples of these are bursitis, tendinitis, and arthritis.

Projected (Transmitted or Transferred) Pain. Projected pain is perceived to be transmitted along the course of a nerve either with a segmental (dermatomal and sclerotomal) or a peripheral distribution, depending on the site of the lesion. Examples of projected pain with segmental distribution are the pain of radiculopathy caused by herpes zoster or other diseases involving the nerve root or nerve trunk before it divides into its major peripheral branches. Examples of projected pain with peripheral distribution include trigeminal neuralgia, brachial plexus neuralgia, and meralgia paresthetica.

Referred Pain. Referred pain is referred from a deep somatic or visceral structure to a distant region within the same segment, with or without hyperalgesia and hyperesthesia, deep tenderness, muscle spasm, and autonomic disturbances (see Chapter 9). No changes are seen, however, in the reflexes, and no muscle weakness or atrophy is present. This type of pain, the mechanisms of which are discussed in Chapter 9, is found in visceral disease and deep somatic disorders. In patients with this type of pain the segments involved are identified, and all somatic and visceral structures innervated by these segments are carefully examined for a pathologic process. Shoulder pain seen with a subphrenic abscess is an example of referred pain.

Reflex Sympathetic Pain. Reflex sympathetic pain does not conform to any segmental or peripheral nerve distribution or to any other recognizable pattern and is associated with hyperalgesia, hyperesthesia, and vasomotor and trophic changes. It is best exemplified by causalgia and other reflex sympathetic dystrophies. This type of pain has been relabeled *complex regional pain types I and II* to emphasize that the involvement of the sympathetic nervous system is neither required nor sufficient to explain the clinical syndromes (5).

Psychogenic Pain. The location and distribution of pain caused primarily by psychological or psychiatric disorders usually does not fit the normal neuroanatomic patterns. Examples include pain with glove or stocking distribution, pain involving the entire body, or various pains scattered all over the body. Although this is a commonly used label for pain without observable pathology, it certainly is not malingering or caused entirely by mysterious processes in the mind of the patient. Most often, this is pain behavior engendered by environmental factors. Other patients have myofascial pain syndromes that have been overlooked by their physicians. The

proper use of this diagnostic term requires positive findings that suggest that mental processes are the sole cause of the patient's complaints. It should not be a diagnosis of exclusion when no clear–cut physical findings explain the patient's symptoms. We have found that the label *psychogenic pain* is usually a sign that the physician does not like or believe the patient. Criteria such as those used in *Diagnostic and Statistical Manual* , fourth edition, are not well suited for the identification of patients who fit in this category. The reader should consult Chapter 26 for more discussion of this topic.

Quality. The quality of pain, as emphasized in Chapter 8 and Chapter 9, is a most important distinguishing characteristic because it indicates whether the causative factor is superficial or deep. Pain associated with a superficial lesion is usually sharp, burning, and well localized, whereas pain caused by deep somatic or visceral disease is dull, diffuse, and poorly localizable. Such assessment instruments as the McGill Pain Questionnaire can provide useful information about the qualities and intensity of the patient's pain.

Severity or Intensity. The severity or intensity of pain is another important characteristic. It is perhaps the most difficult aspect of pain to evaluate because it cannot be measured precisely (refer to Chapter 15 for a detailed discussion of the subject). Evaluation of the intensity of pain must rely on the patient's statements and on the examiner's ability to appraise the patient's personality and physical status. In the usual clinical setting, the patient is asked to rate the pain intensity on a 0 to 10 scale, 0 being no pain and 10 being the most severe or intolerable pain imaginable. As discussed in Chapter 15, others use descriptors such as *mild, moderate, severe, very severe* , and *excruciating* . A variety of psychometric tests have been developed to assess pain intensity and the sensory as well as affective components of pain (6).

Duration and Periodicity. The duration and other temporal characteristics of the pain are also determined because they suggest its mechanism, thus aiding the diagnosis. The patient should be asked whether the pain is continuous, intermittent, pulsatile, or characterized by a wavelike rise and fall in intensity because these factors are relevant. Determination of the length of the interval between painful episodes is important in aiding the diagnosis. In connection with these temporal factors, Lewis (7) suggested the use of a time– intensity curve (Fig. 12-1). The curve portrays the manner in which pain starts, the rapidity of its increase, the duration and smoothness at its height, and the manner of its decline. Pain can be experienced in various ways: as a brief flash, as in tic douloureux; in rhythmic pulses, as in inflammation of dental pulp or migraine; in longer and less rhythmic phases, as in intestinal colic; rising gradually or suddenly to a plateau that is maintained for a long period without any fluctuation before vanishing, as in angina pectoris or burns; and continuous but fluctuating in intensity, as in aches that arise from the musculature of the limbs. In addition to the time– intensity curve, the relations of the pain to the time of day, week, or season, weather conditions, and emotional stress or environmental cues also provide important information.

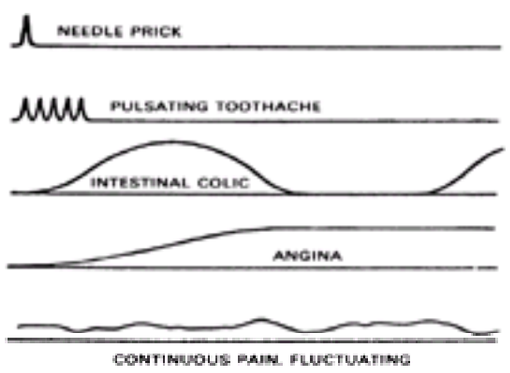


Figure 12-1. Time–intensity curve of various well–known pains. (From Lewis T. *Pain*. New York: Macmillan, 1942:176.)

General Outline of the History

The history of the pain, as for all clinical histories, usually begins with obtaining demographic data (if not already available), including the patient's name, address, sex, age, marital status, occupation, race, nationality, and religion. This demographic information may be collected by a written survey vehicle that the patient completes before the interview with the physician. A statement of the patient's major or presenting complaint is then obtained, which in this case is pain. This is followed by a description of the symptoms and course of the present illness, with a chronologic account of its development. This type of information gathering can be facilitated by using a standardized form that the patient completes before the physician interview, but such a form is never adequate for the full understanding of the patient's history.

History of the Pain

Pain at Onset. Detailed information should be obtained regarding the precise date of onset and the circumstances contributing to the causation of the pain. The location and distribution, quality, intensity or severity, and duration of the first pain should be ascertained. The type of onset, gradual or sudden, should be determined. If the pain was motion related, patients should be asked to demonstrate the position they were in and the action they were performing when the pain first occurred. For example, if the patient gives a history of onset of pain during a lifting maneuver, it should be ascertained whether the pain occurred during bending or raising of the trunk. Was the pain localized, or was it distributed along a limb? Was it shooting and sharp or dull and aching pain? How long did the pain last at the time of onset? Was the patient able to continue activities that day or was the pain immediately disabling? If the injury was job related, determining the interpersonal relations in the work setting at the time, as interpreted by the patient, is important. In addition, the patient should be questioned regarding any associated sensory (e.g., numbness), motor, or autonomic disturbances at the time the pain was first noticed. The patient should be questioned about the treatment received at the time of onset of pain and its effect.

Pain during the Interval. Detailed information about the course of the pain during the interval between the onset and time of evaluation is of great diagnostic value. Did the pain get better or worse with time? Did the location and spread change or remain the same? Were the quality, severity, and temporal characteristics of the pain and associated disturbance modified during the interval? It is essential to obtain detailed and precise data about the diagnostic and therapeutic procedures that have been carried out and the results achieved. It must be carefully and precisely determined whether the pain after surgery or any other therapy was the same as the pain before the procedures. Iatrogenic complications caused by inappropriate procedures add to the pain and suffering of many patients. For example, multiple abdominal surgeries, whether properly indicated for diagnosed organic disease or carried out under pressure of the patient's complaint of persistent pain, can lead to the formation of more adhesions and thus more pain. Every operation or diagnostic study carries with it a message that there may be a “broken part” causing the pain and may further increase the patient's somatic preoccupation and complaint of pain. In other cases, chronic use of medication over a long period can produce unwanted physical and psychological side effects.

Special care should be exercised early in the interview to determine whether the patient takes significant amounts of medication. Some chronic pain patients are confused and have impaired memories because of drug–induced cognitive defects. If such is the case, the patient should be placed on a detoxification program (see Chapter 16 and Chapter 18) before a diagnostic evaluation is continued and completed.

Present Pain. The patient should be asked to describe in detail the quality, site, distribution, intensity, and temporal characteristics of the pain at the time of evaluation and to indicate whether any of these factors has changed since the onset or during the interval. The patient is then asked what factors aggravate the pain, relieve the pain, and have no effect on the pain. Also, the patient should be asked what effect emotional disturbances, movement of the part, exercise, local pressure, heat or cold, coughing, sneezing, straining, and deep breathing have on the severity, quality, and distribution of the pain. The physician should be especially sensitive to the patient's description of the present pain and record it. If the patient describes the pain in unusually colorful terms that make no anatomic sense or implies some external and unusual causative factor, the likelihood of the pain resulting from a pathologic lesion decreases. Such phrases as “fishhooks in the mouth,” “red hot poker,” or pain “traveling down the leg and jumping to the opposite knee” should alert the physician to expect significant affective and environmental factors in the maintenance of the patient's pain. When the pain is constant and does not fluctuate with any physical or emotional activity, it is again more probable that a structural lesion is not the primary cause of the patient's complaint. Another clue that a specific lesion is unlikely to be found is when the patient states that the pain levels are always 10 out of 10.

Detailed information should be obtained about the effect of the pain on the patient's activities, the amount of time the patient is up and about (up time), and the amount of time the patient spends sitting or lying down (down time) while awake. This type of information is best elicited through the use of a 2–week diary in which

the patient records the physical activities, medication taken, and intensity of the pain during each waking hour. It is also important to obtain information on the effect of pain on sleep. Does the pain make it difficult to fall asleep? Does the pain awaken the patient from a sound sleep? (This subject is discussed in more detail in Chapter 16 and Chapter 18).

Elicitation of this part of the history, in which similar questions are asked repeatedly, can tax the patient as well as the physician. Patients should be impressed with the importance of providing detailed information and repeatedly encouraged to sustain their efforts during this long and tedious part of the evaluation. The physician must allow ample time for these patients because they present complex medical, psychological, and social problems, often associated with multiple areas of pathology.

Past Medical History. The past medical history is especially important in the evaluation of the patient with chronic pain in regard to developing the therapeutic strategy and predicting the outcome. The general health of the patient before the onset of the pain is elicited and recorded, followed by a history of past illnesses, operations, and accidents or injuries sustained, with the date and nature of each, period of disability, and sequelae (3). If the patient's health was normal before the onset of the pain problem, a return to normality can be expected with effective therapy. If, however, there have been many serious physical or psychological illnesses and the patient has been dependent on health care with a long history of health care–seeking behavior at times of stress, it is unrealistic to expect improvement beyond the previous best level of functioning.

In relating past illnesses and injuries, the patient might list only the serious or outstanding ones and fail to mention individual symptoms that could be of diagnostic significance (3). Consequently, detailed questioning is important to diagnose systemic and psychophysiologic illnesses. Symptoms referable to the various organs and systems can be investigated by inquiring about the function or dysfunction of the eyes, ears, nose, and throat, the cardiovascular and respiratory systems, the gastrointestinal and genitourinary systems, and other parts of the body that might be relevant to the present pain.

Family History. It is important to obtain information about the health of the parents and siblings and to determine whether they suffered frequent painful disorders and disability. Evidence exists that *modeling* is an important factor in the development of chronic pain behavior (8). Another relevant aspect of the family history is to ascertain tactfully and considerately whether the patient was the subject of childhood abuse. This factor also plays an important role in the development of chronic pain behavior (9).

Psychological and Psychosocial History. The psychological and psychosocial part of the history helps to determine the contribution of affective or environmental factors to the patient's pain complaint. Often, the factors generating pain at the onset of the disease are not those that are present when the patient is eventually seen by the pain specialist. Although this subject is discussed in detail in Chapter 16, some brief comments are made here for the sake of completeness.

A properly conducted psychological evaluation should delineate the contribution of environmental reinforcers to pain behaviors, the role of avoidance behaviors, and the presence of depression (10). A history of prior psychological disorders, substance abuse, vocational problems, family role models of chronic illness or pain, and recent stressors can enhance the understanding of the patient's current problem. Selection of the optimal treatment strategy also depends on this type of information.

The psychological assessment is based on a structured interview; the sequence of topics should be constructed so as to reduce the patient's restraints by first focusing on the pain problem (see previous discussion). Once this has been done, the physician can explore environmental and social issues and finally approach psychological, psychosocial, and marital or family problems.

The history of drug use is important from both the medical and psychological perspectives. It is best to start by questioning the use of prescription drugs, progressing to over-the–counter and alternative (e.g., herbal) medicines, and moving on to questions of smoking and alcohol use and illicit drugs. Physical dependence on drugs is relatively common in those in the chronic pain population, and alcohol dependence is a major problem.

The assessment of environmental reinforcers is a key part of the psychological assessment of the patient with a complex chronic pain syndrome. One must be cognizant of positive reinforcement (something good happens if the behavior is exhibited) and avoidance reinforcement (something bad is avoided by exhibiting the behavior). The latter is much more durable and less obvious to the patient and the observer. Areas to be assessed include activity changes, social reinforcers, avoidance behaviors, vocational factors, compensation–litigation issues, activation of recent stressors, family history, psychological dysfunction, and cognitive dysfunction.

One goal of psychological assessment is determination of the *cost* to the patient of the chronic pain problem. Not only should the economic factors be examined carefully, but also the social and personal costs of the patient's pain behavior. When the cost is high, the pain behavior is probably generated mainly by tissue damage or injury to the nervous system. Activity changes are an effective measure of the cost and reflect the probability that disuse and its secondary effects are contributing to the patient's pain. The conditioning of the heart and lungs reduces exercise tolerance and endurance, whereas decreased range of motion affects strength and speed in various body regions and can generate pain and prevent the patient from performing routine daily activities. Deactivation can also contribute to depression and isolation; social reinforcers can be lost because of decrease in activities.

Another area that requires scrutiny is clinical depression, a common condition in patients with chronic pain. It is necessary to do more than ask about the patient's mood. Other clues are persistent irritability, insomnia, chronic lassitude, weight gain or loss, and suicidal ideation. Depression is common in the elderly patient, but pain behavior also can be a cover–up for cognitive slippage in this age group (11).

Finally, it is important to carry out a vocational assessment, a topic discussed in detail in Chapter 17.

Physical Examination

Because pain is the most common symptom that causes the patient to seek medical counsel, physical examinations are most often performed to ascertain the cause of pain and its relation to an underlying disease. It might seem unnecessary, therefore, to emphasize the importance of such an examination, but those managing pain syndromes sometimes focus their whole attention on the pain without further inquiry. Because pain in general and chronic pain in particular have widespread effects (as emphasized in Chapter 10), an appraisal of the general physical, neurologic, musculoskeletal, and mental status of the patient must be done if a proper diagnosis is to be made. The physical examination is also important in establishing the physician's standing and competence in technical medical matters to the patient. In addition, it emphasizes that the physician has a high degree of concern for this particular patient and that the patient's complaints are taken seriously.

The physical examination of the chronic pain patient is often a demanding and lengthy process. It involves not only a general physical examination, but also more careful neurologic and musculoskeletal studies than are indicated for most other types of medical patients. Clinical assessment of the patient's functional abilities is also required, which is usually a tiring procedure for the patient and invariably involves maneuvers that exacerbate the pain. If the patient appears to be fatigued after obtaining the lengthy history it might be advisable to carry out a superficial preliminary examination and to postpone a more definitive study to a later date.

General Physical Examination

The general appearance of the patient is noted. The observations made during taking of the history are correlated with those made after the patient has disrobed. Any outward manifestations of pain should be noted in particular. The appearance and color of the skin, distribution of fat and hair, evidence of weight loss, emaciation, weakness, abnormal attitudes, contractions, contractures or deformities, atrophies or hypertrophies, enlarged glands, and presence of vasomotor or trophic changes are important points to observe and record. One should observe the posture of the patient and note the presence of lordosis, scoliosis, kyphosis, rounded shoulders, ptotic abdomen, flat feet, and if one shoulder or hip is lower than the other.

The facial expression and presence of flushing or paleness, sweating, pupillary dilatation, tears, tremors, muscular tension, or the appearance of anxiety, fear, or depression are important manifestations of pain, which should be noted. The gait is ascertained by having the (disrobed) patient walk in a straight line, backward, sideways, and on the toes and heels. The temperature, pulse, respiratory rate, blood pressure, height, and weight of the patient are recorded.

The skin and mucous membranes should be examined and their appearance, color, temperature, consistency, texture, elasticity, and any abnormalities noted. Nails of the patient whose history suggests a diagnosis of a complex regional pain syndrome, formerly called *reflex sympathetic dystrophy* , should be closely examined, with particular attention paid to texture, smoothness, and presence of fissures. The hair of such patients should also be examined in regard to amount, distribution, and

color and particularly to texture, because changes of this feature are a common manifestation of complex regional pain syndrome.

Examination of the Painful Region

After this general inspection, the specific region of the pain complaint is examined. This is done before proceeding with the rest of the physical examination because the patient expects the investigation to begin in the area in which the discomfort is located. Some patients feel resentful when the initial examination involves areas other than the painful region. The examination consists of inspection, palpation, and percussion, and sometimes auscultation of the region.

Inspection. Inspection of the area provides definitive data that can be correlated with the story given by the patient and with the information obtained by palpation, percussion, and special tests (3). The appearance and color of the skin overlying the painful area are observed closely and note is made of trophic manifestations, hypertrichosis, hyperhidrosis, cyanosis or flushing, cutis anserina (*goose flesh*), and visible evidence of muscle spasm. Gunn and Milbrandt (12) point out that presence of cutis anserina is a common manifestation of autonomic dysfunction caused by damage to nerve roots or to formed nerves during their exit through the intervertebral foramina, resulting in denervation supersensitivity (Fig. 12-2). Gunn and Milbrandt (12) emphasized that this manifestation is seen immediately when the patient undresses and cool air plays on the exposed skin, provoking the pilomotor effect in the dermatomes of the affected segmental level, and further stated that it is essential to watch the patient undress, examining the skin carefully because the reflex might be present only briefly. They believe that this pilomotor reflex can be reinforced or induced by firm digital pressure over any tender motor point within the affected segment (12).

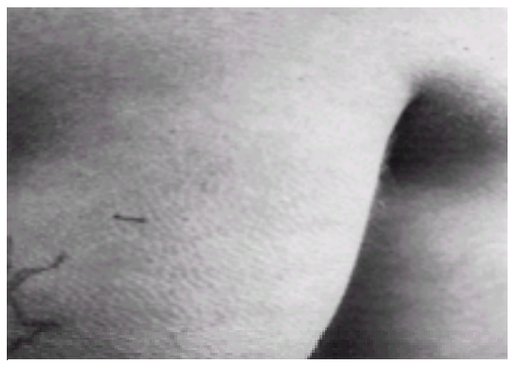


Figure 12-2. A readily seen signal of neuropathy affecting the autonomic system is an isolated patch of *goose bumps* created by a super-sensitive pilomotor reflex responding to exposure while undressing. Here it appears locally at the shoulder and arm, indicating trouble related to segments C-5 and C-6.

Palpation. Palpation of the region provides further information about the pain. Deep tenderness is best elicited by digital palpation, using the middle finger to exert firm deep pressure on the painful site. The area of tenderness is mapped out, and the neural segments involved are ascertained. If any doubt regarding the existence of a pathologic basis for the pain patient's complaint is present, the findings can be confirmed or discounted by repeated palpation, approaching the region from a different direction each time. If this is done while the patient is distracted, evocation of pain in the same region is some indication of a pathologic process. During palpation of the region, these evocations of pain should be correlated with subjective (symptoms) and objective (signs) manifestations of the painful disorder, and a determination made of whether any discrepancy exists between them. Subjective pain behavior includes grimacing, groaning, shouting, writhing, and other verbal and nonverbal expressions. The degree of such subjective behavior expected for a particular condition varies greatly with the cultural and ethnic backgrounds of the patient; writhing and groaning on the part of an ordinarily stoic individual can signify a more noxious condition than the same behavior from a customarily flamboyant person. Likewise, such behavior can be more marked in an anxious or depressed person with a given condition than in someone without these emotional problems. Objective signs associated with some painful conditions are those that are not wholly under the voluntary control of the patient, and include manifestations of autonomic discharge such as sweating, flushing, tachycardia, elevated blood pressure, and muscle spasm.

In patients with a pathologic process, palpation provides not only a qualitative reaction but also quantitative data proportionate to the stimulus used. Therefore, the response of the patient to palpation of the opposite symmetric nonpainful side when it is palpated in exactly the same manner should be noted. This also provides important information regarding the sensitivity of the patient to noxious and nonnoxious stimuli, as well as information about the sensitivity of the painful region.

To determine whether the tenderness and pain provoked by palpation are caused wholly or in part by overlying skin allodynia, hyperalgesia, or hyperesthesia, the brush test, pinch test, pinprick test, and scratch test are used. The brush test consists of lightly stroking the skin with a cotton wisp or something similar; the report of pain indicates allodynia and is suggestive of spinal cord dysfunction. The pinch test consists simply of pinching the skin between the thumb and index finger, applying the pressure along close parallel lines beginning over the adjacent nonpainful area, and continuing over the painful part and then beyond to the farther asymptomatic area (Fig. 12-3). The pinprick and pin scratch tests are used similarly to examine superficial pain sensibility and are described in detail in connection with the neurologic examination (see following discussion). These procedures should also be carried out over the opposite and corresponding nonpainful areas as controls to obtain an index to the patient's response to stimuli, to show the patient what to expect, and to provide a subtle, subconscious basis of comparison when the affected side is examined. Response should be evaluated by noting any wincing, groaning, or voluntary complaint by the patient, or by the onset of reflex muscle spasm. The patient is asked only neutral and nonsuggestive questions. These tests should always be used as complementary procedures to maneuvers intended to elicit, reproduce, or evaluate pain and tenderness by percussion, jarring, or pounding, because such percussion tests are positive in the presence of cutaneous hyperesthesia, which contributes greatly to misdiagnosis if unrecognized. The presence of objective signs tends to suggest a significant organic or pathologic substrate underlying the patient's pain complaint, whereas excessive subjective signs in relation to objective signs tend to indicate a major psychological component to the patient's complaint but do not rule out underlying structural pathology.

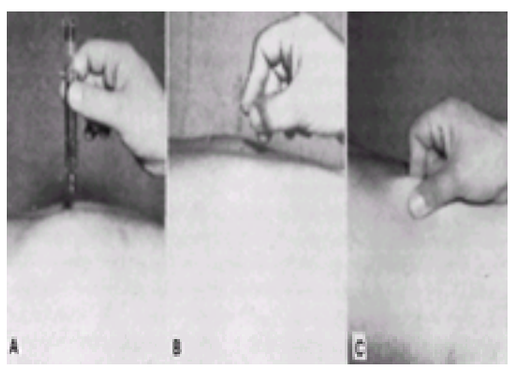


Figure 12-3. Techniques used for testing pain sensation. **A:** Pinprick test. **B:** Pin scratch test. **C:** Pinch test (see text).

Gunn and Milbrandt (12) mentioned two other objective signs that are manifestations of denervation sensitivity consequent to damage to spinal nerves that can be provoked by palpation. Both signs are manifestations of trophedema, in which a gradual thickening of subcutaneous tissue is seen and the overlying skin tends to be fissured and prone to heavy folds. This alteration in the quality of skin produces a *peau d'orange* effect similar to that described for malignant lumps of the female breast and is similarly accentuated when the skin is gently squeezed together or when the back is fully extended (Fig. 12-4). Trophedematous subcutaneous tissue has a boggy inelastic texture when rolled between the thumb and finger, distinguishable from subcutaneous fat. When a patch of skin and subcutaneous tissue a few centimeters in diameter is gently squeezed together it neatly forms a fold of flesh; in contrast, trophedematous tissue does not budge or finally yields altogether, with a sudden expanding movement similar to that of inflating a rubber raft. A second test that indicates trophedema is the matchstick test. Trophedema is nonpitting to digital pressure, but, when the end of a match is used, the indentation produced is clear–cut and persists for several minutes, distinctly longer than that seen over normal skin (Fig. 12-5). This test result may be positive and produce a deep indentation over an extensive area, or in milder cases it might only cause a slight

indentation over the skin overlying the tender motor points.

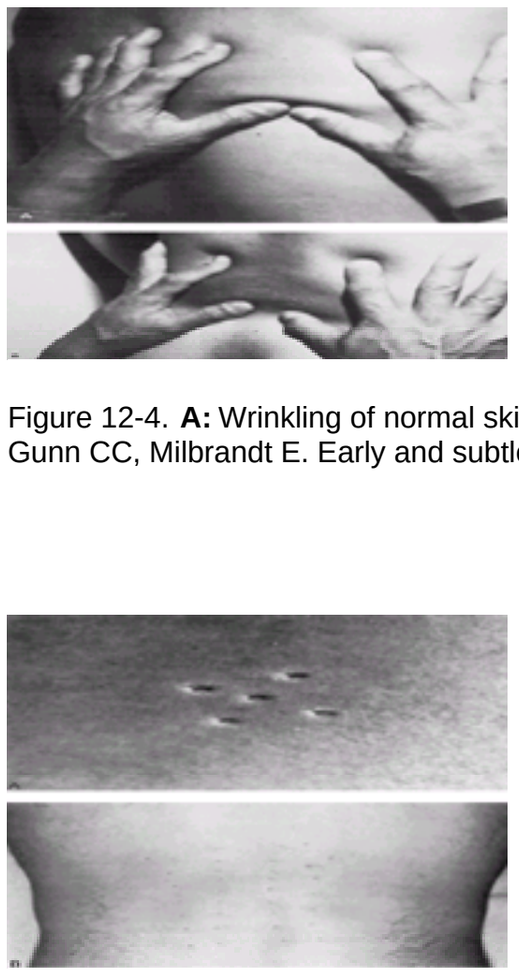


Figure 12-4. **A:** Wrinkling of normal skin when gently squeezed together. **B:** Trophedematous skin when gently squeezed together, the *peau d'orange* effect. (From Gunn CC, Milbrandt E. Early and subtle signs in low-back sprain. *Spine* 1978;3:267–281.)

Figure 12-5. **A:** The matchstick test. Trophedema may be found by pressing on the suspected area using the end of a matchstick. The deeper the indentations, and the longer they last (up to many minutes), the more severe the neuropathy. **B:** In low back pain, the matchstick test result is often positive over an area that is more widespread than the painful area. This patient had symptoms only in the low lumbar back, but indentations are seen at all lumbar levels, which indicates that even though pain is limited to one level the neuropathy is more extensive. (**A** from Gunn CC, Milbrandt E. Early and subtle signs in low–back sprain. *Spine* 1978;3:267–281.)

Other Procedures. In addition to these procedures, the pain is further evaluated by other methods. Factors or circumstances that reproduce, aggravate, or relieve the pain are determined, because they represent important and often conclusive evidence in making the diagnosis. One should particularly determine the effect on the part of pain of palpation, motion, application of heat and cold, exercise, walking up steps, deep breathing, coughing, sneezing, straining, digital pressure over the regional arteries, assumption of the prone, supine, and upright positions, and Valsalva's maneuver. In Bonica's experience, the intravenous administration of small amounts (100 mg) of thiopental sodium provided insight into the intensity of the noxious stimulus in body structures. Whereas this amount normally causes patients to manifest uninhibited overreaction in the presence of severe noxious stimuli, patients in whom the pain has little or no nociceptive basis manifest complete relief. This is not the case, however, in patients with central pain, in whom small amounts of intravenous barbiturate provide relief, whereas larger doses of narcotics do not. This is discussed in detail in Chapter 23.

Examination of Other Regions

Like many other clinicians, we believe that in any but the most obvious and simple cases the rest of the examination should be done because it frequently reveals pertinent data that cannot be obtained otherwise. The head, neck, chest, abdomen, back, and extremities are carefully examined and evaluated, but because these are discussed in detail in the introductory chapters on pain in various body regions, and because they are well known, they are not considered further here.

Neurologic Examination

After a complete history and general physical examination, which must be considered to comprise the cornerstone of the diagnostic evaluation of the patient with a pain complaint, a neurologic examination is carried out. In this section we present a screening neurologic examination that should be performed on all patients. A detailed examination of selected aspects of the nervous system relevant to specific regional pain syndromes is discussed in the introductory chapter to the various regional pain syndromes in Part IV of this book. A more detailed discussion of the examination of the nervous system can be found in works by De Jong (3) and by Wilkins and Rengachary (13). A discussion of the anatomy of the peripheral somatic and autonomic nervous systems is presented in Chapter 8, which contains illustrations of the dermatomes and sclerotomes.

Screening Neurologic Examination

A minimum neurologic examination should be performed on every new patient without regard to the region or type of pain. It takes only a few minutes to perform such a screening neurologic examination and is just as essential as auscultation of the heart and lungs and usually more valuable in the assessment of the patient with pain. It requires only the following simple instruments: clean safety pin, cotton applicator stick, tuning fork (128 or 256 cps), reflex hammer, and ophthalmoscope–otoscope. It is easiest for the examiner to have a clear-cut system and to follow the same routine whenever a patient is evaluated. The following procedure has worked effectively for us, but alternate schemes are certainly equally valid (Table 12-1). The patient should be comfortably seated on an examination table clad only in underwear or a loosely fitted gown.

Nerve or central nervous system location	Function tested
Cranial nerves	
II (optic)	Visual acuity and fields
III (oculomotor)	Extraocular muscles
IV (trochlear)	Pupillary constriction
VI (abducens)	Ocular movement
Cervical sympathetic	Pupillary dilatation
V (trigeminal)	Sensation in face and anterior two-thirds of the scalp; corneal reflexes; muscles of mastication
VII (facial)	Facial muscles
VIII (auditory)	Hearing, balance
IX (glossopharyngeal)	Gag and swallow
X (vagus)	Gag and swallow
XI (accessory)	Shoulder shrug, head rotation
XII (hypoglossal)	Tongue movement
Funduscopic examination	Retina, papilledema, vascular changes
Spinal nerves	
Sensation	Light touch, pinprick, vibration, position sense
Motor	Reflexes, strength, gross atrophy
Coordination	Gait, Romberg's test, rapid alternating movements, finger-to-nose testing
Cerebrum	Orientation, language, memory, mood

TABLE 12-1. Screening neurologic examination

Function of Cranial Nerves. The neurologic examination commences with the assessment of cranial nerve function. Visual acuity is easily tested by either a pocket

Snellen's chart or reading newsprint; visual fields can be evaluated by confrontation and contrasting the perimeters of the patient's fields to those of the examiner. This is a rather crude method, and significant visual field deficits can be missed unless formal perimetry is obtained (cranial nerve II). The functions of extraocular muscles and pupillary activity are then assessed. Conjugate gaze should be observed in the cardinal positions, nystagmus should be noted as present or absent, and the pupillary size, equality, and response to accommodation should be ascertained (cranial nerves III, IV, and VI).

The trigeminal nerve is quickly evaluated by checking corneal reflexes, facial light touch and pinprick sensation, and jaw deviation on opening (cranial nerve V). Facial muscles are assessed by observing facial tone and symmetry with grimace and eye closure (cranial nerve VII). Hearing is assessed by placing a watch adjacent to each ear or by rubbing the fingers together (cranial nerve VIII). The gag reflex is checked along with elevation of the uvula by placing an applicator stick lightly in each tonsillar region (cranial nerves IX and X). Strength in the trapezius and sternocleidomastoideus muscles is evaluated by shrugging the shoulders and by turning the head against resistance (cranial nerve XI). Tongue protrusion and lateral movements complete the screening examinations of the cranial nerves (cranial nerve XII). After the cranial nerves have been assessed, the ophthalmoscope is used to evaluate pupillary light reaction and the fundi. Every patient deserves funduscopic examination.

Function of Spinal Nerves and Neuraxis. Sensation over the trunk and extremities is rapidly screened; a tuning fork quickly tests vibration sense in each hand and foot. A cotton wisp is used to ascertain light touch in each extremity and over the chest and abdomen; a safety pin, discarded after use on each patient (or sterilized), is used to test pinprick sensation distally and proximally on each extremity and bilaterally over the chest and abdomen. The superficial abdominal and cremasteric reflexes are ascertained by stroking the abdominal and mesial thigh skin with the pin.

Screening motor evaluation is simple and rapid: gross strength in flexors and extensors at shoulders, elbows, wrists, finger abduction and adduction, and thumb opposition are determined, as is that of hips, knees, and ankles in flexion and extension. Myotactic reflexes at triceps, biceps, quadriceps (knee jerks), and gastrocnemius (ankle jerks) are readily tested with a reflex hammer (Fig. 12-6). Reflexes should be graded on a 0 to 4+ scale, and strength on a 0 to 5 scale. The presence or absence of Babinski's responses must be noted. (The innervation of specific muscles is presented in Table 8-2 in Chapter 8.)

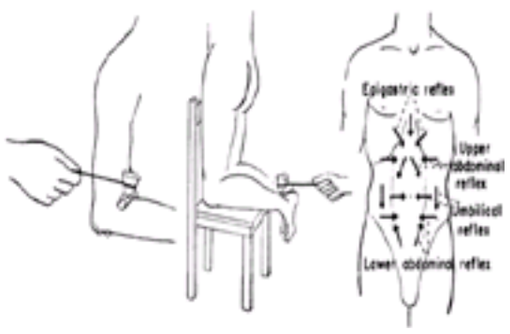


Figure 12-6. Methods for eliciting reflexes. **A:** Biceps reflex. **B:** Achilles tendon reflex. **C:** Sites for eliciting superficial abdominal reflexes.

Coordination can be assessed by observing sitting and standing balance, gait, finger-to–nose testing, and rapid alternating movements such as hand clapping or placing the thumb on the other fingertips. Romberg's test (standing with feet together and eyes closed) completes this segment of the examination.

Sympathetic Function. Sympathetic function is examined by measuring vasomotor, sudomotor, and pilomotor activities. Sudomotor function can be evaluated by observing the patient's sweating pattern in a warm room, by performing a formal sweat test, by means of an infrared skin temperature probe, or by measuring cutaneous resistance, because the major factor contributing to lowered skin resistance is the presence of sweat.

Pilomotor function can be examined by observing for the development of cutis anserina (goose flesh) on gentle stroking, tickling, or scratching of the skin. Vasomotor function can be evaluated by observing the flushing of the skin associated with vasodilatation and the pallor caused by vasoconstriction. The limb can be heated or cooled with the application of hot or cold towels and the skin inspected visually. Alternatively, one can measure skin temperature directly by application of a thermocouple to the skin and comparing temperature in one part of the body with that of the homologous region. Vasomotor activity also can be evaluated by more sophisticated technology, such as a laser Doppler device, which actually measures skin capillary blood flow. Measurement of skin temperature by ultraviolet photography or liquid crystal thermography devices are other highly sensitive methods of determining regional differences in skin blood flow. Thermography has no direct link to diagnosis or magnitude of pain.

Cerebral Function. The final portion of the screening examination is determination of cerebral function, which has already been evaluated to some degree during the history and physical examination. It is customary to assess orientation to time, place and person, recent and remote memory, parietal sensory function (e.g., right–left orientation, two–point discrimination, double simultaneous stimulation), language function, and purposeful coordinated movements. The assessment of mood is also essential (see Chapter 16).

The use of terms to describe sensory abnormalities is often confusing (6). *Hypesthesia* denotes decreased sensation or increased threshold for sensation, anesthesia denotes no sensation, hypalgesia means decreased response to a painful stimulus, and analgesia denotes absence of pain on noxious stimulation (see Chapter 2). *Paresthesia* means the report of an abnormal sensation, either spontaneous or evoked by stimulation; patients often use such terms as pins and needles. *Dysesthesia* denotes an unpleasant abnormal sensation. *Allodynia* is a term used for pain caused by a nonnoxious sensation, as in complex regional pain syndromes types I and II. It usually characterizes central hyperactivity after a nerve injury. *Hyperpathia* is a painful syndrome characterized by increased reaction to a stimulus, especially a repetitive stimulus, and an increased pain threshold. It is common to have paresthesia and dysesthesia after nerve injury; any combination of sensory aberrations can be found.

General Principles

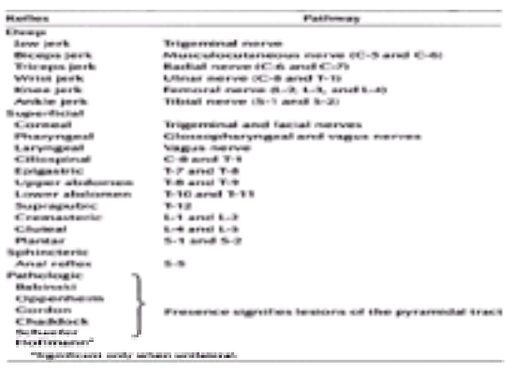
The question of what is normal or abnormal is often difficult for those who are not neurologists or neurosurgeons. A few general principles are helpful.

Except for strength, the right and left sides of the body should be identical on neurologic testing. Depending on occupation and physical condition, the dominant side of the body can be stronger (especially the grip) and the muscles have more bulk. Any asymmetry of sensation or reflex is abnormal.

A wide latitude of normal is seen on myotactic reflex testing (Table 12-2); absent reflexes are never normal, nor is clonus (4+ reflex). Table 12-3 lists the commonly tested superficial and deep reflexes and their segmental and peripheral nerve supplies.

Grade	Observation
0	Absent reflex
Trace	Reflex present only with facilitation
1+ to 3+	Normal range; asymmetry is significant
4+	Pathologically hyperactive; sustained clonus is present

TABLE 12-2. Grading of reflexes



Reflex	Pathway
Deep	
Jaw jerk	Trigeminal nerve
Biceps jerk	Musculocutaneous nerve (C-5 and C-6)
Triceps jerk	Radial nerve (C-6 and C-7)
Wrist jerk	Ulnar nerve (C-8 and T-1)
Knee jerk	Femoral nerve (L-2, L-3, and L-4)
Ankle jerk	Tibial nerve (S-1 and S-2)
Superficial	
Corneal	Trigeminal and facial nerves
Pharyngeal	Glossopharyngeal and vagus nerves
Laryngeal	Vagus nerve
Ciliospinal	C-8 and T-1
Epigastric	T-7 and T-8
Upper abdomen	T-8 and T-9
Lower abdomen	T-10 and T-11
Suprapubic	T-12
Cremasteric	L-1 and L-2
Gluteal	L-4 and L-5
Plantar	S-1 and S-2
Sphincteric	
Anal reflex	S-5
Pathologic	
Babinski	Presence signifies lesions of the pyramidal tract
Oppenheim	
Gordon	
Chaddock	
Schaefer	
Hoffmann*	

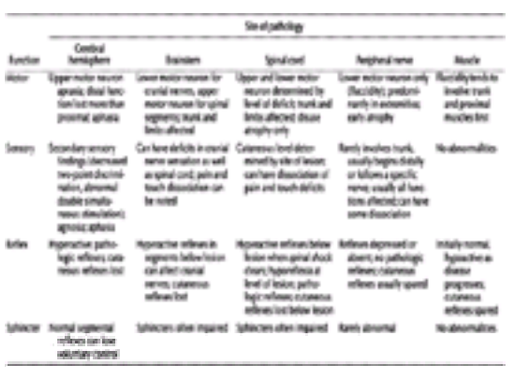
*Significant only when unilateral.

TABLE 12-3. Reflexes and their pathways

Neurologic deficits rarely end at the exact midline and tend to follow the territories of peripheral nerves, dermatomes, or hemibody. Deficits that are exactly horizontal are not likely to have a structural corollary: On the trunk, the dermatomes slope downward from the posterior midline. Somatically preoccupied patients often report profound sensory loss without apparent loss of function (e.g., the patient who claims to have an anesthetic hand can hold a pencil or grasp a key). Another sign of hysterical deficit is a sensory change that ends abruptly at the midline. Because nerves overlap somewhat from either side, such a finding is incompatible with a structural neurologic deficit. Similarly, the report that a vibrating tuning fork cannot be perceived on one side of the sternum or calvarium is a sign of hysterical sensory loss.

Patients with significant drug or alcohol intake often give bizarre neurologic examination results that revert to normal when drug effects abate. This is particularly true of the chronic pain patient receiving multiple narcotic and sedative-hypnotic drugs.

It is essential to describe the examination findings in writing before attempting to localize the lesion(s) and guess at the pathology. If the examiner has written down the findings, others can use the information to aid in establishing diagnosis and therapy. Variations in nerve territories and dermatomes occur. The patterns depicted in Chapter 8 are the most common, but by no means absolute, findings. Every physician should be able to characterize the findings on history and physical examination as suggesting a disease of muscle, peripheral nerve, spinal cord, brainstem, or cerebral hemispheres (Table 12-4).



Function	Site of pathology: Cerebral hemisphere	Brainstem	Spinal cord	Peripheral nerve	Muscle
Motor	Upper motor neuron signs; dorsal horn cell more than proximal aphasia	Lower motor neuron for cranial nerves, upper motor neuron for spinal segments; trunk and limbs affected	Upper and lower motor neuron determined by level of deficit; trunk and limbs affected; disuse atrophy only	Lower motor neuron only (flaccidity); predominantly in extremities; early atrophy	Fasciculity; tends to involve trunk and proximal muscles first
Sensory	Secondary sensory findings; observed two-point discrimination, abnormal double simultaneous stimulation; agnosia; aphasia	Can have deficits in cranial nerve sensation as well as spinal cord; pain and touch dissociation can be noted	Cutaneous level determined by site of lesion; can have dissociation of pain and touch deficits	Rarely involves trunk, usually begins distally or follows a specific nerve; usually all functions affected; can have some dissociation	No abnormalities
Reflex	Hyperactive pathologic reflexes; cutaneous reflexes lost	Hyperactive reflexes in segments below lesion can affect cranial nerves; cutaneous reflexes lost	Hyperactive reflexes below lesion when spinal shock clears; hyperreflexia at level of lesion; pathologic reflexes; cutaneous reflexes lost below lesion	Reflexes depressed or absent; no pathologic reflexes; cutaneous reflexes usually spared	Initially normal; hyporeactive as disease progresses; cutaneous reflexes spared
Sphincter	Normal segmental reflexes can lose voluntary control	Sphincters often impaired	Sphincters often impaired	Rarely abnormal	No abnormalities

TABLE 12-4. Clinical manifestations of neurologic pain

Common diseases are more likely than rare ones. Most patients do not harbor more than one active disease affecting the nervous system.

Sensory examination requires a high level of patient attention and cooperation if the results are to be meaningful. All sensory responses are subjective; it is only the recognition of a familiar pattern that causes the examiner to believe that some sensory findings are objective. It is wise to perform the sensory examination before the patient is fatigued. The patient must be alert, relaxed, and informed if the results are to be significant. Patients in severe pain often cannot give an accurate sensory examination.

Examination of the Musculoskeletal System

A screening examination of the musculoskeletal system indicates or excludes functional impairment of this system. If an abnormality is revealed, a more detailed examination of the region is indicated, as discussed in various chapters in Part IV. The occupation of the patient may be highly relevant to the complaint of pain (14). The following is the sequence recommended by Clawson and associates (15) and incorporates strategies described by Waddell and Turk (16).

The patient must disrobe with the exception of underwear. The patient is inspected from the front, side, and back. Attention is directed to body type and posture, abnormal spinal curvature, deviation from normal alignment of the limbs, and other deformities, such as abnormalities of the foot arches and toes. It is important to note the symmetry of the shoulders, the overall symmetry of the arms, elbows, forearms, and hands, and the symmetry of the pelvis, thighs, knees, legs, and feet.

Inspection of the patient from the side permits assessment of the degree of cervical lordosis, dorsal kyphosis, and lumbar lordosis, whereas inspection from behind the patient permits determination of lateral curvature if the spine is in balance. The term *balance* describes the patient with scoliosis whose head is in line over the middle of the pelvis. If the head is lateral to the middle of the pelvis, progressive deformity can be expected.

The patient is then asked to walk in the examining room or large area outside the examining room, and any abnormal forward or backward movements or other irregularities of gait are noted. In addition, the arm swing, stride length, and the push off and heel strike should be observed and recorded. As the patient walks toward the examiner, abnormal side–to–side movements of the trunk and other abnormal movements are looked for. The patient should next be asked to walk on the toes, holding the examiner's hand if necessary for stabilization to test the motor function of the S–1 nerve. The patient is then asked to walk on the heel (again holding the examiner's hand if necessary), a maneuver that assesses the innervation of the dorsal flexors of the ankle, which are innervated primarily by the L–5 nerve.

In examining the muscular system one should observe the strength and power, tone, volume, and contour of the muscle, noting any atrophies, hypertrophies, or signs of irritability such as fibrillary twitching (2,10,14). For proper evaluation of muscle strength it is necessary to know the normal function of each muscle or muscle group as well as the peripheral and segmental nerve supplies (see Table 8-2). The following brief outline can be used as a preliminary or screening appraisal of the strength and function of important muscle groups. These can be evaluated by observing their motions and comparing them with those of the opposite side, or by applying passive resistance to the movement or having the patient resist the examiner's active attempt to move fixed parts.

Neck Muscles

The range of motion of the neck is measured in full flexion, extension of the neck, and lateral and rotatory movement of the head. Normal function requires that in full

flexion the chin touch the chest and in extension the examiner's finger be trapped between the occiput and the C–7 spinous process, whereas rotation should be more than 70 degrees from the sagittal plane (Fig. 12-7; see also Chapter 55 and Fig. 55-1, Fig. 55-2, and Fig. 55-3).

Figure 12-7. Maneuvers for testing muscle function. **A:** Lateral flexors of the neck. **B:** Biceps brachii. **C:** Flexors of the thigh.

Upper Extremity

The function of the muscle of the upper extremity is evaluated by testing the hand grip, raising of the shoulder, abduction of the arms, flexion, extension, supination, and pronation of the forearm, flexion and extension of the wrist, abduction and adduction of the fingers, and touching the fifth finger with the thumb. The patient is asked to stretch out the arms horizontally in front of the body with the fingers spread to check symmetry. The function of the palmar intrinsic muscles is assessed by the examiner's attempt to press the fingers together against the patient's resistance to the movement.

The patient is asked to abduct the arms fully, placing the palms together above the head. Normally the arms touch the ears, with the head and cervical spine in the vertical position. This maneuver tests the functional range of the shoulder, acromioclavicular, and sternoclavicular joints as well as the functional range of lateral rotation of the humerus.

The patient is asked to bring the arms to the side, rotate the humerus medially, and move the forearm up to place the thumb on the back between the scapulae. Normally, the hand should reach the level of the inferior angle of the scapula. The range of movement of the elbow is also tested in this manner and painful affliction, deformities, and muscle weaknesses are thus revealed. The symmetry of the two sides should be ascertained.

The patient must grasp the index and long fingers of each of the examiner's hands. The examiner attempts to move the patient's arms in all directions (up, down, laterally, and medially) while maximum resistance is offered by the patient. This is an effective, although somewhat crude, method of assessing strength of the muscles of the hand, wrist, and elbow, and even of the shoulder. Pain in any of the joints in the upper limb can result in failure to offer resistance.

Trunk Muscles

The muscles of the trunk are evaluated by asking the patient to take a deep breath, get up from a recumbent to a sitting position with the arms folded on the chest, and to flex, extend, and rotate the trunk. The patient is asked to bend forward and attempt to touch the floor while keeping the knees extended. The presence or absence of scoliosis is best demonstrated in this position. The lumbar spine is further tested by having the patient extend as far back as possible, and the thoracic spine is tested by performing rotation movements. To test rotation of the spine effectively, the physician stabilizes the pelvis and asks the patient to rotate as far as possible. The greatest range of rotation occurs in the thoracic spine.

Lower Extremity

The function of the muscles of the lower extremity is evaluated by having the patient step up, raise the leg, and rise from a squat position; resistance abduction and adduction of each limb as well as flexion and extension of the leg, foot, and toes are tested also. Having the patient squat with the feet flat on the floor and the knees and hips fully flexed is an excellent way to assess the function of all major joints of the lower limbs. Watching the manner in which the patient gets down and up provides an accurate impression of the muscle power of the limbs.

The history and physical examination are the cornerstones of diagnosis for the patient with acute or chronic pain. Those who have not perfected the art of obtaining both of these are at peril in the management of the patient with pain.

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CHAPTER 13

Electrodiagnostic Evaluation of Acute and Chronic Pain Syndromes

Walter C. Stolov

The common association of somatosensory and somatomotor systems involvement in acute and chronic pain syndromes requires a complete evaluation of these systems to establish an accurate diagnosis. Although the clinical history and the physical examination can suggest involvement, and structural radiologic examinations can imply damage to the central and peripheral somatic systems, only direct examination can confirm or deny that function has been lost or impaired.

This chapter reviews the reactions of nerve and muscle to injury and defines the terminology likely to be present in a report of an electrodiagnostic medicine examination. The subsequent discussion includes common entrapment syndromes, radicular syndromes, traumatic syndromes, systemic syndromes, and functional syndromes that are associated with pain and are electrodiagnostically analyzable. For more detailed discussions, several standard texts can be consulted (1,2,3,4 and 5).

BASIC CONSIDERATIONS

The reactions of nerve and muscle to injury are relatively small in number. Their detection and localization, however, can be elusive if the electrodiagnostic medicine examination is inappropriately designed. In electrocardiography or electroencephalography, in which electrode placements are standard, the test can be administered by a technician and the data later interpreted by the appropriate physician. Electrodiagnostic examinations, on the other hand, are highly individualized, and rarely are any two examinations alike. In electrodiagnosis, the plan of the examination is more important than the interpretation of the results. An incomplete study whose results are properly interpreted can lead to incorrect diagnoses, and subsequently inappropriate treatment.

For illustration, consider an electrodiagnostic study of a patient with hand pain and numbness in which the distal motor and sensory conduction of the median nerve from the wrist to the hand is found to be prolonged. A conclusion that a carpal tunnel syndrome is present would indeed be consistent with the data. It might be incorrect, however, because of the failure to include a more proximal examination of median nerve conduction and a study of other nerves to ensure that a peripheral neuropathy is not present. In the latter, distal segments of all the peripheral nerves are likely to show slowed conduction, no more or less so than the median nerve, making a carpal tunnel syndrome diagnosis highly unlikely.

The electrodiagnostician has a large number of muscles that can be studied and peripheral nerves and segments of peripheral nerves that can be examined. Also, many central evoked responses can be studied on peripheral stimulation to provide information on spinal cord and cerebral function. Central responses from stimulation of all the peripheral nerves can be examined.

In view of the number of available elements that can be tested, an effective electrodiagnostic examination must first begin with a plan of what should be examined, based on historic and examination data. Specifically, the initial plan is based on the following items:

- The differential diagnostic possibilities of concern to the referring physician
- The additional diagnostic possibilities suggested to the electrodiagnostician after review of the patient
- Knowledge of the anatomy and physiology of the neuromuscular and musculoskeletal systems
- The electrodiagnostic findings expected from the various reactions of nerve and muscle to injury and disease
- The effect that premorbid disease or trauma can have in modifying results
- The level of sophistication of equipment available

Furthermore, examination plans are not static. They can be modified as the examination evolves, for results initially obtained might suggest additional diagnostic possibilities not previously considered.

For the electrodiagnostic examination to contribute effectively to the analysis of acute and chronic pain syndromes, it must be done by a physician trained in electrodiagnostic medicine, not only for the interpretation but also for the actual performance of the examination, because of the on-the-spot judgments that need to be made.

A useful measure of competence is successful passage of the rigorous written, practical, and oral examinations of the American Board of Electrodiagnostic Medicine, admittance to which requires documented training.

The current terminology for an electrodiagnostic study is an *electrodiagnostic medicine examination (or consultation)*. *Electromyography* (EMG) has in part become a generic term inclusive of all the available studies, as has the term *electromyographer* to describe the examiner. Strictly speaking, electromyography refers exclusively to needle electrode evaluation of action potentials seen in skeletal muscles at rest and on volition, and hence parallels the definition of electrocardiography and electroencephalography. The terms *electrodiagnostic medicine* and *clinical neurophysiology* are mostly used to describe the laboratories in which electrodiagnostic medicine examinations are performed. The glossary prepared by the American Association of Electrodiagnostic Medicine, which is adhered to by many, has standardized the definition of many terms that are used (6). For the purposes of this review, the following definitions are used:

EMG refers to direct examination of skeletal muscle via needle electrodes.

Nerve conduction studies (NCS) refers to examination of conduction along peripheral motor and sensory nerves and plexuses.

Late responses refers to potentials evoked by peripheral stimulations that evaluate spinal cord or near spinal cord function.

Somatosensory-evoked potential (SEP) *responses* refers to potentials detected over the spinal cord, brain, or both on peripheral nerve stimulation, and on stimulation of the skin over dermatomal sites and over peripheral sensory nerve fields.

Reactions of Nerve and Muscle to Injury

Nerve

Peripheral motor, sensory, or mixed nerves contain myelinated and unmyelinated fibers. NCS largely focuses on the faster-conducting myelinated fiber, and of this group the larger diameter, fastest-conducting fibers are the ones most easily studied. Conduction in such fibers can be slowed or blocked through disease or injury to

the myelin, the axon, or both. The effect of disease or trauma can be local or diffuse, and in any given whole nerve it can affect some or all of the fibers.

A primary demyelinating process can include a denuding at the nodes of Ranvier, a diffuse or relatively localized thinning of the myelin with a resultant decrease in diameter, or a more general disorganization, again diffuse or segmental. An intussusception of the myelin at the nodes can occur also. Thinning and denuding result in a slowing of conduction and can progress to induce a reversible or irreversible conduction block. When remyelination occurs, the new myelin is thinner and the nodes of Ranvier end up closer together, resulting in slow conduction even if the causal factor has been removed.

In a reversible conduction block, a natural or electrically induced action potential (e.g., traveling wave of depolarization) fails to continue through the region of damage. In such a situation, stimulation of the nerve fiber on the distal side of the block results in conduction. The axon in this example remains relatively healthy, hence the myelinated fiber distal to the block remains unaffected. Such a block remains reversible if it is possible to remove the cause of demyelination or axolemma damage and permit the healing process to take place. If the primary demyelinating process progresses to cause axonal degeneration, the block becomes irreversible. On the distal side of such a lesion, wallerian degeneration occurs and the distal nerve segment can no longer conduct impulses until axonal regrowth occurs (Fig. 13-1).

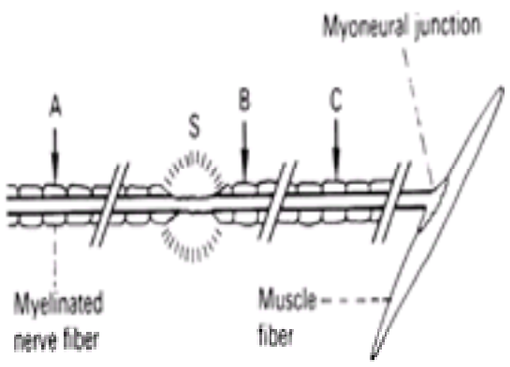

Figure 13-1. Schematic of nerve-muscle complex illustrating conduction block. In the normal situation, stimulation at point A elicits a response at points B and C and at the muscle. If a reversible block (neurapraxia) exists at site S, then stimulation at point A will not elicit a response at points B or C or at the muscle. Stimulation at point B, however, elicits a response at point C and at the muscle because the nerve segment distal to the block is still capable of conduction. If an irreversible block has developed at site S, stimulation at point B will not produce a response at point or at the muscle because the nerve segment distal to the block has undergone wallerian degeneration.

Primary axonal disease can also induce slowing of conduction through a reduction in fiber diameter. Slowing so induced is of a lesser magnitude than the slowing induced by a demyelinating process. Axonal disease is generally associated with metabolic disorders and diffusely affects the entire length of the axon (e.g., diabetes, uremia, folate deficiency). Primary axonal disease is not associated with reversible conduction blocks. The most distal segment of the axon, however, can progress to degeneration. The greater the distance from the nourishing cell body, the more likely degeneration and loss of conduction. Hence, the signs are more pronounced distally. Primary axonal disease can induce secondary demyelination. It is therefore not uncommon, in processes that are primarily demyelinating or primarily axonal, for the electrodiagnostic medicine examination to exhibit features of both.

Processes that affect nerve fibers, be they axonal or myelin in origin, and their associated slowing or conduction blocks can occur in the central and peripheral somatomotor and somatosensory systems and, hence, are potentially uncoverable through the electrodiagnostic medicine examination. Axon and myelin disease processes do not affect all nerve fibers equally. Because electrodiagnostic NCS or SEP studies involve examination of the responses from whole nerve stimulation, the results reflect the collective effect of all the nerve fibers in the group.

Muscle

The response of skeletal muscle to injury of primary importance in EMG and NCS is that which occurs secondary to denervation.

The muscle fibers in skeletal muscle are organized into motor units, the number of muscle fibers per unit ranging from approximately 10 in the extraocular muscles to 2,000 in the large muscles of the leg. A motor unit is made up of a single anterior horn cell, its axon, the terminal branches of the axon, and the muscle fibers that are attached to each terminal branch via the myoneural junction (Fig. 13-2). Thus, in a healthy motor unit, depolarization of an anterior horn cell on volition or of an axon through external stimulation results in an ultimate depolarization and contraction of all the muscle fibers of the motor unit to which it is connected. The wave of depolarization successfully travels in all the branches of the axon and induces, through acetyl choline release at the myoneural junction, a depolarization wave along the individual muscle fibers of the unit to initiate the excitation-contraction coupling process.

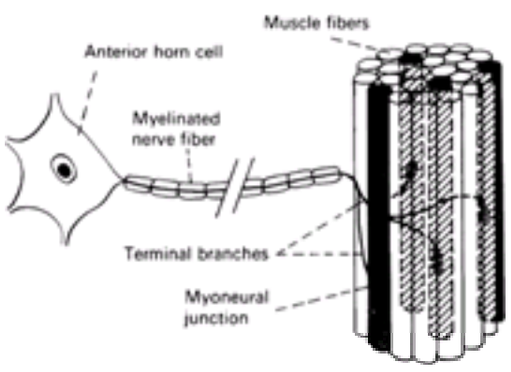

Figure 13-2. The components of a single motor unit. The muscle fibers of the unit (*shaded*) are interspersed among fibers of other units. The myoneural junctions are located approximately midway between the ends of the muscle fibers.

The muscle fibers of a single unit in the muscle are interspersed among muscle fibers of other units; in a large muscle a single unit can have a cross-sectional diameter of as much as a centimeter. Furthermore, the number of fibers per unit within a single whole muscle is variable and obeys the size principle. Smaller anterior horn cells have thinner axons, fewer terminal branches, and a smaller number of muscle fibers per unit, and they are more easily depolarized on volition. When externally stimulated, however, the thicker axons of the larger anterior horn cells have lower thresholds and are depolarizable at lower current strengths than are the thinner axons of the smaller anterior horn cells.

At rest, although nerve and muscle cell membranes are polarized, the positive charge densities on the outside and the negative charge densities on the inside contribute no net electric field externally. Hence, the environment of the cells is electrically silent at rest. Should a depolarization wave be induced, either on volition or by external stimulation, the uniformity of the charge densities is disrupted and measurable electric fields are induced. The resultant action potentials are detectable along the nerve or in the muscle.

When denervation occurs, the reaction of the muscle fibers is the same regardless of cause. The myoneural junction degenerates, and the entire muscle fiber membrane becomes sensitive to acetylcholine. The membrane potential becomes unstable and circulating acetylcholine can spontaneously depolarize the cell at any site along its membrane, inducing the excitation-contraction coupling process and causing the fiber to fibrillate. The time course from axon death to fibrillation varies. It depends on the distance from the site of axon death to the target muscle. The longer the nerve fiber, the more *nutrition* it contains and the longer it takes for

fibrillation to occur. In the case of damage to a nerve root, for example, the paraspinal muscles may begin to fibrillate 7 to 10 days after axonal death, whereas the distal muscles of the lower extremities may not fibrillate for 17 to 21 days.

Muscle fiber atrophy commences with denervation and degeneration of the denervated fibers may begin to occur within a year. Some fibers last a long time in an atrophic, denervated state.

In primary muscle disease (e.g., dystrophy, myositis), a relatively similar response occurs in diseased muscle fiber. Muscle fiber membranes become unstable and can spontaneously fibrillate. Furthermore, in primary muscle disease the number of muscle fibers per motor unit decreases as individual muscle fibers die. This occurs without damage to the nerve fiber, although in myositis the inflammatory process can also involve distal terminal nerve branches.

Nerve-Muscle Repair

If axon death occurs through, for example, compression, blunt trauma, or section, the distal segment of the nerve degenerates. Regeneration of this segment can occur as long as the cell body remains intact and connective tissue continuity is preserved or can be fashioned. In compression or blunt trauma, the endoneurial connective tissue sheath of the axon is preserved, providing a conduit for regrowth of the nerve fiber. In nerve rupture or clean sections, surgical approximation of the proximal and distal nerve ends or a nerve graft is required to permit reinnervation to occur.

After axon interruption, it takes approximately 1 month for the cell body to prepare itself for the regrowth process. The regrowth rate itself varies from 2.5 to 4.0 cm per month (7). Rules of thumb that can be used are a millimeter per day, a centimeter per week, or an inch per month. In motor nerves, an additional month may be required to establish new myoneural junctions once the regenerating nerve fiber has reached its muscle. Using these time frames for cell body preparation, linear growth, myoneural junction recovery, and the length of the nerve segment of interest, one can predict when reinnervation will occur if regeneration is possible. When muscle fibers are reinnervated, they cease to fibrillate and are subsequently restored to their more normal diameter.

Regenerating nerve is of small diameter and at first either nonmyelinated or only partially myelinated. It therefore conducts impulses more slowly than a normal fiber. Even when fully mature, a normal conduction velocity might not be achieved and the size of the new motor unit might not equal that of the preinjury state. Furthermore, the number of muscle fibers reinnervated depends in part on how far away the target muscle is from the initial site of axon interruption. Some muscle fiber degeneration may have occurred by the time regenerating nerve fibers reach the muscle. Reinnervated muscle fibers of a unit are more likely to be clumped together rather than dispersed and intermingled with fibers from other units.

Denervated muscle fibers do not last indefinitely if not reinnervated. Some begin to disintegrate at 1 year, and most, if not all, are gone by 3 years and the muscle becomes fibrotic. Even if regrowing axons arrive, no muscle fibers exist to innervate.

A second healing process, collateral reinnervation, also exists; it occurs much more rapidly if not all of the motor nerve fibers to a given muscle are damaged. In collateral reinnervation, undamaged motor nerves are signaled, in an as yet unknown way, to grow new branches, which then seek to reinnervate the denervated muscle fibers. This process yields an increase in the number of motor fibers per motor unit and can be detected within 1 month of injury.

Electrodiagnostic Medicine Examination and Its Terminology

All of the reactions to injury of nerve and muscle and the healing processes described are detectable in an appropriately designed electrodiagnostic medicine examination. The electrical equivalents of these processes have a specific vocabulary. The data displayed in the electrodiagnostic report are described in specific ways. This section defines and clarifies how the EMG, NCS, late response studies, and SEP examinations reveal injuries to nerve and muscle. It must be remembered that the descriptions of the reactions of nerve and muscle to injury were expressed in terms of single nerve fibers, single muscle fibers, and motor units. In the electrodiagnostic medicine examination, whole nerves or whole muscles are studied and explored. The responses that are seen in these examinations can thus be a mix of normality and abnormality because disease or trauma affects individual nerve fibers, muscle fibers, motor units, and central nervous system elements in variable and incomplete ways.

Electromyography

In an EMG, individual skeletal muscles are explored with monopolar or concentric needle electrodes to detect membrane instability, alterations in the character of the individual motor units, and the number of motor units (i.e., volitionally active motor neurons) in the muscles. The examination begins with the skeletal muscle at rest.

Insertion activity refers to the responses obtained when the needle is moved in small increments through the muscle (Fig. 13-3A). The slicing of the needle through the muscle cells disturbs the uniform charge density distributions, producing local currents and recordable high-frequency short-lived potential changes. This activity is sustained during the movement and ends when needle movement ceases. If many muscle fibers have already degenerated, insertion activity is reduced because a reduced number of viable, excitable cells are present. If membrane instability is present, either from denervation, primary muscle disease, or, in some instances, upper motor neuron disease, two additional responses are seen after needle movement ceases: positive sharp waves and fibrillation potentials, representing abnormal spontaneous single muscle fiber discharges.

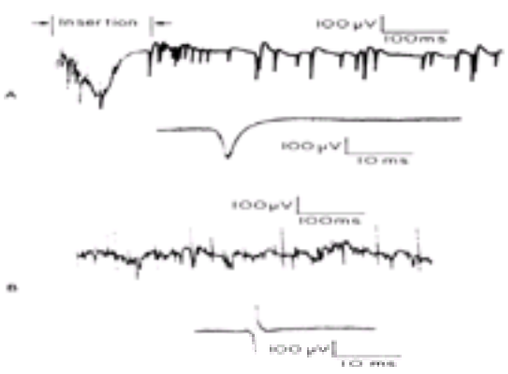

Figure 13-3. Involuntary needle electromyography action potentials at rest (negative values are above the baseline). **A:** Insertion potentials are seen in the first 250 ms of this record. They were produced as the needle sliced through muscle fibers. The insertion potentials are followed by a train of positive sharp waves. A single positive sharp wave is also illustrated. **B:** Fibrillation potentials. The sharp spikes are seen against a background of positive sharp waves. A single fibrillation potential is also illustrated.

Positive sharp waves are electrical potentials that persist following cessation of needle movement (see Fig. 13-3A). These potentials have characteristics that make them easily recognizable. They occur in muscle fibers whose membranes are partially unstable but usually not so unstable that they fibrillate spontaneously. Needle injury of these partially unstable fibers induces a regular frequency discharge, which generally progressively decreases in amplitude, slows in frequency, and ultimately ceases. Positive sharp waves in a progressive lesion are generally followed in several weeks by the second sign of membrane instability—namely, that associated with fibrillation.

Fibrillation potentials are seen in association with fully unstable muscle fiber membranes (Fig. 13-3B). These are single muscle fiber action potentials associated with spontaneous fibrillation. Fibrillation potentials are also easily recognizable and are distinguishable from positive sharp waves. They can also be triggered by needle movement as the local currents induced by movement depolarize nearby susceptible unstable fibers.

The amount of positive sharp wave and fibrillation potential activity is often graded from 1+ to 4+. This grading scale is nonlinear (e.g., 2+ does not mean there is twice as much damage when compared with a 1+ response). The amplitudes are also examined; if small (less than 100µV) they may reflect responses from atrophic fibers and suggest that the instability is chronic or at least of approximately 6 months' duration. Positive sharp waves and fibrillation potentials on recently diseased

muscle fibers are generally larger.

Fasciculation potentials are also examined for, with the patient at rest. They are involuntary discharges of whole motor units or parts of motor units and are neurogenic in origin. Discharge frequencies are irregular and range from approximately 3 to 20 per minute. Their size and shape resemble those of motor unit action potentials (MUAPs; described in this section). The site of the initial depolarization can be at the anterior horn cell (e.g., amyotrophic lateral sclerosis) or along the axon from an external irritation (e.g., compression, trauma).

Complex repetitive discharges can also be seen with the patient at rest. They are involuntary and highly localized. The action potentials associated with these discharges are of high frequency, and the discharges are continuous, usually of a collection of individual muscle fibers depolarized by ephaptic excitation. They start and stop abruptly and are nonspecific in that they can be seen in chronic or old neurogenic or myopathic disease.

After examining the muscle with the patient at rest, the examiner asks the patient to perform weak volitional activity and examines the action potentials produced. The MUAPs are the responses seen when all of the muscle fibers of a particular motor unit are depolarized in a relatively synchronous manner. These potentials are much larger in amplitude and longer in duration than positive sharp waves and fibrillation potentials (Fig. 13-4). With weak contraction, the motor units initially recruited are the type I motor units, which discharge at rates of 5 to 10 per second. Normal MUAPs are usually triphasic in character. In stronger contractions, type II motor units are recruited. These have larger amplitudes and longer durations. Maximum contractions in a normal muscle reveal a discharge of many MUAPs, which flood the screen. The development of this recruitment pattern is carefully examined. In abnormal states, a reduced recruitment pattern on maximum contraction can be caused by a loss of lower motor neurons or loss of upper motor neuron drive. Functional and pain inhibition also produces a reduced recruitment pattern. The patterns for each are different and easily recognizable by the experienced examiner.

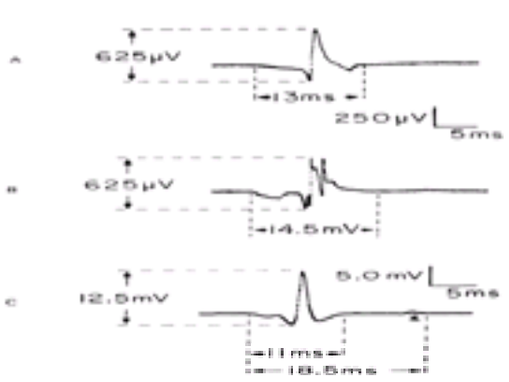

Figure 13-4. Samples of motor unit action potentials recorded by monopolar needle electrodes. **A:** Normal triphasic wave. **B:** Polyphasic (eight phases) wave of longer duration and of similar amplitude. **C:** Large amplitude potential with a triphasic basic component and a small late component, a satellite potential (*). Note amplitude calibration in **C** compared with that in **A** and **B**.

In disease states, individual MUAPs can show decreases in amplitude and duration (e.g., a reduced number of muscle fibers per motor unit) or an increase in amplitude and duration (e.g., a greater than normal number of muscle fibers per motor unit) and excessive polyphasicity (see Fig. 13-4B). Polyphasicity can be caused by a reduction in the number of muscle fibers in a motor unit, as is common in primary muscle disease, or loss of synchronous discharge of the muscle fibers because of increased variability in conduction velocities of terminal nerve branches. Polyphasic potentials are usually associated with a decrease in the amplitude and duration of the MUAP. Small-amplitude, short- or long-duration polyphasic MUAPs also occur after nerve fiber regeneration. Polyphasicity with normal or larger amplitude MUAPs is seen in association with collateral reinnervation processes. MUAP amplitude, duration, phasicity, and the recruitment pattern on volition can be measured quantitatively or qualitatively and assessed for increases or decreases with regard to normal expectations.

Single-fiber electromyography (SFEMG) is a specialized technique not usually useful in the analysis of pain syndromes. The response of a single muscle fiber from a single motor unit, discharging during a weak volitional contraction, is examined with a special needle. If the needle picks up a synchronous discharge from other individual muscle fibers of the same unit within the region of the needle, an increased density of fibers within the unit can be surmised and suggests a state of reinnervation (8).

Peripheral Nerve Conduction Studies

Motor Nerves. External stimulation of a mixed or pure motor nerve induces contraction of the target muscle it serves. If the electrical stimulus is supramaximal (e.g., all motor neurons stimulated), then all motor units within the target muscle are depolarized relatively synchronously. A biphasic potential (M wave) is usually recorded if the recording surface electrode is placed over the motor point of the muscle (Fig. 13-5).

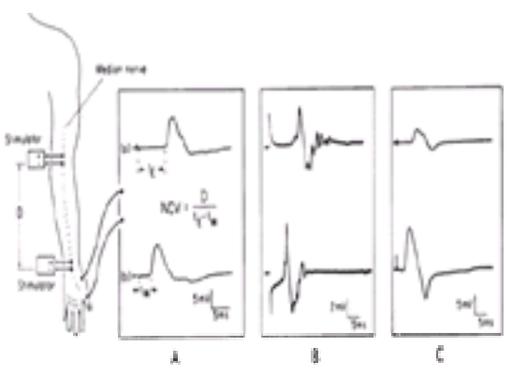

Figure 13-5. Schematic representation of the determination of median nerve motor conduction velocity (NCV) from the elbow to wrist, illustrating three different types of responses: t_E and t_W are the latencies from time of stimulation to time of onset of response of the muscle, from elbow and wrist stimulation, respectively. *D* is the distance between the two points of stimulation. **A:** A normal response. Note that the amplitude of the response from the elbow and wrist stimulations are essentially equal, as are the wave shapes. **B:** Temporal dispersion associated with segmental demyelination. Note the smaller amplitude of the response on elbow stimulation compared with stimulation at the wrist as well as distortion of the wave when the elbow response is compared with the wrist response. **C:** Partial neurapraxic block between the two points of stimulation. Note the much smaller response from elbow stimulation without distortion of wave form when compared with the response on wrist stimulation.

The *latency* of the response is the length of time from initiation of the stimulation to the beginning of the muscle response. It is a measure of the speed of the fastest conducting motor neurons in the nerve bundle. If the nerve can be accessed in at least two places, both proximal to the target muscle, the velocity of conduction of the fastest motor neurons in the nerve segment between the points of stimulation can be obtained. A subtraction of the distal latency from the proximal latency removes any need to consider neuromuscular transition time.

Conduction velocity is determined by dividing the distance between the two sites by the difference in the two latencies, because this difference reflects the time the depolarization wave, induced at the proximal site, took to reach the distal site of stimulation. The *amplitude* of the response is a measure of the number of motor units present within the target muscle. The *duration* of the response reflects the range of velocities of all the motor neurons in the nerve bundle to the muscle. The amplitude of the response from the more proximal stimulation is generally smaller than that obtained from the more distal stimulation, whereas the duration is generally longer. In a normal situation, an amplitude decrease of approximately 20% or a duration increase of approximately 15% occurs because of normal temporal

dispersion. The dispersion occurs because, as the distance traveled increases, the differential time of arrival of the fastest and the slowest nerve fibers at the muscle from the proximal stimulation is greater than that from the more distal stimulation.

An increase in temporal dispersion occurs when the range of values of the slowest to the fastest fiber has increased through segmental demyelination (see Fig. 13-5B). This increase is manifested by a larger decrease in amplitude, a longer duration, and a wave shape distortion when the response to proximal stimulation is compared with the response to distal stimulation. A large decrease in amplitude, when one is comparing the proximal with the distal stimulation without an associated increase in duration, usually means that at least a partial neurapraxia exists between the two points of stimulation (see Fig. 13-5C). Some of the fibers, stimulated proximally, are blocked, and the depolarization wave does not reach the muscle.

Sensory Nerves. The parameters of latency, amplitude, and conduction velocity and the possibility of neurapraxia pertain also to peripheral sensory nerve examination (Fig. 13-6). Action potential duration is usually not useful. Conduction velocity determination requires only a single stimulation because the evoked response is sampled at a point over the nerve itself. Velocity is determined by dividing the distance between the site of stimulation and the location of the sampling electrode by the latency of the response. Amplitudes reflect the number of viable sensory fibers capable of conducting impulses from the stimulating to the sampling electrode. Sensory nerves can be measured orthodromically (in the direction they physiologically conduct) or antidromically. The amplitudes of the sensory-evoked responses are on the order of magnitude of microvolts and are more difficult to measure than those evoked over muscle on motor nerve stimulation, which are usually on the order of magnitude of millivolts.

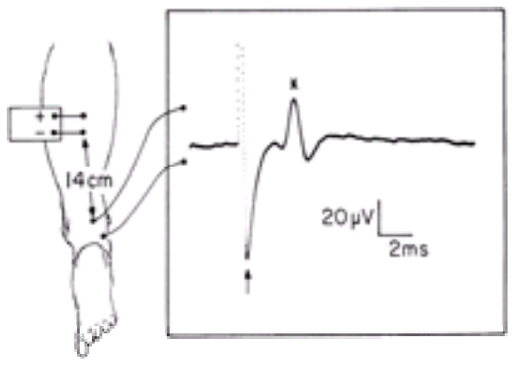

Figure 13-6. Sural nerve sensory conduction. The nerve was stimulated at the calf, and the antidromic response was sampled behind the lateral malleolus. The stimulus artifact is indicated by the arrow, and the sensory-evoked response by the asterisk. The distance between the cathode of the stimulator and the response electrode was 14 cm. The latency of the response measured to the peak of the negative deflection was 3.4 milliseconds, yielding a conduction velocity of 41 m/sec.

Late Responses. Peripheral stimulation also produces peripheral responses that are evoked after the action potential induced on peripheral stimulation has traveled to the spinal cord or brainstem and returned. Some are true reflexes (e.g., H wave, tibial sensory–tibial motor; blink reflex, cranial V–VII; bulbocavernosus reflex, pudendal sensory–pudendal motor), whereas others (F waves) are not.

The H-wave response is the electrical equivalent of the ankle deep tendon reflex, when the tibial nerve is stimulated. It is a monosynaptic reflex response. Stimulation is performed over the tibial nerve behind the knee via current selections that favor stimulation of the group 1A afferent fibers in the nerve. The synapse occurs in the spinal cord at approximately the level of the S-1 root entry zone. After the synapse, discharge of the anterior horn cells induces the motor response (Fig. 13-7A). The response is sampled via surface electrodes over the gastrocnemius-soleus group. The latency of the response, as modified by age, length, or both, and the amplitude are the parameters examined. Disease or injury anywhere along the pathway (tibial nerve, S-1 root, vertebral canal, spinal cord) induces abnormalities.

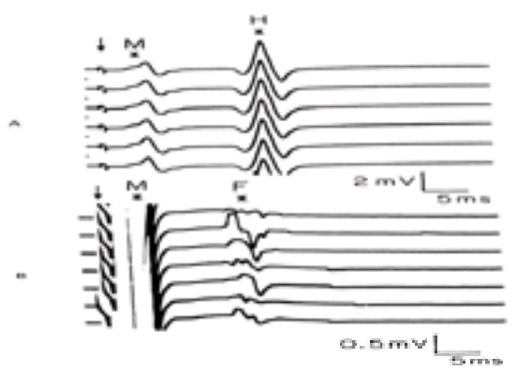

Figure 13-7. Late responses. **A:** H-wave response on tibial nerve stimulation in the popliteal fossa recording over the gastrocnemius-soleus. The M wave is the direct response. The H wave, which results from stimulation of sensory nerve fibers (i.e., group 1A) of the tibial nerve, represents the motor response after a single synapse in the spinal cord. **B:** Median nerve F-wave response on stimulation of the median nerve at the wrist. The M wave represents the direct response of the thenar muscle. The delayed F wave results from antidromic motor nerve fiber stimulation. No synapse occurs at the cord. The small F-wave response represents the small number of anterior horn cells that induced a rebound discharge.

Femoral nerve stimulation at the inguinal ligament can also elicit a monosynaptic reflex response over the quadriceps muscle. This response is the electrical equivalent of the patellar tendon reflex. No other H-wave responses are generally obtainable in the lower extremity and no consistently useful ones are obtainable in the upper extremity, except perhaps in infants.

The F wave is more universally obtainable (Fig. 13-7B). Although it requires adequate spinal cord function as well as peripheral nerve function, it is not a reflex. It is obtained on stimulation of motor nerves antidromically and supramaximally. Approximately 5% of the motor neuron fibers so stimulated *rebound*, and, as a result, a late second response is sampled over the target muscle of the nerve (2). The first response seen is the M wave. Rebound occurs because, for some of the anterior horn cells, the axon hillock refractory period ends before the local currents in the spinal cord have dissipated, and an orthodromic discharge down the motor nerve occurs. Each simulation usually induces the F-wave response in a different 5% of the motor neurons. As a result, latency and amplitude of the F-wave response vary (see Fig. 13-7B). Latency is also related to age and limb length. Usually, the shortest latency response in a set of stimulations is the parameter selected, although average latency, the range between the fastest and the slowest F-wave responses and the number of F waves elicited in a train of stimulus (penetrance) can also be useful.

F waves can be elicited from all mixed or motor nerve stimulations in the upper or lower extremity. When late responses are combined with peripheral studies, the most proximal portions of the nerve or its spinal roots can be evaluated. Appropriate combinations of F- and M-wave latency measurements are also capable of measuring the conduction velocity of fibers carrying the F- wave response (2). For the H and the F wave, the spinal cord *turnaround time* is estimated at 1 millisecond.

Somatosensory-Evoked Potentials

Measurement of SEPs permits analysis of syndromes that induce, in particular, proximal sensory nerve or root or spinal cord impairment. SEPs are evoked on peripheral stimulation of mixed or pure sensory nerves and on skin (dermatomal) stimulation (9,10,11 and 12). The responses evoked can be tracked to the somatosensory cortex. From periphery to brain, three synapses occur for the primary arrival short-latency response on sensory or mixed nerve stimulation: at the nucleus cuneatus and nucleus gracilis in the mid medulla, in the thalamus, and at the cortex. The predominant pathway in the spinal cord is in the posterior columns (13,14). The amplitude of the responses is small, on the order of magnitude of a few or even less than 1 μV. Single stimulations are not detectable at the regions

where responses are usually sampled because of biologic and electrical noise interference. Special averaging equipment is necessary to cancel out the noise and extract the signal. As many as 100 to 2,000 responses might need to be averaged. Supramaximal stimulation is not necessary, and most patients can be studied.

Responses to stimulation of lower extremity sensory or mixed nerves are sampled over the leg, the lumbar spine root entry zones, and at the scalp (Fig. 13-8) (15,16). In the upper extremity, Erb's point, the cervical spine, and the scalp areas are sampled (Fig. 13-9) (9,10,17,18). Dermatomal skin stimulation responses in the lower extremity or trunk are recorded at the scalp, and in the upper extremity they are also recordable as well at Erb's point and over the cervical spine (12,19).

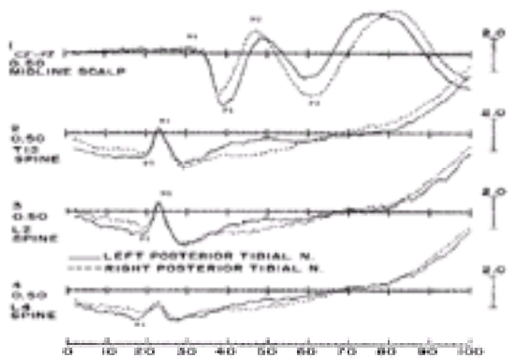

Figure 13-8. Normal somatosensory-evoked potential responses on tibial nerve (n.) stimulation at the ankle. The L-4, L-2, and T-12 responses were obtained with surface electrodes over the respective posterior spines with the reference electrode placed laterally. The scalp response occurred between the active surface electrode 2 cm behind the skull vertex (CZ') and a frontal reference (FZ). The amplitude calibrations on the right are in microvolts, and the time calibration is in milliseconds. The labels *N* and *P* refer to negative or positive peaks.

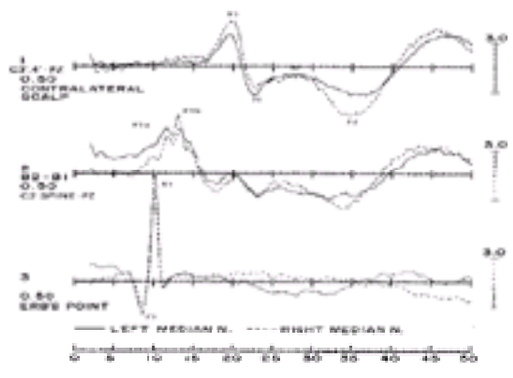

Figure 13-9. Normal somatosensory-evoked potential responses on stimulation of the median nerve at the wrist. The response at Erb's point is between a surface electrode at Erb's point on the ipsilateral side referred to the contralateral Erb's point. The second cervical spine response is between a surface electrode over the spinous process of C-2 and a reference electrode over the midfrontal area of the scalp (FZ). The contralateral scalp response is over the sensory cortex area of the parietal lobe (C_3 or C_4) referred to the frontal region (FZ).

The parameters measured include latencies and amplitudes, and, in particular, at the scalp, the configuration of the response. Sensory impairment in the periphery, in the plexuses, within the vertebral canal, in the spinal cord, and more proximally are detectable. Coupling of SEP results with those of peripheral studies and late-response examinations permits a more complete evaluation of the somatosensory system than peripheral studies alone.

Summary

The techniques described and the data they reveal permit a physiologic evaluation of the somatosensory and somatomotor systems. When abnormalities are seen on EMG, NCS, late responses, and SEP studies, the nature and location of the disease or injury process can be obtained. The results of the electrodiagnostic medicine examination alone, however, cannot reveal the cause of the damage to the system. Determination of the cause (e.g., tumor, trauma, degeneration, inflammation) requires the integration of the results of the electrodiagnostic medicine examination with the history, physical examination, and structural radiologic examinations, together with an understanding of the anatomy of the neuromusculoskeletal system and its variants.

CLINICAL SYNDROMES

The sections that follow indicate the electrodiagnostic abnormal groupings that permit the decision making necessary to suggest the presence or absence of entrapment, radiculopathy, trauma, systemic disease, and functional syndromes as possible causes of an acute or chronic pain complaint. Electrodiagnostic studies cannot, however, quantify pain, nor can they confirm that the neuromuscular abnormalities detected are causally related to the pain complaints. Therefore, it does not necessarily follow that elimination of the abnormalities eliminates the patients' complaints. At the end of each of the following sections, a case example is given to illustrate the application of the methods described.

Entrapment Syndromes

Entrapments involving mixed nerves are more likely to produce motor and sensory symptoms and physical examination signs, as well as motor and sensory electrodiagnostic abnormalities. For pure or relatively pure motor or sensory nerves, the abnormalities are likely to be respectively exclusive. In evaluating a patient for the possibility of entrapment, one must recognize that the sensory symptoms of pain or numbness do not occur exclusively in the referred territory of the sensory nerve. Entrapments can produce a vaguely described discomfort in areas more proximal to the exclusive distal distribution of the sensory innervation. Furthermore, because so- called pure motor nerves (e.g., no skin distributions) can carry muscle and joint afferents, entrapment of such nerves can also induce a deep diffuse discomfort.

Table 13-1 lists the more common nerve entrapments in the upper and lower extremities (20). The type of nerve (mixed, motor, or sensory) is included as well as the location of the entrapment.

Site	Nerve
Cervical rib	Lower trunk brachial plexus
Scalenus anticus	Lower trunk brachial plexus
Suprascapular notch	Suprascapular nerve
Quadrangular space (below glenohumeral joint)	Axillary nerve
Spiral groove of humerus	Radial nerve
Ligament of Struthers (above elbow)	Median nerve
Ulnar cubital tunnel (elbow)	Ulnar nerve
Pronator teres (forearm)	Median (anterior interosseus branch) nerve
Supinator (forearm)	Radial (posterior interosseus branch) nerve
Carpal tunnel (wrist)	Median nerve
Canal of Guyon (wrist)	Ulnar nerve
Hook of hamate (palm)	Ulnar (deep branch) nerve
Inguinal ligament	Lateral femoral cutaneous
Fibula head	Peroneal nerve
Above ankle	Superficial peroneal nerve
Tarsal tunnel (medial ankle)	Tibial nerve

TABLE 13-1. Sites of potential nerve entrapments

Entrapments that are chronic and not transient lend themselves best to electrodiagnostic approaches. Chronic entrapments can appear as relatively acute from a symptom point of view. Usually, a phase exists during which the entrapment is symptomatically silent. During the silent phase, fiber diameters can decrease as a result of the compression, without inducing a conduction block. Furthermore, even if conduction block occurs or axonal degeneration occurs, a certain magnitude of loss must occur before a patient's *ordinary activities* become impaired, be they motor or sensory, or before irritation of the nerve reaches a level sufficient to induce a noxious afferent stimulation from the site. In addition, the small fibers, particularly those carrying pain stimuli, are more resistant to compression.

Transient entrapments, in which a change in body position can relieve the pressure, are more difficult to detect electrodiagnostically. Testing in such cases can require that the study be performed when symptoms are occurring or can be induced.

The electrodiagnostic approach for evaluating entrapment is fairly similar from nerve to nerve. For motor nerves or motor components of mixed nerves, the following situations should be considered:

- If the nerve can be stimulated above and below the suspected site, and the evoked amplitude of its target muscle can be measured, a reduction in motor conduction velocity of the nerve segment containing the entrapment can be obtained. The reduced conduction velocity signifies fiber thinning through demyelination and remyelination. A reduced amplitude of the evoked response from the proximal stimulation, compared with the response obtained from the more distal stimulation, signifies a partial neurapraxia (see Fig. 13-5C). An increase in temporal dispersion can also occur.
- If the nerve can be stimulated above the suspected site but not distal to it, because of accessibility problems, then a latency measure from the time of stimulation to the time the motor-evoked response is obtained is compared with normal values or with the value obtained in the opposite extremity, in unilateral problems. A prolonged latency should result if the entrapment has been sufficient to result in fiber thinning. Again, amplitudes of the two sides can be compared.
- If the suspected site is too proximal to permit stimulation proximal to the site of entrapment, then examination of the F-wave response to the target muscle can be studied and compared with normal values or with that obtained with the opposite extremity, in unilateral problems.
- The target muscles of the suspected motor nerve must also be studied with needle EMG. If motor axon degeneration has occurred, membrane instability is seen, and on maximal volition, a reduced number of MUAPs is noted. Such a reduced recruitment also results from a partial neurapraxia, but if neurapraxia alone is present, no membrane instability is seen. If membrane instability is found, other muscles in the general region or area need to be studied, particularly when other underlying diseases might be present, to be certain that the membrane instability is unique to the nerve and to the entrapment in question. In addition, individual MUAPs can have abnormalities of amplitude, duration, and phasicity in chronic entrapment, secondary to collateral reinnervation.

For sensory nerves or sensory components of mixed nerves, similar stimulation techniques can be used:

- If antidromic stimulation can be delivered proximal to the site of the suspected entrapment and the sensory-evoked response can be sampled distal to the site, conduction velocities or latencies can be determined for evidence of conduction slowing. Amplitudes can be examined; if they are reduced, a conduction block or axonal degeneration is suggested. Orthodromic stimulation is also used.
- For entrapments involving sensory nerves that are too proximal to permit stimulation proximal to the site but can be stimulated orthodromically at a distal site, the SEP response can be examined and compared for latency to indicate slowing and for amplitude to indicate conduction block or axonal degeneration, with normal values or against contralateral responses in unilateral conditions.

Case Example

A 42-year-old woman with a 6-month history of progressive left arm and hand numbness was suspected of having either a C-7 radiculopathy or thoracic outlet syndrome. Numbness first appeared in the middle finger and subsequently ascended up the medial side to the axilla, with some sharp pain laterally. Symptoms at night made sleep difficult. Recently, the numbness was present during the day, and weakness in the left hand was increasing. Physical examination documented decreased grip strength. Strength was reduced in the biceps, triceps, and deltoid, probably from arm discomfort. Decreased light touch was present over the medial arm and forearm.

Needle EMG results of the muscles of the upper extremity, encompassing roots C-5 through T-1, including thenar and hypothenar intrinsics and cervical paraspinal muscles, were negative.

Conduction studies of the motor and sensory components of the median and ulnar nerves are shown in Table 13-2.

Nerve	Segment	Distal latency (ms)	Velocity (m/sec)	Amplitude (μV)
Left median motor	Elbow to wrist	4.2	52	8.5 M
Left median sensory	Wrist to digit 2	4.2	NA	46 D
Left median sensory	Wrist to digit 3	4.2	NA	36 D
Left ulnar sensory	Wrist to digit 5	3.2	NA	58 D
Left ulnar motor	Axilla to below elbow	NA	##	12.0 M
Left ulnar motor	Below elbow to wrist	2.8	45	12.5 M
Left ulnar F-wave	Wrist to spinal cord	26.8	##	NA
Left ulnar F-wave axillary loop	Axilla to spinal cord and back to axilla	11.8	NA	NA

NA, not applicable.

TABLE 13-2. Conduction studies of median and ulnar nerves

The normal needle EMG confirmed the absence of an active motor radiculopathy. The normal ulnar nerve motor conduction velocities, ulnar F-wave conduction velocity, axillary loop latency, and amplitude of the ulnar sensory-evoked response confirmed the absence of ulnar neuropathy, including at the thoracic outlet level. The prolonged median nerve sensory latency from the wrist to digits 2 and 3, compared with the normal ulnar sensory latency from the wrist to digit 5, all three of which were obtained over the same length (14 cm) of nerve, confirmed a left carpal tunnel syndrome. The median motor distal latency was also slightly prolonged, almost two standard deviations greater than normal. The smaller median sensory amplitudes, compared with that of the ulnar sensory amplitude, suggested median sensory axonal loss. Finally, the reduced conduction velocity of the median motor nerve, compared with the ulnar, suggested a retrograde distortion of the median motor nerves proximal to the carpal tunnel. The absence of membrane instability in the needle EMG examination of the thenar muscles confirmed that the carpal tunnel syndrome had not yet induced motor nerve axonal degeneration.

The patient had a surgical carpal tunnel release, and all symptoms cleared within 10 days (see Figure 13-10 for additional examples).

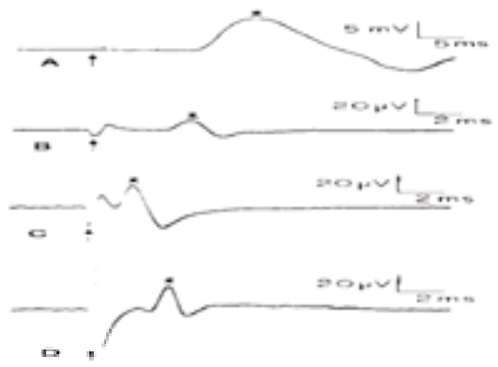

Figure 13-10. Carpal tunnel syndrome with sensory nerve neurapraxia. **A:** Thenar muscle evoked response (*asterisk*) on stimulation of the median nerve at the wrist proximal to the carpal tunnel at a standardized distance of 8 cm from the electrode over the thenar muscle. The latency of this response from the stimulus artifact (*arrow*) to the beginning of the response is 4.2 milliseconds (ms), which is on the slow side but within normal limits. **B:** Sensory response (*asterisk*) sampled at the index finger 14 cm distal to the point of stimulation of the median nerve proximal to the carpal tunnel. The latency of this response measured from the stimulus artifact (*arrow*) to the peak of the negative deflection (*asterisk*) is 4.2 milliseconds. The amplitude of the deflection measured from the negative peak to the subsequent positive peak is 30 μV. **C:** Sensory-evoked response over the index finger from stimulation of the median nerve in the midpalm distal to the carpal tunnel. The latency of this response is 1.9 milliseconds, and its amplitude is 50 μV. **D:** Sensory-evoked response (*asterisk*) over the fifth finger 14 cm distal to the point of stimulation of the ulnar nerve at the wrist. The latency of this response is 3.0 milliseconds, and its amplitude is 34 μV. The longer sensory latency on median nerve stimulation at the wrist compared with ulnar nerve stimulation at the wrist for the same 14 cm of nerve length implies slowing through the carpal tunnel. Similarly, the comparison of the 1.9 ms from midpalmar stimulation to the 4.2 milliseconds latency for wrist stimulation implies slowing in the region from the wrist to the midpalm in the median sensory nerve. The larger amplitude of the median sensory nerve response on midpalmar stimulation compared with wrist stimulation (50 versus 30 μV) indicates a sensory neurapraxia, because 20 μV of amplitude has been lost.

Radicular Syndromes

Damage to nerve roots at or proximal to the intervertebral foramen, where the sensory ganglia are located, encompasses the radicular syndromes. Included in this group are lesions affecting the cauda equina within the vertebral canal below the conus medullaris. An electrodiagnostic medicine examination that concludes a radiculopathy is present does not reveal the cause of the damage. A radiculopathy induced by an extruded disk, tumor, arteriovenous malformation, or even diabetes, for example, can all produce the same electrodiagnostic abnormalities.

Because there are only seven cervical vertebrae and eight cervical nerves, the cervical nerve roots, C-1–C-7, exit above the pedicles of the corresponding vertebrae, and the C-8 root exits above the pedicles of the T-1 vertebra. Beginning with the T-1 root and below, the roots exit below the pedicles of their corresponding vertebrae.

Immediately on exiting the intervertebral foramen, the spinal nerve divides into its anterior and posterior primary divisions. The posterior primary division turns dorsally, looping over the posterior facet joint formed by the articular processes of the vertebrae above and below. The motor branches innervate the paraspinal musculature, extending as much as two levels above and two levels below the immediate region. All spinal nerves from C-3–S-1 contain posterior primary divisions that are distributed in this way. The anterior primary division from C-5–T-1 forms the brachial plexus, and the anterior primary divisions from L-1–S-2 similarly form the lumbosacral plexus. Only in the thorax (T-2–T-12) do the anterior primary divisions remain isolated and distribute as thoracic nerves.

As a result of plexus formations and redistributions of spinal nerve fibers into the terminal peripheral nerves of the plexuses, all muscles of the upper and lower extremities are innervated by the fibers of more than one spinal nerve.

Root disease can be motor or sensory if the anterior and posterior roots are separately involved, or mixed if both are damaged. An injury, as in an entrapment syndrome, can induce only a conduction block, or, if severe or long-standing, axonal degeneration. In the case of the anterior root, distal axonal degeneration leads to denervation of some or all of the muscles supplied by the anterior primary division in the extremities and to denervation of the paraspinal musculature supplied by the posterior primary division. In sensory axonal degeneration that occurs proximal to the sensory root ganglia, the axon distal to the ganglia remains capable of supporting the conduction and does not degenerate.

Needle EMG and SEPs are the main electrodiagnostic aids for the determination of radiculopathy. Late responses and the examination of amplitudes of motor-evoked responses on peripheral nerve stimulation can also contribute. The flow diagrams in Figure 13-11 and Figure 13-12 suggest approaches based on how soon after an acute insult the different studies can be considered. It is useful to group the discussion of the electrodiagnostic approaches into cervical, thoracic, lumbosacral, and low sacral radiculopathies. The following discussion assumes that the examination is being performed on patients without prior back surgery.

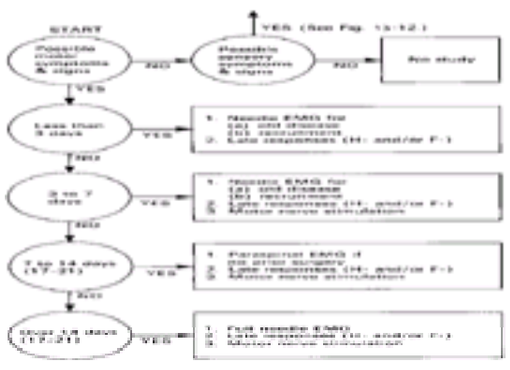

Figure 13-11. Flow diagram of appropriate electrodiagnostic studies in the evaluation of radiculopathy if signs or symptoms of weakness are present. The studies to consider are based on the duration of the symptoms and signs. See Figure 13-12 for appropriate approaches if only sensory symptoms and signs are present. (EMG, electromyography.)

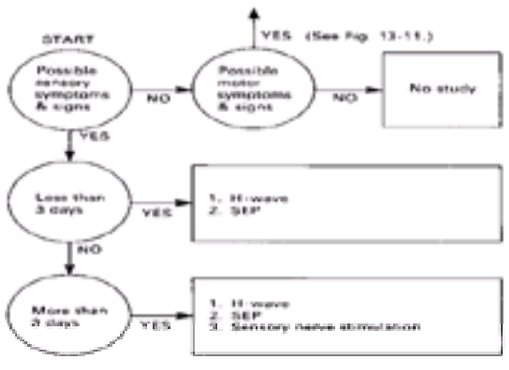

Figure 13-12. Flow diagram of appropriate electrodiagnostic examinations to consider for sensory symptoms and signs and in the evaluation for possible radiculopathies: See Figure 13-11 for appropriate approaches if motor symptoms and signs are present. (SEP, somatosensory-evoked potential.)

Cervical Radiculopathies (Roots C-5–T-1)

Even though only one specific root is suggested by the clinical examination, needle EMG of the upper extremity muscles should be carried out so that at least two muscles with innervation from each of the roots (Table 13-3) are sampled. From such an examination, a clear pattern can emerge. The presence of membrane instability in a muscle implies motor axon degeneration and generally is associated with a reduced recruitment pattern. A reduced recruitment pattern alone, without membrane instability, implies the existence of only a conduction block without axonal degeneration. Fasciculation can also appear, indicating an irritating focus. The membrane instability in peripheral muscles and in the paraspinal muscles is diagnostic for radiculopathies because it signifies involvement of both the anterior and posterior primary divisions and, hence, a lesion at or proximal to the intervertebral foramen.

Muscle	Spinal nerve roots
Deltoid	C-5, C-6
Biceps	C-5, C-6
Pronator teres	C-6, C-7
Extensor carpi radialis longus and brevis	C-6, C-7
Triceps	C-7, C-8
Extensor carpi ulnaris	C-7, C-8
Extensor digitorum communis	C-8, C-7
Flexor carpi ulnaris	C-8, C-7
Thenar group	T-1, C-8
Hypothenar group	T-1, C-8

TABLE 13-3. Dominant root innervations of some upper extremity muscles easily accessed by needle electromyography

Within 7 to 10 days after onset of axonal degeneration, paraspinal muscles show membrane instability, whereas 17 to 21 days may be necessary for the more distal muscles of the extremity.

Dermatomal SEPs provide information on the status of the sensory root. Skin stimulation of the lateral shoulder (C-5) and over the digital nerves of the thumb (C-6), middle finger (C-7), and little finger (C-8), and recording at Erb's point, at the cervical spine, and at the scalp, with contralateral comparisons, can reveal a conduction block or sensory axonal degeneration proximal to the dorsal root ganglia.

Abnormal F-wave responses (e.g., absent or of prolonged duration) at the thenar and hypothenar muscles elicited by median and ulnar nerve stimulation, respectively, suggest C-8, T-1, or both kinds of root involvement. F-wave responses for more proximal roots are not readily accessible.

A softer, but sometimes useful, sign is a reduction in amplitude of the motor-evoked responses on peripheral stimulation (e.g., thenar for C-8–T-1 on median stimulation, flexor carpi ulnaris for C-8 on ulnar stimulation, triceps for C-7 on Erb's point stimulation, extensor carpi radialis for C-6 on radial nerve stimulation, and biceps for C-5 on Erb's point stimulation). For the amplitudes to be reduced, motor axonal degeneration must have occurred; hence, needle EMG results should also be positive for membrane instability. Peripheral sensory-evoked amplitudes are normal and unaffected in lesions proximal to the dorsal root ganglia.

Thoracic Radiculopathy (T-2–T-12)

Needle EMG is limited to the paraspinal muscles and to the abdominals. The rectus abdominus, served by T-7–T-12, is easily accessed. Membrane instability is likely the only finding of interest because recruitment patterns are not useful. Fasciculations, however, can be helpful.

Careful SEP serial dermatomal stimulation with left-right comparisons of scalp recordings can permit detection of sensory root disease.

No F-wave or peripheral stimulation techniques are useful.

Lumbosacral Radiculopathy (L-1–S-1)

The approach of the needle EMG in these radiculopathies parallels that of the cervical area. All of the EMG abnormalities discussed also apply here. Muscles sampled should be broad enough to confirm a pattern obeying a root distribution (Table 13-4). Again, the finding of membrane instability in peripheral and paraspinal muscles confirms anterior and posterior primary division involvement and a lesion proximal to the intervertebral foramen.

Muscle	Spinal nerve roots
Vastus medialis	L-4, L-3
Rectus femoris	L-4, L-3
Adductor longus	L-4, L-3
Anterior tibialis	L-5, S-1
Extensor hallucis longus	L-5, S-1
Tensor fascia lata	L-5, S-1
Medial hamstrings	L-5, S-1
Lateral hamstrings	S-1, L-5
Medial gastrocnemius	S-1, L-5
Lateral gastrocnemius	S-1, L-5

TABLE 13-4. Dominant root innervations of some lower extremity muscles easily accessed by needle electromyography

The tibial H wave is a late response useful for S-1 root disease, particularly in the absence of clear-cut EMG findings. A prolonged H- wave latency or a markedly reduced amplitude of the response when compared with the uninvolved side can be caused by disease in the afferent or the efferent limb of the reflex. An abnormal H wave in the presence of a normal EMG would suggest sensory root involvement or motor root conduction block. Although less useful, a peroneal nerve F wave recorded at the extensor digitorum brevis muscle can be studied to assist in the diagnosis of L-5 lesions.

SEP studies of the response to posterior tibial nerve stimulation at the ankle (mostly S-1) and the peroneal nerve at the knee (mostly L-5), with recording over the back at the root entry zones and at the scalp, can be useful in detecting sensory root conduction block or slowing of conduction. In addition, scalp recordings of the response to dermatomal stimulation of L-5 and S-1 over the foot, L-4 below the knee, and L-3 above the knee focus more specifically on the individual roots.

Peripheral motor stimulation, with comparison of evoked amplitudes over the muscles of the involved and uninvolved sides for the detection of motor axon loss, are also considered. Peroneal nerve stimulation with the measurement of evoked amplitude at the extensor digitorum brevis, mostly for L-5 lesions, and tibial nerve stimulation with measurement of the evoked amplitude over the abductor hallucis, mostly for S-1 lesions, have been used.

Low Sacral Radiculopathies (S-2–S-4)

Limited, although useful, approaches exist for low sacral lesions. These lesions are further clarified by urodynamic studies.

Needle EMG for low sacral radiculopathies is restricted to the anal sphincter. Membrane instability, reduced tonicity at rest, and a reduced recruitment pattern on volition can all be detected.

The bulbocavernosis reflex can be electrically studied for abnormalities in the S-2–S-4 roots, the pudendal nerve, or both. This is a polysynaptic reflex response elicited by penile or clitoral skin stimulation with needle or surface recording in men over the bulbocavernosus muscle and in women in the urethral sphincter or over the surface of the perineum. It is more easily elicited in men simply because of the easier accessibility of the penis and the bulbocavernosus muscle. The afferent and efferent limbs of the reflex travel in the pudendal nerve served by the S-2–S-4 roots.

An SEP study of the scalp response to penis or clitoris skin stimulation can also be useful for deficits in the pudendal nerves.

Paraspinal Electromyography in Postsurgical Backs

The usefulness of paraspinal EMG is diminished in regions in which previous laminectomies have been performed (21). Paraspinal muscle stripping to access the lamina causes denervation of the paraspinal muscles because the procedure usually damages the posterior primary divisions. Approximately 2 or more years might be necessary for reinnervation to be completed or, if not completed, for the residual denervated fibers to degenerate. During this period, membrane instability on needle EMG is likely to be seen. A qualitative impression of old or newly denervated muscle fibers can sometimes be made when the amplitudes of the fibrillation potential and the positive sharp waves are closely examined. Old fibers are more atrophic, and their membrane and instability responses are of comparatively low amplitude.

Multiple Root Syndromes

The cauda equina syndromes of lumbar spinal stenosis and arachnoiditis deserve special mention because their electrodiagnostic findings are usually different.

Lumbar spinal stenosis is a slowly progressive process that, if compromising lumbar and sacral roots, does so at a rate that permits adaptation. Furthermore, when symptoms are produced, the patient is usually able to assume a position that causes the symptoms to fade, giving the involvement a transient character. A gradual diminution in diameter of the nerve fibers slows conduction through the region of impairment without necessarily inducing axonal degeneration. Even if axonal degeneration is induced, it occurs in insufficient numbers at any one time. As a result, needle EMG may not show membrane instability but may show decreased recruitment patterns, and the individual MUAPs may show increased amplitude and durations because of prior collateral reinnervation. SEP data, on the other hand, may be particularly abnormal because of the thinning of the fibers and attenuation of the incoming signal (Fig. 13-13). Dermatomal SEP abnormalities may show multiple root abnormalities, but in varying degrees and rarely with full left-right symmetry, as might be seen, for example, with a peripheral neuropathy. They also have a greater sensitivity than EMG for spinal stenosis (22,23,24).

Figure 13-13. Somatosensory-evoked potential responses at the scalp in a patient with spinal stenosis. The responses to skin stimulation of various dermatomes are shown. The response to L-2 dermatome stimulation is normal and shows left-right symmetry. No response is seen at the scalp to left and right L-3 and L-4 dermatome stimulation. Tibial nerve stimulation at the ankle and L-5 and S-1 dermatome stimulation also did not show a response at the scalp (not shown). Electromyographic examination in the patient documented active radiculopathy bilaterally only in the S-1 roots. Myelography documented vertebral canal narrowing from L-1 to L-5, with nerve root encroachment of the left L-5 and the right L-4 and L-5 roots. At surgery, severe stenosis was seen from L-3 to S-1. Decompressive laminectomy at L-4 and L-5, partial laminectomy at L-3, partial diskectomy at L-3–4 and L- 4–5, and nerve root decompression foramenotomies at L-3, L-4, and L-5 were performed. Symptoms improved after surgery.

In arachnoiditis, the lesion is more aggressive. Membrane instability on EMG is usually present bilaterally across many muscles and roots, and SEP responses similarly show more symmetry than in spinal stenosis. In both conditions, F- and H-wave responses are abnormal.

Case Example

A 56-year-old man complained of intermittent bilateral numbness over the first, second, and third digits of his left hand for 6 months. Recently, the numbness had spread to include the fourth and fifth digits and grip strength had decreased. Tinel's sign was elicited over the ulnar groove at the elbow, and atrophy and weakness of the left hand were present.

Needle EMG of the left deltoid (C-5), biceps (C-5), pronater teres (C-6), extensor carpi radialis (C-6), triceps (C-7), extensor carpi ulnaris (C-7), flexor carpi ulnaris (C-8), extensor digitorum communis (C-8), and the flexor digitorum superficialis (C-8) was normal. The thenar (C-8–T-1), first dorsal interosseous (C-8–T-1), and hypothenar muscles (C-8–T-1) all showed positive waves and fibrillation potentials and a decreased number of MUAPs. Needle EMG of the lower cervical paraspinal muscles also showed membrane instability.

Conduction studies of the ulnar nerve were done. These revealed conduction velocities of 60 m per second from Erb's point to the axilla, 56 m per second from the axilla to below the elbow, and 55 m per second from below the elbow to the wrist, all of which are normal. Stimulation of the ulnar nerve and recording of the evoked sensory response over the fifth digit revealed an amplitude of 3 µV, which was 14 and 20 times less, respectively, than the sensory-evoked responses obtained at the first and third digits on median nerve stimulation at the wrist. The ulnar nerve F-wave response recorded over the hypothenar muscles on stimulation of the ulnar nerve at the wrist revealed a normal (56 m/sec) conduction velocity of the F-wave response from the wrist to the spinal cord.

Normal ulnar nerve peripheral conduction and F-wave responses indicated no entrapment. The normal F-wave response, coupled with the positive needle EMG findings in the small muscles of the hand innervated by both the median and ulnar nerves, coupled with the positive paraspinal findings, implied C-8 or T-1 root disease. The reduced sensory-evoked response in the fifth digit favored C-8 root disease with involvement of the posterior root ganglion.

Radiography revealed marked degenerative joint disease at the C-5–C-6 level, and cervical myelography was inconclusive for root encroachment. An anterior diskectomy at C-5–C-6 and an exploration at C-7–T-1 on the left were performed. At the C-7–T-1 level, free disk material was found encroaching on the C-8 spinal nerve in the intervertebral foramen.

Traumatic Syndromes

Given the plethora of ways accidents and injuries take place, nerve and muscle damage can occur literally anywhere in the body. Frank nerve section can result from sharp objects or bullets or internally in association with fractures. Traction injuries are common in high-speed accidents. Blunt trauma or compression injuries can induce total nerve damage without separation. Muscle trauma and the associated inflammation can induce compartment syndromes and yield primary muscle destruction, as well as nerve damage to terminal branch elements or to nerves traversing the compartment.

The anatomy of the peripheral nervous system and the anatomic relationships between the peripheral nervous system and the musculoskeletal system suggest some specific regions of vulnerability where trauma can injure the nervous system and provide a source for pain complaints in need of evaluation. Table 13-5 lists these vulnerable sites, the type of trauma inducing the damage, and the nerve elements likely to be involved. All of these can be evaluated electrodiagnostically.

Trauma and site	Vulnerable nerve(s)
Acute lateral flexion of head and neck	Brachial plexus
Glenohumeral dislocation	Axillary nerve
Scapular fracture	Suprascapular
Humeral fracture	Radial
Elbow fracture or dislocation	Ulnar
Wrist fracture (distal radius)	Median
Forearm trauma and compartment syndromes	Median (anterior interosseus) and radial (posterior interosseus)
Pelvis (pubic rami) fractures	Obturator
Hip fracture and dislocations	Sciatic (peroneal, tibial)
Knee derangements	Peroneal
Below-knee anterior compartment syndromes	Peroneal (deep branch)
Ankle fractures	Tibial and peroneal

TABLE 13-5. Sites vulnerable for traumatic nerve injury

The electrodiagnostic approach to the evaluation of trauma depends on whether the examination is done in the acute phase or 3 to 4 weeks or more after onset. Examination in the acute phase is usually directed at determination of injury location, the presence or absence of muscle paralysis, and whether nerve continuity has been lost. A high index of suspicion for nerve damage must also be considered even when not particularly obvious, to ensure that reduced muscle function, surmised simply as pain inhibition, is not also actual nerve damage. An electrodiagnostic examination performed in the acute phase can lead to an earlier recognition of nerve damage than might be evident, leading to more appropriate treatment. In particular, if head injury is present or cognition is impaired, electrodiagnostic studies should be considered in the acute phase because the clinical examination might be incomplete.

In the chronic phase, some of the same questions can be addressed that were asked acutely but were unanswered because life-saving measures took precedence. In addition, after the effects of acute trauma have settled down, more definitive assessments of damage than those obtained acutely are possible and beginning assessments of prognosis can be made.

Acute Phase

Needle EMG of target muscles of motor nerves suspected of damage permits a determination if any nerve fibers are able to conduct impulses through the region of trauma. Volitional contraction is asked for, reflex responses via tendon taps are induced, and noxious stimulation is delivered to assess whether any MUAPs are detectable and to what degree. If any are detected, nerve continuity in some degree must exist. If no MUAPs are detected, clearly no conduction through the region is present. An absent response, however, is the same whether complete nerve separation, total crush injury without separation but with total axon destruction, or a complete physiologic conduction block (neurapraxia) exist.

No membrane instability is seen, even in total sections, in the acute phase, because an insufficient length of time has elapsed for wallerian degeneration to take place and for acetylcholine sensitivity to appear.

Motor nerve stimulation proximal to the site in question, with either a surface or needle electrode placed on the target muscle, further adds to the solution of the continuity question. Any response in the target muscle from the proximal stimulation concludes that at least some continuity exists. Proximal stimulations may be more useful than needle EMG with volitional effort because pain may inhibit the latter. An absent response on proximal stimulation is also compatible acutely with complete section or a complete reversible physiologic block. Motor nerve stimulation distal to the suspected region still yields a normal response because the distal segment of even a severed nerve remains capable of conduction until wallerian degeneration has occurred. It may take anywhere from 2 to 10 days, depending on the length of the distal segment, before distal stimulation fails to induce muscle contraction. Serial studies of latency and amplitude after a severing injury may suggest severance before complete conduction failure has occurred.

Peripheral sensory nerve stimulation is also useful, provided the nerve can be accessed on either side of the region of injury. If this can be done, then the same type of data results as in peripheral motor stimulation.

Late responses, in particular F waves, are useful if the region of injury is too proximal to permit stimulation of motor nerves proximal to the site. Stimulation of the motor nerves distal to the site and examination for the presence or absence of an F-wave response is performed. If a response is present, nerve continuity through the site is present. If the F-wave response is absent, again the same reasons for blocked conduction apply.

SEP responses permit assessment of a block at the site of injury for sensory signals. Distal stimulation of mixed nerves or pure sensory nerves or of skin dermatomes with an evoked response determination over the spine or scalp can determine if injury has produced an interruption of conduction. Again, the interruption of conduction would be the same for nerve section, nerve compression with complete axonal destruction, and nerve compression with a purely physiologic block.

Chronic Phase (after 3 to 4 weeks)

Needle EMG of target muscles now becomes quite useful. If nerve section or axon death at the site of injury has occurred, membrane instability on the needle EMG examination documents the loss. No voluntary MUAPs are seen if interruption is complete and membrane instability is present. If some MUAPs are present along with membrane instability, the loss is incomplete.

Peripheral NCS of motor nerve segments distal to the site of injury with sampling electrodes over the target muscles now permit differentiation between the physiologic conduction block and axon interruption. If complete axon interruption has occurred, the distal nerve segment is not excitable, and no target muscle response is seen. If only some of the axons have been interrupted, the amount of axon loss can be estimated from the amplitude of the evoked response on stimulation of the distal nerve segment. The estimate of amount of loss is best obtained by a comparison of the amplitude with that achieved on the contralateral uninvolved side. If only a physiologic block has occurred, the target muscle demonstrates a normal response. Stimulation proximal to the injury can document a healing conduction block if serial examinations demonstrate a progressively increasing amplitude in the target muscle response.

Similarly, peripheral sensory NCS, distal to the lesion site, can be used to document sensory nerve degeneration. A response seen immediately after injury that later disappears confirms axon death through nerve section or a major compression.

SEPs coupled with peripheral sensory NCS permits determination of whether an injury is proximal to the sensory root ganglia, particularly in brachial plexus injuries. For example, the persistence of a peripheral sensory-evoked response in the thumb, coupled with an absent SEP response over the brain on thumb stimulation, implies root avulsion rather than trauma to the upper trunk of the plexus. In the latter case, no peripheral response and no SEP response is seen.

Case Example

A 33-year-old man fell while mowing his lawn and landed on his right wrist in the volar-flexed position. He experienced immediate wrist pain. After the acute pain subsided, he noticed an inability to dorsiflex the wrist. The next day radiographic results were negative, and paralysis of voluntary wrist and finger extension was apparent. An electrodiagnostic examination was performed 10 days after injury.

Needle EMG revealed absent membrane instability in the triceps (all heads), brachioradialis, extensor carpi radialis longus and brevis, extensor carpi ulnaris, extensor digitorum communis, supinator, and extensor indicis. On volition, recruitment was normal in all three heads of the triceps; however, only a few scattered voluntary MUAPs were seen in the brachioradialis, extensor digitorum communis, supinator, and extensor indicis. No voluntary MUAPs were seen in the extensor carpi radialis longus or extensor carpi ulnaris.

Stimulation of the radial nerve at Erb's point, recording over the triceps, evoked a normal response with a latency of 4.6 milliseconds. No response was present over the extensor carpi ulnaris on Erb's point stimulation. Recording over the brachioradialis produced a normal latency of 6.2 milliseconds, but the evoked amplitude was only 600 µV. Stimulation of the radial nerve above the elbow produced a normal response in the brachioradialis and the extensor carpi ulnaris. Furthermore, tetanic stimulation of the radial nerve above the elbow produced excellent contraction of wrist and finger extensors.

The lack of a response at the extensor carpi ulnaris on Erb's point stimulation with an excellent response on stimulation above the elbow, coupled with the much greater response over the brachioradialis, on above-elbow stimulation compared with Erb's point stimulation, documented the presence of a conduction block (neurapraxia) of the radial nerve proximal to the branch of the nerve to the brachioradialis and distal to the radial nerve branches to the triceps. The block was deemed reversible, because, if it had destroyed axons, the radial nerve would no longer be stimulatable distally. The absence of membrane instability was expected because 10 days had elapsed since the injury.

The presence of some voluntary MUAPs in some of the muscles distal to the block led to the diagnosis of an incomplete neurapraxia of the radial nerve, proximal to the brachioradialis branches. The block was probably induced by a forceful contraction of the lateral head of the triceps when the patient hit the ground and a resultant compression of the radial nerve as it winds around the humerus. Retesting in 2 weeks was recommended to assess for the existence of a partial denervation component. It was estimated that significant recovery could be expected in 4 to 6 weeks.

One month later, the patient had normal wrist and finger extension function. No further needle EMG was performed, because it was presumed that the block had been completely reversible and that no axonal loss had occurred.

Case Example

A 24-year-old man, 7 weeks before electrodiagnostic examination, was hit with an axe in his left neck. Radiography documented C-4 and C-5 vertebral fractures on the left, and the neurologic examination confirmed a Brown-Séquard syndrome. The persistent flail character of the left upper extremity raised the question of whether the flaccidity was secondary to a brachial plexus lesion, which might suggest the need for surgery.

Muscle strength testing revealed extremely weak musculature in the C-5 and T-1 innervated muscles and possible in C-8, with essentially no function through muscles innervated by C-6 and C-7. Light touch sensation only was present in the lateral shoulder (C-5). Sensation was absent in the thumb (C-6), middle finger (C-7), and little finger (C-8). Sensation was normal in the medial upper arm (T-1).

Needle EMG confirmed the presence of membrane instability (positive sharp waves and fibrillation potentials) in all muscles of the upper extremity innervated from C-5–T-1. The number of voluntary MUAPs was markedly decreased in muscles served by the C- 5 and T-1 roots, with essentially absent voluntary MUAPs in the muscles innervated by the C-6, C-7, and C-8 roots.

Motor nerve stimulation of the median and ulnar nerve at the elbow and at the wrist, recording over the thenar and hypothenar muscles of the hand, respectively, demonstrated normal conduction velocities with markedly reduced (50% of normal) amplitudes in the evoked responses. Stimulation of the radial nerve above the elbow produced no response in the wrist or finger extensors.

Sensory nerve stimulation of the median nerve at the wrist and the radial sensory nerve in the forearm, with recording of the evoked response in the thumb (C-6) using ring electrodes, produced normal responses of 60 and 14 µV, respectively. Sensory nerve stimulation of the median nerve at the wrist, recording over the middle finger (C-7), also produced a normal response of 60 µV, and sensory nerve stimulation of the ulnar nerve at the wrist, recording over the little finger (C-8), produced a normal response of 55 µV.

SEPs on median nerve stimulation at the wrist revealed normal responses at Erb's point, a weak to near absent response over the cervical spine, and no response at the scalp. SEPs on direct stimulation of the thumb, middle finger, and little finger revealed no responses at the scalp (Fig. 13-14).

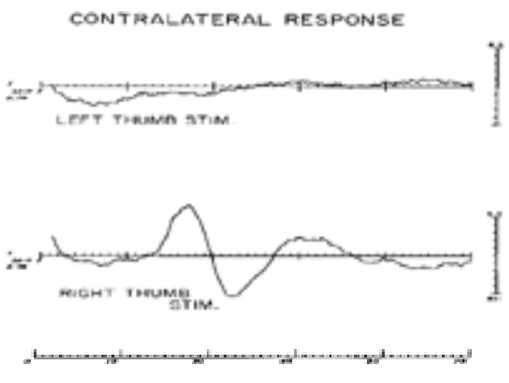

Figure 13-14. Somatosensory-evoked potential responses at the scalp to left (upper) and right (lower) stimulation of digital nerves of the thumb (C-6). Note absence of a response to left-sided stimulation and a normal response to right-sided stimulation. Amplitude calibration is in microvolts, and time calibration is in milliseconds. The lesion in this example was proximal to the C-6 posterior root ganglion, because peripheral sensory stimulation was normal (see text).

The excellent sensory responses, over digits 1, 3, and 5 on distal, radial, median, and ulnar nerve stimulation confirmed intactness of sensory axons up to and including posterior root ganglia in the intervertebral foramen of spinal nerve roots C-6, C-7, and C-8, as did the excellent Erb's point response on median nerve stimulation at the wrist. Absent scalp responses in the SEP studies confirmed the accuracy of the patient's assessment of absent sensation in his hand and led to the conclusion that the block in conduction of sensory signals was proximal to the dorsal root ganglia.

The median and ulnar motor nerve responses confirmed some T-1 motor function, and the absence of a response to radial nerve stimulation confirmed motor neuron loss through the C-6, C-7, and C-8 roots or cord centers.

The conclusion was drawn that the persistent flail weakness of the left upper extremity was not secondary to a brachial plexus lesion, but rather secondary to a lesion proximal to the intervertebral foramen, involving either or both nerve roots and the cervical cord centers for motor and sensory fibers.

Systemic Syndromes

In diffuse, relatively symmetric pain syndromes, electrodiagnostic examination may be necessary and should be considered to assist in the diagnosis. Polymyositis, for example, could be present with chronic, diffuse muscle pain and tenderness with varying amounts of weakness. A more acute symmetric pain presentation can

occur in Guillain-Barré syndrome.

In polymyositis, NCS, late responses, and SEPs are normal, but needle EMG shows abnormalities. Membrane instability is present if muscle destruction is occurring. In fact, needle EMG can be helpful in monitoring corticosteroid dosages. A well-controlled myositic patient is less likely to show membrane instability than one whose corticosteroid dosage is too low. In addition, MUAPs have characteristic features. The loss of individual muscle fibers within a motor unit shows MUAPs of decreased amplitude, decreased duration, and increased polyphasicity. Voluntary recruitment patterns are full, but maximum amplitudes are reduced.

In Guillain-Barré syndrome, the lesion is in the peripheral nerve. Segmental demyelination can be documented by motor NCS. Velocities are slowed, and temporal dispersion is increased. Abnormal F- and H-wave responses may be the earliest sign because disease can first attack the proximal segments of nerves and leave the distal segments undisturbed. Thus, normal peripheral NCS with delayed or absent F-wave responses indicates proximal slowing or a conduction block. A response of a target muscle on peripheral motor NCS in the presence of profound weakness signifies a conduction block secondary to demyelination proximal to the site of stimulation. Needle EMG of paralytic muscles can be used to determine whether demyelination has caused secondary axonal death by documenting muscle fiber membrane instability. A normal response on peripheral nerve stimulation is also produced if spinal cord or brain damage has affected the upper motor neurons to cause a profound weakness. For situations in which pain is suspected as secondary to ischemic neuropathy, electrodiagnostic examination can be helpful. In particular, the mononeuropathy or polyradiculopathy of diabetes is easily studied by the NCS and EMG techniques described. Furthermore, these particular syndromes are generally distinguishable from the diffuse distal axonal sensorimotor symmetric peripheral neuropathy of diabetes on which it is superimposed.

Case Example

A 63-year-old man was referred with the possible diagnosis of nerve root compromise secondary to spinal stenosis. Chronic low back pain was intermittent for several years, with a recent increase in discomfort aggravated by ambulation and associated with radiation into the buttocks and thighs. In addition, during ambulation, his legs felt “wooden” and he felt a “burning” in the soles of his feet. The burning was also frequently present without ambulation. Examination of the neuromuscular system was unremarkable except for reduced ankle deep tendon reflexes and bilaterally atrophic extensor digitorum brevis muscles. Position sense was normal, and no clear sensory impairment was present. The patient had an 8-year history of diabetes, which he indicated was well controlled by diet.

Needle EMG bilaterally in the vastus medialis, rectus femoris, anterior tibialis, extensor hallucis, medial and lateral hamstrings, medial and lateral gastrocnemii, and lumbar paraspinal musculature was unremarkable. Recruitment patterns were normal, and no membrane instability was seen.

Late response studies of tibial H waves, performed bilaterally, were symmetric with latencies of 35 milliseconds (2 milliseconds greater than expected values), and with a small amplitude of 0.2 mV. Motor and sensory nerve conduction studies were performed the next day to determine whether the delayed H wave was a sign of S-1 nerve root abnormalities or was associated with a diabetic peripheral neuropathy.

Conduction studies, all on the right side, are shown in Table 13-6.

Nerve	Distal latency (ms)	Conduction velocity (m/sec)	Amplitude (μV)
Median motor	3.6	51	6.3 K
Median sensory	4.4	43	18.0
Ulnar motor	3.2	58	7.0 K
Ulnar sensory	4.0	51	28.0
Peroneal motor	4.7	34	0.6 K
Peroneal sensory	Not applicable	34	1.5
Sural sensory	4.7	30	9.0
Tibial motor	4.8	39	5.5 K

TABLE 13-6. Results of motor and sensory nerve conduction studies

The negative needle EMG examination result confirmed the absence of an active radiculopathy. The motor and sensory conduction studies, however, confirmed a significant peripheral neuropathy, largely axonal. Specifically, sural nerve conduction was three standard deviations (SD) away from normal, evoked amplitude was 2 SD below normal; peroneal sensory velocity and amplitude were 2 SD below normal; peroneal motor conduction velocity was greater than 2 SD below normal, and the amplitude was greater than 3 SD below normal; and tibial motor velocity was 2 SD below normal. In the upper extremity, median motor velocity, median sensory latency and velocity, and ulnar sensory velocity were also abnormal. A systemic axonal, sensory, more than motor, and lower extremity, greater than upper extremity, peripheral neuropathy was concluded.

The patient was referred for endocrinologic studies, which revealed the diabetes to be poorly controlled. The patient was placed on chlorpropamide, and the back pain was treated conservatively, with good results.

Functional Syndromes

The physician who does not maintain a high degree of suspicion that the weakness or sensory loss seen in the chronic pain patient may be functional does so at his or her own peril and that of the patient as well. Too many operations have been performed on backs, necks, legs, and arms for weakness, paralysis, or sensory deficits that were presumed to be organic but were actually functional inhibitions or frank conversion reactions unassociated with malingering.

Weakness, paralysis, and sensory loss should be viewed, until proven otherwise, as part of the pain behavior complex discussed in Chapter 25 and Chapter 26. Humans have an amazing capacity to subconsciously inhibit motor function and sensory input in the presence of physiologically normal somatomotor and somatosensory systems. The electrodiagnostic examination can detect such functional inhibition by the responses seen in peripheral motor and sensory NCS, needle EMG, and SEPs.

If even the slightest suggestion occurs to a physician that the patient's behavior, weakness, and sensory complaints do not fit or make sense with the medical history and physical examination, electrodiagnostic examination might be the next thing to consider.

The most difficult of the functional patterns to detect are those that *grow out of* or are associated with an initially *legitimate* injury or disease process. For example, after an ankle sprain or even a fracture, in which ankle dorsiflexion was inhibited initially because of pain, the dorsiflexion weakness might persist long after healing of the acute process should have occurred. The documentation of functional inhibition in such a case is achieved by demonstration of a normal response on stimulation of the peroneal nerve at the knee and the ankle and the demonstration that no membrane instability is present on needle EMG of the *paralyzed* muscles.

Lower extremity functional inhibitions are more prevalent than those affecting the upper extremity. Both appear as inhibitions that affect performance of work-related activities of an inherently distasteful character to the patient or activities that produce stresses with which the patient has difficulty dealing.

Lower extremity functional problems are usually apparent on ambulation. Some gait patterns that suggest a functional origin and indicate a need for an electrodiagnostic examination are presented here:

- Full knee extension throughout the stance phase
- Knee buckling at the end of the stance phase just before heel strike of the swinging opposite limb
- A dropped foot during swing
- An absent heel strike at the beginning of stance
- Toe walking during stance

- Foot inversion during stance
- Use of the hand on the anterior aspect of the thigh during stance
- Use of the hand to help advance a leg during swing
- Continuous contact and dragging of the foot on the floor during swing in a position of hip and foot external rotation
- A decreased duration of stance phase of the involved leg
- Use of a cane or a crutch on the *same* side as the affected leg

The electrodiagnostic examination findings that suggest functional inhibition are listed here:

- Normal M-, F-, and H-wave responses on stimulation of peripheral motor nerves, serving muscles that appear to be weak or paralyzed on voluntary effort
- Normal peripheral sensory nerve-evoked responses and normal central SEP responses on peripheral sensory nerve stimulation in regions in which the patient reports absent or reduced sensation on direct examination.
- No membrane instability and normal MUAPs on needle EMG examination in patients with profound weakness presumed to be caused by a lower motor neuron problem. The needle EMG examination also detects irregular noncontinuous bursts of MUAP activity as the patient engages in largely ineffectual and *rachety* voluntary effort.

Case Example

A 43-year-old man suffered a displaced fracture of the tip of the medial malleolus of his right ankle 14 months before his electrodiagnostic examination. An open reduction with internal fixation was initially performed, and the ankle was immobilized in a plaster cast. The immediate postoperative period was complicated by a superficial *Pseudomonas* infection. Chronic pain and continued ambulation difficulty persisted after cast removal and even after metal screw removal. The persistent gait abnormality was manifested by toe-drag during the swing phase of the right leg. On clinical examination, no voluntary function was seen in the anterior tibialis, peroneal, or toe extensor muscles. In addition, leg edema and superficial dysesthesias were present.

Needle EMG of the anterior tibialis, extensor hallucis, peroneus longus, and extensor digitorum brevis revealed absent membrane instability (i.e., positive waves or fibrillation potentials). On voluntary effort, a marked reduction in the number of voluntary MUAPs was seen. Those that were present were of normal configuration. The recruitment effort was unsustained with occasional bursts of MUAPs, suggesting cerebral inhibition.

Conduction studies of the right peroneal nerve, stimulating at the fibula head and at the ankle and recording over the extensor digitorum brevis, produced a conduction velocity of 52 m per second (normal) and an evoked response at the extensor digitorum brevis of 12 mV (normal). In addition, a normal F-wave response was seen over the extensor digitorum brevis on stimulation of the deep branch of the peroneal nerve at the ankle. Comparison of the evoked responses at the extensor digitorum brevis on stimulation at the knee and at the ankle revealed normal temporal dispersion.

The excellent response on peroneal nerve stimulation revealed the nerve to be fully viable. The normal F-wave response indicated that the peroneal motor nerve fibers were intact clear into the spinal cord. The absence of membrane instability of the needle EMG confirmed no loss of motor axons to any of the muscles served by the peroneal nerve. The diagnosis of functional inhibition as the cause of the gait abnormality and the weakness was made.

Psychological and social review revealed much stress. The treatment program, directed at relieving the stresses, at reambulation, and at restoration of voluntary ankle dorsiflexion, eliminated the gait abnormality, resolved the edema, and caused the dysesthesias to fade.

CONCLUSIONS

The symptom of pain usually implies nervous system involvement. The complaint, as discussed in Chapter 9 and Chapter 10, is derived from myriad factors. Whereas a correctable lesion can be present, the more chronic the complaint, the less likely a localizable lesion is the cause. Before any therapeutic considerations, particularly a surgical approach to correct a suspected lesion that might involve the somatomotor or somatosensory system, careful and complete diagnostic evaluations are essential. The power of the electrodiagnostic examination for the detection of neuromuscular disease has been clearly established.

In this chapter, the essential ingredients of available electrodiagnostic studies have been reviewed. Specifically, the way in which needle EMG, peripheral motor and sensory NCS, late responses, and SEP analysis can be used to evaluate entrapment syndromes, radiculopathies, traumatic syndromes, systemic syndromes, and functional syndromes have been discussed.

All physicians faced with patients with pain complaints should establish a relationship with a physician skilled in electrodiagnostic medicine for assistance when somatomotor and somatosensory involvement is suspected, even if the history and the physical examination have obvious features. The likelihood of misdiagnosis and faulty treatment is therefore reduced.

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CHAPTER 14

Imaging Pain Patients

Alexander B. Baxter and Kenneth R. Maravilla

Primary imaging studies for the patient with acute pain aim to confirm or exclude a diagnosis based on history and physical examination. For patients with recurrent or persistent pain whose diagnosis remains obscure, or for patients with pain that appears to be solely related to degenerative disease, the role of imaging is expanded. Specialized techniques can help detect subtle evidence of disease, direct therapy, and select patients for surgical or radiologic intervention.

A comprehensive discussion of computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and radionuclide examinations is beyond the scope of this chapter and can be found in most general radiology textbooks. Refinements in CT, MRI, and spinal interventional procedures have led to new applications in evaluating and treating patients with chronic pain syndromes. This chapter reviews the imaging approach to several regional pain syndromes as well as imaging techniques that can be used to select surgical candidates among patients with back pain, tic douloureux, and peripheral nerve entrapment syndromes. Techniques and indications for MRI of the cranial nerves and posterior fossa vasculature, diskography for nonradicular back and neck pain, and high-resolution MRI of the brachial plexus and peripheral nerves are discussed. The role of imaging in conjunction with diagnostic and therapeutic nerve blocks is also addressed.

HEADACHE

Headache is a common symptom, and choosing the patient who should have a cranial imaging study can be challenging (see Chapter 48). The diagnostic yield of neuroimaging examinations in patients with headaches and a normal neurologic examination, or in patients with typical migraine, is low (Table 14-1) (1). Certain clinical situations, however, should prompt cranial imaging: Acute onset of an extremely severe headache, worsening subacute headache, headache associated with focal neurologic signs or cognitive impairment (in patients without a history of migraine), new headache in patients older than age 50, and headache in immunocompromised patients or patients with known malignancy (2,3). Patients over the age of 65 with new onset of pathologic headache have a 15% incidence of serious intracranial disease, including temporal arteritis, tumor, and infarct. In contrast, patients younger than age 65 have only a 1.5% incidence of detectable underlying pathology (4).

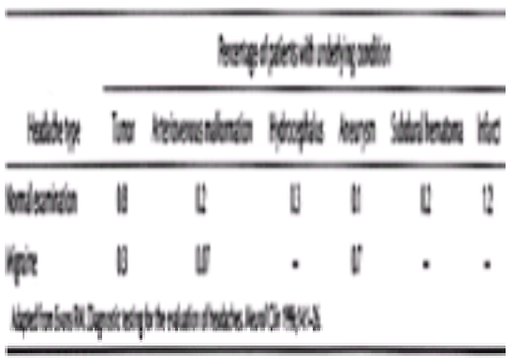

TABLE 14-1. Neuroimaging yield in headache

Acute Headache

Severe, acute headache, especially if associated with neurologic abnormality or depressed sensorium, suggests possible subarachnoid hemorrhage (SAH). The devastating consequences of untreated ruptured aneurysm require prompt exclusion of SAH in this setting. Diagnosis is best made by CT demonstration of hyperdense blood in the subarachnoid space or detection of xanthochromic cerebrospinal fluid (CSF) on lumbar puncture in patients with a negative CT examination (5). CT sensitivity for detection of SAH is reduced as the time interval from hemorrhage increases. Ninety-five percent of SAH are identified on CT in patients scanned within 24 hours of aneurysm rupture. At 3 weeks, only 30% of SAH are detected by CT (1). If SAH is present, subsequent imaging is directed at detecting an aneurysm (Fig. 14-1) or arteriovenous malformation (Fig. 14-2). Venous sinus thrombosis (Fig. 14-3 and Fig. 14-4) (6,7), benign perimesencephalic SAH (8), arterial dissection (9) (Fig. 14-5), migraine, and benign thunderclap headache can also present as acute, severe cephalgia.

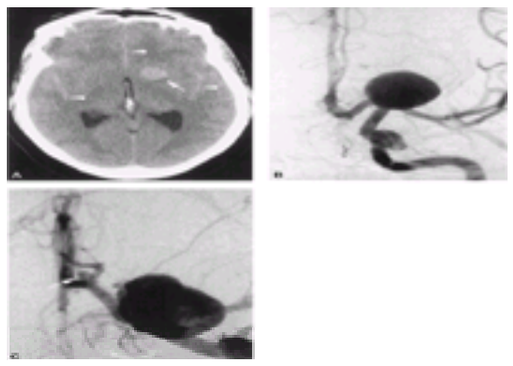

Figure 14-1. Subarachnoid hemorrhage caused by ruptured terminal internal carotid artery aneurysm. **A:** Nonenhanced computed tomography shows hyperdense aneurysm (*arrow*) and blood within interhemispheric and sylvian fissures (*arrowheads*). The ventricles are mildly enlarged and clot is present within the third ventricle. **B:** Left internal carotid artery arteriogram shows a 2-cm aneurysm arising from the termination of the internal carotid artery.

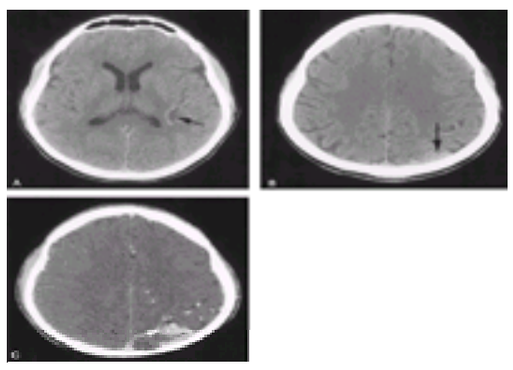

Figure 14-2. Arteriovenous malformation. A 39-year-old man with several days' headache. **A:** Noncontrast computed tomography shows enlarged, slightly hyperdense vessels in the sylvian fissure (*arrow*). **B:** Hyperdense, dilated veins at the varietal vertex (*arrow*). **C:** Computed tomographic angiography shows the arteriovenous malformation nidus as well as dilated feeding arteries and peripheral draining veins.

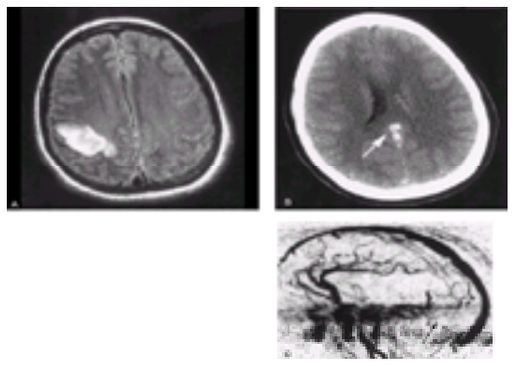

Figure 14-3. Venous sinus thrombosis with cortical infarct. A 26-year-old postpartum woman with headache and left hemiparesis. **A:** Axial FLAIR image at level of centrum semiovale shows increased signal in precentral gyrus, indicating cortical infarct. **B:** Nonenhanced computed tomography shows high attenuation in vein of Galen and straight sinus (*arrow*). **C:** Magnetic resonance venogram shows absence of flow through straight sinus with patent sagittal and transverse sinuses.

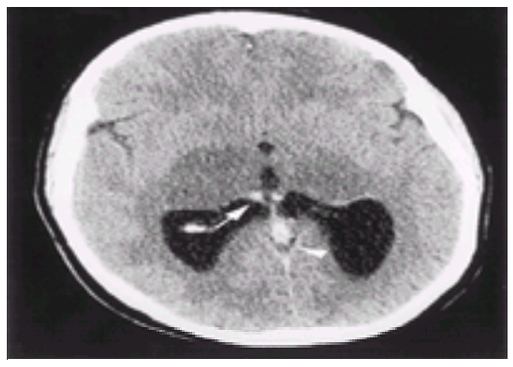

Figure 14-4. Venous sinus thrombosis with bilateral thalamic infarcts in a 24-year-old woman with 4 days of headache followed by several hours nausea and depressed consciousness. Nonenhanced computed tomography shows low attenuation changes in both thalami, with increased attenuation in the internal cerebral veins (*arrow*) and straight sinus (*arrowhead*).

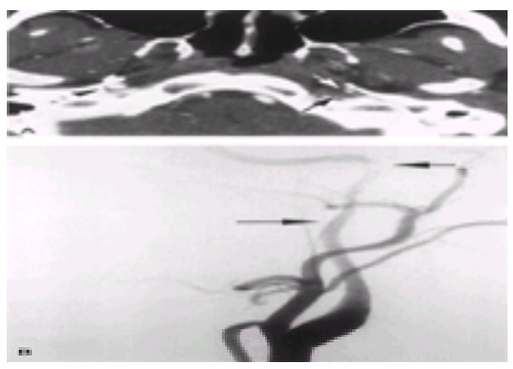

Figure 14-5. Internal carotid artery dissection in a 37-year-old man with headache and left pupillary constriction. **A:** Computed tomographic angiography at skull base shows decreased caliber of left internal carotid artery (*white arrow*) at the skull base. Intramural hematoma surrounds the narrowed lumen (*black arrow*). Normal right internal carotid artery (*arrowhead*). **B:** Left internal carotid arteriogram shows smooth narrowing of distal cervical internal carotid with near complete occlusion at the skull base (*arrows*).

Imaging the patient with suspected SAH should begin with nonenhanced CT. Cisterns and sulci must be carefully examined for hyperdense acute blood, which can be subtle if the amount of hemorrhage is small, or if the bleed occurred more than 24 hours before CT. Although nonenhanced CT has a sensitivity of 97.5% when obtained within 12 hours of symptom onset, lumbar puncture can detect xanthochromic CSF in patients with SAH but normal CT scan results. This is particularly important in patients who are evaluated 12 or more hours after headache onset (5,10). Red cells detected by lumbar puncture performed immediately after the onset of symptoms may not permit distinction between spontaneous hemorrhage into the CSF and traumatic lumbar puncture. In the absence of SAH, nonenhanced CT can detect signs of other pathologies, including increased density within a thrombosed dural venous sinus, venous infarction, and edema associated with intracranial mass lesions. If subtle abnormalities are found on nonenhanced CT, further imaging evaluation includes contrast-enhanced CT or MRI. In the absence of SAH, MRI is a more sensitive technique to evaluate the patient for other causes of headache, including dural venous sinus occlusion, venous infarct, and intracranial infection. If SAH is detected, cerebral arteriography is generally used to further evaluate the location and features of an aneurysm or arteriovenous malformation.

Magnetic resonance angiography (MRA) and CT angiography are useful for rapid, noninvasive diagnosis of intracranial vascular lesions. CT angiography is a dynamic, CT-based angiographic technique in which thin slice images are obtained rapidly and continuously during the first pass of the arterial phase of an intravenous contrast infusion. In this manner, axial images covering several centimeters of the cervical or cerebral vessels can be acquired in less than 1 minute. Using rapid computer processing, planar and three- dimensional reconstructions can be created to display the enhanced blood vessels in a manner analogous to the projection images from catheter arteriography. CT angiography or MRA can assist in the rapid diagnosis or exclusion of aneurysms and arteriovenous malformations in the acutely ill patient, or to clarify subtle findings in patients with questionable abnormalities on nonenhanced CT. Similarly, carotid dissection can be detected by imaging the upper cervical vasculature with either technique (see Fig. 14-5) (11,12).

Chronic Headache

Imaging findings are unrevealing in most cases of isolated chronic headache. Nonetheless, intracranial lesions sometimes present only with headache, although they are usually associated with other neurologic signs or symptoms (13). When headaches are caused by underlying pathologic disorders, the differential diagnosis is broad. Serious primary conditions include intraparenchymal, dural, or skull base tumors (14); unruptured aneurysms (15); abscesses; arterial dissection (16); venous sinus thrombosis; and arteriovenous malformations. CT or MRI without intravenous contrast excludes most intracranial masses, and if the results are normal, can reassure the clinician and justify continued clinical observation and symptomatic treatment. If the clinical evaluation points toward metastasis, abscess, or a vascular process, then contrast-enhanced CT or MRI is an appropriate study.

Acute sinusitis is a common cause of headache or facial pain and can be diagnosed by plain film or CT (see Chapter 52). Screening sinus CT is more sensitive than plain radiography and is now used routinely at our center. Designed as a rapid, limited CT examination targeted only at the paranasal sinuses, this study can be performed at only a modestly increased cost compared with plain films. CT has the additional advantages of evaluating the middle ear and mastoid air cells, as well as the subtle bony and mucosal changes reflecting chronic sinusitis. In the patient with recurrent sinusitis, thin section coronal CT assists in planning of endoscopic sinus surgery (Fig. 14-6) (17).

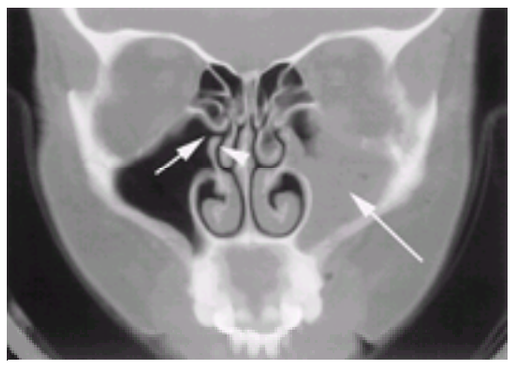

Figure 14-6. Chronic sinusitis. Coronal, nonenhanced screening sinus computed tomography through the face shows opacification of the left maxillary sinus caused by chronic inflammation (*long arrow*). The osteomeatal unit (*short arrow*) and uncinate process (*arrowhead*) are clearly demonstrated on the opposite side.

The syndrome of CSF hypotension is characterized by positional headache and variable symptoms of nausea and vomiting and visual, auditory, or vestibular disturbances. Normal CSF pressure in the recumbent position, and in the absence of prior lumbar puncture, is between 7 and 18 cm H_2O. CSF hypotension can be caused by spontaneous development of a CSF leak (18) or may result from diagnostic lumbar puncture, epidural anesthesia, myelography, head injury, or overdrainage of CSF shunts (19).

Spontaneous, posttraumatic, and postlumbar puncture CSF hypotension probably reflect chronic leakage of CSF through a dural defect (20). Cranial MRI with gadolinium demonstrates smooth, continuous enhanced dural thickening, subdural effusions, and downward vertical displacement of the brain. In some cases, the dural thickening may extend inferiorly to involve the spinal canal as well. These findings may disappear with resolution of CSF hypotension after successful treatment by blood patch, epidural saline injection, or surgical repair of the defect (21,22 and 23). Headache with MR findings of diffuse enhanced dural thickening, not explained by prior surgery or infection, should prompt a diligent search for occult spontaneous CSF leak. Such occult, spontaneous leaks may recur through the skull base, or, less frequently, via a spinal dural defect (Fig. 14-7).

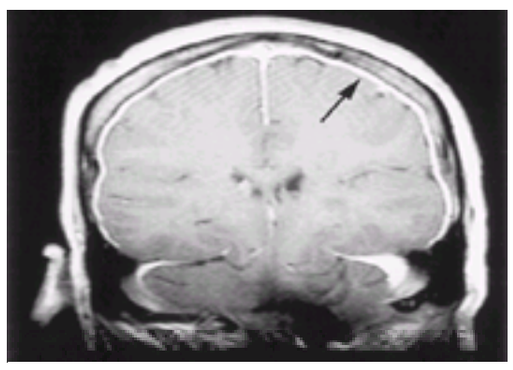

Figure 14-7. Cerebrospinal fluid hypotension caused by overshunting. A 54-year-old woman with ventriculoperitoneal shunt. Diffuse dural thickening and enhancement (*arrow*) caused by shunt valve with insufficient resistance. Similar findings may be seen in patients with postlumbar puncture, dural tears, or posttraumatic cerebrospinal fluid leaks.

FACIAL PAIN

Intractable trigeminal neuralgia (tic douloureux) can be related to a branch of the superior, anterior, or posterior inferior cerebellar artery that contacts the cisternal portion of the fifth cranial nerve (24) (see Chapter 47). Surgical intervention with placement of a prosthesis to separate the offending vessel from the root entry zone of the cranial nerve is often effective in relieving symptoms (25). Diagnosis of vascular loops in the prepontine cistern and cerebellopontine angle was difficult before the development of MRI. Thin section high-resolution MRI and MRA, using specialized, phased array radiofrequency receiver coils and multiplanar or three-dimensional reformatting can accurately demonstrate all relevant posterior fossa structures and aid in identification of surgical candidates (26,27 and 28).

The diagnosis of vascular loop syndrome is made by demonstration of a blood vessel contiguous with, or preferably distorting, a cranial nerve close to its origin from the brainstem at the root entry zone (Fig. 14-8). This portion of the nerve is sensitive to irritation from pulsations in the contacting artery. The diagnosis is based on appropriate clinical symptoms as well as definitive MRI/MRA findings, because a small number of asymptomatic patients show vascular loops contacting the cranial nerve origins. Imaging findings alone do not justify surgical treatment, which is based on symptom severity and failure of medical therapy. Other causes of trigeminal nerve dysfunction include meningioma, schwannoma, arachnoid cyst, chordoma, and chondrosarcoma. These can be diagnosed by conventional cranial MRI and CT.

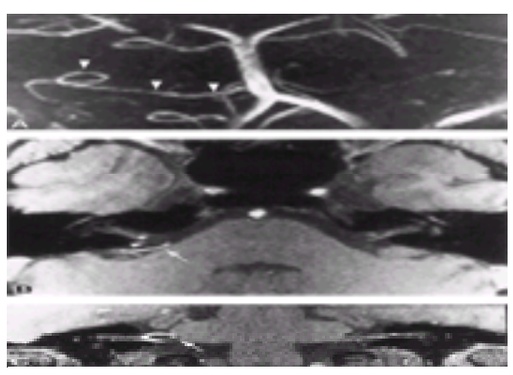

Figure 14-8. Vascular loop compression of the eighth nerve. **A:** Anteroposterior projection of a magnetic resonance arteriogram (MRA) of the vertebral basilar arterial system shows a good demonstration of a prominent right anterior inferior cerebellar artery (*arrowheads*). However, this standard MRA display does not allow one to determine the relationship of the looping portion of the vessel to the underlying neural structures. **B:** Axial source image of the MRA now shows a good demonstration of a vascular loop (*arrow*), which lies contiguous with the eighth nerve near its origin from the brainstem. **C:** Coronal reformatted image from the MRA data set confirms the contiguous position of the vascular loop with the eighth nerve near its root entry zone (*arrow*).

Vascular loops can compromise other cranial nerves in the basal cisterns. Chronic vertigo can be caused by posterior fossa vessels contacting the root entry zone of the eighth nerve (see Fig. 14-8) and compression of the intracisternal seventh nerve can result in hemifacial spasm. High-resolution MRI/MRA can be used to identify potential vascular loop syndromes causing these symptoms.

SPINAL PAIN

Technical advances in surgical fusion of lower lumbar vertebrae have resulted in safer, less invasive operations and have generated renewed interest in diagnostic tests that might predict a favorable surgical outcome for the back pain patient (29,30 and 31) (see Chapter 76). Conventional MRI, CT, and CT myelography can accurately evaluate spinal canal or neuroforaminal stenosis, lumbar disk protrusion, extrusion, or sequestration in the patient with pain and radiculopathy (32). Gadolinium-enhanced MRI can distinguish between postsurgical scar and recurrent disk herniation in the patient with prior back surgery and persistent or recurrent pain (33). Because of the prevalence of degenerative changes, annular tears, and herniated disks in asymptomatic patients, CT or MRI findings alone do not prove that a given disk is the cause of the individual patient's pain (34).

Before the advent of spinal CT and MRI, diskography was the only radiologic technique for directly assessing the anatomy and integrity of the intervertebral disk. From this anatomic standpoint, CT and MRI have replaced diskography (35). Indeed, its present role is as a provocative test, with the aim of selecting patients with a greater likelihood of improvement after spinal fusion procedures. Diskography involves injection of radiographic contrast material into an anatomically abnormal (suspect) disk and one or two normal (control) disks, and recording the patient's reported pain sensations during injection (Fig. 14-9) (36).

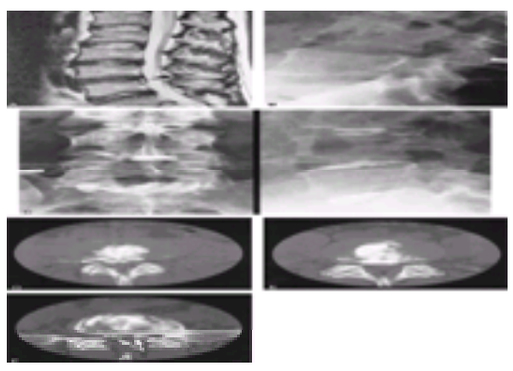

Figure 14-9. Diskogram. A 34-year-old man with chronic lower back pain with radiation to left leg. **A:** Sagittal T2-weighted lumbar magnetic resonance imaging examination demonstrates an annular tear at L-4–5 as well as mild disk dessication at L-3–4 and L-5–S-1. **B:** Lateral fluoroscopic spot film showing placement of 25-gauge Chiba needles within the intervertebral disks at L-3–4, L-4–5, and L-5–S-1.

C: Anteroposterior (*left*) and lateral (*right*) fluoroscopic images after injection of contrast material. During contrast injection, the patient reported no pain at L-3–4, mild (2/10) pain similar to clinical symptoms at L-4–5, and minimal (1/10) pain unlike clinical symptoms at L-5–S-1. **D:** Postdiskography axial computed tomography through L-3–4. Internal fissures and small central annular tear (*arrow*). **E:** Axial computed tomography through L-4–5. Internal fissures.

F: Axial computed tomography through L5–S1. Internal fissures and annular tear with focal herniation (*arrow*).

Diskography is performed with fluoroscopic guidance and meticulous sterile technique. The risks of the procedure, including nerve root injury, contrast media reaction, diskitis, osteomyelitis, and epidural abscess are reviewed with the patient (37,38 and 39). After sterile preparation of the skin over the flank and generous local anesthesia, 22- or 25-gauge needles are placed into the center of both suspect and control disks via an oblique coaxial approach. One milliliter to 2 mL of nonionic contrast material is injected into each disk, and the patient is questioned as to the severity of pain with contrast injection and whether it is similar, different, or exactly the same as their usual back pain. Fluoroscopic and CT images are obtained at each disk level to evaluate disk morphology and to confirm appropriate placement of contrast. A positive test result is indicated by reproduction of the patient's symptoms during injection of a morphologically abnormal disk, without similar discomfort on injection of control disk levels (40).

Diskography is a unique provocative test for diskogenic pain, but patients' reporting of symptoms during disk injection can be affected by psychological factors as well as interview technique (41,42). The diskographic identification of a painful disk also does not guarantee that the patient will respond to surgical fusion at that level (43). Because ongoing controversy exists as to its accuracy and value (44), diskography is probably best indicated before proposed surgical therapy in the setting of severe, intractable back pain without radiculopathy or CT or MRI evidence of disk herniation. In this setting, diskography may confirm the levels of symptomatic disks, or may be nondiagnostic, with pain at both suspect and control levels.

MAGNETIC RESONANCE NEUROGRAPHY

Neurogenic pain involving the neck, shoulder, and the upper extremity can result from cervical nerve root compression, brachial plexopathy, thoracic outlet syndrome (TOS), ulnar nerve entrapment at the elbow, or median nerve compression at the carpal tunnel (see Chapter 56). Precise definition of the level of nerve compression or injury can be difficult, even with electrodiagnostic studies. MRI of the cervical spine and brachial plexus and MR neurography permit direct visualization of the brachial plexus and peripheral nerves and can confirm the presence of neural irritation, edema, or compression (45,46 and 47). Pathologic states caused by variant anatomy, prior trauma, scar tissue or mass lesion, and musculoskeletal causes of pain can be excluded (Fig. 14-10, Fig. 14-11 and Fig. 14-12). MRI of distal musculature can provide evidence of denervation in the distribution of a given peripheral nerve (Fig. 14-13 and Fig. 14-14).

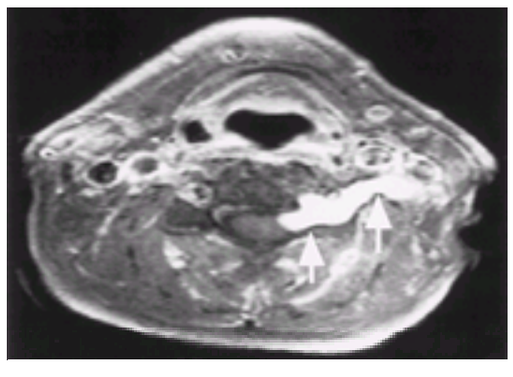

Figure 14-10. C-5 schwannoma. An 81-year-old man with 4 years of left upper extremity pain and dysesthesia. Axial and coronal short tau inversion recovery images

reveal a dumbbell-shaped high signal intensity extradural mass involving the left C-4/5 neural foramen (*arrows*).

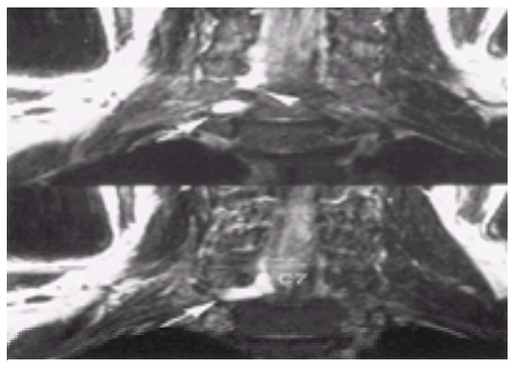

Figure 14-11. Nerve root avulsion. A 25-year-old man with traumatic injury to the right brachial plexus following a motorcycle accident that resulted in a flail upper extremity. After the accident he suffered from daily, intermittent, lancinating pain. Electromyography demonstrated absent cortical and brainstem response to stimulation of median and ulnar nerves and upper trunk of brachial plexus (C-6–8 roots). Coronal T1 and short tau inversion recovery images show proximal meningeal diverticuli at C-6, C-8, and T-1 (*arrow*) as well as abnormal signal in the right brachial plexus.

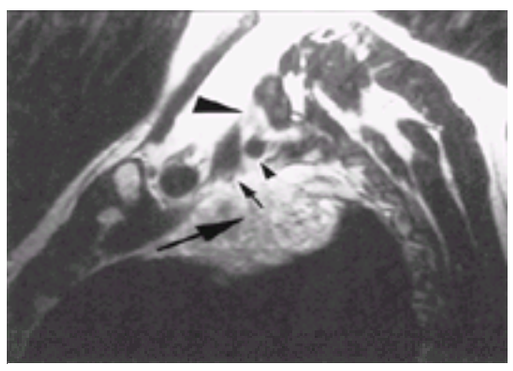

Figure 14-12. Pancoast's tumor. A 42-year-old man with mild cough. Posterior superior mediastinal mass was identified on plain radiograph. Sagittal T2 images demonstrate the pulmonary apex mass that abuts but does not surround the subclavian artery. At surgery, the mass was found to be a hemangioma. Magnetic resonance imaging is useful for evaluating the extent of chest wall tumors as well as brachial plexus and vascular invasion.

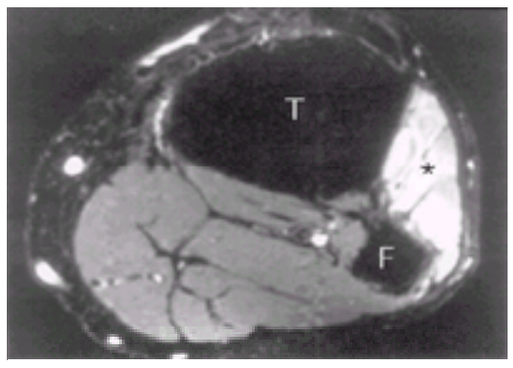

Figure 14-13. Subacute denervation in the distribution of the peroneal nerve. This axial short tau inversion recovery image of the proximal calf at the level of the fibular head (F) and the tibial metaphysis (T) demonstrates markedly hyperintense signal intensity within the anterior compartment muscles (*asterisk*). Note the muscles of the posterior calf for comparison, which show normal signal intensity. This illustrates the typical appearance of acute and subacute denervation that in this case followed severe injury to the left common perineal nerve.

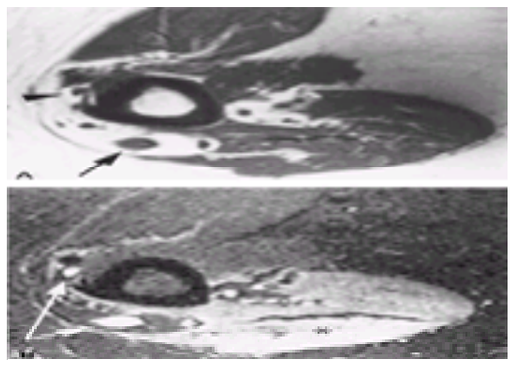

Figure 14-14. Ulnar and radial nerve injury. This patient suffered a severe left brachial plexus injury, with radial and ulnar neuropathy. **A:** T1-weighted axial image through the left upper arm showing location of the radial (*arrow*) and ulnar (*arrowhead*) nerves. T1 sequences generally demonstrate anatomic relationships better than corresponding short tau inversion recovery sequences. **B:** Short tau inversion recovery image showing increased signal in radial and ulnar nerves (*arrows*) as well as increased signal in triceps muscle (*asterisk*).

Brachial plexus, cervical root, or sacral MRI is optimally performed using a phased-array surface coil and large matrix size. Coronal and sagittal T1-weighted images provide superb anatomic definition. Fast spin echo T2 and short tau inversion recovery (STIR) sequences are sensitive to changes in normal signal intensity within the roots, trunks, and cords of the brachial plexus. STIR sequences suppress signal from fat, increasing the conspicuity of abnormal nerves. It is often helpful to image both sides of the patient simultaneously for comparison with the asymptomatic side (48). Optimal MR neurography at the elbow, wrist, or arm also requires high-resolution surface coils, a large matrix size, T1, fast spin echo T2, and STIR sequences. Imaging is conducted in the axial plane (perpendicular to the nerve) and either the coronal or sagittal plane. Acute and subacute denervation of muscles supplied by peripheral nerves is evident as increased signal on T2 and STIR sequences, loss of muscle volume, and sometimes enhancement after gadolinium administration. Chronic denervation results in marked loss of muscle mass together with fatty infiltration. The increased T2 changes seen in acute and subacute denervation are not seen. Axial T2 or STIR images of the musculature supplied by an injured peripheral nerve can identify denervation and are an indirect but effective means of determining the affected nerve and level of injury (see Fig. 14-13 and Fig. 14-14) (45).

Abnormal changes in peripheral nerves identified by MR neurography include focal or generalized enlargement of the nerve, increased signal on T2 and STIR

sequences, loss of fascicular architecture, enhancement after administration of gadolinium, and displacement or compression of the nerve by soft tissue or osseous masses. MR neurography requires specialized surface coils and high-resolution techniques for optimal imaging. It is particularly useful for patients with unexplained neuropathy, for whom surgical intervention is planned, or when the anatomic site of abnormality remains unclear after clinical examination and electrodiagnostic studies (49,50).

ENTRAPMENT SYNDROMES

Extremity pain, dysesthesia, and weakness can result from entrapment of nerve roots, compression, injury, or infiltration of the brachial, lumbar, or sacral plexi and compression of peripheral nerves at several sites (51,52). Anatomic diagnosis is not always clear and may require imaging of the spine or trunk as well as the affected extremity.

Cervical spine MRI, CT, or CT myelography demonstrate intervertebral disk herniation, spinal canal and neuroforaminal stenoses, and degenerative changes in evaluating radiculopathy. Contrast-enhanced MR can identify spinal cord and vertebral tumors in addition to postoperative scars. Brachial plexus and pelvic MRI, using high-resolution phased array coils, can define the course of nerve roots, trunks, divisions, and cords in the patient with plexopathy, as well as detecting masses, traumatic injuries, and inflammatory changes (48) (see Fig. 14-10 and Fig. 14-11). Direct imaging of peripheral nerves at common sites of entrapment can confirm the location of injury or tumor, and patients who might benefit from decompressive surgery can be identified (Fig. 14-15; see Fig. 14-14) (50).

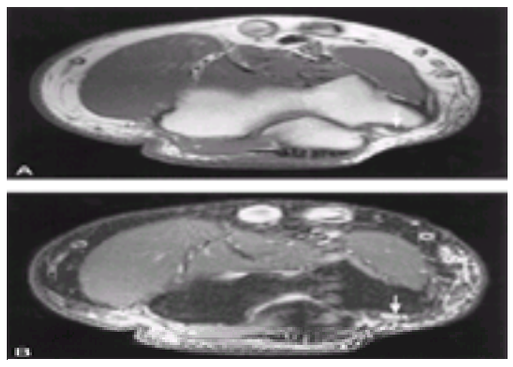

Figure 14-15. Ulnar entrapment. Axial T1 (**A**) and short tau inversion recovery (STIR) (**B**) images of the right elbow taken at the level in which the ulnar nerve passes through the cubital tunnel. **A:** On this T1-weighted image, a normal sized right ulnar nerve is nicely demonstrated surrounded by perineural fat (*arrow*). **B:** The STIR image, however, demonstrates abnormally increased hyperintensity within the nerve that is abnormal (*arrow*) and that, in the presence of appropriate symptoms, is an indication of ulnar nerve entrapment.

Brachial Plexus

The true TOS is a rare condition caused by compression of the lower trunk and or medial cord (C-8 and T-1 nerve roots) of the brachial plexus between the first rib, the anterior scalene, and the middle scalene muscles (see Chapter 55). Most patients have a controversial syndrome characterized by variable supraclavicular and upper extremity pain, dysesthesia, and weakness without the presence of an anomalous cervical rib or objective physical examination or electromyographic findings of nerve abnormality (53). A minority of patients have a predominately vascular form of TOS with symptoms resulting from subclavian artery compression or venous insufficiency and possible thrombosis (54). Because musculoskeletal inflammatory conditions, complex regional pain syndromes, and distal compressive neuropathies can have similar symptoms, the diagnosis of TOS can be extremely difficult. Although decompression of the inferior brachial plexus and subclavian vessels by transaxillary resection of the first rib has been successful in management of some patients with TOS, generally after a trial of physical therapy, the decision to operate is rarely straightforward.

The role of imaging in suspected TOS is not clearly established at present and is currently under evaluation. Panegyres and colleagues reported sensitivity of 79% and specificity of 87.5% for the detection of distortion or displacement of the brachial plexus or subclavian vessels in 20 patients with symptoms of TOS who underwent bilateral brachial plexus MRI examination. They also described soft tissue bands arising from the C-7 transverse process in 75% of symptomatic sides and 16% of control sides (55). In contrast, Poole and colleagues did not identify soft tissue bands in any of the 23 patients with clinical TOS who had MRI examinations. They believed history and physical examination were the most helpful predictors of good surgical outcome, and that imaging and electrodiagnostic studies were valuable primarily in identifying other sources of pain (56). Continuing improvements in high-resolution MR examination of the brachial plexus may help to identify surgical candidates on the basis of nerve signal abnormalities, but prospective studies have not yet been published.

Peripheral Nerve Entrapment Syndromes

Carpal tunnel syndrome is the result of median nerve compression at the carpal tunnel (see Chapter 59). Clinical features, usually sufficient for diagnosis, include paresthesia and hyperesthesia in the median nerve distribution, radiation of pain along the volar aspect of the forearm, nocturnal pain, exacerbation with repetitive movements, and atrophy of the thenar muscles. Carpal tunnel syndrome is most often caused by repetitive injury of the median nerve within a compromised carpal tunnel volume, but can also be caused by focal space-occupying lesions, local inflammatory processes, or metabolic derangements related to systemic illness (57,58). Proximal nerve entrapment in the cervical spine, thoracic outlet, and along the course of the median nerve can mimic carpal tunnel syndrome. The pronator syndrome, and the anterior interosseous syndrome are distal median nerve compression syndromes in which the nerve is compressed by the two heads of the pronator, or after the branching of the anterior osseous nerve, along the interosseous membrane, respectively. Both of these syndromes can produce symptoms identical to carpal tunnel syndrome (49).

Although ultrasound and CT have been used to evaluate anatomy of the carpal tunnel and visualize the median nerve (59), MR is superior to these technologies in confirming the diagnosis of carpal tunnel syndrome, by virtue of its greater contrast sensitivity and its ability to detect abnormal signal intensity changes within a compressed median nerve. A coronal T1 scout image allows selection of axial scan levels through the wrist. Axial T1 and STIR (or T2) images should be obtained at the distal radiocarpal joint, proximal carpal tunnel, distal carpal tunnel, and metacarpal bases. Dedicated phased-array coils are valuable in increasing image quality to better demonstrate these small structures (Fig. 14-16) (45).

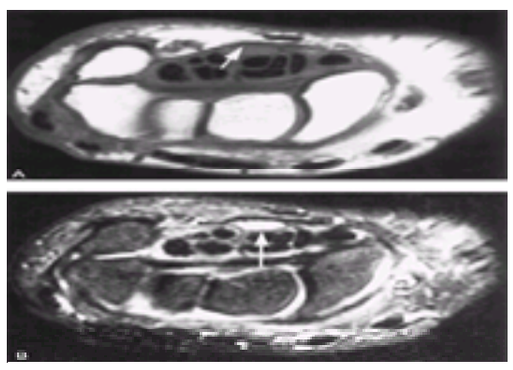

Figure 14-16. Carpal tunnel syndrome secondary to tenosynovitis. **A:** Axial T1 image through the carpal tunnel shows increased girth of the median nerve and bowing of the flexor retinaculum (*arrow*). **B:** Corresponding axial short tau inversion recovery image shows increased signal in the median nerve (*arrow*), as well as high signal fluid surrounding the tendon sheaths.

Findings in carpal tunnel syndrome include increased girth of the median nerve proximal to the carpal tunnel, flattening of the nerve within the tunnel, increased bowing of the flexor retinaculum, and increased signal intensity of the median nerve on T2 and STIR sequences. Ganglion cysts, lipomas, posttraumatic or degenerative bony deformities, and other soft tissue tumors are easily identified on MRI. Thickening or separation of tendons with increased signal changes on T2 or STIR sequences indicates tenosynovitis. Often idiopathic, it can also be caused by trauma, rheumatoid arthritis, and chronic infection. Amyloid, gout, acromegaly, hypothyroidism, and other systemic diseases associated with carpal tunnel syndrome are generally diagnosed on the basis of clinical, laboratory, and plain film findings (60,61,62 and 63).

Similar entrapment syndromes are also found in the ulnar canal at the elbow, peroneal nerve behind the knee, and at Guyon's canal, in which the distal ulnar nerve enters the wrist (64). High-resolution, surface coil MRI can be diagnostic, but its application requires careful attention to the anatomy of the particular nerve involved (45).

Imaging studies play an important role in the facilitation of diagnostic and therapeutic nerve blocks (see Chapter 102, Chapter 103 and Chapter 104). Accurate placement of needles for the injection of local anesthetic or neurolytic substances can be confirmed by radiographs, fluoroscopy, or CT scanning. These imaging techniques can prove the localization of a needle at a specific anatomic site and confirm the actual nerve or nerve root that is being blocked. The injection of a contrast agent with a local anesthetic solution can reveal the distribution of the agent used and confirm which nerves have been exposed to the anesthetic solution. This is particularly important when a surgical decision is based on the responses to nerve blocks. These techniques are particularly useful in patients whose anatomy has been distorted by disease processes or prior surgical procedures. The development of open magnet MR scanning may lead to an increase in the use of this imaging technology in the performance of nerve blocks.

Radiography is commonly used to confirm the placement of needles in the performance of facet joint blocks, paravertebral somatic nerve blocks, or transsacral blocks. Fluoroscopy is used in the placement of epidural electrodes or catheters. Surgical procedures such as gangliolysis of the trigeminal nerve or radiofrequency rhizolysis or spinal nerves are performed with fluoroscopy. CT scans are commonly used for celiac plexus block. Modern imaging techniques facilitate the use of nerve blocks by providing proof of the exact location of the needle or the spread of injectate.

CONCLUSIONS

Diagnostic imaging in patients with acute pain has a clearly defined role in establishing or confirming a pathologic diagnosis, and directing medical, surgical, or radiologic intervention. Patients suffering from chronic, recurrent, or intractable pain from degenerative disease, anatomic variations, chronic inflammatory conditions, neoplasm, and postoperative or posttraumatic scarring may benefit from specialized imaging examinations for the determination of etiology, treatment planning, and prediction of the outcome of directed therapy.

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CHAPTER 15

Measurement of Pain

C. Richard Chapman and Karen L. Syrjala

This edition of this book, like its predecessors, emphasizes that pain is a complex perceptual experience. When pain is acute, it is often psychologically inseparable from fear and general distress. When it is chronic, it can become the focal element in a complex network of suffering that involves depression, somatic preoccupation, physical limitation, sleep disturbance, and hopelessness. Despite this complexity, meaningful evaluation of a patient with pain, and successful treatment, typically require quantification of the patient's pain.

Monitoring the severity and duration of pain can enhance patient care and improve the fit of the treatment to the patient. Such monitoring is essential for quality patient care in circumstances with fluctuating pain intensity: postoperative settings, intensive care environments, management of the cancer patient, and during the performance of invasive diagnostic procedures. The ability to quantify relevant dimensions of chronic pain also is critical for successful patient management because (a) chronic problems have a relatively stable baseline and permit rigorous assessment to determine outcomes of interventions; (b) evaluating treatment effects protects against the dangers of overmedication and repeated surgery; and (c) when a poor fit exists between demonstrable organic disease and pain behavior, treatment of chronic pain is often a process of rehabilitation that requires documentable increases in activity level and functional capability. Certain dimensions of pain, but not others, might indicate the success or failure of treatment. Furthermore, some patients or some types of problems are better suited for certain interventions than for others. Optimal matching of patient and treatment strategy depends on accurate and comprehensive assessment of the pain problem.

This chapter provides an introduction to the measurement of pain in clinical environments. We offer an overview of current methods for the assessment of acute and chronic pain and discuss basic issues to consider when measuring pain. Finally, we provide guidelines for measuring pain in different settings and maintaining a clinical database. For a comprehensive treatise on pain measurement, the reader can consult the *Handbook of Pain Assessment* by Turk and Melzack (1).

BASIC CONSIDERATIONS

Progress in Pain Measurement

Bonica published the first edition of this book in 1953. The ensuing decades have produced substantial progress in pain assessment, theory, and technology. Theorists and clinical researchers now agree that pain is a complex experience rather than a simple sensation. Simplistic concepts such as pain threshold have largely disappeared from contemporary parlance in the field of pain. Elegant methods of multidimensional assessment of pain have emerged to replace them. Many of these have attempted to exploit the words used to describe pain in the construction of rigorous test instruments. Increasingly, clinical investigators are assessing both sensory and affective dimensions of pain. Some have extended assessment to include the ways that pain interferes with daily living.

The importance of the cardinal distinction between acute and chronic pain, which Bonica emphasized in the first edition (2), has gained wide acceptance, and many care providers now understand that pain complaint can reflect complex psychological and even sociologic factors in addition to sensory and emotional experience. Many new tools for measuring pain in clinical settings have emerged in the 1990s. The most recent reveal an increasing tendency to measure syndrome-specific pain states. No single standard exists for quantifying pain in all circumstances.

Noteworthy progress has occurred in measuring pain associated with life-threatening diseases such as cancer and acquired immunodeficiency syndrome (AIDS). Also, both theoretical and technological advances have led to the development of tools for the assessment of functional impairment related to pain states. Increasingly, clinical investigators are finding that subjective measures of pain intensity, taken alone, are rarely adequate as indicators of patient well-being or as gauges of response to intervention. Pain causes fatigue, impairs concentration, prevents restorative sleep, and makes normal or productive behavior difficult. Accordingly, the newer pain measurement tools assess the subjective phenomenology of pain together with its effect on daily living (see Chapter 16).

The challenge of reliably quantifying pain still remains, but progress continues in this area. Enthusiasm for improving pain measurement has not waned within the scientific or clinical community. Thanks to the precedents of the pain guideline documents produced by various organizations, including the Agency for Health Care Policy and Research at the National Institutes of Health (3,4), recording pain has become standard practice in many hospital and other clinical settings.

Pain Assessment in Acute Versus Chronic Pain

As other sections of this book emphasize, acute pain is a transient, continuously changing state that differs radically from normal daily life (see Chapter 1). It relates intimately to intense emotional arousal, it typically has at least a rough association with tissue pathology, and it usually has clear, well-focused sensory location and characteristics. Acute pain states can be brief, lasting moments or hours, or they can persist, lasting weeks or months until the disease or injury heals. Chronic pain, in contrast, is an enduring condition that has become a component of the daily life of the patient. This definition excludes many forms of cancer pain or rheumatoid arthritis but includes pain associated with other persistent musculoskeletal, neuropathic, visceral, and degenerative disorders, and pain problems with behavioral components. Its sensory characteristics are more often, but not always, multifocal and vague, sometimes inappropriate for the organic pathology evident, and relatively similar across time. As with headaches or postherpetic neuralgia, the problem can become a chronic part of someone's daily life even while the pain itself may come and go. Although the same technology applies to the measurement of acute and chronic pain, the goals of assessment and the interpretation of the measures are usually different.

Some psychologists emphasize the difference between state and trait psychological measures. The term *state* refers to a situation -specific condition linked to, and defined by, specific circumstances. Postoperative pain, therefore, is clearly state variable. A *trait*, in contrast, is a relatively enduring tendency to feel or behave in a certain way across most circumstances much of the time. Chronic low back pain, that endures for years or decades and limits normal behavior in all areas of life, is a trait variable. The interpretation of measures differs for state versus trait variables although the actual measurement tools may be the same.

In assessing a patient or evaluating an intervention, one should conceptualize the state versus trait distinction clearly to predict treatment-related changes in either state or trait indicators. State changes in measures drawn from chronic pain patients, although easy to obtain (e.g., ratings of pain intensity), are usually of limited value because it is the trait variable that is in question. Trait measures, in contrast, allow the clinician to determine whether the chronic pain has really changed; they are often indicators of pattern or trend. Goals of measurement with acute and chronic pain can be viewed as analogous to short-term and long-term variability in the values of market stocks. Day-to-day levels are highly variable and of limited use in predicting the success of a long-range investment. Trends of values over months (traits), on the other hand, provide useful predictors for long-term investment. If, in contrast, one plans to withdraw funds from the market by next week, the long-range trend is less relevant than the short-term movement. The treatment of pain in a chronic pain patient is clearly like a long-range rather than a short- range investment. Therefore, assessment of chronic pain must involve trends and long-range change. In addition, it usually extends beyond the measurement of pain intensity alone to the measurement of the effect of pain on patterns of physical and psychosocial functioning.

APPROACHES TO MEASURING PAIN

Below, we present the major approaches to the quantification of pain and attempt to describe their advantages and limitations.

Pain as Self-Report on a Single Dimension

Category Scales

Category scales consisting of verbal or visual descriptors offer patients a simple method for reporting the private intensity of pain. These scales require only the choice of the best word or picture from the patient. For example, Melzack and Torgerson (5) introduced the following scale for pain intensity: mild, discomforting, distressing, horrible, and excruciating. Alternatively, one can use an eight-point facial expression picture scale for pain assessment (6) (Fig. 15-1). In developing countries, picture scales with differently sized familiar objects, such as cooking fires or coins, have worked well for scaling pain intensity. These approaches may be most effective for older people unaccustomed to scaling their experiences, those with limited language or verbal fluency, the young, or poorly educated populations, because scaling of this sort is not limited to words. The disadvantages of this scaling approach include the need to remember or have a printed form for the words or pictures and the limited possible range of responses to the number of words or pictures in the list. Statistical manipulation of category data is usually limited to nonparametric methods, which reduces the robustness of such scales. Moreover, on some scales, patients tend to use the middle rather than the ends of category scales, thus distorting the judgment process and further reducing the possible range of responses.

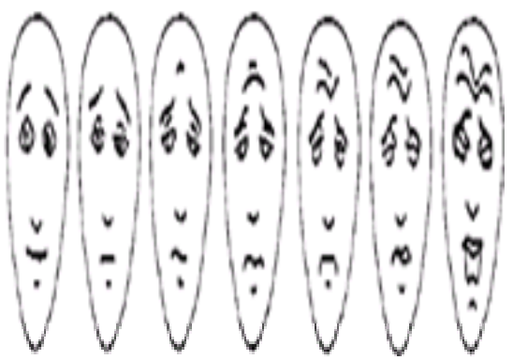

Figure 15-1. Faces Pain Scale for Adults and Children. (From Bieri D, Reeve RA, Champion GD, et al. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties. *Pain* 1990;41:139–150, with permission.)

Numeric Rating Scale

In clinical settings, it is often important to be efficient and minimize staff and patient burden when collecting data. The simplest and most frequently used approach to assessing pain states is a numeric rating scale (NRS). Patients indicate how intense their pain is on a scale from 0 to 10, on which 0 typically represents “no pain at all” and 10 “the worst pain imaginable.” Such tools typically scale pain severity or intensity, but some clinical investigators use them to study the aversiveness or bothersomeness of pain (its affective dimension). Most patients readily understand this type of scale, and a nurse or physician can administer it either orally or in written form. McGrath and colleagues (7) developed a scale for children that uses color to code sensory intensity and faces with varying expressions to code affect. The child gives a nonverbal response on each dimension, but the instrument provides the caregiver with a corresponding NRS. This approach demonstrates the possibility of extracting a numeric score from a measurement device having a nonnumeric interface.

Visual Analog Scale

An equally simple and efficient to administer alternative is the visual analog scale (VAS), which usually consists of a 10-cm line anchored at one end by a label such as “no pain” and at the other end by a label such as “the worst pain imaginable” or “pain as bad as can be.” The patient simply marks the line to indicate pain intensity, and the provider then measures the length of the line to the mark on a 101-point scale (8). A slide rule–like device with the line on the patient's side and numeric score on the obverse facilitates clinical assessment. The main disadvantage of the VAS is the time required to measure the scale. For busy clinicians or researchers with large volumes of data, this can be an impediment to assessment. Although these tools are relatively straightforward, researchers have reported that 7% to 11% of patients are unable to complete the VAS or find it confusing (9,10), and one reported that 26 of 98 patients in a particular sample could not complete a VAS (11). Examples and practice using common pain problems, such as headaches of varying intensity, can help patients who seem not to understand use of the scale.

Nonwritten versions of the NRS or VAS work with very sick patients if the provider instructs them to give a number from 0 to 10 or asks them to hold up from 0 to 10 fingers, or if someone runs a pencil slowly along a VAS while the patient nods his or her head at the point that corresponds to current pain.

Fig. 15-2 provides examples of several simple pain scaling instruments. Clear patient instruction in their use is essential for meaningful data collection. For the NRS and VAS, patients must understand the labels at the two end points and that they are free to indicate a response at any point in the scale.

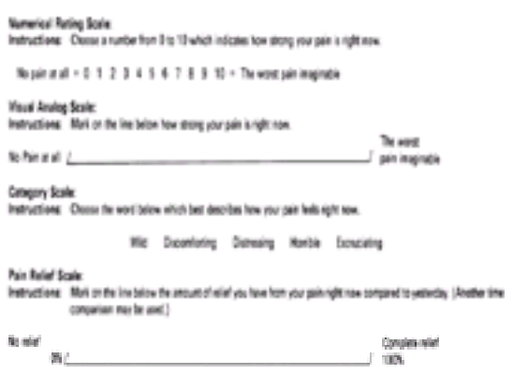

Figure 15-2. Single-dimension, self-report measures. These include the following scales: Numerical Rating Scale, Visual Analog Scale, Category Scale, and Pain Relief Scale.

Carlsson (12) critically evaluated the VAS as an indicator of pain state or pain relief in chronic pain patients, comparing different forms of the scale. Reliability, as judged from consistency of response to the two forms, was low, and Carlsson concluded that the validity of VAS procedures for chronic pain populations might be unsatisfactory (see also reference 13). Other research, however, has supported the reliability and validity of the VAS as a sensitive measure of pain and change in pain (14).

Mantha and colleagues (15) advocated using statistical confidence intervals (CIs) with VAS data. A CI provides a range of values based on the observed data that contains, with a specified probability, a true but unknown variable typifying a population of scores, usually the mean. In other words, instead of reporting a simple mean VAS score, an investigator might report the mean together with the 95% CI for that mean. This has practical value in studies of analgesic effect. If we define as *effective* a treatment that reduces pain to a level within 0 to 30 on a 100-point VAS and then carry out a study, we need to determine whether the treatment really worked. If the entire 95% CI for the posttreatment scores falls within the 0- to 30-point range, then we may assume with confidence that the treatment was effective. If only the mean falls within that range, our confidence in the outcome is less. This approach lends itself well to graphic depiction.

A plethora of other, more subtle issues about scale construction and presentation have emerged in the literature but do not merit detailed description here. The important point is that even a simple and rapidly administered tool can fail if the provider does not exercise sufficient care to ensure accurate, valid, and reliable reporting. The primary limitation of single dimension subjective scaling of pain resides in the strong risk of oversimplifying assessment of the pain problem by not adequately addressing the complex nature of the experience. A simple, subjective indicator of pain intensity provides, for example, no information about the effect of the pain on sleep or function.

Pain as Self-Report on Multiple Dimensions

For all but the most brief, predictable, procedural pain, competent measurement requires, at minimum, that clinical investigators ask patients to report intensity, qualities of the pain (e.g., burning, aching, throbbing), location(s), and interference with function (16,17). Location is usually indicated by having patients point to where on their bodies they feel painful sensations or by having them mark a body drawing (Fig. 15-3). Although location is difficult to use as research data, other than descriptively, it assures clinicians that they understand where the patient feels pain and assists in defining etiology. Interference with function is important when pain occurs while patients are expected to perform other activities. Without interference ratings, a clinician would consider a patient with pain intensity of 3 on a scale from 0 to 10 to have good pain treatment. However, if the clinician discovers that the pain is only at a 3 because the patient does not move off the couch, pain management is clearly less than adequate. Verbal descriptors of the sensory qualities of pain are increasingly important as we define treatments specific to different characteristics. The major distinction currently is between somatic or visceral pain versus neuropathic pain. Verbal descriptors and precise location description are the best measurement tools for differentiating these etiologies. Words selected from the McGill Pain Questionnaire (MPQ; see following discussion) can be used to distinguish burning, shooting, electric, or pins and needles pain from throbbing, aching, heavy pain, and these two groupings have been used effectively to define appropriate treatment (18).

Figure 15-3. The McGill Pain Questionnaire. (From Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;1:277–299, with permission.)

Some investigators compensate for the unidimensionality of NRSs and VASs by using several of them, each designed to assess a different dimension of pain such as intensity or unpleasantness. With this approach, it is difficult to ensure that the response to the first scale administered does not influence the response to following scales. Carlsson (12) emphasized that patients must respond to each scale without the opportunity to compare the present response with other, previous VAS estimates.

Alternative approaches offer multidimensional scaling, but they do so at the cost of increased responder burden. Many investigators prefer to develop instruments that simultaneously measure pain on multiple dimensions, sometimes combining VASs, NRSs and category scales. Below, we review several instruments that illustrate the variety in multidimensional pain measurement approaches.

McGill Pain Questionnaire

The MPQ (19) is one of the more extensively tested multidimensional scales available. It scales pain in three dimensions: sensory, affective, and evaluative (see Fig. 15-3). The test instrument consists of 20 sets of words that describe pain. Patients select the sets that are relevant to their pain and circle the words that best describe the pain within any selected set. Each set has from two to six words that vary in intensity for the quality described by the set. The first ten sets represent sensory qualities, the next five are affective, set 16 is evaluative (intensity), and the last four sets are miscellaneous words. It is possible to score each dimension and to obtain a total score. An adjunct questionnaire, termed the *Dartmouth Pain Questionnaire,* can supplement the MPQ through the assessment of three additional factors over and above pain quality. These include a general affective dimension, the time course and intensity of pain, and behaviors affected by pain (20). One advantage of the Dartmouth Pain Questionnaire is its consideration of remaining positive aspects of functioning rather than just impairment. As Sacks (21) has emphasized in his discussion of impaired neurologic patients, evaluation of patient weakness and limits to the exclusion of strengths and assets is an incomplete evaluation and possibly a disservice to the patient.

Statistically, numerous studies have supported the factor structure of the MPQ, its reliability, and its concurrent validity (22,23). The MPQ takes between 5 and 15 minutes to complete, however, and thus it places a larger burden on the patient than a VAS or NRS; some patients cannot handle the vocabulary of the instrument; and the scoring procedures available have limitations (22). Walsh (11) commented that when patients complete the MPQ in the presence of their spouses, the spouse may interfere by offering alternatives or urging changes. Turk and colleagues (24) critically evaluated the MPQ and various approaches to its scoring. They concluded that the total score is valid as a general measure of pain severity, but one should not interpret individual scale scores. They could not demonstrate adequate discriminative validity to support scaling at the level of sensory, affective, and evaluative dimension subscales. This paper calls to question the multidimensional scaling capability of the MPQ.

As a clinical tool, the MPQ helps define the quality of a patient's pain, both in its sensory dimensions and its affective effect. It is helpful to review the words with patients to ensure that they understand the meaning of each word, and it is possible to administer the scale orally, reading each word set and having patients indicate which word in the set, if any, describes their pain. With this method, even quite sick patients have been able to complete the measure. Research indicates, however, that oral and written responses to the MPQ are not necessarily equivalent. Therefore, one should maintain a standard format to compare scores obtained in two ways (25).

One can use the MPQ in combination with other tools. Haas and Nyiendo (26) evaluated the diagnostic value of the MPQ for low back pain, combining it with the Oswestry Disability Questionnaire. They found the combination of these inventories valuable for ruling out nonspecific low back pain and ruling in radiculopathy, with and without neurologic deficits. This suggests that the MPQ in combination with measures of function may prove clinically useful.

Memorial Pain Assessment Card

Perhaps the fastest means of assessing multiple dimensions of the pain experience in sick patients, or those undergoing evaluation for pain control is the repeated use of a VAS. The Memorial Pain Assessment Card scales pain, pain relief, and mood on VASs and adds a set of adjectives reflecting pain intensity (27). The card is illustrated in Figure 15-4. The advantages of this measurement tool are that it takes only seconds to use, it is correlated with other, longer measures of pain and mood, and the provider can fold the card so that the patient sees only one scale at a time.

Figure 15-4. The Memorial Pain Assessment Card. (From Fishman B, Pasternak S, Wallenstein SL, et al. The Memorial Pain Assessment Card: a valid instrument for evaluation of cancer pain. *Cancer* 1987;60:1151–1158, with permission.)

Pain Perception Profile

A radically different approach to multidimensional scaling comes from a psychophysical technique, known as *cross-modality matching*, that quantifies a sensory experience by matching it to the experience of a precisely controlled stimulus in a different sensory modality. For example, one might match the intensity of a toothache produced by electrical tooth shock to the perceived loudness of a controlled tone. The technology by which spontaneous pains of natural origin are matched to controlled stimuli is too complex to warrant description here. The typical procedure involves matching words describing pain to measurement in another dimension (e.g., line length or hand grip strength), matching both to experimental pain, and then deriving scaling standards for the relationship of words describing pain to actual pain. One can apply such methods to clinical pain assessment. Some investigators use them to assess multiple dimensions of pain, such as intensity and unpleasantness, as demonstrated by Gracely and colleagues (28).

The Pain Perception Profile (29) uses cross-modality matching. It (a) measures sensation threshold; (b) uses magnitude estimation procedures to judge induced pain; (c) measures pain on intensity, reaction, and sensation dimensions via psychophysical scaling of verbal pain descriptors; and (d) allows the user to administer the three dimensions of psychophysically scaled verbal descriptors in a diary format for repeated assessment over time. Compared with the MPQ, cross-modality matching is shorter and less demanding once the psychophysical scaling is complete. Doctor and colleagues (30) used this approach to develop the Descriptor Differential Scale of Pain Intensity. It offers potentially more reliable and valid data than the simpler VAS scales. However, this approach and that of Gracely and colleagues (28) require validation work for different patient populations. This necessitates experimental pain testing and a substantial amount of development before clinicians can interpret data from a broad sample of patients confidently. These methods seem promising as measurement tools for the future.

Pain as a Multidimensional Experience that Includes Effect on Daily Living

Clinicians often measure pain to assess the effect of an intervention to relieve it. A single pain rating, or even ratings that include sensory and affective components, cannot provide a comprehensive indicator of patient well-being or functional capability. If, after treatment, a patient experiences increased levels of physical activity, less fatigue, better mental concentration, and more social interaction, but the same reported average pain intensity, then the clinic may take satisfaction in a job well done. On the other hand, if the patient reports good pain relief but demonstrates no improvement in physical activity and other functioning, then the pain report is either spurious or an incomplete indicator of treatment effect. Ultimately, a cost-effective intervention for pain must relieve the negative effect of pain on daily living. What patients can do after treatment is as important as what they say about their subjective sense of pain relief.

The impetus for development of new instruments that assess pain and impairment of function is economic as well as clinical. Pain clinics must demonstrate that their sometimes costly interventions have made a difference in pain patients' ability to work, worker productivity, and health care use. A growing literature now underscores the importance of assessing the functional capability of chronic pain patients, and it offers several instruments that can scale the impact of pain on daily living.

The measurement of function in chronic pain patients is problematic for two reasons. First, different pain syndromes appear to require different measures of pain effect. The effect of low back pain on a patient differs from that of temporomandibular joint pain or shoulder pain. Therefore, measurement instruments are becoming specific for syndromes. Second, the relationship of the disease causing the pain (e.g., arthritis) to the degree of impairment is rarely, if ever, strong. This makes it difficult to interpret the relationship of pain as a subjective state to functional impairment. Finally, sex differences exist in daily function that require different norms for men and women (31). Generic indices of functional status do not take these into account, and this can become problematic for some highly specific pain syndrome instruments. Similarly, the activities of daily living change over age. A single instrument might fare poorly for adolescents and geriatric patients if its designers had middle-aged people in mind. Thus, before using any measure, identification of the sample in which the instrument was standardized is important.

Brief Pain Inventory

Cleeland and Ryan (32) described the history of the Brief Pain Inventory (BPI) (Fig. 15-5), its reliability and validity across cultures and languages, and its particular usefulness for cancer pain research. The design of the BPI reflects an important principle. The goal of pain relief is to reduce two targets: the subjective intensity of pain and the disability that pain causes. The BPI quantifies both targets.

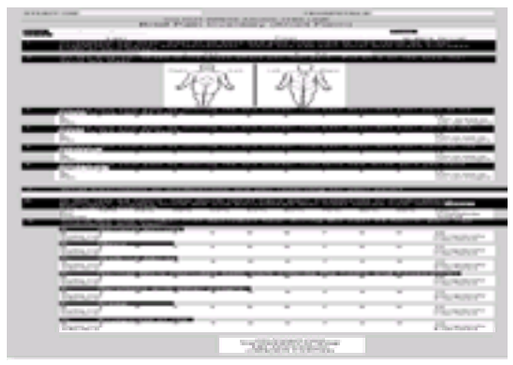

Figure 15-5. Brief Pain Inventory. (From Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994:23:129–138, with permission.)

The BPI is a quick, multidimensional pain measurement tool with demonstrated reliability and validity in patients with cancer, AIDS, and arthritis (33,34 and 35). In 5 to 15 minutes, patients provide subjective ratings of pain intensity (pain worst, pain least, pain average, and pain right now), and, importantly, they also report the effect

of pain on multiple functions (general activity, mood, ability to walk, normal work, socializing with others, enjoyment of life, and sleep). All but 6% of 1,200 hospitalized cancer patients selected for study were well enough to complete the questionnaire, and only 7% refused to participate in the study. Thus, this measure is a good choice for multidimensional pain measure in patients with progressive diseases. Portenoy and colleagues (36) and Breitbart and colleagues (37) used a pain-related functional interference index (sum of the seven item BPI subscales) in a study of pain and functional impairment in patients with life-threatening disease. This instrument is available in several languages, including French, Spanish, and Chinese (38).

Investigators studying cancer pain are on the lookout for simple measures that correlate strongly with both intense pain and major impairment of function. Serlin and colleagues (39) explored the relationship between numeric ratings of pain severity and ratings of pain's interference with such functions as activity, mood, and sleep. They used interference measures to grade pain severity. They grouped severity scores into three categories: mild, moderate, and severe. Based on the degree of interference with cancer patients' function, severity ratings of 1 to 4 corresponded to mild pain, 5 to 6 to moderate pain, and 7 to 10 to severe pain. Thus, brief measures of pain severity can convey information about expected levels of functional impairment in cancer patients.

West Haven–Yale Multidimensional Pain Inventory

The West Haven–Yale Multidimensional Pain Inventory provides an alternative to the MPQ (40). This questionnaire, by design, is shorter and more classical in its psychometric approach to multidimensional scaling than the MPQ. The 56-item inventory comprises three parts: (a) five general dimensions of the experience of pain and suffering, interference with normal family and work functioning, and social support; (b) patients' perceptions of the responses of others to displays of pain and suffering; and (c) frequency of engagement in common daily activities. The instrument is linked to cognitive-behavioral theory and assesses constructs beyond subjective distress, including effect of the pain problem on general functioning. As such, it represents a broader approach to scaling than the MPQ. The Multidimensional Pain Inventory has found wide use with diverse pain syndromes, and various studies have replicated the scale structures.

The West Haven–Yale Multidimensional Pain Inventory assesses dimensions relevant in chronic pain problems. With acute or persisting pain problems of progressive nature, such as cancer or rheumatoid arthritis, extensive evaluation of social contingencies for pain behavior is not always necessary. Furthermore, with patients who are quite ill, one must balance needs for speed and minimal response burden against the value of multidimensional assessment.

Sickness Effect

The presence of persisting pain can limit and frequently disable a patient. For the patient with low back pain (the best-studied type of patient in the chronic pain population) this effect consists of increased hours spent reclining or in bed rest, restriction of normal social and recreational pursuits, emotional distress, and expressed inability to maintain gainful employment. The concept of sickness effect is for most practical purposes interchangeable with that of disability.

No comprehensive, validated objective indicators of sickness effect exist at present. Instead, investigators use behaviorally oriented subjective report procedures. Activity diaries, which provide a daily record of up time or down time, medication use, and type of activity, provide a common example of this approach (41). One can tabulate a variety of variables obtained from diary forms and plot them over time. It is possible, however, to go well beyond the daily diary in an attempt to scale systematically the physical, social, and psychological limitations imposed by (or adopted in response to) sickness.

One of the most carefully developed and fully validated of the behaviorally oriented instruments is the Sickness Impact Profile (SIP) (42,43). This instrument is a general indicator of health status and health-related dysfunction rather than a pain-specific test. An interviewer can administer it, or the patient can complete it. Patients respond only to the sickness-related behavior change items that describe them appropriately. The SIP provides general scores along three dimensions of disability (physical, psychosocial, and overall) and 12 specific category scores that include, for example, communication, social interaction, and home management. Its measures are derived from responses to 136 items.

Follick and colleagues (44) studied the SIP scores of 107 patients seen at a multidisciplinary pain clinic, 75% of who were receiving worker's compensation payments. The outcomes supported the validity of this instrument as an indicator of functional status in patients with low back pain. The psychosocial dimension of the SIP correlated significantly with Minnesota Multiphasic Personality Inventory scores; the physical dimension score related inversely to independent measures of standing and walking and correlated positively with down time as recorded on activity diaries. These authors concluded that the SIP is a useful means of assessing functional impairment in patients with back pain. The SIP is gradually gaining validation in other populations of patients with chronic pain. The Chronic Illness Problem Inventory (45) shows promise as a useful alternative measure of dysfunction in chronic low back pain patients because it is shorter and easier to score than alternatives.

Back Pain and Function

Functional limitation and disability are an important part of the low back pain syndrome (46). A set of largely objective physical function measures is available for use with patients with low back pain (47). This group of rehabilitation-focused indicators, which works in concert with a battery of psychological measures, includes eight categories of measurement: range of motion, cardiovascular fitness and muscular endurance, gait speed, timed simulation of daily activities, static lifting, lifting under load, isometric and isokinetic dynamic trunk strength, and a global effort rating. A definitive study repeated these measures through the course of treatment and provided feedback on functional capacity to patient and surgeon. Although 92% of patients were unemployed before treatment, only 18% failed to work when treated with this objectively derived rehabilitation model combined with psychological intervention. Again, although not direct measures of pain, these measures of functioning may offer as much or more value in successful treatment or treatment planning as self-report of pain intensity. It is worth noting that even with the high rehabilitation rate of the patients in the study cited, and with a significant decrease of self-reported pain, these patients maintained a mean VAS pain report of 77 out of a possible high score of 150. Clearly, in the treatment of chronic pain, one must define goals and priorities to determine which measures indicate successful treatment.

Many alternatives exist for assessing disability associated with back pain. The Quebec Back Pain Disability Scale (48,49) quantifies functional disability for patients with low back pain, operationalizing disability in terms of perceived difficulty in performing simple physical activities. It is a 20-item scale that assesses six empirically derived categories of activity associated with back pain. Beurskens and colleagues (50) assessed and compared four instruments designed to quantify functional status in low back pain patients: Oswestry, Million, Roland, and Waddell disability questionnaires. The validity and responsiveness of all four seemed favorable. These authors commented that “Functional status measures are not currently used in many settings in which they would be valuable.”

Manniche and colleagues (51) introduced the Low Back Pain Rating Scale, a tool that quantifies pain intensity, disability, and physical impairment. By design, the scale monitors the outcome of clinical trials of low back pain treatment. Westaway and colleagues (52) developed the Patient-Specific Functional Scale and demonstrated that it is an efficient and valid measure for assessing disability and change in disability in persons with low back pain and knee dysfunction.

Pain as Behavior

Many pain states entail certain consistent behavior patterns. For example, studies have shown that patients with back pain tend to grimace, guard their movements, rub themselves, and sigh (53; see Chapter 25). When clinical pain is operationally defined as behavior, one can use objective measures. Clinical researchers can identify selected behavior patterns related to pain, quantify them in terms of frequency or rate of occurrence, and assess them via direct or videotaped observation of patients in settings involving specific task performance. Because behavioral patterns are complex, many of the newer behavioral measures are multidimensional.

Measurement of Pain Behaviors

Medication use (daily amount, frequency of self-administration) is a common measure of pain behavior, although this approach does not provide an adequate measure of pain intensity. It represents an objective measure in a hospital setting, but it is subject to some bias if dependent on patient self-report (see Self-Reports of Behaviors, later in this chapter). A number of other examples exist in the literature of how one can quantify pain behaviors; in general, the method tallies behaviors over time and scores them in terms of frequency. Keefe and Block (54) developed an observational system for scoring pain behavior in patients with chronic back pain. They assessed guarded movement, bracing, rubbing, and sighing. These indexes proved reliable and valid (in relation to reported pain), and the behaviors were more frequent in pain patients than in normal persons or control patients with depression. Keefe and Hill (53) extended this approach by placing pressure transducers in patients' shoes to assess the parameters of walking. Patients and normal persons were required to walk a 5-m course while being videotaped. Patients walked more slowly than normal persons, took smaller steps, did not show normal symmetric gait patterns, and exhibited more pain behaviors. Patients receiving disability payments had significantly longer stride length and longer limb swing time than other patients. This approach thus appears promising for the assessment and objective quantification of back pain, although it is sometimes difficult to separate the effects of pain from those of other causes of functional limitations.

When designing pain behavior measures, the clinical investigator should observe patients in activities likely to evoke pain behavior but not to induce pain. For the patient with back pain, these activities would include walking and changing position, and for the patient with facial pain they might include talking and eating. The pain behaviors one might record for frequency or occurrence or nonoccurrence should be common indicators of pain in the location of interest. These might include grimacing, sighing, or holding the afflicted area. It is then essential to test the consistency of the observers, evaluate the reliability of the measure, and assess validity. Typically, the investigator must infer validity by comparing predicted changes before and after treatment, by examining the relationship of observed behavior scores to self-report of pain and other measures of functioning (see next section), and by looking for expected differences in rates of behavior between the target group and patients with pain at other locations or patients who do not have pain.

Weiner and colleagues (55) examined a group of elderly community-dwelling patients with back pain and lumbosacral osteoarthritis. They compared behavioral observation methods to self-report instruments and the degree to which pain and pain behavior related to disability. They used types of behavioral observations: One was identical to that of Keefe and Block (54), and the other simulated activities of daily living that involve an axial movement activities of daily living protocol. Self-report included a VAS scale and the MPQ. Correlational results revealed that self-reported pain was associated with pain behavior frequency. The association was stronger for the activities of daily living protocol than for the Keefe and Block protocol. The association between pain and disability was modestly strong with both self-report instruments and pain behavior observation under activities of daily living protocol conditions, but not with the Keefe and Block protocol. These authors concluded that observation of elders during performance of activities of daily living may be a more sensitive and valid way of assessing pain behavior than observing pain behavior during sitting, walking, standing, or reclining. Measures of behavior are particularly valuable for patients who are cognitively impaired or otherwise unable to produce self-report of pain. The major limiting factor is that correlations between self-reported pain and pain behavior are modest at best.

A significant limitation of the behavioral observation approach is that pain behaviors are highly specific for each pain syndrome. Patients with shoulder pain or headache, for example, might be indistinguishable from normal subjects on the Keefe and Hill (53) test. Keefe and colleagues (56) undertook behavioral evaluations of pain in patients with cancer of the head and neck to address this issue. They found that such patients displayed their pain primarily through facial expression rather than through guarded movements. Several investigators have developed syndrome-specific pain behavior and disability measures. For example, Heald and colleagues (57) developed the Shoulder Pain and Disability Index, and Vernon and Mior (58) developed the Neck Disability Index.

The search for more global indicators of pain behavior that might have broad application to different clinical populations continues but does not appear promising. Linton (59) investigated the hypothesis that reported pain intensity is inversely related to general activity level in patients with back pain (as measured by self-monitoring or observed behavior in a test situation). He found no relationship between activity level and intensity of chronic pain. Thus, behavioral indicators, used in conjunction with other measures, seem useful as highly specific and precise ways to quantify certain pain problems, but thus far they are not viable options as broad indicators of pain states. Much more definitive work is needed before we can use this approach to address a wide range of pain problems.

Self-Reports of Behaviors

One way to gather information about patients' behavior patterns and habits is to ask the patient, spouse, or some other day-to- day observer. This approach combines the simplicity and efficiency of self-report methods with the theoretical perspective of the behaviorist. It presupposes, however, that the patient (or the spouse) is a reliable and accurate historian. Ready and colleagues (60) found that patients with chronic pain, when asked to report medication use, gave information that was 50% to 60% below actual drug intake. Kremer and colleagues (13) compared patient records with staff observations of patient activity of social behavior and found significant discrepancies. Sanders (61) studied automated monitoring of up time in healthy control subjects, psychiatric inpatients, and patients with chronic back pain. He found moderate positive correlations between self-report and automated monitoring. All groups averaged less self-reported up time than the automated report indicated, the discrepancy being greatest for patients with chronic back pain.

These observations call into question the validity of some self-reports about behavior. When other observation measures are not available, however, and for clinical use, it is often desirable to have a patient complete a daily pain diary, rather than merely report retrospectively on a persisting or chronic pain problem. A *pain diary* is a log of pain-relevant activities broken down into small blocks of time, such as hourly or quarter-hourly segments. The diary form divides activity into such categories as sitting, walking, and reclining, and the patient reports the specific activity under the appropriate category and the time the activity occurred. Typically, diary forms require that the patient rate the pain level on a 0 to 10 numeric scale for each hour and record medication use (Fig. 15-6).

Figure 15-6. A pain diary page for 1 day.

The use of a pain diary with chronic pain patients offers several advantages: (a) Because patients complete the diary each day, it is less subject to distortion based on the patient's current pain experience at the time he or she visits the doctor's office (see Temporal Referent in Self-Report of Pain , later in this chapter); (b) it provides information on patterns of normal activity relative to patterns of pain behavior (or pain-linked inactivity) that is not available from other behavioral assessments; (c) it is inexpensive; and (d) it provides direct information about patient behavior in the home. From the pain diary it is possible to determine behavioral patterns, defined in terms of the time of day or activity, that result in high pain levels versus average pain levels. It can also yield information about time the patient spends in various activities or inactivity over a week. In general, it helps clarify the relationship between pain, activity, and medication use.

The limitations of the pain diary merit comment. For example, the reliability of the pain diary is unknown, because it depends on the accuracy of the patient and the patient's compliance. Some patients complete the form on a daily or hourly basis as directed, but others fill out the form incompletely or do it retrospectively just before their office appointments. With these limitations in mind, we believe that this measure is a useful supplement to subjective pain report when other behavior observation data are unavailable.

SOME SPECIAL CONSIDERATIONS IN PAIN MEASUREMENT

Temporal Referent in Self-Report of Pain

Patient memory for pain, while the patient is in a relatively pain-free state, is reasonably accurate up to a week after postsurgical pain (62,63). For pain problems that do not remit, research has demonstrated that current pain intensity produces systematic distortions of memory for prior pain, independent of treatment outcome (64). This influence of current pain on memory of past pain in persistent or chronic situations suggests that the most unbiased measure of pain would specify current level.

In acute pain circumstances, clinical investigators most commonly ask patients to rate their current pain. With persistent pain, patients more often rate their worst pain in the past 24 hours and their average or usual pain in the past 24 hours. Although more vulnerable to deficits in memory, clinicians sometimes ask about pain in the past week.

Assessment of Pain in Children

Measurement of pain in children requires awareness of developmental stages (see Chapter 44). Just as verbal fluency and the ability to follow instructions develop

with age, pain behavior also appears to vary with development. When assessing pain in infants, one must rely on gross motor indicators of generalized body reaction, reflex withdrawal, and crying. Toddler pain behavior can include pressing the lips together, rocking, rubbing, kicking, hitting, biting, attempting to run away, or opening the eyes wide (65). Although categorizing neonatal and toddler responses is progressing, none of these behaviors is unequivocally pain specific; reliable behavior observation measures available for assessing pain at these early ages are still at issue.

For pediatric patients from age 3 and older, a range of tools is available for self-report and behavior observation. In the area of self-report, a number of studies have indicated that children from approximately age 5 are able to reliably complete a VAS (66,67). With a young child, it is helpful to practice with a VAS on familiar pain problems, such as a skinned knee, to be certain the child understands the scaling before assessing the current pain problem. For children younger than age 5 or those who have difficulty with a VAS, a number of alternatives exist. These include a NRS in the form of a thermometer (68), a color-matching technique in which children choose a color that best represents their pain (69), the *Oucher*, a picture scale validated with children as young as 3 (70), or the Faces Pain Scale (71,72), validated in children from 4 to 8, with good validity and rank order as well as approximate ratio scaling properties. These scales are strictly single-dimension ratings of pain intensity. For multidimensional self-report, some investigators hold that the MPQ is valid for children down to age 12 (65).

Development of behavior observation measures specific to children has focused on pain associated with invasive diagnostic procedures in cancer patients. Researchers have recognized that these children often cannot discriminate between the affective (anxiety) dimension and pain intensity; and consequently these measures tend to be a composite index of distress. Katz and colleagues (73) found that young children display a greater variety of anxiety behaviors over a longer time than older children. As children age, they tend more toward withdrawal and muscle tension behaviors in response to painful procedures. Several researchers have developed behavior checklists with similar types of observed activities (73,74 and 75). Jay and colleagues (74) have revised and developed the work of Katz and colleagues (73) to produce the Observation Scale of Behavioral Distress. The categories in this measure are weighted according to intensity and include crying, screaming, physical restraint, verbal resistance, requests for emotional support, muscular rigidity, verbal expression of fear, flailing, nervous behavior, and information seeking.

As with adults, the multidimensional measurement of pain in children enhances ability to determine appropriate intervention and to assess treatment outcome. In addition to measuring pain intensity and pain behavior in children, it is valuable to assess parental anxiety, because a significant relationship exists between child behavioral distress and parental anxiety (74).

Assessing Pain in the Elderly

Adults of any age may be capable of completing any of the assessment measures described previously (see Chapter 45). However, when patients are older, examiners should anticipate a number of factors that are less often considered in younger adults (17). The areas to assess are the same. The selection of instruments may need some adaptation. Disputes in research results make it unclear whether the elderly are more likely to make errors in completing VAS format pain intensity ratings or other types of intensity scales (9,76,77). If questions exist as to whether a patient is able to understand the VAS or NRS, the Faces Pain Scale for the elderly (6) has been well validated and demonstrates excellent rank order and test-retest reliability, with even some support for ratio scaling. Recommendations from Herr and Mobily (17) are worth repeating. Avoid time pressure; if necessary, select fewer instruments rather than trying to rush an elderly patient who may be having difficulty with comprehension or vision. Evaluate impairments in hearing, vision, dexterity, comprehension, and articulation, along with ability to communicate verbally. One option is to have the patient read a part of the assessment tool to evaluate some of these capabilities. Even mild hearing problems can reduce concentration and understanding if background noise is interfering. Common visual impediments must be considered in selecting tools. These include reduced visual acuity, rate of visual accommodation, color discrimination, and adjusting to glare of lights on paper or eyes. Large, simple, upper and lower case letters help, as does greater space between lines. For their Faces Pain Scale, Herr and colleagues recommend 4-cm-high drawings, with heavy, dark lines (6). Keeping the content simple and providing practice examples can help the patient to comprehend and pay attention. Oral response to items, or scales that allow pointing, can ease some visual and dexterity difficulties. If self-report capability is limited, observer reports may be needed. No tools yet exist that offer clear, reliable, and sensitive behavioral methods for use with cognitively impaired elderly (78).

Cultural factors may inhibit pain report in the elderly. Reasons that patients may be less inclined to acknowledge pain include the following: (a) a belief that pain is expected and must be lived with as one ages; (b) fear that pain may lead to further loss of independence; (c) fear that pain may forebode serious illness or death; (d) unfamiliarity with what others may consider common terms in pain language; (e) justifiable concern that pain complaints will be dismissed as elderly hypochondriasis and lead to people avoiding them; and (f) stoicism (17,78). Other factors that influence perception of pain in the elderly lead to unpredictable modes of pain presentation. Although pain perception does not necessarily decrease with age (17,78,79), atypical presentations are not uncommon, particularly absent or mild pain report with serious illness such as myocardial infarction, peptic ulcer, appendicitis, and pneumonia. Conversely, pain complaints may be used to solicit interaction or may be heightened by boredom, loneliness, and depression. In their study of 758 nursing home elderly, Parmalee and colleagues (79) concluded that, although cognitively impaired, patients may underreport pain; their self-reports, when made, were as valid as those who were cognitively intact.

In summation, pain assessment in the elderly must be undertaken by planning to use the same tools as used with younger patients, but prepared for a wider range of evaluation before assessment and for adaptation of the assessment strategy if the factors described previously apply to the individual patient.

Physiologic Indicators of Clinical Pain

Pathophysiologic changes accompany acute and chronic pain (22,23). When pain is acute, it can be associated with motor reflexes that produce muscle spasm or splinting. When surgical or other trauma has occurred to the chest or abdomen, such reflexes impair ventilation. Autonomic reflexes also accompany acute pain and can inhibit gastrointestinal and genitourinary function, producing ileus and smooth muscle spasm (80). Less specific patterns of autonomically mediated arousal can contribute to distress and fear. Liberation of catecholamines increases blood pressure and cardiac output and increases rate of ventilation.

Secretion of b-endorphin (and b-lipotropin, a precursor) often occurs during acute pain, and in their presence pain intensity is diminished. Szyfelbein and colleagues (68) observed that the concentration of endorphins in plasma was negatively correlated with acute pain report. The greater the levels of b-endorphin, the lower the reported pain. Because endorphins are also linked to stress, however, their presence does not provide objective evidence of the presence of nociception. Therefore, plasma endorphin concentrations might be better indicators of endogenous pain modulation than of pain itself.

Pathophysiologic changes sometimes characterize the area of painful focus in patients with chronic pain. Skin temperature is perhaps the best studied. Some physicians use thermography, the measurement of skin temperature, in evaluation of certain types of chronic pain (81). Complex regional pain syndromes are characterized by temperature changes in the extremities (82). Myofascial pain syndromes, certain cancer pain syndromes, and certain other pain problems manifest low skin temperature in the area of the painful focus, which is indicative of altered sympathetic nervous system function. Pain accompanying some arthritic or rheumatologic conditions is associated with abnormal warmth because of acute inflammation.

Trophic changes occur with some types of chronic pain. When pain is related to trigger points in middle-aged and older patients, it is often accompanied by subtle indicators of autonomic dysfunction, such as enhanced pilomotor segmental reflex, vasomotor and sudomotor disturbances of the skin, and trophedematous changes in subcutaneous tissue (83).

Other physiologic correlates of pathologic pain states exist. Pupil dilation occurs with certain types of migraine headache. Cluster headaches classically involve skin flushing in facial areas. None of these signs, however, proves the presence of pain; nor does the absence of such signs mean that pain is not present. The presence of such correlates increases the probability that pain is present, but correlates do not validate or definitively indicate pain.

Measurement of Analgesia and Pain Relief

Analgesia strictly denotes complete absence of pain, but the term is ubiquitously misused to indicate any diminution of response to a painful stimulus or any relief of existing pain. To facilitate communication, we use the term *analgesia* rather than *hypalgesia* here to indicate reduced pain sensibility (diminished response to a painful stimulus rather than complete absence of ability to feel pain), but we distinguish it from the relief of clinical pain because the latter is a different concept. The term *pain relief* represents the therapeutic alleviation of clinical pain, as determined by subjective report.

The relationship of analgesia to pain is in some ways like the relationship of cold to heat. One can only define cold as the absence of heat, and it is necessary to measure cold in heat units. Similarly, analgesia by definition is the absence of pain in the presence of a normally painful stimulus. We must quantify analgesia in the pain units. The analogy breaks down somewhat, however, because pain is a complex perception that cannot be measured on a single scale, and pain is inherently

subjective. Just as many operational definitions for pain exist, so there can be many operational definitions of analgesia.

Many different analgesic phenomena exist. The mechanism of the analgesia caused by injection of a local anesthetic at a peripheral nerve is not the same as that induced by hypnosis, infusion of an opioid, or administration of a nonsteroidal antiinflammatory drug. In selecting a measure of pain for the evaluation of analgesia, it is important to recognize these differences and select an operational definition of pain that fits the phenomenon in question. Just as no generic index for pain suits all applications, so no all-purpose procedure exists for assessing analgesia. In general, however, the measurement of analgesia requires a pain challenge stimulus. Therefore, analgesia is defined in terms of the difference between a patient's normal or baseline response to the pain challenge and his or her response after an intervention.

Pain relief has occurred when a patient reports reduction in a subjectively defined clinical pain state after intervention. Clinical interventions of many sorts can relieve a pain state without reducing a person's ability to perceive a pain challenge stimulus, such as a pin prick. Nonanalgesic pain relief occurs when a treatment enhances endogenous inhibitory pain modulation mechanisms (e.g., the release of b-endorphin), blocks excitatory pain modulation mechanisms such as algogesic substances or sympathetic nervous system hyperactivity, or selectively blocks or eliminates the pathologic origin of the pain.

Scaling pain relief differs from measuring analgesic effect. It does not require a pain challenge stimulus, and it does not rely on pain scores. Patients typically estimate the amount of pain relief they have experienced in percentage units. They may report this scaling orally from 0% to 100%, or perhaps they use a VAS with anchors of “no change” to “100% pain relief” (see Fig. 15-2). This form of assessment presupposes that the underlying pain is relatively constant (if not chronic) and well known to the patient. Therefore, although this approach could prove problematic in assessing the benefits of a treatment for a postoperative pain that is novel to the patient and variable in intensity over hours or days after surgery, it might work well for cancer patients. Kaiko and colleagues (84) administered morphine to patients with cancer when their pain was either moderate or severe. Patients used a categorized scale to report pain relief: no relief (0), slight relief (1), moderate relief (2), lots of relief (3), and complete relief (4). Patients reported pain relief hourly for up to 6 hours. They constructed a total morphine pain relief score by summing the hourly pain relief scores. Total morphine pain relief varied with dose of drug, initial pain intensity, and site of pain. Complex differences in pain relief were also associated with age and race.

Caregiver Ratings of Pain and Pain Relief

It is sometimes necessary (never do if expedient, only if no other choice) to use judgments made by physicians, nurses, or family members about the patient's pain rather than the patient's own reports. Such data usually take the form of simple category scales such as no pain, slight pain, moderate pain, or severe pain. In some cases, scales incorporate judgments of what the patient can or cannot do on certain tasks, such as bending over to pick up a weight. Sometimes providers judge the success of a therapeutic intervention on an arbitrary scale, such as no pain relief, slight pain relief, moderate pain relief, or total pain relief.

Advantages exist to using such procedures in some populations. For example, patients who are too sick to make reports, are mentally incompetent, are heavily medicated, are on respirators, cannot speak English, or are too young to defy assessment by other than caregiver ratings. Moreover, it is efficient and inexpensive to collect data in this way.

The limitations of caregiver pain judgments are many in acute and chronic settings. First, caregiver judgments are not true measurements and cannot fully substitute for true measures. Pain is a subjective experience, and another individual can never truly observe a patient's pain. One can only infer pain in a patient. In acute care settings, confounding factors can distort such judgments (e.g., the rater's expectations, past experience, or belief about the patient's situation). Knowledge of the patient's organic condition can also bias the pain rating. Moreover, some raters stereotype patients. It is easy to say, for example, that Norwegians are always stoic after surgery, that Italians always vociferate even if the surgery is minor, that women cannot bear pain as well as men, all redheaded patients are hyperreactive, and that children are not as sensitive to pain as adults. These or other stereotypes might be accurate some of the time, but individual patients vary widely and no justification exists for gross generalizations, even when the literature has demonstrated trends in certain directions. If allowed to influence the data, stereotypes can greatly damage the quality of a study. Caregiver rating data are meaningful only when a well-trained rater generates them, using well-defined criteria for judgment. Often it is best to use multiple trained raters.

In the chronic pain setting, in which the efficacy of therapeutic interventions is at issue, different biases can affect rater judgments. Interactions between patient and therapist can lead to positive or negative bias in the therapist's judgments. Moreover, for many clinicians it is impossible to respond independently to each patient. The clinician's perceptions of success or failure concerning the day's preceding cases can greatly affect the ratings of pain relief made for any given patient. In such settings, it is often necessary to rely on a rater who has not been involved directly in the care of the patients undergoing assessment.

Caregiver perception of pain in an older pediatric patient population has proven problematic. Vetter and Heiner (85) compared patient VAS self-report of pain intensity with trained caregiver judgments (multiple raters, satisfactory interrater reliability). The patient-generated and caregiver-generated pain scores correlated poorly.

The limitations of the caregiver rating approach are evident in the literature. Many early studies of acupuncture analgesia, for example, obtained no actual measures of pain or pain relief. Instead, clinician investigators published their own ratings of therapeutic outcome. This was also true of early Chinese studies of acupuncture for pain control. It seemed expedient at the time to rush into print with minimal data, because acupuncture was a pressing mystery. History has dismissed most such studies as inconclusive, and these studies have had no effect on the way Western medicine views acupuncture.

We recommend using caregiver rating data to assess pain and treatment effect only when the patients in question are unable to answer for themselves or when the data are for medical records that will never be used for scientific purposes. If it proves necessary to use such ratings, it is worthwhile to develop and maintain rigorous criteria for the judgments made, to have multiple raters and periodically test their percentage agreement, and, if possible, to have collateral measures of pain or pain relief.

Limitations and Problems in Pain Measurement

In the process of measurement the clinician must (a) conceptualize the patient's pain problem clearly; (b) decide which attributes of the pain to quantify (i.e., the dimensions to scale); (c) decide on the goal of the measurement; and (d) initiate a process that attaches numbers to pain, either by clinician judgment, patient report, or both. Several limiting factors make the clinical measurement of pain a difficult challenge.

- Because no satisfactory objective indicators of pain exist, pain is a fundamentally subjective state. Even when the clinician elects to gather objective indicators of behavior in measuring pain, it is necessary to validate such measures with subjective reports of pain. This restriction to subjectivity reduces pain to a scientific metaphenomenon and forces the investigator or clinician to depend on the patient for accurate and reliable data. Moreover, clinical pain intensity does not vary directly with the extent or severity of clinical pathology or even with the number of nociceptors stimulated. For example, a poor relationship exists between reported pain and the size of a surgical wound (86) as well as between the severity, location, and extent of a burn injury and the pain of the patient (87).
- Pain is a multidimensional experience. The clinician can quantify it on a single dimension using, for example, a single VAS, but this approach risks potentially significant oversimplification (12). Pain has sensory, emotional, motivational, cognitive, and behavioral dimensions.
- The characteristics of pain worth quantifying depend on the patient population in question, the purpose of the assessment, and perhaps the theoretical orientation or scientific assumptions of the clinician investigator. No default standard exists for pain measurement. As emphasized elsewhere in this book, many ways exist to define pain as a clinical problem. Definition depends on the patient population at hand and the basic assumptions of the clinician or investigator. A neurologist approaching chronic pain as a sensory problem might well use operational definitions that are different from those of a behaviorist or a psychoanalytically oriented psychiatrist. No universal index of pain is equally useful for all health care professionals.
- The greatest difficulty in measuring pain is the intrinsic predicament of measuring subjective states of any sort. Measurement is only valid when the numbers obtained correspond in a one-to-one fashion to the underlying variable undergoing measurement. One can never test this validity in the assessment of pain states; consequently, numbers obtained from patients or test instruments as pain measures are not so much actual scores as estimates of pain. One can readily obtain numbers that appear to be measures of pain but in fact are not valid. Inexperienced clinicians may err by oversimplifying the problem (e.g., by measuring only pain intensity in a chronic pain patient), using a weak or unreliable scaling method, or by failing to clearly instruct patients about how to report their pain in numbers.

GUIDELINES FOR SELECTING TEST INSTRUMENTS FOR PAIN EVALUATION

What makes a satisfactory instrument for pain measurement? Most test instruments are based on patient self-report, although it is possible to restrict measurement to

the quantification of behavior alone. In general, clinical pain assessment requires that instruments for subjective report the following: (a) place a minimal burden on patients; (b) be understandable from the patient perspective; (c) produce a wide range of scores and show sensitivity to analgesic or psychological intervention; (d) demonstrate appropriate reliability and validity; and (e) have appropriate norms. For a given application, the choice of a testing device or procedure depends on the unique needs and theoretical bent of the clinician and the limitations of the patient population. No substitute exists for careful planning and forethought in the selection of assessment procedures; no single instrument or procedure is a standard for all applications.

Defining the goal of the assessment is the first step in determining an appropriate choice of measures. In an acute pain situation lasting minutes, and in which the goal is to determine an appropriate medication level, a brief numeric rating of pain intensity from 0 to 10 before and after medication administration might suffice for assessing the adequacy of intervention or the need for further assessment. In chronic pain situations, however, it is nearly always advisable to assess pain with a multidimensional model that includes self-report, behavioral observation, and functional evaluation.

Pain problems exist in which various aspects of multidimensional assessment are uniquely important. For example, the patient who talks cheerfully to family but tearfully complains of pain when alone might require assessment of observed pain behavior and functional status as well as self-report of pain. The same is true for the patient with acute pain who wakes up long enough to ask for medication but is asleep again before the medication arrives. Measurement goals might be defined beyond a generic determination of appropriate treatment. Diagnosis of disease state might be the primary target of assessment. Alternatively, it might be useful to assess the effect of pain on functioning, to define areas of remaining function or well-being, or to evaluate the dependence of pain behavior on environmental factors. Setting clear goals permits the clinician to choose measures within and beyond pain assessment *per se* that provide the most comprehensive yet selective information required for the problem.

The algorithm in Figure 15-7 provides an example of how one might select pain measurement tools for different clinical situations. For immediate purposes, we have defined *brief acute pain* as that which lasts minutes, hours, or days and for which appropriate brief medical intervention is usually the defined goal. *Acute persistent pain* is defined as that which lasts weeks or even months, with slowly healing organic pathology, but has a clear nociceptive origin. Proper diagnosis or adequate medication coverage might be the primary goal of assessment, but it might also be necessary to assess the effect of pain on functioning, to look at environmental contingencies that might support the development of a chronic problem, or to assess the potential effectiveness of an intervention over and above administration of medication. When pain is related to progressive diseases, acute episodes might emerge intermittently in response to nociceptive events (e.g., the painful diagnostic procedures repeatedly performed on cancer patients). In addition, the level of functional impairment varies from individual to individual as a function of factors other than pain intensity alone. Therefore, optimal selection of measurement tools depends on the goal of assessment and the individual being assessed. With chronic pain problems that are not progressive, it is nearly always advisable to assess pain behavior and general functioning in addition to self-reported pain level. In many cases, it is also important to evaluate the personality and environment of the patient in planning appropriate treatment.

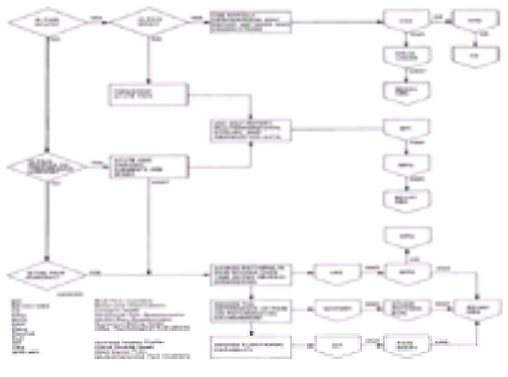

Figure 15-7. Algorithm for selection of pain measurement instruments.

Although thoroughness is of value in treatment planning and assessment of treatment effectiveness, redundancy in information provides only copious information for its own sake and risks alienating or decreasing the motivation of the patient. Unless one is testing the validity of a number of measures for use in a certain population, it is advisable to choose a single measure to assess each of the required dimensions. As an example, if a clinical investigator measures pain quality with the 20-word sets of the MPQ and pain intensity by a VAS, it would not then be necessary to complete the pain intensity ratings of the McGill questionnaire or to complete other measures of pain quality. Establishing a preset plan for pain assessment—a readily available set of forms, scoring procedures, and, most important, plans for use of the resulting information—can ease the work for staff and patient while ensuring that effort has value.

Developing a Clinical Database

A clinical database for pain can greatly facilitate patient management and evaluation of therapy. Until the 1990s, only university clinics or large medical centers could collect, store, and analyze patient data. With the advent of personal computers and easy to use software, the individual physician in practice or the private clinic can afford a small system and the required programs.

Value of a Database

The advantages of a database are obvious. The computer can retrieve and graph important data on patients from all previous visits. From such records, trends in activity level, reported pain, social behavior, or other relevant factors are readily available for examination. This makes it inexpensive to evaluate the effects of changes in medication, surgery, behavioral interventions, or other treatments. Below, we offer some basic guidelines for the physician who wishes to develop a database for pain patients and demonstrate the effectiveness of intervention for third-party payers.

Guidelines for Database Development

Design the Data Layout Carefully from the Beginning

Most commercial database programs assist in data layout, but they are for business rather than for medical applications. Therefore, the physician must plan carefully or enlist the aid of a programmer with expertise in database work. It is often best to find the programmer before buying the software. A database consists of a matrix of rows, which are cases, and columns, which are variables. If the database is poorly structured, one may have trouble with information retrieval or graphics.

Consider Automated Data Collection

In most settings, it is feasible to collect data from patients via a computer interview conducted at an office terminal or via palm-top devices that patients can take away. The latter option exploits rapidly expanding technical possibilities for automated two-way communication between providers and patients. Technological advances offer at least three important benefits to clinicians: (a) automated data collection is economically advantageous; (b) computer technology is more accurate and reliable than human data collection; and (c) technology can accompany the patient in virtually all settings 24 hours a day. Experience shows that most patients are comfortable with, and like, the computer interview. Many believe that automated processing increases their privacy.

The economic advantages of computer technology stem largely from the reduced manpower requirements. With paper-based technology, an office needs a nurse or psychometrist to administer the test forms and score the instruments when data collection is complete. Entry of scores into the database requires that someone hand-enter data into the computer. To ensure accuracy, standard psychometric practice dictates that someone enters the data a second time and examines all discrepancies in the two entered records. Computer technology ensures accurate scoring and data entry automatically, thus saving substantial day-to-day manpower costs.

The accuracy and reliability advantages of computer technology derive from the greater computational power and accuracy of computers. Putting standard testing inventories onto a computer is straightforward. Computer administration differs from paper administration in that the computer can insist that the patient respond to all

items, and it can perform ongoing checks to ensure that all scores are in the expected range. Sophisticated testing programs can detect contradictions and nonsensical responses. This ensures a cleaner and more complete data record than one would normally obtain with paper instruments.

Finally, computers offer a great advantage because they can track the activity, medication intake, and pain levels of patients in their home and work environments. It is possible to beep or otherwise request that patients activate an interactive data collection program on a pocket-sized electronic interview instrument, or even call a phone number and use the phone number pad as the response method. This allows for powerful examination of chronologic pain patterns, including breakthrough pain, and it also provides a basis for tracking or facilitating medication compliance. The simplest approach requires patients to bring the hand- held computer device to every office visit. The nurse can quickly download its contents into the database. More sophisticated, and increasingly common, approaches involve transmitting the data on a daily basis from the patient's hand-held device to the clinic via telephone or, in some cases, radio signals.

Automated data collection systems sometimes offer a fourth advantage for clinical practice. A sophisticated system can update a centralized patient record almost instantaneously. Building on this, physicians can design interactive records that display data in summary form. For example, for a cancer patient a data record could chart pain and opioid side effects across days or weeks, thus affording visual pattern recognition of trends. The physician on rounds could look at pain and side effects patterns across time at the nurses' station. Gleaning the same information from a printed chart would take hours, and this clearly is infeasible in today's economic climate. We expect revolutionary progress in automated data records within a few years of the publication of this volume.

Avoid Collecting Too Much Data

A common mistake of inexperienced clinical database developers is the tendency to collect copious information for its own sake. It is easy to assume that data collected now might prove useful later. However, extra data collection burdens the patients, degrading their motivation and compliance in a way that compromises the overall quality of the measurement process, and it diffuses the focus of the investigation. In some instances, the clinician may fail to collect critical information because a hurried patient or a busy nurse has given priority to obtaining the extra information instead of data for the core testing devices. Moreover, when data collection involves complex test devices, the scoring of test data can become costly and time consuming. Costs of patient evaluation and research escalate in proportion to the amount of data collected. It is therefore important to streamline data collection and minimize patient information demand.

Be Sure the Test Instruments Fit Your Patient Population

Some testing forms or instruments demand more of certain patients than they can provide. For example, the MPQ uses a vocabulary that is too complex for poorly educated patients. Other tests are not useful with patients from certain cultural subgroups because the tests presume that patients engage in activities that they never perform. Still others are too great a burden for very sick or heavily medicated patients, such as certain cancer or AIDS patients. Always check the appropriateness of an instrument's norms for the population at hand.

Take Care to Collect Responses to All Items on All Forms

As we noted previously, patients who use paper forms sometimes feel uncertain about how to answer particular items and therefore leave them blank. The result is a missing element in the database. Large amounts of missing data render the database useless. Clear instructions, a minimal responder burden, and a quick check by the nurse or data gatherer at the end of testing help minimize lost data.

SUMMARY

The measurement of pain remains a knotty problem, but it has received considerable attention and there has been substantial progress in the development of theory and technology. Most clinicians now recognize that the perception of pain is a complex phenomenon and that it is prudent to guard against oversimplification in assessing pain. Sensory, emotional, functional, motivational, and cognitive aspects of pain merit evaluation in many settings. New instruments for pain measurement have taken this complexity to account in various ways. For a comprehensive review, see the Turk and Melzack volume (1). Subjective report and behavioral observation methods have advanced in recent years and promise to continue evolving in valuable directions.

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CHAPTER 16

Psychological and Psychosocial Evaluation

Judith A. Turner and Joan M. Romano

Chronic pain that is associated with significant physical and psychosocial dysfunction poses a difficult, often refractory, problem for the patient, his or her family, the clinician, and society. In such cases, a comprehensive psychological evaluation can provide information useful in identifying psychological and behavioral factors that may be contributing to the individual's pain and disability, as well as elucidate the impact that a chronic pain problem may have on physical, psychological, and social functioning. The psychological evaluation can also provide information essential to the planning and implementation of successful treatment.

Current conceptual models of chronic pain are based on the recognition that, in addition to whatever pathophysiologic factors may underlie a pain problem, psychological or behavioral factors often contribute to the persistence and severity of chronic pain and disability. As a pain problem persists over time, greater opportunity arises for psychological and behavioral processes to influence the course of pain and disability. The experience of pain, as well as of associated loss of vocational, home, family, recreational, and social activities and roles, can have profoundly negative effects on mood, self-image, and interpersonal relationships. These changes, in turn, can contribute to persistent suffering and disability, in a vicious circle. Causal relationships are difficult to delineate, but for patients with disabling chronic pain, a complex mix of physical, psychological, and behavioral factors almost always perpetuates dysfunction. Defining these factors is critical to designing effective treatment for such patients. Failure to address these issues can result in poor response to traditional somatically focused treatments. The psychological evaluation can also be useful in selecting particular therapeutic approaches for given patients. For example, evidence of severe depression, stress-related problems, family conflict, or alcohol abuse indicates the need for specific interventions beyond those for pain.

In this chapter, we discuss indications for and purposes of the psychological evaluation of the patient with chronic pain, preparation of the patient for the evaluation, the important components of the evaluation (including interview topics for both the patient and significant other), and several instruments that may be used to supplement the clinical interview.

BASIC CONSIDERATIONS

Indications for Psychological Evaluation

A psychological evaluation can be useful in all cases in which pain interferes significantly with a patient's ability to engage in normal activities, in which pain has adversely affected interpersonal relationships, and in which the patient shows signs of significant psychological distress (e.g., depression, anxiety). Psychological assessment is also indicated when the patient repeatedly and excessively uses the health care system, persists in seeking invasive investigations or treatments after being informed these are not appropriate, or uses opioid or sedative-hypnotic medications or alcohol in a pattern of concern to the patient's physician (e.g., escalating use).

Purposes of a Psychological Evaluation

The psychological evaluation is useful for delineating specific psychological and behavioral factors involved in pain, suffering, and disability. These can include such diverse processes as social and environmental reinforcement of pain behaviors, depression, and avoidance of activities believed to cause pain. The psychological evaluation can also reveal aspects of the patient's psychosocial history that are relevant to the current problem. Knowledge of history of psychological disorders (e.g., depression), substance abuse or dependence, vocational problems, family role models of pain or chronic illness, and recent life stress can often enhance understanding of the patient's current pain problems. A further purpose of the evaluation is to determine which psychological and behavioral treatment strategies are indicated for a particular patient and the conditions necessary for optimal chances of successful treatment.

The psychological evaluation cannot give definitive information about the cause of the pain. The presence of psychological factors likely to be influencing pain and disability does not exclude the possibility of organic pathology, just as the presence of positive physical findings does not necessarily imply the absence of important psychological influences. Conversely, the absence of positive physical findings does not indicate that the pain must be “psychogenic.” A number of problems are associated with the use of this term. Such labeling tends to obfuscate the specific psychological and behavioral factors contributing to the pain problem. It perpetuates the outdated conceptual dichotomy between “organic” and “psychogenic” or “functional” pain, an oversimplification that does not consider current concepts of pain that acknowledge the role of psychological factors in pain, regardless of cause (see Chapter 26). Furthermore, it underestimates the complexity of most chronic pain syndromes, in which some mixture of psychological and pathophysiologic influences is found.

Another problem associated with the use of the term “psychogenic” arises in physician-patient communication. Patients typically interpret the term to mean unreal or imagined and react with anger and defensiveness if their pain is so labeled. This interferes with the physician-patient relationship and creates a negative setting for seeing the psychologist. Many patients seen in pain clinic settings have been told or have the impression that their physicians think that the pain is “all in their head,” and often much effort needs to be expended to convince the patient that those on the staff accept the validity of the pain. In such circumstances it is difficult to develop a working alliance.

The psychological evaluation can identify risk factors for poor response to surgery, although it cannot lead to a precise prediction of whether a particular patient is going to respond well or poorly to surgery for the pain problem (see Chapter 76). Although a number of studies (1,2,3,4 and 5) demonstrated a moderate statistical association between various psychological factors or *Minnesota Multiphasic Personality Inventory* (MMPI) results and surgical response, the strength of such associations is not sufficient to warrant reliance on such techniques for making surgical decisions in individual cases. The decision for or against surgery must be made on the basis of the patient's history, physical examination, and diagnostic test findings, but the psychological evaluation can be useful in identifying patients with psychological characteristics that are associated with poor response to surgery. Such patients may benefit from psychological treatment as an adjunct to medical and

surgical management.

Preparation of the Patient for Psychological Evaluation

Patients with chronic pain may be concerned that referral for a psychological evaluation implies that their physician believes that their pain is “not real” or that they have a mental disorder, or both. Patients may not see the relevance of such an evaluation to their pain problem, which they view as having a biomedical etiology. When compensation or litigation issues are present, patients can be sensitive to the financial implications of the psychological evaluation report. Careful explanation of the reasons for recommending the assessment can reduce guardedness and defensiveness and enhance patient receptiveness to and cooperation with the evaluation.

Whether the psychological evaluation is a routine part of the practitioner's or facility's assessment procedure, or the patient is referred to the psychologist after a medical evaluation has been completed, adequate preparation of the patient is invaluable. It is helpful to state explicitly that the evaluation is to be conducted not because it is believed the pain is psychogenic or not real, but because the evaluation can provide information useful both in determining factors that might be increasing suffering and functional disability and in suggesting specific treatments for managing pain and enhancing the ability to engage in normal activities. This can be illustrated in a way personally meaningful to the patient by pointing out symptoms the patient has reported (e.g., sleep disturbance, fatigue, depression) and stating that such problems are frequently associated with chronic pain and can make the pain and suffering worse, thus creating a vicious circle. The patient can then be told that certain psychological techniques can improve these symptoms, as well as help him or her to manage the pain better.

COMPONENTS OF THE PSYCHOLOGICAL EVALUATION

General Format

This chapter describes a comprehensive psychological evaluation and areas important to address in such an evaluation. Even when conducted by an experienced psychologist, such an evaluation can require as many as 3 hours, including a review of relevant medical records, interviews with patient and significant other, feedback to the patient, and report preparation. We recognize that in many situations and settings it is necessary to conduct a less time-consuming and hence less comprehensive assessment. In such situations, the psychologist must consider the purpose(s) of the evaluation in deciding what topics to cover and in what detail. Major psychological disorders can be screened for by asking a few questions or by asking the patient to complete self-report questionnaires before the interview. If the psychologist will continue to see the patient in treatment after the initial evaluation, some topics and questions can be deferred to a subsequent session.

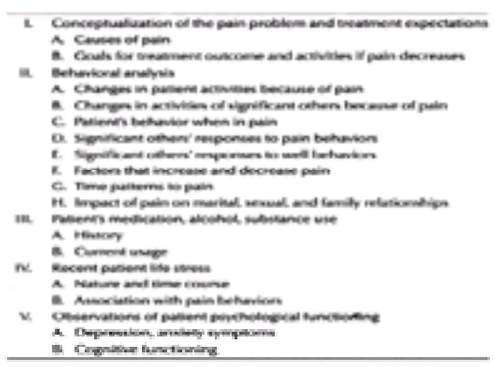
In addition to an interview with the patient, it is extremely useful, if at all possible, to separately interview the patient's spouse, family member, or close friend who has had regular contact with the patient over a long period (for the sake of brevity, we refer to such a person as a “significant other”). The reasons for this should be discussed in advance with the patient. Patients can be given the rationale that such interviews greatly increase the information needed to understand the patient's pain problem thoroughly and can provide another perspective on pain-related changes that have occurred over time. It might also be helpful to mention that family members are affected by the pain problem as well and often appreciate the opportunity to express their views and feelings.

It is most helpful to spend a small portion of the evaluation in an initial conjoint interview with the patient and significant other to observe how they interact and the remainder of the time in separate interviews. Patients and spouses alike typically speak more freely and openly in the absence of the other. The clinician conducting the evaluation, however, needs to be alert to issues of confidentiality. At times, problems can arise when the patient or significant other requests that important information be withheld from the other or from professionals involved in the patient's care. Such problems can often be resolved by discussing the reasons for wanting this information withheld and then frankly addressing the limitations this imposes on clinical recommendations and care. Alternatively, some clinicians may want to ask the patient and significant other before the interviews begin if it is acceptable to openly discuss with one partner all information conveyed by the other. Discrepancies in information given by the patient and significant other (e.g., concerning drug or alcohol use or sexual functioning) must be clarified in a sensitive manner. In cases in which assessment or treatment decisions are influenced by this information, it is usually best to achieve clarification at the time of the evaluation by openly discussing the discrepancies with the couple. The patient and significant other should be informed at the beginning of the interview of the limits of confidentiality, as required by law (e.g., the requirement that child abuse and elder abuse must be reported).

The sequence of topics covered in the interview is important. The interview can be structured, as shown in Table 16-1, so as to decrease patient guardedness and increase patient ease by initially focusing on the history of the pain problem and the patient's current subjective experience of the pain and then by exploring activity and functional changes, pain behaviors, and responses of others. Questions about substance use and symptoms of psychological disorders are best deferred until later in the interview, when rapport has been established and the patient presumably feels more comfortable.

TABLE 16-1. Patient interview topics

Table 16-2 provides an outline that might be used for a separate interview with the significant other. Important areas to assess include the significant other's conceptualization of the cause(s) of the patient's pain and goals for treatment. In addition, questions should be asked about pain-related activity changes for the patient and spouse, with attention to how these relate to any changes in the marital relationship and family functioning. Pain behaviors observed and the responses of family members to these are also of great importance, as are the significant other's observations of the patient's medication and alcohol intake and of stressors affecting the patient. Finally, the significant other can provide important observations concerning symptoms of psychological disorders. These points are discussed further below.



I.	Conceptualization of the pain problem and treatment expectations
	A. Causes of pain
	B. Goals for treatment outcome and activities if pain decreases
II.	Behavioral analysis
	A. Changes in patient activities because of pain
	B. Changes in activities of significant others because of pain
	C. Patient's behavior when in pain
	D. Significant others' responses to pain behaviors
	E. Significant others' responses to well behaviors
	F. Factors that increase and decrease pain
	G. Time patterns to pain
	H. Impact of pain on marital, sexual, and family relationships
III.	Patient's medication, alcohol, substance use
	A. History
	B. Current usage
IV.	Recent patient life stress
	A. Nature and time course
	B. Association with pain behaviors
V.	Observations of patient psychological functioning
	A. Depression, anxiety symptoms
	B. Cognitive functioning

TABLE 16-2. Interview outline for significant other

General areas to assess in the patient interview are outlined in Table 16-1 and below. The categorical distinctions we make are of necessity somewhat artificial and arbitrary because areas overlap. Each area pertains to the overall goal of determining the specific psychological and behavioral factors that may be associated with pain, physical and psychosocial disability, and appropriate treatment strategies.

History of Pain and Current Subjective Pain Experience

It is important to determine when and how the pain started and what the pain experience (i.e., qualitative, quantitative, and temporal) has been over time. The circumstances of onset may be associated with current psychological dysfunction, as in the case of posttraumatic stress disorder (discussed later in this chapter) or anger at perceived negligence in an accidental injury. Information about the pain experience, of course, must be interpreted in light of the type of pain syndrome (e.g., low back versus headache versus phantom limb) and any associated physical findings that could influence clinical presentation and course. Identification of times of the day or particular situations associated with increased or decreased pain can provide data as to potential environmental reinforcers for pain behaviors, stressors associated with increased muscle tension, and other possible contributors to ongoing pain and suffering.

Patient and Significant Other Pain Explanatory Model, Expectations, and Goals

In planning treatment and in optimal preparation of the patient for treatment, it is important to understand the patient's and significant other's conceptualizations of the cause(s) of the patient's pain (explanatory model) and his or her expectations and goals regarding treatment. Does the patient want or expect medical diagnosis and treatment to eliminate the cause of the pain, or is the patient receptive to learning ways to better manage the pain? It is frequently the case that the patient or significant other believes that the medical workup has been inadequate, that further medical diagnosis is necessary, and that the only appropriate treatment is surgery to eliminate the cause of the pain. Similarly, a patient's and significant other's goal of obtaining or continuing on disability compensation is inconsistent with treatment aimed at improved physical functioning and return to work. Unless such beliefs are addressed and some consensus is reached between patient and clinician as to problem conceptualization and treatment goals, behavioral and other psychological treatment efforts are unlikely to succeed.

Previous and Current Treatments

It is useful to inquire about previous and current pain treatments and the effects of these so that this information can be used in planning future interventions. Assessing the nature and extent of treatments is important. Patients might state that they have unsuccessfully tried a particular treatment modality (e.g., physical therapy, biofeedback, antidepressant medication), yet might not have had an adequate trial of treatment for reasons of misapplication, patient noncompliance, or failure to persevere with the intervention for a sufficient period of time to test it adequately. “Failure to respond” under such conditions does not necessarily preclude that particular treatment from being tried again, provided that patients are given an adequate rationale for doing so. Patients should be asked not only about traditional medical treatments but also about chiropractic treatment and other complementary treatments (e.g., herbal therapy, massage therapy, vitamin therapy, homeopathy, acupressure, acupuncture, naturopathy), because use of these may be associated with their explanatory models of their pain problem.

Medication and Alcohol and Substance Use

Obtaining a clear picture of the extent and pattern of a patient's use of analgesic and sedative-hypnotic medications, as well as of alcohol or illicit substances, is important for several reasons. First, medication and substance use may be affecting a patient's physical and psychological functioning. Second, information concerning the effects of past and current medication regimens on pain and functioning is useful to physicians in making decisions concerning whether such medications should be continued, modified, or discontinued. Third, some patients with chronic pain problems may exhibit patterns of problematic or escalating use of these medications in the absence of progressive disease (6,7). This is a frequent reason for patient referral to a multidisciplinary pain center for evaluation. Fourth, abuse of or dependence on alcohol or other substances can interfere with efforts to treat pain and disability and may require specialized treatment beyond that used for pain.

Although the use of long-term opioid therapy may be appropriate for some patients with chronic noncancer pain (8), the circumstances under which such therapy should be considered need to be defined on an empiric basis, and this remains an area of controversy within the field of pain management. An in-depth discussion of the pros and cons of this practice is outside the scope of this chapter (see Chapter 84). However, as part of the psychological evaluation of patients with difficult, disabling pain problems, it is important to elucidate patterns of medication and substance use as accurately as possible to identify their potential contributions to patient physical and psychological functioning, and the resulting implications for treatment.

Inappropriate medication use and substance abuse complicate assessment of the pain problem for a number of reasons. Excessive alcohol, sedative-hypnotic, and opioid use may contribute to dysphoria, irritability, mood swings, decreased energy, sleep disturbance, cognitive impairment, and appetite and weight changes, which may not be recognized as substance- or medication-related (9). In a minority of patients, pain behaviors may function to legitimize drug-seeking and use.

As part of the patient psychological evaluation, inquiry about previous and current medication use can easily follow from other questions concerning previous treatments for the pain problem and the patient's response to those. Having patients keep 1 to 2 weeks of diaries of medication use can also be helpful, although patients may underreport use (10). Questions about alcohol and other substance use are best asked later in the interview, when patient-interviewer rapport and patient comfort with the interview are likely to be higher. The CAGE questions (11) may be used to screen for possible alcohol problems (Have you ever felt the need to *C*ut down on drinking? Have you ever felt *A*nnoyed by criticism of drinking? Have you ever had *G*uilty feelings about drinking? Have you ever taken a morning *E*ye opener?). Sensitive questioning concerning current and past patterns of alcohol and substance use, driving under the influence of alcohol or substances, or any history of alcohol- or substance-related interference in work or family life can provide detail necessary to decide whether a referral to a chemical dependency treatment program may be warranted.

Because patients may be reticent to disclose alcohol and substance use or may underestimate consumption, it can be informative to ask significant others about these issues. We also find that questioning the significant other about the effects of medications on the patient's physical and cognitive functioning, mood, and behavior can provide important information not obtained from the patient.

It is usually necessary to refer patients for whom substance abuse or dependency is a major problem to a chemical dependency treatment program before treating the pain problem. Most pain programs are not equipped to treat such problems, which are likely to interfere with maintenance of improved function after treatment. Tapering of prescribed opioid and sedative-hypnotic medications can usually be accomplished as part of a pain treatment program.

Behavioral Analysis

One of the primary aims of the psychological evaluation is to determine whether behavioral factors may be playing a role in a patient's pain behaviors and disability (see Chapter 25). Reinforcement of pain behaviors by social or environmental contingencies may contribute to ongoing patient disability, in addition to the influence of other factors, such as guarding, deactivation, depression, and other psychological disorders. A behavioral analysis is an important part of the comprehensive psychological evaluation of the chronic pain patient and can yield information crucial to treatment planning. This analysis entails identifying, at least on a presumptive basis, social and environmental factors that may contribute to the maintenance of pain behaviors and disability, and assessing the feasibility of modifying these factors in treatment.

Contingencies maintaining pain behaviors may take the form of direct positive reinforcement—for example, pain behaviors may be followed by greatly increased support and expressions of caring from significant others. In other cases, reinforcers may involve the avoidance of aversive situations or activities, such as family conflict or a stressful or dangerous work environment. Often, reinforcers may be quite subtle and difficult to identify. Pain behaviors may function to elicit involvement from an otherwise uninterested spouse or may allow patients and significant others to avoid dealing with stressful problems such as sexual dysfunction or cognitive deterioration.

A thorough behavioral analysis, based on interviews with the patient and significant other, can provide a basis for generating hypotheses to be tested in further observations and interactions with the patient and for treatment planning. Fordyce (12) provides a detailed description of the theoretical background and method of conducting a behavioral analysis. The two major foci of the behavioral analysis, patient and significant other pain-related activity changes and social responses to pain behaviors, are discussed in the following sections.

Activity Changes

A careful analysis of how the patient's activity patterns have changed since pain onset can be a rich source of information bearing on possible reinforcers for pain behaviors as well as factors contributing to depression and stress in the patient's life. Activity changes can suggest that learning factors may play an important role in the maintenance of pain behaviors and disability, as well as highlight significant losses in the patient's life that may be related to emotional distress and that may be important to address in treatment.

Patients typically describe major changes in their activities and lifestyle as a result of their pain problem. Often they describe significant decreases in work, home, social, and recreational activities and a concomitant increase in sedentary activities such as watching television or resting during the day. Patients frequently describe such changes as distressing and as resulting in increased boredom and isolation. However, the assessment can also reveal positive consequences of the pain problem for the patient, such as increased closeness to or support from family, removal from a stressful or dangerous job situation, reduction in family conflict or demands, or increased amounts of time available to spend with a spouse or children. The presence of such consequences does not imply malingering but can suggest the influence of operant (learning) factors on pain behaviors and the need to address these factors in a pain management program (see Chapter 88). It should be noted that positive and negative consequences for pain behaviors (such as those listed above) may coexist, complicating the assessment process and contributing to difficulties in rehabilitation. Although patients understandably may focus on the losses they have experienced as a result of pain, it is important to examine the overall balance of positive and negative consequences for pain behaviors in assessing readiness to engage in rehabilitative treatment. As part of this analysis, it is also important to identify patient readiness to pursue behavioral goals and acquisition of pain coping strategies, alternative strategies the patient may have available to obtain social and financial support, and whether the patient has or can develop effective strategies for coping with stressors.

Another line of inquiry that often proves fruitful concerns what future activities the patient and significant other would like to and realistically could perform if the pain posed fewer limitations. The identification of activities that were highly reinforcing for the patient in the past and that might be targeted as part of a rehabilitation program can be useful in planning goals for treatment. A rehabilitation program is unlikely to be successful unless such behavioral goals can be identified.

The interviewer conducting a behavioral analysis can start by asking patients to list specific vocational, home management, social, and leisure activities that they used to do until the pain began but are doing less or are not doing now. It can be informative to ask the same questions of the significant other separately, with the aim of learning how frequently each activity was performed before the onset of pain, as well as which activities were pleasurable and which were not. Some patients may state that they used to do many pleasurable things (e.g., sports) that they no longer can do; careful questioning sometimes reveals that these activities were actually engaged in rarely immediately preceding the onset of pain. It is useful to observe the degree of congruence between the patient's current affective state (depression versus apparent comfort in current lifestyle) and activity change (major losses versus no major losses in pleasurable activities). If marked incongruence is present, further questioning may reveal additional relevant information that was missed previously.

Inconsistencies in activities that have been reduced or eliminated because of pain can help to identify positive and negative reinforcers of pain behaviors. An example is the situation in which one usual activity is performed, but another, with similar physical demands, is not. Often, the former activity is found pleasurable by the patient, whereas the latter is aversive. Not uncommonly, however, an activity is avoided, not because it is aversive, but because the patient fears that it will produce increased pain. This issue is discussed further in the section on guarding.

Social Relationships and Reinforcers

The behavioral analysis includes an examination of how the patient's significant others respond to his or her pain behaviors and how this might affect the patient's pain behaviors, coping, and functioning. To assess the probability of direct social reinforcement of pain behaviors, it is necessary to ask the patient and the significant other how others know when the patient has increased pain and how others respond at those times. Even if patients do not complain directly of pain, significant others frequently report that they infer pain from behaviors such as facial grimacing, lying down, limping, or taking medications. The responses of significant others to these behaviors need to be detailed, as well as whether these are viewed positively or negatively by the patient and significant other.

The significant other's responses to “well behaviors”—that is, behaviors inconsistent with the sick role—must also be determined. If patient activity, such as beginning a household task, is followed by the significant other's attempts to discourage that activity or take it over or if patient behaviors associated with being well are followed by withdrawal of affection and attention or renewed demands, or both, rehabilitation can be difficult unless these responses are modified. Also, it is important to identify aspects of the patient's pain and disability that are reinforcing to family members, with or without their awareness. Shifts in family members' roles and responsibilities can occur in response to patients' pain problems and can be highly reinforcing. Patients' attempts to resume their former roles and duties can meet with some resistance if family members' needs are not addressed.

Behavioral formulations of chronic pain problems (e.g., 12) have noted that responses by the significant others to patient pain behaviors and well behaviors may be one factor contributing to ongoing pain behaviors and dysfunction (see Chapter 88). Solicitous behaviors—that is, behaviors characteristic of taking care of someone who is ill or disabled (e.g., encouraging rest and reduced activity, taking over tasks, comments and actions conveying concern or sympathy for the patient's physical condition)— have been examined most frequently in this regard. Such behaviors would appear to have high potential for reinforcing pain behaviors, given that they are frequently provided on a pain-contingent basis and many patients describe such responses in positive terms, as evidence of significant others' care and support.

Empiric support for solicitousness as a potential reinforcer of pain behaviors has come from studies demonstrating that solicitous responses of significant others to patient pain behaviors are associated with higher pain ratings and lower patient activity level (13,14), more frequent pain behaviors (15,16), and higher levels of disability (16). If family members frequently respond to the patient's verbal and nonverbal pain behaviors, it is likely that social reinforcers are important in maintaining pain behaviors and should be addressed in treatment. However, social reinforcement of pain behavior may take forms other than solicitous responses, including ignoring or expressions of irritation or anger, and must be evaluated in the context of the relationship. For example, in a conflicted marriage, being left alone may be quite reinforcing. Social reinforcers of pain behaviors thus must be defined on the basis of their impact on behavior, not on their presumed positive or negative qualities.

It is helpful to ask about the quality of the marital relationship over time and about the effects of the pain problem on the relationship. Patients and significant others often report changes in the marital relationship due to the patient's pain problem and associated dysfunction. Often patients become more irritable and depressed, causing increased interpersonal conflict. Consistent with this, several studies have reported increased rates of marital dissatisfaction and psychological distress among the significant others of patients with chronic pain (17,18,19 and 20). In other cases, however, patients and significant others may report increased closeness as a result of coping with chronic pain.

It is also important to assess the effect of the pain problem on the couple's sexual relationship. Many couples report a decrease in sexual activity since pain onset, due to the patient's decreased sexual desire, due to increased pain caused by sexual activity, or both. Significant others may avoid sexual activity due to fear of causing increased pain. A decrease in sexual activity or quality of the sexual relationship can be very distressing to one or both partners and can negatively affect the marital relationship. However, changes in marital satisfaction or sexual activity can also be the result of long-standing conflicts within the relationship, perhaps exacerbated by or explained in terms of pain. Pain may also legitimate avoidance of intimacy in some individuals (e.g., if sexual activity had been aversive, as is sometimes the case because of its association with previous trauma, such as sexual abuse). Thus, the evaluation of relationship changes and effects of pain can be fully understood only in the context of the history of the relationship and of each partner.

It is also important to consider the relationship implications of changing the patient's functioning in treatment. In some cases, the marital system may depend on the patient being “ill” to maintain stability; in such situations, one partner may, at some level, fear that the other will leave if the patient becomes more functional and independent. Alternatively, the spouse may fear that the patient will no longer “need” the significant other if he or she gets better. Such relationship issues may form formidable barriers to patient improvement if not recognized and addressed (e.g., with marital therapy).

Guarding, Deactivation, and Activity Pacing

Many patients show guarding behaviors—that is, they avoid certain activities or body movements that have been associated with increased pain. Fordyce and his associates (21) described certain pain behaviors (e.g., limping) that can effectively reduce nociceptive input during the acute phase after an injury. Over time, such behaviors become habitual, and the patient no longer allows himself or herself the opportunity to engage in activities, such as normal limb use, due to fear of provoking increased pain. Such patterns of avoidance may lead to disuse syndromes, and initial attempts to reverse this pattern are likely to lead to increased pain,

confirming patients' beliefs that such activity is painful and likely damaging. If this appears to be the case for a particular patient, treatment should be aimed at helping the patient learn that not engaging in the guarding behaviors is safe and at gradually shaping normal use of the affected part of the body. As Fordyce and colleagues (21) emphasized, this must be achieved by setting up a program in which the patient gradually increases performance of the feared behavior, because information provision alone is unlikely to produce a change in beliefs or behaviors (see Chapter 88). It is important to inform patients that such a program typically results in increased discomfort initially, but this does not mean it is harmful, and that such treatment is necessary to regain normal use patterns involving the affected part of the body and to prevent further complications of disuse.

A problem closely related to avoidance learning is deactivation or deconditioning. This is a common accompaniment to chronic pain, especially common musculoskeletal pains such as low back and leg pain. Many patients find that pain is worsened by activity and reduced by rest. Because this pain reduction positively reinforces resting behavior, resting is likely to occur more frequently in the future (22). Excessive resting over time often results in decreased physical strength, flexibility, stamina, and conditioning. This sets up a vicious cycle in which any attempt at activity results in increased pain, which punishes such attempts and reinforces inactivity. This also reinforces the patient's fears that activity is harmful. As this cycle progresses and patients become progressively more deactivated, they lose opportunities to engage in positive activities that would have physical and psychological benefits for them, such as social or recreational activities, and have increased opportunities to think and worry about pain, both of which can contribute to depression and further withdrawal. Such patterns can result in profound physical and emotional deterioration, with some patients spending nearly 24 hours a day reclining and having difficulty engaging in even basic self-care activities because of this progressive pattern of deactivation and pain. Activity diaries, described below (see also Fig. 16-1), are a useful means of determining the frequency and duration of time spent in rest versus activity each day. Excessive time spent resting indicates the need for a treatment program that involves gradual systematic increases in activity.

Figure 16-1. Activity diary.

Another pattern seen with frequency in patients with chronic pain is dysfunctional activity pacing. Many patients respond to periods of decreased pain with overactivity (”I'll get all the house and yard work done now while I can”). This overactivity causes increased pain, and the patient responds by resting until he or she feels better. Patients who tend to have cycles of underactivity followed by overactivity often benefit greatly by learning how to plan activities in advance so that they are paced and there are periodic breaks.

Vocational Assessment

Obtaining a vocational history and clear picture of current vocational status and future prospects is often critical in understanding the pain problem and in treatment planning. If the patient is not currently working, is return to work a desired and realistic goal? If so, is the patient's former job available and feasible? Is vocational retraining necessary? If so, how could this be funded? This is a very complex area. Many patients injured at work receive wage replacement income, and these patients may, understandably, be afraid of losing this steady income, especially if the customary job is aversive or no longer available, if income from the job is unreliable (as in seasonal work), or if the patient fears reinjury or increased pain if he or she returns to work. Patients whose medical conditions prevent them from returning to work at their accustomed jobs can find this loss and the financial ramifications very distressing. Patients involved with workers' compensation systems may be angry if they perceive they are being treated unfairly or forced to return to work at a lower-paying job. Any such pertinent issues must be addressed directly before and as part of treatment; otherwise, chances of successful treatment are greatly diminished.

Compensation and Litigation Issues

The extent to which financial compensation for disability (e.g., wage replacement after a job injury) or unresolved litigation related to the pain influences the maintenance of pain behaviors and the response to treatment is of great clinical and economic importance. Some studies have suggested that patients with chronic low back pain who do not receive financial compensation and who do not have pending litigation have better treatment outcomes than do those who are on workers' compensation or have pending litigation (23,24 and 25). The ways in which various compensation and litigation systems influence the maintenance of pain problems and response to treatment are complex and might well interact with other patient characteristics.

In clinical settings, knowledge of compensation and litigation issues can help to clarify contingencies that the patient perceives to be associated with getting better versus those involved with remaining disabled. We have observed that many patients have unrealistic expectations concerning the duration of wage replacement payments and the amount of settlement awards likely to be received. It is frequently valuable to discuss these issues openly with the patient (and the patient's attorney) before treatment begins to ensure that all concerned have the same expectations regarding future financial compensation and its relationship to treatment outcome.

Social History

Obtaining a brief childhood and family history can yield valuable information concerning patients' prior learning experiences regarding pain and illness behaviors, significant role models for pain and disability, and the characteristic response of the family to health problems. A history of chronic pain and disability in the family can result in learning-restricted and maladaptive behavioral responses to illness and discomfort. This can be explored by questioning the patient and significant other about the range of responses to pain and illness shown by the patient and family members. For example, is there a history of long periods of time off work after injury; financial compensation for disability; or significant disability in normal vocational, avocational, and household roles? Significant others can be asked similar questions about their personal and family history to determine if they are responding to the patient's pain behaviors in maladaptive ways based on past learning experiences.

A family history of depression or other psychological disorders can alert the clinician to the potential contribution of such factors to the patient's current situation and developmental history through biological predisposition, learning patterns, or both. Similarly, familial alcohol or drug abuse and childhood abuse or neglect are often seen, suggesting the need to assess their impact on the patient.

We have observed, and studies have reported, high rates of childhood and adult sexual abuse in women with chronic pain problems, especially chronic pelvic pain (26,27 and 28) (see Chapter 70). If the clinician wishes to assess for a history of abuse, a thorough assessment involves specific questions about emotional, physical, and sexual abuse. The clinician's responses, of course, are important. As noted by Jacob and DeNardis (29), it is unhelpful to imply disbelief, ask questions that are perceived as intrusive, challenge the patient's responses, or minimize the importance of the abuse. It is helpful to respond in a sensitive manner, expressing concern and asking about the patient's comfort after disclosure. Jacob and DeNardis (29) suggest, and we agree, that it is not appropriate to obtain a detailed history of abuse experiences in a pain management setting, in which the focus should be on a general understanding of the abuse and how it might bear on the patient's pain problem. A referral to someone with special expertise in treating victims of abuse can be offered if the patient has symptoms or concerns related to the abuse.

Cultural Factors

In any assessment of chronic pain, the influence of cultural factors on the expression of somatic complaints and pain behaviors should be acknowledged. Cultural values and beliefs can affect patients' responses to chronic pain and illness, patient-provider relationships, and providers' responses to patients' problems (30,31).

Although few studies have examined the role of culture in pain behaviors and pain-related health care use, attention to such relationships might help the clinician to understand the meaning of a patient's pain and health care–seeking behaviors within the context of family and culture more clearly and suggest ways to prepare the patient and family for pain treatment approaches. An evaluation by a psychologist should always be conducted in accordance with the ethical principles of psychologists (32), which recognize that ethnic and cultural differences (among other factors) may significantly affect the process of psychological assessment and treatment. Additional training or consultation should be obtained, or an appropriate referral made, if needed, to ensure that competent services can be provided to patients of different ethnic backgrounds.

Stress

Many reports have considered the relationship between stress and disease, injury, and illness behavior (33). Within this broad area, attention has increasingly focused on basic research in underlying psychophysiologic processes and adaptational and coping mechanisms thought to mediate stress responses. An association has been reported between life stress and pain description in some patient samples (34,35), but these relationships appear to be complex, possibly influenced by a number of factors requiring further clarification.

We have often seen such an association in our clinical experience, although patients can initially deny or minimize the contributions of stress to their pain problems. The interview with the significant other frequently reveals information about stresses affecting the patient. In many cases, no major stressor can be identified as associated with pain onset, but current stressors in the patient's life can contribute to psychophysiologic dysfunction, such as increased levels of muscle tension, illness behavior and disability, and use of medications or alcohol as coping strategies (33).

Of course, pain, inability to engage in normal social, recreational, vocational, and homemaking activities, and worry about the prognosis or cause of the pain are themselves often sources of major stress. Worry about the cause of the pain and its implications can profoundly affect the patient's emotional functioning and interpersonal relationships. Identification of stressors and of their effects on pain, suffering, and family functioning indicates directions for treatment, which include stress management training, relaxation training, and psychotherapy, as well as techniques aimed at altering stressful situations (e.g., marital or family therapy).

Psychological Disorders

Psychological disorders, especially depression and anxiety disorders, are common in patients seeking health care but are frequently undiagnosed in medical patients (36,37). This is probably a result of a number of factors, including patient denial or minimization of psychological symptoms, patient attribution of psychological symptoms to pain or physical disease, and lack of physician time spent with patients in discussing psychosocial issues. Certainly, the emotional impact of chronic pain and disability can result in mood disturbance, and the psychological evaluation needs to address these issues in detail.

Depression is a particularly prevalent and treatable disorder in chronic pain populations (38,39) and should therefore be assessed routinely as part of the psychological evaluation. For purposes of descriptive evaluation and consistency of communication across disciplines and settings, the *Diagnostic and Statistical Manual* (4th ed) (40) criteria specified by the American Psychiatric Association are recommended (see Chapter 26). Assessment of depression should not be limited to asking about depressed mood, because patients may deny or minimize this. Other depressive symptoms, such as decreased interest or anhedonia, fatigue, insomnia, and suicidal ideation, may be present but not reported spontaneously by the patient. All patients should be asked questions to assess possible suicidality, and an assessment of the patient's risk for suicide should be included in the report of the psychological evaluation. Identification of clinically significant depression among chronic pain patients is facilitated by the use of brief self-report questionnaires, as described below, but such testing does not serve as a substitute for a thorough clinical interview and evaluation.

A brief screening for other psychological disorders should be included in a comprehensive psychological evaluation. Anxiety and somatization disorders, for example, are seen with some frequency in chronic pain patients. It is important to obtain a thorough history from the patient and significant other, and from records of the past medical history, to determine whether the patient has a history of multiple medical problems and treatments suggestive of somatization disorder.

Posttraumatic stress disorder (PTSD) may be present in individuals whose pain stems from a motor vehicle accident (MVA) or other traumatic event or situation experienced or witnessed by the patient and involving actual or threatened death or serious injury. This disorder is characterized by persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the event, and symptoms of increased arousal (40). There appears to be a high prevalence rate of PTSD and also of depression in individuals with chronic pain associated with an MVA (41,42,43,44,45,46 and 47) and a high prevalence of chronic pain in combat veterans with PTSD (48). Thus, it may be useful to screen for PTSD symptoms as well as for depression in all individuals with pain due to an MVA or serious injury. The PTSD Checklist can be used as a brief screening instrument for PTSD (49). The presence of PTSD may increase suffering and disability associated with chronic pain and requires specialized treatment (42).

In older patients, previously undiagnosed dementia is common. Pain can be used as an excuse to avoid certain activities the patient finds difficult to perform because of intellectual deficits. Intact social skills can mask the severity of the cognitive impairment, and a structured mental status examination is a useful screening tool for dementia (50). The *Mini-Mental State* (51) (Table 16-3) is a brief measure that is a useful screening tool; however, it is highly sensitive to education, and a well-educated individual with a mild to moderate level of dementia can perform well on this measure. Furthermore, the *Mini-Mental State* cannot provide information about the source of cognitive impairment (e.g., depression, medication, Alzheimer's). Subtle impairment might not be detected by the mental status examination, however, and formal neuropsychological testing is a more sensitive indicator when clinical observation and family report suggest some deterioration of cognitive function.

TABLE 16-3. Some measures useful in the psychological evaluation of the patient with chronic pain

INSTRUMENTS FOR ASSESSMENT

A number of instruments are useful for supplementing information obtained through interviews (see Table 16-3). Those most frequently used and clinically relevant instruments are highlighted below. For a more detailed review of self-report assessment instruments developed for use with chronic pain patients, see Turk and Melzack (52).

Minnesota Multiphasic Personality Inventory

The MMPI (53) and the MMPI-2 (54) are commonly used in the assessment of personality characteristics of chronic pain patients. The original MMPI is a 566-item true-false questionnaire developed in the 1930s and 1940s that describes a patient on three validity scales and 10 scales designed to assess psychological disturbance. A revised version of the instrument, the MMPI-2, designed for use with adults aged 18 or older, was published in 1989 and includes 567 items and the same scales as those in the original (54). A number of items on the original MMPI were eliminated or modified, and the normative sample for the MMPI-2 is more representative of the U.S. population. The MMPI-2 has less objectionable and more contemporary item content than the original MMPI. In general, an individual's profile types are similar when tested with either version; however, MMPI-2 profiles are slightly less elevated than MMPI profiles. A thorough discussion of the MMPI is

beyond the scope of this chapter; interested readers can find more information in several sources (54,55,56,57,58 and 59).

Of particular interest is Keller and Butcher's (60) book on the use of the MMPI-2 in the assessment of patients with chronic pain. This book presents MMPI-2 data from 502 patients who participated in a chronic pain rehabilitation program in Minnesota from 1985 to 1987 and recommends using a standardized score (T-score) cutoff of 65 and above to indicate clinical significance instead of the traditional T-score of 70.

The MMPI can be used to corroborate clinical impressions and to generate hypotheses about a patient's personality and psychological factors involved in a patient's pain problem. A substantial body of research has demonstrated low to moderate associations between certain MMPI scales and profile configurations and particular behavioral characteristics of patients with chronic pain (61,62).

Perhaps the most extensively researched area is the ability of the MMPI to predict response to medical and surgical therapies for pain. Although some negative results were reported, a number of studies (1,2,3,4,63,64,65,66 and 67) found an association between elevations on the hypochondriasis and hysteria scales and poor response to medical and surgical treatments for back pain. Caution is warranted in applying these findings to individual patients, however, because the association is moderate and, although statistically significant, can only be suggestive rather than prescriptive in clinical application.

Interpretation of the MMPI requires training and specific experience with the patient population of interest. As noted previously, although certain scale elevations and profile patterns can be statistically associated with certain patient characteristics, such an association might not be present in a particular person. MMPI interpretations should be regarded as providing probable hypotheses regarding patient functioning rather than definitive conclusions.

A number of drawbacks are associated with the use of the MMPI. It is lengthy, and many patients view it as irrelevant to the evaluation of their pain problem. Despite its drawbacks, however, much information exists about the meaning of MMPI scores. In the hands of someone skilled in its interpretation with patients with chronic pain, especially in conjunction with clinical interview data, the MMPI is useful in assessment and treatment planning.

Depression Inventories

Because depression is such a common and treatable disorder in patients with chronic pain, self-report depression measures are a useful supplement to the clinical interview. The *Beck Depression Inventory* (68,69) and the *Center for Epidemiological Studies- Depression Scale* (70) are commonly used. A study found both measures to be valid in identifying major depression in patients with chronic pain (71).

Activity Diary

Fordyce et al. (21) described diaries in which patients record, on an hourly basis, all medications used (type and amount), activities, position (sitting, standing or walking, or reclining), and pain intensity for 1 or 2 weeks (see Fig. 16-1). Although several studies found that patients with chronic pain typically underreport medication use and activity levels (10,72,73), another study (74) reported high positive correlations between patient and spouse diaries of patient lying and standing-walking time and medication use (number of pills). This study also found that lying, sitting, and standing-walking times and medication use were relatively consistent over a 1-week period. Patients and spouses knew that they were recording the same variables at the same time, which might explain the higher agreement found in this study.

Despite the unresolved issue of the degree of accuracy of diary information, in our experience, diaries are generally sufficiently representative of a patient's activity level, medication use, and pain intensity patterns to provide valuable information of assistance to the clinician. For example, the diary can be used as an indication of whether medication use may be excessive or inappropriate. Regular use of opiate or sedative-hypnotic medication every few hours may be a sign of medication dependence.

The diary also indicates the degree to which the patient is deactivated. Patients seen in pain clinic settings not infrequently record up to 20 hours or more spent reclining each day. Such a pattern indicates the need for a reactivation program involving exercise that gradually increases in duration and intensity. This may be initiated in physical therapy, using a “quota” system (12), and continued in a regular unsupervised exercise program and in a volunteer or job station program of gradually increasing daily duration.

The activity diary can also reveal consistent patterns in pain intensity. Such patterns might be temporal—that is, pain is consistently worse at a certain time of day or on certain days of the week, and the reasons for these patterns can be explored with the patient in the interview. Fluctuations in pain levels reliably seen in tandem with certain events can help in identifying situations found by patients to be physically or psychologically stressful. Identifying these situations and assessing the associated stresses can shed light on factors potentially maintaining pain and disability, as well as indicate directions for intervention.

ADDITIONAL CONSIDERATIONS

As this chapter indicates, the psychological evaluation of chronic pain problems is a highly complex task, involving a broad range of clinical questions and issues. In light of the current health care environment, it is important to note that the complexity of such a psychological evaluation might not be recognized by managed care organizations. Efforts to communicate what can and cannot be done in the time authorized are needed to avoid misunderstandings and to educate managed care organizations about the amount of time required for, and the usefulness of, a comprehensive evaluation.

The overriding theme of the psychological evaluation is the delineation of psychological and behavioral factors involved in persistent pain, disability, and suffering, with a view toward prescription of appropriate interventions for altering these patterns. The outcome of this evaluation is a synthesis of the information gathered, resulting in a list of problems reflecting the contribution of specific psychological and behavioral processes to the maintenance of suffering and disability. The appropriateness of various treatment strategies should be suggested by the data gathered in the course of the evaluation. Decisions as to the intensity and duration of treatment are affected by the extent to which factors such as medication dependence, deactivation, and entrenched patterns of social reinforcement appear to maintain illness behaviors. The degree to which variables such as social reinforcement, patient beliefs about pain, patient cognitive and behavioral responses to pain, marital and family conflict, depression, and stress play a role in pain problems determines whether the intervention program should incorporate strategies such as behavioral therapy techniques, cognitive-behavioral therapy, marital or family therapy, and antidepressant medication.

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CHAPTER 17

Evaluation of Function and Disability

James P. Robinson

The purpose of this chapter is to outline some of the problems that surround disability determination in patients who claim incapacity because of pain. Problems are described at the level of individual physicians who try to make disability determinations and at the level of public policy. Also, practical suggestions are provided for the clinician who is asked to make disability determinations about patients whom he or she is treating.

Two caveats are appropriate at the outset. First, the scientific underpinnings of disability evaluation in painful conditions are weak. As a result, any discussion of the subject must be tentative and speculative. The goal of this chapter is not to “solve” the problem of disability evaluation in painful conditions but rather to explore some of the factors that have made solutions so difficult to achieve. Second, this chapter focuses almost exclusively on problems associated with pain and disability in the United States. This reflects the practical fact that my knowledge of disability systems is limited to those that operate within the United States. Clearly, other countries are struggling with the problem of pain and disability (1,2,3 and 4), and the issues considered in this chapter may well be relevant to these countries. As the following discussion demonstrates, however, generalizations across countries and even across disability systems within a single country are hazardous.

OVERVIEW OF THE PROBLEM

Some people with chronic pain seek assistance from society because of incapacity associated with their pain. The requests for assistance take various forms. For example, some may claim that they are unable to walk long distances and request disabled parking stickers. They may say they are unable to manage routine chores at home and request subsidized chore worker services. Or, they may claim that they are incapacitated from work and request work disability benefits under various private, state, or federal disability programs. This chapter focuses on the problems associated with the evaluation of work disability secondary to pain. For simplicity, the term “disability” is used as a synonym for “work disability.”

The problem of disability secondary to pain is an elusive one that yields conflicts and contradictions at multiple levels of analysis. At a clinical level, conflicts and distrust frequently develop between disability applicants and the physicians and disability adjudicators who are involved in their claims. Independent medical examiners and attorneys often become participants in these conflicts. Patients often think that physicians and others discount their complaints. Physicians and adjudicators experience doubt or outright skepticism about complaints of pain in the absence of corroborating physical findings.

At an administrative level, disability programs are run by bureaucracies that have certain imperatives. For example, the Social Security Administration (SSA), which runs the two largest disability programs, strives for uniformity, objectivity, and cost containment in its disability evaluation procedures (5). However sensible these goals are from a bureaucratic standpoint, they often are at odds with the clinical realities of patients with chronic pain (6).

At a societal level, additional concerns and perspectives emerge. Disability programs reflect an ethical commitment to support citizens who are incapable of working. If a program is too restrictive, it may consign needy applicants to poverty; if it is too lax, it may encourage disability applications from people who are actually capable of working. Even if a program is meeting its ethical mandate quite well, it may strain the financial resources of the country to the breaking point. This is precisely the concern that is now being voiced about many of the programs run by the U.S. SSA.

At a scientific level, issues related to disability are usually unanswerable because the research underpinnings for “disability evaluation science” are so meager. Moreover, the search for scientifically valid conclusions about disability may be compromised by the adversarial settings in which disability evaluations are made and the enormous financial stakes involved.

Finally, at a philosophical level, the problem of disability evaluation in chronic pain rests on an epistemologic dilemma—the information available to an individual experiencing pain is fundamentally different from the information available to any external observer who attempts to assess the pain. Scarry succinctly captured this dilemma when she said, “To have pain is to have certainty; to hear that another person has pain is to have doubt” (7). In clinical situations, chronic pain patients frequently communicate the sense that they are severely incapacitated by pain and ask physicians to support their claims. Typically, physicians who evaluate these patients cannot identify tissue damage or organ pathology that make the limitations communicated by the patient seem inevitable or even plausible. The physician then has the dilemma of integrating the subjective reports of a patient with the objective evidence of tissue damage or organ pathology to come up with some final judgment about the extent to which the patient really is incapacitated. At one extreme, a physician might simply ignore a patient's self-assessments and make a disability determination based strictly on objective findings of tissue damage or organ pathology. At the opposite extreme, the physician might accept the patient's definition of the situation and give a disability rating that is congruent with the patient's self-assessment. Most physicians feel uncomfortable with either extreme, but it has proved extremely difficult to find some middle ground in which both objective evidence and self-assessments by patients can be incorporated into disability evaluations.

BASIC CONCEPTS: IMPAIRMENT AND DISABILITY

Any discussion of pain and disability runs the risk of foundering on the heterogeneity of disability systems. In the United States, these include the 50 state workers' compensation systems, the three federal workers' compensation systems, two disability programs run by the SSA, a Veterans Administration disability program, and several disability programs offered by private insurance companies. Because of the multitude of disability programs, virtually any statement about disability is likely to have exceptions, and it is difficult even to define concepts unambiguously. The following discussion attempts to mitigate this problem by focusing on the largest disability programs.

Impairment is defined in the American Medical Association's (AMA's) *Guides to the Evaluation of Permanent Impairment* (4th edition) as “an alteration of an individual's health status. [It] is assessed by medical means and is a medical issue. An impairment is a deviation from normal in a body part or organ system and its functioning” (8).

Disability is a more difficult term to define. The AMA *Guides* defines it as “an alteration of an individual's capacity to meet personal, social, or occupational demands, or statutory or regulatory requirements, because of an impairment. Disability refers to an activity or task the individual cannot accomplish” (8). This definition is general; it refers to activity limitations in any arena. In contrast, agencies that administer work disability programs have developed a variety of more restricted

definitions of disability. The definition of disability used by an agency identifies the criteria a patient must meet to be eligible for benefits. For example, the SSA defines disability as “the inability to engage in any substantial gainful activity . . . by reason of any medically determinable physical or mental impairment that can be expected to result in death or that has lasted or can be expected to last for a continuous period of not less than 12 months” (9). In contrast to the definition in the AMA *Guides*, the one used by the SSA refers only to a person's ability to work.

As a practical matter, there are different “kinds” of disabilities, based on the regulations and definitions of the different agencies that administer disability programs. For example, disability can be total (meaning that an individual is judged to be incapable of any employment) or partial (meaning that the individual is judged to be incapable of certain kinds of work). It can be permanent or temporary. Some programs (e.g., workers' compensation) emphasize causation—that is, they award disability only if a worker's incapacity has been caused by an injury or illness at work. In other programs, such as the SSA's disability programs, causation of a patient's incapacity is irrelevant. Some programs provide a single cash settlement to compensate an individual for his or her disability; others provide ongoing wage replacement payments. This chapter focuses on disability programs administered by the SSA and uses its definition of disability.

A close relation exists between impairment associated with pain and disability associated with pain. This is because all disability systems construe impairment as a necessary condition for disability. The logic underlying this requirement is simple. Disability programs are designed to assist individuals who are unable to compete in the workplace because of a medical condition. In essence, disability programs attempt to partition individuals who fail in the workplace into two large groups: ones who fail because of a medical condition and ones who fail for other reasons (e.g., advanced age or lack of demand for their skills). Therefore, disability programs require evidence that an applicant has a medical problem underlying his or her workplace failure. Impairment provides the needed evidence, as it can be viewed as a marker that an individual has a medical problem that diminishes his or her capability. Conversely, if an individual has no impairment, this means that he or she does not have limitations due to a medical condition.

In addition to the qualitative requirement that a disability applicant must be impaired, informal observation strongly suggests that disability programs act on the assumption that the probability of disability increases as the severity of impairment increases. This hypothesis is difficult to prove because the decision-making rules of most disability agencies are not open to public scrutiny. But some of the largest disability administrations, including the SSA and the California workers' compensation system, openly state that severity of impairment is one important consideration in disability awards (10,11).

The discussion so far indicates that impairment is necessary, but not sufficient for disability. This raises an obvious question: What factors other than impairment are considered in disability determinations? No single answer to this question exists because different disability programs have different criteria for identifying an individual as disabled. In a general way, however, disability programs attempt to integrate medical information regarding a disability applicant with nonmedical factors that bear on his or her ability to compete in the workplace. For example, as described under Pain and the Social Security Administration Disability Evaluation Process, the SSA considers not only an applicant's impairment, but also his or her age, education level, and past work experience.

Another key question is the following: Who gathers information about disability applicants, integrates medical data with nonmedical data, and ultimately decides which applicants receive disability awards? Again, the answer varies from one disability program to another, but in general, both physicians and nonmedical adjudicators play a role. Physicians are expected to determine the diagnoses of disability applicants and the severity of their impairments. Also, physicians are often asked to give opinions about the vocational implications of patients' medical problems (e.g., to state whether a patient is capable of light, medium, or heavy work). Physicians who provide this information occupy a variety of niches within disability systems. In some instances, the physician who is treating a patient provides medical information. In other instances, independent medical examiners are commissioned by insurance companies, disability agencies, or courts to examine disability applicants and provide necessary medical information. Independent medical examiners function as consultants to disability agencies rather than employees. Their impartiality can be questioned, as each side in a disputed case wants its own examiner(s). Finally, disability agencies sometimes hire physicians to provide the information needed.

Regardless of the specific niche they occupy, physicians typically report their findings and opinions to nonmedical disability adjudicators. It is the adjudicators who actually make disability decisions, after combining medical and nonmedical data on applicants.

This chapter uses the term *disability evaluation* to describe the evaluations that physicians perform on applicants for disability benefits. Physician disability evaluations generally include assessments of impairment, but they also address other issues. Thus, an impairment rating is construed here as a component of a physician disability evaluation. A physician disability evaluation, in turn, is only one component of the overall evaluation that a disability applicant undergoes. It is supplemented by information gathered and interpreted by nonmedical adjudicators. For simplicity, this chapter focuses on the challenges that physicians face during disability evaluations; it ignores the roles that nonmedical professionals play in the disability determination process.

PAIN AND THE AMERICAN MEDICAL ASSOCIATION IMPAIRMENT RATING SYSTEM

Because impairment represents the medical component of disability, it is critical to consider the manner in which impairment associated with pain is assessed. I do this in relation to the impairment rating system developed by the AMA because it is the one that is used most widely in the United States.

It is helpful to start an analysis of the AMA approach to impairment associated with pain by considering problems in which pain and other subjective complaints do not play a major role (e.g., an amputation in a patient who has no significant pain complaints). Complications introduced when the system is applied to painful conditions can then be addressed.

General Features of the American Medical Association Impairment System

The AMA impairment system represents an ambitious attempt to quantitate impairment affecting essentially all organ systems and body parts. The first step in an impairment rating is for a physician to give a quantitative measure of loss of function in an organ or body part. The measure is supposed to be based on objective, publicly available information. For example, an amputation at the metacarpophalangeal joint of the thumb corresponds to a 40% impairment of the hand (8).

The rating process then involves a series of abstractions so that a measure of “whole person impairment” can be achieved. For example, the patient with an amputation at the metacarpophalangeal joint of the thumb would be judged to have a 36% impairment of the upper extremity (8) and a whole-person impairment of 22% (8). Whole-person impairment is conceptualized as a unidimensional scale running from 0% (for an individual with no measurable deficit) to 100% whole-person impairment (for a person who is comatose or has some other type of problem that is totally incapacitating). The whole-person impairment concept thus has two essential features: It measures the severity of impairment (with a range from 0% to 100%), and it permits direct comparisons to be made among impairments involving different organs and different diseases.

The AMA system raises several obvious questions:

1. *Can the functioning of organs be measured objectively? How should this be done? How reliable are the measurements?* As an example of problems in this area, experts have debated the appropriateness of range of motion measurements in the assessment of impairment associated with disorders of the spine. As a result, two different systems are described in the fourth edition of the AMA *Guides*. The range of motion model includes spinal range of motion as one factor in determining impairment; the injury model completely eliminates range of motion in impairment ratings. The duality of the AMA's present approach to spine impairment rating reflects lack of consensus among experts about the reliability with which spinal motion can be measured and the relevance of the measurements (12,13 and 14).
2. *Is it possible to interpret measurements of organ function throughout the range from completely normal to completely absent or dysfunctional?* Often, the impact of organ impairment on whole-person functioning is relatively easy to measure at the extremes. For example, if there is no impairment of the organ, there is no associated deficit in an individual's activities. If an organ or body part has essentially no function, the individual either dies (if the affected organ is a vital one) or demonstrates fairly predictable activity deficits (e.g., as in T-8 complete paraplegia). But the impact of partial organ impairment is often difficult to assess and may be modified by a variety of psychosocial characteristics of the affected person. Some people are resourceful and determined in overcoming impairments. Their activity limitations are likely to be smaller than would be anticipated on the basis of their impairments. Other patients show different patterns of adaptation to impairment and have relatively large activity limitations. The personal factors that modify the impact of a partial loss of function in an organ are extremely difficult to quantify and factor into an impairment rating.
3. *Is valuable information lost in the process of abstraction that occurs when specific deficits are converted to whole-person impairment?* For example, a patient with an amputation of an upper extremity at the shoulder and one with significant renal insufficiency might both have whole-person impairments of 60%, but the specific activity deficits of the two patients would be entirely different.
4. *What does the concept of whole-person impairment mean? Is the concept supported by research that demonstrates its construct validity?* Because the AMA

> construes impairment as existing at the level of specific organs or body parts, the meaning of whole-person impairment is unclear. One could construe it as a global measure of a patient's activity deficits. This meaning is suggested at one point, when the AMA *Guides* states, “An impairment percentage derived by means of the *Guides* is intended, among other purposes, to represent an informed estimate of the degree to which an individual's capacity to carry out daily activities has been diminished” (8). However, this interpretation makes whole-person impairment similar to the AMA's concept of disability. Surprisingly, the AMA *Guides* contains only a brief discussion of whole-person impairment and says nothing about how it compares with disability.

Given the ambiguity of the whole-person impairment concept and the strong possibility that critical clinical information is lost when an examiner converts an assessment of organ impairment into a whole-person impairment rating, there is an obvious need for research to validate the whole-person impairment construct. Presumably, such research would focus on relations between quantitative measures of whole-person impairment and quantitative evidence of limitations in activities of daily living. However, virtually no such research exists (15). In essence, whole-person impairment is a concept that is at best questionable as far as face validity is concerned and lacks validation through research.

American Medical Association's Rating System for Painful Conditions

The discussion so far has explored generic problems with the AMA impairment system rather than problems specific to the assessment of impairment secondary to pain. When the AMA system is applied to painful conditions, new strains emerge in the relations among disease, organ impairment, whole-person impairment, and activity limitations. The essential new element introduced by pain is the tension between objective and subjective perspectives on impairment. As noted earlier, the AMA system rests on the assumption that organ impairment can be assessed objectively. This is precisely the assumption that is challenged by patients who report incapacity secondary to pain. The recurring problem is that the patients report incapacitation that exceeds any objectively measurable evidence of organ dysfunction.

The issues surrounding impairment assessment in painful conditions vary from one pain problem to another. A key point is that chronic pain is frequently one of many manifestations of a chronic medical condition. The pain associated with the medical condition often cannot easily be abstracted from the other manifestations of the condition. For purposes of analysis, most painful conditions can be placed in one of five categories on the basis of relations among the pain, other manifestations of the underlying disease, and impairment: incidental pain, expected pain, magnified pain, unverifiable pain, and psychogenic pain.

- Incidental pain—Pain occurs along with evidence of organ dysfunction severe enough to produce severe impairment by itself. Example: a patient with congestive heart failure and angina pectoris.
- Expected pain—Pain occurs in the context of objective evidence of organ dysfunction. The pain appears to be consistent with the objective findings and is a major reason for the patient's incapacitation. Example: A patient with imaging and electrophysiologic evidence of a persistent L-5 radiculopathy reports pain in an L-5 distribution of the affected leg and does not demonstrate any evidence of symptom magnification. Significant atrophy of the affected leg exists.
- Exaggerated pain—Pain occurs in the context of objective evidence of organ dysfunction and is a major reason for the patient's incapacitation. An examining physician, however, judges the pain to be exaggerated relative to the objective findings. Example: a patient with the same clinical syndrome as in incidental pain, but the patient reports severe pain in both legs, reports that he is spending 22 hours per day in bed because of his pain, and demonstrates several nonorganic signs (16) on examination.
- Unverifiable pain—Pain occurs in the context of a medical condition that normally does not produce objective signs of organ dysfunction. Examples include chronic headache and fibromyalgia.
- Psychogenic pain—Pain is judged to be a manifestation of a psychiatric disorder—that is, a somatoform disorder, such as pain disorder associated with psychological factors (17).

Relations among pain, disease, and impairment for each category are diagrammed in Figure 17-1.

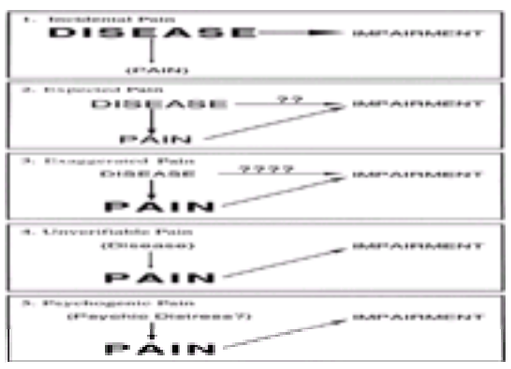

Figure 17-1. Categories of pain, based on relations among pain, impairment, and an underlying disease. 1. Incidental pain: The underlying disease directly causes impairment, regardless of whether there is associated pain. Pain may or may not be present but is not a central determinant of the impairment. 2. Expected pain: Disability agencies treat conditions in this category as if the disease leads directly to impairment; however, as the figure indicates, this causal chain is questionable. Although the disease may cause objectively measurable impairment, the major driver of the patient's activity restrictions is pain. The apparent severity of the patient's pain and pain-related restrictions appears to be appropriate to the disease. 3. Exaggerated pain: The connection between pain and impairment is even more questionable for conditions in this category. There may be objectively measurable impairment, but the objective findings are grossly inadequate as an explanation of the patient's apparent activity restrictions. Also, the link between disease and pain is questionable for conditions in this category—that is, the patient's apparent pain exceeds what would be expected for the disease. 4. Unverifiable pain: In this category, the disease postulated to underlie pain and impairment is inherently not objectively measurable. A disease may be inferred by an examining physician, but the inference is completely dependent on the patient's pain behavior—that is, the presence of the disease can be established only by asking the patient about his or her pain. Thus, although a disease is presumed to exist, it is “invisible.” 5. Psychogenic pain: In the extreme, there is no disease at all underlying the patient's pain complaints—that is, there is no anatomic or physiologic abnormality that can be construed as the source of the patient's complaints. As noted in the text , concepts surrounding psychogenic pain are poorly developed. Some experts suggest that psychic distress or unresolved emotional conflict “takes the place” of an abnormally functioning organ as the source of pain. Although the patient refers his or her pain to an organ or body part, the source of the pain is “in the mind” rather than in the organ or body part.

The above typology highlights the variety in relations among impairment, pain, and other manifestations of disease. In terms of this typology, the AMA *Guides* is devoted almost exclusively to patients with incidental pain or expected pain. A discussion of pain as a manifestation of a psychiatric disorder is included, but no details are given either about how to place a patient in the psychogenic pain category or how to rate impairment in such a patient. No useful information is provided on the rating of patients with exaggerated pain or unverifiable pain. Thus, the AMA impairment system is probably adequate for some categories of pain but not for others. More generally, it is quite possible that any system for evaluating impairment associated with pain will need different approaches for the different categories outlined. However, with the exception of the Report of the Commission on the Evaluation of Pain (18), discussions of pain and disability have rarely dealt with the implications of different categories of pain. The implicit assumption has generally been that the problem of impairment from pain could be discussed without any detailed consideration of the ways in which pain and other manifestations of disease interrelate.

Expected pain deserves special consideration. For practical purposes, the AMA impairment system seems to work fairly well for this category. However, a system that rates conditions with expected pain on the basis of objective findings can be confusing conceptually because its emphasis on objectivity obscures the factors that actually create impairment. As an example, consider a patient with a chronic right L-5 radiculopathy severe enough to produce essentially complete loss of function in the right L-5 spinal nerve. Because of the objective findings, such an individual might well be eligible for benefits under various disability programs. But in what sense would he or she be severely impaired? At the level of organ function, it would be said his or her spine is impaired. To understand this statement, the biological functions of the spine should be considered. Briefly, the lumbar spine plays four major roles: It contributes to structural support for the person (e.g., provides attachment points for muscles and space for vital organs such as the lungs and abdominal viscera), permits upright posture, permits motion, and protects spinal nerve roots. Only the last function is significantly compromised in an L-5 radiculopathy, and the functional loss can readily be compensated for with a short leg brace. In fact, an individual with an L-5 radiculopathy is not incapacitated by loss of function of the lumbar spine but rather by pain. At best, the patient's clinical findings (e.g., epidural scarring around the L-5 root, weakness, and atrophy of the right leg) validate that the individual has sustained a significant lumbar radiculopathy—they do not demonstrate substantial loss of function of the spine.

In a monograph on the SSA's disability programs, Osterweis et al. emphasize the distinction between loss of function of an organ and incapacitation from pain as follows:

> The notion that all impairments should be verifiable by objective evidence is administratively necessary for an entitlement program. Yet this notion is fundamentally at odds with a realistic understanding of how disease and injury operate to incapacitate people. Except for a very few conditions, such as the loss of a limb, blindness, deafness, paralysis, or coma, most diseases and injuries do not prevent people from working by mechanical failure. Rather, people are incapacitated by a variety of unbearable sensations when they try to work (6).

A CLOSER LOOK AT THE PROBLEM OF INFERENCE IN PAIN ASSESSMENT

Physicians must use complex inferential processes when they make judgments about whether patients with chronic pain are disabled. This is inevitable because no clear-cut rules exist for deriving disability judgments from clinical data on these patients. The inferential processes underlying disability judgments are typically implicit and may well differ from one evaluator to another. However, these processes have received little attention in research, so the following discussion is based mainly on informal observation. Although it is speculative, the discussion highlights possible reasons why these evaluations are so difficult and contentious.

Implicit Beliefs and Cognitive Dissonance

As noted under Overview of the Problem, only the patient directly experiences his or her pain. Any other person can only make inferences about the patient's pain based on his or her pain behavior. As Fordyce and others (19,20) have forcefully argued, pain behavior has multiple determinants so that its interpretation is frequently ambiguous. At one level, the distinction between the pain experience of a sufferer and the pain behavior that others can observe is simply a restatement of the conundrum of solipsism that has occupied philosophers for thousands of years. But there are specific aspects of pain experience and pain behavior that go beyond the generic issue of subjective versus objective information.

Every human being has multiple experiences with pain and develops conceptual models about pain on the basis of these. These models are difficult to articulate rigorously because they are typically implicit (21). Common beliefs about pain probably include the following:

1. Pain usually signifies a significant injury or illness.
2. Pain can be incapacitating (most people have episodes of pain that completely dominate consciousness and behavior).
3. Although the severity of pain is usually correlated with the severity of the underlying disorder, it is possible to have incapacitating pain in the absence of a catastrophic or even serious medical condition (e.g., migraine headaches and acute back sprains).
4. Physicians are limited in their ability to interpret pain. It is thus possible for a patient to have pain whose significance is missed by a physician.
5. Activity limitations because of pain are typically not absolute. Pain frequently makes activities difficult but rarely makes them completely impossible.
6. Patients can “fake” pain—that is, they can deliberately exaggerate its severity and impact.
7. More generally, pain behavior is often at least partly under voluntary control. Even if a person is not deliberately faking pain, his or her pain behavior may well be influenced by its consequences.

Taken together, these assumptions highlight the variety and ambiguity of relations among disease, pain experience, and pain behavior. A patient's complaints might signify anything from malingering to a serious medical condition that physicians have missed. Thus, the daunting task for a disability examiner is to determine the significance of pain behavior in an individual patient. Moreover, it is highly likely that examiners differ significantly in their conceptual models of pain. These differences may well underlie some of the conflicts that occur among different physicians, between physicians and adjudicators, and so forth as they attempt to reach a common understanding of a patient's pain.

The discrepancy between the incapacity reported by a patient and the objective markers of incapacity available to an observer is sometimes extreme, and it is in this setting that the dilemma of interpreting pain reports becomes most acute. For example, many patients with fibromyalgia report overwhelming incapacitation in the absence of any objective markers of disease except tender points (22,23 and 24). A physician evaluating such patients might understandably think that he or she is faced with extreme choices. One is to accept what seem like extraordinary statements by the patient about the severity of his or her incapacitation more or less at face value. The alternative is to reject the statements. This alternative is likely to set up cognitive dissonance (25,26) within the examiner. The dissonant cognitions are (a) “I respect Mr. X, and believe that he, like most patients I see, is honestly trying to tell me about his pain” and (b) “Mr. X has just told me things about the severity of his pain and the impact of pain on his life that I find preposterous.” The simple resolution to this pair of dissonant cognitions is to conclude that the patient is telling preposterous tales because he or she is a liar or has some significant psychiatric disorder. Thus, the examining physician often experiences difficulty in distinguishing between evaluation of the patient's medical condition and evaluation of the patient as a human being. That is, the physician often believes that he or she has only two choices: to ally with the patient and accept the patient's view of his or her condition or to reject the patient's condition and impugn the integrity or mental status of the patient.

It may well be that the pressure to line up with the patient or against the patient underlies some of the frustration and hostility that not infrequently surface during treatises on pain and disability (27,28 and 29). As an interesting example of the pejorative attitude that some physicians have toward pain patients, consider the terms that have evolved to describe individuals with persisting symptoms (usually pain) after a compensable event. Mendelson (30) gives a list of 37 such terms, including *accident neurosis*, *aftermath neurosis*, *American disease*, *attitudinal pathosis*, *Greek disease*, *greenback neurosis*, *justice neurosis*, *railway brain*, and *unconscious malingering*.

The pressure toward extreme positions vis-à-vis a pain patient may be accentuated by a simplistic tendency among some physicians to group patients broadly into two classes: (a) ones who honestly describe their problems to a physician and (b) malingerers. This dichotomy fails to do justice to the richness of interactions between patients and physicians. It is beyond the scope of this chapter to review this complex area (30,31), but a few observations are in order. First, the extensive literature on the operant conditioning of behavior suggests that the manner in which patients present themselves may well be shaped by previous interactions with various health providers (19). Because most chronic pain patients have large numbers of interactions with these providers, there is ample opportunity for their stories about themselves to be shaped in ways that maximize their apparent incapacitation. This process may go on without any conscious planning or intent to deceive. Second, patients engage in impression management when they interact with physicians, just as all people (and even infrahuman organisms) do whenever they engage in social interactions (30,3233 and 34). As Shorter points out, patients do not want to be ridiculed when they describe their problems to physicians (29). In their attempts to be taken seriously, some pain patients undoubtedly “overplay their hands,” making exaggerated statements that sound improbable to an examining physician. This may reflect poor social judgment but not necessarily malingering.

A realistic view of the subtleties of social interaction between patients and physicians makes it quite probable that patients are often incorrect in their statements about their pain but are not malingering or deliberately lying. Thus, a physician who is aware of these subtleties might feel comfortable in rejecting a patient's statements about incapacity but not impugning the moral or psychiatric status of the patient. But it is difficult to find this middle ground. The message from many pain patients is, “I live with my pain and know more about it than anyone else. I demand that you accept what I say about my pain at face value.”

Cannot versus Will Not

Regulations governing disability systems often demand that patients receive benefits only if their incapacitation is both objectively determinable and categorical. The demand for categorical incapacitation is manifested in the wording of questions to physicians. Physicians are asked whether patients can or cannot do certain kinds of work, how many pounds they can lift on a frequent basis, and so forth. This wording presupposes a sharp delineation between what a person with a medical problem can and cannot do. The dichotomous categories of can and cannot often do not match the realities of activity restrictions that patients face, even when pain is not a factor. For example, Brodal (15) wrote a thoughtful essay about his functioning after experiencing a stroke. He pointed out that many of his deficits could be overcome by strenuous effort—that is, there was no sharp line between what he could do and what he could not do.

In general, activity limitations can be stated fairly precisely when there is complete loss of function in an organ or body part. Thus, a patient who is completely blind cannot use visual cues; a patient with complete T-6 paraplegia cannot use his or her legs, and so forth. But when there is incomplete loss of function, the distinction between cannot and chooses not to becomes blurred. For example, a patient with lower extremity paresis secondary to an incomplete T-6 spinal cord injury might well be able to walk but would demonstrate gait abnormalities and show poor endurance when walking. It might be said that this patient can walk, but not as well or as long as someone with a normal spinal cord. It would be anticipated that there would be no single, precise time when such a patient would report fatigue that prevented

further walking. Thus, the boundary between being able and unable to walk would be fluid and would be influenced by the patient's motivation to succeed, use of coping strategies, and so forth. It would be difficult for an external observer to decide whether the patient's activity limitations reflected what he or she could not do or what he or she chose not to do.

Although the distinction between what a person cannot do and what he or she chooses not to do is difficult in many conditions, it is especially acute in the interpretation of incapacitation from pain. A person with chronic pain is much more similar to a patient with an incomplete spinal cord injury than to one with a complete spinal cord injury in that he or she usually can do a wide range of activities. But the quality of performance may be reduced, the duration of activity may be reduced, and the patient may report aftereffects of the activity in the form of a pain flare-up.

The activity restrictions in a patient with chronic pain can best be modeled as shown in Figure 17-2, in which pain is conceptualized as an aversive drive that tends to produce inhibition of activities that provoke it (36,37). The strength of this aversive drive can be inferred from the strength of the incentive that must be provided to induce a person to engage in the painful activity. The effects of different strengths of the aversive drive are divided into three zones. In the unrestricted zone, the aversive drive is either completely absent or so trivially small that any incentive can override it and induce the person to engage in the “painful” activity. At the opposite extreme, in the compulsory zone, the aversive drive is so strong that no incentive induces the person to engage in the behavior. For all practical purposes, the person cannot do the activity. In the middle is the discretionary zone. When the strength of the aversive drive is in this region, the person engages in the painful activity, but only in response to substantial incentives. One might say that the person can engage in the activity, but with difficulty.

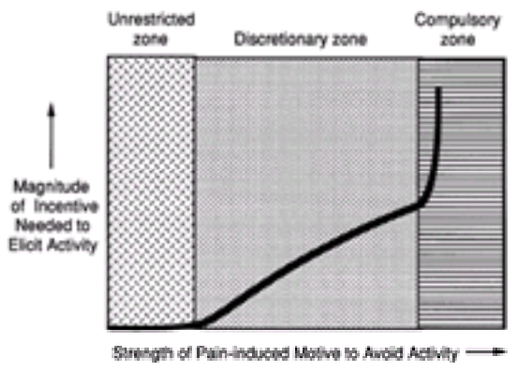

Figure 17-2. Motivational consequences of pain.

Although the model shown in Figure 17-2 is quite abstract, it appears that many physicians who examine patients with chronic pain follow something like it. In particular, examiners typically look for evidence of inconsistency in the activity levels of pain patients, especially when the inconsistency is predictable on the basis of changes in incentives. If, for example, a back pain patient shows severe activity restrictions during an independent medical examination but is shown playing volleyball on a surveillance videotape, a physician is likely to be skeptical about the activity limitations described and demonstrated during the examination.

The previous discussion focuses on personal factors, such as motivation, that blur the boundary between can and cannot in a patient with chronic pain. It is worth noting briefly that the boundary is also indistinct because of factors extrinsic to the patient. Many of the work restrictions imposed by medical conditions—including painful ones—can be circumvented by appropriate modifications of the workplace. As a simple example, a paraplegic cannot walk up stairs but can have access to all floors of a building equipped with an elevator. The potential for work site modifications (or accommodations, as they are described in the Americans with Disabilities Act) to offset activity restrictions complicates the assessment of what a patient can do in two ways. First, an evaluator has to define the patient's activity limitation carefully. In the preceding example, the paraplegic is incapable of walking up stairs but may be capable of reaching all the floors of the building where he or she works. Second, the evaluator must consider the availability and practicality of various job site accommodations that might mitigate the detrimental effects of a medical condition.

Changes over Time

Changes over time in the apparent incapacitation associated with painful conditions should be analyzed at two levels. At the level of individuals, some patients with pain problems seem to become more focused on their pain as time elapses and to lose their motivation to remain productive despite pain. Clinicians often observe these trends among individuals who have sustained disabling work injuries—that is, they see injured workers who become worse rather than better as time elapses after an injury and who seem to use medical information to buttress the conviction that they are disabled. A paucity of systematic data exists to validate or invalidate these clinical observations. Studies have shown that work disability after various industrial injuries follows something like an exponential decay curve, as shown in Figure 17-3 (38). Basically, the curve indicates that most people recover quickly after a workplace injury, but that the recovery curve flattens out over time so that, for example, individuals who are disabled more than 3 months tend to remain disabled for extended periods. It is possible that people in the “tail of the curve”—that is, those with very prolonged disability—have learned to emphasize their pain and incapacity as a result of interacting with the complex, often contradictory environment that injured workers face (39,40,41,42 and 43). The term *disability syndrome* is sometimes used to describe the behavioral and attitudinal changes that are thought to lead to prolonged disability in these injured workers. It is important to note, however, that although the concept of disability syndrome is clinically plausible, it is highly speculative. It is not really known why some injured workers end up in the tail of the recovery curve (44).

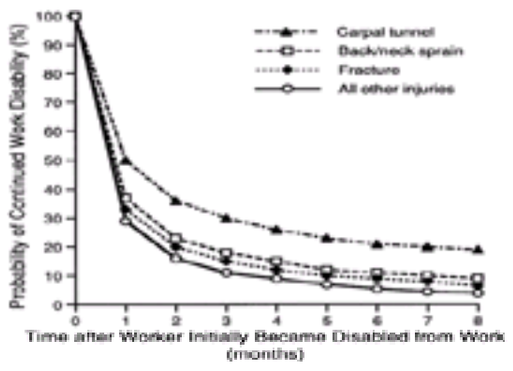

Figure 17-3. Recovery curves after industrial injuries. (Adapted from Cheadle A, Franklin G, Wolfhagen C, et al. Factors influencing the duration of work-related disability: a population-based study of Washington State workers' compensation. *Am J Public Health* 1994;84:190–196.)

At a societal level, there is evidence that the apparent incidence and prevalence of painful disorders change as a function of social conditions and public policies regarding disability (45,46,47 and 48). One possible explanation for these changes is that large groups of people gradually learn the “templates” for certain diseases and present to physicians with symptoms that adhere closely to these templates (30). That is, patients may interpret bodily sensations in terms of disease templates available in their culture; then hone, modify, and selectively process the sensations; and then organize their communications with physicians in ways that render the symptoms coherent and understandable in terms of an accepted disease. This hypothesis is a broad one that is difficult to prove or disprove conclusively, but there are historical instances that at least make it plausible. For example, repetitive strain injuries (RSIs) of the upper extremities became a major problem in the Australian workforce during the early 1980s and then rapidly diminished in apparent incidence and severity after legislative action and court decisions reduced the probability that workers could receive benefits for the condition through the industrial compensation system (49,50,51,52,53,54 and 56). Littlejohn (52) gave a detailed account of the social forces that influenced the rapid spread of RSI, describing the roles played by physicians, unions, the media, patient support groups, ergonomic specialists, the compensation system, and litigation. For example, he described the role of unions as follows:

> Unions played a prominent role in the epidemic. It was through the publicity generated by the unions that most workers developed knowledge of RSI. Workers were warned to look for the first early symptoms of the condition. Any ache or pain was suggested as a sign of early RSI. Publicity was generated to indicate that the condition occurred in a graded fashion; a staging system was suggested and adopted by the unions with vigor. Patients were warned that they would pass from stage 1 (mild transient aches) through to stage 3 (severe intractable aching) and on to long-term crippling without any chance of cure (52).

This and other statements by Littlejohn suggested that publicity surrounding RSI sensitized workers and persuaded them to interpret various sensations in terms of the RSI construct.

Another possible example is fibromyalgia. It appears to have increased substantially in prevalence since 1980, and at least one historian (30) has emphasized that this epidemiologic trend is attributable to the spread of information about the condition. If the “template” concept applies to fibromyalgia, the year 1990 must be considered pivotal because it was in that year that a group of prominent rheumatologists published diagnostic criteria for fibromyalgia (57). Perhaps in response to the growing awareness of fibromyalgia, disability awards for the condition in the Canada Pension Plan increased by a factor of six between 1987 and 1993 (4).

The possibility that individual patients or large segments of society learn pain behaviors that make them convincing has implications both for the clinical evaluation of disability in chronic pain and for social policies involving pain and disability. The individual examiner must consider the possibility that he or she is seeing manifestations of disease that have been modified by the past experiences and selective reinforcement to which a patient has been exposed. Policy makers must consider the possibility that pain may be “elastic”—that is, that the apparent amount of pain-related disability in the United States depends on how social policies regarding pain and disability are crafted.

Decision-Making Strategies

Physicians frequently attempt to assess the credibility of patients during disability examinations. They may rely on the Waddell signs (16) or a variety of other tests and signs to decide whether a patient is exaggerating or falsifying information. The decision a physician reaches about the credibility of a patient depends not only on the data he or she collects on the patient, but also on the decision-making strategy that he or she uses to interpret these data. As a hypothetical example, consider a population of chronic pain patients that is made up of two distinct subpopulations—honest reporters and malingerers. Imagine that an examiner uses a 50- item “malingering test” to gather information about whether each patient is an honest reporter or a malingerer. The examiner needs to develop some cutoff point for the malingering test, so that patients who score above the cutoff point are designated as malingerers, whereas ones who score below it are designated as honest reporters. As shown in Figure 17-4, the cutoff points developed by the examiner will probably be influenced by two factors—(a) the examiner's beliefs about the relative sizes of the honest reporter and malingerer subpopulations and (b) the costs he or she associates with different classification errors.

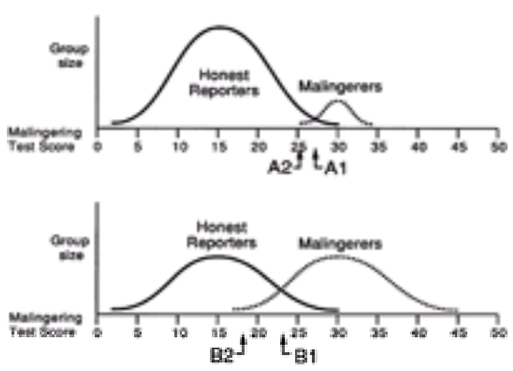

Figure 17-4. Cutoff points for honest reporters versus malingerers. In **A,** honest reporters outnumber malingerers. In **B**, malingerers are thought to be more common. See text.

Figure 17-4A shows a situation in which the examiner estimates the honest reporter subpopulation to be much larger than the malingerer subpopulation. The arrow labeled *A1* shows the cutoff point the examiner might use if he or she was equally concerned about misclassifying malingerers as honest reporters and honest reporters as malingerers. The arrow labeled *A2* shows the cutoff point when the examiner wants to be sure not to miss a patient who is malingering.

Figure 17-4B shows a situation in which the examiner believes that the malingerer subpopulation is as large as the honest reporter subpopulation. The arrow labeled *B1* designates the cutoff point the examiner might use if he or she was equally concerned about the two kinds of classification errors; the arrow labeled B2 designates the cutoff point that might be chosen if the examiner wants to be sure not to miss a patient who truly is a malingerer.

As Figure 17-4 demonstrates, the cutoff points A1, A2, B1, and B2 are all different. The figure thus highlights the fact that even when two examiners have the same information about a patient, they can differ markedly with respect to their conclusions about the credibility of the patient. The differences are often the result of implicit assumptions that different examiners make about the relative frequencies of different subpopulations of pain patients and the costs that they associate with different kinds of classification errors. These decision-making issues underlie some of the distrust that frequently exists between independent medical examiners and treating physicians.

PAIN AND THE SOCIAL SECURITY ADMINISTRATION DISABILITY EVALUATION PROCESS

To understand how a disability system handles applications by patients with pain problems, one must look at the details of its procedures for awarding disability to applicants in general. These procedures differ from one disability agency to another. The discussion focuses on the way in which the SSA evaluates disability applicants. The SSA administers two disability programs— Social Security Disability Insurance (SSD) and Supplemental Security Income (SSI) (58). They are by far the largest disability programs in the country. They are virtually identical in terms of their definitions of disability and the procedures they follow to determine disability; the two programs differ only with respect to nonmedical eligibility requirements.

The operating rules of the SSD/SSI evaluation process can be seen by examination of the five steps that are followed in evaluating an applicant. These are shown in Figure 17-5. In essence, evaluators address questions in the sequence indicated and determine the eligibility of each applicant on the basis of the answers. A few issues stand out:

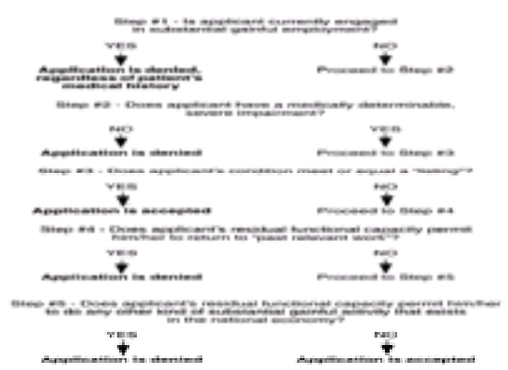

Figure 17-5. Steps in the evaluation of Social Security Disability Insurance and Supplemental Security Income applications.

1. An applicant is rejected at step 2 unless he or she has a medically determinable, severe impairment. Thus, impairment is a necessary condition for an SSD/SSI award. In a comprehensive review of the role of pain in SSD/SSI awards, Osterweis et al. (6) pointed out that many applicants with pain problems are rejected at step 2 of the evaluation process.
2. The SSA has developed a set of “listings” for various medical conditions. A listing typically incorporates a medical diagnosis plus some markers of severity. If an applicant has an impairment that meets the criteria for a listing, his or her application will be accepted without further ado.
3. The SSA permits a disability award to be granted if an applicant has several different impairments that cumulatively are believed to be as disabling as a listed condition.
4. In steps 4 and 5, evaluators specifically consider “vocational factors” as well as an applicant's impairments. These include the applicant's age, educational level, past work history, and transferable skills. For example, an older applicant with a poor educational background might be awarded disability even when his or her impairment is not severe enough by itself to warrant the award.

In essence, the SSD/SSI evaluation process provides alternative routes by which an applicant might be awarded disability. Medically determinable, severe impairment is a necessary condition for an award (see step 2). Among applicants with a medically determinable, severe impairment, the ones who receive awards may follow at least three different “paths” *en route* to the awards:

1. The applicant's main problem might be characterized as an impairment that meets criteria for a listing.
2. The applicant may have a combination of impairments that cumulatively are disabling enough to equal a listing.
3. The applicant may receive an award on the basis of a combination of an impairment and vocational factors.

The disability evaluation procedures of the SSA have been subjected to far more public scrutiny than those of any other disability agency. Of special relevance to the present chapter, the federal courts have played a significant role in defining the manner in which the SSA should interpret pain. The judicial history in this area is complex. Relevant decisions through the mid-1980s are summarized in Osterweis et al. (6). More recent cases are reviewed by Wolfe and Potter (59). They summarize various standards that have been considered by the courts as follows:

> [In] a landmark decision of the Ninth Circuit in 1991 . . . , the court considered three competing standards that might be used in evaluating disabling pain. The first . . . held that a finding of disability could be made without requiring that the claimant produce medical evidence of an impairment. The court rejected this standard. . . . The second standard . . . is known as the Cotton standard. It requires “the claimant to produce medical evidence of an underlying impairment which is reasonably likely to be the cause of the alleged pain. When this evidence is produced, the Cotton standard does not require medical findings that support the severity of the pain and, thus, the adjudicator may not discredit the claimant's allegations of the severity of pain solely on the ground that the allegations are unsupported by objective medical evidence.” The third standard . . . required not only objective medical evidence of impairment, but also corroborating medical evidence of the severity of the alleged pain. The Ninth Circuit . . . rejected [this] standard [and supported the Cotton standard] (6).

The Cotton standard supports the role of a physician in determining that a disability applicant with chronic pain has an impairment and in determining whether the impairment is likely to produce symptoms similar to the ones the applicant alleges. But it rejects the idea that a physician can objectively determine how severely an applicant is affected by the impairment.

If the severity of pain-associated impairment (or activity limitation) cannot be determined objectively by a physician, how can it be determined? SSA adjudicators are instructed to consider two issues: the activity limitations actually demonstrated by an applicant, and the credibility of the applicant. To get actual data on an applicant's activity limitations, adjudicators communicate with people close to him or her, such as family members and coworkers. As far as credibility assessment is concerned, a recent SSA ruling states

> When the existence of a medically determinable physical or mental impairment(s) that could reasonably be expected to produce the symptoms has been established, the intensity, persistence, and functionally limiting effects of the symptoms must be evaluated. This requires the adjudicator to make a finding about the credibility of the individual's statements about the symptoms(s) and its functional effects. Because symptoms, such as pain, sometimes suggest a greater severity of impairment than can be shown by objective medical evidence alone, the adjudicator must carefully consider the individual's statements about symptoms with the rest of the relevant evidence in the case record in reaching a conclusion about the credibility of the individual's statements. It is not sufficient for the adjudicator to make a single, conclusory statement that “the individual's . . . allegations are (or are not) credible.” The determination or decision must contain specific reasons for the finding on credibility, supported by the evidence in the case record, and must be sufficiently specific to make clear to the individual and to any subsequent reviewers the weight the adjudicator gave to the individual's statements and the reasons for that weight (60) .

The emphasis that the SSA places on assessing credibility is interesting. On the one hand, assessment of the credibility of a pain patient is crucial if one acknowledges (as the SSA does) that the effects of pain of functioning cannot be determined fully by objective measures of organ impairment. On the other hand, there is evidence that clinicians have difficulty assessing the credibility of statements made by patients with various subjective complaints (61,62).

In summary, the SSA has a multilayered algorithm for evaluating disability applicants. Problems associated with disability evaluation in painful conditions have been subjected to detailed scrutiny in the federal courts. The SSA's solutions to these problems are at odds with central assumptions in the AMA *Guides*. In particular, the SSA evaluation process embodies the assumption that physicians are frequently not able to assess objectively the severity of pain-related impairment.

EPIDEMIOLOGY OF PAIN-RELATED DISABILITY

Important questions about the epidemiology of pain-related disability include the following: How many individuals in various communities experience chronic pain? How many of them experience significant activity restrictions because of their pain? How many of them receive disability benefits because of their pain? However, these questions are difficult to answer because of a number of methodologic issues.

Several population-based surveys have shown that chronic pain is a common complaint among individuals in the United States (63,64); western European countries (65,66,67 and 68); and various countries in Africa, South America, and Asia (69). The exact prevalence of chronic pain is difficult to determine because the apparent prevalence depends on a number of methodologic issues such as the exact wording of questions posed to respondents (70). Crombie (71) cited six epidemiologic studies in which the reported prevalence of chronic pain varied from 7.0% to 63.5%; the mean of the rates published in the six studies was 31%. It is beyond the scope of this chapter to attempt to reconcile these discrepant data, but it appears that perhaps 20% to 30% of residents in the United States and western European countries experience chronic or frequently recurring pain.

A different picture emerges when disability associated with chronic pain is investigated. Epidemiologic studies have used varying definitions of “disability,” but it has typically been defined in terms of self-reported activity restrictions rather than in terms of whether a respondent is receiving disability benefits. Von Korff et al. (64) demonstrated the importance of distinguishing between chronic pain and disabling chronic pain. Although 63.5% of their subjects reported chronic pain, only 8.1% reported associated disability—that is, reported that during the previous 6 months they had experienced days when their pain had prevented them from carrying out usual activities. These data strongly support the idea that although chronic pain is common, it does not necessarily cause disability (in the sense of self-reported activity restrictions).

A similar conclusion was reached in a study of chronic pain among primary care patients in 15 countries (69). The authors found that 31% of their chronic pain subjects were judged by interviewers to be moderately or severely disabled in work, homemaking, or volunteer activities (versus 13% of subjects without chronic pain). Although disability was thus fairly common among chronic pain subjects, more than two-thirds of the subjects did not appear to be disabled by their chronic pain. Moreover, the authors point out that the statistical association between pain and disability was not consistent across participating countries. (In contrast, chronic pain was strongly and consistently related to anxiety, depression, or both.)

In summary, epidemiologic studies highlight the fact that in countries throughout the world there is a large reservoir of individuals with chronic pain. These individuals can be viewed as the group at risk for seeking disability benefits because of pain. At significantly greater risk are the people who report substantial activity restrictions because of pain. It is somewhat heartening that this subgroup represents only a minority of individuals with chronic pain, but the subgroup is large enough to

underline the importance of questions related to disability evaluation in painful conditions.

PAIN AND DISABILITY IN THE SOCIAL SECURITY SYSTEM

None of the preceding studies addresses pain-related disability in the sense of receiving benefits through a disability program. Disability in this sense can meaningfully be examined only in relation to specific disability systems because eligibility rules differ from one system to another. The present discussion focuses on chronic pain as the basis for SSD or SSI awards.

Two important questions regarding the epidemiology of pain-related disability in the SSD and SSI programs are the following:

1. Are substantial numbers of patients with chronic pain receiving disability benefits?
2. How adequately does the SSA distinguish disabled from nondisabled people among applicants with chronic pain—that is, what are the reliability and validity of its decisions?

Information related to both of these questions is sketchy. During the 1980s, the problem of pain as a reason for disability was believed to be important enough that two major studies of the role of pain in SSD/SSI awards were undertaken (6,18). Both expert panels concluded that data on the outcomes of SSD/SSI evaluations of patients with chronic pain were inadequate. However, with the exception of research undertaken by Rucker and colleagues (discussed later in this section), the situation is not much better today (76). Reasons for the lack of adequate data include the following:

1. As noted earlier, chronic pain is frequently one of many manifestations of a medical condition. The pain associated with a medical condition often cannot easily be abstracted from the other manifestations of the condition. Thus, if a person with a painful condition is awarded SSDI, the role of his or her pain in the award is often ambiguous. For example, a patient with chronic congestive heart failure and angina pectoris has pain (the angina) and would generally qualify for SSDI. His or her pain, however, might be only a minor factor in the decision by the SSA to grant benefits. The SSA makes no attempt to identify the role that pain plays in its decisions. In fact, as Osterweis et al. (6) noted, the SSA is likely to obscure the role of pain by its emphasis on objectively determinable impairment.
2. The problem of "disentangling" pain from other manifestations of disease is magnified by the fact that in the *International Classification of Diseases,* Ninth Revision (*ICD-9*), medical conditions are classified in multiple ways. For example, a person with a low back problem could be given a diagnosis (e.g., 724.2, low back pain), which highlights the fact that he or she has back pain, but he or she could also receive a diagnosis based on the suspected pathophysiology underlying his or her symptoms (e.g., 722.2, lumbar disc herniation). Virtually all disability agencies, including SSA, use diagnoses that emphasize biological derangement (e.g., lumbar disc herniation) rather than ones that emphasize symptoms.
3. In its publications, the SSA groups disability recipients into 15 broad diagnostic categories (72). This grouping completely obscures the role that pain may be playing in SSD/SSI awards. For example, patients with fibromyalgia, lumbar disc disease, and rheumatoid arthritis are all lumped into the category "musculoskeletal disorders."
4. The SSA is an administrative agency that operates in a political arena. As such, it often does not have the luxury of doing scientific research and making policy based on the results. The history of the continuing disability review program during the early 1980s is a compelling example (5). Continuing disability reviews are reevaluations of the functional and medical status of individuals who are already receiving SSD or SSI benefits. In theory, continuing disability reviews permit the SSA to improve the accuracy of its decision making because doing so gives the agency a second chance to consider the extent to which an individual is incapacitated. In 1980, a study of SSD beneficiaries indicated that more than 500,000 of them were not disabled severely enough to deserve benefits. The SSA responded to this information by intensifying its program of continuing disability reviews on beneficiaries and ended up dropping approximately 450,000 of them between 1981 and 1983 (73). This led to a flood of legal appeals and outcries by members of Congress. Finally, in 1984 a beleaguered SSA cut its continuing disability review program back drastically and has never reinstituted it on a scale that approaches its intensity during the early 1980s. In essence, for a program like SSD, scientific questions about the validity of decisions are entangled with societal concerns about justice and with the politics of interest groups.

Despite the limitations described, at least some data bear on the question of whether SSD/SSI benefits are frequently awarded to patients with chronic pain. Wolfe et al. (74,75) present data on the frequency with which patients with fibromyalgia are awarded SSD. In their first study, they demonstrated that the prevalence of fibromyalgia in the community is approximately 2%. The second study dealt with self-reported disability among fibromyalgia patients who were attending one of six university-based rheumatology clinics around the United States. Twenty-six and one-half percent of the 1,144 respondents reported that they had received disability payments of some kind during their lifetimes. SSD was by far the most common source of disability payments, with 16.2% of respondents reporting SSD benefits. Wolfe et al. noted that among subjects who began receiving disability benefits after 1988, 44.4% reported that the award was granted for a diagnosis of fibromyalgia. (Other respondents reported receiving disability for a variety of diagnoses, including back conditions, miscellaneous other musculoskeletal conditions, systemic lupus erythematosus, miscellaneous other medical conditions, and psychiatric conditions.)

Wolfe et al.'s data are subject to a variety of interpretations. As the authors note, their subjects were patients at university-based rheumatology clinics and therefore may not have been representative of fibromyalgia patients as a whole. Also, more than one-half of the patients who received disability payments reported that they were nominally given the payments for a condition other than fibromyalgia. But despite these caveats, the data clearly show that individuals are getting SSD benefits for conditions characterized mainly by chronic pain. In this regard, it is important to note that in terms of the categories given earlier, fibromyalgia should be classified as an unverifiable pain problem—there are no truly objective findings. Thus, Wolfe et al.'s data indicate that the SSA, despite statements about the need for "medically determinable severe impairment," actually grants SSD to many individuals strictly on the basis of reported pain. Moreover, the number of SSD awards for fibromyalgia appears to be high. If we multiply the number of adults in the United States (approximately 200,000,000) by the prevalence of fibromyalgia (2%) by the probability of being on SSD among fibromyalgia patients (16.2%) by the proportion of fibromyalgia patients who receive benefits on the basis of a diagnosis of fibromyalgia (44.4%), we would conclude that approximately 290,000 individuals are currently receiving SSD benefits because of fibromyalgia. This figure is undoubtedly too high, but Wolfe et al.'s data forcefully make the general point that substantial numbers of Americans are being awarded SSD for conditions characterized by chronic pain in the absence of other manifestations of disease.

I am not aware of data on SSD awards among any other patient groups with chronic pain. As noted, statistics published by SSA are virtually useless in determining how many awards are given primarily because of pain. There are suggestions, however, that pain is a common problem in SSD and SSI applicants. For example Rucker, who has done extensive research in conjunction with the SSA, cites unpublished data suggesting that pain is at least a factor in 40% to 60% of all SSD and SSI awards (76).

The fact that some disability applicants are awarded benefits largely on the basis of pain says nothing about the reliability or validity of the decisions that the SSA makes on these applicants. The SSA does have a quality control program and keeps track of the reproducibility of decisions made when individuals submit their initial applications for disability. These initial applications are evaluated by adjudicators and physicians who work for a Disability Determination Service (DDS) in the applicant's community. When applicants' files are randomly reevaluated by staff at one of the SSA regional offices, the concordance rate between their decisions and the decisions made by evaluating DDS teams is approximately 95% (77). These data suggest that the disability determination process is highly reliable. However, the interpretation of the data is unclear for two reasons. First, the SSA quality-control program deals with all applicants—it does not give information about the reliability of decisions regarding applicants with chronic pain. Second, and more important, 24% of the individuals whose applications are denied during the initial SSA evaluation are awarded benefits on appeal (64). Thus, although the decisions made by DDS teams agree well with decisions made by reviewers at the SSA regional offices, the SSA decision-making system as a whole is unreliable because judgments made at the DDS level are frequently overturned on appeal.

As far as predictive validity is concerned, research conducted by Rucker and colleagues (76,78) provides the most useful data. They were commissioned by the SSA to develop a system to assess disability applicants with chronic pain. They developed the Multiperspective Multidimensional Pain Assessment Protocol (MMPAP) to accomplish this goal. It consists of a questionnaire for patients to fill out, a standardized physical examination, and standardized physician ratings of patients' behavior. The MMPAP was administered to 691 individuals who were filing initial disability applications (either for SSD or SSI). All subjects were described as having chronic pain, defined as pain lasting at least 6 months. No detailed medical information was reported on the subjects. All subjects went through an initial MMPAP assessment. To test the reliability of assessments, the researchers recruited 20% of the subjects to return for a repeat assessment approximately 4 weeks later. Subjects were contacted 8 months later, and their employment status assessed by self-report. Key findings were the following:

1. The MMPAP demonstrated adequate test-retest and interrater reliability.
2. One hundred fifty-seven of the subjects (22.8%) were awarded disability; the other 532 (77.2%) were denied. [This award rate is lower than the initial award rate of 31% for all disability applicants (73).]
3. Applicants who were awarded disability were less likely to be working at follow-up than ones who were denied disability (chi square = 6.78, p <.01). It is worth noting, though, that even among the denied patients, only 14% were employed at follow-up.
4. Discriminant function analysis revealed that approximately 65 of the items from the MMPAP were predictive of whether a subject would be employed or

unemployed at follow-up. The authors noted that the predictors came from several domains, including rated pain intensity, mental health status, physical examination findings, activity limitations reported by the subject, and functional abilities rated by a physician examiner.

Rucker et al.'s research provides some support for the validity of the SSA's decisions regarding applicants with pain problems. Specifically, the investigators found that at 8-month follow-up, 14% of individuals rejected by SSA were working, as opposed to 6% of those who received disability awards. This difference was statistically significant at the .01 level, but it is hardly impressive. In fact, the most parsimonious explanation of Rucker et al.'s data is that disability applicants with chronic pain do poorly as far as return to work is concerned, regardless of whether their disability applications are accepted or denied. It is also noteworthy that the acceptance rate for Rucker et al.'s patients was low compared with the acceptance rate among all disability applicants.

In theory, continuing disability reviews could provide some information about the validity of the SSA's decisions. As a practical matter, however, the SSA has done few continuing disability reviews since the early 1980s (79). At this point, individuals who get SSD awards almost all stay in the system until either death or age 65 years (when they become eligible for old age insurance) (80). Because few continuing disability reviews are done, there are no useful data about the actual medical status of individuals who are receiving benefits or about the predictive validity of the decisions that the SSA makes when it initially awards benefits. In essence, political considerations make it difficult for the SSA to study individuals after they have received awards.

Longitudinal studies on disability applicants who were denied benefits might also provide important information about the validity of the SSA's decision-making procedures. Aside from Rucker et al.'s 8-month follow-up study, however, research in this area is virtually nonexistent.

CLINICAL MANAGEMENT OF DISABILITY ASSOCIATED WITH PAIN

The discussion so far has focused on conceptual and public policy quandaries involved in the evaluation of pain-related disability. At a more practical level, physicians are frequently confronted with the task of evaluating disability in chronic pain patients whom they are treating. This is often an uncomfortable task for several reasons:

1. They frequently feel pressured to do the evaluations. Insurance companies typically create pressure by threatening to withhold benefits from the patient or payment from the physician if disability forms are not filled out.
2. Often, they are not familiar with the disability systems with which they are interacting. For example, they may not grasp the implications of signing a job analysis or stating that a patient has reached maximal medical improvement (MMI). Thus, they worry that they may inadvertently prejudice disability applications of their patients.
3. They may not be familiar with the types of medical issues that should be addressed in contested situations that may end up in court. For example, they may not make a clear distinction between subjective and objective findings, or they may not be familiar with the mechanics of performing impairment ratings according to the AMA system.
4. They often implicitly recognize the difference between the clinical role they normally play when they treat patients and the adjudicative role that is required during a disability evaluation. Informal observation as well as examination of the limited literature on these roles (81,82,83,84) suggests the differences shown in Table 17-1. Physicians probably recognize that significant ethical issues arise when they switch back and forth between these two roles (84). As a result, many of them feel uncomfortable making adjudicative judgments on patients they are treating.

Clinical role	Adjudicative role
The physician's primary obligation is to his or her patient. It is appropriate for the physician to be a patient advocate and to do everything possible to help his or her patient return to health.	The examiner is not a patient advocate and is not obligated to meet the needs of the patient being evaluated (some critics would assert that independent medical examiners often function as advocates for insurance companies).
A patient's history provides 90% of the clinical information that a physician needs. The physical examination and laboratory tests are important but secondary sources of information.	The emphasis in an evaluation should be on objective findings (e.g., on physical examination or imaging findings) rather than on the patient's complaints.
When there is doubt about the accuracy of a patient's statements, the patient is given the benefit of this doubt.	Be skeptical of patients' reports.
A major task of a physician is to diagnose a patient's problems—that is, to identify the pathophysiology underlying the patient's symptoms.	The focus should be on legal causation of a patient's symptoms.
A physician's job is to provide medical or surgical assistance, not to become embroiled in a patient's legal problems.	The major job of the independent medical examiner is to relate a patient's clinical condition to applicable laws or administrative regulations that define the responsibilities of third-party payers.

TABLE 17-1. Role expectations for physiciansclinical versus adjudicative

5. Partly because of the role conflict noted, clinicians often end up feeling caught in the middle between their patients and disability systems. Disability agencies might seem bureaucratic and unenlightened; they might make demands for documentation that seem unreasonable to the clinicians. At the same time, patients might express a degree of incapacitation that seems extraordinary and then try to enlist the physicians as advocates during negotiations with disability agencies.

The purpose of this section is to outline skills and strategies that physicians may use as they attempt to negotiate the turbulent waters of disability evaluations of patients they are treating. Broadly speaking, when clinicians address disability issues in patients they are treating, they need special skills in two areas—evaluating patients and interfacing with disability systems.

Patient Evaluation

In the usual clinical situation, a physician evaluates a patient by eliciting a history, performing a physical examination, and perhaps performing ancillary investigations such as laboratory studies. The goals of the evaluation are to diagnose the patient's problem and to develop a treatment plan. These skills are all essential in a setting where the clinician is evaluating the disability status of his or her patient, but a number of additional issues must also be addressed:

1. *Are the patient's examination findings "subjective" or "objective"?* There are at least two reasons why this distinction is important. First, disability systems typically require physicians to identify the objective findings on which their conclusions are based. Second, the distinction highlights a problem that physicians must consider when they treat patients who are also interacting with a disability system. It is that the behavior of such patients might be subtly altered by their involvement with the system. In this context, it is important for the physician to distinguish between findings that are completely beyond the control of the patient and ones that are at least partially under the patient's control (and therefore subject to change in response to environmental influences).

   However, the distinction between subjective and objective findings is not entirely clear-cut. At the extreme, a subjective finding is a report by a patient of something a physician cannot directly observe (e.g., "My arm is beginning to tingle"), whereas an objective finding is one that is completely unrelated to any voluntary response of the patient. To state it differently, a completely objective finding is one that could be obtained in a comatose patient or one who was completely uncooperative or disingenuous. Examples include x-ray findings and laboratory findings. In actual clinical settings, there are many physical examination findings that are "semiobjective," in the sense that they are partially under the control of a patient. Examples include muscle spasms or tenderness, restricted range of motion, and some deep tendon reflex abnormalities. The attorneys and disability agency adjudicators who routinely ask for objective findings are generally unaware of the subtleties.
2. *Is there a clear-cut diagnosis?* Sometimes a patient's signs and symptoms represent a textbook case of some medical condition. In this instance, the physician can at least be reasonably comfortable that his or her diagnosis is correct. However, many patients—especially ones with chronic pain problems—present with a set of symptoms and signs that only loosely fit a well- defined medical condition. In this situation, the clinician is faced with ambiguity from the outset because he or she cannot be sure what (if any) medical problem the patient has.

   A related issue involves the consistency of the patient's symptoms and signs over time. A clinician can be most confident of his or her diagnosis when the patient demonstrates the same clinical picture over a series of assessments or shows the kind of progression of symptoms and signs that is typical of the condition that has been diagnosed.
3. *How much impairment is usually associated with the diagnosed condition? What kinds of activity restrictions are typical?* An experienced clinician has a general idea about the kinds of activity limitations that are expected in a patient with a certain medical condition. For example, patients with acute lumbar radiculopathies frequently do not tolerate sitting, bending, or lifting and can be severely incapacitated. Patients with carpal tunnel syndrome are often intolerant of repetitive hand activities and are often awakened at night by uncomfortable paresthesias.

The clinician should be alert to a patient who either claims much greater incapacitation than one would expect for a given medical condition or reports activity restrictions that are qualitatively different from the ones that are expected. These kinds of mismatches should prompt the clinician to consider carefully the reasons for the patient's atypical presentation.

4. *Is there any evidence of symptom magnification or nonorganic findings?* If these are present, they should alert the clinician that the patient's apparent limitations are probably not explainable entirely in terms of the biology of his or her medical condition. The physician should consider hypotheses to account for nonorganic symptoms or signs.
5. *How credible is the patient's presentation overall?* This is a global judgment that takes into account items 1 through 4.
6. *Has the patient reached MMI?* A patient is said to have reached MMI after an injury when three conditions have been met: (a) The patient has had the benefit of therapies considered appropriate for the injury, (b) enough time has elapsed that healing is likely to be complete, and (c) the patient has reached a plateau as far as functional improvement is concerned. The issue of MMI comes up routinely on disability forms. Most disability programs operate on the premise that long-term decisions about a disability applicant should be made when the applicant has reached MMI. Some, such as SSD/SSI, reject applicants if there is reason to believe that they will improve within a year. However, the concept of MMI is fraught with ambiguity. It is beyond the scope of this chapter to review all the complexities related to the term, but a key issue is whether a patient who experiences chronic pain can be considered to have reached MMI when he or she has not had the opportunity to undergo a vigorous pain rehabilitation program. More generally, a patient who has failed to benefit from curative therapies such as surgery might still benefit from a structured physical restoration program. To certify a patient as disabled before any attempt at rehabilitation is not an adequate standard of either health care or disability determination.
7. *What are the patient's physical capacities and physical limitations?* Most clinicians realize that it is difficult to assess a patient's activity limitations on the basis of a medical examination only. At best, such an examination leads to a diagnosis and broadly identifies the types of limitations that might be expected. Medical examinations, however, are not well suited to determining a patient's activity limitations in detail. One way for a clinician to obtain more detailed information is to refer his or her patient for a functional capacity evaluation (sometimes called a *physical capacities evaluation*) (85). Even a physical capacities evaluation is not totally objective, however. If even more detailed behavioral data are needed, the clinician can refer a patient to various programs that provide ongoing assessments of patients over weeks, along with attempts to increase the patient's activity capacities. Even a physical capacities evaluation is not totally objective, however. For example, pain rehabilitation programs (86), functional restoration programs (87), and work hardening programs (88) all provide extensive observational data on the capacities of chronic pain patients.
8. *How does the patient's medical condition affect his or her ability to work?* This is a key question in disability evaluations but an extremely difficult one for physicians to answer. At the very least, an intelligent answer requires a physician to match the activity limitations imposed by a patient's medical condition to the activity demands of various potential jobs. This is difficult to do for several reasons. First, as discussed throughout this chapter, activity limitations secondary to pain are difficult to quantify. Second, physicians rarely have detailed information about the physical demands of various jobs. Third, the workplace factors that influence pain patients' ability to function are often subtle. For example, Yelin (89) found that patients with rheumatoid arthritis are more likely to maintain employment if they have significant control over the pace of their work activities. Thus, even if a physician has information about the physical demands of a job, he or she may be uncertain about subtle aspects of the job that are likely to influence the ability of a patient to meet these demands.

   Some disability agencies assist physicians by hiring vocational rehabilitation counselors and providing treating physicians with job analyses—that is, detailed descriptions of various jobs for which a patient is being considered. But even with this help, physicians face ambiguity when they render opinions about the ability of patients to work.

Interfacing with Disability Agencies

Even after a physician has done the kind of detailed assessment discussed above, he or she may not be ready to respond to the questions raised by a disability agency. There are several reasons for this.

1. The specific questions addressed to physicians vary widely from one agency to another. Sometimes physicians are asked to state the physical limitations of a patient (e.g., to state how many hours the patient can sit during a day, how many pounds he or she can lift, and so forth). In other situations, they are given detailed information about specific jobs and are asked whether their patient can perform the essential functions of the jobs. These job analyses typically request much more than a simple yes or no answer by the physician. For example, they often ask whether the worker can do the job on a full-time versus a part-time basis, whether modifications in the job would help, what these modifications should be, and so forth. Other agencies ask the physician to state in broad terms the category of work in which a patient can engage—from sedentary to heavy. In still other situations, physicians are asked whether their patients can go back to their usual line of work and, if not, whether they can perform any kind of work. In essence, physicians who have completed a detailed assessment of their patients must still carefully study the questions posed to them by a disability agency and see whether the medical information they have obtained permits them to answer these questions.
2. More generally, the rules of different disability systems differ so dramatically from each other that a physician is unlikely to be able to interface with a particular one unless he or she understands it in some detail. The following discussion considers two systems—the Department of Labor and Industries (DLI) (the main workers' compensation carrier in Washington state) and the SSA. The SSA follows the same rules throughout the United States, so the following information is relevant regardless of where a physician practices. The procedures followed by workers' compensation systems vary widely from state to state, however. The following information about DLI may be relevant in states other than Washington, but the only way physicians can be sure is to study the rules in their state carefully.

Disability Evaluation in the Washington State Department of Labor and Industries

A key feature of the Washington State DLI is that it requires treating physicians to make sequential disability judgments regarding injured workers. The physician who initially evaluates an injured worker is required to complete an accident report, as shown in Figure 17-6. The form includes several items about disability. Item 45 requires the physician to list objective findings that support his or her diagnosis. It thus raises the issue of subjective versus objective perspectives on incapacitation. Item 47 asks about causation—that is, whether the patient's condition was caused by an exposure at work. Item 48 asks the physician to assess the effect of the work injury or illness on the patient's ability to work.

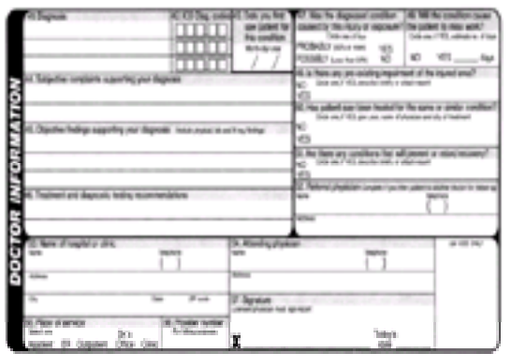

Figure 17-6. Selected questions from the Washington State Department of Labor and Industries accident report.

It is typical for physicians in emergency rooms and other immediate care facilities to address disability issues during their first encounter with a patient. If the worker remains off work for an extended period, the treating physician is asked to make a series of judgments that bear on the worker's disability status. The judgments include the following:

1. Responses to job analyses submitted by vocational rehabilitation counselors. If a treating physician indicates that the patient can perform the essential activities for one of these jobs, the patient's time-loss benefits are terminated.
2. Responses to physical capacities evaluations.
3. Judgments about whether a patient has reached MMI from treatment.

4. Comments on independent medical examinations commissioned by the DLI.

In addition, the treating physician is invited to conduct a formal closing examination on a worker who is thought to have reached maximal medical benefit from treatment. In such an examination, the physician is asked to comment on the causation of any medical condition diagnosed, to indicate whether the patient has achieved MMI, to rate the impairment associated with each condition, and to indicate whether the patient is employable.

Disability Evaluation for Social Security Disability Insurance and Supplemental Security Income Applicants

Rules and procedures governing the SSD and SSI programs have been described (under Pain and the Social Security Administration Disability Evaluation Process). The demands on the treating physician imposed by these programs are entirely different from those imposed by workers' compensation systems. In particular, the SSD/SSI programs are designed only for individuals who have reached MMI and are severely disabled. The concepts of temporary disability or partial disability do not exist in the SSD/SSI programs. One consequence is that the treating physician is typically contacted only once for information about an SSD/SSI applicant. Typically, physicians are sent letters requesting that they address the issues listed in Table 17-2.

History and physical examination findings
Progress notes
X-ray reports
Description of joints to include deformities and inflammation
Range of motion
Gait and station
Evidence of muscle spasms
Neurologic findings
Pertinent lab work
Operative reports
Description of pain (what causes it; what relieves it)
Type and duration of treatment
Prognosis

TABLE 17-2. Information typically requested from treating physicians regarding applicants for Social Security Disability Insurance or Supplemental Security Income

The SSA takes the perspective that treating physicians should provide objective information about the medical status of disability applicants but that it is the job of adjudicators with a DDS to make the final decision about whether an applicant is really disabled. Thus, in theory the role of the treating physician is limited. In practice, however, a treating physician can influence the disability determination process in several ways (58). For example, one step of the sequential evaluation process used for SSD/SSI applicants is the determination about whether their problems meet a “listing.” A treating physician who is familiar with the criteria for various listings (10) can provide information about whether a patient has the findings that qualify him or her for a listing.

It is common for workers with prolonged disability from work injuries to apply for SSD while their industrial compensation claims are still open. In that instance, the treating physician ends up interacting with two disability systems simultaneously.

Practical Suggestions for Interfacing with Disability Systems

No simple “cookbook” exists that treating physicians can follow when they address issues related to the disability of patients they are treating; however, a few general guidelines are provided:

1. An enormous difference exists between temporary, short-term disability and permanent or long-term disability. For example, a person with a low back strain might well be incapacitated for several days, and it is entirely reasonable for a treating physician to support the individual's statement that he or she cannot work. Workers' compensation systems generally acknowledge this reality by accepting more or less at face value a physician's assertion that the patient is temporarily disabled from work. Problems arise when the patient's apparent work incapacity continues for weeks or months or when the patient applies for permanent disability. The following discussion focuses mainly on permanent or long-term disability.
2. The disability evaluations that physicians make on their patients permit them not only to respond to questions posed by a disability agency, but also to manage the patients more effectively. The reason for this is that treating physicians have the potential to alter the disability status of their patients rather than simply to assess it. This is particularly important in the treatment of recently injured patients who are on short-term disability (e.g., through a workers' compensation claim). In that setting, physicians can use management strategies to reduce the likelihood of long-term disability. No proven set of strategies exists, but informal experience suggests the following:
   a. “Watching the clock.” Disability seems to feed on itself. Once a patient has been on disability for a long time, the probability of going off disability drops, as does the probability of the patient's responding positively to treatment.
   b. Protecting the worker's job. Long-term follow-up studies indicate that workers are more likely to reintegrate into the workforce if they return to the job where they were injured (90,91). A treating physician can sometimes take steps to foster constructive interaction between an injured worker and his or her employer.
   c. Knowing risk factors for chronicity. No single, definitive list of factors exists that predicts the probability that a patient will become chronically disabled; however, several tentative “red flag” lists have been developed on the basis of expert consensus (92,93) or literature reviews (94).
   d. Intensifying treatment for high-risk patients. If a patient seems likely to fail conventional treatment approaches and remain disabled, the treating physician can attempt to direct the patient toward a variety of more intensive rehabilitative interventions, including psychological evaluation and treatment, work hardening, and pain center treatment.
   e. Assessing the credibility of patients. These assessments are crucial because treating physicians typically make key management decisions on the basis of statements made by patients. Credibility assessment is a difficult area, and there are no proven guidelines. In the area of low back pain, the nonorganic signs and symptoms developed by Waddell (17) can be extremely helpful. The lists of “red flags” for chronicity that various investigators have developed (92,93) may be relevant to the assessment of patient credibility, although the set of factors thought to represent red flags for chronicity is broader than the set of factors that suggest low patient credibility (e.g., poor educational background and history of multiple surgeries are thought to predict chronicity but do not necessarily imply poor patient credibility).

   Sometimes it is useful to turn the issue around and identify a “green flags” list—that is, a set of factors associated with high patient credibility (Table 17-3). Physicians should be concerned when they see a patient who fails to match several of the factors on this list. Remember, however, that this list has not been subjected to validation research.

No preexisting condition
No medical co-morbidities
Definite stimulus (e.g., crushed by a tree)
Definite tissue damage (e.g., fracture)
Symptoms, signs, activity limitations fit expectations for the medical problem
Consistent findings over repeated examinations
No exaggerated pain behavior
No inconsistencies between symptoms and signs noted in the physician's office and behavior outside the office
No chronic psychiatric disorders or long-term psychosocial risk factors
No reactive psychiatric problems (e.g., anxiety disorder, depression)
Patient motivated to return to productivity
Job opportunities exist
No incentives for disability

TABLE 17-3. Characteristics associated with high patient credibility

3. Treating physicians are likely to assume that when they support disability applications of their patients, they are acting in the patients' interests. It is therefore

important to highlight the fact that the long-term interests of patients might actually be harmed when their treating physicians support disability rather than return to productivity. At least two considerations are relevant:

   a. Most patients are not well served by long-term disability systems. For example, the payment levels for SSD recipients are low (95) so that beneficiaries face the strong possibility of financial hardship. In general, the economic needs of an injured person are much more likely to be met if he or she remains in the workforce than if he or she remains in a disability system for an extended period (96).
   b. As discussed under Changes over Time, many injured workers seem to become more dysfunctional as they interact with the industrial compensation system (43). The dehumanizing effects of interacting with the bureaucracy are pervasive. Thus, physicians generally serve the long-term needs of their patients best when they encourage the patients to extract themselves from the system as soon as possible.

4. For physicians to interact successfully with a disability system, they should understand its rules and policies in detail. These differ sharply from one system to another. No substitute exists for spending the time needed to become familiar with some of the common ones.

   It can be particularly enlightening to learn what attorneys say about disability systems. For example, Ruskell (97) has written a book for attorneys who represent SSD/SSI applicants that provides detailed, practical information about the SSD/SSI application process.
5. A treating physician sometimes feels overwhelmed by the bureaucratic machinery of a disability system. This sense may be heightened when a group of independent medical examiners renders opinions different from the ones he or she has expressed. It is therefore important to understand that courts have required disability agencies to weigh the opinions of treating physicians heavily. Thus, if a treating physician forcefully communicates opinions about his or her patient, it will have an impact on the decision that a disability agency makes.
6. Patients who are actively seeking disability benefits often see support from their treating physicians as crucial to their disability applications. A physician who does not support such an application should discuss this issue openly with his or her patient. In many instances, conflict about a disability application will cause serious strains in a doctor-patient relationship that is otherwise entirely positive.
7. Many patients seek legal representation when they are applying for disability. A treating physician thus should consider how to interact not only with the patient and the disability system, but also with the patient's attorney.

IDEAS FOR CHANGE

There is no dearth of scientific literature on the general issue of disability evaluation. A MEDLINE search done in April 1998 with “disability evaluation” as key words yielded 2,323 articles published in English since 1990. However, virtually all of them are irrelevant to the present discussion because “disability” is generally defined in terms of self-reported activity limitations. The literature on individuals who have applied for or have been awarded SSD, or both, is much smaller, and the literature on pain and SSD is virtually nonexistent. However, new ideas that warrant discussion are on the table.

1. Numerous discussions about the assessment of pain exist in the medical literature and in other chapters of this book. I have not included an assessment protocol because essentially none of the ones in current use has been validated for the problem under discussion here—the determination of disability in chronic pain patients. The only exception is the work of Rucker and colleagues (76). As noted, they have developed reliable and valid tools for the assessment of disability applicants with pain problems. The project is a model for the approach that is needed if scientific progress is to be made in the processes by which SSD/SSI applicants are evaluated. Rucker's team did the basic work of developing an assessment battery, determining its metric properties, and assessing its validity on a cohort of disability applicants. At this point, their work stands alone as the one systematic attempt to answer questions about pain and the SSA rigorously. More studies of a comparable character are needed to address the assessment of pain as a cause of disability.
2. The National Center for Health Statistics conducts an annual national survey (the National Health Interview Survey) dealing with health problems of U.S. citizens. One of the areas covered in depth is self-reported activity limitations. The surveys provide a rich picture of the distribution of various disabling problems in the United States (98). However, the survey format to date does not include any questions about whether respondents are receiving disability benefits. In future surveys, these questions will be included (M. LaPlante, personal communication, March 1998). This will permit the National Health Interview Survey to collect population-based data on the self-reported activity limitations of individuals who are, versus ones who are not, receiving disability benefits.
3. Physicians with expertise in fibromyalgia have been involved for several years in a vigorous and sometimes rancorous debate about disability among fibromyalgia patients (42,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139 and 140). The debate has been wide ranging, dealing not only with the assessment of disability in fibromyalgia, but also with the question of how causation of fibromyalgia can be assessed and with the issue of the nature and reality of the condition. Although this debate has not led to any obvious resolution, it has at least brought critical issues related to pain and disability to the attention of physicians. In essence, fibromyalgia raises questions about pain and disability in pure form because patients often complain of overwhelming incapacity but have no conclusive evidence of a disease process that can be assessed objectively by a physician. At this point, the dialog on disability in fibromyalgia represents the best discussion in the medical literature about how disability agencies and individual physicians might respond to alleged disability in painful conditions.
4. The fourth edition of the AMA *Guides to the Evaluation of Permanent Impairment* has a chapter on the evaluation of disability secondary to chronic pain. It includes important concepts about chronic pain and some guidelines about how to evaluate the impact of pain systematically. However, the chapter does not provide any method for quantifying the impairment associated with pain, and the information in it is not integrated into the entire AMA system for impairment rating. In essence, the chapter on impairment from pain is rather redundant with other chapters in the AMA *Guides* and is generally ignored by disability examiners. As a practical example, an examiner evaluating a patient with a chronic lumbar spine condition would almost certainly ignore the chapter on pain and instead use the impairment ratings given in the chapter on the musculoskeletal system.

   On the positive side, however, the AMA is committed to upgrading its system of evaluating pain-related impairment. The editor of the upcoming fifth edition of the *Guides* has contacted the American Pain Society, the American Academy of Pain Medicine, and various experts in disability in an attempt to strengthen its discussion of pain-related impairment (L. Cocchiarella, personal communication, February 1998).
5. A monograph edited by Fordyce et al. (45) focuses on problems associated with the current concepts regarding low back pain and work disability. In essence, this group argues that impairment cannot be assessed validly in nonspecific low back pain, because (a) an examiner's assessment of impairment from low back pain depends on the performance of a patient during an examination and (b) a back pain patient's performance during an examination is determined not only by the severity of the anatomic and physiologic functional loss he or she has sustained, but also by a variety of psychosocial factors. In their words, “Not all potential impairments can be confirmed by verifiable measures of their presence independent of performance by the person purported to be impaired. Because performance is also 'effort-related' as well as related to anatomical or physiological capabilities, it is inevitably linked to and influenced by such factors as attitudes, motivation and personality” (45).

Fordyce promotes the idea that patients with nonspecific low back pain should be classified as “unemployed” rather than disabled if they “persist . . . in activity intolerance beyond the allotted time for medical treatment and temporary disability status” (45). Thus, patients with persistent nonspecific low back pain would, for benefits purposes, be classified with people who are unable to find work who do not have a rated disability.

It is important to note that Fordyce makes recommendations for disability policy only in relation to nonspecific low back pain; they do not consider any other chronic pain conditions. Also, although their recommendations about disability policy rest on their pessimistic view of the ability of physicians to determine impairment accurately in patients with nonspecific low back pain, they do not provide any data to buttress this view. In essence, their monograph is a consensus document rather than a presentation of empiric data. However, in view of the eminence of its authors, *Back Pain in the Workplace* is a provocative work that should be read carefully. It clearly identifies the need to separate the availability of health care from disability status and to recognize the “moral hazard” of disability insurance.

WHERE DO WE GO FROM HERE?

This chapter was meant to have a sober tone. It is common knowledge that many people seek disability because of painful conditions; however, the societal responses to these requests are incoherent for many reasons:

1. No accepted system exists for classifying painful conditions in a way that is relevant to disability evaluation.
2. Partly as a result of the preceding reason, there are virtually no useful data on how many patients seek disability because of pain and how many actually receive benefits.
3. Similarly, little is known about the long-term activity limitations and workplace disadvantage of people who perceive themselves as disabled by pain.
4. There has been no agreed-on solution to the problem of integrating subjective information and objective information in the evaluation of patients who claim work incapacity.
5. The scientific study of disability evaluation is woefully lacking. Only fragmentary information is available about the reliability with which physicians evaluate patients claiming work incapacity. Studies on the validity of these judgments are virtually nonexistent, and there are significant problems in determining, even at

a theoretical level, how such studies should be designed.

6. The process of disability determination is entangled in the insurance and legal systems. The effects of these entanglements are difficult to assess, but, in a general way, they act as barriers to information exchange and scientific research (141).

Given the preceding, there is a real risk that the chapter on pain and disability in the next edition of *Bonica's Management of Pain* will be as inconclusive as the present chapter has been. If we are to move forward, we have to start by acknowledging the holes that exist in our present approaches to pain-related disability and work toward a set of concepts and empiric research that could properly be called *disability evaluation science*. This will be hard work, and there will be no "quick fix." A short list of the issues that should be addressed includes the following:

1. *Break the problem down.* It is quite possible that impairment rating systems currently in use are adequate for assessing patients with "expected" pain. In contrast, there is no good method available for rating unverifiable pain or psychogenic pain. These important distinctions are lost if statements about pain and disability are framed in global terms.
2. *Clarify the meaning of psychogenic pain and the manner in which impairment associated with psychogenic pain should be assessed.* Psychogenic pain is probably the most ambiguous category of pain (142). It involves philosophic conundrums (143,144) and conceptual leaps whose implications have not been carefully explored. When physicians evaluate most pain patients, they start with the assumption that the patient's pain is somehow "grounded" in a pathophysiologic process that can be understood in traditional medical terms. In psychogenic pain, pathophysiology (in the sense of injury or disease of a body part) is irrelevant. Thus, it is not clear what clinical evaluation tools are relevant to psychogenic pain. Also, it is not clear how psychogenic pain differs from abnormal illness behavior (145). In the extreme, a paradox is encountered in which it is concluded that every patient (other than a malingerer) who reports incapacitating pain must be severely impaired. If the patient has objective evidence of a medical condition that explains his or her symptoms, the impairment is attributed to that condition. If no such objective evidence is found, it is concluded that the patient must be severely impaired because of psychogenic pain. This syllogism is obviously specious, but it highlights the conceptual confusion that surrounds psychogenic pain.
3. *Develop methods for aggregating patients into large groups without losing critical clinical information.* Many problems exist in this area. The *ICD-9*, the most widely used diagnostic system, is difficult to use in studies on large groups of patients, in part because a condition such as low back pain is compatible with multiple *ICD-9* diagnoses. Ambiguities associated with *ICD-9* diagnoses are magnified by the fact that physicians and disability agencies often choose diagnoses on the basis of factors other than accuracy. Physicians tend to choose diagnoses that maximize their chance of being reimbursed by insurance companies; disability agencies tend to choose diagnoses based on their congruence with eligibility criteria for benefits [e.g., workers' compensation systems tend to code all noncatastrophic low back conditions as lumbar strains (847.2), whereas the SSA is more likely to diagnose lumbar degenerative disc disease (722.52) or displacement of lumbar intervertebral disc dislocation (722.10)]. A further complication arises when survey methods are used to obtain self-reported health data (98). Interviewers in surveys are not medically trained and typically do not have access to physical examination findings or laboratory data. As a result, the "diagnoses" made in the course of health surveys are not necessarily comparable to diagnoses made by physicians. The general point is that research on pain-related disability should deal with a paradox: Large patient cohorts are needed to identify statistical trends, but information vital to the clinician may be lost when patients are aggregated into large groups.
4. *Develop strategies for making inferences about pain on the basis of diagnostic information.* Assuming that one has access to *ICD-9* diagnoses for a group of patients, one still has to determine whether pain is a major component of the problems with which the patients presented. This requires a careful consideration of the role that pain is likely to play in various medical conditions. For example, paraplegia is a condition associated with substantial impairment even when pain is not a problem. In contrast, for most patients with lumbar disc conditions and for all patients with fibromyalgia, pain is essential to the impairment.
5. *The SSA should keep more detailed medical records on beneficiaries.* As noted previously, the SSA uses such broad medical categories in its research and statistical reports on beneficiaries that the role of pain in SSD or SSI awards is difficult to determine.
6. *Study correlations between reported incapacity from pain and objective measures of organ dysfunction or activity restriction*. Some research in this area has already been done (24,146). The broad question is whether the statements that patients make about their abilities and restrictions match objective assessments that external observers make. If the match is close, then it might be reasonable to weigh subjective estimates of incapacitation heavily in disability evaluations.
7. *Study long-term functional outcomes among patients who seek disability benefits because of pain.* This would include follow-up research both on individuals who receive disability benefits and ones whose benefit applications are denied. The research of Rucker et al. (76,78) provides an example of the kind of work that is needed in this area.
8. *Study the effect of social policies on the apparent incidence and prevalence of painful conditions*. As previously noted, many experts are concerned that if disability programs dispense benefits liberally on the basis of subjectively determined incapacity, the result will be a sharp increase in the number of people who request benefits because of pain and other symptoms. This hypothesis can and should be tested.
9. *Evaluate the hypothesis that patients with chronic pain become more incapacitated as a result of interactions with agencies that administer disability programs* (39,40,41,42 and 43).
10. .*Consider methods for determining disability in the face of uncertainty*. Statisticians deal with uncertainty on a regular basis, and statistical methods, such as regression analysis, have been developed to optimize decision making when data are incomplete. It might be possible to apply some of these methods to decisions about disability—that is, to use "statistical" rather than "clinical" decision making (147). This would require a paradigm shift because disability systems seem to operate on the assumption that detailed clinical evaluation of an individual applicant will permit an optimal decision to be made regarding that applicant.
11. .*Do validity research on pain assessment systems that have already been developed*. It is possible that multidimensional pain assessment systems, such as the one developed by Rucker et al., will turn out to have construct and predictive validity in the evaluation of patients seeking disability because of pain. Research is needed to determine whether this is so.
12. *Examine the extent to which findings about pain-related disability can be generalized across disability systems and across cultures*. Some investigators have suggested that the apparent incapacitation associated with painful conditions varies widely from one culture to another (148,149). Within the United States, there is evidence that patients receiving workers' compensation are more likely than noncompensation patients to remain disabled despite seemingly appropriate treatment (150,151,152,153,154,155,156,157 and 158). In a general way, a detailed understanding of the ways in which biological, psychological, and social factors interact to produce pain- related disability is lacking (43). As a practical matter, findings from research on any single disability system or culture will need to be replicated in other settings before they can be considered firmly established.

The preceding points provide a flavor of the work that should be done if there is going to be movement toward a well-developed science of disability evaluation for patients with chronic pain. At this point, so little work has been done that it is not known how difficult the project may be; however, the problem of pain and disability is important. At one extreme, the risk is run of abandoning citizens who, by any reasonable standard, are incapable of competing effectively in the workplace. At the opposite extreme, the risk is run of driving social support systems into insolvency by granting disability awards to individuals who are not really needy. To find some middle ground between these two extremes, research is needed to provide answers to the questions that have been raised in this chapter.

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CHAPTER 18

Multidisciplinary Pain Assessment

John D. Loeser

The growing awareness that reports of chronic pain and subsequent disability are influenced by psychosocial and environmental factors as well as physical changes within the patient's body has led to the continued development of multidisciplinary/interdisciplinary (M/I) pain treatment facilities. In this section I will describe the M/I process of screening patients with chronic pain as it is implemented at the Multidisciplinary Pain Center of the University of Washington (1). Different types of evaluation are presented and the roles of a variety of health care providers in the evaluation process are discussed. I emphasize the importance of the sharing of information by the assessment team and how an integrated treatment recommendation is generated by the assessment team. The conceptual framework discussed in the Introduction to Part II of this book determines the type of assessment that is used. These diagnostic strategies have been developed from the pioneering work of W. E. Fordyce and by our physicians and psychologists since 1970 and provide us with a rational basis for assessing and treating patients disabled by chronic pain. Other authors have described evaluation strategies at their institutions; often these are based on the concepts that evolved at the University of Washington (2,3,4,5 and 6). The objectives of this type of assessment are to identify those patients who could benefit from a physical and psychological rehabilitation program based on cognitive-behavioral principles of effecting behavior change and pain reduction; to rule out those patients who have a medical or psychological contraindication to such a program; to identify other, perhaps more effective, methods of treatment; and to help establish appropriate therapeutic goals.

REFERRAL TRIAGE

Pain centers should maintain their position as referral and not as primary care institutions. The first contact in reference to a patient is usually made by either a letter or a telephone call from another physician or, on occasion, from another type of health care provider. Rarely is a referral made by a claims manager, but when this occurs, we immediately contact the primary care physician to make sure that he or she supports such a referral and wishes to have the pain center involved in the care of the patient. A pain center physician reviews each referral letter or speaks to the referring physician to ascertain the nature of the patient's problem and the type of assessment required. At times, a nurse or another highly trained staff member may participate in the preliminary triage of incoming referrals. The processes described below can apply equally well to an inpatient or an outpatient treatment service. One of six options is chosen (Table 18-1):

Screening evaluation
Consultation
Rejection of referral
More information needed
Emergent treatment required
Unresolved medical issues must be addressed

TABLE 18-1. Triage outcomes

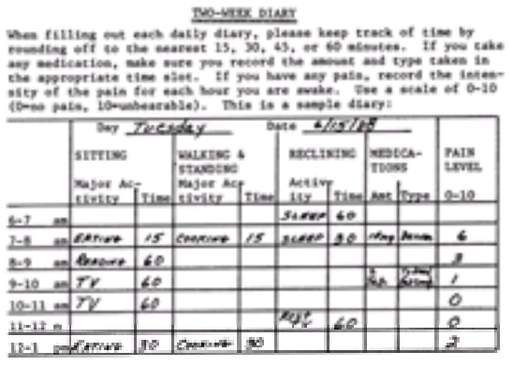
1. M/I evaluation: The patient has a complex chronic pain problem requiring comprehensive evaluation. These are most often patients with long-standing pain problems that have failed to respond to traditional health care interventions. They are often inappropriately using medications. Approximately one-half of these patients have experienced low back and leg pain. We have used the term *screener* to describe this type of patient.
2. Consult: The patient has a straightforward pain problem that one of our physicians or psychologists can handle, at least initially.
3. Reject: The patient is not suitable for further assessment or treatment at our facility.
4. Additional information required: Further information is required before a decision can be made by our staff as to the suitability of the patient for our center. Usually this means that the referring physician did not forward the appropriate medical and psychological records, which must be reviewed before any decision can be made. Sometimes the issue is the lack of current imaging studies in a patient who has had prior surgical procedures or whose clinical status has changed since his or her most recent evaluations.
5. Emergent treatment required: The patient has a severe chronic pain problem that cannot await outpatient diagnostic evaluation and requires direct admission to our inpatient service for both assessment and pain control. This is an uncommon scenario. It often relates to problems with medication. Some cancer pain patients present in this group.
6. Unresolved medical issues: The patient clearly has unresolved medical issues that must be addressed before referral. Attempts should be made to assist the referring physician to place the patient in the appropriate treatment facility. These patients should be reconsidered when their medical status has been resolved. Common examples include inadequately treated chronic diseases or new findings in the patient with cancer. At issue here is the presence of medical issues that must be addressed in parallel with or before pain management.

SCREENING, CONSULTATION, AND REJECTION OPTIONS

Screening Evaluation

Screening is the usual evaluation format for a patient with chronic pain caused by a nonmalignant disease who has failed routine health care and who does not have a specific pain syndrome such as tic douloureux or peripheral neuropathy. Few patients with pain caused by cancer are initially scheduled as screeners, but many are eventually seen both by our physicians and our psychologists. As we can screen only two patients each working day, efforts are made to avoid stacking up a long waiting list for these limited slots. Consultations are therefore the first encounter with the pain center for the majority of patients.

Most referrals to M/I pain centers concern patients with long-standing disability resulting from pain caused by nonmalignant disease. They have complex medical and psychological histories, and the pain center must first sort out the facts. When the reviewing physician determines that the patient needs an M/I evaluation, a letter is sent to the referring physician requesting the transmittal of all relevant records and imaging studies. The patient is contacted by telephone, and the names and addresses of any other treating physicians or psychologists are requested. Every effort is made to assemble the most complete documentation available before the patient's initial visit. Once the relevant information is obtained and the patient is deemed appropriate for a screening evaluation, the patient is scheduled for an appointment. At that time he or she is sent a demographic and history questionnaire and 2 weeks of pain, activity, and medication diaries, which are to be completed and brought to the initial visit (Fig. 18-1). Patients are informed of the importance of the completion of these forms in detail to ensure the appropriate evaluation of their pain problem. Failure to complete the diaries or forms often results in a partial evaluation and the rescheduling of the clinic visit for a later date.



TWO-WEEK DIARY

When filling out each daily diary, please keep track of time by rounding off to the nearest 15, 30, 45, or 60 minutes. If you take any medication, make sure you record the amount and type taken in the appropriate time slot. If you have any pain, record the intensity of the pain for each hour you are awake. Use a scale of 0-10 (0=no pain, 10=unbearable). This is a sample diary:

Day Tuesday Date 4/15/85

	SITTING Major Activity	Time	WALKING & STANDING Major Activity	Time	RECLINING Activity	Time	MEDICATIONS Amt	Type	PAIN LEVEL 0-10
6-7 am					SLEEP	60			
7-8 am	EATING	15	COOKING	15	SLEEP	30	1Tsp	Bran	6
8-9 am	READING	60					1	Tylenol	3
9-10 am	TV	60					2	Tylenol	1
10-11 am	TV	60							0
11-12 n					REST	60			0
12-1 pm	EATING	30	COOKING	30					2

Figure 18-1. Part of a completed pain clinic diary.

Patients are informed that they must be accompanied to the initial pain center appointment by the spouse or significant other. This individual is an important part of our evaluation process. We have learned that the evaluation of a patient with chronic pain requires assessment of the family and home situation and information about the patient that only another person can provide. Thus, we will not schedule an appointment for screening unless a significant other will be accompanying the patient. It is also important that patients be informed of the nature of the assessment and that more than just medical issues will be explored. Patients should be prepared, both on the basis of what the pain center provides in written and oral information for prospective patients and by their referring physician, for the thorough medical, psychological, and vocational assessment that they will undergo. The mere presence of a psychological evaluation makes many patients feel that their symptoms are not accepted as valid and that they are thought to harbor a mental illness. It is imperative that this belief be dispelled quickly by all members of the assessment team.

The screening evaluation occupies an entire morning for the patient and significant other (Fig. 18-2). The patient is seen by a physician and a complete history and physical examination are obtained using the patient-completed survey form as a starting point. The patient and the patient's family member are interviewed separately by the psychologist. The patient completes the Minnesota Multiphasic Personality Inventory (MMPI), that is immediately scored by a medical assistant and interpreted by the psychologist. The vocational counselor is also part of the initial assessment team when there are any work-related issues. The information gleaned from the patient's survey forms, MMPI, physician evaluation, psychologist evaluation, and vocational counselor evaluation is then used in a face-to-face meeting of the evaluation team.

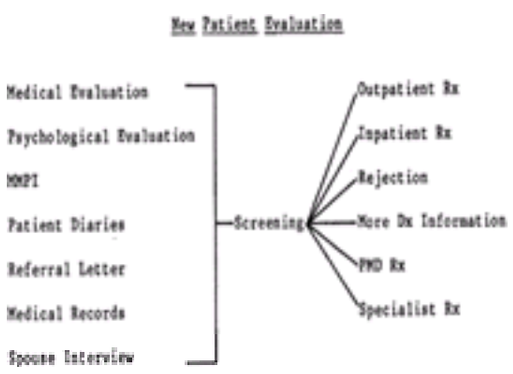


Figure 18-2. Diagrammatic representation of screening process. See text for details. (Dx, diagnostic; MMPI, Minnesota Multiphasic Personality Inventory; PMD, private medical doctor; Rx, treatment.)

Types of Screenings

We have two types of screening patients—long-distance screeners (LDSs) (the patient resides more than a 3-hour drive from our clinic) and local screeners. LDSs are individuals who live far enough from Seattle so that coming in for a screening evaluation and returning home again only to come back shortly thereafter for treatment is a hardship. The University of Washington Multidisciplinary Pain Center attracts patients from the entire Pacific Northwest region, including Alaska; long travel distances are common for its patients. Their records and letters from referring physicians have been carefully reviewed, and they appear to be patients who are candidates for our 3-week structured program treatment. If they are suitable candidates and agree to participate, they are entered into a treatment group immediately after screening. Preauthorization for their assessment must be obtained by our patient care coordinator before scheduling the patient for screening.

Local screeners reside within easy commuting distance of the University of Washington. If they are accepted for treatment, they are scheduled into the next available opening in the structured program after authorization for care has been obtained. If more appropriate, both LDSs and local screeners may be entered into other treatment programs in the pain center or in other clinical departments, whether within the University of Washington or closer to their homes.

Role of the Physician

The physician and the psychologist have complementary roles in the screening process. The physicians function as pain patient managers. Currently, five anesthesiologists, a neurologist, two neurosurgeons, a psychiatrist, and three physiatrists comprise the medical staff. In our experience, the discipline of the physician has proven irrelevant; rather, an appropriate philosophical approach and certain specialized knowledge and skills are required. The primary tasks of the physicians are the following:

1. To unravel the patient's history and document how the patient has achieved his or her present status as a chronic pain patient
2. To evaluate past medical treatments and their sequelae
3. To describe the current physical condition accurately
4. To determine whether any additional diagnostic studies are necessary
5. To identify any medical limitations on treatment

This requires that the prior medical records be carefully reviewed to reconstruct the medical events that have led the patient to the present state. Imaging and electrodiagnostic studies and other laboratory tests must be examined, often with the assistance of the specialist in these areas. Judgment must be used in identifying a real need for additional diagnostic studies. Needless repetition of tests must be avoided. The medical evaluation of the chronic pain patient is carried out by the physician as described previously in Chapter 12.

Role of the Psychologist

The task of the psychologist is to ascertain the role of cognitive, affective, and environmental factors in the genesis, exacerbation, or maintenance of the patient's pain behavior and disability. As previously noted, we use 2 weeks of diary information completed by the patient to obtain information about pain levels, medication consumption, the amount of time the patient spends up and about and sitting and lying down, and the types of activities engaged in. A patient whose days are filled with activities such as woodwork, needlework, watching television, reading, and visiting friends, all identified by the patient as positive and pleasurable, is viewed somewhat differently from a patient who has had to eliminate pleasurable hobbies and activities. The McGill Pain Questionnaire is also part of our diagnostic array, as are pain drawings, the Beck Depression Inventory, and a structured questionnaire for collecting additional information. The MMPI is used to describe the likelihood that the patient is responding to environmental or affective factors with pain behaviors, as well as in helping to assess level of depression; covert expressions of suffering, pain, and distress; possible cognitive impairment; and other serious mental disorders. Most important, however, is the psychologist's assessment of the

patient and spouse based on the interviews in the screening evaluation. Observation of the patient's behavior and the responses of the significant other during the interview are particularly important. The psychologist also attempts to identify the antecedents and consequences of pain behaviors. Data from all of these sources are considered by the psychologist when determining what are the appropriate diagnoses, what form of treatment is most likely to succeed, and whether there are impediments to participation in a pain management program.

Role of the Vocational Counselor

The role of the vocational counselor is to ascertain the contributions of workplace factors to the patient's pain behavior and to evaluate outcome potentials in the employment sphere. In other pain treatment facilities, occupational therapists or rehabilitation nurses may undertake some aspects of this role. The current workplace environment as well as prior work experiences and the opportunities for future job modifications are investigated. The vocational counselor also communicates with claims managers and outside vocational counselors to glean further information about the patient and address administrative issues.

In effect, our screening process asks the physician to identify the roles of tissue damage or injuries to the nervous system; the roles of the patient's appraisals, beliefs, expectations, affective disturbances, and environmental factors are assessed by the psychologist and workplace factors by the vocational counselor. Consistent with the literature, we have not found any single test or scheme to be highly reliable either for diagnosis or treatment outcomes (7,8,9 and 10). The professional judgments of our physicians, psychologists, and vocational counselors are not infallible, either. The assessment process does yield information that predicts likelihood of treatment success, probably by identifying those who are likely to fail (2).

Management Conference

The management conference that follows the patient's assessment by the physician and vocational counselor and the patient and the spouse assessment by the psychologist are critical to our evaluation and to the establishment of treatment goals. This conference usually lasts 30 to 45 minutes. The physician presents the medical history and physical findings, the psychologist presents the psychological and social history and the MMPI interpretation, and the vocational counselor reports work-related findings and issues. A consensus is reached regarding both diagnosis and treatment options. The process of obtaining a consensus is one of the most important aspects of the M/I evaluation. It requires that the team members be able to break through their disciplinary approaches and share in the give and take of a problem-solving exercise.

The patient and the family member or significant other are then brought into the room for the feedback portion of the management conference. The process of evaluating and meeting with the patient and significant other is labor intensive, but it seems to be required both for diagnosis and the establishment of meaningful treatment plans. Chronic pain patients have been a puzzle to their prior health care providers. We attempt to fit the pieces of this puzzle together. The face-to-face meeting of health care providers to formulate a single, mutually acceptable diagnosis and treatment plan is a critical part of multidisciplinary pain management. The feedback component is also an important educational experience for the patient and the significant other. After this feedback conference, a written report is generated, and the referring physician is informed of our diagnosis and treatment recommendations.

Other Issues in the Screening Process

At times, the screening evaluation is inconclusive because of unresolved medical or psychological issues and because additional information is needed before diagnosis and treatment can be determined. In such cases, the patient is asked to undergo the appropriate diagnostic tests and is brought back for another conference when the necessary information has been obtained. If the patient has pending litigation that is relevant to the pain problem, we always ask the patient's permission to contact the attorney before embarking on a treatment program. Litigation is not by itself an exclusionary factor. Although a number of studies have reported that compensation and litigation status are impediments to rehabilitation, they are not primary determinants of treatment eligibility, but rather are viewed as important pieces of information that are included in the determination of the appropriate treatment (11,12 and 13).

In the event patients manifest drug toxicity (from multiple medications) such as impaired mentation and confusion, they are placed on the “drug detoxification” program (described in detail in Chapter 88) and then reevaluated. Experience has impressively demonstrated that after they are detoxified, such patients have been able to provide more precise information, are able to better cooperate, and frequently state that they have less pain.

Purpose of Screening

The purpose of our screening evaluation is to identify those patients for whom a structured, 3-week, intensive program of physical, psychological, and vocational rehabilitation will launch a return to functional existence both at home and in the workplace. The goals of this program include the following:

1. Reduction of pain level
2. Improvement of physical conditioning, strength, and flexibility
3. Management of medications
4. Improvement of psychological well-being
5. Identification of reasonable vocational goals and movement toward them
6. Education about mind and body function
7. Education about prudent health care consumption
8. Alleviation of depression

The actual treatment program is discussed in detail in Chapter 109. It has been our experience that approximately 50% to 70% of the patients who are accepted for screening are referred to our structured rehabilitation program. The “hit” rate is a function of the type of patient as well as the source of funding for health care. Ideally, we would like to have a higher “hit” rate, but our triage system has been biased toward evaluating the maximum number of referrals for humane reasons and to try to assist physicians in the community.

Consultation

When the referral letter indicates a chronic pain problem that appears to have a specific diagnostic or treatment requirement, we schedule the patient for a consultation with a physician or psychologist at the pain center. Some patients are referred by other physicians in our pain center for psychological assessment only. The special training and interests of our physicians dictate the referral of patients for consultations. Thus, in our pain center, headache and peripheral neuropathy problems are referred to our neurologist, our neurosurgeon sees patients with tic douloureux and other neuropathic states, physiatrists see patients with musculoskeletal problems, and so forth. All of our physicians participate in the assessment of chronic pain patients referred as candidates for our structured 3-week rehabilitative program. Some patients with specific physical issues may be referred to physical therapy or occupational therapy for additional evaluation.

Sometimes what appeared on referral to be a straightforward problem turns out to be a complex issue requiring additional study. The consulting physician may then refer the patient to a psychologist. Conjointly they plan the patient's evaluation and subsequent treatment. Such a patient may eventually be admitted into our structured program. Patients who are seen in consultation may be managed by the consulting physician or may be returned to the care of their primary physician, with treatment recommendations from our consultant.

Rejection

Certain factors can lead to refusal to evaluate a patient. Many physicians consider the phrase *pain clinic* to be synonymous with *garbage pail* and cannot understand why every referral should not be seen. It is important for a pain center to be able to control the types and numbers of patients that it sees; otherwise a considerable amount of time can be wasted evaluating patients for whom the pain center has little to offer.

We have learned that our pain center strategies are ineffective in the management of addiction based on illegal (“street”) drugs. It is easy to taper patients off their medicine using the “pain cocktail” technique (see Chapter 88), but such patients are almost certain to resume their drug-seeking behavior immediately after discharge from the pain center. The factors that lead to addiction appear to be quite different from those that lead to tolerance and habituation because the chronic pain patient is not likely to return to medication usage after the treatment program has been completed. The factors that lead to addiction, both biological and psychological, are not present in the vast majority of chronic pain patients who have been prescribed opioids to alleviate pain and suffering. Chronic pain patients, if their pain is relieved

by some other means, can be rapidly tapered off opioids and do not engage in subsequent drug-seeking behaviors.

Patients who have already failed to benefit from similar pain rehabilitation programs are usually not accepted for evaluation or treatment. Their acceptance must be based on a significant change in the patient's physical condition or the affective and environmental factors. We have learned that pain management strategies are not effective with severely emotionally disturbed patients. Moreover, the group treatment program may be disrupted by the inclusion of such patients, thereby impairing other patients' treatment. When the referral letter indicates that the patient has long-standing major psychopathology that antedates the pain problem, we do not evaluate the patient. Although many patients have a history of excessive alcohol usage, patients currently abusing significant amounts of alcohol should be referred for the treatment of alcoholism before acceptance to our pain rehabilitation program.

Different pain management programs have evolved their own evaluation strategies that can make use of the services of a wide array of health care providers and include different physical and psychological strategies for patient assessment. Comparative data are lacking on relative efficacy and costs. Thus, there is no empiric basis for the determination of optimal inclusion or exclusion criteria.

Basic Requirements for Patient Assessment

It is certainly true that many pain practitioners desire to practice M/I pain management but lack the resources of a university center or a large, multispecialty hospital. The minimal resources required to provide an M/I service include a physician, a psychologist or psychiatrist, and someone to undertake the assessment of vocational issues. As is true for M/I pain centers, the role of the physician is to ascertain medical diagnoses and the suitability from the physical perspective for a rehabilitation program. The role of the psychologist or psychiatrist is to determine the contribution of cognitive, affective, and environmental factors in the patient's symptoms. A vocational counselor or someone competent to assess vocational issues must also be available. The physician and the psychologist and other team members should all participate in the decision of whether to treat a particular patient. The entire team must also share in the design of a treatment program that addresses the physical, psychosocial, and behavioral factors associated with the patient's suffering, emotional distress, maladaptive attitudes and beliefs, and the maintenance of inappropriate pain behaviors, all of which may interfere with effective rehabilitation. The assessment team must meet face to face to discuss their findings and agree on treatment recommendations. Finally, a feedback conference for the patient and his or her significant other must complete the assessment process. The interactions between the providers and the interaction with the patient are essential components of this assessment process. It is preferable that the physician and the psychologist have some experience with and understanding of chronic pain patients. It is not safe to assume that the necessary knowledge base or implementation skills are imparted in standard training programs for the education of physicians, psychologists, or vocational counselors.

An essential product of a pain center evaluation is the letter that is sent to the referring physician and the sponsoring agency. Such a document needs to state clearly but concisely the patient's medical, psychological, and vocational history and the diagnoses that have been established by the evaluation. It should also state the prognosis if no further treatment is offered. The treatment recommendation section should indicate the reasonable treatment options, their relative likelihood of success, and how the patient's status will be altered by successful treatment (outcome goals). In the managed care environment of the United States, this letter must contain all of the information that is required to obtain authorization for care.

Evaluation for Nonmedical Purposes

Pain centers are often asked to perform a variety of administrative evaluations that have little to do with patient care. These include such things as a physical capacities evaluation and a medical evaluation to ascertain disability status. Such activities may be a method of generating revenue for individual health care providers, but they have little to do with improving the patient's well-being. Whereas there is no violation of the doctor-patient relationship when such an evaluation is performed on an individual who is not receiving care in an institution or from the evaluating physician, there are many reasons to be cautious about providing such administrative ratings on someone who has confided in his or her physician for reasons of health care. Indeed, such rating activities could easily be a violation of the doctor-patient relationship (14). In addition, there is very little evidence to support the validity of either a physical capacities evaluation or a medical evaluation. When the matter arrives in a court of law, each side is able to produce expert witnesses who solemnly swear that the individual is either fully disabled or not disabled at all. The time is long overdue for such trials by combat to be eliminated from the disability determination system. Pain centers should have a circumspect viewpoint on participating in such administrative charades (see Chapter 17).

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CHAPTER 19

Painful Neuropathies

Misha-Miroslav Backonja

Injuries and diseases of the peripheral nerves are relatively uncommon among the large numbers of patients with chronic pain, but pain is a frequent symptom of injuries to and diseases of peripheral nerves. Painful neuropathies are not too rare in general medical practice and, of course, they are concentrated in pain management practice. They have diverse etiologies and, as a consequence, their clinical course varies from disease to disease. However, many symptoms and signs are common to all painful neuropathies, and it has been postulated that they share many similar, if not the same, pathophysiologic mechanisms. Painful neuropathies are classified under the rubric of neuropathic pain syndromes.

Painful neuropathies can be classified by major etiologic categories: toxic-metabolic (endocrine, chemotherapy and chemical exposure associated, nutritional), posttraumatic (complex regional pain syndrome types I and II), compressive (nerve entrapment syndromes), autoimmune (vasculitic, paraneoplastic, parainfectious), infectious, and hereditary (1,2). Nerve entrapment painful neuropathies and posttraumatic neuropathies are discussed in many other chapters of this textbook, so they are not treated here. Complex regional pain syndrome is presented in Chapter 20. One of the infectious neuropathies, herpes zoster, is also discussed in Chapter 22. This chapter concentrates on painful neuropathies with the other common etiologies.

General issues that are common to all neuropathic disorders are discussed first. Among these are the pathophysiologic mechanisms underlying the pain of painful neuropathies, pain and other symptoms assessment, approaches to diagnostic evaluation and testing, treatment principles, and a review of the frequently used pharmacologic therapies. When discussing pathophysiology, the emphasis is on how an understanding of these common issues affect pain assessment and therapy. This chapter then reviews a few examples of painful neuropathies related to diabetes, human immunodeficiency virus (HIV) infection, Guillain-Barré syndrome (GBS), and vasculitis, with the accent on specific issues in diagnosis and therapy for these neuropathies.

Because of limited space, rarer types of painful neuropathies cannot be covered in this chapter. The textbooks edited by Dyck and colleagues (1) and Schaumburg and colleagues (3) and the issue of *Seminars in Neurology* devoted to diabetic neuropathies (4) are excellent sources of additional information. Table 19-1 lists painful neuropathies according to etiology.

Toxic-metabolic	Endocrine (e.g., diabetic)
	Chemotherapy (e.g., isoniazid)
	Chemical exposure associated
	Nutritional (e.g., beriberi)
Posttraumatic	Complex regional pain syndrome types I and II
Compressive	Nerve entrapment syndromes (e.g., carpal tunnel syndrome)
Autoimmune	Vasculitic
	Demyelinating
	Paraneoplastic
	Parainfectious
Infectious	Viral (e.g., human immunodeficiency syndrome, herpes zoster)
	Spirochetal (e.g., Lyme)
	Guillain-Barré disease
Hereditary	Fabry's
	Amyloid

TABLE 19-1. Etiology of painful neuropathies: major categories

EPIDEMIOLOGY

The epidemiology of painful neuropathies is not well known for many reasons. Diverse etiologies prevent systematic epidemiologic study of painful neuropathies as an entity (Fig. 19-1). The epidemiology of painful neuropathic disorders varies greatly from country to country depending on the socioeconomic status and the disease incidence and prevalence for any given country. In poor countries, one would expect to see more painful neuropathies caused by nutritional deficits, whereas in industrial countries one sees more toxic and metabolic disorders, such as diabetes-related neuropathies. With more and more patients surviving cancer and acquired immunodeficiency syndrome (AIDS), chemotherapy-related painful neuropathies have increased in incidence. The emergence of new diseases, such as AIDS and Lyme disease, and their spread in the population have been associated with increasing numbers of painful neuropathies associated with these disorders. With the exception of diabetes, which has been well studied in Western countries, data for most other types of painful neuropathies are not available. We have learned from observing the course of diabetes that with the progression of the disease an increase occurs in the prevalence of neuropathy, from approximately 8% at the time of diagnosis up to 50% after 25 years of the disease (5). However, the severity of painful symptoms and the associated morbidity are not known (6).

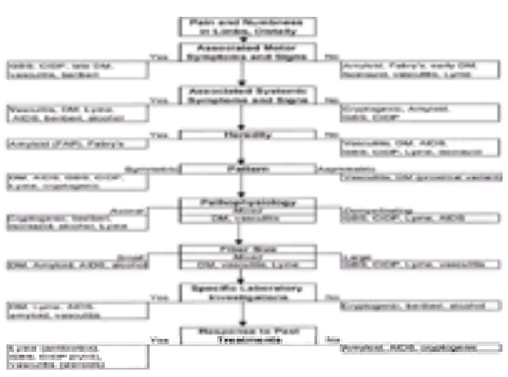

Figure 19-1. This algorithm is provided as a guide to consider major steps in diagnosis of painful neuropathies. It should be kept in mind that these are only suggestions for categorization for each diagnostic step; the designation into each category is likely but not exclusive categorization. For example, Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) present most commonly in their idiopathic form and are not necessarily associated with systemic symptoms, but on the other hand, GBS is frequently preceded by a viral and most often systemic illness, whereas CIDP can be associated with many systemic illnesses. It should be also noted that the designation into any category is tentative, because many neuropathies change their characteristics as the disease process progresses or the same disease can have several presentations. For example, diabetic neuropathy can present with or without motor involvement. (AIDS, acquired immunodeficiency syndrome; DM, diabetes mellitus; FAP, familial amyloid polyneuropathy; IVIG, intravenous immunoglobulin.)

PATHOPHYSIOLOGY OF NEUROPATHIC PAIN IN PAINFUL NEUROPATHIES

Advances in the neuroscience of pain have significantly helped our understanding of the mechanisms underlying symptoms and signs of neuropathic pain. Descriptions of pain after nerve injury and dysfunction date as far back as the late eighteenth century and have been described in greater detail in the late nineteenth century (7). Pathologic studies of human peripheral nerves demonstrating preferential loss of nerve fibers in certain painful neuropathies, such as postherpetic neuralgia (8), laid the groundwork for theories postulating the loss of myelinated fibers as the precursor of neuropathic pain. These ideas subsequently formed the basis for the gate- control theory of pain (9). However, pathologic studies demonstrating the loss of other fiber types as well, including small unmyelinated fibers, called for additional explanations for the underlying pathophysiology of neuropathic pain. After an extensive review of this topic, Scadding concluded that the loss of a particular fiber size did not predispose patients to develop pain, nor did it prevent them from developing pain as part of peripheral neuropathy (10).

Human psychophysical studies performed in the first half of the twentieth century set the stage for the developing concept of sensitization of neurons in the peripheral and central nervous system (CNS) (11,12). It was, however, the introduction of animal models (13,14) that dramatically enhanced our understanding of the pathophysiologic mechanisms of such abnormal phenomena as allodynia and hyperalgesia (15), both of which are common symptoms of neuropathic pain. This topic is discussed in detail in Chapter 3.

Pathophysiologic Mechanisms Underlying Abnormal Sensations

The primary pathology in peripheral neuropathies is in the peripheral nervous system, so that primary pathophysiologic mechanisms are those of the peripheral nervous system. However, it is overwhelmingly clear from basic science research that the CNS undergoes changes when the peripheral nervous system is injured and dysfunctional (16). The concept that has been evolving is that peripheral generators of abnormal activity are responsible for chronic pain symptoms (17,18 and 19). Consequently, efforts should be made to correct the abnormalities in the peripheral nervous system to improve overall symptomatology.

A large number of human laboratory and clinical studies, as well as animal research on sensory symptoms and signs of neuropathic pain syndromes, point to the many peripheral and central mechanisms whose interactions lead to the manifestation of neuropathic pain. Enough experimental and clinical evidence exists from peripheral nervous system research to suggest some common mechanisms as a cause for neuropathic pain (20). These mechanisms include receptor sensitization and spontaneous afferent activation (17,20). On the other hand, all symptoms cannot be explained by peripheral pathophysiology. An increasing body of basic science information suggests that CNS mechanisms play a significant role, and central sensitization is the best example of how CNS mechanisms lead to the development of chronic neuropathic pain (19). An exciting development has been the realization that peripheral sensitization can initiate and maintain central mechanisms of neuropathic pain (17,18,21).

A large body of research exists on peripheral mechanisms of neuropathic pain and associated phenomena. Sensitization of nociceptors (20) has been documented even in a human patient (22), and it is probable that this sensitization occurs as a result of the release of many chemical mediators of inflammation, the so-called inflammatory soup (20,23). Sensitization of primary afferents has been documented in animal and human research and it presents with ectopic generation of nerve impulses at the site of injury caused by increased sensitivity of adrenergic receptors (20,24,25 and 26). Continuous spontaneous activity of sensitized primary afferents is the probable mechanism of ongoing pain (23,27,28 and 29). Upregulation of sodium channels is possibly a more specific explanation of mechanical allodynia and hyperalgesia (24). Hyperalgesia to heat appears to be mediated by sensitized small fiber nociceptors (22,30,31). Sympathetic catecholamine sensitization of the primary afferents may be the mechanism by which the sympathetic nervous system adversely affects primary afferents resulting in hyperalgesia and allodynia (32,33,34 and 35). Ephaptic transmission between the sympathetic nervous system and primary afferents has been suggested (36). Activation of *silent* nociceptors could explain ongoing pain and pressure pain (20,37). Ectopic discharges of dorsal root ganglion cells have been documented in animal models of neuropathic pain (38,39 and 40) and could also explain ongoing pain.

CNS plasticity changes, particularly in neuropathic pain, play a significant part in the development and maintenance of chronic pain syndromes and their symptoms and signs. The symptoms and signs related to the phenomenon of central sensitization were recognized in the late 1930s (11,12) and have been well characterized in human laboratory models (41,42). Clinical research has confirmed what the laboratory models had demonstrated: Neuropathic pain phenomena, such as ongoing pain, allodynia, and hyperalgesia, are to a significant degree the result of central mechanisms. Research in animal models contributed significantly to the understanding of some of the basic mechanisms. The phenomenon of *wind-up* at the dorsal horn level was recognized as early as 1966 (43), but received much deserved attention only over the 1990s. Physiologic and pharmacologic studies of spinal cord neuroplasticity changes after neuropathic injuries have contributed to a better understanding of wind-up and central sensitization (19,44). It was found that excitatory amino acid neurotransmitters, in particular *N*-methyl-d-aspartate (NMDA) receptor-related activity, play a crucial role in the genesis and maintenance of chronic neuropathic pain and associated symptoms and signs (45,46). Our understanding of pathophysiologic mechanisms underlying neuropathic pain has advanced considerably, and it is becoming clear that neuropathic pain is a complex biological phenomenon with many components. A better understanding of the pathologic mechanisms of neuropathic pain and its components should contribute to a better evaluation and treatment of patients with neuropathic pain, including painful neuropathies (see Chapter 3).

PHYSICAL EXAMINATION

Physical Examination in General

Traditionally, different specialists examine pain patients by a method that is centered on the skills that define their specialty. However, the evaluation of patients with neuropathic pain also requires a systemic examination, particularly an examination of the nervous and musculoskeletal systems. A general neurologic examination should be performed on all patients with chronic pain, but is not discussed in great detail here (see Chapter 12). The emphasis in this chapter is on those aspects of the neurologic examination that are related to pain evaluation that lead to a more specific neuropathic pain diagnosis. A thorough documentation of the patient's history is the first step (Table 19-2).

Onset	When and how did the pain start?
Location/site	Where is the pain located?
Temporal profile	What has happened since onset?
Characteristic/quality of pain	Describe the pain.
Severity	How severe is the pain?
Unpleasantness/distress	How unpleasant is the pain?
Associated symptoms	Are there any other symptoms, such as numbness, weakness, uncontrollable movements, bowel/bladder dysfunction, or insomnia?
Psychological factors	Does the patient suffer from depression? Anxiety? Posttraumatic stress disorder?
Aggravating factors	What makes the pain worse?
Alleviating factors	What makes the pain feel better?
Effect on function and activities	How are work, daily activities? Is the patient engaged in recreational activities? Workers' compensation? Family responsibilities affected? System adding barriers to return to enjoyable pain/employment?
Response to past treatments	What prior treatments have been used?
Habits	Does the patient smoke? Drink? Use illegal drugs? If yes, how much and how often?
Coping skills	How is the patient coping with pain?
Chronic regional pain syndrome-specific symptoms and signs	In the painful region, are there abnormal skin color changes? Skin temperature changes? Abnormal swelling? Abnormal sweating or skin dryness?

TABLE 19-2. Neuropathic pain and symptoms assessment

Neurologic Examination

Several aspects of the examination specific to neuropathic pain should be attended to while performing the standard neurologic examination of the patient whose history suggests possible neuropathic pain. These specific tests are part of the sensory examination and are helpful in confirming the presence or absence of a neuropathic pain disorder. It must be noted that the lack of significant physical findings, including those discussed here, does not rule out the possibility of neuropathic pain, nor should their absence be interpreted as psychogenic pain or malingering (see Chapter 26).

Sensory Examination

Sensory signs are obtained by the patient's report during sensory examination. Indeed, it cannot be emphasized enough that the patient with neuropathic pain, like the patient with any kind of pain, is still the only and the best judge of his or her pain symptoms (47). The examination itself is carefully described beforehand to the patient, and the patient is reassured that the limits of the examination are set by the patient himself or herself.

The sensory examination consists of three steps that, when undertaken sequentially, help to better differentiate between sensory signs in patients with possible neuropathic pain. The first step is to establish whether a stimulus is perceived as normal. The second step is to establish whether a stimulus is a negative phenomenon (i.e., felt as less) or a positive phenomenon (i.e., felt as more). Third, if a stimulus is perceived as a positive phenomenon then the patient's own description is obtained, and these descriptions should help in differentiating between types of sensory abnormalities.

When performing the sensory examination, there are many ways of communicating with the patient to obtain information regarding sensory phenomena. When performing the first two steps, the patient is asked to answer whether the stimulus is normal or different, increased or decreased. Questions are simply phrased, requiring a simple answer: *yes, no*, or *do not know*. This is the basic rule of psychophysical testing. The stimulus should first be applied to the normal body part. This introduces the stimulus to the patient and establishes how the examination is to be conducted. During the application of the stimulus, the examiner should ask the patient to describe the perceived sensation. The questions are simple, unambiguous, and should ask only if the perceived sensation is normal or abnormal, uncomfortable, unpleasant, or painful. The area of abnormal sensation determined by application of stimuli is then mapped.

Sensory signs can manifest as negative or positive sensory phenomena (48). When the patient has negative sensory phenomena, this means that a stimulus such as light touch, pinprick, cold, warm, vibration, joint position sensation, two-point discrimination, or sensory neglect is perceived as decreased or less. Sensory signs can also manifest as positive sensory phenomena. Positive sensory findings include allodynia, hyperalgesia, and hyperpathia, and application of any of the earlier named stimuli is perceived as increased or more. Positive sensory signs can be caused by mechanical or thermal stimulation. Positive sensory signs are associated with additional sensory phenomena, such as stimulation-induced paresthesia, dysesthesia, summation, and aftersensation. Neglect of the pain-affected area or a body part was described in 1995. The patient's perception is that the pain-affected body part or a limb does not belong to him or her (49).

The following paragraphs review sensory abnormalities (50) that may be observed in patients with neuropathic pain disorders and should be tested for during the neurologic examination. These terms are briefly defined in Chapter 2. Proposed pathophysiologic mechanisms underlying each phenomenon are discussed as well.

Mechanical allodynia is the abnormal sensation of pain from usually nonpainful mechanical stimulation and is elicited by lightly touching the painful region with a fingertip, cotton swab, or paint brush. Mechanical allodynia may be one of the most disabling physical symptoms, forcing the patient not to wear clothing, rendering the patient homebound. The pathophysiologic mechanism underlying this sensory phenomenon is central sensitization and activation by fast conducting A-b afferents (20,51). Mechanical allodynia can be static when a single stimulus is applied, such as light pressure. Dynamic allodynia is the pain from repeated innocuous stimuli such as when the area being examined is repeatedly stroked with a cotton swab (19,20,51).

Thermal cold and warm allodynia is the abnormal sensation of pain from usually nonpainful thermal stimulation, such as cold or warmth. For example, a patient may describe a worsening of pain when the painful region is exposed to a cold or warm external environment. Examining the patient for thermal allodynia entails placing a cool stimulus, such as a cool tuning fork, and a warm stimulus, such as a warm test tube of water or warm tuning fork, directly on the painful region for a few seconds. Patients with thermal allodynia report that thermal stimulus, although innocuous, is irritating and painful and frequently continues longer than stimulus application. Thermal warm allodynia is the result of C nociceptor sensitization (22), and cold allodynia comes as a result of central plasticity changes (20).

Summation refers to an abnormally increasing painful sensation to a repeated stimulus although the actual stimulus remains constant. The patient describes the pain as growing and growing as the same intensity stimulus continues. Summation is frequently seen as a part of hyperalgesia and hyperpathia (see following discussion), although it could be seen in mechanical allodynia from repeated light touch stimulation or from vibration. Summation is a sign of central sensitization (20,52), and it is a clinical equivalent of what has been described in electrophysiologic laboratory studies as the *wind-up phenomenon* (43).

Aftersensation refers to the abnormal persistence of a sensory perception provoked by a stimulus even though the stimulus has ceased. After nonpainful and painful stimuli, neuropathic pain patients may report that the pain, dysesthesia, or paresthesia lingers and continues for seconds or minutes after mechanical, thermal, or painful stimuli. Aftersensation could be the result of stimulus-evoked exaggeration of ongoing primary afferents' ectopic generators (19,22,53) or could be caused by a wind-up phenomenon (43) as a manifestation of central sensitization.

Hyperalgesia is an exaggerated pain response from a usually painful stimulation, either mechanical or thermal. Hyperalgesia does not have a symptom analogue and can only be determined by physical examination. Hyperalgesia can also be mechanical or thermal. Examining the patient for mechanical hyperalgesia entails stimulating the painful region with a sharp object, such as a safety pin, using a single pinprick stimulus and multiple pin-prick stimuli. Repeated stimuli are applied to the same area for a few seconds or as long as it is tolerated by the patient. At the bedside, the simplest way to test for thermal hyperalgesia is by using a glass tube filled with ice cold water. A variety of responses may be seen in neuropathic pain patients. Hyperalgesia is present if an exaggerated pain response is observed and reported by the patient. Summation and aftersensation are frequently present. Often areas of hyperalgesia are adjacent to areas of sensory deficits within the region of neuropathic pain (i.e., sensory changes may be patchy within the neuropathic pain-affected region). Mechanical hyperalgesia is a result of activation of myelinated afferents (19,20,54).

Hyperpathia is the most complex abnormal sensation. Hyperpathia refers to an abnormally painful and exaggerated reaction to a stimulus, especially to repetitive stimuli, in a patient who at first perceives the stimulus as less intense. Then the patient experiences explosive pain and usually cries out. Summation and aftersensation are usually present. For example, during repetitive stimulation with a pin the patient may at first perceive little, but after a few seconds the patient reports a great deal of pain and responds with an increased reaction.

Paresthesiae are abnormal and unusual sensations that are described by the patient as neither unpleasant nor painful. Paresthesia can be a spontaneous sensation, such as the report of pins and needles perceived at rest, or it can be evoked on physical examination by nonpainful or painful stimulation, such as light touch, thermal stimuli, or pinprick.

Dysesthesiae are abnormal sensations described as unpleasant and disturbing. As with paresthesiae, dysesthesiae may be spontaneous or provoked by maneuvers on physical examination. Once the patient reports the provoked sensations as painful they should be considered to be allodynia or hyperalgesia.

These abnormal positive sensory signs are most often indicative of a neuropathic pain process. However, allodynia and hyperalgesia may be seen in cases of acute injury and pain, such as burns, but their natural history is one of a gradual resolution of pain, allodynia, and hyperalgesia. On the other hand, in instances of neuropathic pain, allodynia and hyperalgesia persist after the initial injury or disease process has healed. Any or all of the sensory symptoms and signs are considered diagnostic for a dysfunctional sensory nervous system and are, therefore, likely to signify neuropathic pain if pain is part of the clinical presentation.

Motor System

Patients with neuropathic pain experience motor symptoms and signs that could also be viewed as negative and positive. On the level of the motor system, negative signs include hypotonia, decreased muscle strength, and decreased endurance (55). Positive motor signs include increased muscle tone, tremor, dystonia, and dyskinesiae (56,57). Incoordination, ataxia, and apraxia can be seen on examining patients with neuropathic pain syndromes as well. The type and the degree of motor abnormalities vary from syndrome to syndrome depending on how much the motor system is affected, either directly or indirectly. Motor symptoms and signs are

frequently overlooked during the pain evaluation, although they are significant indicators that the nervous system is affected beyond the pain-transmitting fiber.

LABORATORY STUDIES AND INVESTIGATIONS

Blood and serum studies for specific agents are performed any time a specific condition, such as HIV or diabetes, is suspected. Additional laboratory studies to confirm a specific diagnosis, such as cerebrospinal fluid (CSF) for the diagnosis of GBS, may be necessary. Their use with specific pain symptoms is discussed later in this chapter.

Neurophysiologic investigations of nerve conduction velocity (NCV) study and electromyography (EMG) are performed to confirm the presence of neuropathy and to help provide additional information that can help in differentiating different types of neuropathies (58) (see Chapter 13). For example, NCV and EMG can specifically diagnose entrapment neuropathies and can help differentiate neuropathies caused by demyelination versus axonal loss. The role in the early diagnosis of GBS is especially important. However, like every test, NCV and EMG have a number of limitations, and these include false-negative results. More specifically, these studies can show normal results in neuropathies of recent onset and in neuropathies affecting predominantly the small fibers.

In contrast, quantitative sensory testing provides a sensitive measure of large and small diameter fiber function (59,60). The quantitative sensory testing provides quantitative values for many sensory modalities, including thresholds for vibration, touch, pinprick, two- point discrimination, warm, cold, heat pain, and cold pain. Values can be obtained for individual patients and compared with control values. Based on functional properties of the different nerve fibers and their associated pathways, the abnormal values of quantitative sensory testing for a particular patient would suggest a type of sensory nerve dysfunction as the cause of the neuropathy. However, this method of investigation also has limitations, primarily its susceptibility to the patient's cognitive status and other neuropsychological dysfunctions.

More invasive evaluations such as nerve biopsy can be done to confirm the diagnosis and delineate the pathology. Nerve biopsy may be helpful in the investigation for the presence of chronic demyelination, amyloidosis, vasculitis, and hereditary neuropathies. Nerve biopsy for cryptogenic polyneuropathies, those without clear-cut etiology, has the most utility if one wants to rule out amyloid polyneuropathy. The value of this method in metabolic disorders and alcoholic and nutritional neuropathies is limited because findings are nonspecific. Genetic analysis using recombinant DNA technology is rapidly gaining wide use (61) for the diagnosis of hereditary neuropathies. Skin punch biopsy is a novel method for staining small nerve fibers; it is still in development, but it holds the promise of being useful in diagnosing small fiber neuropathies, including painful neuropathies. Microneuronography is a novel electrophysiologic method that can be used to record from individual nerve fibers and to study the generation and maintenance of pain, but it remains strictly a research tool without practical clinical applications.

The diagnosis of the majority of neuropathies is easily made based on the history and physical examination and confirmed with appropriate laboratory and electrophysiologic tests (see Cryptogenic Polyneuropathies and Neuropathies Caused by Undetermined Causes , later in this chapter). Differential diagnosis becomes more challenging when two neurologic conditions coexist (e.g., a patient with diabetic neuropathy can have compression neuropathies, such as carpal tunnel syndrome in the upper extremities and tarsal tunnel syndrome in the lower extremities).

TREATMENT OF PAINFUL NEUROPATHIES

General Principles of Therapy

Therapy for painful neuropathies can be viewed at two levels. At the primary level, therapy is targeted at the underlying disease process (e.g., nutritional supplementation for neuropathies caused by nutritional deficiencies). Whenever practical, such therapy should be administered as soon as possible, because it is most likely to control and even reverse the process that initiated the disease in the first place. With reversal of the disease, the pain is highly likely to be alleviated. At the secondary level is symptomatic therapy, such as analgesia and symptom control, which should also be administered as soon as possible and parallel to the treatment of the underlying disease. One does not exclude the other. This chapter concentrates on analgesia and symptom control.

Guidelines for Pharmacotherapy

The general principles of pharmacologic treatment are individualization of therapy and titration of pharmacologic agents with close attention paid to effect on the one hand and side effects on the other (62,63 and 64). *No response* should not be accepted as an outcome until a sufficient period of time has passed to judge the efficacy of the drug. The pharmacologic agents best studied and longest used for pain relief in painful neuropathies are tricyclic antidepressants (TCAs) and antiepileptics. With advances in the neuroscience of pain, however, other agents are being introduced, such as systemically administered local anesthetics and NMDA blockers. Opioids may be useful, although their efficacy in the treatment of neuropathic pain has been questioned (65). Causes of and possible strategies to overcome opioid resistance in neuropathic pain states are under investigation (44,66,67). Controlled data for long-term use of opioids for chronic neuropathic pain are lacking, and consequently the medical literature generally does not advocate their use. The confusion regarding definitions of tolerance, dependence, and addiction, and the consequent fear of addiction, has been the ultimate barrier for use of opioids for chronic pain (68). However, the marked improvement in pain assessment and the utility of multidisciplinary and interdisciplinary approaches to pain management are leading to reconsideration of opioids for neuropathic pain. Destructive surgery on the peripheral or central afferent nervous system in the case of neuropathic pain always implicates further deafferentation and thereby provides an increased risk for a persistent deafferentation type of pain. For that reason, stimulation methods are favored over destructive procedures whenever surgical therapies are contemplated (69).

Frequently, patients are labeled as *treatment failures* because of inadequate medication trials. Many patients are subsequently successfully treated with drugs that were in the past deemed as failures, once those drugs are appropriately prescribed and administered. Two common reasons exist why patients do not respond to a particular medication. One is inadequate dose titration, often seen when a patient does not achieve pain relief or side effects. The second reason is the initiation of polypharmacy at the onset of the treatment trial; it is then not possible to ascribe either effects or side effects to any particular medication.

Guidelines for the treatment of painful polyneuropathies suggest that (a) one drug is titrated at any give time; (b) the dose of each drug is started at the lowest possible level; (c) titration is performed slowly by increasing the dose by one additional unit dose every 3 to 7 days, as determined by the patient's characteristics (i.e., age, prior medication experience, comorbidities, other medications patient is using at the time); and (d) titration is continued and the dose is further increased until one of the following endpoints is attained: significant pain relief, intolerable side effects, or *toxic* serum levels. The last applies only to antiepileptics and mexiletine. A medication is continued for the foreseeable future if all of the following criteria are met: significant pain relief, tolerable side effects, and improved patient activity and function.

The examination and pain assessment should lead to a specific neuropathic pain syndrome diagnosis, or in some cases, to more than one pain diagnosis. The treatment plan is based on the severity of pain, associated symptoms and comorbidity, and the complexity of the patient's medical presentation. The patient is apprised of the possible analgesic treatment goals, which should be modest, because most of the neuropathic pain syndromes are difficult, if not impossible, to cure and relieve completely.

Role of Polypharmacy and Duration of Treatment

Many patients require more than one drug to obtain satisfactory pain relief; it appears that more than one pathophysiologic mechanism may be causing the pain (70,71). As a practical guideline, one drug should be continued and another drug added only if the first drug produces only partial but still unsatisfactory pain relief. It should be kept in mind that only one drug should be titrated at any given time. No controlled studies demonstrate the efficacy of this treatment model, but data from basic science strongly support this concept.

A similar lack of clinical trial data exists to answer how long any given therapy, including pharmacologic treatments, should be administered. No attempts have been made to evaluate whether successful treatment with an analgesic medication alters the natural history of pain. Do patients who report significant pain relief with a certain medication need to be treated with that particular medication at that dose for the rest of their lives? One suggestion is to taper the medication every 6 to 12 months for the reassessment of the patient's pain level without the medication and basing the need for therapy on that *no medication trial*. Most of the medications have been used on a long-term basis for treatment of other disorders (e.g., for epilepsy and depression) so that long-term use for pain relief would be justified as safe as long as the treatment is monitored and the medications provide satisfactory pain relief.

Pharmacologic Agents Used for Treatment of Neuropathic Pain

Neuropathic pain in general has always presented a challenge because it does not respond to standard doses of opioids (65). The first class of pharmacologic agents demonstrated to be effective in the treatment of neuropathic pain were TCAs, but their effect is modest. With advances in the neurobiology of chronic neuropathic pain, new options for treatment could be considered, and with the development of novel pharmacologic agents these possibilities have been realized. The group of pharmacologic agents that provides relief of pain in neuropathic pain through mechanisms other than mu-opioid receptors is termed adjuvant analgesics (see Chapter 85 and Chapter 86). Categories of pharmacologic agents used for treatment of neuropathic pain include TCAs, antiepileptics, a-adrenergic agents, systemically administered local anesthetics, gamma-aminobutyric acid agonists, and NMDA blockers (Table 19-3). In addition, opioids have been reconsidered and have been found to be effective in some patients with neuropathic pain but at doses that are often higher than for those used for patients with nociceptive pain.

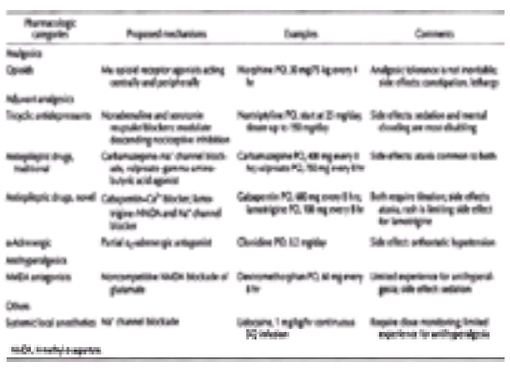

TABLE 19-3. Pharmacologic therapeutic agents used in treatment of neuropathic pain syndromes including neuropathies

Analgesics

Opioids. Opioids are still the drugs of choice for the treatment of acute episodes and acute exacerbations of neuropathic pain. Opioids strongly inhibit central nociceptive neurons mainly through interaction with mu-opioid receptors producing neuronal membrane hyperpolarization. Opioids are clearly effective in postoperative, inflammatory, and cancer pain. In some neuropathic pain syndromes, intravenous morphine is clearly analgesic when compared with placebo. However, no long-term studies have been performed on oral opioids used in the treatment of neuropathic pain. Surveys and uncontrolled studies indicate that a small fraction of the patients suffering from postherpetic neuralgia (72,73 and 74) or other neuropathic pain syndromes (75) can obtain and maintain adequate pain relief with oral opioids. Even without solid scientific evidence, the opinion of many pain clinicians is that opioids can and should be used as a part of comprehensive pain treatment program. Given that some patients with neuropathic pain may obtain considerable pain relief, opioids should be tested early in the treatment of neuropathic pains and a trial of opioids should not be delayed as a last resort. Administration of opioids requires specific treatment programs for patients with a history of chemical dependence and caution in patients with pulmonary disease. Prophylactic treatment of common side effects, notably nausea or constipation, can improve patient compliance and satisfaction with opioid therapy.

Adjuvant Analgesics

Tricyclic Antidepressants. TCAs are the best-studied group of pharmacologic agents and the most widely prescribed drugs for the treatment of neuropathic pain disorders (see Chapter 85). They have been shown to have analgesic effects, although often modest and not in all patients. Controlled studies have demonstrated their efficacy in painful diabetic neuropathy independent of their effect on depression (76). Solid evidence suggests that the serotonin and noradrenaline reuptake blocker amitriptyline and the selective noradrenaline blocker desipramine produce pain relief in diabetic or postherpetic neuropathy (24,25,26 and 27,76,77,78,79,80,81 and 82). A systematic review of antidepressants for the treatment of neuropathic pain concluded that these drugs are effective: “of 100 patients …30 will obtain more than 50% pain relief” (83). Contrary to prior teaching, when these agents are effective, they may relieve the constant burning and deep pains, as well as lancinating pains.

TCAs inhibit reuptake of monoaminergic transmitter peptides. Selective serotonin reuptake blockers are no more effective than placebo (84); this would suggest that efficacy of TCAs for neuropathic pain depends in a significant part on a noradrenergic component (79). It has been postulated that the site of analgesic activity is the CNS brainstem–dorsal horn nociceptive modulating system, in which the drug may alter serotonin and norepinephrine activity (85).

The TCA drugs bind to a variety of receptor sites, not only serotonin and norepinephrine, but also histaminergic, cholinergic, and adrenergic neurotransmitter sites. The significant variability in pain relief and side effects experienced by patients among the different TCAs may be explained by the fact that each tricyclic possesses a distinct profile of activity at each of these neurotransmitter sites. TCAs also have sodium channel blocking characteristics, and this could contribute to their efficacy.

Treatment with a tricyclic should be initiated with a dose of 10 or 25 mg in the evening, a few hours before bedtime to avoid early morning sedation. The lower 10-mg dose should be prescribed for the elderly, frail, or side effect–prone patient. The dose is titrated by one tablet, 10 or 25 mg, every 5 to 7 days if the patient has poor pain relief and does not complain of intolerable side effects. If effective, the majority of patients report significant pain relief or intolerable side effects within the dose range of 30 to 150 mg. The mean dose that results in pain reduction for amitriptyline is 75 to 150 mg per day, and that dose is smaller than doses necessary to achieve antidepressant effects. Onset of the analgesic effect occurs within 1 to 2 weeks and peaks around 4 to 6 weeks (76,80). Improvement in sleep, mood, and anxiety can further add to the improvement of pain control.

The most common side effects of the tricyclics are caused by their anticholinergic activity: constipation, dry mouth, blurred vision, slight cognitive changes, tachycardia, and urinary hesitancy. a-Adrenergic receptor blockade may result in orthostatic hypotension. Importantly, all of these potential side effects can be minimized by following the guideline of slow titration. Contraindications to the tricyclics include closed-angle glaucoma, benign prostatic hypertrophy, and acute myocardial infarction. Sedation and weight gain may occur from histaminic activity. The tricyclics are often prescribed solely for their positive effects on sleep. Sedation without weight gain is not possible, as both result from histaminergic activity.

The clinical experience with the TCAs for pain relief is poor to fair. Many patients obtain clinically insignificant pain relief and more often than not they report intolerable side effects. Although TCAs have been important in the field of neuropathic pain, their clinical utility is marginal and more effective agents are needed.

Antiepileptic Drugs. Antiepileptic drugs (AEDs) have garnered significant interest as agents for the treatment of neuropathic pain, because they have therapeutic effects on many neurotransmitter and ion channel systems that are implicated in the genesis and maintenance of neuropathic pain (86). Although they all have different mechanisms, they are grouped together because of their clinical utility for control of seizure and epileptic disorders.

As with all drugs used to treat neuropathic pain, significant variability exists with regards to efficacy, dose, and serum level of antiepileptics. Some patients may report significant relief with serum levels that are far below the *therapeutic* range for epilepsy, whereas other patients require *toxic* serum levels before pain relief is obtained and still remain without intolerable side effects. Therefore, a medication should, as a rule, be started at the small dose and slow titration should be initiated, as with all other medications for pain control.

Phenytoin and Carbamazepine. Phenytoin and carbamazepine act primarily by having an effect on sodium channels. Phenytoin and carbamazepine as pain relievers are deemed effective, but “minor adverse effects occurred as often as benefit” (86). Several controlled trials have reported benefit using these classic anticonvulsants. Phenytoin has been shown to be effective in well- controlled trials of diabetic polyneuropathy (87) and pain in Fabry's disease (88). Carbamazepine was found to be effective in two double-blind placebo-controlled studies for control of pain in diabetic neuropathy (89,90). The clinical experience with these two older anticonvulsants has been unsatisfactory. Many, if not most, patients when treated with these older anticonvulsant drugs either do not experience significant pain relief or develop intolerable side effects.

Gabapentin (Neurontin). Gabapentin is a novel antiepileptic with an unknown mechanism of action. A multicenter placebo- controlled study demonstrated significant pain reduction with gabapentin for the treatment of painful diabetic polyneuropathy (91). Gabapentin has also demonstrated analgesic efficacy in control of other neuropathic pain syndromes, such as postherpetic neuralgia (92). Even before these reports were presented, gabapentin had been extensively prescribed for the treatment of many neuropathic pain syndromes, based on the drug's excellent efficacy, side-effect ratio, remarkably low incidence of intolerable side effects, and the ease with which it may be prescribed, with no need to monitor any blood and serum parameters (93). Another added benefit of gabapentin is that the drug is not metabolized, and thus there are no drug–drug interactions.

The starting dose is 300 mg every 8 hours and is titrated by 300 mg per dose every 3 to 7 days until the patient reports pain relief, intolerable side effects, or a dose of 4,500 mg per day has been reached. Clinical experience has shown that a majority of the responders obtain relief at doses in the range of 1,800 to 3,600 mg. Gabapentin is much more expensive than the older anticonvulsants.

Lamotrigine. Lamotrigine is a novel antiepileptic agent that blocks voltage-sensitive sodium channels and inhibits the release of glutamate. An open-label survey revealed that this drug provided significant pain relief in most patients with painful diabetic neuropathy (94). To date, however, the clinical experience of the treatment of painful polyneuropathies with lamotrigine is limited.

Other Antiepileptics. Clonazepam and valproic acid have an effect on gamma-aminobutyric acid and could potentially help control neuropathic pain, but they have not been formally studied for that indication. However, the clinical experience is limited for both agents. A couple of novel AEDs, topiramate and vigabatrin, could potentially have analgesic effects similar to other AEDs, but data are not available, and these medications are frequently associated with bothersome side effects that could limit their usefulness.

Systemically Administered Local Anesthetics. Systemically administered local anesthetics block ectopic discharges caused by experimental injury and in axotomized dorsal root ganglion cells of the peripheral nerves (38), probably by blocking sodium channels (23), although central effects have been proposed (95). Local anesthetics have been administered systemically also for the control of cardiac arrhythmias and they are categorized as type Ib antiarrhythmic drugs. Systemically administered lidocaine, mexiletine, and tocainide were demonstrated to have analgesic effect for control of neuropathic pain in diabetic or postherpetic neuropathy (73,96,97 and 98). Reviews of the experience with use of these drugs revealed success for treatment of various neuropathic pain syndromes (99); no well-controlled studies and accepted standards exist for their long-term administration. Therefore, care needs to be taken when administering them. In the first edition of this text, Bonica championed the use of intravenous procaine for the treatment of neuropathic pain, based on his clinical experience. Contraindications include cardiac electric conduction abnormalities, reduced left ventricular function, and severe liver and renal disease. Properly conducted clinical trials cannot be identified.

Antihyperalgesics: N-*Methyl-D-Aspartate–Receptor Antagonists.* NMDA receptors have been demonstrated to play an important role in the genesis of neuropathic pain (see previous discussion). Clinically available compounds that are demonstrated to have NMDA-receptor–blocking properties include ketamine and dextromethorphan. Memantine is available outside the United States. NMDA-receptor antagonists have demonstrated analgesic effects in human laboratory and clinical studies (100,101,102 and 103), including in a long-term trial with diabetic neuropathy (104). Toxicity and side effects of these agents at analgesic doses are limiting factors for their wider use, but advances in neuropharmacology hold promise and hope for more effective and less side-effect–prone agents.

CLINICAL SYNDROMES

Polyneuropathies can be diagnosed only by the patient's history, metabolic findings, and diseases in other organs; their clinical manifestations are not distinctive (Table 19-4).

Type of fiber loss	Neuropathy
Selective large fiber loss	Isoniazid neuropathy
	Pellagra neuropathy
Selective small fiber loss	Fabry's disease
	Dominantly inherited sensory neuropathy
	Diabetic neuropathy
	Amyloid neuropathy
Nonselective fiber loss	Alcoholic neuropathy
	Myeloma neuropathy
Unknown	Guillain-Barré neuropathy (acute inflammatory)
	Beriberi neuropathy
	Strachan's syndrome
	Burning feet syndrome
	Arsenic neuropathy
	Chloramphenicol neuropathy
	Metronidazole neuropathy
	Misonidazole neuropathy
	Organophosphorus neuropathy
	Thallium neuropathy

TABLE 19-4. Painful polyneuropathies

Diabetic Painful Neuropathy

Patients with diabetes develop a variety of peripheral neuropathies as their disease progresses. One of the presenting features of diabetes is symmetric distal polyneuropathy, which can affect predominantly either small or large fibers. Small fiber neuropathy manifests most commonly with pain and paresthesiae, whereas large fiber neuropathy presents with sensory ataxia. Polyneuropathy is seen in insulin-dependent and noninsulin-dependent forms of diabetes. Focal diabetic neuropathies are common as well. Two possible mechanisms lead to focal neuropathies. One is focal ischemia, and the other is an abnormal susceptibility to compression injuries. At times, focal neuropathies present with involvement of multiple nerves as mononeuritis multiplex, and this presentation then makes the differentiation from polyneuropathy more important. Any and all of the diabetic neuropathies might be associated with pain or dysesthesiae, but most commonly small fiber distal neuropathy and ischemic mononeuropathy are painful. In a few patients presenting with primarily proximal pain and weakness, termed *diabetic amyotrophy*, evidence exists of autoimmune inflammatory neuropathy resembling vasculitis (105,106 and 107), and on pathologic review of nerve biopsy, evidence of demyelination and axonopathy exists (105).

The cause of common distal neuropathy is likely to be multifactorial. Pathologically, evidence exists of demyelination and axonal degeneration in most patients. The pathogenesis is uncertain, but direct injury of axons and their supporting structures caused by either metabolic abnormalities or affliction of nerve microvasculature remains the most readily accepted hypothesis (108,109 and 110). The putative pathologic mechanisms include accumulation of sorbitol, formation of glycosylation end products, free radical–mediated oxidative stress, abnormalities in essential fatty acids, and deprivation of nerve-growth factors (6). No differences existed in morphometric studies of the sural nerve biopsy from patients with and without neuropathic pain (111). However, based on the clinical examination and according to neurophysiologic studies, patients with diabetic neuropathy who experience pain have evidence of small fiber dysfunction (112).

Differentiation of two forms of distal painful polyneuropathy syndromes in patients with diabetes is possible. One is acute and the other is chronic. Acute painful polyneuropathy is most frequently precipitated by the initial administration of insulin. The syndrome manifests with many severe pains distally in feet and legs and is associated with marked allodynia and hyperpathia (113). Pain in the hands is less common. Sensory and motor findings are usually slight, although clear evidence exists of abnormal thermal perception. Acute polyneuropathy, and many focal neuropathies as well, run a more benign course, with pain abating spontaneously after months to years. Pathophysiologic mechanisms are not well known, but observations suggest that insulin has a vasoactive hypoxic effect, and this may offer an explanation (114). Chronic painful neuropathy has an insidious onset of symptoms, such as numbness, leg weakness, ataxia, and paresthesiae. Symptoms and signs of autonomic dysfunction are present in varying degrees. Most commonly, patients experience aching pain with superimposed shooting pains. Improvement of glucose control can slow down the progression of polyneuropathy, but this improvement has little effect on manifestations of pain.

Diagnosis

Diagnosis of painful diabetic neuropathy is usually straightforward. It is made on the basis of painful neuropathy in patients with known diabetes. Because diabetes is one of the most common causes of distal painful neuropathies in the Western countries, any patient presenting with painful neuropathy deserves diagnostic evaluation for diabetes. In addition to serologic studies performed to corroborate the diagnosis, electrophysiologic studies of NCV and EMG can be performed for

better definition of the type of neuropathy. Quantitative sensory and autonomic testing could also bring additional information regarding the type and the extent of neuropathy.

Therapy

Recommendations for tight blood sugar control are the standard of care for all diabetics, and it has been repeatedly shown that the onset and progression of diabetic neuropathy are delayed with normoglycemia (115,116). More advanced therapies with combined pancreatic transplantation and kidney transplant can lead to clinical improvement and substantial recovery of mean motor and sensory conduction velocities, although no improvement in sensory thresholds or autonomic function have been shown (117). Patients with autoimmune painful diabetic amyotrophy should be considered for treatment with immunosuppression (107).

Any therapy for diabetic neuropathy should start with general medical care, such as striving for as rigorous blood sugar control as possible, good skin care, and particularly good foot care. Symptomatic pain treatment for diabetic neuropathy is in general similar to other painful neuropathic disorders. Pain assessment and the examination should lead to a specific diabetic pain syndrome diagnosis or, in some cases, more than one pain diagnosis, as discussed earlier. Treatment plans are based on the appreciation of the severity of pain, associated symptoms and comorbidity, and the complexity of the patient's medical presentation. The patient is apprised of the possible analgesic treatment goal, which should be modest. The patient with acute polyneuropathy can be reassured that eventually a good outcome exists regarding spontaneous resolution of pains. TCAs have been best studied for treating pain in patients with diabetic neuropathies (76,80,118,119). Although in clinical trials up to 60% to 70% of patients receive satisfactory or good relief of pain, clinical experience has not been as favorable. Most patients cannot titrate the dose because of the side effect of sedation and other anticholinergic side effects. Antiepileptics, carbamazepine and phenytoin have been studied and used as adjuvant analgesic therapy with modest effect (6). The newer antiepileptic, gabapentin, has demonstrated good analgesic efficacy in a multicenter study, and with its benign side-effect profile it is a welcome addition (91). Other antiepileptics, such as valproate and lamotrigine, are considered for treatment of pain in diabetic neuropathy, although controlled studies are lacking. Long-term use of opioids for chronic neuropathic pain may be considered in patients with well-defined pain syndromes who show good response to a trial of opioids. New and exciting possibilities suggested by the preliminary studies of nerve growth factors that might help regeneration of nerves damaged in diabetes (120) may have an important effect on pain control and diabetic care in general (121).

Topical capsaicin has been widely used, although evidence regarding efficacy is conflicting. Its application is frequently reported as messy and requires great skill and diligence in how it is applied. Vitamins and gangliosides are widely prescribed, but only a few controlled studies have assessed their efficacy. At best, the results are conflicting (116).

Physical therapy modalities are an important part of any chronic pain treatment, and this also applies to painful diabetic neuropathy. This is especially important for those with diagnosed musculoskeletal problems and with significant muscle pain. Psychological methods of pain control are used at all times and are an integral part of pain management in general. Another important aspect of psychological therapy is the establishment of realistic treatment goals.

A more challenging situation is the treatment of the patient who has more than one type of pain. For example, burning and stabbing pain caused by distal neuropathy, localized ache and sharp pain caused by entrapment neuropathy, and severe cramping deep pain caused by vascular insufficiency can present in the same patient. That patient would need, in addition to pharmacologic therapy for neuropathic pain, therapy for vascular insufficiency and would need to be considered for decompressive surgery.

Stimulation therapies may be used as well. Transcutaneous electrical nerve stimulation can help some patients with neuropathic pain. Spinal cord stimulation has been used with increasing frequency and success and may ameliorate pain even in those refractory to all other medical intervention (122). However, controlled clinical trials still have to confirm these preliminary observations before this invasive method of therapy could be routinely recommended.

In addition to analgesia, other symptoms are treated in parallel. Insomnia is one of the most disabling results of unrelieved pain; once pain is relieved, it is easier to aid sleep by introducing small doses of TCAs, which themselves have analgesic action. Nausea, diarrhea, constipation, itching, and fatigue could be part of diabetes and should be treated specifically. It should, however, be kept in mind that these symptoms are also frequently seen as side effects of many analgesic medications, so careful monitoring of any therapy is necessary.

Neuropathies Caused by Connective Tissue Disorders and Vasculitis

Vasculitis syndromes are autoimmune disorders characterized by inflammation and necrosis of blood vessel walls. Vasculitis syndromes are a heterogeneous group of disorders, and they can be classified as falling into several groups depending on their relationship to the neuropathies: systemic necrotizing, hypersensitivity vasculitis, giant cell arteritis, and localized vasculitis. This classification is particularly important for the planning of therapy (123).

Peripheral neuropathy is a common component of the vasculitis syndromes in systemic and localized vasculitis. Localized vasculitis is more frequently associated with peripheral neuropathy, which is usually painful. Vasculitis is frequently insidious at the time of presentation, and for that reason is difficult to diagnose, leading to long delays from initial presentation until the time of diagnosis (124). Most patients with neuropathy caused by vasculitis experience varying degrees of numbness and weakness in addition to severe pain, depending on the extent and the severity of vasculitis. The pain usually has characteristics of acute neuropathic pain with severe ongoing pain and frequent spontaneous paroxysms of pain and hyperalgesia. Involvement of other organs varies from one vasculopathy syndrome to another and may include skin, kidneys, gastrointestinal, sinuses, and joints.

When the diagnosis of vasculitis is suspected, a comprehensive workup is necessary, starting with serologic studies, such as sedimentation rate, antinuclear antibody panel, and other more specialized autoimmune tests. The suspicion of this diagnosis may make obtaining combined muscle and nerve biopsies necessary (125). The diagnostic histologic finding is inflammation of the medium-sized arteries in the epineurium, multiple areas of demyelination, and patchy destruction of axons. The lymphocytic infiltration of the arterial wall and the thrombotic occlusions of inflamed arteries are diagnostic findings. Occlusion of medium and small vessels leads to interruption of the blood supply to the nerves through their nutrient vessels. The extent of the occlusive disease determines whether distal polyneuropathy or mononeuritis multiplex occurs. Frequently, electrophysiologic investigation with NCV and EMG can help in the differential diagnosis of these two syndromes that can be difficult to distinguish on clinical grounds alone.

The primary treatment goal in case of neuropathy caused by vasculitis is the control of the underlying disease process. Treatment is based on high-dose immunosuppressive therapy that typically includes corticosteroids, cyclophosphamide, azathioprine, and chlorambucil. Specific treatment guidelines regarding the specific agents and duration of therapy are established for different types of vasculitis (123). For example, the simplest is the treatment for giant cell arteritis with prednisone for up to 5 months, and the most complex therapy is for peripheral nerve vasculitis with systemic necrotizing vasculitis, and consists of prednisone and cyclophosphamide for at least 1 year, depending on the response. Immunosuppressive therapy can control motor as well as painful sensory symptoms. Neuropathic pain should be treated with opioid and adjuvant analgesics, as discussed earlier in this chapter in the section Treatment of Painful Neuropathies (see Table 19-3).

Autoimmune Demyelinating Neuropathies: Acute Inflammatory Demyelinating Polyneuropathy or Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyneuropathy

Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

GBS is an inflammatory polyneuropathy with an estimated crude average annual incidence rate of 0.4 to 1.7 per 100,000 (126), which means that a large hospital is likely to receive several patients with GBS each year. GBS is an immunologically mediated disorder, usually triggered by cytomegalovirus or Epstein-Barr virus, and reports exist of GBS occurring after vaccination and surgery. The syndrome is characterized by ascending motor weakness; approximately 10% of patients develop disease severe enough to require ventilatory support that leads to admission to the intensive care unit for weeks. Pathologic studies show an inflammatory process affecting the peripheral nerves and nerve roots, consisting of lymphocytic and macrophage infiltration and demyelination. GBS can last for a number of months, but eventual spontaneous recovery takes place in 90% of patients. Developments in intensive neurologic care and advanced critical care facilities have resulted in low mortality of approximately 1%. Therapy targeted toward the underlying mechanisms is based on the removal of the antigen and consists of plasma exchange and intravenous immunoglobulins. Once the patient begins recovery, the treatment focus is physical therapy and rehabilitation.

Pain and dysesthesia are relatively common in GBS, found in 40% to 75% of patients in one series (127). In most cases, however, they do not constitute a major source of inconvenience to the patient, to whom the loss of motor function of legs and arms is usually far more distressing. However, pain can be severe, often of a burning quality and associated with allodynia and hyperpathia. In this situation, prompt amelioration of pain is of paramount importance. Sensory changes are usually

mild but detectable in 25% to 50% of patients, especially affecting the functions subserved by large-diameter fibers. It is obvious from a number of clinical and neurophysiologic observations that most pain in GBS is neurogenic in origin. Other types of pain may occur as well, perhaps secondary to prolonged immobility and neuritis-induced myofascial mechanisms. One review lists several types of pain: backache, meningism, muscle pain, joint pain, and visceral pain (127).

Moulin and colleagues reported that pain is a presenting symptom in more than three-fourths of patients with GBS, and in many it precedes weakness. Pain is present throughout the course of GBS; in one-half of those patients, it is rated as severe. Pain intensity on admission correlated poorly with neurologic disability on admission and throughout the period of the study. Patients who present with severe pain do not necessarily progress to severe paralysis or have a poor prognosis (128).

The major pain syndromes observed in GBS are back and leg pain, dysesthetic extremity pain, and myalgic-rheumatic extremity pain, which are most directly related to the GBS, and visceral pain, headache caused by dysautonomia, pressure palsies, and sacral decubiti as an indirect consequence of GBS.

Approximately two-thirds of patients experience back and leg pain at some time during the course of the GBS. Pain is usually described as a deep, aching, or throbbing pain in the low back, frequently radiating to the buttocks, thighs, and occasionally to the calves. These symptoms are the most frequent cause of what patients describe as horrible or excruciating pain. Back and leg pain is exacerbated with straight leg raising, and this phenomenon would suggest that traction on inflamed nerve roots could be responsible for this pain. Pain exacerbation by nerve root traction maneuvers could be mistakenly diagnosed as an acute radiculopathy caused by herniated disk. A strong component of muscular pain occurs as a mechanism for back and leg pain in the acute phase of GBS. Acutely paralyzed large muscles are commonly painful, and this parallels the elevation of serum creatinine kinase (129). Muscle calf pain can be difficult at times to differentiate from deep venous thrombosis, so a number of patients are subjected to venous studies.

Dysesthetic extremity pain, described as burning, tingling, or shocklike, involves the legs more frequently than the arms and is also common in GBS. This type of pain is present in a minority of patients on admission, although approximately one-half experience dysesthetic pain sometime during the course of the illness. It may persist indefinitely in 5% to 10% (128). It is postulated that neuropathic pain of this type is likely caused by ectopic impulse formation at sites of demyelination and axonal degeneration and regeneration along the peripheral nerve (53).

Myalgic and rheumatic extremity pain, described as an aching or cramping type of pain, is less frequent than radicular low back pain. This pain is usually associated with the complaint of joint stiffness. This pain is most notable during the passive and active- assisted exercises associated with physical therapy.

Visceral pain is often related to constipation and usually responds to an aggressive bowel regimen. Headache caused by malignant hypertension can also occur as a result of dysautonomia. Bedridden patients are prone to sacral ulcers and painful pressure palsies; they can be prevented with the use of air mattresses, careful turning of patients, and positioning of limbs. The use of padding over elbows and knees can prevent pressure palsies.

Pain Management in Guillain-Barré Syndrome A wide range of pharmacologic agents can be used for management of pain in GBS. It is most efficient to attempt to match the underlying pathophysiologic mechanisms with a class of pharmacologic agent. For example, nociceptive pain of the low back type is best treated with nonsteroidal antiinflammatory agents and opioids, depending on the severity of pain, and dysesthetic pain is best treated with anticonvulsants.

In a prospective study (128), 75% of patients required oral or parenteral opioids to provide adequate pain relief. Patients with severe pain who are in the intensive care unit on ventilatory support are best managed with a continuous intravenous opioid infusion using either morphine or hydromorphone. Starting doses of an intravenous morphine infusion are usually in the range of 1 to 3 mg per hour. Epidural morphine is an acceptable alternative to systemic opioids in ventilated patients with primarily low back and leg pain (130). In nonventilated patients in the acute stage of illness, opioid analgesics must be titrated carefully because of increased risk of respiratory depression. However, starting doses of sustained-release morphine in the range of 15 to 30 mg twice a day with dose titration to 60 to 90 mg twice a day are usually well tolerated (128). During the recovery phase, when muscle and joint pain are routinely precipitated by passive and active exercises, immediate-release codeine or morphine can be given an hour or two before treatment to facilitate compliance with physiotherapy. Most patients do not require opioid analgesics beyond the first 8 weeks of illness.

Corticosteroids, including methylprednisolone, may relieve severe pain in GBS (131), and this may be caused by its antiinflammatory effects at the nerve root level.

A tricyclic antidepressant such as amitriptyline or nortriptyline represents the first line of treatment for dysesthetic extremity pain seen in GBS. If a tricyclic antidepressant is intolerable or does not control the pain, mexiletine (132) or clonidine (133) may be useful. Mexiletine is usually prescribed in gradually increasing doses to 200 mg orally three times a day. Clonidine can be given orally or transdermally in a total daily dose of 0.3 mg daily. Gabapentin, a newer anticonvulsant, has shown promise in the management of chronic neuropathic pain states (134). Gabapentin can be rapidly titrated to 300 mg three times a day orally to a maintenance dose of 900 mg three times a day.

Studies on the efficacy of plasma exchange and immunoglobulins concentrate on improvement in motor weakness and overall disability. It is not clear whether these therapies relieve pain or help to prevent it from occurring in prolonged cases.

No controlled studies exist on the efficacy of any treatment of pain associated with GBS. Most authors have adopted a common-sense approach, recognizing the neurogenic nature of most pains in this condition and adopting well-known pain-relieving methods, including TCAs and anticonvulsants.

Occasionally, pain becomes a major problem in those patients treated in the intensive care unit for weeks or months. It should be noted that as the patients in this setting are disabled for a long time, without exception they need some type of psychological support. Because of the inflammatory nature of this pain, nonsteroidal antiinflammatory agents are occasionally effective. However, the patients are at an increased risk for developing peptic ulcers, and the prolonged use of nonsteroidal antiinflammatory agents cannot be advocated. Similarly, although corticosteroids seem to provide temporary alleviation (131), their long-term use is not recommended.

In summary, GBS is an acute and often frightening paralytic disease that commonly has a significant pain component. Accurate diagnosis, careful monitoring, early therapeutic intervention with intravenous immunoglobulin or plasma exchange, good intensive care unit care, active pain management, and active rehabilitation are all essential in the treatment of GBS.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic peripheral nervous system disorder that can have progressive, relapsing-remitting, and monophasic courses. The incidence is probably less than GBS, but, because of its prolonged course, its prevalence is greater than GBS. Association with preceding viral illnesses is less common, at 20% to 30% of patients, in contrast to GBS, in which the incidence is close to 70%. Many autoimmune and infectious disorders, such as lupus, HIV, paraproteinemias, and diabetes mellitus, are associated with CIDP. Malignant cell dyscrasias and monoclonal gammopathies can also lead to CIDP. Presenting symptoms are the insidious onset of numbness and weakness, primarily affecting distal limbs first, but a great variability occurs. Pain may or may not occur, and it has all of the features of neuropathic pain. Pain in CIDP is probably more prevalent than previously reported (135). A notable sparing of cranial nerves takes place, which contrasts with GBS (136). Therapy is aimed at treating the underlying disease process with intravenous immunoglobulin, plasmapheresis, and oral corticosteroids. Pain management should follow the basic principles of neuropathic pain pharmacologic therapy.

Brachial Plexopathy

Idiopathic brachial plexopathy (Parsonage-Turner syndrome) is an infrequent peripheral neuropathy syndrome that occurs primarily in younger adults, usually 20 to 40 years of age. The etiology of this syndrome is not well established, although cases with a preceding viral illness would suggest the possibility that this disorder results from an autoimmune process similar to GBS. Idiopathic brachial plexopathy is usually a self-limited disease with good recovery. On the other hand, prognosis of symptomatic brachial plexopathy depends on the underlying disease process.

Predominant symptoms are pain in the affected shoulder and weakness of the shoulder girdle muscles. The weak muscles are usually serratus anterior, deltoid, supraspinatus and infraspinatus, and triceps, in isolation or various combinations. Muscle atrophy develops 2 to 3 weeks from the onset of pain and weakness. If the long thoracic nerve is affected, the diaphragm may be partially paralyzed. Pain is usually described as deep and aching. It is made worse with movements of the affected limb. Pain is not made worse by coughing or sneezing, which helps to differentiate this syndrome from cervical radiculopathy. Despite the pain and weakness, minimal sensory deficits occur. EMG is useful in documenting the extent of nerve involvement. Differential diagnosis includes traumatic causes of brachial

plexus, invasion of brachial plexus by lung or breast malignancies, postradiation brachial plexopathy, cervical radiculopathy, and a number of rheumatologic syndromes affecting the shoulder joint. Differential diagnosis also includes hereditary liability to brachial plexopathy, which can be diagnosed from an adequate family history.

Because most cases of brachial plexopathy are idiopathic, no specific therapy exists for this disorder. Treatment of pain may require mild to strong analgesics, and in chronic forms of brachial plexopathy other treatments such as TCAs, antiepileptic drugs, or systemically administered local anesthetics are used. Early rehabilitation is important to prevent capsulitis (frozen shoulder).

Hereditary Neuropathies

Hereditary neuropathies present a wide spectrum of peripheral nerve disorders and syndromes, but only a few of them are painful. Some of the hereditary sensory-motor neuropathies and porphyria may have pain as one of the presenting symptoms, but pain is always overshadowed by symptoms of sensory and motor deficits. However, in the presentation of Fabry's disease, pain is the cardinal symptom.

Fabry's Disease

Fabry's disease is a multisystem disorder, affecting peripheral nerves, kidneys, heart, and skin. It is caused by an X-linked recessive gene and the symptoms start in childhood or adolescence. The biochemical abnormality in this disorder is deficiency of a-galactosidase, a lysosomal enzyme.

The clinical features include red punctate skin lesions in lower body and thighs, corneal opacifications, cardiac and renal failure, and polyneuropathy. Renal and cardiac failure usually requires intensive care treatment, and can be terminal for these patients. Constant burning pain in hands and feet is the prominent feature of this neuropathy. Another type of pain these patients can experience is spontaneous paroxysms of severe excruciating burning pain. On examination, surprisingly minimal abnormalities are evident. Sensory and motor function and stretch reflexes are usually preserved. Electrophysiologic studies of NCVs and EMG are almost always normal. Antiepileptic medications, such as carbamazepine (137) and phenytoin (88), can be used for control of pain. In addition to pain, patients with Fabry's disease have marked autonomic abnormalities manifested by episodic diarrhea, vomiting, urinary retention, and diminished sweating. These have been reported to be exacerbated by carbamazepine (137), so this medication should be used with caution. Gastrointestinal symptoms can be relieved with metoclopramide.

Amyloid Neuropathy

Peripheral neuropathy is a common, early, and often most prominent manifestation of amyloidosis (138). Most of the cases of amyloid neuropathy belong to the hereditary (familial) form, although some cases are of sporadic type. Several distinct clinical groups of hereditary amyloidosis exist, but all of them have an autosomal dominant pattern. The initial symptoms are numbness, paresthesiae, and pain in the feet and lower legs. Autonomic involvement is also important, manifested by abnormal pupillary reflexes and myosis, anhidrosis, orthostatic hypotension, diarrhea alternating with constipation, and impotence. Cranial nerve involvement is seen late in the disease. Primary (nonfamilial) systemic amyloidosis has a similar neuropathic presentation as does hereditary (familial) amyloidosis. Approximately one-half of the patients have at the onset predominantly neuropathic symptoms, and one-half have systemic disorders of cardiac, hematologic, and renal function (138). Patients with familial amyloid polyneuropathy can benefit from liver transplantation (139). Most of the patients with systemic (nonfamilial) amyloidosis die because of major organ failures within 6 to 12 months after the diagnosis (3).

Toxic and Nutritional Neuropathies

Neurotoxic substances impair a number of neural processes, such as protein synthesis, axonal transport, and myelin maintenance. Exposure to several industrial toxins is known to lead to polyneuropathy. These usually cause motor symptoms and signs, although painful and dysesthetic symptoms may ensue in a minority of patients. Few pathologic studies have been conducted in humans. *N*-hexane, a common ingredient in household glue, and methyl-*n*-butyl ketone, used as an industrial solvent, are known to cause focal swelling of axons to two to three times their normal diameter and can result in painful neuropathies (3).

Several drugs may cause painful polyneuropathy. Cytotoxic and immunosuppressant drugs are especially important in this respect because of the rapid onset of polyneuropathy and its dose-limiting influence on treatment. Vincristine, cisplatin, paclitaxel (Taxol), paxitaxel, and docetaxel all cause polyneuropathy with pain and dysesthesia. These are reversible if the drug is discontinued, and preventable to a certain extent if low doses are used. Concomitant adrenocorticotropic hormone may help to reduce, but not prevent, cisplatin neuropathy (140). A potent immunosuppressant FK506 or tacrolimus causes CNS and painful sensory-motor demyelinating multifocal neuropathy. The latter improves after plasma exchange or intravenous immunoglobulins (141).

Many other drugs are known to cause polyneuropathy, which is usually but not always painful. Among these are isoniazid, gold, disulfiram, nitrofurantoin, amiodarone, and bezafibrate. In the category of toxic-metabolic neuropathies are included neuropathies that are related to nutritional deficiencies, primarily caused by vitamins from the B family.

Isoniazid-Related Polyneuropathy

Isoniazid is an effective and the least expensive antituberculosis drug, but it is associated with distal neuropathy when administered in higher doses (3). Patients with genetic predisposition for slow metabolism of isoniazid are more susceptible to this adverse effect. Isoniazid interferes with enzymes related to vitamins from the B_6 group leading to axonal damage. This axonopathy affects small and large fibers, causing sensory and motor deficits and pain. Physical examination confirms these deficits as well as positive sensory phenomena. Pain is described as deep aching pain in calf muscles and burning paresthesiae in upper and lower extremities. The treatment consists of administering pyridoxine in doses of 30 to 100 mg per day; doing so can prevent development or reverse existing isoniazid neuropathy. When administering pyridoxine, excessive doses should be avoided because pyridoxine itself can cause neuropathy if given in excess (3).

Beriberi Neuropathy

Beriberi is the most widely recognized nutritional neuropathy; it is a disease of peripheral nerves and heart (138,142). If the heart is affected, patients present with heart failure (wet beriberi). The majority of patients present with neuropathy with or without heart disease (dry beriberi). Presenting symptoms are slowly progressive weakness, paresthesiae, and pain in distal limbs, worse in lower than upper limbs. On rare occasions, there could be a rapid progression of symptoms over a period of only a few days. Multiple pain symptoms occur, including dull, constant ache, lancinating brief pain similar to tabes dorsalis, tightness in calves, bandlike sensation in the legs, and burning. Because burning in the feet could be a presenting symptom of beriberi, it could be mistakenly diagnosed as *burning feet syndrome*. In beriberi, burning usually involves hands early in the disease. Physical examination reveals symmetric sensory loss in all modalities as well as positive phenomena of allodynia, hyperalgesia, and hyperpathia, all of which are worse distally. Also, distal muscle weakness and absent reflexes occur, as beriberi can be documented on nerve conduction study (143). The emphasis of therapy is nutritional supplementation with thiamine and all other B vitamins, but pain and symptom control have an important part. The prognosis in treated beriberi neuropathy is good, but recovery takes a long time because regrowth of nerves is slow (138).

Pellagra Neuropathy

Pellagra is a nutritional disorder that, when fully developed, affects skin, gastrointestinal tract, hematopoietic, and nervous systems. Nervous system manifestations include encephalopathy, myelopathy, and neuropathy. Neuropathy is infrequent, but it can be disabling. Neuropathy symptoms and physical findings are indistinguishable from other nutritional neuropathies (138).

Alcohol-Related Painful Neuropathy

Chronic alcohol intoxication is associated with many disorders of liver, heart, muscles, and nervous system. The neurologic complications of chronic alcoholism include dementia, cerebellar ataxia, and polyneuropathy. Alcohol polyneuropathy is probably caused by multiple nutritional deficiencies, and the clinical presentation is similar to any other nutritional deficiency disorder (138). Treatment of alcoholic neuropathy should be given as a part of a comprehensive treatment program, which includes alcohol abstinence and psychological alcohol addiction therapy, improved nutrition, and vitamin supplementation. Pain relief may be attempted with antidepressants and anticonvulsants; opioids should be used cautiously.

Human Immunodeficiency Virus Infection–Related Neuropathies

Peripheral neuropathies are among the most frequent neurologic complications in HIV infection (see Chapter 39). A few peripheral neuropathic pain syndromes occur in patients with HIV infection, and they tend to be specific to the stage of HIV infection. Inflammatory demyelinating polyneuropathies occur early in the course of HIV infection; distal sensory neuropathy occurs late in the disease; vasculitis-related neuropathies occur midcourse in the disease. Incidence and prevalence of neuropathies in HIV patients are as low as 2.6% in Japan (144) and as high as 44% in a cohort from Zimbabwe (145). In the study by Parry and colleagues (145), in a randomly selected group of HIV-positive subjects in Africa, with clinical manifestations ranging from asymptomatic to AIDS, 44% had evidence of neuropathy based on history, clinical examination, and electrophysiologic abnormalities. Major categories of neuropathies included subclinical (56%), acute inflammatory demyelinating polyneuropathies (acute inflammatory demyelinating polyneuropathy) (15%), and distal symmetric polyneuropathies (22%). Subclinical neuropathy was found in all categories, whereas acute inflammatory demyelinating polyneuropathy predominated in the symptomatic category and distal symmetric polyneuropathies in individuals with AIDS. The pattern and frequency of neuropathies seen in the African-American population are similar to those reported for other continents. In the late stages of the disease, as documented in biopsy and autopsy series, the incidence of neuropathy is 100%.

Acute demyelinating polyneuropathies occur in early stages of HIV infection, and often may be a presenting syndrome in patients who are otherwise asymptomatic for any other HIV symptoms (146). Chronic demyelinating polyneuropathies also develop as one of the early manifestations. Demyelinating polyneuropathy is assumed to be on an autoimmune basis. Brachial plexopathy and focal neuropathies also occur during early stages of HIV infection (147). Neuropathies caused by vasculitis may develop in the course of HIV, and this diagnosis should be suspected, especially in patients who develop multiple mononeuropathies (mononeuritis multiplex).

The pathologic mechanisms in neuropathy caused by HIV are not well understood, and it has been argued that it is not from the direct effect of the virus itself (146). The virus, which is not found within ganglionic neurons or Schwann cells but only within the endoneurial macrophages, may generate a tissue-specific autoimmune attack by secretion of cytokines that promote trafficking of activated T cells and macrophages within the endoneurial parenchyma (148). Antisulfatide antibodies are therefore one of the humoral factors responsible for demyelinating diseases in AIDS patients (149).

Distal symmetric predominantly sensory polyneuropathy is commonly seen in the late stage of the disease in full-blown AIDS. Patients frequently suffer from severe painful burning dysesthesiae, especially in the feet.

Differential diagnosis is complicated by the fact that anti-HIV medications such as ddI (Didanosine) and ddC (Zalcitabine) can themselves cause neuropathies. The wide use of the neurotoxic antiretroviral nucleoside analogues ddC, ddI, d4T (Stavudine), and 3TC (Lamivudine) exacerbate or trigger subclinical neuropathy in many of these patients. Like HIV-associated sensory neuropathy, ddC- related toxic neuropathy is a predominantly sensory, length-dependent, symmetric, painful neuropathy. Dose reduction has lessened the severity of symptoms, although objective signs of neuropathy persisted. Patients with subclinical neuropathies or who are at significant risk, such as diabetics, may be poor candidates for ddC therapy (150). Patients who developed peripheral neuropathy while continuing treatment with ddI, ddC, and d4T had acetyl-carnitine deficiency. The normal levels of total carnitine in the study group appear to indicate the specificity of the defect and rule out coexisting relevant nutritional problems. The critical role of acetyl-carnitine for the metabolism and function of the peripheral nerves supports the view that the acetyl-carnitine deficiency found in these subjects may contribute to the neurotoxicity of ddI, ddC, and d4T, even though the interference with mitochondrial DNA synthesis is regarded as the main cause of their toxicity.

Opportunistic infections are a serious possibility in HIV patients and may lead to neuropathies; cytomegalovirus polyradiculoneuritis and herpes zoster neuropathy should be kept in mind. Differential diagnosis of painful neuropathy in the HIV patient also must include cytomegalovirus infection of the dorsal root ganglia with polyradiculoneuritis, especially in patients who present with cauda equina syndrome.

Treatment of neuropathic pain syndromes in HIV patients is complicated by the fact that pain in HIV patients in general is underdiagnosed and undertreated. Pharmacologic treatment of neuropathic pains in this condition is analogous to that of neuropathies caused by cancer (151). The specific issues are the multiple diagnostic possibilities that may require specific considerations such as cytomegalovirus treatment with acyclovir or treatment of demyelinating neuropathy with plasmapheresis or intravenous immunoglobulin.

Lyme Neuropathy

Neuropathies were documented early, when Lyme disease was initially described. This spirochetal infection, which is transmitted to humans by deer ticks, causes multisystem disease including dermatologic, rheumatologic, cardiac, and neurologic symptoms and signs. Neurologic manifestations include neuropathy, polyradiculoneuropathy, myelopathy, multiple cranial nerve dysfunction, and encephalomeningitis (152). Presenting neuropathy symptoms are paresthesiae and dysesthesiae (153), but later, in the chronic phase of the disease, distal painful sensations predominate (154). The Lyme neuropathy is reversible if the patient is treated with systemic antibiotics such as oral doxyxicycline. If symptoms are severe with positive cerebrospinal fluid findings, intravenous ceftriaxone, 2 g per day for 2 weeks, should be used. Symptomatic pain control should be administered as long as symptoms interfere with the patient's function.

Cryptogenic Polyneuropathies and Neuropathies Caused by Undetermined Causes

Surveys that looked for causes of neuropathies have concluded that, for a number of patients with neuropathy, 32% to 70% cannot be accurately diagnosed (155,156). A number of these patients have sensory disturbances, including pain, paresthesiae and dysesthesiae, and muscle cramps (157,158 and 159). However, as suggested by a few authors, intensive reevaluation with comprehensive techniques leads to improvement in diagnostic rates (157). According to a large series by Dyck and Lambert (157), of the 205 patients who were originally unclassified, most (42%) had inherited disorders, followed by autoimmune disorders in 21% of patients, inflammatory demyelinating polyradiculoneuropathy in 13%, and other causes accounting for 13%. Even after comprehensive reevaluation, 24% of patients remained without diagnosis. In the series of 519 patients reported by McLeod and colleagues (158), approximately 13% of patients were without a specific diagnosis. Consequently, the possibility exists that patients presenting with pain and paresthesiae in distal limbs could not be diagnosed with a specific polyneuropathy at initial workup, but reevaluation is recommended because it is likely to provide a specific diagnosis that permits the administration of more specific therapy. In the interim, symptomatic treatment should be administered.

CONCLUSIONS

Painful neuropathies are a diverse group of disorders with many clinical similarities. The natural course of the disease for each disease entity is determined by the underlying etiology. The approach to pain and symptoms assessment and the treatment strategies are similar, although the treatment of each clinical entity should be based on the underlying etiology. A growing number of adjuvant analgesics offer an opportunity for control of pain in these disorders.

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CHAPTER 20

Complex Regional Pain Syndromes—Type I: Reflex Sympathetic Dystrophy, and Type II: Causalgia

Bradley S. Galer, Lauren Schwartz, and Roger J. Allen

Of all the chronic neuropathic pain syndromes, none has perplexed patient, clinician, and scientist more than the complex regional pain syndromes (CRPS), heretofore known as *reflex sympathetic dystrophy* (RSD) and *causalgia*. Although much has been written about these disorders, unknowns include the pathophysiology, natural history, and useful therapies for these syndromes. Much of the past literature was descriptive, based on authorities' personal clinical experience, which most likely does not adequately reflect the true clinical spectrum of these disorders and also suffers from selection bias. Thus, writings that have been accepted more or less on faith as clinical fact are being reanalyzed and scientifically evaluated to assess whether they are scientifically sound or rather merely clinical folklore. Several task forces of the International Association for the Study of Pain (IASP) have been formed to try to answer many crucial questions in the quest for a better understanding and improving the treatment of the CRPS disorders.

Throughout this chapter the currently accepted taxonomy, *CRPS*, is used when CRPS and RSD or causalgia can be used interchangeably. However, when older writings and studies have described or assessed patients with *RSD* or *causalgia*, these older terms are used to be true to these reports.

HISTORICAL PERSPECTIVE

Causalgia

The initial reports of causalgia stem from descriptive writings of wartime injuries. In 1862, Paget described patients with “distressing” pains in the fingers after nerve injury that had associated “nutritional changes” (1). The term *causalgia* was first used by Silas Weir Mitchell in an 1867 monograph, *United States Sanitary Commission Memoirs* (2):

> Causalgia—There is, however, one species of pain arising out of nerve wounds which had never been described except by my colleagues and myself, although the state of skin which is usually found with it had been spoken of by Mr. Paget, who seems to have seen it only in association with common neuralgic pains. In writing this peculiar kind of suffering, I felt that it would be well to give it some more convenient name than merely “burning pain,” and in accordance with the suggestion of my friend, Professor Robley Dunglison, I have therefore adopted the term Causalgia as being both descriptive and convenient.

Mitchell also described localized skin changes, “glossy skin,” and increases in skin temperature, which he stated may or may not accompany causalgia (3). In 1920, the Nerve Injuries Committee of the British Medical Research Council defined *causalgia pain* as: (a) spontaneous; (b) hot and burning in character, intense, diffuse, persistent, but subject to exacerbations; (c) excited by stimuli that do not necessarily produce a physical effect on the limb; and (d) tending to lead to profound

changes in the mental health of the patient (4).

During World War II, nerve injuries were also noted at times to result in causalgia pain that may be associated with other focal changes. At that time, it was thought that the intermittently occurring temperature changes, skin color changes, and bone changes developed as an independent problem, and perhaps were related to disuse of the limb secondary to the severe pain and were not necessarily caused by a distinct pathophysiologic event (5).

Reflex Sympathetic Dystrophy

The first reported descriptions of a nonneuralgic chronic pain disorder associated with localized vasomotor changes were in 1877 by Wolff (6) and in 1895 by Kummell (7). Similar case descriptions were published by Sudeck in 1900 (8), Fontaine and Herrmann in 1933 (9), Detakats in 1937 (10), Livingston in 1938 (11), and Homans in 1940 (12). Evans was the first to use the term *RSD* in 1946 to describe a group of patients with chronic pain and skin changes (13).

In the 1953 first edition of this text, Bonica suggested that all conditions with pain and associated focal vasomotor abnormalities should be “consider[ed] …under one all-inclusive term …reflex sympathetic dystrophy” (14). Before this time, many differently named syndromes had been described by different medical specialists for apparently the same disorder, such as *minor causalgia, posttraumatic spreading neuralgia, posttraumatic vasomotor disorders, Sudeck's atrophy, sympathalgia, algodystrophy*, and *shoulder-hand syndrome*. All of these disorders reflected a similar symptom complex characterized by pain, vasomotor skin changes, functional impairment, and various degrees of trophic changes that usually followed a musculoskeletal trauma, although certain characteristics may have been more prominent in certain of these conditions. Thus, because of these similarities, Bonica suggested that “all of them be considered under the generic term ‘reflex sympathetic dystrophy’” (14).

Bonica and many of his colleagues believed that the major underlying etiology of RSD was a disturbance in the sympathetic nervous system. This belief stemmed from their own clinical experience that most of their patients with RSD reported pain relief with sympathetic nerve block. In addition, it was thought that the unusual associated vasomotor changes associated with RSD, such as the focal skin color and temperature changes, had to be caused by abnormal sympathetic tone in the involved limb, hence the term *dysautonomic signs*.

Complex Regional Pain Syndrome

Many medical disorders have no clear single diagnostic “gold standard” (e.g., known measurable etiologic process or laboratory test result) that unequivocally indicates the presence or absence of the disorder. Most disease states reflect a spectrum of associated signs and symptoms. Often no prototypic signs and symptoms define the presentation of a given disorder across all cases. Thus, development of standardized, reliable diagnostic criteria and decision rules to identify disorders is the only way to allow adequate generalizability for appropriate treatment selection and identification of reproducible research samples. Medicine continually attempts to classify symptoms and signs into distinct categories with the goal of achieving standardized diagnostic criteria and hence leading to improved understanding of symptom/sign pathophysiology and eventually to improved treatment (15).

Why Rename the Clinical Syndrome?

Even though Bonica's intent was that the “all-inclusive term (reflex sympathetic dystrophy) serve the very purpose of coordinating and crystallizing our thoughts about the general subject, and in this manner helps to avoid confusion” (14), over the ensuing decades confusion continued because no single diagnostic criterion had been widely accepted by clinicians and researchers worldwide. Hence, patients evaluated by one physician or researcher diagnosed with RSD (or causalgia) may or may not have obtained the same diagnosis from another evaluating physician. This lack of consensus and the confusion with regard to RSD and causalgia diagnostic criteria have retarded clinical research. Little progress has been made regarding these disorders' pathophysiology. Therapy and patient outcomes continue to be poor.

In 1993, a consensus group of pain medicine experts (a Special Consensus Workshop of the IASP) gathered with the defined task of reevaluating the clinical syndromes of RSD and causalgia (16). It was agreed by this group that these disorders were characterized by controversy and confusion with regard to diagnostic criteria, pathophysiologic mechanisms, and effective therapies. Therefore, this international consensus group agreed to dismantle the terms *RSD* and *causalgia*, to admit the field's ignorance, and to think anew about patients who present with severe disabling pain after soft tissue injury or nerve injury associated with regional abnormalities in skin color, skin temperature, abnormal sudomotor activity, skin sensitivity, and motor difficulties. Additionally, it was increasingly apparent, with increased worldwide clinical experience, that many, if not most, patients with this clinical syndrome did not obtain cures or even significant long-term benefit from sympathetic nerve blocks. This feature was an important tenet to Bonica's and others' writings. As Boas, a participant in the 1993 conference, wrote:

> …there was agreement that not all patients referred under this RSD banner met the classical case scenario, and many of those who met diagnostic criteria responded poorly to long-term treatment. Variability in symptoms and signs over time, a lack of consistency in supportive diagnostic testing, and lack of responsiveness to sympathetic blockade belied the simplistic elements inherent in the mechanistic label of RSD. Participants agreed that the use of the term RSD had lost its usefulness as a clinical designation and had also become an indiscriminate diagnosis for patients showing elements of neuropathic pain or resistance to therapy. Therefore, the need to develop alternative concepts and nomenclature was accepted (17).

Thus, at the historic meeting of 1993 it was decided to rename these syndromes as CRPS for several reasons. First, little agreement existed among those from different medical fields and among those from different parts of the world as to the diagnostic criteria and appropriate therapies for RSD and causalgia. Second, much medical folklore exists with reference to RSD and causalgia based on early anecdotal personal physician experiences that have either not been proven in a scientific manner or are not consistent with a more extensive worldwide clinical experience. Last, most authorities agree that many patients do not demonstrate the classically described *dystrophic signs*, such as atrophy and changes in skin, nails, and hair.

Complex Regional Pain Syndrome Criteria

The diagnostic criteria for CRPS as defined in 1993 were accepted by the IASP classification committee and published in 1994 (18). These diagnostic criteria were meant to be a starting point, not to be written in stone. The criteria should and must evolve and change after the results of scientifically performed validation studies, something that had not been done with RSD and causalgia.

Unlike the prior criteria of RSD and causalgia, the diagnostic criteria for CRPS are purely clinical (i.e., no need exists for laboratory testing or sympathetic block). All that is needed is a history, pain and symptom description, and physical signs meeting the needed diagnostic criteria. [Clinically based diagnostic criteria without laboratory testing have been successfully used in psychiatry (i.e., *Diagnostic and Statistical Manual*) and headache (i.e., International Headache Society Criteria).]

The consensus group divided the disorders based on the type of injury that apparently initiated the disorder: Type I follows a soft tissue injury, akin to RSD, whereas type II follows a well-defined nerve injury, akin to causalgia. Types I and II are otherwise identical, with the exact same diagnostic symptoms and signs. Although the two types of CRPS differ in the type of inciting injury, different pathophysiologic events that follow their respective trauma and result in CRPS I or II have not been identified. In addition, as noted later, differences in responsiveness to therapeutic interventions also have not been noted. Furthermore, at times, it is not possible to state whether a patient's CRPS followed injury to nerve, soft tissue, or both, such as CRPS that develops after carpal tunnel surgery.

Complex Regional Pain Syndrome Type I

- The presence of an initiating noxious event, or a cause of immobilization
- Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event
- Evidence at some time of edema, changes in skin blood flow (skin color changes, skin temperature changes more than 1.1°C difference from the homologous body part), or abnormal sudomotor activity in the region of pain
- This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Complex Regional Pain Syndrome Type II

- The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve
- Evidence at some time of edema, changes in skin blood flow (skin color changes, skin temperature changes more than 1.1°C), or abnormal sudomotor activity in the region of pain

- This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Acceptance of the Complex Regional Pain Syndrome Criteria

Since its inception, the CRPS criteria have been criticized by some as being too vague and perhaps allowing for the overdiagnosis of this syndrome. For instance, as it is currently written, it is unclear how many symptoms and signs are necessary to make the diagnosis. The phrase “at some point in time there must be evidence of” is ambiguous. How many symptoms are necessary? How many signs must be documented on physical examination? The current criteria do not adequately define the minimal requirements for diagnosis.

Another issue with the CRPS diagnostic criteria is that these empiric criteria discarded several symptoms and signs that had been used in prior diagnostic constructs, including burning pain, dystrophic symptoms and signs, and motor abnormalities. Was it correct not to include these abnormalities in the new diagnostic criteria?

Complex Regional Pain Syndrome Validation Studies

The CRPS criteria are plastic and were written with the intent of performing validation studies, the results of which should refine the criteria. Thus, it was acknowledged that part of the process must be to study the consensus-written CRPS criteria and then reshape them as the data dictate.

Thus, to address these issues and to validate the new criteria, the IASP has formed a multicenter CRPS research group. Several members of this group first reported a small single-center empirical validation study that concluded that the 1994 CRPS criteria overdiagnose the disorder and that patient-reported symptoms can be useful diagnostically without confirmatory physical signs (15). Data from this small study confirmed that several of the classic symptoms and signs that had been discarded in the CRPS criteria, such as burning pain and dystrophic symptoms and signs, were not useful, but that the addition of motor neglect signs to diagnostic criteria may improve diagnostic accuracy (15). This study also demonstrated an extremely high false-positive percentage using the criteria as currently written, noting that nearly 40% of painful diabetic neuropathy patients met the sign and symptom diagnostic criteria for CRPS.

An extensive six-center study of 123 patients meeting IASP criteria for CRPS also analyzed the signs and symptoms of CRPS for internal validity (19). Based on the results of this comprehensive analysis, the authors proposed the following as a first revision of the CRPS criteria: (a) criterion 1 (presence of an initiating event) should be dropped; (b) the presence of symptoms and signs should be divided into distinct necessary criteria; (c) patients must have at least two of the following *symptoms*: sensory (hyperesthesia), vasomotor (temperature, skin color abnormalities, or both), sudomotor/fluid balance (edema, sweating abnormalities, or both), and motor (decreased range of motion, weakness, tremor, neglect, or all); (d) patients must have at least two of the following *signs*: sensory (allodynia, hyperalgesia, or both), vasomotor (objective temperature, skin color abnormalities, or both), sudomotor/fluid balance (objective edema, sweating abnormalities, or both), and motor (objective decreased range of motion, weakness, tremor, neglect, or all). These newly recommended CRPS criteria will be evaluated and validated as the process continues.

Sympathetically Maintained Pain

Definition

The term *sympathetically maintained pain* (SMP) is commonly used by clinicians to describe patients who have CRPS (Fig. 20-1). However, all too frequently the term is used incorrectly. SMP is defined as “pain that is maintained by sympathetic efferent innervation or by circulating catecholamines” (16). Thus, SMP is not a clinical diagnosis, but rather an assumed pain mechanism. The term SMP should only be used in clinical practice to describe a patient's report of pain relief after a sympatholytic procedure (i.e., if a patient reports good pain relief after a sympathetic block, then that patient can be said to have SMP).

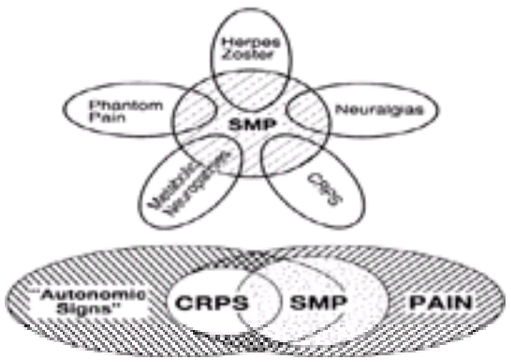

Figure 20-1. Relationship between sympathetically maintained pain (SMP) and selected painful conditions. This is meant to be a conceptual framework and the magnitude of the intersection between sets is not intended to represent a quantitative relationship. Sympathetically maintained pain may exist as an entity not associated with any other condition. The list of associated conditions is not meant to be exhaustive. (CRPS, complex regional pain syndrome.) (From Stanton-Hicks M, Janig W, Hassenbusch S, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain* 1995;63:127–133, with permission.)

Complex Regional Pain Syndrome and Sympathetically Maintained Pain

SMP cannot be used interchangeably with CRPS. SMP is a pain mechanism, whereas CRPS is a clinical diagnosis. By definition, SMP cannot be established by the presence of *dysautonomic* symptoms and signs, such as skin color changes, skin temperature changes, and sudomotor abnormalities. Patients with CRPS may or may not have SMP. In fact, it is believed that the majority of CRPS patients do not have SMP, but instead have sympathetically independent pain. Moreover, response to sympathetic block may be partial and thus, at least theoretically, a CRPS patient may have components of SMP and sympathetically independent pain.

Additionally, patients with other distinct chronic neuropathic pain syndromes without these symptoms or signs, such as peripheral neuropathies and postherpetic neuralgia, may also report significant pain and symptom relief with sympathetic blockade, and thus could be said to have SMP as well (17,20,21 and 22).

Flawed Sympathetically Maintained Pain Assumptions

If a patient reports pain and symptom relief after a sympathetic block, it has been assumed that the mechanism of relief is caused by the anesthetic effect on the sympathetic fibers (i.e., a reduction in focal sympathetic hyperactivity) (14,23). However, such simplistic thinking may be faulty based on several lines of evidence: (a) after selective sympathetic blockade (with normal volume), systemic absorption of local anesthetic results in local anesthetic serum concentrations similar to those obtained with intravenous lidocaine infusion, thereby potentially altering activity in other regions of the nervous system besides the sympathetic nervous system (22,24,25); (b) spillage of local anesthetic onto adjacent nonsympathetic nerve fibers has been documented after selective sympathetic blockade (26); (c) degree of sympathetic dysfunction does not correlate with degree of pain relief obtained from sympathetic blockade (20,27,28); (d) time of onset and duration of pain relief do not correlate with the timing of sympathetic block (22,29); and (e) no correlation has been reported between RSD affected limbs' catecholamine concentration and pain relief after sympathetic blockade (30).

Thus, a CRPS patient who reports pain relief after a sympathetic block by current definition has SMP. Yet whether this patient's pain is generated by abnormal hyperactivity in the regional sympathetic nervous system innervating the CRPS body region is not known (22,31). Therefore, stating that a patient's pain is being generated by abnormal activity in the autonomic nervous system based on a report of pain relief from sympathetic blockade can only be considered a hypothetical assumption.

EPIDEMIOLOGY

No well-designed prospective study has assessed the epidemiology of CRPS, RSD, or causalgia in the general nonmilitary population. Although several studies have reported some epidemiologic data, they suffer from selection bias and therefore cannot be generalized to the CRPS population as a whole. Only a few published reports have obtained even basic demographic data.

Age

A prospective study of RSD patients from a tertiary referral surgical clinic in the Netherlands reported a median age of 41 years (range, 4 to 84 years old), with a mean duration of RSD of 405 days (range, days to 20 years) (32). A retrospective study of 134 patients referred to a tertiary university pain center in the United States reported a mean age of 41.8 years (range, 18 to 71 years), mean age at time of injury of 37.7 years (range, 14 to 64 years), and a mean duration of CRPS symptoms before pain center evaluation of 30 months (range, 2 to 168 months) (33).

Gender

The large study from the Netherlands found a female to male ratio of 3:1 (32), and a 2.3:1 ratio was found in the U.S. pain clinic study (33).

Location

Most patients have CRPS involving a single limb. Involvement of the upper versus lower limb has been reported fairly equally, with one study observing 59% upper extremity and 41% lower extremity involvement (34) and another 44% upper extremity and 48% lower extremity involvement (33). This latter study reported CRPS occurred in 38% on the left and 46% on the right. Bilateral limb involvement has been reported to occur in 11% to 16% of patients (33,34).

Inciting Injury

The large prospective study from the tertiary surgical clinic reported 65% followed trauma, usually a fracture, 19% an “operation,” 2% an inflammatory process, and 4% “after various other precipitants, such as injection or intravenous infusion” (32). The United States study from a chronic pain clinic reported 77% of their patients had a known event that resulted in the development of CRPS, 29% strain or sprain, 24% postsurgical, and 11% contusion or crush injury (33). Additionally, both studies identified patients with no known precipitating cause, ranging from 10% to 23% (32,33).

Direct damage to central nervous system structures has also been reported to be an initiating cause of RSD, including spinal cord injury (35) and brain injury (36).

Legal and Workers' Compensation Issues

As most cases of CRPS develop after a traumatic event, it is reasonable to expect issues regarding on-the-job injury and other potential litigious issues to arise. Of a group of patients evaluated in a United States chronic pain clinic, only 17% had a lawsuit, whereas 54% had a workers' compensation claim related to their CRPS (33) (this clinic had a contract with the state workers' compensation system and thus biases these data).

Only one study has assessed the type of job in which the injury occurred that resulted in the development of CRPS. This chart review study found that of the work-related injuries, 14% occurred in service occupations, such as restaurant workers, bakers, and police officers; 8% in clerical and sales professions; 7.4% in manual labor workers such as construction workers; 5.2% in professional, technical, or managerial; 5.2% in agricultural, fishing, or forestry occupations; 4.4% in benchwork occupations, such as assembly workers; 2.2% in machine trades, such as mechanics; and 4.4% in miscellaneous occupations, such as bus drivers and truck drivers; in 5% of the cases, the occupation could not be determined from the chart (33).

Health Care Use

Of patients referred to a university-based chronic pain clinic in the United States, the mean number of physician evaluations before the pain clinic evaluation was 4.8 (range, 1 to 20) (33). Before and during treatment in this multidisciplinary pain center from 1992 through 1997, the majority of CRPS patients were given medication trials, including 78% tricyclic antidepressants (whether these drugs were prescribed for pain, sleep, a psychological disorder, or all is unclear), 38% selective serotonin reuptake inhibitor antidepressants, 60% anticonvulsants, and 70% opiates (33). This study also noted 88% obtained physical therapy, 45% occupational therapy, 82% nerve blocks (mean of six blocks per patient; range, 0 to 20), 50% psychological treatment, and 6% spinal cord stimulation. Whether these data can be generalized is unclear, because treatment of CRPS most likely varies tremendously between individual providers, different medical specialties, types of clinics, and region of the world in which treatment is obtained.

Risk Factors to Developing Complex Regional Pain Syndrome Do Exist

No definitive risk factors have been identified that predispose individuals to developing CRPS. Factors that have been postulated include extensive immobilization (and disuse), cigarette smoking, genetic predisposition, and psychological factors.

Immobilization

Although not well studied, available clinical data suggest that immobilizing an injured limb for an extended period of time may be a risk factor for the development of CRPS. A prospective study demonstrated CRPS symptoms and signs in normal individuals casted after an orthopedic procedure; however, these patients immediately participated in an active physical therapy program and did not develop CRPS or any other chronic pain syndrome (37). Similar findings of abnormal symptoms and signs akin to CRPS have been documented in animal models of limb immobilization (38,39). Retrospective chart review studies have reported rates of prior immobilization in established CRPS patients of 42% to 47% (33,40).

Smoking

One retrospective survey of refractory RSD patients identified smoking as a possible risk factor for the development of RSD (41). However, a similar retrospective survey did not confirm this association (42). Clinical experience minimizes this finding, because many CRPS patients do not smoke, many who do smoke can show improvement, and some nonsmoking patients may be refractory to treatment. Neither study performed relevant multifactorial analysis or used chronic pain patients as controls.

Genetic Factors

One small pilot study reported a possible genetic predisposition to the development of CRPS (43). Also, a retrospective clinical study hypothesized that rare individuals afflicted with RSD may then be predisposed to recurrences (34). These studies are preliminary and are based on an extremely small number of patients; therefore, definitive conclusions should not be drawn from these data.

Psychological Factors

It is important to note that the mind plays a role in all forms of suffering and dysfunction, and it is the mind that copes and adapts or fails to do so (44).

Researchers and clinicians have posed the question as to whether specific psychological factors may predispose certain individuals to develop RSD (45,46 and 47). Many claims have been made, most in the clinical literature, that certain long-standing psychological factors or issues predispose individuals to develop RSD, such as history of psychological or psychiatric disorders or childhood abuse. In addition, some authors have proposed the existence of psychological characteristics of patients may be etiologic risk factors for the development of RSD. For instance, Lankford stated, “It has long been recognized, but seldom discussed in the literature, that only a certain type of patient develops RSD” (48). However, it must be stressed that the research has not borne out this claim. Models that consider multiple etiologic factors are more appropriate conceptually for this disorder, especially when considering the role of psychological, psychiatric, and behavioral factors.

Most research studies have not shown evidence for an *RSD personality* or specific personality factors that predispose a person to develop CRPS. A thorough review of the literature concluded that these concepts do not hold up to scientific scrutiny (49). Other studies have found that anomalies in personality and behavior decreased after relief of the pain, suggesting that such abnormalities were likely the sequelae of causalgia or RSD rather than the cause (47,50). A few studies have attempted to evaluate premorbid personality characteristics retrospectively. One such study found that 12 of 19 active duty servicemen with RSD had records indicating conflict with authority and slow promotion rates (51), whereas another study reported that 6 of 11 patients who developed RSD as a procedural complication had evidence of premorbid dependent personality characteristics (52). Interpretation of these studies is limited by their small sample size and by the lack of appropriate comparison groups.

Regarding major psychological or psychiatric illness, most studies have focused on a history of depression, anxiety disorders, or substance abuse in this population, as with other chronic pain conditions. It has been proposed that a history of psychological difficulties may be evidence of a vulnerability that may limit adaptive coping with an injury, thus promoting more intractable pain, disability, and unusual somatic symptoms. Another interpretation has been that the RSD symptoms and disability may be a mask for more serious underlying psychiatric disorder. This latter theory has received more attention in the literature.

A long history of discussion exists in the general chronic pain literature regarding the intimate relationship between chronic pain and depression (53). It is well known that individuals with all types of chronic pain have higher rates of depression, and individuals with depression have higher rates of chronic pain. Clinical lore and research suggest that although treatment of psychological and psychiatric symptoms is often significantly helpful in decreasing pain, disability, and improving response to pain treatment (54,55), it is rarely the magic cure for chronic pain. The current belief is that for the majority of patients, chronic pain is not a mask for depression or other psychiatric disorder, although a high rate of co-occurrence exists, and both warrant clinical attention and treatment. A specific study evaluating this issue for individuals with CRPS has not been conducted.

In a retrospective chart review of 134 CRPS patients evaluated at a chronic pain clinic in the United States, 26% had a premorbid history of depression and 24% had a history of problems with anxiety, based on a clinical interview using *Diagnostic and Statistical Manual*, third edition, criteria conducted by a licensed psychologist (56). Another study reported that 37% of RSD patients had a history of psychiatric problems or *emotional disturbances* before the onset of RSD (57); specifics regarding the nature of these psychological difficulties were not detailed in this report. As with other chronic pain conditions, no study has been able to determine the role of psychiatric disorders in the development of CRPS. More likely, psychological disorders are comorbid conditions that develop because of the pain, disability, and poor coping abilities associated with CRPS.

The literature suggests wide variance in substance abuse rates among individuals with chronic pain that may not be significantly higher than the general population. A study of CRPS patients evaluated in a pain clinic observed that 30% of patients with CRPS had a history of substance abuse, as defined by *Diagnostic and Statistical Manual*, third edition, criteria (56). The reported prevalence of drug and alcohol abuse or dependence in general chronic pain patients ranges from 3% to 19% (58). The national alcoholism prevalence is thought to be 14% to 18%. Thus, preliminary research suggests that CRPS patients may have slightly higher rates of substance abuse history than patients with other chronic pain disorders. However, this finding needs to be verified by other studies. Furthermore, clinical experience suggests that a small minority of patients presenting to a pain clinic with CRPS have a true addictive disorder.

As with many other chronic pain conditions, the issue of child abuse history among patients with CRPS has been raised (44,59). However, only one study has systematically evaluated reported histories of child abuse among patients with RSD. This study reported that sexual, physical, and emotional abuse, as well as cumulative trauma experiences, were equally distributed among all three of the chronic pain groups studied, RSD, chronic local neuropathy, and back pain (60).

Thus, although some studies have found higher rates of psychological difficulties among RSD patients as compared with non-RSD chronic pain patients (61,62), the findings are far from consistent (63,64). In any chronic disorder, failures of coping and adaptation among patients frequently occur, especially among specialty (pain) clinic samples. The data suggest that psychological and psychiatric difficulties occur in CRPS patients as frequently as in other chronic pain disorders, and that such difficulties exacerbate the patient's overall suffering and impair coping efforts. Additionally, the prevalence of psychiatric disorders and psychological difficulties is highest in the most refractory cases, such as those patients seen in specialty pain clinics. As Ciccone and colleagues have stated, “[data] raises further doubt about supposed psychological origins of RSD …and the burden of proof is upon those who advocate the non-organic hypothesis” to provide credible evidence of primary psychological factors in the etiology of RSD (60).

PATHOPHYSIOLOGY

The pathophysiology of CRPS is not known. Although much has been learned with regard to the mechanisms underlying pain after peripheral nerve injury, minimal progress has been made in understanding the pathophysiologic events that result in the evolution of CRPS, whether after a well-defined nerve injury or soft tissue trauma. Most likely, CRPS develops and is maintained by abnormalities throughout the neuraxis, including peripheral nervous system, central nervous system, and autonomic nervous system. In addition, at least in some patients, the involvement of regional myofascial dysfunction may play an important role in CRPS development. The degree to which each system is involved probably varies from patient to patient (Fig. 20-2). Furthermore, the entire nervous system and musculoskeletal system are further altered by psychological factors, ongoing stress, and disuse that occur after the development of CRPS. Thus, CRPS is most likely not reflective of a single pathophysiologic event, but rather is a heterogeneous disorder with several different underlying pathophysiologic mechanisms that result in similar clinical symptoms and signs.

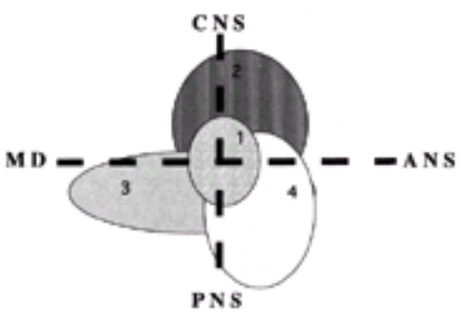

Figure 20-2. A model for understanding the heterogeneity among pathophysiologic processes and sites involved in the development and maintenance of complex regional pain syndrome (CRPS). Potential sites of abnormality among CRPS patients include the peripheral somatic nerves (PNS), the central nervous system (CNS), which includes spinal cord and all supratentorial events, such as psychological processes, the autonomic nervous system (ANS), both its peripheral and central components, and myofascial dysfunction (MD), which may be primary or secondary. Four theoretical CRPS patients are depicted: Patient 1 has an equal degree of PNS, CNS, ANS, and MD abnormal function responsible for CRPS symptoms; patient 2 has mostly CNS, ANS, and MD dysfunction; patient 3's symptoms derive mostly from ANS and MD; and patient 4's CRPS symptoms develop from PNS and ANS pathophysiologic processes.

More Questions Than Answers

Some basic questions regarding the pathogenesis of CRPS remain to be answered:

- Why do only a small minority of patients develop CRPS after a simple soft tissue injury, such as strain, sprain, or contusion? Quite often, these patients have had similar injuries in the past and did not develop the symptoms of CRPS.
- Why do only a small minority of patients with a well-defined nerve injury develop CRPS? Some patients with apparently the same injury do not develop chronic pain, others only develop a chronic neuropathic pain without *dysautonomic signs*, and a rare few develop a chronic neuropathic pain associated with CRPS signs and symptoms.
- Are there structural differences in the injuries to soft tissue or nerve that cause CRPS?
- Does the nervous system react to the injury aberrantly, causing CRPS?

- Was the patient's internal or external environment different at the time of injury, thus resulting in an altered physiologic response to the injury resulting in CRPS?
- Is the sympathetic nervous system involved in the development or maintenance of CRPS?
- Can some or all of the symptoms and signs of CRPS be explained by disuse alone?
- Is there a genetic predisposition to CRPS?
- Why do patients with CRPS vary significantly with regard to the type and degrees of vasomotor, sudomotor, and motor abnormalities?
- Is there only one pathophysiologic mechanism? Or could there be several different possible initiating mechanisms that resemble one another in their clinical presentation? Thus, could subtypes of CRPS exist with distinct pathophysiologic mechanisms that respond differentially to different therapies?

Postulated Mechanisms

Many authorities have hypothesized potential pathophysiologic mechanisms that result in the development of CRPS. Some of these postulated mechanisms are based on animal data, others on clinical experience, and others on pure speculation. No mechanism has definitive evidence proving its involvement in CRPS.

Aberrant Healing Response

After tissue injury, the body responds in such a way so as to promote healing, prevent complications, and thereby ensure survival. Thus, all aspects of healing should aim to improve the organism's odds of efficiently regaining full use of the injured body. Healing is promoted by the inflammatory response. Further bodily injury is prevented by guarding and protecting the damaged bodily region. CRPS has been hypothesized to be caused by an aberrant healing response, including exaggerated and persistent inflammation and guarding.

Exaggerated Inflammatory Response

Sudeck first hypothesized that RSD may be caused by the inflammatory reaction (65). Rubor, calor, dolor, tumor and functio laesa, the classic signs and symptoms of the inflammatory response, are all present in CRPS. Inflammation is a complex neuroimmunologic reaction. At the site of injury, peripheral A-d and C-fiber nociceptors transmit signals interpreted as pain in the brain and also release substance P and calcitonin gene–related peptide (CGRP) into the damaged tissues, which result in vasodilatation and increased vascular permeability (66). These neuropeptides cause the physical findings associated with inflammation, redness, warmth, and swelling. Also released into the injured tissues are bradykinin, leukotrienes, histamine, prostaglandins, and serotonin, all of which heighten these vascular changes in the local environment and cause nociceptor sensitization (66).

As part of the normal inflammatory response, the area of pain, skin sensitivity, and tenderness spreads into adjacent regions after a bodily injury. This spread of pain is thought to be caused by *secondary hyperalgesia*, central nervous system alterations resulting from the abnormal ectopic input from the periphery. These changes in the central nervous system have been hypothesized to involve *N*-methyl-D-aspartate receptors, substance P, CGRP, and nitric oxide (67,68). Thus, many of the hallmark signs and symptoms of CRPS are present in the normal postinjury setting, including skin color change, abnormal skin temperature, edema, and spreading pain and skin sensitivity. However, this symptom and sign complex normally remits spontaneously within several weeks of the injury, whereas in the CRPS patient these symptoms and signs continue and even progress seemingly inexplicably.

The authors of a large prospective study of 829 RSD patients concluded that their data support the concept of “an exaggerated regional inflammatory response” (32). Data also supporting this hypothesis include the observation of increased microvascular permeability for high-molecular-weight proteins in early RSD (69) and high-energy phosphate metabolism impairments in affected RSD limbs (70). Several studies, however, have demonstrated that bone-scan changes thought to be associated with an inflammatory response that subside with time in chronic RSD patients (69,71).

Protective Disuse

Another normal part of the postinjury reaction may explain some of the maintenance and progression of the CRPS symptom and sign complex: protection and decreased use of the injured body part. After injury, the organism naturally protects and guards the injured body part to optimize healing and prevent reinjury. With normal healing, the organism gradually increases the use of the injured region, which then aids in the eventual full recovery and reintegration of the body part into the organism's normal sense of self. However, the CRPS patient continues to protect and guard the injured and painful limb either directly because of recommended medical treatment, such as casting or splinting, because of the patient's volitional disuse for fear of pain exacerbation, or because of a neurologic neglectlike syndrome.

The classic teaching has been that this prolonged guarding of the involved limb is volitional, caused by the patient's fear of heightened pain if the limb is reinjured or accidentally touched (14). A more recent hypothesis, that a neurologic neglectlike disorder may be present in some CRPS patients of this phenomenon, has been postulated (72). Similar to a stroke patient with a neglect syndrome, such CRPS patients' involved limbs are seemingly out of conscious awareness. The patient states the need to bring full attention, mental and visual, to the CRPS limb to move it proficiently, so-called motor neglect, which is confirmed on physical examination testing. In addition, the patient may state that the limb “feels like it is not part of me anymore” or “feels disconnected from my brain and body” (72). It has been postulated that this neglect may be caused by neuroplastic changes in the brain, perhaps involving the central autonomic nervous system (72).

Regardless of the reasons underlying the disuse of the limb, the lack of normal movement of the body part most likely causes further bodily dysfunction in the soft tissues and nervous system. Many of the symptoms and signs of CRPS may, at least in part, be solely caused by the patient's lack of use of the limb. For instance, by not using an extremity over an extended period of time it may become swollen (dependent edema), cold (decreased blood flow), and develop trophic changes (decreased blood flow). A small prospective study revealed that patients who have been casted after an orthopedic procedure for 4 to 6 weeks develop many of the CRPS symptoms and signs, but these resolve once the patients partake in the normally prescribed active physical therapy (37). Brain-injured patients may develop RSD in a limb that has been weakened or is part of a neurologic neglect syndrome (36).

Several animal studies have demonstrated pain and nervous system changes caused solely by disuse of a limb. One study showed that immobilizing a rodent wrist with a plastic cast for 3 to 4 weeks resulted in significant allodynia and neuroplastic changes within the dorsal horn similar to those caused by nerve injury (i.e., sensitization of dorsal horn neurons) (38). Another rodent study demonstrated the presence of mechanical and cold allodynia that persisted for several weeks after 7 days of hind paw immobilization (39).

Dysfunctional Sympathetic Nervous System

The classic teaching has been that RSD and causalgia were caused by hyperactivity of the sympathetic nervous system (14). This belief has come under serious scrutiny during the 1990s, with much scientific and clinical evidence dismissing this hypothesis. The following evidence argues against the sympathetic hypothesis:

- The majority of patients who meet diagnostic clinical criteria for RSD do not obtain significant pain relief from sympathetic blocks (73,74).
- Some patients without the signs and symptoms of RSD and causalgia report pain relief with sympathetic blocks (20,74).
- Plasma catecholamine concentrations are actually lower in RSD-affected limbs (30,75).
- Laser Doppler flowmetry results suggest that vascular disturbances in RSD are not caused by constant overactivity of sympathetic vasoconstrictor neurons (76).
- Microneurography testing shows no increase in sympathetic activity or discharge pattern in RSD patients subjected to arousal and mental stress (77).
- No histochemical evidence of an atypical distribution of sympathetic fibers is found in CRPS hyperalgesic skin (78).
- Skin temperature does not correlate with the activity of sympathetic vasoconstrictor neurons (79).

Involvement of the autonomic nervous system has been hypothesized to occur via adrenergic supersensitivity that develops in the peripheral nervous system or within the spinal cord, or both (30). Others have postulated that an upregulation of a $_1$-adrenoreceptors on nociceptor afferents results in pain and SMP (80). Further evidence for a possible role of adrenergic supersensitivity is the observation that locally infused adrenaline results in a worsening of pain in RSD patients (81). However, similar findings of a worsening of pain and allodynia with subcutaneous injections of epinephrine have been documented in a controlled study of postherpetic neuralgia patients (82).

An alternative hypothesis has been published postulating that, after a limb is injured, endogenous opioid modulation normally increases in regional sympathetic ganglia to prevent excessive autonomic activity in the limb, but that in patients with RSD this local opioid modulation does not occur, resulting in “autonomic features of opioid withdrawal” (pain, increased pilomotor activity, increased sweating, and vascular instability) in the affected limb, which are then perpetuated by disuse of the

limb (83).

Myofascial Dysfunction

Several studies have documented significant myofascial dysfunction in many CRPS patients. Evans remarked on the seemingly high occurrence of “muscle cramps and spasms” in RSD patients (13). Also, Livingston's “vicious cycle” hypothesized excessive muscle spasm resulted in hypoxia and metabolites, which were an additional source of symptoms (84). A prospective study of 41 CRPS patients referred to a chronic pain clinic reported 61% had identifiable myofascial dysfunction in the proximal musculature, in which trigger point palpation resulted in a worsening of pain and other CRPS symptoms in the CRPS body region (shoulder girdle musculature for upper extremity CRPS and gluteal and lumbar paraspinous muscles for lower extremity CRPS) (85). This study also reported a higher prevalence of myofascial dysfunction in CRPS patients with upper (70%) versus lower (47%) extremity pain, a positive correlation between the presence of myofascial dysfunction and motor neglect, but no association between duration of CRPS symptoms and myofascial dysfunction.

If present, myofascial dysfunction may be primary or secondary. Because the patients in the previously mentioned study were evaluated many months after the onset of CRPS symptoms, these patients' myofascial dysfunction could have been present at onset and possibly be primarily responsible for the development of CRPS or, on the other hand, evolved from dysfunctional disuse and overuse of soft tissues. Regardless of whether myofascial dysfunction is primary or secondary, clinical experience suggests that, if myofascial dysfunction is present, patient improvement of pain and symptoms occurs when myofascial trigger points resolve.

Central Nervous System Abnormality

It is now accepted as scientific fact that adaptive changes occur acutely and chronically in the central nervous system after injury to the nervous system (68). Thus, damaged or dysfunctional peripheral nerve and soft tissue that result in the development of CRPS must also involve abnormal processes in the spinal cord and brain. The exact sites and pathophysiologic processes within the central nervous system that result in and maintain the pain and other signs and symptoms of CRPS are unknown, yet various sites have been postulated.

Spinal Cord. Leriche first hypothesized that a vicious cycle develops initially from a peripheral source that then results in chronic changes within the spinal cord (86). Later, Livingston proposed that abnormal impulses developed in self-sustaining loops within the dorsal horn, by either small peripheral nerve endings or major nerve trunks, which also eventually involved other neuronal systems, including the motor horn cells, which resulted in abnormal muscle activity and spasm (87) (Fig. 20-3). Roberts postulated a spinal cord mechanism in which sympathetic outflow stimulates low-threshold, myelinated mechanoreceptors, resulting in sensitized wide dynamic range neuronal activity (23).

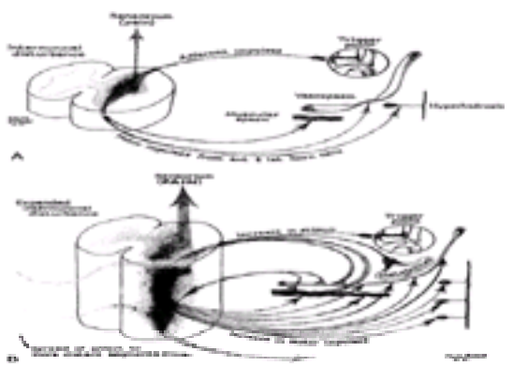

Figure 20-3. **A:** Schematic diagram to depict the physiopathologic mechanism of causalgia and other reflex sympathetic dystrophies. The early stages of the disturbances initiated by a fracture are shown. The afferent impulses from this trigger point reach the spinal cord wherein they set up disturbances of the internuncial pool. This results in increased activity of the anterior and lateral horn cells, which in turn produces increased motor activity of the affected segment. **B:** The fully established vicious circle with expansion of the internuncial disturbances and consequent involvement of other segments. (From Bonica JJ. *The management of pain*. Philadelphia: Lea & Febiger, 1953:973, with permission.)

Brain Mechanism. In 1943, deTakats and Moser each suggested that the brain may be mechanistically involved in RSD (88,89). The thalamus was hypothesized to be the primary area of dysfunction by Moser and Zikeyev (89,90). More recent evidence continues to point to the brain as being possibly involved in the development and maintenance of CRPS. After all peripheral bodily events, including peripheral nerve injury, neuroplastic changes in the brain occur (68). Data supporting the brain's involvement include the occurrence of RSD after brain injury and the anatomic distribution and spreading of CRPS symptoms and signs (91). Positron emission tomographic scanning has demonstrated altered thalamic activity in CRPS patients (92). Also, a neglectlike syndrome has been observed in CRPS patients (72), which, if present, must be the result of altered higher brain processing. Laser Doppler flowmetry results suggest that abnormal patterns of sympathetic vasoconstrictor neurons may be caused by thermoregulatory and emotional stimuli originating from the brain (76). It has been hypothesized that an important functional neuroanatomic region involved in CRPS is the central autonomic nervous system, which includes the insular cortex, amygdala, hypothalamus, and the periaqueductal gray; this central autonomic nervous system could theoretically link the complex clinical picture of CRPS, including the pain, vasomotor changes, sudomotor alterations, and motor abnormalities (72).

Psychological Factors

Similar to the discussion of proposed psychological risk factors for CRPS, several psychological and behavioral factors have been suggested as being integral in the pathophysiology of CRPS, including stress around the time of the injury and an abnormal behavioral response to the injured body part. A possible psychophysiologic mechanism that has been focused on is sympathetic nervous system hyperarousal.

An intriguing, but as yet unproven, hypothesis is that psychosocial stress at the time of injury or during the time of healing may play a role in CRPS development. It has been reported that a significant stressful event occurred before or concurrent with the inciting injury that precipitated RSD or CRPS in some patients. One study observed that 31 of 32 RSD patients referred for psychological or psychiatric evaluation reported experiencing a major life stress around the time of the onset of their RSD (46). Another observed that eight RSD patients recalled experiencing “an extraordinarily difficult period” coincident with the injury or trauma that triggered the RSD (93). A chart review study of CRPS patients referred to a chronic pain clinic found that 30 of 45 patients reported a significant stressful event 6 months before or after the inciting injury that precipitated their CRPS, with most of the patients reporting the event occurred within 6 months before the inciting injury (56).

It is well known that sympathetic arousal or stimulation can increase pain (50). Ecker suggested that RSD pain may be maintained or exacerbated by a feedback system of sympathetic arousal (94). Chronic states of hyperarousal could theoretically predispose an individual with an injury or trauma to developing CRPS. Some believe that sympathetic hyperactivity can account for certain RSD symptoms (95). It has been proposed that RSD symptoms, particularly hyperalgesia, may be related to a-adrenergic activity and that for an individual with a nerve injury, increased a-adrenergic activity associated with anxiety, life stress, or depression may contribute to the development and maintenance of RSD symptoms through sensitized receptors in the area of the injury (45). It has been demonstrated that life stress in the preceding 6 months results in disturbed a-adrenergic activity (96).

Overall, however, limited scientific data exist to support these theories beyond the seemingly high incidence of reported stress occurring before or immediately after the inciting injury or trauma. Additionally, the classic belief that RSD is primarily caused by hyperactivity of the sympathetic nervous system has come under scrutiny. Sympathetic nervous system mechanisms may only partially explain the development and maintenance of CRPS in all patients, or, more likely, may play a significant role in only a subset of CRPS patients.

It has also been hypothesized that patients' behavioral responses to an injury may be a key contributing factor in the development of RSD after a relatively minor injury (44). These responses can range from minimal guarding of the limb to complete immobility and atrophy of the affected area. Such guarding and disuse of the CRPS limb may be explained by extraordinarily high levels of fear of reinjuring the area, fear of worsening of pain with movement, neglect, or all three. Additionally, poor motivation caused by disincentives for wellness may account for at least part of the disuse phenomenon. However, it is almost impossible to assess the extent to

which a person's behavior reflects the experience of pain versus a reaction to more external factors (e.g., stress, solicitous responses from family, or compensation system demands); moreover, both factors may operate simultaneously in some patients. Patients' guarding and disuse behaviors can seem extreme and unusual to the outside observer and therefore are often misinterpreted. Further understanding of the possible roots of such behavior within the context of psychological and physical factors is crucial. Accurately evaluating the causes of such behavioral responses can be difficult, but it is critical when working clinically with these patients.

Psychogenic Factors

Finally, examining the usefulness of the dichotomy frequently discussed between *psychogenic pain* and *organic pain* is important. Ochoa and colleagues have written extensively that RSD and CRPS are primarily psychogenic in origin (97). This group bases their hypothesis on the fact that neurophysiologic testing does not show any defined abnormality and that many of their CRPS patients show *placebo responses* to their interventions. This line of reasoning is scientifically invalid and clinically dangerous for several reasons. First, by definition, a patient's electrodiagnostic testing must be normal to make the diagnosis of CRPS 1. Second, currently available electrodiagnostic and other neurophysiologic testing does not have the ability to assess many important neuropathophysiologic events that may be relevant to CRPS in humans, such as altered receptor affinity, aberrent synapse formation, altered central nervous system processing, and so forth (98). Third, most of their patient placebo responses are associated with single-blind placebo trials, in which conclusions may be biased, making such responses uninterpretable (99). Last, clinicians and scientists must realize that in all illness and disease, symptoms are most often the result of coexistent psychological and physiologic components. After all, psychological processes are actually neurophysiologic events, and physiologic processes may develop, worsen, or improve with different psychological states. These points are often forgotten, if not entirely overlooked, by Ochoa and colleagues. Thus, the schism between the psyche and the body is an artificial one that a true multidisciplinary approach replaces with a realization that a person's body, nervous system, and spirit are one.

Pathophysiology Conclusion

As outlined previously, much has been hypothesized about the possible pathogenesis and anatomic sites of dysfunction in CRPS. Although many authors of such hypotheses have discounted others' postulations, it is feasible that all hypothesized pathophysiologic sites and events may occur simultaneously or in sequence. Moreover, it may be that underlying the clinical picture of CRPS is a heterogeneous group of pathophysiologic mechanisms, which includes dysfunctional peripheral, central, and autonomic nervous systems, myofascial dysfunction, and psychological states, that result in a common set of clinical signs and symptoms. It also should be remembered that each of these *distinct* systems is integrally related to all others: One system does not act independently of all the others. Psychological distress (a neurobiological event) has direct physiologic effects on the entire neuraxis and the musculoskeletal system. Thus, each CRPS patient may differ with regard to the overall role each system plays in the development and maintenance of his or her unique set of CRPS symptoms and signs (see Fig. 20-2).

SYMPTOMATOLOGY

Few studies have prospectively evaluated RSD and CRPS patients' symptoms, signs, or both. The largest prospective study included 829 RSD patients and reported the following symptoms: paresis, 95%; pain, 93%; altered skin temperature, 92%; skin color change, 92%; limited range of motion, 88%; hyperpathy, 79%; hyperesthesia, 76%; hypoesthesia (stocking/glove), 69%; edema, 69%; altered nail or hair growth, 60%; muscle atrophy, 55%; incoordination, 54%; tremor, 49%; hyperhydrosis, 47%; and skin atrophy, 40% (32). A prospective multicenter study of 123 CRPS subjects evaluated by pain specialists reported the following frequencies of symptoms: color change, 86.9%; burning pain, 81.1%; decreased range of motion, 80.3%; edema, 79.7%; temperature asymmetry, 78.7%; weakness, 74.6%; hyperesthesia, 65.1%; sweating change, 52.9%; hypoesthesia, 44%; skin change, 24.4%; tremor, 23.7%; nail change, 21.1%; and dystonia, 20.2% (19).

Clearly, not all patients with CRPS suffer from the same constellation of symptoms or suffer to the same degree from each symptom. CRPS presents itself with a tremendous amount of variable symptoms. A spectrum of symptoms exist. It remains to be seen whether subpopulations of patients with CRPS exist within this large diagnostic category.

Correlation between Symptoms and Signs

When diagnostic criteria rely on a patient's self-reported symptoms, questions often arise about their validity. However, it should be noted that other diagnostic criteria that rely solely on patient self-reported symptomatology have undergone the rigors of validation studies, including the International Headache Society criteria for migraine and *Diagnostic and Statistical Manual* criteria for depression. Two studies have assessed the validity of using self-reported symptoms for the diagnosis of CRPS. These studies have reported that although patient self-reported symptoms are more frequent than objective signs, the pattern of frequencies is similar across signs and symptoms, suggesting that patient self-reported symptoms produce a more global assessment of the condition versus the objective signs, which reflect only a small *snapshot* of a CRPS patient's overall condition, which fluctuates from hour to hour and day to day (15,19). Thus, it appears that symptoms reported by patients have an important role in evaluating patients for CRPS.

Location of Symptoms

As with the classic descriptions of RSD and causalgia, CRPS most commonly occurs in a distal limb (i.e., foot or hand), although RSD has been reported in other body regions, such as the head, proximal limb, and genitalia (100). Applying the current diagnostic criteria, one finds that CRPS may occur in any body regions covered by skin; thus, CRPS cannot occur in the teeth, for instance, because changes in skin temperature, skin color, sudomotor activity, or all three are necessary. Why CRPS occurs more commonly in the extremities is not known, although possible reasons include the fact that limbs are involved most commonly in soft tissue injuries and, perhaps, because of the neuroanatomic and neurophysiologic uniqueness of these body regions.

Spreading and Recurrence

It has been well described that CRPS symptoms may spread proximally or to other body regions, including the contralateral limb, coined *mirror RSD* (18,84,100). However, it is important to distinguish between true spread of CRPS and the more common scenario of a spreading of symptoms apparently caused by myofascial dysfunction. For instance, most patients with upper extremity CRPS also develop shoulder girdle pain, neck pain, and often referred headache, whereas the lower extremity CRPS patient develops buttock and hip pain and low back pain.

An analysis of 1,183 consecutive RSD patients reported a recurrence incidence of 1.8% per patient per year (34). Recurrences occurred in the same or other limbs. This study noted that 53% of these recurrences were of spontaneous origin (i.e., no known precipitating injury), and that the duration between first and second RSD had a tremendous range, from 3 months to 20 years.

Pain Quality

Although the classic pain quality that has been ascribed to RSD and causalgia is burning pain, two separate CRPS validation studies have shown this not to be true (15,19). Bonica also mentioned that these patients may not describe their pain as burning (14). In fact, the pain of CRPS is typically described by its sufferers with several different pain descriptors. A prospective study using the Neuropathic Pain Scale reported that the most prevalent pain descriptors endorsed by CRPS patients were deep, sharp, sensitive, and hot (101). Many CRPS patients complain most of a deep aching pain, described by them as “like my limb has just been removed from freezing water and is thawing out.”

Pain Triggers

As with many chronic pains, the pain and other associated symptoms of CRPS may be worsened by physical contact, changes in environmental temperature, and emotional stress (14,18).

Edema

The painful body region may have mild to frank pitting edema. Not uncommonly, patients may describe a sensation of swelling or fullness without actual physical evidence of edema (“like when a dentist gives you Novocain and your lip feels big”).

Skin Temperature Changes

The involved body region may be hotter or colder than the contralateral region. Moreover, in any one patient, the same region may fluctuate from hot to cold within hours (76). Fluctuations in abnormal skin temperature have also been demonstrated in animal models of nerve injury (102). The difference in temperature between the affected and unaffected limb has been shown to be dependent on the external temperature (103).

Although not well described or differentiated in the literature, when patients admit to temperature changes, it may mean two different things: (a) the CRPS body region's skin has a palpable skin temperature difference as compared with the contralateral limb; or (b) to the patient, the body region may feel abnormally hot or cold; when actually touched, however, it feels the same temperature as the other side. The frequency of each of these has not been evaluated, and the implication of this difference has not been studied.

Skin Color Changes

The CRPS region may have observable skin color alterations, typically described as mottled, deep purple, pale, or bright red. Like skin temperature, the skin color may vary in any one patient over time (76). Frequently, patients state that the skin color changes are correlated with the temperature of the limb, coldness associated with a deep purple skin color and hotness with a red skin color. Uncommonly, patients may describe and have observable frank rashes or peeling of their skin.

Sweating

Alterations in sudomotor activity within the CRPS region may occur. Although the classic description is of profuse sweating, increased or decreased sweating may occur. Patients may describe an abnormal skin dryness in the CRPS affected region.

Motor Dysfunction

Motor abnormalities have been minimized in prior authoritative texts regarding RSD (14). Others, however, have noted that “reflex sympathetic dystrophy is as much a movement disorder as a painful condition” (83). The largest prospective study of RSD demonstrated that motor dysfunction is nearly universally present, with 95% having weakness, 54% muscular incoordination, and 49% tremor (32). In addition, this study noted that 15% of RSD patients had no active movement with normal electromyography tests and were deemed to have a *pseudoparalysis*, thought to be neurologic in nature (32). Another study described RSD patients who displayed clinically significant motor abnormalities, including “focal dystonias, weakness, spasms, tremors, difficulty initiating movement, and increased tone” (40).

CRPS patients commonly describe a vague weakness of the involved limb, even though neurologic muscle testing may be normal. Frequently, patients with CRPS of the hand complain that objects fall out of the hand suddenly, and those with the disorder in the feet may describe stumbling or tripping.

Guarding and Neglect

A classic image of the CRPS patient is one with the upper limb held tightly against the chest with minimal spontaneous and voluntary movement. The historic explanation for this abnormal body position has been that these patients *guard* the involved body region (i.e., they develop a protective posture and tend to avoid its use to minimize a worsening of their pain). Thus, it was generally assumed that this lack of movement was volitional.

However, one report has postulated that the abnormal motor weakness, abnormal posturing, and lack of spontaneous and volitional movement may be caused by a neurologic neglectlike syndrome (72). In other words, these patients do not use their limbs normally because their central nervous system has *shut off* the limb from conscious awareness. Another report noted “inability or difficulty in initiating movements” (40). These patients note that to initiate and perform volitional motor tasks with the CRPS limb they need to look directly at the limb and focus all of their conscious attention on the limb for it to move as desired. Additionally, these CRPS patients describe the involved limb as though it has been disconnected from themselves, for instance, “it's as if my arm is not connected to my brain” or “my mind tells my hand to move, but it won't” (40,72). For some patients, this motor neglect is more disabling than the pain.

Myofascial Pain

Patients with CRPS of the limb develop a secondary proximal myofascial pain caused by disuse and overuse of other musculoskeletal body regions in compensation of the functional loss of the CRPS limb. Although Bonica mentioned this anecdotally, he did not describe it as an important feature clinically (104). Evans also described “skeletal muscle cramps and spasms” (13), and Livingston described muscle spasms as a key factor in his vicious cycle model (84). The clinical relevance of the muscular component has been overlooked, if not ignored, by most clinicians.

In some CRPS patients, the proximal myofascial pain syndrome may be of primary importance (i.e., by treating the proximally involved myofascial regions, the patient's CRPS symptoms improve). During the evaluation of the CRPS patient, palpating the proximal musculature for trigger points not only may reveal their presence, but also may result in referred symptoms (i.e., an immediate worsening of the patient's CRPS pain and its other associated symptoms). At times, a patient's CRPS signs may become evident or worsen immediately on trigger point palpation (e.g., a hand may become abnormally dusky and cold in conjunction with palpation of a trapezius trigger point).

When examining the patient with CRPS of the hand and upper extremity, it is recommended that the shoulder girdle musculature be examined for myofascial trigger points and the hip, buttocks, and the lumbar paraspinous muscles be evaluated in the patient with CRPS of the foot and lower extremity. Even if the initial injury is in the distal extremity (i.e., hand, wrist, foot, or ankle), over time proximal myofascial trigger points may develop and may even become the primary source of many symptoms. A prospective study of CRPS patients revealed clinically significant myofascial dysfunction in 70% of upper extremity and 47% of lower extremity CRPS patients (85).

Therefore, all CRPS patients should be evaluated for myofascial pain in the respective proximal muscle groups, and if present, should be treated appropriately with active physical therapy and possibly trigger point therapy.

Trophic Changes

Although classically considered part of the syndrome, trophic changes, such as decreased hair growth, brittle nails, muscle wasting, and joint thickness, are less common than once thought. In fact, these are not part of the CRPS diagnostic criteria, and studies, as mentioned previously, show that only a small minority of CRPS patients have symptoms or signs of trophic changes (15,19,32).

Psychological Factors

Most CRPS patients experience significant pain, disability, and emotional suffering. Cross-sectional research studies have examined the psychological symptomatology associated with RSD and also have compared them with patients having other chronic pain conditions. Results have shown that affective disorders are common among patients with RSD and CRPS (45,56,62). A chart review study found that 62% of patients with CRPS meet criteria for major depressive disorder during their initial evaluation in a pain clinic (56). One study found that, compared with hand surgery patients, female RSD patients had higher rates of depression and male RSD patients had higher rates of anxiety (61). Compared with chronic back or non-RSD limb pain patients, RSD patients reported greater psychological distress, but the correlation between distress and pain was strongest for the RSD and non-RSD limb pain patient groups (62). This study also noted that the RSD and non-RSD limb pain patients were similar on nearly all the psychological measures used in the study (62). Elevations of scores on the Minnesota Multiphasic Personality Inventory were more frequent for RSD patients than non-RSD nerve lesion patients; however, the differences were not statistically significant, and the cut-off scores used were not clinically significant (105). Another study reported that RSD patients demonstrate higher pain levels but less psychological distress, as rated on the Symptom Checklist-90, compared with patients with chronic back pain and headache (63). Thus, most studies have concluded no consistent significant differences exist on psychological measures between RSD patients and patients with other chronic pain conditions (60,62,63 and 64).

CLINICAL SPECTRUM

Natural History

The natural history of CRPS is unknown. No long-term prospective longitudinal study has assessed the natural history of these disorders. The symptoms of RSD may begin within hours, days, weeks, or months after injury (14). The 1994 IASP taxonomy monograph states, “the onset of symptoms usually occurs within one month of the inciting event” (18). Although pain may begin fairly abruptly in relation to an injury, the other symptoms of CRPS may be delayed for several months and, in some, may be associated with prolonged decreased use of the involved body region. The progression of symptoms and signs appears to vary from patient to patient, and there appears to be a spectrum of natural histories.

Bonica reported that pain persists for more than 6 months in 85% of patients and longer than 1 year in 25%, but these data are based solely on his personal clinical experience (105). One survey reported that two-thirds of RSD patients were officially disabled, retired, or unable to return to prior employment 14 months after last treatment (106). Most reports, however, are based on observations made on patients referred to pain specialists and thus may not adequately reflect a true population-based sample. For instance, one such study observed that the average time duration between injury date and initial pain clinic consultation in the United States was 30 months (33). It may be that these patients are distinctly different (or similar to) other CRPS patients who are evaluated and treated by primary care physicians.

Does Reflex Sympathetic Dystrophy Have Stages?

Historically, it has been written that RSD progresses through certain distinct stages. Initially, Steinbocker described stages of the *shoulder-hand syndrome* (107). Bonica, in the first edition of this text (1953), described the following three stages of RSD:

> The first stage is characterized by constant pain, usually of a burning quality and of moderate severity and localized to the area of injury. The pain is aggravated by movement and is associated with hyperesthesia. There is also localized edema, muscle spasm, and tenderness. All of these factors are conducive to limitation of motion. At this stage the skin is usually warm, red, and dry (vasodilation) …in mild cases the first stage lasts a few weeks, and then subsides spontaneously or rapidly responds to treatment. In severe cases this stage may last as long as six months.
>
> The second stage is characterized by gradual decrease in pain, spread of edema, and increasing stiffness of the joints and muscular wasting. The skin is moist, cyanotic, and cold; the hair is coarse and nails show ridges and are brittle. Signs of atrophy become more prominent…. During this stage, which usually lasts three to six months, proper treatment may be effective in reversing the process.
>
> The third stage is characterized by marked trophic changes which eventually progress to an irreversible degree. The skin becomes smooth, glossy, and drawn; its temperature is lowered and it is pale or cyanotic in color. The hair is long and coarse, the nails are ridged with lateral arching and brittle. The subcutaneous tissue is very atrophic, as are the muscles …extreme weakness and limitation of motion …contractions of the flexor tendons …pain may be mild to severe, and is usually aching in character, although it may be throbbing or burning…. Hyperesthesia and paresthesia are occasionally present (14).

No long-term longitudinal prospective study has been published that follows the natural history of RSD. However, the largest prospective study of referred RSD patients did not confirm a correlation between duration of RSD and differing sets of symptoms and signs (32). One study demonstrated that increased skin temperature was correlated with a shorter duration of pain in RSD and non- RSD painful limbs, but direct autonomic testing did not support a correlation with pseudomotor activity (74). Another study that categorized patients solely by patient perception of skin temperature (stage I, stationary warmth; stage II, intermittent warmth and cold; stage III, stationary cold) reported thermoregulatory skin blood flow as measured by laser Doppler flowmetry was increased in stage I and decreased in stages II and III, perhaps reflecting an initial decrease in efferent sympathetic nerve impulses and then later an increase in skin microvessel sensitivity to circulating catecholamines (108). However, this latter study noted that the skin blood flow changes tended to correlate more with skin temperature than the duration of the syndrome. The authors of this study concluded that large interindividual differences with respect to skin blood flow “may reflect dissimilar rates with which pathophysiologic processes take place” (108). Furthermore, some of the clinical signs and symptoms described in Bonica's stages 2 and 3 may be caused by disuse of the limb and may not necessarily be caused by the underlying pathophysiologic process responsible for CRPS.

Several authorities do not recommend using a staging system (100,109). In fact, a staging system may be counterproductive in the clinical setting, because it paints a negative prognostic outlook for the later stages, adding to the patient's sense of doom and gloom when such negativity is actually not based on scientific study. Patients who would technically meet Bonica's criteria for stage 3 have been observed to make clinically significant improvement with proper long-term multidisciplinary treatment.

Is Early Intervention Important?

Most texts and reviews recommend early treatment for RSD, stating that early intervention may prevent chronicity and refractoriness. Bonica was a strong advocate for early aggressive sympathetic blockade with physical therapy (14,104). However, although early aggressive treatment makes intuitive clinical sense, no controlled prospective study has proven this clinical assumption to be true. It has also been assumed that early CRPS responds to sympathetic blockade, whereas later-stage CRPS does not. This long-standing tenet also has never been assessed in a controlled fashion and it too is based on clinical folklore rather than scientific validity. Moreover, because the natural history of the syndrome is not known, patients reported to be cured by a treatment may in fact be manifesting the natural history of their disease (10).

Regardless of when the diagnosis is made, aggressive therapies as outlined in this chapter should be immediately initiated. Even patients who are diagnosed with CRPS several years after actual CRPS onset may respond to appropriate therapies that have not been attempted in the past. To be unduly pessimistic with long-standing CRPS patients, especially those who have had inadequate treatment, is unwise and not based on any solid definitive data.

LABORATORY TESTING

Based on the CRPS criteria, no need exists for any laboratory testing for diagnostic purposes. Authors have suggested that certain laboratory testing may be helpful as diagnostic aids for RSD and causalgia. However, laboratory testing is not necessary for CRPS diagnostic purposes, nor is it useful in defining appropriate therapies or assisting in prognosticating. Thus, it is questionable as to whether any laboratory testing is ever warranted once the diagnosis of CRPS is made.

Radiologic Testing

Plain radiographic findings of bony demineralization have been noted in some patients with RSD, and this finding may aid in the diagnosis of RSD (111). However, these changes are nonspecific to CRPS, and most patients do not demonstrate this abnormality. In addition, demineralization may occur because of disuse of the limb *per se* and is therefore not specific to CRPS.

Bone Scan

Kozin and colleagues described using bone scintigraphy as a useful diagnostic laboratory tool in RSD (111,112). Bone scan changes described as consistent with RSD include distinctive patterns of radiotracer uptake, especially in the delayed phase of the test (111). Using his personal criteria for RSD, Kozin reported bone scintigraphy has a sensitivity of 67%, a specificity of 86%, and a positive predictive value of 86% (111), whereas another similar study reported a sensitivity of 44%, a specificity of 92%, and a positive predictive value of 61% (113). This latter retrospective study also demonstrated that only 21% of their RSD patients had bone scan abnormalities consistent with RSD (113). A retrospective study of patients with a proven diagnosis of CRPS referred to a chronic pain clinic observed that of the 38% of the 134 patients who had received a bone scan before referral, 53% had a positive scan result, and 47% had a negative scan result (33). Moreover, the test's ability to predict response to sympathetic block has been evaluated in a prospective study, which revealed no correlation between three phase bone scan changes and pain relief after sympathectomy (114). Thus, based on these studies, the clinical utility of bone scan in CRPS has not been demonstrated.

Thermography

Thermography can assist in documentation of abnormal skin temperature. As asymmetric skin temperature in the painful region is one of several possible signs of CRPS, thermography is of potential use but not a necessity for diagnosing CRPS. More inexpensive tools may be used to accurately document skin temperature abnormalities, such as skin temperature probes or infrared thermometers. One study assessing the validity of thermography as a diagnostic tool for RSD concluded that an asymmetry cutoff of 0.6°C provided optimal sensitivity and specificity (115).

Autonomic Testing

Quantitative sudomotor axonal reflex testing can document abnormalities in the autonomic nervous system (116). Although potentially useful in research, the extent to which quantitative sudomotor axonal reflex test is useful in the clinical setting has not been established. One retrospective study reported that resting sweating output was found to have diagnostic specificity for RSD (74). However, such autonomic testing devices are not readily available in clinical practice and therefore have limited use.

Electrodiagnostic Studies

Electrophysiologic studies, electromyography, and nerve conduction velocity testing can confirm the presence of large fiber peripheral nerve injury for the diagnosis of CRPS type II. At present, however, it is unclear whether electromyographic or nerve conduction velocity documented nerve injury evidence has any prognostic or therapeutic relevance with regard to CRPS. Another neurologic test, quantitative sensory testing, can provide information on the function of large and small peripheral nerve fibers and the central nervous system's interpretation and perception of thermal stimuli. Again, the clinical relevance of these findings is not known. However, the combination of microneurography and quantitative sensory testing may permit a classification of pain syndromes, including CRPS, on the basis of mechanisms rather than symptoms and signs.

TREATMENT

> It is probably a truism to state that most physicians and surgeons are so trained and skilled at treating organic pathology that they are unable, unskilled or disinterested in the demands imposed by a CRPS patient who has neither a focal injury nor is amenable to a disease based therapy (21).

Many claims have been made that described treatments result in CRPS/RSD/causalgia cures. The reality is that no such treatment exists. Although many treatments for RSD or causalgia have been reported and recommended, the majority are descriptive and anecdotal and are not based on the results of controlled clinical trials. The overall clinical experience with all medical and procedural treatments is poor, with the majority of patients not reporting clinically meaningful pain relief or improved function with any monotherapeutic treatment approach.

Several detailed treatment review articles have been published and are recommended reading (116,117 and 118). These extensive critical reviews of the published literature by Kingery and Tanelian clearly delineate the lack of controlled clinical trials (116,117 and 118). No scientifically established treatments exist for CRPS. Although a few treatments have some controlled trial data suggesting efficacy, no treatment has been shown to cure CRPS. In addition, good long-term efficacy data are lacking for all therapeutic interventions. A failure of all published trials to date is their lack of long-term functional outcome measures. As is described here, even the classic teaching of sympathetic nerve blockade for the treatment of these conditions has no significant supportive data suggesting long-term efficacy and thus is no longer recommended as the mainstay of CRPS treatment (109,116,117 and 118).

One potential reason for such poor outcomes overall with all treatments for CRPS is that CRPS is a heterogeneous disorder with many possible underlying mechanisms responsible for its pain and symptoms. In other words, perhaps CRPS is actually composed of multiple patient subgroups with different pathophysiologic mechanisms and environmental factors, all of which need different therapeutic approaches. Thus, it would be unrealistic to expect a single modality treatment to be beneficial for all CRPS patients.

Multidisciplinary Treatment

The key disciplines needed for the management of CRPS include medicine, psychology, and physiotherapy (Fig. 20-4). The primary goal of multidisciplinary management is to achieve functional restoration of the CRPS body region through long-term, quota-based physical and occupational therapy. The physician's role is to provide pain and symptom relief via medication or procedures and to lead the treatment team. The psychologist's role is to identify comorbid psychiatric conditions, such as depression, posttraumatic stress disorder, and anxiety disorder. Psychological treatment approaches include cognitive-behavioral techniques and supportive psychotherapy, with the goal of teaching the patient pain-coping skills. The role of the physiotherapist, probably the key interventionist and therapeutic provider, is to organize and manage the daily rehabilitative treatment of the patient. All medical providers must be experienced in the care of CRPS patients and work closely as a cohesive team, with frequent team meetings to address patient progress. Multidisciplinary management of CRPS can be painstakingly slow (for patient and providers), taking several months to a year or even longer. The key is slow, gradual, persistent documented functional improvement.

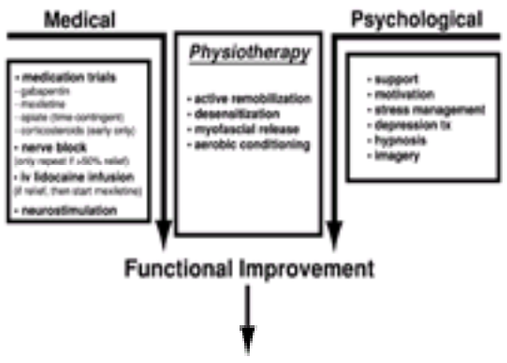

Figure 20-4. Multidisciplinary treatment.

Validation of Symptoms

CRPS patients often believe their symptoms are invalidated by the health care system. Because the symptoms of CRPS are unusual, are not readily explainable or measurable by our current knowledge of pathophysiologic events, cannot be confirmed by any laboratory testing, and do not improve with customary therapies, many physicians who are not familiar with CRPS (and even some who are familiar with CRPS) communicate to patients, either directly or indirectly, that the pain and symptoms are all in their heads or that the problems are not organic but psychogenic. Such conclusions are countertherapeutic and most certainly worsen a patient's physical and psychological state. Health care providers must first and foremost validate the CRPS patient's symptoms: Yes, your symptoms are real; yes, other patients with your condition complain of similar symptoms; and yes, we hope we can lessen the intensity of your symptoms and improve your functioning and quality of life. CRPS patients often state that this validation of their symptomatology is one of the most important therapeutic interventions provided.

Education

When given a diagnosis of a chronic disorder, most patients want information regarding the disorder's etiology, underlying pathophysiology, therapeutic options, known treatment outcomes, and prognosis. For patients with CRPS, answers to all of these appropriate questions are not available. In this day and age of cyberspace, many patients search the Internet for answers and are often provided with misinformation and reasons for pessimism. Thus, patients are often left with a

sense of hopelessness.

That CRPS patients often become fearful and anxious of the unknown and develop a sense of pessimism is understandable. Therefore, these issues must be directly addressed during the initial consultation visits with each specialist. Enough time should be spent with each CRPS patient to address these fears with education. A physician should answer patient questions about pathophysiology and treatments honestly, yet with optimism. A clinical psychologist should also address these concerns therapeutically. A patient psychotherapy and education group, led by a knowledgeable CRPS health care provider, can be helpful, especially if the group includes former CRPS patients who have made functional improvements.

Setting Treatment Goals

The following realistic goals must be set for each CRPS patient:

- The physician attempts to provide pain and symptom relief through safe procedures or medications, although clinically meaningful pain relief is not guaranteed.
- Even if pain relief is found through such therapies, it will not be a cure.
- The patient should be open to nonpharmacologic treatments, such as those offered by the clinical psychologist.
- The most important element of CRPS treatment is the patient's own persistence and efforts at long-term active physical therapy, which may initially exacerbate the symptoms, but are necessary for improvement.

Physiotherapy

The role of physiotherapy in the treatment of CRPS is varied. Although some interventions in this branch of treatment may result in the attenuation of pain or allodynia, the primary responsibility of the physical therapist is the restoration of function through activity (119,120,121,122 and 123). To this end, the fundamental approach is to help the patient work toward achieving a normal quality of movement of the affected limb and allowing it to once again become an integral participant in daily activity.

The therapist works with the patient to promote bilateral symmetry of movement. This may help restore motion, strength, and dexterity to the affected limb while also helping to prevent the contralateral limb or proximal joints from taking on an increased biomechanical burden. Often the *spread* of CRPS may be traced to the mechanical result of increased forces at aberrant joint angles, caused by movement substitution, in an effort to favor the painful part.

Diminished use of the limb and the prolonged maintenance of maladaptive guarding postures have been observed to result in significant soft tissue contractures from adaptive shortening, an accompanying loss of range of motion at the joints, and disuse atrophy of the limb's musculature (124). The patient may also present a history of decreasing overall physical activity level through the reduction, or elimination, of participation in work or recreational activities in an effort to guard against increases in pain. The result can be an overall physical deconditioning and the possibility of increased focal and global discomfort from deactivation pain as muscles shorten and decrease their oxidative capacity, joints stiffen, soft tissue becomes fibrotic, and peripheral breakdowns begin in articular cartilage.

Treatment Goals

Therapeutic activities are guided by functional goals, established in conjunction with the patient. When asked what their goals are in therapy, patients often respond with “I want the pain to go away,” or “I want my arm (hand, leg, foot) to be normal again.” Pursue the issue by asking what things the patient could do if the patient's arm were normal that he or she cannot do now; doing so may yield specific functional activities that can help set the course for therapy. Toward building capacity to facilitate functional outcomes, the following general therapeutic goals are included:

- Eliminate guarding postures and substitute movements.
- Restore normal active range of motion, strength, and motor control.
- Establish equal weight bearing for lower extremities.
- Increase standing duration tolerance with equal weight bearing.
- Increase ambulation distance using a normal, symmetric gait pattern.
- Increase stair climbing ability with symmetric step pattern.
- Increase aerobic capacity and general conditioning.
- Increase total day activity time.
- Increase touch tolerance.
- Decrease pain responses to nonnoxious stimuli.
- Build physical capacity to meet specific requirements for returning to work, when appropriate.

Physiotherapy Assessment

A comprehensive assessment provides insight into the nature of the patient's physical and functional condition and serves to establish multiple quantitative baselines that can be used to objectively evaluate patient progress and responses to therapy. In addition to a relevant medical history, the assessment should include activities and conditions that aggravate or relieve symptoms and modes of treatment and responses to prior physiotherapy.

Essential is obtaining information from the patient regarding his or her current or former occupation (with a general sense of its physical and postural demands), activities of daily living currently restricted or eliminated secondary to pain or its physical complications, and estimated number of daily waking hours the patient currently spends in bed or reclining.

Physical findings should include measurements of active range of motion and muscular strength for both the affected and contralateral limb, documentation of motor abnormalities (e.g., dystonia, apraxia, movement latency, increased tone, intention tremors, involuntary movements, and motor neglect), postural evaluation with specific attention to protective guarding patterns, gait characteristics (i.e., abnormalities, asymmetry, maximum distance walked, need for assistive devices, and ambulation speed over a short standardized distance), duration of aerobic activity tolerance at an age-specific target heart rate, and stair climbing ability. Proximal sites (e.g., the shoulder girdle and periscapular region for upper extremity cases or hip, gluteal and low back regions with affected lower extremities) should be palpated for the presence of myofascial trigger points. For lower extremity cases, uncued standing weight bearing on each leg should be documented. With affected upper extremities, hand grip and key pinch strength should be assessed bilaterally, along with an appropriate standardized measure of functional hand and upper extremity dexterity.

Physiotherapy Treatment

To address the multifaceted goals leading to functional restoration, diverse physiotherapy interventions may be used (125). No appropriately controlled clinical studies exist that adequately address the efficacy of individual physiotherapy methods for the treatment of CRPS. Some authors insist range of motion work and strengthening should only be done under pain-free conditions (126,127 and 128) (i.e., physiotherapy sessions should only follow sympathetic, central, or peripheral nerve blockade). Yet this recommendation is faulty on several accounts. First, many, if not most, CRPS patients do not obtain even temporary relief with nerve blocks. Second, even if such meaningful relief is attained, such practice, although benevolent, is far from being practical. To be effective, the frequency of physiotherapy treatment would require an unreasonably high number of blocks to be performed. Therefore, the therapist is practically faced with the task of working to restore function within a painful limb, without increasing the patient's long-term discomfort. Some clinicians now recommend the use of transcutaneous electric nerve stimulation units during therapy to attenuate pain during the treatment session (128). Again, no controlled studies have appeared that support transcutaneous electric nerve stimulation use to be either effective in temporarily blocking CRPS pain, or producing faster or more complete functional recovery. Additionally, responses to heat and cold as palliative modalities are highly varied and unpredictable, even for an individual patient over time.

Desensitization techniques are used to reduce allodynia (125). Desensitization is a progressive technique to gradually habituate the patient to the presence of nonnoxious stimuli, which previously elicited a pain response. A sequence of materials are selected that progress from soft, light textures to extremely course, irritating surfaces. The patient lightly rubs affected areas with the most nonirritating material for several minutes, rests, then rubs again for several minutes. After a number of sessions, the patient gradually becomes accustomed to the presence of this texture on his or her skin and the painful response diminishes. He or she then moves to the next material in the sequence of increasingly coarse textures and repeats the procedure. Gradually, the affected limb habituates to increasingly irritating

textures, until the patient can easily tolerate the touch of clothing, bed sheets, towels, and so forth during normal activities of daily living. To complete desensitization training, materials triggering diverse sensory modalities should be employed, such as pressure and cold.

To restore range of motion, strength, and motor control, as well as build functional tolerance to activities such as standing, sitting, or walking, appropriate dosing of exercise is critical. For this purpose, a quota-based progression system may be used, as first outlined by Fordyce (129). For each individual activity or specific exercise, a baseline is first established. In setting baselines, the patient is instructed to perform and continue the activity (usually quantified as the number or repetitions of a compete movement cycle, or elapsed time), until he or she just begins to feel the first signs of any of the three following sensations: increased pain, muscle weakness, or fatigue. During the next treatment session (or home exercise session), the patient is instructed to perform just 80% of the number of baseline repetitions (or tolerated elapsed time). During each subsequent session, the number of repetitions is increased by one (or 5% to 10% for activities based on elapsed time). With progressive resistive exercises for strength building, when the number of repetitions reaches 15, resistance is increased, repetitions are dropped to eight, and the progression begins again. This formula allows the individual to begin exercising at a level that is well within his or her reasonable level of exercise tolerance and then progress at a gentle, reasonable rate. Each day, each exercise has a specified quota for number of repetitions. Patients are instructed to perform exactly that number or repetitions, not more or less, regardless of temporal pain. The implementation of quota-based exercise dosing helps the individual to progress in functional physical ability, while decreasing the oscillation cycles of activity tolerance inherent in pain-contingent dosing of activity.

Attempts to restore range of motion begin by instructing the patient in passive arthrokinematic joint mobilization and techniques of active assisted range of motion for joints displaying functionally limited movement. As functional levels of passive and active assisted motion are reached, the patient advances to active range of motion exercise using the muscles directly controlling the joints in question. Active assisted range of motion and active range of motion exercises should have a baseline established for reasonable tolerance and progress on a quota-based system. As the patient begins to display increases in active range of motion, appropriate progressive resistive exercises may be introduced to build muscle strength. Each resistive exercise should have an individual baseline established and progress via the quota formula. Progression should be linear, with daily exercise intensity specified by the quota progression, not pain contingent.

Building tolerance for sustained aerobic activity, as well as functional tasks, such as sitting, standing, walking, writing, or using a keyboard, may also be approached using a quota-based system. Baselines are established using an appropriate measure, such as time, distance, number of written lines, and so forth. A quota progression is then created, beginning at 80% of the baseline value and linearly increasing daily in increments of between 5% and 10% of the original baseline. All functional activities should be performed with appropriate mechanics and without movement substitution or asymmetric distribution of effort. Standing quotas should be met with equal weight distribution and walking with symmetric movement and release of guarding postures. That the functional task be accomplished during a therapy session is less important than that it be done with correct patterns of movement, thereby encouraging reeducation of appropriate neuromotor behavior.

In cases of lower extremity CRPS (and sometimes caused by an expanded guarding pattern in upper extremity CRPS), proper walking mechanics and symmetry may be restored via gait-shaping protocols. Initial and continuous emphasis is placed on equal weight bearing. As equal weight bearing and symmetric gait are established, variable surface training may be used to build ambulatory adaptability to irregular walking surfaces and also enhance proprioception. Weaning from assistive devices, such as canes or crutches, may be facilitated with a quota-based gradual reduction in their use.

Some weight-bearing activity for upper extremity CRPS may also have utility in helping resolve symptoms. Using *stress loading* protocols, balanced weight-bearing tasks may be practiced with the upper extremity (130,131).

Managing edema may also be an issue essential to restoration of appropriate movement. For lower extremities, frequent ankle pump exercises should be performed, whereas for the upper extremities gentle hand grip and release may be used. Self-administered unidirectional massage, along the lines of lymphedema protocols, may aid in swelling resolution and also provide further practice with touch desensitization. When available, hydrotherapy, via warm water pool work, is highly recommended. The pressure gradient created by standing in water facilitates edema management and relieving weight from weight-bearing joints affords an excellent opportunity for building strength and range of motion.

Many CRPS patients manifest proximal myofascial components, which may be limiting movement and exacerbating pain through referred patterns. Typical techniques of myofascial release, involving *spray and stretch* or deep tissue work (132), may not be tolerated with hyperalgesic limbs and may provoke symptoms for a considerable period of time. Complete therapeutic intervention should, however, assess and address potential myofascial trigger points. Myofascial release work may be accomplished when appropriate windows of opportunity present themselves, such as coordinating the timing of therapy sessions with medication schedules. Patients may also be taught self-applied techniques of manual myofascial release for incorporation into their home programs.

Additional physiotherapy modalities have been suggested, but have yet to demonstrate controlled clinical efficacy, or in several cases have yet to establish sound pathophysiologic foundation for their use. These include the use of transcutaneous electric nerve stimulation and high-voltage pulsed current for managing edema, neuromuscular electric stimulation to build strength, and thermal biofeedback to restore normal patterns of peripheral blood flow.

No established standards exist for the frequency and duration of physiotherapy sessions. Much depends on the individual patient's needs. The key decision factor involves how frequently a patient should be seen in the clinic to ensure compliance with quota-based activity. The importance of a home program cannot be overemphasized. To successfully treat CRPS, the patient must be committed to integrating treatment concepts into the daily routine outside the clinic. This includes appropriately pacing physical activity, as well as adhering to instructions to extinguish guarding, and using the affected limb in normal activities of daily living at gently advancing levels of intensity and involvement. The patient should be continually encouraged to generalize movement gains made in the clinic to the routine performance of daily activities at home. Transferring physical and functional gains to activities of daily living is essential.

Progress and Outcome Measures

An extremely useful facet of physiotherapy treatment is that it lends itself easily to direct objective progress measures across multiple parameters. This is of benefit to the therapist in assessing response to treatment modalities and to the patient in perceiving clear progress toward measurable goals, and provides a rich source of quantitative variables for future research. Patient outcomes may easily be quantified and documented on any number of dimensions, including the following: symmetry of lower extremity weight bearing; aerobic activity tolerance, assessed as minutes of continuous activity maintained at a target heart rate; manual or isokinetic testing of muscular strength; grip and pinch strength, measured in kilograms; active range of motion, measured in degrees, or linear distances from anatomic landmarks; ambulation distance with appropriate symmetric gait pattern; ambulation speed over a standardized distance; number of stairs that can be ascended and descended without a rest stop; tolerance for lifting weight to and from varied heights and carrying over a given distance; and the ability to independently perform relevant functional, work-related, or both kinds of activities with the affected limb, which had been discontinued because of limitations of pain, strength, endurance, motion, or motor control.

Outcome Factors

No studies have been reported that use large enough samples to adequately assess factors that may predict a successful response to therapy. However, based solely on clinical experience, there appear to be a few exogenous and endogenous factors that have been associated with a reasonably rapid return to function. Exogenous factors include the speed with which therapy is commenced after the precipitating event or onset of symptoms (120,133) and adequate access to relatively frequent therapy sessions. Using records from 36 pediatric patients, one study reported that physiotherapy sessions conducted as frequently as twice daily were most likely to lead to resumption of activity (134). Large-scale studies on the requisite dosing of physiotherapy are not available.

Endogenous factors typically associated with relative success involve a willingness on the part of the patient to adhere to strict pacing of activity and an intrinsic desire to increase function and return to work or daily activities, as opposed to simply reducing pain. With properly applied and paced physiotherapy, many CRPS patients who possess a real desire to return to normal activity can experience a significant restoration of physical abilities, an improved quality of life, and a meaningful reduction of their symptoms.

Psychological Treatments

Psychological intervention is a crucial part of the multidisciplinary treatment for patients with CRPS. Psychological therapies can help to remove barriers to rehabilitation, such as fear of reinjury and worsening pain, depression, anxiety, disincentives for wellness, and third-party systems issues (e.g., worker compensation, legal, and insurance systems). A thorough psychological evaluation by a psychologist or psychiatrist well versed in chronic pain can be crucial in ferreting out these issues, as well as in diagnosing depression and anxiety disorders. Although many reports in the literature emphasize the importance of psychological factors in CRPS

and RSD, little research has been conducted on the effectiveness of psychological therapies for this condition. Currently, most of what is known and used is based on the general chronic pain treatment literature (53,135,136).

Identify Psychological Comorbidities

As mentioned previously, rates of depression and anxiety are much higher in individuals with all types of chronic pain as compared with non pain community samples. Emerging reports suggest that rates of posttraumatic stress disorder may also be higher in chronic pain populations. Additionally, anger issues can be a significant factor for these patients; although anger related to third- party systems may be understandable given the patient's situation, it may nevertheless tax the patient's ability to manage pain and effectively deal with these issues. If left unchecked, negative emotional states, most likely a consequence of chronic pain and its effects on the patient's quality of life, are likely to exacerbate the pain and other symptoms of CRPS, worsen disability, and hinder efforts at rehabilitation. Appropriate therapies, including psychotherapy and pharmacotherapy, are critical in the overall treatment of CRPS.

Cognitive-Behavioral Psychotherapy

Most of the psychological strategies suggested for the treatment of patients with CRPS are those cognitive-behavioral therapies used in the treatment of general chronic pain conditions (53,136). Standard cognitive-behavioral psychotherapy for depressive and anxiety disorders can be helpful for individuals with CRPS. Therapeutic techniques, such as thought monitoring (e.g., decreasing catastrophizing thoughts and beliefs), cognitive restructuring, goal setting, stress management, and increasing participation in pleasurable activities, can be the most useful interventions for such patients (53,135,136).

Group Psychotherapy

Group psychotherapy for individuals with CRPS is an extremely helpful therapeutic modality to address the comorbid psychological issues and to decrease the social isolation that many of these patients experience. CRPS patients often feel isolated, depressed, and enigmatic, believing that they are unusual and suffer from bizarre symptoms. Introducing patients to other individuals who have had similar experiences with CRPS with regard to symptoms, relationships with health care providers, and systems issues, is a positive experience for many CRPS patients. It is particularly useful to have patients in the group who are in various stages of treatment to provide hope and a model of recovery for the patients who are just starting treatment. These groups should include both a didactic component regarding issues related to CRPS (e.g., sleep and mood management, self-management strategies, family issues, and how to deal with the health care system) as well as supportive psychotherapy approaches. The group should not be allowed to focus entirely on negative issues, but rather focus on more adaptive ways to cope and function with CRPS.

Symptom-Specific Psychological Treatments

Specific psychological techniques may be of particular benefit for individuals with CRPS. The role of biofeedback (137) and hypnosis (138,139) as adjuncts to more traditional cognitive-behavioral psychotherapy has been highlighted in the literature. However, most of these studies are limited by small sample size, and many are single case reports.

Biofeedback. One study found that thermal biofeedback on the affected RSD limb promoted a decrease in RSD-associated symptoms in 20 *treatment refractory* patients (137). At 1-year follow-up, 14 of 20 of these patients were reported to be working. Another study reported that biofeedback was helpful when used as part of a multidisciplinary treatment approach to RSD symptoms (130). Biofeedback can be useful for this population in terms of facilitating learning of relaxation skills and possibly decreasing pain, other CRPS symptoms, and distress via an increased sense of self-control and perhaps by reducing the patient's autonomic stress response.

Hypnosis. Hypnosis with CRPS patients has also been proposed as an effective therapy in reducing some of the symptoms associated with RSD. A case report observed that three RSD patients achieved warming in their affected limb and some relief of other RSD symptoms (138). One study reported that integrating hypnosis into a multidisciplinary approach, which also included psychotherapy and myofascial therapy, was useful for approximately two-thirds of RSD patients who were considered *highly hypnotizable* (139).

Additional Psychological Treatment Issues

As noted elsewhere, validation of the CRPS patient's clinical and life situation seems to be particularly important for this patient population. Because of the bizarre nature of many of the symptoms associated with CRPS, many of the patients believe that the validity of their symptoms has been questioned by other doctors and third-party systems, and therefore they get caught in a bind of trying to convince representatives of such systems, and often significant others, that their symptoms are real. This only serves to compound patient disability and pain behaviors. A lot of mileage can be gained in working with these patients by validating their experiences in the beginning and throughout treatment. For a significant majority of these patients, a trusting relationship with a physician is crucial to treatment success. Equally important is compassionately dispelling unwarranted catastrophic thinking, such as belief in an eventual need for amputation or that “RSD is spreading throughout my entire body.” Psychotherapy can be a useful adjunct to working on these issues while the patient goes through reactivation physical therapy and medical management of the CRPS symptoms.

Medical Therapies

Sympathetic Blockade

> Current neurophysiologic evidence does not support the direct inference of pathogenic mechanism, site, or transmission pathway from observations during neural blockade. Complex physiologic events may confound the simple interpretation of diagnostic blocks…. On the basis of the published material reviewed, we conclude that there are many limitations that weaken the theoretic basis for neural blockade as a diagnostic or prognostic tool. In addition, these procedures in general lack thorough documentation of clinical usefulness (22).

Classic teaching strongly recommends treating RSD and causalgia with sympathetic blocks (14,104). Sympathetic blocks continue to be the first-line and mainstay of treatment by many treating physicians. One study reported that an average of six blocks (range, 0 to 38) was performed without significant benefit on CRPS patients before being evaluated in a chronic pain clinic (33). It is imperative to realize that the data used to support the notion of sympathetic blocks for the treatment of RSD are not based on controlled clinical trials and, in addition, the supportive reasoning behind this notion is circular because prior diagnostic criteria required a positive response to such a nerve block. Thus, it is likely that only RSD and causalgia patients with SMP were treated with sympathetic blocks (and thus the reported high success rate), whereas those who did not report pain relief with sympathetic blocks were not considered to have RSD or causalgia and hence were excluded from study results. Therefore, most of the prior RSD and causalgia reports need to be interpreted with great caution, because the subjects were a selected subgroup of CRPS patients and these studies were not placebo controlled.

Another major issue with sympathetic blocks is their true mechanism of pain and symptom relief. This significant issue has not been questioned. It has been assumed that pain relief after sympathetic blockade results from decreasing an abnormally hyperactive sympathetic tone in the involved body region (14,104). Yet, the acquisition of more recent data brings this assumption into question. For instance, with regional ganglion sympathetic block, there are systemic absorption of local anesthetic and spillage of local anesthetic onto adjacent nerve fibers, which likely result in distinct nervous system activity apart from the local effect on the sympathetic ganglia (22,24,25). Also, several studies have demonstrated no correlation between degree of sympathetic dysfunction and degree of pain relief obtained from sympathetic blockade (20,27,28). Lastly, the time of onset and duration of pain relief do not correlate with the timing of sympathetic block (22,29).

Several techniques exist for sympathetic blockade, including selective sympathetic ganglion blockade, stellate ganglion block for the upper extremity and lumbar sympathetic block for the lower extremity, intravenous regional guanethidine/bretylium block, and intravenous phentolamine infusion. All of these techniques, except phentolamine infusion, have technical factors that may affect the efficacy of the block, including the physician's experience and technique and the patient's anatomy (22). All of these techniques, including phentolamine infusion, have nonspecific effects that could explain their apparent success.

Is There a Need to Perform a Series of Nerve Blocks?

Another clinical practice, based more on folklore than scientific evidence, is that of automatically performing a series of sympathetic nerve blocks to all patients with

CRPS. No controlled published studies have verified the efficacy of this practice. Although it is still recommended that a CRPS patient have one sympathetic nerve block to assess whether SMP is present (realizing the pitfalls of interpretation thereof), if the patient does not report significant pain relief after one well-performed sympathetic block, then further sympathetic blocks are not recommended.

Selective Sympathetic Ganglion Nerve Block

Several problems exist regarding the efficacy studies for selective sympathetic ganglion nerve block and stellate ganglion and lumbar sympathetic block for the treatment of CRPS. First, the actual success rate of blocking the sympathetic activity with these blocks is not known (22). Second, no placebo-controlled trials have been published. Third, the mechanism of pain relief when achieved may be local anesthetic activity on peripheral somatic nerve fibers and not sympathetic fibers via local anesthetic systemic concentration or local spillage (22,24,25). In fact, patients who have reported transient pain relief with sympathetic block may also report similar degrees of pain relief with intravenous lidocaine infusion and then obtain chronic relief with oral mexiletine.

Intravenous Regional Sympathetic Block

Studies have assessed the efficacy of intravenous regional sympathetic blockade using several different agents. Guanethidine is commonly used and is thought to act by depleting norepinephrine, although the drug has also been shown to have serotonergic and anticholinergic activity (140). Based on seven controlled trials (141,142,143,144,145,146 and 147), a critical review of the literature concluded that intravenous regional sympathetic blocks with guanethidine “are ineffective analgesics compared to placebo or no treatment” (117). One of these studies also demonstrated that a series of guanethidine blocks produced similar ineffective results as a single block (147).

Bretylium is also frequently used as the agent in intravenous regional sympathetic block. Bretylium, like guanethidine, is thought to be of potential benefit in SMP because of its activity of depleting norepinephrine. Only one non–placebo-controlled study of intravenous regional sympathetic block with bretylium has been published, comparing bretylium with lidocaine in 12 subjects, which reported bretylium resulted in a significantly longer duration of pain relief than did lidocaine (148).

Other controlled trials of agents administered as intravenous regional sympathetic block include droperidol, ketanserin, reserpine, and atropine. Droperidol, an a-adrenergic antagonist, resulted in no pain relief in six subjects who had responded to a prior stellate ganglion nerve block (149). Ketanserin, a serotonin type 2 antagonist, was studied in nine patients with the report of significant pain relief for several weeks as compared with saline (150). Two controlled studies assessed reserpine, another norepinephrine-depleting drug, in subjects who had a positive prior response to stellate ganglion block, and reported no significant pain relief (142,143). No pain relief was also reported for the anticholinergic atropine in patients who had previously responded to intravenous regional sympathetic guanethidine block (151).

Besides lacking firm positive data from controlled clinical trials, another significant issue with intravenous regional sympathetic blocks has been raised. Pain relief associated with this procedure may result solely from the ischemic tourniquet block and not be caused by the injected medication. Significant A-b and A-d fiber conduction block with clinically evident sensory changes have been documented with only the tourniquet block (152).

Intravenous Phentolamine Infusion

Phentolamine's primary mechanism of activity is believed to be via a $_1$-adrenergic antagonism, although the drug also has serotonergic, histaminergic, and cholinergic activities (29) and local anesthetic properties (153). Controlled clinical trial results are mixed, and methodology of these trials is poor. The one trial with positive results always administered the placebo immediately before the phentolamine (154). One of the trials with negative results also always administered the placebo at the same time and, additionally, was a single-blind study (155). One study reported that phentolamine infusion was less sensitive but more specific than stellate ganglion block for the diagnosis of SMP (28). An uncontrolled report observed that some RSD patients experience days to weeks of pain relief after one phentolamine infusion, and that patients may report a delay of peak pain relief for several days after phentolamine infusion (29).

Phentolamine infusion has advantages over other sympathetic blocks in that it is minimally invasive, is not technician dependent, and has systemic activity that allows for treatment of multiple body regions with SMP. It is unclear whether phentolamine has a dose-response relationship and thereby some patients may need higher doses for an effect (156).

Epidural Clonidine

One double-blind controlled trial reported statistically significant pain relief with epidural clonidine injections for RSD patients who had SMP (157). However, this study also reported significant adverse events both with the single injection and with the open- label continuous epidural infusion.

Predictors of Sympathetically Maintained Pain

One retrospective study reported that RSD patients with early disease (less than 6 months) associated with increased skin temperature and edema were more likely to report pain relief after sympathetic block (74). This and another study also reported that patients with allodynia were more likely to respond to sympathetic blocks, but this was true for RSD and non-RSD limb patients (20,74).

Placebo Blocks

Much discussion has taken place with regard to the need for placebo blocks. When performing and interpreting clinical trials in which a group of subjects' responses to a treatment are being evaluated, placebo treatment is always necessary, especially in a syndrome, such as CRPS, in which the natural history is unknown and no gold standard treatment exists. Thus, in clinical trials research, the response of an overall group of subjects to an inert placebo block must be compared with the response when the active medication is injected.

The use of placebo blocks in clinical practice, however, needs to be seriously questioned (see Chapter 81). It is currently accepted clinical practice to perform placebo blocks on individual CRPS patients to assess for the patient's individual placebo response. Although commonly practiced, this procedure is fraught with multiple problems that make interpretation of the patient's responses impossible, including the following problems:

- There is no such thing as a *placebo responder*. Every person can (and will) respond to a placebo given certain conditions (158).
- An individual's response to a placebo is plastic, not static, and this response changes from day to day, and even minute to minute (159).
- Treatment responses to all treatments and for all medical conditions always have two components, one directly related to the physiologic activity of the treatment and the other evolving from nonspecific treatment effects (159). Thus, a patient who has a true physiologic response to an active block may also have a similar response to a placebo block and report pain relief to both blocks.
- A patient's response to placebo is affected by many variables outside of the treating physician and patient's control, including patient expectation, physician expectation, patient anxiety, environmental setting, patient experience with similar treatments, and physician experience with similar treatments.
- Single-blind procedures are uninterpretable. One prospective study revealed that physician expectation was more important than patient expectation with respect to subsequent response to therapeutic pain procedures, thus questioning the validity of single- blind procedures, in which only the patient is blinded to the medication administered (99).
- An inert substance, such as saline, used as the placebo may not truly be inactive. Injection of saline has physiologic effects and therefore can result in altered sensations. In addition, the simple procedure of needle insertion for the block may actually result in a physiologic response if the needle penetrates a myofascial trigger point. The simple maneuver of the ischemic tourniquet block used for intravenous regional sympathetic blocks results in peripheral nerve alterations and changes in sensory perception (153).

Thus, placebo blocks performed in an individual patient to assist in treatment planning cannot be interpreted with certainty and therefore are not recommended. Non-specific effects including placebo are discussed in Chapter 81.

Are Patients with Complex Regional Pain Syndromes Placebo Responders?

It has been written and promulgated that CRPS patients tend to be placebo responders (97). The data used to validate this postulation are based on single-blind procedures (156), which are uninterpretable (99). In addition, most authorities' clinical experience is that most CRPS patients do not respond to any medical interventions (17,99,109,116) and if indeed CRPS patients tended to be placebo responders one would expect the opposite, positive reports of pain relief after most medical therapies.

Medication

As with sympathetic blockade, no medication has definitive controlled clinical trial evidence and long-term clinical experience as a gold standard for CRPS treatment (Table 20-1). The modus operandi for prescribing medication is still trial and error, with subsequent drug trials. As with the treatment of other neuropathic pains, the key with currently used medication is the need for dose titration until good pain relief or intolerable side effects are reported by the patient. Also an important strategy is titrating one drug at a time, although some patients eventually may require polypharmacy. Many CRPS patients have no success with all currently available drug therapies because of poor pain relief and intolerable side effects.

Antiarrhythmics
Anticonvulsants
Antidepressants
Calcitonin
Calcium channel blockers
Corticosteroids
Opiates
Regional sympathetic blockade
Ganglion block
Intravenous regional
Spinal/epidural
Systemic sympathetic blockade
Oral
Intravenous
Topical local anesthetic
Transcutaneous electric nerve stimulation
Peripheral nerve stimulator
Spinal cord stimulator
Spinal opiates (and other drugs)
Sympathectomy

TABLE 20-1. Medical treatments for complex regional pain syndrome

Corticosteroids

Pulse doses of corticosteroids (60 to 80 mg per day) for 2 weeks have been reported in a small uncontrolled case series to be beneficial in RSD patients (112). Two small single-blind trials of 10 and 17 early RSD subjects, within 2 to 3 months of injury, also reported clinical improvement after 4 or 12 weeks of oral corticosteroid treatment (159,160). None of these studies, however, reported long-term follow-up data. Clinical experience with corticosteroids in CRPS patients who have had symptoms for over 6 months is poor. Also, many patients report a return of their pain and symptoms after the corticosteroids are tapered. Chronic corticosteroid treatment is not recommended.

Gabapentin

Uncontrolled case series have described successful treatment of CRPS pain and other associated symptoms with titrating doses of gabapentin (161). No controlled clinical trial has been published to date. Clinical experience has been good with gabapentin, with approximately 30% of CRPS patients reporting noticeable pain and symptom relief and tolerable side effects (a good percentage for CRPS). The dose can be titrated to a maximum of 6,000 mg per day if needed. Because of gabapentin's excellent safety and side- effect profile, it should be prescribed early with aggressive titration.

Oral Sympatholytic Agents

Like the sympathetic blocks, oral sympatholytic agents theoretically should provide pain and symptom relief to CRPS patients with a component of SMP. No randomized prospective controlled study has assessed the efficacy of these agents, although case reports and case series have reported benefit from prazosin (162), phenoxybenzamine (163), and terazosin (164). Clinical experience has shown that these drugs are often poorly tolerated, resulting in orthostatic hypotension and depression, therefore limiting their clinic utility.

Clonidine

A small, uncontrolled study of transdermal clonidine reported that several RSD patients with a component of SMP obtained relief of allodynia only in the skin region directly under the transdermal patch (165). No controlled clinical trial or long-term prospective outcome study has been published assessing the efficacy of systemic clonidine. Clinical experience has been poor with systemic clonidine, although a rare patient may report significant relief without intolerable side effects (166,167).

A new formulation of topical clonidine gel with minimal systemic activity has been studied in an open-label pilot study. This uncontrolled study observed decreased allodynia and hyperalgesia in some CRPS patients (168).

Tricyclic Antidepressants

No study, controlled or uncontrolled, has assessed the efficacy of tricyclic antidepressant medication in CRPS. Clinical experience is poor, unlike its use for the treatment of other neuropathic pains. Most CRPS patients do not report substantial pain relief and many experience intolerable side effects. As with many other chronic pain states, tricyclics may be of benefit as a sleeping aid to many CRPS patients.

Calcium Channel Blockers

A small, uncontrolled case series reported improvement using the calcium channel blocker nifedipine (169). No randomized controlled trial has been performed using these agents. Clinical experience is poor for these agents, although rarely a CRPS patient reports significant relief.

Beta Blockers

A placebo-controlled trial did not show efficacy for propranolol (170), although relief was reported in case reports (171). Clinical experience is poor.

Calcitonin

Calcitonin has been shown to be of no benefit in two controlled studies, one with subcutaneous administration (172) and another via intranasal route (173) in early RSD, within 8 weeks of injury. One controlled study of intranasal calcitonin, however, demonstrated positive benefit in early RSD after 8 weeks of treatment (174). The clinical experience using intranasal calcitonin for the treatment of CRPS is limited, and no study has assessed efficacy in CRPS patients with a duration of symptoms longer than 2 months.

Local Anesthetic Antiarrhythmics

As mentioned, a potential mechanism of selective sympathetic ganglion block is systemic activity of local anesthetic (24,25). Intravenous lidocaine infusion has been shown in uncontrolled trials to produce transient reductions of pain in some patients with RSD and causalgia (175,176). Although the use of oral mexiletine has not been studied, clinical experience has shown it to be of potential benefit for some CRPS patients.

A new formulation of topical lidocaine patch was reported to produce clinically significant pain relief under the application site in several patients with RSD in an uncontrolled case series (177).

Opiates

As with the treatment of all neuropathic pains, the use of opiate medication in CRPS is controversial, with advocates (116) and detractors (100). Neither side has any solid controlled clinical trials supporting their claims. It is currently recommended that a trial of opiates should use time-contingent dosing, titrating the dose until the patient reports significant pain relief or intolerable side effects. Clinical experience is that most CRPS patients experience the latter and thus do not do well with opiates. However, some CRPS patients experience clinically meaningful pain reductions without significant side effects and thus report increased daily functioning on time-contingent opiates.

Implantable Devices

Over the 1990s, there has been a tremendous increase in the use of implantable devices, such as spinal cord stimulation and intrathecal opioid pumps, for the treatment of chronic pain, including CRPS. Here, too, controlled clinical data are lacking.

Neuroaugmentative Procedures

Spinal cord stimulation (178,179) and peripheral nerve stimulation (180) have been reported to produce pain and symptom relief in uncontrolled case series. A case series of 18 patients treated with spinal cord stimulation reported 4 patients failed the initial 1-week trial, 5 experienced moderate relief, 6 good relief, and 7 patients had technical problems with the hardware (181). A retrospective case series of 12 patients with RSD reported excellent pain relief in 8 and good results in 4, with an average follow-up of 41 months (178). Clinical experience is divided between those who strongly advocate spinal cord stimulation use in CRPS and others, whose poor experiences with these devices suggest limited utility.

Intrathecal Opioid Therapy

Once again, controlled clinical trial data are nonexistent. Most published reports describe patients with a variety of nonmalignant pain diagnoses, of which RSD may be a small group with moderate improvement (182,183). One small uncontrolled report discussed the outcome of three RSD patients, observing 50% to 70% pain relief in two of the patients at 1-year follow-up (184). At this time, intrathecal opioid therapy should be reserved for those who have had no success with other medical and nonmedical therapies.

Neurosurgical Therapies

Neuroablative Procedures

The response rate for surgical sympathectomy varies from 12% to 97%, depending on the series and duration of the follow-up period (185). Besides the inherent risks to surgery and neurolytic blocks, a return of the pain has been documented after sympathectomy in some patients within 6 to 12 months (186). One prospective study assessed the recurrence rate in 66 World War II veterans who underwent surgical sympathectomies for causalgia and reported that all 66 had resolution of the burning pain, 30 had good results maintained for 2 to 8 years, and 6 had good results for less than 2 years (187). A fairly common complication of lumbar sympathectomy is *postsympathectomy syndrome* in up to 44%, characterized by pain in the anterior thigh and thought to be caused by irritation or inflammation in the L-2 and L-3 nerve roots (188).

Because of the lack of good controlled data and of its invasiveness, ablation of sympathetic ganglia, chemical or surgical, should be considered only in patients who report transient pain and symptom relief with a series of different nonablative sympathetic procedures. Specifically, it is recommended a CRPS patient must report clinically meaningful relief of at least several days' duration after at least five sympathetic blocks, each with similar degrees of relief. Moreover, before considering sympathectomy, a CRPS patient should have experienced no success with nonsurgical approaches. Even in this small subset of CRPS patients who meet these criteria, long-term significant relief after appropriately performed surgical sympathectomy is by no means guaranteed.

CONCLUSIONS

Recommended Current Treatment

The key to treating CRPS is to validate the patient's symptoms and initiate a multidisciplinary treatment plan with the goal of functional restoration over months of therapy. The treating physician should be aggressive with medical therapies, systematically initiating different pharmacotherapeutic regimens if the patient continues to report significant pain and other CRPS symptoms. Psychological therapies, including stress management, supportive psychotherapy, and treatment of psychological comorbidities, should be initiated early and be an integral component of the multidisciplinary approach. Probably the most important component of the multidisciplinary treatment is active physiotherapy, which should include a slowly progressive active therapy program. It is imperative that the CRPS patient is cared for by a cohesive team that meets regularly to discuss the patient's progress and shares treatment philosophies and approaches.

Lastly, besides performing nerve blocks and prescribing medication (both activities that rarely significantly alleviate the CRPS patient's pain and suffering), all health care providers must provide the CRPS patient with all of the following: (a) a model for understanding their symptoms, (b) validation of their symptoms and suffering, (c) rewards for even the smallest functional improvement, and (d) a sense of optimism.

Recommendations for Future Clinical Research

As the field moves forward with the primary aim of improving the treatment of patients with CRPS, several recommendations for future treatment outcome studies can be made:

- Future clinical trials should be placebo controlled.
- If possible, a crossover design should be used because of the significant individual variability and the likelihood of subpopulations of CRPS patients with distinct pain mechanisms.
- Outcome measures should include the treatment's effect on the following: (a) various pain descriptors, such as with the Neuropathic Pain Scale (101), (b) various CRPS symptoms and signs, and (c) patient function.
- Post-hoc analyses should be performed to assess whether certain subpopulations of CRPS patients respond to the treatment, perhaps based on the presence of certain pain descriptors, symptoms, or signs, even if an overall treatment effect on CRPS was absent.
- Neuroimaging studies, such as positron emission tomographic and functional magnetic resonance imaging, should be performed, assessing baseline and treatment alterations in brain functioning of CRPS patients.
- Prospective studies should be done of acutely injured patients after surgery and soft tissue and nerve injuries to assess potential risk factors for the development of CRPS, including medical, psychological, and environmental variables.

CHAPTER REFERENCES

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CHAPTER 21

Pain after Amputation: Phantom Limb and Stump Pain

John D. Loeser

This chapter discusses the pathogenesis and management of two of the most vexatious forms of chronic pain: postamputation stump pain and phantom limb pain. Although clinical similarities exist between these pain syndromes and the pains that develop after spinal cord injury, brachial plexus avulsion, injuries to nerves in the extremities, and severe polyneuropathies, those conditions are discussed elsewhere in the book. It is also likely that the mechanisms that generate these pain syndromes are shared by all neuropathic pains.

Postamputation pain syndromes have also been described after the loss of other body parts, including the nose, tongue, breast, fingers, teeth, testes, penis, bladder, and anus (1,2,3,4 and 5). The incidence of these types of pain is unknown; however, there are few data for meaningful discussion. Although amputation of a breast is far more common than the loss of a limb, only a few reports discuss phantom breast sensations or pain. Mastectomy has been reported to lead to a phantom sensation in 22% to 64% of the women who have had this operation, and some women also report phantom pains (6). Most of these women do not report their symptoms to their physicians; the role of psychological and social factors is unclear. The lessons learned from the study of the loss of an extremity can be applied to some degree to these less well-described forms of phantom pain. A pain syndrome likely occurs in proportion to the amount of tissue loss and the number of axons that are destroyed.

Little has changed in the management of stump and phantom limb pain since 1953, when Bonica (7) summarized the situation in the first edition of this book:

> [T]his type of pain taxes the psychologic as well as the physical endurance of the patient and the therapeutic skill of the physician to the utmost. . . . Many of these patients go from one physician to another and from clinic to clinic seeking relief that, all too frequently, does not come. They undergo a succession of medical and surgical measures, each one tried with a great deal of hope and anticipation that it will be *the one* that will effect a cure, only to fail as miserably as the previous ones.

Phantom limb and stump pain was certainly recognized by Ambroise Paré (8) in the middle of the sixteenth century. Like so many of the physicians who have written on this type of pain, he obtained his experience as a military surgeon. In the 1870s, S. Weir Mitchell (1) emphasized the magnitude of suffering with this type of pain in his medical studies and literary essays based on his observations in the American Civil War. Apparently he was the first to use the term *phantom limb pain*. Every major war for the past 140 years has produced another set of articles on this topic. Yet, a survey by Sherman and Sherman (9) could not identify differences between civilian and military amputees. Since 1980, studies of the anatomic and physiologic changes associated with amputation neuromata and spinal cord changes after nerve injury have led to dramatic advances in our understanding of some of the potential mechanisms of these types of pain (see Chapter 3 and Chapter 4). The reader who wishes to obtain more clinical information is referred to major works by Cronholm (10), Solonen (11), Sunderland (12), Livingston (13), Sherman and Sherman (14), and Jensen et al. (15).

DEFINITIONS

Phantom Limb Sensation

Virtually all amputees describe phantom limb sensations (1,12,15,16,17 and 18). These are a variety of positive sensory phenomena, including the perception that the limb is still present, although usually foreshortened and often distorted in position. The phantom sensation is almost always more vivid in the distal extremity. With time, the phantom part may telescope into the stump. Paresthesias may be reported in the phantom. Many patients report the ability to cause the phantom to move by conscious thought. The phantom usually fades during the first year after amputation (12). The vast majority of patients who have phantom sensations do not have phantom limb pain (12).

Phantom Limb Pain

Phantom limb pain is a chronic pain perceived in the absent body part. It can be a minor problem or can totally consume the patient's life. The incidence of phantom limb pain is variably reported from 0% to virtually 100% (10,11 and 12,15,18). Such a wide range must imply differences in physician and patient labeling of pain.

Stump Pain

Stump pain is a chronic pain perceived in the region of the amputation; the pain is perceived to be located in existing body parts. The incidence of stump pain is between 10% and 25% (12,15,18). It may be diffuse or focal and is often associated by patients and physicians with palpable neuromata in the amputation site. However, all amputees have neuromata and not all have phantom or stump pain. A patient can have stump pain alone, or it can be associated with phantom limb sensations or phantom limb pain. It is critical that stump pain be recognized as distinct from phantom limb pain; treatment strategies for the two conditions are quite different. Whether they have any etiologic similarities is unknown.

PHANTOM LIMB PHENOMENA

Phantom limb sensation, which probably occurs in all amputees, is a vivid, highly articulated image of the lost part, and it contrasts with the poorly defined phantom sensations of the anesthetic body parts in paraplegics and quadriplegics. The vividness of phantom limb sensation in amputees suggests that the spinal segmental apparatus plays a role in the genesis of the phantom that characterizes the loss of a limb; when the spinal cord has been transected, a much vaguer image is created by the remaining more rostral neural structures (19).

Pathophysiology and Mechanisms

Phantom limb sensations can be created by caudal, spinal, or regional anesthesia (20,21,22 and 23). Occasionally, these phantom sensations are considered painful by the patient. Such immediate phantoms after local anesthetics must be caused by the abrupt cessation of peripheral nerve electrical activity. This hypothesis is confirmed by the observation that as soon as any sensation returns, the phantom disappears. Wall (24) suggested that C-fiber silence leads to phantom limb sensations, but the evidence for this is not conclusive. The study by Nyström and Hagbarth suggested that C fibers were active in patients with phantom limb pain (25).

Because many peripheral sensory nerves synapse in the dorsal horns of the appropriate spinal cord segments, it has been presumed that these second-order neurons play a key role in the genesis of phantom sensations. It must be remembered, however, that axons that form the dorsal columns only send collaterals to the segmental apparatus; their first synapse is in the medulla, raising the possibility that abnormal activity in the dorsal column nuclei could also play a role in phantom sensations (see Chapter 4). Kjerulf and Loeser (26) showed that forelimb deafferentation in the cat led to abnormal spontaneous and evoked activity in the lateral cuneate nucleus.

Although rapid changes in sensory fields of dorsal horn neurons have been described after dorsal rhizotomy or peripheral neurotomy, even these are not instantaneous (27,28). Clearly the segmental spinal mechanisms cannot be sufficient for the production of phantom sensations, because alterations in their output must reach higher centers to cause the patient to become aware of a phantom. Lesions occurring higher in the nervous system are well known to influence the presence or absence of phantom sensations (12,29,30 and 31).

Patients with phantom limb phenomena can develop radicular pains secondary to a herniated nucleus pulposus. When this occurs, the patient complains of low back pain that radiates into the stump and phantom, just as if the normal limb were present. Removing the disk alleviates the radicular pain but does not change the phantom itself (7,32). Cohen (33) has made another interesting observation on the referral of the pain of angina pectoris to an amputated left arm. The several patients who have manifested this phenomenon described pain typical of angina, clearly distinct from other phantom sensations or phantom limb pain.

Phantom limb sensations do not depend on the abnormal electrical activity generated in the neuroma. As described above, phantom sensations can follow local anesthesia in which there is not peripheral electrical activity. Mechanically stimulating the neuroma does not alter phantom sensations. Instead, it produces an electricity-like pain that radiates into the peripheral nerve distribution of the transected nerve (34). Blocking the nerves leading into the stump or their neuromata usually does not change phantom sensations either (25).

Clearly, the above observations include a paradox: Phantom sensations can be due to the loss of afferent input, but when some afferent input is reestablished by the development of electrical activity in the neuroma (which takes a few weeks in humans), the phantom sensations do not disappear. This strongly suggests the development of long-term central changes after deafferentation. Yet it is common for the phantom sensations to recede and eventually disappear over a year or more (10,12,35,36).

The vividness and, indeed, the presence of a phantom can be influenced by conscious and unconscious mechanisms. We do not know if the fading of the phantom is the result of changes at the spinal segmental level or in higher centers. Lesions in the spinal cord or brain that would be expected to render a body part anesthetic will abolish phantom sensations but do not often eliminate phantom limb pain. This is another clue that the same central processing systems that deal with normal sensory phenomena are involved in the perception of a phantom body part.

Congenitally absent limbs or those lost early in childhood seem to be less likely to lead to phantom phenomena, implying that the phantom depends on an intact body map in the cerebral hemispheres (37). On the other hand, Poeck (38) and Weinstein et al. (39) have described patients with limb aplasia and loss of limbs in infancy who did have typical phantom sensations. They also found a few other examples in the literature. Smith and Thompson have reported that phantom limb pain in children after amputation for extremity cancer was more common than after amputation for trauma and that chemotherapy increased the likelihood of developing phantom limb pain (40). More studies are needed to accurately determine what the likelihood of phantom phenomena and phantom limb pain is in aplastics or children who sustain early life limb loss.

Symptoms and Signs

If asked, almost all patients who lose a limb or major portion thereof report phantom sensations (10,35,36,41). The likelihood of developing phantom sensations after amputation seems to increase from infancy to approximately 8 years of age, at which point phantom sensations are virtually certain (37). Simmel (42), however, noted that lepers who gradually lost their distal extremities did not develop phantom sensations; when surgical amputation was performed for infection or major trauma, phantom sensations were reported. Price's (43) study suggested that lepers did have phantom phenomena; however, they were not associated with paresthesias and dysesthesias but were instead a sensation that the normal missing part was present. A similar phenomenon has been described in some patients with phantom limbs, but most patients describe active distortions of sensation and not just a feeling that a normal limb is present.

Although there have been a few contradictory reports, it does not appear that the development of a phantom sensation is related to the level of the amputation (whether the amputation involves the upper or lower extremity) or to the rapidity of loss of the extremity or the age of the patient past childhood. Phantom sensations are usually present immediately after amputation but may take a few weeks to develop.

Phantom limb experiences can be divided into three categories: kinesthetic (distortion of positional sensation), kinetic (sensation of movement), and exteroceptive (surface sensations such as pins and needles, buzzing, heat) (44). The patient describes a limb that has a position in space as well as definite length and volume. The limb may be movable, fixed, normal in posture, or distorted. The kinesthetic sensations often change over time; the phantom becomes less normal. Most phantom limbs have the sensation of movement. Exteroceptive sensations are common, but they are often diffuse. All sensory modalities have been reported, and they frequently fluctuate in nature and intensity. Some report that their phantom feels like a normal limb; others describe sensations of paresthesias, dysesthesias, and distorted positions (18).

Phantom sensations usually abate over time, but they can suddenly recur. Older amputees appear to have a more fixed phantom sensation; younger patients can voluntarily influence their sensations to a greater degree (45). Characteristically, the phantom limb “telescopes”; the proximal part of the limb disappears first. A patient may report that his or her hand is attached directly to the stump and that he or she has no sensation of the intervening arm or forearm. Because the perception of superficial tissue damage is one of the exteroceptive sensations, it is not clear that phantom limb pain is qualitatively different from other sensations such as heat, cold, pins and needles, or numbness. What differs may be the behavioral response of the patient to this sensory illusion. In conclusion, phantom experiences clearly depend on changes in the peripheral and central nervous system as well as affective, cognitive, and environmental factors.

Treatment

Phantom sensations, by definition not painful, can be frightening to the unprepared patient. Although there is no reasonable, effective treatment in the medical sense, there certainly is a need for patient counseling and education, which should begin before amputation whenever possible. Meeting an amputee who has successfully rehabilitated him- or herself can be helpful. Explaining to the patient that phantom sensations are normal and not a sign of mental illness is also important. As is true for any type of pain problem, the health care provider can be of great value to the patient by offering education, reassurance, and compassion.

STUMP PAIN

Many authors have not discriminated carefully between stump pain and phantom pain; this failure makes the literature confusing. Stump pain is ubiquitous immediately after amputation; this is simply postoperative pain and can be expected to disappear in a few weeks, as is true for pain after any major operation. Some amputees have stump pain that long outlasts healing time; the reported incidence varies from 13% to 71% (10,46). Some have averred that stump pain is more likely to occur if there has been pain before amputation, but this relationship is not supported by reports of all observers.

There appear to be two categories of stump pain: that due to local pathology and that due to the injury to peripheral nerves and the central nervous system responses to nerve injury. Careful examination of the stump; judicious use of imaging studies, bone scans, thermography, and plethysmography; and proper fitting of the prosthesis can help identify local pathology. As noted by Zborowski (47) and subsequent observers, environmental and cultural factors can also play a role in the

genesis of stump pain.

Etiology and Pathophysiology

There are several recognized causes of pain in an amputation stump: surgical trauma, ischemia, inflammation, skin infection or trauma, bone spurs, local scarring, ill-fitting prosthesis, neuromata, and central changes due to deafferentation (12). The pain of surgical amputation should not last more than a few weeks and almost always disappears as the wound heals. This pain is due to the activation of nociceptive nerve fibers of the A-d and C-fiber spectra.

The stump may have inadequate blood supply due to vascular disease proximal to the stump or to poor vascularization of the muscles and skin of the stump itself. Infection, either superficial or deep, can also lead to stump pain. Osteomyelitis is a frequent form of infection. Poor skin hygiene with pressure areas or ulceration can result from inadequate personal hygiene, marginal blood supply, or a poorly fitting prosthesis. A poorly trimmed bone can lead to pressure on innervated structures; new bone growth can also be a source of pain. All of these provoke nociceptive types of pain (peripheral mechanisms), and they do not necessarily involve any pathology intrinsic to the nervous system.

Stump pain often appears to be due to the presence of neuromata. All amputations result in neuromata not only of the major nerves but also of the smaller nerves in skin and deep structures. Because only a fraction of amputees develop stump pain, the presence of neuromata *per se* cannot be the cause of pain. When a neuroma is repeatedly traumatized by weight bearing or a prosthesis, however, it clearly can be one of the causes of stump pain. In a stump with extensive scarring, neuromata may be mechanically traumatized with any movement. The extreme sensitivity of the axon sprouts in a neuroma to mechanical or chemical stimuli is probably the basis for this type of pain (48). Changes in the dorsal root ganglia and the dorsal horn secondary to nerve injury and neuroma formation can also be contributors to stump pain (see Chapter 3).

There is also the possibility that autonomic nervous system abnormalities play a role in stump pain, even in the absence of local pathology. Some patients experience causalgic symptoms in their stumps, including burning, aching pain and vasomotor, pilomotor, and sudomotor abnormalities. Animal studies have shown ephaptic connections and sprouting axons ascending the proximal nerve stump that involve sympathetic postganglionic axons (49). Sympathetic fibers also grow onto the dorsal root ganglion cells after peripheral nerve injury (50).

Finally, there is a large group of patients who complain of stump pain in whom none of the above factors seems to be playing a role. Almost always, such patients have both phantom limb pain and stump pain. In such patients it is possible that spinal cord or more rostral neural structures are the sites for the genesis of the pain.

In summary, stump pains are varyingly present after healing of the amputation site. They are of diverse etiology and vary widely in their sensory and temporal characteristics (12). Any or all of the mechanisms that underlie neuropathic pain states may be operative in the patient with stump pain (see Chapter 3 and Phantom Limb Pain, below).

Symptoms and Signs

Stump pains may be continuous or intermittent, focal or diffuse. They may be triggered by stimulation of the stump or by emotional stress. The pain can be described as cramping, burning, shooting, hot, cold, aching, or any combination of these. Many patients have movements of the stump in association with their pain. Myoclonic jerks and chronic contractions of agonists and antagonists are seen. Some patients have clear-cut attacks of pain with pain-free intervals. Patients with severe stump pain often also have phantom limb pain and vice versa.

Treatment

As mentioned earlier in this chapter, stump pain can be associated with pathology in the stump itself. Although this does not appear to be the common cause of this complaint, it happens frequently enough to mandate that a painful stump be carefully examined. The presence of a skin lesion, bone spur, osteomyelitis, deep abscess, or circulatory insufficiency requires appropriate medical or surgical therapy. Revision of the stump has had its proponents, but in the absence of demonstrable pathology most experts would doubt the wisdom of this procedure (12,51,52).

Stump pain can be due to a poorly fitted prosthesis. Therefore, careful evaluation of the stump and the prosthesis by an expert prosthetist is always warranted. If the pain is believed to be due to a neuroma, management becomes more complex. Obviously, prevention of a painful neuroma is highly desirable; many have reported surgical strategies that they believe reduce the rate of painful neuromata (53,54). Whether encapsulation of the cut nerve, fascicle ligation, or self-implantation of the nerve reduces the incidence of painful neuromata and stump pain is unknown. In his review of the U.S. Army experience in World War II, White (55) listed several procedures that should never be undertaken to relieve stump pain: repeated resections of neuromata, neurectomies at higher levels, reamputation for pain relief, periarterial sympathectomy, intrathecal alcohol, and dorsal rhizotomy. He believed that the following procedures were useful: single resection of a painful neuroma, sympathectomy, and anterolateral cordotomy. He emphasized that the first two procedures should only be carried out when relief of the stump pain occurs with appropriate prognostic nerve blocks. My observations suggest that only patients with allodynia or dysesthetic stump pain respond to sympathectomy— that is, only when the pain resembles complex regional pain syndrome type I does it respond to sympathectomy. The likelihood that a cordotomy will provide pain relief for more than 2 years appears to be small (see Chapter 106).

Finding other reports that separately consider stump pain and its management is difficult. Clearly, many of the remedies discussed under Phantom Limb Pain have also been used for stump pain; there are not sufficient data to discuss these independently. Some aspects of the management of stump pain are therefore contained in the following section, Phantom Limb Pain.

PHANTOM LIMB PAIN

Epidemiology

The incidence of phantom limb is not known precisely; reports vary from 2% to 97% of patients who have undergone limb amputation (11,12,14,44,50,56,57,58,59 and 60). It is clear that the patient and the observer may vary in what they consider to be a significant amount of pain and where they localize it. All that can be said about incidence is that phantom limb pain is a well-recognized problem in a fraction of the amputees. Surveys with more reliable methodology suggest a prevalence of phantom limb pain of approximately 70% that is stable over many years (Table 21-1).

Time since amputation	Prevalence of phantom limb pain	Primary author
8 days	72%	Jensen (1983)
16 wk	59%	Pohjolainen (1991)
6 mo	67%	Jensen (1983)
1 yr	53%	Pohjolainen (1991)
2 yr	59%	Jensen (1985)
5 yr	73%	Steinbach (1982)

TABLE 21-1. Prevalence of phantom limb pain

Etiology

The role of preamputation pain in the genesis of phantom limb pain is unclear. Some have suggested that pain before amputation increases the likelihood of severe phantom limb pain (1,10,44,61,62,63 and 64). Others have not found this association (14,35,65). Whether “preemptive analgesia” reduces the likelihood of phantom limb pain is uncertain, in my opinion (66,67). Many patients report that their phantom sensations and phantom limb pain are similar to the position of the limb and the sites of pain immediately before amputation, yet a study of patients whose amputations were performed for extremity cancer (65) indicated that most patients' phantom limb pains were unrelated to preamputation pain.

The relationships of the level of amputation and the reason for amputation to the presence of phantom pain are unclear. Use of a prosthesis and lower age at amputation appear to be correlated with a lower incidence of phantom limb pain (56). The extensive survey by Sherman and Sherman (14) failed to note any correlation between preinjury factors and incidence of phantom limb pain. In summary, there is conflicting evidence on the relationships between preamputation factors and phantom limb pain. Moreover, little evidence exists to support the allegation that postamputation factors play a major role in the genesis or perpetuation of phantom limb pain.

It is unclear whether phantom limb pain is part of a continuum that begins with the phantom limb sensations or is a distinct phenomenon with its own neural substrate. Some patients report that their phantom limb pain began at the time of amputation, and others state that the pain developed weeks, months, or even years later.

Pathophysiology and Mechanisms

The hypotheses for the pathophysiology of phantom limb pain can be divided into four categories: (a) peripheral (i.e., due to loss of peripheral nerve activity or development of abnormal activity in the neuroma or dorsal root ganglion cells), (b) spinal segmental (i.e., deafferentation effects), (c) central (i.e., due to changes in thalamus and cerebral cortex), and (d) psychological (implying that mental processes led to the patient's symptoms) (17,68,69).

In the patient who develops phantom limb pain immediately after amputation, the sudden absence of nerve signals from the periphery may trigger changes in the spinal cord or even more rostral structures that lead to the report of pain (24). Another possibility is that a massive discharge of axons at the time of injury or amputation leads to central changes that generate the report of pain (excitatory amino acid toxicity) (see Chapter 3). This explanation has led to the concept of *preemptive analgesia*: dense local anesthetic blockade of the plexus leading to the limb before amputation. Conflicting evidence as to the efficacy of this approach has been published (66,67). Whether preemptive analgesia is effective is impossible to determine on the basis of the published articles; additional clinical trials are required to resolve this debate.

Peripheral Factors

Because the development of phantom limb pain can be delayed and the nature of the abnormal sensations can vary, multiple etiologies must be considered. Animal studies have indicated potential peripheral factors in the genesis of pain that include the following: (a) ephaptic connections, (b) spontaneous activity in the neuroma or in dorsal root ganglion cells whose axons are involved in the neuroma, (c) abnormal sensitivity to mechanical and chemical stimuli in the neuroma, (d) alterations in conduction velocities in damaged nerves, and (e) reflex changes in sympathetic activity (24,49,69,70).

The microneurographic studies of two patients with phantom limb pain by Nyström and Hagbarth (25) clearly showed that spontaneous C-fiber axonal activity could be recorded in transected nerves. Local anesthetic applied to the stump neuroma stopped both the evoked electrical activity and the stump pain reported by the patient when the neuroma was mechanically stimulated, but neither the phantom limb pain nor the spontaneous electrical activity in the nerve was altered by the neuroma blockade. These results imply that the phantom limb pain and some of the activity in the peripheral nerve are generated proximally to the neuroma, either in the dorsal root ganglion, dorsal horn, or more rostral structures.

Dorsal Horn Changes

Changes in the segmental dorsal horn afferentation have also been postulated to be a factor in phantom limb pain. On the basis of clinical observations, Howe (71) proposed that nerve transection leads to the loss of high-threshold input to dorsal horn neurons; new connections are made by low-threshold afferents. This hypothesis would account for the patient's reporting that nonnoxious stimulation of other regions of the body could trigger phantom limb pain. Many years earlier, Haber (72) noted that the skin of an amputation stump was much more sensitive to a wide range of stimuli than the homologous region on the opposite extremity. These observations certainly strengthen the arguments for changes in the dorsal horn connections as key factors in phantom limb and, perhaps, stump pain.

Many observations attest to the role of the stump and its neuromata in the genesis of phantom limb pain (12,24). It has been argued (without much evidence) that special treatments of the transected nerves in the amputation stump reduce the likelihood of phantom limb pain (73). Sensory and autonomic abnormalities are often described in the stumps of patients with phantom limb pain. Local and regional anesthetics and resection of the neuromata usually result in the temporary cessation of phantom limb pain (7,74). Mechanical stimulation or deformation of the stump often alters the pain (1). The fact that *N*-methyl-d-aspartate receptor blockade can relieve phantom pain suggests central sensitization by the peripheral nerve injury (75).

Central Factors

Other observations emphasize the importance of central nervous system factors in the genesis of phantom limb pain. Phantom pain can be present without stump pain or any evidence of disease in the stump or painful neuromata. Often neither section of the dorsal roots nor cordotomy relieves phantom limb pain. The pain often develops immediately after the amputation, before the development of neuromata that could lead to peripheral nerve abnormal activity. Stimulation of a stump neuroma does not activate phantom limb pain (34,35). Surgical repair of a stump usually does not alter phantom limb pain. The phantom sensations and pain can be influenced by affective factors and sensory changes in other parts of the body.

Spinal anesthesia can unmask phantom limb pain at a time when the patient does not have any complaints of phantom limb pain before the administration of spinal or epidural local anesthetic (7,76). The phantom pain persists only as long as the complete loss of proprioception and movement. Such observations imply that the spinal segmental input to rostral structures plays an important role in the sensations that the patient reports. Clear-cut evidence of cortical reorganization suggests that phantom limb pain can be the result of sensory cortex neuronal field changes (77,78).

On the basis of these and other clinical and experimental observations, it appears that both peripheral and central factors play a role in phantom limb pain. We do not know why some individuals become chronic pain patients after amputation and others do not. Certainly, a phenomenon that occurs in a fraction of the amputees cannot be blamed solely on the anatomic injury. Perhaps there are genetic predisposing factors that will be difficult to elucidate in humans. In the dorsal horn and in thalamus and cerebral cortex, there is good evidence that reorganization of sensory fields occurs after amputation; how these changes are related to the genesis of pain remains unclear.

Psychological and Emotional Factors

The psychological aspects of phantom limb pain have been the object of much speculation. Some have argued that this is a psychosomatic disease (79,80 and 81). Bailey and Moersch (61) reviewed 55 cases from the Mayo Clinic and concluded that no physiologic explanation for this type of pain could be discerned. They proposed that phantom limb pain was a “psychic” disease. Certainly, the absence of understanding of physiology does not establish the diagnosis of psychopathology.

Others have noted that stress and emotional factors can aggravate the pain (82). Almagor et al. (83) showed that double amputees were more likely to have phantom limb pain in their dominant extremity, but that the patient's response to his limb loss did not seem to influence the incidence of phantom limb pain. Parkes and Napier (82) described characteristic psychosocial factors: rigid, self-reliant to a fault, unemployed. These individuals were more likely to have significant pain complaints. The psychiatric literature is cluttered with theoretical explanations that cannot be verified by any rational means (79,84): “[T]he phantom, like the dream, is a product of unconscious wishes or drives.” Patients who complain of phantom limb pain are more depressed, have more complaints of other types of pain, and have more interpersonal problems than amputees who do not have phantom pain (85,86 and 87). Genetic factors could also play a role.

The emotional status of an amputee is clearly a function of the setting in which the amputation has occurred and the patient's personality and social environment. The study by Shukla et al. (88) indicated that two-thirds of an unselected group of civilian amputees had significant psychiatric symptoms in the first few months after

amputation. There are very few data on the correlation between early psychiatric symptoms and the persistence of phantom limb pain. Gallinek (89) argued that the hallucinations of psychotics were distinct from the phantom phenomena seen in amputees, although there is no reason to suggest that the mechanisms underlying these two phenomena have any commonality.

Obviously the brain is the organ of behavior, and emotional factors are due to electrochemical events in higher centers. We are so far from understanding these complex cognitive and emotional behaviors that their explanation is couched in a nonphysiologic language. This situation often leads the reader to believe that psychological processes are somehow not the result of electrical and chemical activities in the brain. The evidence for downstream modulation of afferent processing is strong; this is not unique to the problems of the genesis of phantom limb pain.

Cognitive Factors

One explanation for phantom sensations and phantom limb pain is based on cognitive processes. Ewalt et al. (90) wrote that “phantom pain occurs in those individuals who are having phantom sensations but who, by reasons of psychopathology, interpret the phantom sensations as being unpleasant and painful.” It is well known that the human develops a complex set of maps for both internal and external space. The body image appears to depend on the sensory and motor experiences from each region. When afferent information is suddenly distorted, a mismatch between the central map and afferent signals occurs. How the patient labels this phenomenon may determine whether the patient describes phantom sensations or phantom limb pain. It may not be a difference in the peripheral nerve activity or in the dorsal horn response to deafferentation that determines whether the patient has pain. The critical factor may be the labeling of the abnormal sensory experience. This, in turn, can be based on experience, personality type, genetic factors, age, and innumerable other unknown factors.

Amputation in Animals

It is worthwhile to consider the effects of nerve transection in other mammals. In some species, the animal attacks the denervated part; Wall and his associates (91) have labeled this *autotomy* and believe that it is a model for anesthesia dolorosa. No good evidence exists, however, that the animal is in pain. Different species are more or less likely to manifest the phenomenon. Even within one species, the genetic strain is a major determinant of autotomy (92). The histology and physiology do not appear to differ in animals with and without autotomy. By analogy, no evidence exists to support the concept that events at the neuroma or in the spinal cord differ in patients with and without phantom limb or phantom sensations. It seems more likely that preexisting differences in cognitive and affective information processing play a critical role in the genesis and maintenance of these pain syndromes.

Age

A final factor that seems critical is the age of the patient at the time of amputation. Phantom limb pain is rare in young children and becomes more common as the patient ages (10,37,49). This correlation suggests that plasticity of the nervous system is one of the factors that work against the development of a pain syndrome.

At this time, it is not possible to generate a unitary hypothesis for the pathogenesis of phantom limb pain. Clearly, necessary peripheral events exist, and there must be alterations in the spinal cord and brain function. Whether affective and cognitive factors are in response to the peripheral events or are themselves capable of modifying segmental information processing is unclear.

Symptoms and Signs

In most patients, phantom limb pain begins shortly after amputation; there are a few reports of onset months or even years later (1,61,73). Some of the patients who have phantom limb pain experience spontaneous remission in their symptoms, most often in the first year after the onset of their pain (7,11). Most of the pain is usually reported to be in the distal part of the extremity, usually in the foot or hand, particularly in the instep, heel, toes, fingertips, knuckles, palms, or wrists. Some patients report that the phantom extremity is distorted in a way that would be painful for an intact limb.

Characteristics of the Pain

All types of painful sensations have been reported. The pains can be continuous or intermittent and may occur randomly in severe attacks.

The intensity of the pain varies dramatically between patients. For some, it is only an annoyance; for others, it is almost unbearable and totally disrupts all productive activities and interferes with rest, sleep, and social relationships. Most patients freely admit that attention, emotional states, experiences, and other factors influence the amount of pain they experience. Severe pain is usually associated with paresthesias.

The quality of the pain also varies greatly: It has been described as burning, cramping, aching, gnawing, crushing, pulling, stabbing, or shooting. Approximately one-fourth of patients experience predominantly a burning, aching, throbbing pain, not unlike that of causalgia, which they describe is as if the hand or foot were held too close to a fire. This group may respond to sympathetic blockade. Approximately one-third of patients complain primarily of pain associated with an extremely abnormal position of the phantom limb. The hand or foot may be felt to be in a painful twisted, cramped, rigid, or flexed posture, from which the patient is unable to release it. In many of these patients, the fingers and thumb are tightly flexed, with the nails cutting into the palm. Occasionally, the digits or the hand, or both, or foot are felt to be twisted out of shape. When such sensations are present, patients find it difficult or impossible to change the posture of the malpositioned part. Some patients feel as if the nails of the fingers or toes are being pulled off or lifted from their nail beds. Others experience the feeling of the presence of a tight, wirelike band around the phantom limb that gradually gets tighter or that the phantom limb is being squeezed in a vice.

Careful questioning frequently reveals that the patient also experiences bizarre sensations that he or she is often reticent to discuss, lest someone label him or her insane. There is no information on the relationship between the type of sensation reported and the reason for amputation or any other potentially significant factors.

Numerous factors may aggravate the pain, including fatigue, sleeplessness, persistent worry, and even apprehension from knowing that the stump is going to be examined. The pain may also be aggravated by cooling or warming the stump, or even allowing it to hang. Sometimes such actions as yawning, micturition, or defecation temporarily exacerbate the pain. In contrast to the preservation of more or less free movement in painless phantoms, the presence of pain renders voluntary movement difficult, if not impossible. In some patients, wearing a prosthesis causes the phantom limb to elongate temporarily, and this sensation is associated with aggravation of the phantom pain.

The duration of phantom limb pains is unpredictable. In a few patients, they are transitory and recede in months. In others, the pain disappears after a year or so. The majority of patients seem to have pain that persists for a decade or more. Many patients report a constant background pain but also have superimposed major exacerbations of pain that may have a totally different character. Palpation of the stump or pathology in the stump, such as infection, may increase phantom limb pain in some patients. Patients may experience referral of pain into a phantom limb from stimulation elsewhere in the body or, for example, into a phantom arm from angina pectoris. Manipulation of a neuroma may change phantom limb sensations, including pain.

Treatment

The treatments of phantom limb and stump pain are myriad (Table 21-2), but good data for the efficacy of any method are lacking. Therefore, all I can do is to review the published treatments and summary articles and add some comments based on personal experience (12,30,51). One of the reasons for the apparent poor results of any published treatment is the failure to recognize that individuals may, on rare occasion, have a good result, yet the general population has a poor chance of success. Hence, it may be that one in 10 chronic stump or phantom limb pain patients is relieved by a particular medicine or surgical procedure. From that patient's viewpoint, the treatment was successful. Physicians and financial sponsors may be loath to advocate a treatment with so low a success rate; the informed patient should have the right to choose such a procedure. Obviously, such a predicament requires that the physician begin with the least hazardous treatment strategies. Because many papers do not discriminate between stump and phantom limb pain, analysis of possible outcomes is quite difficult. The review by Sherman (51) provides the best modern overview of this topic. Other large series attest to the low success rates of any single form of treatment (11). Sherman also alleges that the type of phantom limb pain mirrors changes in the stump skin and muscle and that therapies tailored to the pain description and physical examination have superior outcomes (93).

TABLE 21-2. Reported treatments for postamputation pain

Pharmacologic Therapies

Nonnarcotic Analgesics. Nonnarcotic analgesics are, of course, the most commonly used medications for any type of chronic pain. There is no evidence for their specificity in phantom limb pain; to the extent that they help a patient without side effects, they can be freely used (94).

Narcotic Analgesics. No studies have been published on the role of narcotics in phantom limb pain, but most of the physicians who deal with phantom limb pain and other deafferentation pain syndromes agree that it is a rare patient who can control this type of pain with narcotics. The usual picture is of increasing dosage and dependence on the drug, with poorer and poorer pain control, and increasing depression and disability. Nevertheless, there may be a small number of amputees whose phantom limb pain is best ameliorated by narcotics and who can maintain themselves without escalation of the dose. If a patient manifests more than just a verbal response to narcotics and actually increases his or her functional activities, it may be worth a cautious trial with oral narcotics. When activity levels decrease and drug intake increases, it is time to withdraw the patient from narcotics. This is the usual outcome when this class of drugs is used for deafferentation pain. The newer partial agonists do not seem to be any more effective than pure opioid agonists.

When oral or transcutaneous opioids fail, a trial of intrathecal or epidural opioids may be useful. If good short-term response is seen, an implanted catheter and pump may be effective (see Chapter 103). However, this is an expensive technology with frequent complications, and the criteria for selection of patients are not yet well established (95). There is no question, however, that some patients can get excellent pain relief with this method of opioid delivery. A large fraction of the patients requires additional intrathecal drugs to get adequate pain relief, such as clonidine or bupivacaine. These medications do not have Federal Food and Drug approval for intrathecal use at this time.

Other Medications. A few reports exist on the efficacy of anticonvulsants in the management of phantom limb pain (96,97). Carbamazepine is the most commonly used drug; others have included phenytoin, valproate, mephenytoin (Mesantoin), gabapentin, and lamotrigine. None of the reports has involved controlled studies.

Antidepressants have been used, but no good data are available attesting to their efficacy in phantom limb pain (98). They seem to be useful in many types of neuropathic pain and are the first class of drugs to try in a patient with phantom limb or stump pain. Personal anecdotes and unsubstantiated series attest to the efficacy of phenothiazines (99,100).

Propranolol, a beta-blocker, has been used in doses of 40 mg per day, with dramatic responses in a small number of patients (101,102). In contrast, Scadding et al. (103) reported poor results with this drug.

Mexiletine, an absorbable local anesthetic, has been reported as useful in patients with phantom limb pain, either alone or in conjunction with propranolol (104).

Calcitonin was found to be effective in a double-blind controlled study by Jaeger and Maier (105); there are few other reports on the use of this drug.

Sedatives and hypnotics have no role in the treatment of phantom limb pain, because they are not only ineffective in relieving it, but they also tend to be habit-forming and increase depression. Moreover, long-term use does not improve sleep disturbances that may be ascribed to the pain.

Other medications that have been the subject of sporadic reports include vitamins and a wide variety of herbs, nostrums, and chemicals that can be ingested or applied to the painful stump. There is no reason to believe that they are in any way effective.

Local and Regional Anesthesia

In the first edition of this book, Bonica (7) reviewed the extensive literature published up to 1953 and his personal experience in the use of regional analgesia for the management of patients with postamputation stump pain, phantom limb pain, or both. Although there have been few recent reports on the use of this method in the treatment for phantom limb and stump pain (51), Bonica believed it had a definite role in the management of these patients. The most important use is for diagnostic and prognostic purposes, although it may also be useful in a small percentage of patients as a therapeutic method (see Chapter 102).

Diagnostic and Prognostic Blocks. Nerve blocks may be valuable as a diagnostic tool to identify candidates for specific surgical procedures. For example, patients with a burning, throbbing pain in the phantom limb or in the stump frequently respond to block of the regional sympathetic nerve supply to the involved limb with a local anesthetic. Such patients may get a good long-term result from sympathectomy when a series of blocks provide complete but only temporary relief. In this regard, it is essential to ascertain that sympathetic interruption to the limb is complete. Bonica cited a number of patients who had undergone surgical sympathectomy with only partial or no relief of burning pain in the phantom limb, but who derived complete relief of pain with a local anesthetic sympathetic block (7). The obvious reason for the discrepancy is that the solution diffuses to include anomalous pathways, whereas the surgery removes the sympathetic chain and may omit such anomalous sympathetic nerves, which continue to provide sympathetic function to the limb. In addition, surgeons may not resect enough ganglia to completely denervate the extremity (see Chapter 105).

Paravertebral somatic nerve block can also be used as a diagnostic tool in the occasional patient who develops symptoms of radiculopathy in the phantom limb consequent to herniation of the intervertebral disk or other pathologic changes. Properly executed, such a procedure helps to ascertain the level of the nerve root or full nerve implicated in the pathophysiologic process. Another technique that has been advocated as part of the comprehensive evaluation of patients with postamputation pain is differential spinal (subarachnoid) block. The evidence that this procedure is of any value is sparse. The indications for these techniques and the advantages and limitations of these procedures are discussed in Chapter 102.

Therapeutic Blocks. Indications for therapeutic nerve blocks are few because, as for most other methods, long-term benefits appear to be infrequent. However, some patients derive long-term relief from repeated nerve blocks. Bonica cited the extensive experience of Leriche, Livingston, and a number of other investigators, as well as his own personal experience in the use of a series of sympathetic blockades in patients who experienced burning, aching pain in the phantom limb or the stump or both (7). It deserves reemphasis that, to achieve effective sympathetic denervation of the upper limb, it is necessary for the local anesthetic to diffuse extensively and block the middle cervical to the third or fourth thoracic ganglion inclusive. For the lower limb, it is essential to block the lowest two thoracic ganglia, as well as the lumbar sympathetic chain. In patients who derive complete but only temporary relief from blocks with local anesthetics and whose physical condition is too poor to tolerate a major neurosurgical operation, Bonica suggested chemical sympathectomy with phenol or alcohol. This procedure requires extensive experience and extreme care to avoid serious complications.

Infiltration of local anesthetics is sometimes effective in relieving the pain and associated phenomena for varying periods of time. Occasionally, trigger points are found in patients with stump pain and in patients with phantom limb pain who develop musculoskeletal disorders consequent to amputation (see Chapter 29). Gross (106) claimed that local anesthetics injected into trigger areas of the contralateral limb at the site of reported phantom limb pain provided long-term relief after several treatments, but no confirmative reports have been published. Bonica stated that intravenous infusion of procaine was effective in some patients (7). It is possible that

the systemic absorption of local anesthetics reduced ectopic firing in damaged nerves without altering nerve conduction.

Physical Methods

Acupuncture. A few anecdotal reports of successful treatment of phantom limb and stump pain with acupuncture can be found in the literature (107). I am dubious of the long-term efficacy of this method for phantom limb or stump pain.

Percussion or Vibration of the Stump. In 1947, Russell and Spalding (108) claimed that repeated percussion of the stump with a small hammer alleviated phantom limb and stump pain in most amputees. Since then, sporadic reports have included mention of either failure or success of this method (109). It is not commonly used today, perhaps because it seems to be low technology in a high-technology era of medicine. Several authors have claimed that vibration of the stump is effective in treating stump and phantom limb pain (110,111).

Other Physical Methods. Application of external heat or cold, internal heating by ultrasound, massage, manipulation of the stump, and adjustment of the prosthesis all have been claimed to be effective in some patients (109). Data are sparse; these treatments have few complications.

Psychological Strategies

Explanation and Reassurance. Little question exists that phantom sensations, phantom limb pain, and stump pain are not only uncomfortable but also may be inexplicable for the patient. One of the physician's primary roles is to educate the patient about the meaning and significance of his or her symptoms. When possible, this education should begin before amputation. The patient should be told that phantom sensations are ubiquitous and are not a sign of mental illness or complication of amputation. The expected course of acute postsurgical stump pain and the initial steps for the fitting of a prosthesis should be discussed in detail. If chronic stump pain or phantom limb pain occurs, the patient must be given the support and encouragement of a concerned physician who will work with the patient to ameliorate the symptoms. It repeatedly amazes me how many patients with phantom limb pain are referred to our pain center with many years of suffering, never having had a reasonable explanation of the causes of their pain syndrome.

Hypnosis. Hypnosis has been reported to be successful in a small number of patients (51). For this approach to be cost-effective, the patient must be able to learn self-hypnosis. I have encountered a few patients who found this strategy helpful.

Psychotherapy. Patients who have lost a limb are not immune to preexisting or subsequent psychiatric illness. Various forms of psychotherapy can be helpful for such cases. Kolb (79) expressed the viewpoint that phantom limb pain was itself a psychiatric illness and could be treated by psychotherapy. Others have reported successes and failures (51). An association between depression and chronic pain of any type exists; to the extent that a patient with phantom limb pain is depressed, psychotherapy may be valuable. Little question exists that some patients benefit from psychotherapy, but it does not appear to be a form of treatment with high specificity for phantom limb or stump pain.

Cognitive-behavioral Therapy. Cognitive-behavioral therapy has been shown to be effective for chronic pain when the patient's complaints are under environmental control, are related to disuse or deconditioning, and are not due to tissue damage or injury to the nervous system (see Chapter 88 and Chapter 89). A patient with stump or phantom limb pain is not usually a candidate for this type of treatment, but the occasional patient may have complaints and pain behaviors that can be ameliorated by such a treatment strategy.

Biofeedback. Some have reported on the efficacy of electromyographic or electroencephalographic biofeedback of phantom limb pain (51,112). Biofeedback does not appear to be widely used for this type of pain, and data are sparse.

Relaxation Training. Sherman et al. (113) reported on the efficacy of relaxation training in the management of phantom limb pain. Twelve of 14 patients benefited, with follow-up periods of 6 months to 3 years. This method has widespread usage for other types of chronic pain and may be valuable for stump pain and phantom limb pain as well.

Vocational Counseling. Patients who have lost a limb require extensive rehabilitative services to return to as normal as possible a lifestyle. Vocational assessment, counseling, and training are essential for every amputee and reduce the extent of disability. Amputees who complain of stump or phantom pain must have vocational counseling as part of their overall management. It is generally true that people who have something better to do do not hurt as much.

Surgical Therapies

Few published reviews exist of surgical therapies for phantom limb and stump pain. Perhaps the best is by Siegfried and Cetinalp in 1981 (114). White and Sweet (30) have discussed their experiences, and Sherman (51) has published his survey, which indicates that few patients admit to success from any surgical procedure. Falconer (115) provided a good review. There are no good prospective or controlled studies; the follow-up periods are often short or unspecified. This does not distinguish the surgical reports from those involving other methods, but the additional risks and costs of surgery seem to mandate that better data be obtained to justify extensive use of surgical procedures.

Revision of Stump. Stump revision is a useless procedure for phantom limb pain, but it may be indicated in selected patients with stump pain. The indications for this operation are few, and the most likely origin of the need for this procedure is an improper amputation in the first place (116). Only when the patient's complaint of pain can be reasonably ascribed to a pathologic process in the stump is revision warranted. When a stump revision is done solely to treat pain without any sign of disease in the stump, it is almost certain to fail. Baumgartner and Riniker (117) reported excellent pain relief in 87% of 172 stump revisions in 100 patients. Eighty percent of these patients had a diagnosable lesion in their stumps, and this type of patient had the best outcome. The duration of follow-up was not given.

Another long-standing debate exists as to the efficacy of special treatment of the nerves at the time of amputation or stump revision in the prevention of stump or phantom limb pain (44,51,53,54,118). There is agreement that the nerve should be transected at the time of amputation so that the neuroma will lie in healthy muscle in a non–weight-bearing area. Beyond this, there is no consensus. Each surgeon claims that his or her strategy reduces the pain problems seen with everyone else's amputations.

Neuroma resection is warranted only when the patient's symptoms are due to mechanical pressure on the neuroma. This operation never alleviates phantom limb pain but may, in the specific case mentioned above, provide symptomatic relief of stump pain. A neuroma always forms at the proximal end of the transected nerve; it is typical for pain relief to last the 3 weeks that it takes for new growth cones to develop at the transection site (12,51). Reports of pain relief exist in the literature, and I have seen patients who have reported pain relief after neuroma resection, but this is a rare outcome. The history of failure to get pain relief with one or more prior neuroma resections should be an absolute contraindication to another attempt with this procedure.

Dorsal rhizotomy is not often effective for the relief of phantom limb or stump pain (30,44,51). Chapter 106 reviews this operation and discusses the potential reasons for its high failure rate. Whether the addition of ganglionectomy and the use of the operating microscope to guarantee complete root section would improve success rates is unknown. There are no contemporary reports on this operation for phantom limb or stump pain.

Dorsal Root Entry Zone Lesions. This operation has been performed for two decades, and the reported series are small (see Chapter 106). In approximately 24 patients, the success rate is approximately 50% (114,119). How to select patients to improve the chances of success is unclear. On the basis of preliminary data, this operation has some chance of alleviating stump or phantom pain and is probably a wiser choice than any other ablative procedure.

Dorsal Column Tractotomy. Dorsal column tractotomy was described by Pool (120) in 1946; a subsequent report by Browder and Gallagher (121) in 1948 brought the total number of cases to nine. Good results were described with very short follow-up periods. It is not known whether this procedure, which interrupts the dorsal columns, would be more effective than anterolateral cordotomy for patients who describe phantom limb pain in which distortion of the body part is a major component. This operation has not been reported in the past 50 years. Whether it ever received an adequate trial is unknown.

Anterolateral Cordotomy. Anterolateral cordotomy has gotten mixed reviews for both phantom limb and stump pain. It does not appear to be very effective for the burning, dysesthetic types of pain. Reports by White and Sweet (30), Falconer (115), Falconer and Lindsay (122), Rousseaux and Lepoire (123), and others suggest

that approximately half of the patients get good results, at least in the first year or so. Cordotomy is discussed in detail in Chapter 106.

Sympathectomy. For patients who complain of a burning or dysesthetic stump pain or phantom limb pain, sympathectomy may be effective (see Chapter 105). It is essential that a favorable response to sympathetic blockade be demonstrated before a surgical procedure is contemplated. Only when repeated blocks yield temporary but not permanent relief is surgery warranted. The report by Echlin (124) demonstrated that, after transection of the lumbar sympathetic chain, stimulation of the distal segment did not produce pain, but stimulation of the proximal segment reproduced the patient's phantom pain. The sympathectomy relieved the phantom pain for the duration of the 3-month follow-up. Others have reported varying degrees of success, but there are many late failures (31,51,125,126). The literature and our experience at the University of Washington Pain Center suggest that sympathectomy is likely to be effective only when the patient's symptoms are similar to those of causalgia. Long-term success is much less likely than immediate good results (31,44).

Thalamotomy. Stereotaxic lesions in various portions of the nonspecific thalamus and subthalamus and mesencephalon have been used in the treatment of phantom limb pain (114). Short-term results suggest a 20% success rate, but long-term follow-up of patients who have had these lesions indicates an even lower success rate (51). They probably are not a wise choice in the management of stump or phantom limb pain (see Chapter 108).

Cortical Resection. First reported by de Gutierrez-Mahoney in 1944 (127), cortical resection has been extensively discussed and occasionally performed. The extent of postcentral gyrus resection is often not detailed, and the results are therefore difficult to compare. There is some evidence to suggest that the better results are obtained with excisions that include the secondary sensory area as well as the primary area. In a survey of all the reported cases before 1969, White and Sweet (30) found that 4 of 23 patients had good pain relief after resection of the postcentral gyrus. I cannot find any more recent reports; this operation is rarely performed and probably does not have a good long-term success rate. Modern studies have shown that amputation leads to changes in cortical sensory projections that are quite extensive; this might explain many surgical failures (78).

Neurostimulation Techniques

Transcutaneous Electrical Stimulation. Transcutaneous electrical stimulation has been used in large numbers of patients with phantom limb and stump pains. Most reports suggest that approximately 50% of patients report significant pain relief, but few writers report long-term data. When long-term data are reported, the success rates usually fall below 25% (51,128,129 and 130). Some authors have described stimulation of the contralateral limb as an effective means of controlling phantom limb pain. Chapter 98 contains a detailed discussion of transcutaneous stimulation. It is a treatment strategy without complication and probably should be tried in most patients, even though Sherman (51) reported a low overall success rate in his survey.

Peripheral Nerve Stimulation. Direct application of implanted electrodes to peripheral nerves has been possible since the early 1970s. A few patients with phantom limb or stump pain have been treated, but there are few published data (129).

Spinal Cord Stimulation. Spinal cord stimulation is the most commonly used form of implanted electrical stimulation, and the technology has gone through several evolutionary stages (see Chapter 100). The surveys by Siegfried and Cetinalp (114), Krainick and Thoden (130), and Lang (131) indicated that the results for phantom limb pain mirror the overall results from spinal cord stimulation: Approximately half of the patients have good initial relief of pain, but only half of these obtain long-term benefit.

Electrical Stimulation of the Brain. There are two deep target sites in electrical stimulation of the brain—the periaqueductal gray (the enkephalinergic system) and the lateral thalamus-internal capsule—although some neurosurgeons have used other medial thalamic structures (see Chapter 101). The results suggest that phantom limb and stump pain are more likely to respond to stimulation of the thalamic sites than to stimulation of the periaqueductal gray (114,132,133). Mundinger and Neumüller (134) reported a 93% success rate in 14 patients treated with the combination of deep brain stimulation and transcutaneous stimulation. There are probably 100 reported cases of deep brain stimulation for phantom limb pain; approximately 25 patients are said to have had good long-term relief of pain. Reports by Tsubokawa et al. (135) have indicated that stimulation of the motor cortex could be effective for relief of central pain states. Not enough cases have been reported to assess the efficacy of this treatment strategy and its usefulness in phantom limb pain.

CONCLUSIONS

No surgical procedure has a high likelihood of success in relieving phantom limb or stump pain. We need better methods of characterizing the pains seen after amputation to see whether there are criteria for the selection of specific operations that will increase the likelihood of favorable results. If we can isolate the mechanisms that lead to phantom and stump pain, it is possible that patients can be selected for particular pharmacologic or surgical treatments with higher likelihood of success. It is probably wisest to use nonablative procedures initially, for the patient will not risk the loss of neurologic function in the attempt to obtain pain relief. All of the neurosurgeons who have seen significant numbers of patients with phantom limb and stump pain have concluded that any operation is more likely to fail than to succeed in a particular patient (136).

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CHAPTER 22

Herpes Zoster and Postherpetic Neuralgia

C. Peter N. Watson and John D. Loeser

This chapter reviews the features of herpes zoster (HZ), the most common neurologic illness, and the disease's most frequent and feared complication, postherpetic neuralgia (PHN). It is increasingly important to recognize and treat HZ early to prevent viral replication, to relieve acute pain, and to prevent the complications of the disease. PHN is important because its treatment is difficult and also because it is a valuable clinical condition for research into neuropathic pain. It is important not only to emphasize the optimal therapies of PHN but also its intractability; prevention of PHN may be possible. New information about these disorders includes a new definition (zoster-associated pain), epidemiologic data, the prospect of the prevention of PHN with appropriate measures, and controlled drug trials for PHN that support the use of antidepressants, the anticonvulsant gabapentin, as well as the use of opioids in refractory cases.

HERPES ZOSTER

Basic Considerations

Historic Aspects

The Greek word *herpes* means something that creeps and was commonly employed in early Greek medicine to designate chronic cutaneous diseases. The word *zoster* means a belt a warrior used to secure his armor. The common term for HZ, *shingles*, has an ancient derivation from the Latin verb *cingere*, which means *to gird*. The reader is referred elsewhere for details of interesting ancient treatments of HZ (1).

In 1831, Bright (2) suggested the neurologic basis of HZ because the characteristic rash distribution suggested segmental nerve involvement. Von Barensprung (3,4) identified the dorsal root ganglion as corresponding to the levels of rash. In 1892, von Bokay (5) established that HZ and varicella were different manifestations of the same etiologic process. The largest pathologic study in the literature to date is that of Head and Campbell in 1900 (6), in which the authors found that changes were limited to one ganglion. They noted that some ganglia were more predisposed to be affected than others and that these were the thoracic and the ophthalmic divisions of the trigeminal. Head and Campbell also found that some patients appeared to have the clinical manifestations of zoster without the rash. Weber (7) coined the term *zoster sine herpete* for this phenomenon.

The zoster virus was identified with light microscopy by Paschen (8). In 1926, Netter and Urbain (9) successfully showed the similarity of the antigens in vesicle fluids from HZ and varicella. They suggested that HZ was a recurrent manifestation of the primary infection of varicella. The current concept that HZ is a reactivation because of declining immunity of latent varicella virus in sensory ganglia was proposed by Hope-Simpson (10). Cell-mediated immunity is thought to be of importance in conveying protection against reactivation resulting in zoster (11,12 and 13).

Incidence

The overall incidence of HZ has been estimated at 131 per 100,000 person-years (14). No gender difference has been found (10,15). The incidence, however, is directly related to age (Table 22-1), so that a tenfold greater incidence is seen in individuals 75 years and older compared with those younger than 14 years (10,15,16). There is no seasonal occurrence (10,15). The dermatomes affected tend to be truncal as occurs with varicella, particularly the thoracic dermatomes and the ophthalmic division of the trigeminal nerve (10) (Table 22-2). One study has shown that blacks have a significantly lower risk of developing HZ than whites; the reasons for this have been discussed at length (16). In patients with lymphoproliferative disorders, the likelihood of zoster increases with the severity of the disease and with the aggressiveness of radiotherapy and chemotherapy. A small percentage of patients (5%) have a recurrence of HZ (15), and this may have a tendency to occur in the same dermatome (10). A decline of cell-mediated immunity appears to be associated with HZ rather than a decline in humoral immunity (11,12 and 13).

	Source of data	
Age (yr)	Hope-Simpson (10)	Ragozzino (14,15)
0–9	0.74	
10–19	1.3	0.6
20–29	2.58	0.8
30–39	2.29	0.9
40–49	2.92	1.5
50–59	5.09	2.1
60–69	6.79	3.1
70–79	6.42	4.1
80–89	10.1	

[a]Incidence rate reported as 1,000 per year.

TABLE 22-1. Incidence of herpes zoster[a]

Region	Cases (%)
Cranial	15
Cervical	12
Thoracic	55
Lumbar	14
Sacral	3
Generalized	1
All	100

TABLE 22-2. Distribution of herpes zoster

Pathology

It is thought that the virus that causes varicella gains access to the sensory nerves in the skin and passes to the dorsal ganglion cells in which it lies dormant. The latent virus becomes reactivated often when immune mechanisms are impaired. At the time of reactivation, an intense necrotizing reaction is seen in the dorsal root ganglia, peripheral nerves, and dorsal horn of the spinal cord. At this time the virus is thought to be transported in a retrograde fashion via the sensory axons to the skin to produce the rash.

HZ is a vesicular skin eruption characterized by inflammation of the corium, intranuclear inclusion bodies, edema of the epidermal cells, and giant cell formation (17). The initial lesions may become secondarily infected, and necrosis and hemorrhage can occur. The lesions heal by crusting and may leave regions of hypopigmentation and scarring.

The dorsal root ganglion, dorsal horn of the spinal cord and adjacent leptomeninges are the sites of inflammation, hemorrhage, and necrosis (17). The peripheral nerve of the infected ganglion is also the site of demyelination, fibrosis, and cellular infiltration (18). Ophthalmic HZ was studied by Denny-Brown and colleagues (19) in 1944 and virus particles were seen in the peripheral nerves, ganglion, and posterior roots but not within the axons themselves.

Varicella-zoster virus has been isolated from the dorsal ganglion at autopsy of patients with malignant lymphoma or with Hodgkin's disease associated with acute HZ (17). Microscopic examination of the involved ganglion showed coagulative necrosis and hemorrhage, with intranuclear inclusion bodies in both satellite and ganglion cells. Herpes virus virions have been seen with electron microscopic analysis (20).

Clinical Considerations

Symptoms and Signs

HZ usually commences with pain, paresthesiae, and dysesthesia in the afflicted dermatome(s), followed in a few days by a vesicular eruption. The intensity of the pain in the prevesicular and vesicular phases is variable, but in most patients is severe. Older patients are more likely to have severe pain in the acute stage than younger patients (15,21,22). The vesicles usually scab within 1 week and heal in approximately 1 month. On rare occasions a segmental, painful disease can occur without cutaneous vesicles (*zoster sine herpete*). An acute increase in antibody titers suggests that zoster is the etiologic agent. *Zoster sine herpete* is, of course, a difficult diagnosis to establish. Lewis (23) has described various sensory, visceral, and motor signs attributed to *zoster sine herpete*.

Patients may have occasional vesicles scattered over their bodies that are remote from the involved dermatome, but this does not imply an impending generalized infection. Generalized zoster is seen almost exclusively in immunosuppressed persons. Sacral segment involvement can be associated with urinary retention, and motor deficits have also been described in other regions (24). The facial nerve is the most common site of motor involvement. The development of zoster infection of the central nervous system (encephalomyelitis) is uncommon and usually has a favorable prognosis. Although it has been suggested that the occurrence of HZ might indicate an occult malignancy or immunodeficiency, no evidence exists to support this concept, and extensive diagnostic evaluation is unwarranted in the patient who develops segmental HZ (15).

A systemic response to HZ including fever, stiff neck, headache, and nausea, and regional or diffuse adenopathy is seen in approximately 5% of patients. It is not correlated with the likelihood of any complication, including PHN.

HZ in the first division of the trigeminal nerve may jeopardize vision. Conjunctivitis, keratitis, or iridocyclitis may ensue, especially when the nasociliary nerve is involved. Pain can be caused not only by the vesicles but also by the ophthalmic complications. Loss of vision can result from improper ophthalmologic management.

The distribution of HZ has been well described: Although more than 50% of patients are afflicted in the thoracic region, the ophthalmic division of the trigeminal nerve is also one of the more common sites, particularly in the elderly (15,24) (Table 22-2). The segmental distribution of zoster mirrors that of the exanthem of varicella and the virus itself may have a predilection for certain regions.

Recurrent attacks of HZ are uncommon (only 1% to 5% of those who have one episode have another) and may be associated with immunosuppression or underlying malignant disease.

Differential Diagnosis

A similar vesicular rash can be caused by herpes simplex; a patient with focal vesicles may be thought to have simplex when zoster is actually the causative agent. Viral cultures can resolve this ambiguity (25). Other viral infections without exanthems can produce similar symptoms. It may be impossible to differentiate *zoster sine herpete* from radicular pain of any other origin. Factitious scratching of the skin can create an eruption similar to that of acute HZ, but it is rare that such a patient confines the dermabrasion to one or two dermatomes.

Therapy

Symptomatic Treatment. The acute pain of HZ may be treated both topically and systemically. Compresses of Burrow's solution, or calamine lotion or a petroleum jelly impregnated bandage, with or without topical antibiotics, are commonly used. Nonsteroidal antiinflammatories and acetaminophen with codeine or stronger narcotics may be indicated because of the intensity of the acute pain. Long-acting opioids, such as sustained-relief morphine, oxycodone, and hydromorphone or the fentanyl skin patch, may play a role in difficult cases. Good analgesia for HZ pain may prevent alterations in the central nervous system that could be responsible for PHN.

Antiviral Agents. The hope has been that antiviral agents given within the first 72 hours will prevent viral replication and hence reduce the severity of the acute eruption and prevent PHN. Early studies of some agents that have not gained common usage involved idoxuridine (26), adenosine and cytosine arabinoside, (27,28), amantadine (29,30), and adenosine monophosphate (31).

Initial studies with acyclovir (ACV) were difficult to interpret, probably because they did not focus on or adequately evaluate pain. The use of the term *zoster-associated pain* has been developed to overcome this difficulty. A combined analysis of four ACV trials showed a reduction in PHN by 42% (32). Famciclovir (a nucleoside analogue) has greater oral bioavailability and a longer half-life than ACV. A placebo-controlled trial has shown that the median time to pain disappearance was shorter with this drug (33). A trial comparing famciclovir with ACV showed the time to pain disappearance was similar between the two agents (34).

Valacyclovir is a prodrug for ACV and has a higher bioavailability orally. Valacyclovir administered for 7 or 14 days was more effective than ACV in relieving zoster-associated pain (35). In this study there was no difference between 7 and 14 days' treatment duration. A smaller proportion of patients had pain at 6 months' follow-up with valacyclovir (19% versus 26%, $p = .02$).

Corticosteroids. Trial results with corticosteroids have been confusing: Some are favorable and others not. Large controlled trials have shown early resolution of the acute illness but no effect on PHN (36,37). There appears not to be a risk of dissemination of the virus with these agents.

Regional Anesthesia. A variety of uncontrolled studies have purported to show a faster resolution of the acute illness with regional, sympathetic, somatic, or all three kinds of neural blockade. Symptomatic relief of the pain of HZ can be obtained with somatic block and sometimes with sympathetic block as well. Claims have also been made for a reduction of PHN. No controlled trial has settled this issue to date (38).

Other Methods. No good scientific evidence exists that any of a variety of other approaches attenuates HZ or prevents PHN. Bowsher has suggested that the early initiation of low-dose antidepressants, such as amitriptyline, may prevent PHN (39).

Conclusions

The population with HZ at highest risk for severe acute disease and complications is the group over the age of 60. In elderly patients, it is important to treat the

eruption and pain aggressively. Within the first 72 hours an antiviral agent such as valacyclovir or famciclovir should be commenced. Adequate analgesia with opioids, if necessary, is important to relieve acute pain. The early institution of low-dose amitriptyline may help with pain relief and prevent PHN. In patients with refractory pain, it is reasonable to consider regional anesthesia.

POSTHERPETIC NEURALGIA

PHN is the most frequent and feared complication of HZ and is a common cause of chronic pain in the elderly population. The eruption of HZ, the most common neurologic illness (40), is a harbinger of long-standing neuropathic pain in at least 50% of those older than 60 years (41). Lifestyles are dramatically disturbed; many older patients become reclusive, restricted in activities of daily living, and chronically depressed because of this misery. This section of the chapter reviews what is known about the natural history, demography, clinical features, pathology, pathogenesis, and management of PHN. Although the natural history is of slow improvement for many patients, some experience symptoms for years. With judicious choice of agent and careful monitoring, it is possible to provide reasonable pain control to approximately 60% of patients. Approximately 40% remain unsatisfactorily relieved or are intractable; this is why prevention with vaccination or early aggressive treatment of the acute zoster pain may be of critical importance.

Basic Considerations

Definition

PHN has been defined as pain along the course of a nerve after the characteristic acute segmental rash of HZ. It is important to be more precise than this to interpret the results of clinical trials and to define a fairly chronic, stable pain state for the design of uncontrolled trials but also to reduce the numbers required in controlled studies. A commonly used definition of PHN is pain persisting after the rash has healed (usually 1 month). Because of the tendency for pain to further diminish with time after 1 month, some investigators studying therapeutic approaches have chosen longer periods of 2, 3, or even 6 months after the disease onset.

Incidence, Natural History, and Demographics

The incidence of PHN (defined as pain persisting for more than 1 month) has been variously estimated from 9% to 14% (10,15,21). Other work indicates that of an original 100 patients with HZ at 3 months and as few as five and at 1 year, only three patients have persistent severe pain (41). These data emphasize that to minimize the sample in any study of the treatment of this disorder, patients should be included with severe pain at 1 or even 3 or 6 months. Despite this overall low incidence and marked early tendency for PHN to improve with time, the incidence and the severity (as measured by duration) are directly related to age (Table 22-3). Approximately 50% at age 60 years and nearly 75% at age 70 years with HZ develop PHN 1 month or more after the rash (41). This, combined with the knowledge that HZ itself is common and also directly increases with age, means that PHN is already a major geriatric problem in the developed countries and its incidence will increase. Additional factors contributing to the morbidity of this disease are the limited efficacy and untoward effects of pharmacotherapy.

Age (yr)	Patients with pain (%)	Patients with pain longer than 1 yr (%)
10–19	4.0	4.0
20–29	2.0	2.0
30–39	15.0	10.0
40–49	33.0	7.0
50–59	49.0	18.0
60–69	65.0	37.0
70–79	74.0	48.0

Data from de Moragas JM, Kierland RR. The outcome of patients with herpes zoster. *Arch Dermatol* 1966;75:193–196, with permission.

TABLE 22-3. Incidence of postherpetic neuralgia

Most studies have found no gender predilection for PHN when normal demographic change with age is considered (22,42). The dermatomal distribution of PHN has been found to reflect that of HZ in that a predilection occurs for thoracic dermatomes, especially T-5, and for the ophthalmic division of the fifth cranial nerve (43).

Pathology

In 1900, Henry Head and A. W. Campbell reported autopsy findings in 21 cases of HZ (6). Some cases were obviously chronic and had scarring in the sensory ganglia (Fig. 22-1) and nerves; however, in only one of their chronic examples (case 7) was the subject documented as having persistent pain. More recently, this scarring in the peripheral nervous system has been found in several cases of well-established PHN (18,44,45). Evidence exists that the nerve fiber population shifts with a preponderance of small unmyelinated and myelinated fibers and loss of large myelinated fibers (45,46). Atrophy of the dorsal horn of the spinal cord has been documented in several cases (45,46) (Fig. 22-2).

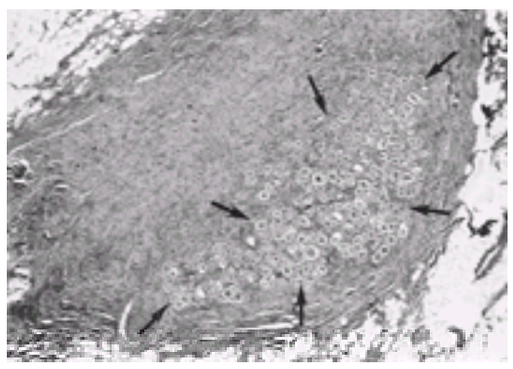

Figure 22-1. Postherpetic neuralgia with scarring in the sensory ganglion and some surviving ganglion cells (*arrows*).

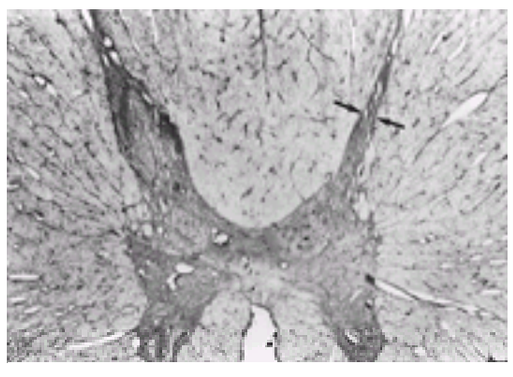

Figure 22-2. Postherpetic neuralgia with atrophy of the dorsal horn of the spinal cord (*arrows*).

The pathogenesis of PHN remains unknown. Noordenbos (46) thought that the pain and hyperesthesia in PHN were caused by preferential destruction of larger myelinated fibers in the peripheral nerve, leaving an excess of the small myelinated and unmyelinated fibers. This would result in a loss of inhibitory (large fiber) input to the spinal cord with unopposed, nociceptive (small fiber), afferent bombardment. Evidence that ongoing small fiber input might be important in painful nerve injuries has been reported (47). This work demonstrates that preferential sprouting of small diameter afferents in experimental neuromas occurs after nerve transection in the rodent. These axons showed spontaneous activity, increased sensitivity to mechanical stimuli, and sensitivity toa-adrenergic agonists and to sympathetic efferent activity. The discovery of pathologic change in the dorsal horn and relief by dorsal root entry zone lesions in some patients with PHN supports the concept of a derangement in that area of hypersensitive neurons. It has been suggested that pain relief in PHN by antidepressants may act by increasing inhibition of pain perception in serotonergic and noradrenergic pathways descending from the brainstem onto the dorsal horn. Occasional patients with PHN have inflammatory infiltrates persisting for many months (45), suggesting that some persistent occult inflammation may play a role in the symptoms and that antiinflammatory or antiviral agents could be useful in some individuals with PHN.

Clinical Considerations

When the acute rash has healed, the affected skin often exhibits a reddish, purple, or brownish hue. As this subsides, pale scarring often remains. Occasionally, severe pain with no residual scar may occur or the scars in cases of long duration are barely perceptible. The scarred areas are usually at least hypoesthetic and often anesthetic, and yet the skin often exhibits marked superficial pain on tactile stimulation (allodynia), increased pain to noxious stimulation (hyperalgesia), or an increased sensitivity to touch (hyperesthesia) (Fig. 22-3). Two types of pain may be found: one a steady burning or aching, the other a paroxysmal, lancinating pain. Both may occur spontaneously and are usually aggravated by any contact with the involved skin, such as friction from even the lightest clothing. Firm pressure on the skin may curiously be soothing but lighter brushing unbearable. Some patients describe unbearable itch, formication, or dysesthesia. As well as clothing contact, these symptoms may be exacerbated by physical activity, temperature change, and emotional upset.

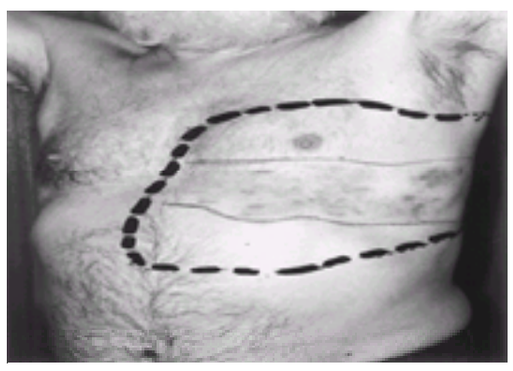

Figure 22-3. Postherpetic neuralgia showing scarring and sensory loss (*solid lines*) and allodynia (*dotted lines*).

The examination of the affected, scarred skin often reveal a loss of sensation to pinprick, temperature, and touch over a wider area than the scars and an even wider area of sensitive or painful skin. This sensitive skin may paradoxically include the anesthetic areas in which it is elicited by skin stroking or skin traction between thumb and forefinger, an effect that is thought to be caused by summation on hypersensitive, deafferented central neurons with expanded receptive fields.

Prevention

As many as 40% of patients with PHN have either incomplete or no relief from our best treatments. Because of this, the future may lie with prevention through vaccination and early aggressive treatment of HZ with antivirals and analgesics to reduce the extent of the nerve damage and sensitization that may correlate with PHN.

Live attenuated varicella vaccine elicits protective immunity against varicella zoster virus in children and adults (48,49,50 and 51), although mild breakthrough cases of varicella may occur. It is possible that waning varicella zoster virus–specific cell-mediated immunity in the elderly can be stimulated by varicella vaccine to prevent the occurrence and severity of HZ and hence PHN.

Early treatment of HZ with the antiviral agent ACV may prevent or attenuate the occurrence of PHN. Initially, studies of ACV were not impressive, but more recent trials that have paid more attention to persistent pain suggest a protective effect of this drug when used in high doses orally (800 mg 5 times a day) (32). Newer antivirals, such as valacyclovir, may prove more effective than ACV in preventing PHN (35).

A number of uncontrolled studies of small numbers of patients with HZ treated with corticosteroids have claimed a reduction in PHN. Two controlled trials have purported to prove such an effect (52,53). These trials have been criticized, and more recent controlled trials have shown no effect (36,37,54,55).

Uncontrolled trials of sympathetic blocks for HZ have claimed relief of the acute pain of HZ and a reduction in the subsequent development of PHN (56,57,58 and 59), although one study showed no effect (60). With the marked natural tendency for improvement of pain with time, it is easy to confuse this with a treatment effect in uncontrolled studies (38).

One placebo-controlled trial supports the preventive effect of amantadine hydrochloride in PHN when used in a dose of 100 mg twice a day at the onset of HZ (29,30). Other unreplicated trials claim a prophylactic effect with levodopa (61) and adenosine monophosphate (31). Good control of the acute pain of HZ with opioids, if necessary, could also be important in reducing PHN.

Treatment of Established Postherpetic Neuralgia

Antidepressants. A large number of studies support the utility of antidepressants in a variety of chronic pain problems (62,63 and 64). An important part of this literature concerns favorable, well-designed trials of the use of these agents in neuropathic pain, particularly PHN. PHN is a good model of neuropathic pain for drug trials because, if patients are chosen carefully, the pain is fairly stable over time and sufficient numbers of cases for trials can be readily obtained. Antidepressant therapy, as opposed to many other putative therapies of this difficult problem, is built on a sound, scientific basis.

Woodforde et al. (65) were the first to recognize that amitriptyline could afford relief in truly chronic postherpetic pain problems. They thought that all 14 of their patients were depressed and used an initial dose of 10 mg four times daily gradually, increasing to 25 mg four times a day; good pain relief was noted in 11 patients from 1 to 11 months. Taub (66) reported successfully treating five subjects with PHN of greater than 3 months' duration with amitriptyline combined with a phenothiazine (fluphenazine, perphenazine, or thioridazine). In a later publication, Taub and Collins (67) used amitriptyline, 75 mg, with fluphenazine, 1 mg three times a day, in 17 patients with pain of greater than 1 year's duration. The patients had good relief in both studies with some mild residual pain after 3 to 6 years of follow-up. The authors commented on their belief in the lack of efficacy of amitriptyline alone. There has been no placebo-controlled trial of a phenothiazine in PHN, and it is proven that the beneficial effects seen with the combination of an antidepressant and phenothiazine are caused by the antidepressant, the efficacy of which has been proven by a number of controlled trials. There are well-known side effects from phenothiazines that can be severe enough to make us cautious about using the drugs unless there are clear-cut benefits. A double-blind, placebo-controlled, crossover trial of amitriptyline found good results in 16 of 24 patients (67%) (68). Most patients were not depressed and pain relief occurred without a change in depression ratings in most patients, indicating that the drug appeared to result in pain relief independently of its antidepressant effect. This pain relief occurred at lower doses than usually used to treat depression (median, 75 mg). Follow-up was a median 12 months with good results maintained in 12 of 22 (55%). A subsequent trial (69) has corroborated these results. Amitriptyline has significant limitations in the long term because of side effects and the fact that relief is rarely complete and occurs in only approximately two-thirds of patients. One of the effects of this drug is to potentiate serotonin and noradrenaline in the central nervous system. Subsequent research has explored whether selective serotonergic or noradrenergic agents

might be more effective and have fewer untoward effects.

Experience with serotonergic agents (clomipramine, trasodone, nefasodone, fluoxetine, and zimelidine) in PHN has been disappointing (43,70,71). The evidence supporting the use of noradrenergic agents is more compelling (72,73 and 74).

Desipramine, a selective norepinephrine reuptake inhibitor, has been shown to be more effective than placebo in PHN. Pain relief with this drug, as well, was found not to be mediated by mood elevation (72). A randomized, double-blind trial comparing maprotiline (noradrenergic) with amitriptyline (73) found that although both were effective, amitriptyline was more so. Nine patients responded equally well to both drugs, seven responded only to maprotiline, and eight other responders required amitriptyline for good relief. All three aspects of the pain of PHN responded to treatment in this study (i.e., steady pain, brief jabbing pain, and pain on tactile skin contact). Side effects were troublesome with both agents, therefore limiting effectiveness. Most patients were not depressed and pain relief occurred in most without a change in depression-rating scales. A comparison of nortriptyline (more noradrenergic) with amitriptyline showed approximately equal efficacy for both drugs with fewer side effects with nortriptyline (74).

Neuroleptics. Farber and Burks (75) used high doses of chlorprothixene in patients with postherpetic pain with a duration of 2 days to 8 weeks. In an uncontrolled study of 30 subjects of unstated age, they found total relief of pain within 72 hours in all but one. Nathan (76) attempted to duplicate this work in established PHN (median duration, 1 year) by the same method and also in a lower dose, double-blind, placebo-controlled study. He concluded that dosages less than 100 mg per 24 hours were ineffective. The high- dose regimen helped approximately one-third of patients, but only in the short term, and was accomplished by a high incidence of side effects. They used an initial dose of 10 mg four times a day, achieving at least good relief in 11 patients for 1 to 11 months. Taub (66) reported treating five subjects with PHN of more than 3 months' duration with amitriptyline and a phenothiazine (perphenazine, fluphenazine, or thioridazine). In a later publication (67), Taub and Collins used amitriptyline hydrochloride, 75 mg every night, with fluphenazine, 1 mg three times a day, in 17 patients with pain of duration more than 1 year. The subjects in both studies had good relief with some mild residual pain at 6 months' to 3 years' follow-up. Taub commented on his impression of the lack of efficacy of amitriptyline alone.

Anticonvulsants. Studies using the anticonvulsants carbamazepine, phenytoin, and valproic acid for PHN have been either unimpressive (77) or difficult to interpret because of the concomitant use of antidepressants (78,79 and 80). Although carbamazepine is a popular agent for the paroxysmal, lancinating pain that commonly occurs, no conclusive evidence exists to justify its use in this fashion. A recent randomized controlled trial suggests a modest effect of gabapentin (81).

Opioids. For many years, there has been a bias against using opioids for nonmalignant pain. Increasing support exists for the view that these drugs can be helpful and justifiable in chronic pain caused by nerve injury (82,83,84,85,86,87,88,89 and 90). One study suggested that opioids did not relieve neuropathic pain, but this study did not include patients with PHN and its conclusions have been challenged.

Survey data in PHN have indicated that opioids are useful for some patients (43). Twenty-five of 90 patients with otherwise intractable pain achieved good to excellent results, and 50 others had 25% to 50% relief in one report (43). A placebo-controlled trial of 50 patients treated with sustained-release oxycodone has shown that 58% of patients had at least moderate improvement with this drug versus 18% with placebo (91).

Topical Agents. A variety of topical agents have been studied in PHN (capsaicin, aspirin, and local anesthetics) (see Chapter 87). Capsaicin, the active ingredient in red peppers and other plants, acts by depleting the neurotransmitter substance P in small primary afferent fibers. Capsaicin has a modest effect (92) and may best be used as an adjunct to other treatments. The burning sensation induced by capsaicin is often unpleasant or unbearable and usually limits therapy. Open-label, uncontrolled studies suggest that aspirin in a variety of vehicles such as chloroform, ether, and Vaseline ointments may help PHN (93,94 and 95). Similarly, a variety of topical local anesthetic agents, such as lidocaine and EMLA (eutectic mixture of local anesthetics) applied under occlusive dressings, may be useful, but again this effect appears modest (96,97 and 98).

Miscellaneous Therapies. Russell and colleagues (99) advocated repeated nerve blocks, interspinal ligament injection of hypertonic saline solution, or skin infiltration with procaine hydrochloride for relief of hyperesthesia and spontaneous pain in PHN. They also discussed the use of a hand vibrator over the injured skin. Of 100 patients, they provided details for only five. No duration of antecedent pain was stated. Taverner (100) reported 16 cases treated with ethyl chloride spray to the scarred area. Symptoms for 12 of these were relieved for 3 to 21 months, with their pain duration being 10 months to 13 years. The spray was applied daily to twice a week. The author commented on the failure of vibration in his experience, cautioning about the risk of skin injury. Todd and colleagues (101) reported on 86 patients with PHN of at least 3 months and found that 58 (67%) obtained relief with a combination of ethyl chloride spray followed by the application of a hand vibrator; follow-up was 6 months to 6 years. Colding (56,57) concluded that sympathetic blocks for established PHN were of no value. Forrest (102) treated 37 patients with postherpetic pain of more than 6 months' duration with three epidural injections of methylprednisolone acetate at weekly intervals. At 1 year, 90% of the patients were free of pain, with “some patients” followed up for more than 3 years. Forrest postulated that the corticosteroid, local anesthetic used, or preservative might have been the effective component. Another study (103) of five patients with established PHN, treated with epidural bupivacaine hydrochloride and methylprednisolone, concluded that no patient had more than 50% relief at 1 and 5 months.

Nathan and Wall (104) used prolonged transcutaneous electrical nerve stimulation (TENS) and found good results in 11 of 30 patients with established PHN. The voltage, pulse width, frequency, site of application, and duration were all controlled by the patient. The subjective sensation of the input was usually nonpainful and tingling. Pain relief often outlasted stimulation by hours. Follow-up duration was not clearly stated for many patients. Gerson and colleagues (79) found the intermittent use of TENS unsuccessful in 17 patients with chronic PHN. Haas (105) concluded that TENS was helpful in 9 of 11 patients, with follow-up over 1 to 18 months. Lewith and colleagues (106) concluded that acupuncture was of little value in PHN when compared with placebo (mock TENS) in 62 patients. Claims have been made for a variety of other therapies, but these studies suffer from small numbers of patients, lack of controls, inadequate data about the patient population, or lack of adequate follow-up.

Surgical Therapy. No proven surgical cure for PHN has been found (see Chapter 105 and Chapter 106). Browder and deVeer (107) reviewed the poor results of cordotomy, rhizotomy, and sympathectomy, but argued for excision of the painful area. Sugar and Bucy (108) reviewed the surgical attacks on this disease in 1951 and concluded that almost every operation was said to work occasionally, but none consistently. White and Sweet (109) came to similar conclusions. Their lists included retrogasserian rhizotomy, avulsion of the supraorbital nerve or gasserian ganglion, greater superficial petrosal neurectomy, trigeminal tractotomy, stereotaxic thalamotomy or mesencephalotomy, sympathectomy, and sensory corticectomy. Resection or undermining of the skin in the involved areas also rarely seemed to provide long-term pain relief, despite initial reports of good results (107,110). Suzuki and colleagues (111) alleged that applying dry ice to the hyperesthetic skin was effective. Cryocautery has some side effects, and is likely to bring only short-term relief (111). Hitchcock and Schvarcz (112) reported that stereotaxic trigeminal tractotomy was successful in three patients with PHN, all with less than one year's follow-up. No reports of this procedure by other neurosurgeons have been published.

Dorsal root entry zone lesions may prove to be effective for PHN, but too few cases have been reported to permit meaningful analysis of data. Friedman and colleagues (113,114) described good results in 10 of 17 patients who underwent this procedure. Certainly, no other ablative procedure has been reported to have this great a chance of providing long-term relief. Whether the results of dorsal rhizotomy would be improved by adding ganglionectomy is unknown.

Stimulation of the nucleus ventroposteromedialis was reported to provide pain relief for some patients with PHN (115). Approximately one in three patients can be expected to obtain good long-term results. Stereotaxically implanted electrodes can also be directed at other nuclear structures, but the ventroposteromedialis appears to be the best target area (116,117).

Conclusions

None of the putative preventive approaches to PHN can be regarded as conclusively established to be effective in preventing this disorder. Pending final proof, it is reasonable to treat patients early and aggressively to relieve the pain of HZ and to hope to prevent PHN if the therapy is safe and well tolerated. It is important to recognize that the population at highest risk for PHN is the age group 60 years and older who may have a risk of 50% or more of developing this complication. Valacyclovir and famciclovir appear safe and modestly reduce the occurrence of PHN. Although no controlled trial has ever been performed of nerve blocks to treat HZ pain or prevent PHN, they are reasonable and safe in experienced hands and may be repeated if effective as symptoms dictate. The use of nonsteroidal antiinflammatory drugs, acetaminophen, and narcotics, are justified to relieve severe pain with the acute illness on an as needed or round the clock basis. The initiation of low-dose amitriptyline may be considered at this stage.

For established PHN (neuropathic pain persisting more than 1 month after HZ) the most consistently effective agents appear to be antidepressants; controlled trials

support this approach. These data indicate that pain may be reduced from moderate or severe to mild in approximately two-thirds of patients. It is reasonable to commence with amitriptyline or nortriptyline in a dose of 10 mg at bedtime in those older than 65 years and with 25 mg in those 65 years or younger. The dose is increased by similar increments at bedtime every 7 to 10 days until relief is obtained or intolerable side effects supervene. If these fail, one can try desipramine or maprotiline in similar doses. Gabapentin may be regarded as a first-line therapy in divided doses of up to 3,500 mg per day. Occasional patients who have no success with these may benefit from a serotonergic drug such as trazodone, clomipramine, or fluoxetine, but no controlled trial has been done and these do not appear useful for the majority of patients. It is also possible that the addition of a neuroleptic such as fluphenazine, 1 mg up to three times a day, may give added benefit in some. A trial and error approach in refractory patients may also include the anticonvulsants carbamazepine, phenytoin, clonazepam, and valproate. For resistant cases, opioids may be safely prescribed on an as needed or round the clock basis. Methadone or long-acting oral forms of oxycodone, morphine, and hydromorphone and the fentanyl skin patch may be of advantage, and trials of different opioids may reveal one that is preferred. The use of topical agents is attractive, as it is simple and free of systemic effects. These include capsaicin, acetylsalicylic acid, and local anesthetic agents. Although for most patients these do not appear useful as sole therapy, they may be a valuable adjunct in some individuals. TENS may be worth trying. Electrode placement, frequency, intensity, and duration of stimulation are a matter of trial and error. Some patients may benefit from nerve blocks that, if efficacious, may be repeated at appropriate intervals. At least 40% of patients remain totally refractory or unsatisfactorily relieved. Our approach with those is to see them regularly, try different narcotics for the limited relief they give, and try any new or older approach that seems reasonable and safe, hoping that improvement will occur with time. Approximately 50% of patients, even those with long-duration pain, improve over the years; approximately one-half of these are receiving no treatment. It is hoped that new and more successful treatments for PHN will be developed in the immediate future. These could include strategies to prevent the onset of HZ in addition to the attempt to prevent the onset of PHN after the onset of HZ.

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CHAPTER 23

Central Pain States

Ronald R. Tasker

Central pain is defined (1) as "pain associated with lesions of the central nervous system" and is among the most spectacular, distressing, and intractable of chronic pain syndromes. It seems amazing that transection of the spinal cord can result in agonizing pain in the body below the level of the lesion or that a stroke can result in such distressing pain on the opposite side of the body. Central pain belongs to the group of neuropathic pain syndromes and shares many features with the pain syndromes induced by lesions of peripheral nerves, plexuses, and roots, strongly suggesting a shared pathophysiology. Table 23-1 lists the more obvious of these shared characteristics, a topic that has been reviewed by many authors (2,3,4,5,6,7,8 and 9). Nevertheless, our understanding of neuropathic pain including central pain syndromes remains meager.

Caused by damage to somatosensory pathways.
Degree of damage variable from slight with no sensory loss to massive with anesthesia.
Pain idiosyncratic (genetic predisposition in animals).
Pain in distribution of sensory damage.
Onset may be delayed.
Brain central pain may be reversible.
Three common components: steady and neuralgic, spontaneous, and evoked.
May be temporarily relieved by proximal, distal, or both somatosensory local anesthetic blockade.
May be temporarily relieved by sympathetic block if evoked element present.
Steady pain better relieved by intravenous sodium thiopental than opiate infusion.
Steady pain not relieved by proximal neural transection but may respond to chronic stimulation producing paresthesia in pain area.
Evoked and neuralgic pain may be relieved by neural transection.

TABLE 23-1. Features of neuropathic and central pain

This chapter is divided into two sections, one dealing with central pain caused by lesions of the spinal cord and the other with that caused by lesions of the brain. Each section deals both with basic and clinical considerations. However, because no satisfactory laboratory models of pain caused by spinal cord or brain injury exist, the human patient is the best research subject, and insight into the pathophysiology of central pain must be derived from studying the clinical features of each patient. A more general discussion of the different types of pain seen after injury to the spine and spinal cord may be found in Chapter 34.

SPINAL CORD CENTRAL PAIN

Clinical Features

The diagnosis of central pain caused by spinal cord injury is rarely in doubt; the causative events usually are obvious. The patient presents for treatment of pain after therapy for the causative condition, usually trauma, has been completed. Rarely is central pain the presenting feature of a spinal cord lesion. In those rare exceptions, the combination of a pain syndrome and the accompanying neurologic signs usually confirms the diagnosis, assisted by magnetic resonance imaging or other imaging and electrical studies (see Chapter 13 and Chapter 14).

Incidence and Etiology

The incidence of spinal cord central pain has been estimated to be between 6.4% and 94.0% of patients who experience spinal cord injury, as shown in Table 23-2. Sved and colleagues (21) performed a prospective longitudinal study of 100 patients with spinal cord injury and showed that the incidence of central pain was not influenced by early surgical treatment of the spinal cord injury.

Incidence (%)	Reference
6.4	10
7.5–10.0	11
10–30	9
18–63	12
25	13
26.8	14
27	15
33–94 (one-third severe)	16
47–96	16
69.5 (49% severe)	17
77	18
80–94	19
94	20

TABLE 23-2. Published estimates of percent incidence of cord central pain after spinal cord injury

Trauma is the most common cause of spinal cord central pain, as shown in Table 23-3, which lists the etiology of pain in my personal series of 127 patients (22). In this series, 76.4% were men, and 57.4% were younger than 40 years at the time of the injury. Forty-two percent of my patients had lesions in the cervical area, 21% in

the T1-9, and 37% in the T-10–L-2 areas; 32% of lesions were clinically complete, 64% incomplete, and 4% of patients had no clinically detectable sensory loss. There appeared to be no correlation between patterns of pain and etiology, level of injury, and completeness of spinal cord transection, although Richards and colleagues (23) found pain more common after gunshot wounds than other lesions.

	% of Patients
Trauma	65
Iatrogenic	12
Inflammatory	9
Neoplasm	6
Skeletal pathology	2
Vascular pathology	2
Congenital lesions	4

TABLE 23-3. Etiology of 127 cases of cord central pain

Eide and colleagues (24) examined 16 patients with spinal cord injury and dysesthetic pain, comparing the somatosensory function in normal, painful, and nonpainful denervated skin. No difference existed between the degree of deficit in dorsal column and spinothalamic tract functions, but allodynia and wind-up were more common in painful than nonpainful denervated areas.

Delayed Onset

Table 23-4 charts the time of onset of spinal cord central pain after the causative event in 72 of my patients (25). When onset was delayed beyond 1 year, 56% of these patients were found to suffer from a syrinx; 37% of those with onset before 1 year did so. Thus, long-delayed onset of pain should alert the physician to the possibility of syringomyelia. This condition was reviewed in detail by Milhorat and colleagues (26).

	% of Patients
Immediate	24
<1 mo	18
1–6 mo	26
6–12 mo	11
1–5 yr	18
>5 yr	3

TABLE 23-4. Timing of onset of 72 cases of cord central pain after causative lesion

Quality of Pain

Patients describe a considerable variety of pain types after spinal cord injury, in addition to the three common components: spontaneous steady, spontaneous neuralgic, and evoked pain including allodynia and hyperpathia. As Boureau and colleagues (27) have shown, the words used by patients are related to the underlying pathophysiology. Table 23-5 lists the descriptions used in 127 of our cases to describe their spinal cord central pain. Ninety-six percent reported steady, burning, dysesthetic, or all three types of pain. Table 23-6 lists the terms used by other authors to describe spinal cord central

Pain quality	% of Cases[a]
Burning	75
Numb, tingling	26
Shooting[b]	31
Evoked[c]	47
Musculoskeletal-like[d]	15
Visceral	3

[a]Some patients had multiple types.
[b]Two percent in isolation.
[c]Four percent in isolation.
[d]Below a complete level of sensory interruption.

TABLE 23-5. Nature of pain in 127 cases of cord central pain

Author(s)	Terms
White and Sweet (51)	Radicular (neuralgic), psychic, diffuse, sympathetic, visceral
Pagni (6)	Visceral, radicular (especially cauda lesions), remote (causalgic, dysesthetic below level)
Pollock et al. (28), Waisbrod et al. (29)	Segmental, diffuse (burning or visceral), lesional (projected or triggered)
Rose et al. (17)	Radicular, 12.4%; constant, 43%
Beric et al. (30)	Central dysesthetic, 13%
Davis and Martin (31)	Shocklike, electric at or below level one-third
Richards et al. (18)	Musculoskeletal (innervated area), radicular (at level and distally), visceral, central (dysesthetic), psychogenic, lesional (at zone of injury), reflex sympathetic dystrophy, limb pain (especially upper limb from compression nonneuropathic)
Hashold (32)	Radicular, segmental, segmental with syrinx, phantom, visceral
Milhorat et al. (26), 71 cases of syrinx	Segmental dysesthetic, 51%; radicular, 36%; headache, 25%; suboccipital cervical, 67%; in back, 17%; in face, 9%
Sidall et al. (33)	Neuropathic (1) at level (a) radicular (b) central (2) below level

TABLE 23-6. Terms used to describe cord central pain

In our patients, little difference existed between the distribution of the steady component between complete and incomplete cases, other than the fact that the prevalence of a band of steady pain at the upper margin of sensory loss was more characteristic of an incomplete lesion, as was the presence of diffuse pain below the level of injury. Visceral, rectal, and perineal pain was more common in complete lesions. Some patients suffered from pain that resembled that of musculoskeletal

disease, such as the pain of spinal instability or muscle tension. Such pain could indeed be associated with such problems in spinal cord–injured patients when it occurred in an innervated area above the level of injury. However, such pain also occurred below the level of injury, particularly in complete lesions, and was presumably not related to musculoskeletal problems. Facial pain was pathognomonic of a syrinx in the cervical area interfering with the descending tract of the trigeminal nerve.

Table 23-7 lists the patterns of sensory loss in 72 of our patients. It is noteworthy that three had no clinically detectable sensory loss, and 16 had dissociated loss of spinothalamic tract function; the rest had varying degrees of loss both of dorsal column and spinothalamic function. Spinal cord injury pain typically begins well after the traumatic event. Although the pain rarely, if ever, subsides on its own, it may change slowly but significantly over time. Patients with spinal cord injuries, like amputees, may experience phantoms below a complete level. These are said to be less prevalent in patients who were comatose at the time of their spinal cord injury than those who were not (34,35). Phantom onset is delayed by days to months, and the phantoms are said to be less vivid than those of amputees, not telescoping with time (35,36 and 37).

Sensory loss	% of Patients
None	3
Dissociated	16
Incomplete, all modalities	39
Complete, all modalities	41
Data missing	1

TABLE 23-7. Patterns of sensory loss in 72 patients with cord central pain

The most common type of central pain after a spinal cord injury is spontaneous steady, burning, or dysesthetic pain, affecting 96% of our patients (Table 23-8). Its severity fluctuated, some patients distraction. It was described as burning in 75% and dysesthetic in 28%; the dysesthetic element was variably described as tingling in 20%, numb in 6%, crawling in 2%, and pricking in 1%. The pain was aching in 13%, had a sense of compression or distraction in 18% (crush, 3%; tight, 2%; squeeze, 2%; pull, 2%; pinch, 2%), whereas it was rhythmic in 9% (throb, 5%; cramp, 3%; pound, 1%; pump, 1%), cold in 4%, and had the feeling of a cut in 2%.

	Distribution (%)	
Pattern	33 Clinically complete	39 Incomplete
Band at upper margin of sensory change	24	3
Diffuse below level	18	36
Patchy below level	36	49
Visceral below level	24	13
Rectal-perineal	15	8
Facial	3	2

TABLE 23-8. Location of steady pain in 72 patients with spinal cord lesions

Forty-seven percent of our patients experienced allodynia, hyperpathia, or both, but only in areas of preserved sensation. This was usually associated with spontaneous pain, although in 4% of our patients evoked pain occurred in isolation. It affected 39% of patients with complete lesions where it usually occurred as a band at the upper level of the sensory loss, and 51% of patients with incomplete lesions. In these it was found diffusely in 67%, patchily in 75%, and as a band at the upper level of the sensory deficit in 18%. Taking complete and incomplete lesions together, in 21% it occurred in a band at the upper level of the sensory loss, in 29% diffusely, and in 50% patchily below the patient's level. It could also occur in radicular distribution from damage to a root near the level of spine injury. Some patients had allodynia alone, and others allodynia accompanied by hyperpathia; the allodynia might be elicited by single or multiple somatosensory modalities such as touch, hair bending, cold, hot, or muscle and joint movements; deep pressure was much less likely to evoke it than other modalities.

Neuralgic intermittent pain can shoot down the legs, especially in patients with lesions of the cauda equina and conus. This type of pain affected 31% of our patients. It usually accompanied steady pain, but in 2% of patients it was the only type of pain present. When it occurred in the presence of other types of pain, it was usually the most severe. In our patients it was described as shooting in 12.0%, shocklike in 8.0%, stabbing and jabbing in 3.1% each, sharp in 2.4%, and knotting and stinging in 1.0% each. It afflicted 27% of patients with complete and 33% with incomplete lesions, and ran up or down the trunk or legs, particularly in incomplete lesions or else around the body at the patient's level, particularly in complete lesions. It was present in 82% of patients with complete T-10–L-2 lesions, and 64% of incomplete lesions at this level. Pain resembling abdominal or pelvic disease usually occurred below a level of complete sensory loss and often led to extensive investigation of the viscera and even to abdominal surgery.

Thus, pain syndromes can accompany the full spectrum of motor and sensory loss, complete or incomplete and at any level. Pain may even occur in someone with normal spinal cord function on clinical examination but who gives a history of past injury or illness that could have damaged the spinal cord even though it has been followed by complete recovery.

Animal Models

The author is aware of few laboratory studies directed at spinal cord central pain. Levitt and Levitt (38) have studied rodent pathways, whose involvement is necessary for spinal cord central pain to develop. They concluded that the anterolateral quadrant of the spinal cord must be sectioned or else hemisection of the spinal cord performed, preserving some sensation in ipsilateral nociceptive pathways for pain behaviors to occur. Pain never followed posterior quadrant section, whereas simultaneous section of ipsilateral, lateral, or anterolateral quadrants in addition to anterolateral quadrant section or hemisection on the other side of the spinal cord did not result in pain. How this observation matches the clinical facts of spinal cord central pain after complete spinal cord section is unclear. One must keep in mind that their marker for the presence of spinal cord central pain was autotomy, which may not have the same implication as the steady, burning, dysesthetic pain seen in humans. Consonant with human studies, pain onset was delayed and morphine administration, subsequent rostral spinal cord transection, or subsequent rostral selective spinal cord lesions, such as the ones that caused the autotomy in the first place, all failed torelieve it.

Functional Imaging

Functional imaging studies are likely to contribute much to our future understanding of the problem of central pain. Pagni and Canavero (39) and Cesaro and colleagues (40) have demonstrated diminished perfusion of the human contralateral thalamus in single photon emission computed tomography (SPECT) and positron emission tomography scans associated with spinal cord injury, stroke-induced, peripheral neuropathic, or cancer pain. These changes could be normalized by relief of the pain by resection of a syrinx in one case of spinal cord central pain or by cordotomy in cancer pain. These observations support the concept of a final common path for pain, regardless of the individual pathophysiology.

Melzack and Loeser (41) concluded that spinal cord central pain was the result of a “pattern generating mechanism” for pain based on the observations that the pain

was not relieved by cordectomy and persisted if the sympathetic chain was cut or blocked as well. This meant that the pain originated centrally to the lesion and was probably related to loss of sensory input.

Treatment

No clear guidelines exist for the early management of spinal cord lesions that would prevent the onset of central pain. In the patient with established pain, one must address general issues such as nutrition, skin care, elimination, pulmonary function, seating, and appropriate ongoing active physiotherapy to maintain surviving muscle mass and strength. Socioeconomic issues must be attended to to restore as far as possible independence, self-respect, and confidence. Spasticity and spasms often require separate care through appropriate seating, bracing, antispastic medications, and, in some cases, intrathecal baclofen infusion. Attention to psychosocial issues is essential to maximize the patient's functional capabilities. Pain is the major reason for failure of rehabilitation after spinal cord injury (42).

General Principles of Treating Central Pain

Figure 23-1 presents an algorithm for the management of spinal cord central pain. Central pain is a particularly refractory pain syndrome. Only one-third to one-half of patients who experience spinal cord central pain have severe pain. Chronic pain syndromes can almost never be eradicated and can only significantly be reduced in less than one-half the patients treated. Even after initially successful treatment, chronic pain tends to recur with time, regardless of the syndrome or treatment modality (43). Therefore, a treatment modality must be selected by the patient on the basis of the patient's reaction to realistic outcome statistics, risks of therapy, and cost.

Figure 23-1. Algorithm for the treatment of cord central pain. (DBS, deep brain stimulation; DCS, dorsal column stimulation; DREZ, dorsal root entry zone.)

Medical Treatment

The initial treatment should be conservative. Although there have been many investigations of the possible pharmacologic bases of spinal cord central pain and of strategies for its relief, a dearth of specific therapeutic guidance exists (44). Drewes and colleagues (45) found valproate of no value in a double-blind crossover study. Chiou-Tan and colleagues (46) found mexiletine of no value. On the other hand, Eide and colleagues (47) in a randomized double-blind crossover study found that the *N*-methyl- d-aspartate receptor blocker ketamine and the μ opioid receptor agonist alfentanil reduced both spontaneous and evoked pain. Ketamine, although it diminished allodynia, did not affect wind-up pain. Taira and colleagues (48) suggest that intrathecal baclofen not only reduced spasticity in spinal cord–injured patients but also brought about a 64% reduction in the central pain of spinal cord as well as of brain origin. The pain diminished within 1 to 2 hours of infusion, and relief lasted 10 to 24 hours. Middleton and colleagues (49) suggest, based on a single case, that the combination of intrathecal baclofen with clonidine is more effective than the use of baclofen alone. Fenollosa and colleagues (50), in a questionnaire study of 380 patients (38% of whom responded) who suffered from spinal cord injury, revealed that 65.5% experienced pain, of which the steady, burning, dysesthetic component was the most common. Their pharmacotherapy strategy was reported as successful in 33 cases (35% by my calculation) and included the use of amitriptyline, clonazepam, nonsteroidal antiinflammatory drugs, and 5-hydroxy-tryptophane. They also found intrathecal morphine infusion useful. Watson (51) recommended the use of carbamazepine in central pain states related to multiple sclerosis. Both this drug and amitriptyline were effective in a three-phase placebo-controlled study of stroke pain (52), but trazodone, a serotonin-potentiating antidepressant, failed to show benefit in spinal cord central pain (53). Desipramine (54), a norepinephrine-potentiating antidepressant, may relieve neurogenic pain. Watson could find no controlled studies of opioids and anticonvulsants in central pain. Further information on drugs for central pain states can be found in Chapter 84, Chapter 85 and Chapter 86.

Most authors recommend the use of nonsteroidal antiinflammatory drugs and simple analgesics to manage the nociceptive musculoskeletal pain and the use of amitriptyline, carbamazepine, diphenylhydantoin, chlorpromazine, and diazepam for the neuropathic pain. In this author's opinion, narcotics are an unwise choice because of the relative insensitivity of the central pain to these drugs and the development of side effects. Anecdotal reports indicate that some patients may have a good response; a trial of opiates may be warranted when other drugs have failed. Depression and other concomitant psychological problems must also be managed. However, few attempts have been made to evaluate the use of different psychological treatment strategies in the management of spinal cord injury pain. However, if central pain is severe, medical therapy is often disappointing (5,6,44), forcing consideration of more invasive strategies.

Surgical Treatment

In the choice of surgery for spinal cord central pain, the general principles mentioned previously must be kept in mind: the limited success and the incidence of complications balanced against the severity of the pain and its effect on life. The simplest and safest measures should be used first. The pain must be analyzed and broken down into its component parts, each with its separate pathophysiology. Then, a procedure must be chosen that addresses the pathophysiology of the primary pain. Before embarking on pain-relieving surgery, the need for any primary spinal procedure must be ruled out and appropriate imaging studies obtained. The latter helps with planning such operations as the dorsal root entry zone (DREZ) procedure and dorsal column stimulation (DCS) and also identifies a secondary syrinx that, if progressive, must be dealt with first. The use of a multidisciplinary approach is essential. Success after pain surgery is not manifest by the score on an analog pain scale alone, but also by the patient's overall satisfaction with the procedure, the beneficial effect on lifestyle, the requests for medication, and subsequent health care consumption (55). Inappropriate narcotic intake should be managed before commencing surgical treatment.

Local anesthetic diagnostic blocks are of little benefit (5,6). They usually yield temporary pain relief in neuropathic pain syndromes whether done proximal or distal (56) to the causative lesion. Repeated local anesthetic blockade in our hands has not reduplicated the therapeutic benefits described by Livingston (7). Permanent section of the same neural structure affected by the block does not lead to long-term pain relief (2,3 and 4,7). Nerve blocks may be useful in monoradicular syndromes by allowing confirmation of the fact that division of a particular root can stop the allodynia or hyperpathia. They also allow an assessment of the degree of sensory loss, particularly position sense, to be expected should that root be divided in an attempt to relieve the pain, which is particularly important in a quadriplegic with allodynia from a root lesion in the arm. Sympathectomy has little utility except in the rare case of complex regional pain syndrome type I that is superimposed on spinal cord injury (see Chapter 20).

Operations for Syrinx. If the preliminary investigation discloses the presence of a syrinx, the first step is to treat it, usually with an appropriate shunting procedure. Syringomyelia should be suspected in long delayed onset of spinal cord central pain and in patients who show delayed changes in their neurologic status. Contrary to general impressions, we and others, including Milhorat and colleagues (26), have found that drainage of a syrinx usually does not significantly improve spinal cord central pain. Milhorat and colleagues reported 37 patients with syrinx associated with spinal cord central pain. After decompression of the syrinx, only 19% of patients were totally, and 41% partially, relieved of their pain after a 6-week interval. Any improvement was maintained for a year in only 24% of patients, all of whom retained unpleasant symptoms. It may be useful in the management of neuralgic pain presumably caused by impingement of the upper level of the syrinx on the spinal cord, but most patients still must be treated for their spinal cord central pain after decompression of the syrinx in the same way as those not experiencing this complication. In summary, the syrinx must be treated to prevent additional neurologic deficits; pain, when present, is not usually alleviated by treatment of the syrinx.

Miscellaneous Procedures. Procedures such as the intrathecal injection of hypertonic saline, cold saline, phenol, or alcohol are seldom reported in the current literature, although selective phenol or alcohol rhizotomy could be useful as an alternative to percutaneous radiofrequency rhizotomy. They have the disadvantage, compared with radiofrequency lesioning, of not easily permitting physiologic corroboration of the target site, of being less discriminate, and of not uniformly

penetrating the target structure.

Significance of the Outcomes of Destructive versus Neuroaugmentative Surgery

This issue is addressed here, before consideration of the individual procedures, because it reflects on the pathophysiology of the pain. Table 23-9 documents our experience with surgical treatment of spinal cord central pain (22). Chronic stimulation that produces paresthesiae in the area of pain has limited efficacy for the relief of spontaneous, steady pain but is not useful for the treatment of intermittent spontaneous neuralgic pain or of allodynia and hyperpathia; the reverse seems to be true for destructive lesions such as cordotomy, cordectomy, and the DREZ operation, the differences being statistically significant.

		Relief by pain type (% of patients)					
		Steady		Neuralgic		Evoked*	
Surgery	No. of patients	Good	Fair	Good	Fair	Good	Fair
Cordotomy	39	6	21	54	32	50	25
Cordectomy	12	8	38	66	49	66	29
Dorsal root entry zone lesion	4	0	1	1100	0	50	50
Dorsal column stimulation	22 incomplete lesions	27	14	0	0	0	25
	19 complete lesions	0	28	0	0	0	0
Paresthesia-producing deep brain stimulation	12	25	17	0	0	0	0

*Allodynia and hyperpathia.

TABLE 23-9. Response of cord central pain to surgery

How can we interpret this? Patients with spinal injury may experience injury to either spinal cord, spinal roots, or both (see Chapter 34). Pain resulting from injury to roots is in fact an example of peripheral neuropathic rather than of central pain, regardless of the quality of the pain. For example, patients with cervical cord lesions may experience disabling allodynia in the distribution of a spared cervical root emerging near the level of injury. However, allodynia and hyperpathia may also occur in patterns compatible only with spinal cord damage. It is now recognized that allodynia associated with peripheral (including spinal root) lesions is the result of altered processing in the dorsal horn of incoming nonnoxious stimuli. This leads to signals being transferred into the spinothalamic tract rather than the dorsal columns and results in the experience of pain (57,58). It would be expected that such allodynia would be relieved by medical or surgical strategies that blocked transmission in the spinothalamic tract either by modulation or transection, which is confirmed when one examines the surgical experience. It is more difficult to understand the mechanism of allodynia or hyperpathia caused by spinal cord lesions, because the causative lesion in these cases is proximal to the dorsal horn. Nevertheless, in such cases the evoked pain is relieved by transection of the spinothalamic tract, the DREZ procedure, and cordectomy (see Chapter 105 and Chapter 106).

The next element of spinal cord injury pain to be considered is the spontaneous, intermittent neuralgic pain that has been recognized by many authors to be associated with conus and cauda lesions (59). Such pain may be the result of root damage. Our experience and that of others is that, like allodynia and hyperpathia, it is relieved by interrupting the spinothalamic tract, by the DREZ operation, or by transection of the spinal cord (22). Like Sindou and colleagues (60), we regard the DREZ procedure as interrupting part of the spinothalamic pathway. In the literature concerning Nashold's DREZ operation (32,61,62 and 63), it is recognized that this procedure, like cordectomy in Jefferson's experience (14), and cordotomy in our own (22) and that of Botterell and colleagues (20), is ineffective for the relief of the spontaneous, steady pain but that it relieves *end-zone* pain, by which Nashold and his group mean pain beginning at the level of the lesion and extending caudally for a variable number of dermatomes as well as radicular pain (32,64). A possible explanation for this type of pain is that injury to a root in the cauda equina or to the spinal cord may establish a focus of ectopic impulse generation that is transmitted proximally in the spinothalamic tract (65,66).

Visceral and musculoskeletal spinal cord pain is so infrequent that conclusions cannot be made about its possible pathogenesis.

There remains the most common element of spinal cord central pain, the spontaneous, steady, often causalgic or dysesthetic element similar to that seen in all types of neuropathic pain. In spinal cord central pain, this is more characteristic of lesions above the level of the conus, although it can also occur in radicular distribution. This is the type of pain that is most difficult to relieve. It is not stopped by spinal cord transection above the level of the injury (14,22,59), but responds best to chronic stimulation that produces paresthesiae in the area of the patient's pain. It is wise to keep an open mind concerning the pathophysiology of such pain, as no theory adequately accounts for it or for its relief by chronic stimulation. Again, as outlined in Table 23-1, its features are that it is not always present after spinal cord injury, it may take time to develop, it may appear after a long interval when the patient develops a syrinx; the change in the pattern of such pain may reflect the fact that the damage caused by a syrinx is now being added to the pain that was already there from the spinal cord injury. This subject has been reviewed by Yezierski and Nashold (16,32).

Various explanations have been offered to explain neuropathic pain as listed in Table 23-10. In reviewing such a list, it is necessary to reconcile the suggested hypothesis with the clinical facts. Ephapses and ectopic impulse generation could explain the generation of neuralgic pain. Pathologic sympathetic drive could be at work in sympathetically maintained pain caused by peripheral root injuries, but it is difficult to see how it could have anything to do with central pain; the same is true for hypothalamic dysfunction. Denervation neuronal hypersensitivity, with its suggested marker of bursting cells, is discussed under Brain Central Pain, later in this chapter. To result in pain, somatotopographic reorganization, which also is discussed under Brain Central Pain, must be capable of occurring through synaptic reorganization rather than sprouting, because in some patients the pain onset is immediate. Whether sprouting is involved later on cannot be easily determined. Other suggestions involve various patterns of activation or disinhibition of pain pathways, and most of these suggestions would be compatible with the clinical facts. Because they are more difficult to review in the case of pain caused by spinal cord injury than by brain lesions, they also are discussed with the latter.

Ephapses at injury site
Ectopic impulse generation at injury sites
Pathologic sympathetic drive
Hypothalamic origin
Denervation neuronal hypersensitivity of either somatosensory-specific or reticulothalamic-nonspecific pathway, usually correlated with presence of bursting cells
Somatotopographic reorganization in response to injury with opening of alternate pathways through synaptic reorganization or sprouting
Irritation of sensory pathways
Disinhibition of pattern-generating systems
Selective neospinothalamic destruction with disinhibition of spinoreticulothalamic system
Interference with inhibitory mechanisms acting on the nociceptive afferents
(a) At thalamus allowing disproportionate nociceptive projection or with loss of inhibition by reticular nucleus on medial thalamus
(b) By loss of retrograde thalamocortical influence
(c) By loss of medial lemniscal dumping of nociceptive fibers

Adapted from Pagni CA. Central pain due to spinal cord and brain stem damage. In: Wall PD, Melzack R, eds. Textbook of pain. Edinburgh, UK: Churchill Livingstone, 1984:481–491, with permission.

TABLE 23-10. Suggested mechanisms for central pain

Percutaneous Radiofrequency Dorsal Rhizotomy. In monoradicular pain syndromes, particularly with allodynia, physiologically monitored radiofrequency percutaneous dorsal rhizotomy may be useful in selected patients after due consideration for the sensory deficit incurred by the loss of that root.

Dorsal Column Stimulation. Peripheral nerve stimulation is rarely feasible in spinal cord central pain, but one of the first surgical procedures that should be considered is DCS, because of its simplicity and low risk (see Chapter 100) (67,68,69,70,71 and 72). It is indicated as a first procedure in any case of spinal cord central pain in whom it is deemed that sufficient dorsal columns survive above the lesion to allow their stimulation to produce paresthesiae in the patient's area of pain; it has no role in the treatment of pain in an anesthetic or near anesthetic part and proves useless in most patients with incomplete lesions because of inability to produce appropriate paresthesiae. It is because of the inability to produce adequate paresthesiae that DCS has such a low success rate in treating spinal cord central pain. Another problem is that spinal cord injury itself or the primary surgical treatment of the pain- causing lesion may have so disturbed the local anatomy that DCS is

rendered impossible or unusually risky. The author prefers the simpler percutaneous technique of DCS to the use of paddle-type electrodes installed at laminotomy.

Usually, a trial of stimulation is performed first, proceeding to implantation of a permanent device only if more than 50% of pain reduction occurs during the trial. Twenty-two of our patients with incomplete spinal cord lesions were treated with DCS, 27% enjoying good (more than 50%) and 14% fair (25% to 50%) relief of steady pain (22). In 11 patients with complete lesions, 20% reported fair relief and then only of pain at the level of their sensory loss. It was most effective in patients with steady pain with incomplete lesions of the conus and cauda equina. Published outcome data are given in Table 23-11 confirming general unsatisfactory experience with this modality in spinal cord central pain. Complications consist of up to a 5% superficial infection rate and 10% technical problems, such as lead migration, equipment failure, and pain at implant sites. Pagni (6) and Nashold (73) concluded that the modality was disappointing for the relief of central pain. Despite the poor outcome, the simplicity and safety of DCS dictate its trial whenever possible.

No. of patients	% Relieved	Reference
19	16	66
9	22 (pass trial of dorsal column stimulation)	67
10	50 (pass trial of dorsal column stimulation)	69
3	33	68
33	18	22
25	18.2 (after 3 yr)	70
101	31 (short term)	71
	18 (longer term)	

TABLE 23-11. Published outcome of dorsal column stimulation for cord central pain

Deep Brain Stimulation. In the author's opinion, when DCS fails in the treatment of the steady component of spinal cord central pain, deep brain stimulation (DBS) to produce paresthesiae in the painful part of the body is the next surgical choice. This can be accomplished by implanting electrodes either in the medial lemniscus if a large part of the body is affected with pain, or more usually, in the tactile relay (Hassler's ventrocaudal) nucleus of the thalamus or the lemniscal radiations for more localized pain. Spinal cord central pain is often bilateral, and this necessitates bilateral implants. The best indication is steady pain in patients in whom DCS failed to produce paresthesiae in the area of pain; in our experience, if DCS produces adequate paresthesiae and fails to relieve the pain, paresthesia-producing DBS also fails (74). Paresthesiae-producing DBS is preferable to periventricular gray (PVG) or periaqueductal gray DBS for the steady neuropathic pain, the latter being preferable for nociceptive pain. This dichotomy in the use of the two types of DBS is supported by the conclusions of Bendok and Levy (75) (Table 23-12). Table 23-13 lists outcome data for DBS in the treatment of neuropathic pain. Complications occur in less than 8% of patients, and death in 0.6% (75).

	Deep brain stimulation			
	Paresthesiae-producing		Periventricular/ periaqueductal gray	
Pain type	No. of patients	% Relieved	No. of patients	% Relieved
Nociceptive	51	0	291	59
Neuropathic	409	56	155	23

From Bendok B, Levy RM. Brain stimulation for persistent pain management. In: Gildenberg PL, Tasker RR, eds. *Textbook of stereotactic and functional neurosurgery*. New York: McGraw-Hill, 1998:1539–1546, with permission.

TABLE 23-12. Response of nociceptive and neuropathic pain to deep brain stimulation

Site	No. of patients	% Relieved	Reference
Paresthesia producing	3	67	75
	5	40	76
	9	22	79,80
	6	17	77
	16	31	73
Periventricular/ periaqueductal gray	5	40	78
	9	0	79,80
	6	50	25
	12	25 good, 17 fair	73

TABLE 23-13. Published outcome data for deep brain stimulation for cord central pain

Treatment of the Neuralgic Component of Spinal Cord Central Pain

In the patient with (usually) a conus/cauda lesion with significant neuralgic pain shooting up or down the legs below this level, relief is unlikely with DCS, although it is probably best to offer a trial of this modality first because of its simplicity. If DCS fails, and it usually does, the next simplest step is a destructive procedure to interrupt the pain pathways such as cordotomy, cordectomy, or DREZ lesion.

Cordectomy. The simplest destructive procedure is to retransect the spinal cord, usually referred to as *cordectomy*, just above the level of the patient's injury, at the expense of elevating the sensory level one or a few segments and of denervating the lower abdominal muscles. The history of cordectomy has been reviewed by Nashold (32), and has usually consisted of small series of patients with unspecified pain types and somewhat inconsistent results. The exception is the work of Jefferson (14), who reported 19 patients treated by cordectomy. He found the procedure successful with lesions below T-10, especially if the pain was referred to anterior thighs and knees and if it was episodic in nature. Twenty-five percent of four patients with lesions at or above T-10 derived slight relief, whereas 47% of 15 patients with lower lesions were completely relieved, 47% more than 70%. The remaining patients reported 50% relief. In 12 of the author's patients undergoing cordectomy for spinal cord central pain, 60% enjoyed good relief and 40% fair relief of neuralgic pain; 80% good relief and 20% fair relief of allodynia, hyperpathia, or both; but only 30% enjoyed fair relief of steady pain. In these days of optimism for eventual restoration of damaged spinal cord function, cordectomy has become a psychologically unacceptable procedure despite its advantages for the patient with a complete lesion.

Cordotomy. Cordotomy, preferably by the percutaneous technique, achieves the same result as cordectomy, interruption of the spinothalamic tract. Various authors have noticed the selective differential benefit of cordotomy on the neuralgic compared with the steady element of the patient's pain (10,11,20,31,83), and our own experience is similar (22). Out of 39 of our own patients undergoing cordotomy, mostly by the percutaneous technique, 54% enjoyed good relief and 32% fair relief of the neuralgic pain, 50% good relief and 25% fair relief of the evoked pain, and 6% good relief and 21% fair relief of the steady elements of spinal cord central pain.

However, percutaneous cordotomy carries a small risk of producing ipsilateral limb paresis and of aggravating bladder dysfunction, crucial matters for the spinal

cord–injured patient with an incomplete lesion. Open thoracic cordotomy can obviate any risk of respiratory or upper extremity dysfunction in patients with thoracic or lumbosacral spinal cord injuries.

It has already been stressed that chronic pain tends to recur after its initial relief by medical or surgical strategies. This is clearly documented by Rosomoff and colleagues (83) in the case of cordotomy. Although we do not know how many of his patients suffered from spinal cord central pain, because of the reported length of follow-up the pain was unlikely to be caused by cancer and the same outcome would be expected in spinal cord central pain as we have found (84). He found that, initially, cordotomy relieved 90% of patients operated on, but that after 3 months relief had fallen to 84%, after 1 year to 61%, after 1 to 5 years to 43%, and after 5 to 10 years to 37%.

Dorsal Root Entry Zone Procedure. Although the pathophysiology corrected by the DREZ operation has not been clarified (63), the work of Sindou (60) with a related procedure has convinced this author that it relieves pain by interrupting the pain pathway from the somatotopographically related area of the body. This procedure has proved equally successful as cordectomy and cordotomy in the relief of the neuralgic and evoked elements of spinal cord central pain. Like cordectomy, it results in an elevation of the patient's sensory level and requires a laminectomy and considerable skill to do. It probably does not share the disapproval of the cordectomy procedure regarding future spinal cord regeneration, and it avoids the risk of paresis from cordotomy. It does have the propensity when performed at the conus, as is usually necessary, to interfere with any surviving bladder function. Table 23-9 lists our own and Table 23-14 lists published outcome data with the DREZ procedure for spinal cord central pain.

No. of patients	% Relieved	Reference
13	50–77	12,62
10	20	84
2	50	85
31	80 end-zone pain, 32 diffuse pain	61
56	50 all patients	86
31	74 end-zone pain	
25	20 diffuse pain	
14	57	87
138	54	86
20	50	88
7	86 end-zone pain	89
39	64	90

TABLE 23-14. Published outcome data for dorsal root entry zone operation for cord central pain

Although I have stated previously that the DREZ procedure is beneficial for the neuralgic element of spinal cord central pain, this is my interpretation of the work of others. Nashold and Bullitt (62) and Friedman and Bullitt (64) found the procedure most useful for the relief of end-zone pain (i.e., pain starting at the level of injury and extending distally), and not so effective for the diffuse, often sacrally distributed pain. Friedman and colleagues (87) found the procedure useful for pain that extended into the dermatomes immediately caudal to the level of injury, which they referred to as *root, radicular*, or *end-zone pain*. Pain extending into areas remote from the injury site described as *phantom, body*, or *diffuse burning pain* was not very responsive.

Stereotactic Surgery. In this author's experience, with his own patients, and reviewing the literature, destructive stereotactic procedures such as medial thalamotomy or mesencephalic pain tract section yield such poor relief of central pain that they are rarely indicated. Meglio (44), who reviewed the overall management strategies for central and deafferentation pain, agrees with this conclusion. I found 22% to 36% of 150 patients with central pain improved after various thalamotomy procedures (92). Nashold's literature review (93) suggested a 50% benefit after mesencephalic tractotomy. My review suggested 27% (94), whereas Cassinari and Pagni (5) suggested 50%, Pagni (95) 50%, and Davis and Stokes (96) 50%. Pagni, reviewing his own cases, found 30% relief (95), and Gybels and Sweet (97) found 44% relief of various neuropathic pains after mesencephalic tractotomy.

Other Procedures. I agree with Nashold (74) that destructive procedures performed on the cerebral cortex are only of historic interest in the treatment of central pain (see Chapter 108). Procedures directed toward the limbic system, hypothalamus, and hypophysis have all been advocated, but data are too sparse to draw conclusions. We do not consider the treatment of spasticity and spasms as within the realm of this chapter, although they may contribute to the problem of the pain. Although it has become popular to use chronic spinal infusion of opiates for the relief of various types of pain, like Meglio (44) we cannot find convincing evidence for the usefulness of spinal opiates in central pain.

BRAIN CENTRAL PAIN

Central pain caused by brain lesions is more enigmatic and more intractable than that arising from the spinal cord. Another example of neuropathic pain, it shares with the latter the peculiar clinical features described under Spinal Cord Central Pain. It can arise from lesions of any etiology between the foramen magnum and the cerebral cortex, whether minimal or massive or associated with minor or major neurologic deficit. Like other types of neuropathic pain, it is idiosyncratic, often has a delayed onset, may occur in the absence of clinically detectable sensory loss, and commonly has three features: spontaneous steady, neuralgic pain, and evoked pain (allodynia and hyperpathia). Whereas in spinal cord central pain, steady pain, and neuralgic pain are most common, in brain central pain, steady pain, and evoked pain predominate. The papers by Riddoch (98) and Dejerine and Roussy (99) are pioneering masterpieces in its clinical description.

Incidence and Etiology

Most cases of brain central pain are caused by strokes. Table 23-15 lists the etiology in 73 of the author's cases. Brain central pain is rare, said to occur in only 1% to 2% of all strokes (9). Andersen and colleagues (100) studied 207 consecutive stroke patients and found that 8% went on to develop central pain, severe in 5%; 7% of the patients had allodynia.

	%
Vascular	90.6
Supratentorial	78.1
Thrombotic stroke	67.1
Spontaneous	57.5
Aneurysm, subarachnoid hemorrhage	2.7
Iatrogenic	
Artery ligation	2.7
Angiography	1.4
Postoperative	1.4
Trauma	1.4
Hematoma	11.0
Spontaneous	9.6
Thalamotomy lesion	1.4
Infratentorial	
Thrombotic stroke	6.9
Lateral medullary syndrome	5.5 } 6.9
Other	1.4
Hematoma	4.2 } 5.6
Hematobulbia	1.4
Infection	
Abscess	2.7
Vaccinia encephalitis	1.4
Trigeminal tractotomy	1.4
Syringobulbia	1.4
Thalamic sclerolysis	1.4
Degenerative, not yet diagnosed	1.4

TABLE 23-15. Etiology in 73 cases of brain central pain

The paper by Dejerine and Roussy (99) planted the notion that stroke-induced pain depended on thalamic lesions, but modern imaging has confirmed what a few pioneering studies, such as that of Biemond (101), had long suggested: Pain can arise from lesions in brainstem, thalamus, subcortical white matter, and cerebral cortex (102,103). When thalamic lesions cause pain, they tend to lie in ventroposterior thalamus (104), although anatomic studies have failed to agree on a specific site [somatosensory relay and posterolateral thalamus (105), lateral posterior and lateral dorsal thalamus (106) being suggested]. On the other hand, brain central pain is rare after craniocerebral injury (107), craniotomy, or cerebral cortical lesions. Electrical stimulation of the brain (25) and epileptic seizures (108) rarely evoke pain. When they do occur, algogenic cortical lesions are usually located in the parietal area, thought by some to include the spinothalamic projection to the second

somatosensory cortex (109), particularly in the white matter deep to the caudal ansa and the opercular region.

It has been noted that when the thalamus is involved in stroke-induced pain, right-sided lesions are more prevalent than left (110,111), because a literature search revealed 63% of 114 cases of stroke-induced pain involving the thalamus were right-sided. In the author's 11 patients with central pain after six isolated thalamic lesions and five that involved thalamic and suprathalamic structures, 82% were on the right side (112). Tantalizing information that has never led to useful therapy includes the anecdotal accounts of relief of brain central pain after a second stroke, such as the report by Soria and Fine (113) in which a second stroke involved the corona radiata interrupting thalamoparietal connections.

Brain central pain can be reversible in other ways. Potagas and colleagues (114) describe a patient with intermittent pain in the right upper limb caused by an otherwise asymptomatic low-grade glioma of the white matter of the parietal operculum whose pain stopped after excision of the tumor. In a personal patient who had a right parietal hemispheral meningioma with contralateral brain central pain, the pain disappeared after removal of the tumor.

Hamby (115) reported relieving posttraumatic brain central pain associated with allodynia by exploring and excising the patient's atrophic, gliotic parietal cortex, stimulation of which had been painful; pain relief persisted for 10 years. Erickson and colleagues (116) reported two patients with *thalamic pain syndrome* relieved by resection of the postcentral gyrus, but that experience does not appear to have been duplicated by others (4).

Functional Imaging in Brain Central Pain

Functional imaging is a promising tool for the investigation of the mechanism of brain central pain. Cesaro and colleagues (117) found that stimulating the affected half of the body so as to produce hyperpathia in two patients with stroke-induced pain associated with hyperpathia produced thalamic hyperactivity in the SPECT scans, but this was not seen after stimulation of the unaffected side. Stroke pain patients without hyperpathia did not show this hypersensitivity to stimulation. They hypothesized that many thalamic inhibitory neurons lie in the nucleus reticularis thalami and project to the medial nuclei. Loss of their function after a stroke involving thalamus could therefore result in disinhibition of the medial thalamic nuclei and possibly pain; no other connections are known between the medial and lateral thalamic nuclei. Canavero and colleagues (118), in a SPECT scan study of five patients with different neuropathic pain syndromes, found reduced perfusion in the parietal lobe further reduced by inducing allodynia and postulated that cortical inhibition was in some way involved in the production of central pain. The injection of propofol reduced brain central pain for 5 minutes, during which time the thalamic hypoperfusion improved.

Hirato and colleagues (119) studied 5 controls and 11 patients with stroke pain using positron emission tomographic scans. Patients with thalamic lesions tended to have *superficial* pain, those without it *deep* pain. In the thalamic group, background neural activity was reduced in the ventral intermediate region and increased in centrolateral nucleus, whereas regional cerebral oxygen consumption was well maintained on the side of the stroke except in the thalamus, including the cerebral cortex surrounding the central sulcus; regional oxygen extraction ratio was increased around central sulcus. In nonthalamic stroke pain patients, neural activity was generally maintained except in centrolateral nucleus, in which it was low, whereas in these pain patients and after strokes that failed to produce pain, regional cerebral oxygen consumption and regional oxygen extraction ratio were reduced in all contralateral brain structures, as was the regional oxygen extraction ratio. They concluded that the function of nonspecific afferents was maintained in thalamic stroke patients and was possibly contributing to the pain. They postulated that the increased bursting activity in thalamus was related to the increased activity in the motor and premotor cortex, which in turn had a facilitating effect on spinal cord dorsal hornd the thalamic intralaminar nuclei. They also postulated that lost activity in the sensory cortex might result in disinhibition and that this disinhibition, as well as the effect on intralaminar nuclei, might be related to the central pain.

Another study (120) described 13 stroke patients. Irregular burst discharges were often encountered in the posterolateral thalamus, their prevalence correlating inversely with the number of sensory responses there. These findings were associated with increased regional cerebral glucose metabolism and the relative value of glucose to oxygen metabolism in the cortical precentral area ipsilateral to the lesion. These factors were reduced in thalamus and cortical postcentral area in all cases. They postulated that sensory cortex damage could disinhibit the motor area, somehow resulting in pain.

Canavero and colleagues (121) reported one patient with poststroke pain from a suprathalamic lesion who demonstrated parietal hypoperfusion on SPECT scan and two with thalamic lesions with either frontal parietal or thalamic hypoperfusion. They considered this evidence of inhibition and went on (122) to suggest that central pain resulted from a chemical imbalance between glutamatergic and GABAergic mechanisms in transmission between sensory thalamus and cortex. They proposed that these imbalances might be corrected by opposing glutamatergic or potentiating GABAergic transmission, for example, by administering ketamine or propofol, respectively.

Clinical Features of Brain Central Pain

Although published data vary, the clinical features of 73 personal cases of brain central pain are summarized here (112): 54.8% of our 73 patients were men, and pain was right-sided in 43.9%, left-sided in 53.4%, and bilateral in 7%. Age of affected patients at the time of onset is shown in Table 23-16. Accompanying neurologic signs are listed in Table 23-17 and lesion sites in Table 23-18, nearly 70% having hemiparesis, which was severe in 21.9%. After a variable delay, pain with three chief features (64.4%) or dysesthetic (31.6%), intermittent (16.4%), and allodynia and hyperpathia (64.9%).

Age (yr)	%
21–30	2.7
31–40	10.9
41–50	17.8
51–60	37.0
61–70	24.7
71–80	5.5
Uncertain	1.4

[a]Range, 26 to 78; mean, 54.3 years.

TABLE 23-16. Age at causative event: 73 cases of brain central pain [a]

	%
Cognitive	9.6
Speech	28.8
Epilepsy	8.2
Tremor	6.8
Dystonia	8.2
Visual	16.4
Cerebellar	
Nystagmus	4.1
Ataxia	20.5
Cranial nerve	13.6
Hemiparesis	69.9
Sensory defect	87.6

TABLE 23-17. Neurologic signs in 73 cases of brain central pain

No. of patients	73	16
Reference	114	125
Lesion site (%)		
Infratentorial	35.9	14.2
Thalamic	12.8	25.7
Thalamic and suprathalamic	15.4	37.8
Suprathalamic	28.2	22.3
Diffuse	2.6	0
Not visible on computed tomography (supratentorial on clinical grounds)	5.1	0

TABLE 23-18. Location of brain lesions causing central pain

Steady pain was usually described as burning (64.4%), although other adjectives were applied (Table 23-19). Distribution of intermittent pain was similar to that of pain overall, as shown in Table 23-20, and so was its association with sensory loss. Allodynia and hyperpathia are characterized in Table 23-21 and Table 23-22. The only feature noted is its relative infrequency in the absence of clinically detectable sensory loss.

	%
Total incidence	98.6
Burning	64.4
Cold	10.6
Numb, tingle, fuzzy, sting, itch	31.6
Ache, bruise, sore, throb, pull, press, swell, cramp, rush, tight, grab, pinch, tear	38.6

[a]Some patients use multiple descriptors.

TABLE 23-19. Steady pain in 73 cases of brain central pain [a]

	%[a]
Total incidence	16.4
½ Body	78 (89)
Face or focal	22 (11)
Associated with evoked pain	55 (65)
Multimodal sensory loss	44 (48)
Dissociated sensory loss	45 (38)
No sensory loss	11 (14)

[a]Numbers in parentheses are percent distribution for pain in all 73 cases.

TABLE 23-20. Intermittent pain in 73 cases of brain central pain

	% of Patients
Overall incidence	64.9
½ Body	23.2
Patchy	42.5
Evoked by	
Single modality	23.3
Multiple	5.6
?	6.8

TABLE 23-21. Allodynia and hyperpathia in 73 cases of brain central pain

	Evoked pain (% of patients)	
Sensory loss	Present	Absent
None	8.3	20.0
Dissociated	33.3	36.0
Multimodal	58.3	44.0

TABLE 23-22. Relationship of evoked pain to sensory loss

Table 23-23 correlates pain type with lesion site and sensory loss. Intermittent pain appears most common with infratentorial lesions, and evoked pain is equally common with lesions at all sites. Dissociated sensory loss was more common in infratentorial lesions.

	Pain			Sensory loss		
	Constant	Intermittent	Evoked	None	Spinothalamic	Multimodal
Infratentorial brainstem	14	3	10	3	4	6
Thalamus only	5	0	5	1	1	4
Thalamus and supratentorial	6	0	3	1	0	5
Supratentorial, not thalamus	11	1	10	0	1	10
None seen, presumably supratentorial	2	0	2	0	1	1
Diffuse	1	0	0	0	1	0

TABLE 23-23. Type of pain in 40 cases of brain central pain and correlation with lesion site

Onset is often delayed; Table 23-24 tabulates the time of onset in 73 personal cases (112) and two published series (100,123). Pain was almost always referred to a part of the body in which sensation was affected except where there was no clinically detectable sensory loss at the time the patient was seen with the pain, although there might have been loss earlier in the patient's history. Distribution of pain varied and bore no relation to any clinical features. Size, side, or location of the lesion; degree of sensory loss; age; and sex all had no effect on the quality or severity of the pain (100,112).

No. of patients	73	16	27
Reference	113	124	101
Delay of onset (% of patients)			
None	29	0	
<1 wk	8	0	63
1 wk to 1 mo	10	52	
1-6 mo	26	26	19
6-12 mo	7	8	
1-2 yr	10	6	19
>2 yr	4	7	
?	7	0	

TABLE 23-24. Delayed onset in brain central pain

It is just as important to cite structures whose damage does not cause pain as those that do. First, the lesion must affect the somatosensory system. Lesions of the nonspecific spinoreticulothalamic tract, limbic system, dorsomedian, centrum medianum, intralaminar and reticular nuclei, and kinesthetic somatosensory pathway (ventrolateral, posterolateral, anterior nuclei of thalamus and globus pallidus and Forel's fields) virtually never cause pain, as attested to by the absence of central pain in the thousands of patients undergoing medial thalamotomy, cingulumotomy, hypothalamotomy, and various lesions for the treatment of movement disorders (4,5,73,124). However, central pain follows 4% to 18% of lesions made in the lemniscal relay nucleus of the thalamus in attempts to (125).

Table 23-25 shows the distribution of sensory loss in our 73 patients. It was confined to the face in 6.9%, in which it was usually dissociated. Pain was usually associated with sensory loss in all modalities, less often dissociated sensory loss, and rarely occurred in the absence of spinothalamic loss. Boivie and Leijon (123), using psychophysical techniques in 63 cases, concluded that all stroke pain patients have sensory abnormalities, with impaired pain and temperature appreciation being the key common factor; they report, however, one additional case outside their study group of 63 patients in whom no clinically detectable sensory loss was present. They found allodynia in 57% of their Swedish patients, 23% of their British ones.

Hemibody, all modalities	46.5
Dissociated sensory	20.5
All modalities but chiefly pain and temperature	8.2
Hyperpathia, allodynia, or both	6.8
Touch, position, vibration alone	5.5
None	5.5

TABLE 23-25. Pattern of sensory loss in 73 cases of brain central pain

Vestergaard and colleagues (126) studied sensory deficit in 11 stroke pain patients, all of whom had increased threshold for pain appreciation in the affected areas, 10 increased threshold for cold, and a less striking increase in the threshold for heat and cold pain. Four of the 11 also had an increased threshold to touch and three to argon laser pain. There was a tendency for neuralgic pain to accompany brainstem lesions as in the case reported by Nashold and colleagues (125), in whom paroxysms of pain seemed to be accompanied by bursting slow wave electrical activity recorded in the midbrain, which was relieved by lesions made there. Leijon (127) correlated steady pain with infratentorial brainstem and extrathalamic supratentorial lesions and lancinating pain with thalamic lesions. This is not in agreement with our observations.

Andersen and colleagues (100) studied 207 consecutive stroke patients, of whom 16 developed central pain, finding that the patients who went on to develop pain had larger lesions and more pronounced abnormalities of sensitivity to cold and warm than did those who did not. These abnormalities consisted of increased sensitivity to cold, decreased sensitivity to warmth, and allodynia or dysesthesia to touch or cold but not to warmth. Stroke pain in the absence of sensory loss has been reported by others (5,6,107), in addition to ourselves (112) and Boivie and Leijon (123). We have seen brain central pain in patients with selective damage to the lemniscal pathway, and one case has been reported in the literature (128). As with spinal cord central pain, not all patients with appropriate sensory abnormalities go on to develop pain, suggesting that neuropathic pain may be related to factors other than neuronal loss.

Bowsher (129) studied 156 stroke and spinal cord central pain patients, finding pain onset usually delayed (between 1 week and 6 years in more than 69% of patients). Right and left sides were equally affected, and two-thirds had allodynia, including movement allodynia. Pain occurred within the area of sensory deficit, the critical component of which was interference with thermal and pinprick appreciation. These losses were particularly prominent in areas of maximum pain. Deficits in mechanoreceptive functions were not so related. He concluded that the best hypothesis to explain the pathophysiology of central pain was upregulation or downregulation of receptors for transmitters, particularly noradrenergic ones that developed over time.

Hoogenraad and colleagues (130) described a case of visually induced pain in the numb side of the body after a right parietal cortical infarction associated with left hemianesthesia. Jensen and Lenz (131) commented on the hyperalgesia and allodynia described in the original paper by Dejerine and Roussy (99) concerning stroke-induced pain. These evoked elements are said to occur in three-fourths of stroke patients by Andersen and colleagues (100). Jensen and Lenz suggest that allodynia and hyperpathia never occur in stroke pain patients without accompanying spontaneous pain. However, we have observed evoked pain in the absence of

spontaneous pain in spinal cord (see Table 23-5) and brain central pain (see Table 23-25), and Pagni (4) reports it in stroke central pain. Jensen and Lenz comment that the essential damage necessary to produce brain central pain is to the spinothalamic tract, but comment on the fact that some patients who have such damage do not have pain.

Relationship to Dyskinesia

The original description of the Dejerine-Roussy syndrome (99) included dystonia on the same side of the body as the pain. Dystonia affected 8.2% of our 73 cases (112), always associated with thalamic lesions. It must be remembered that stroke- induced dystonia occurs regularly in the absence of central pain. Of our 73 patients, 6.8% had tremor accompanying their central pain, especially in the case of brainstem lesions, in keeping with observations on experimentally induced tremor produced by brainstem lesions in experimental animals. Again, tremor can occur after brainstem strokes in the absence of pain.

Pathophysiology of Brain Central Pain

The features of brain central pain are similar to those of spinal cord central pain and to peripheral neuropathic pain, suggesting the possibility of a common pathophysiology. The issue has been partly discussed under Spinal Cord Central Pain, and common theories are listed in Table 23-10. This matter may be easier to pursue in brain than in spinal cord central pain, because imaging identifies the responsible lesions that are then accessible to physiologic exploration during the course of stereotactic surgery aimed at alleviating the pain. Whatever the accepted theory, it must be consistent with clinical facts. It must take into account the features listed in Table 23-1, such as immediate or delayed onset and reversibility after removal of the causative lesion, and it must take into account the causative lesions, the neural deficit produced, and the response to treatment strategies. Although by no means exhaustive, Table 23-10 lists popular theories offered to explain central pain, some of which can be examined physiologically during stereotactic surgery. Ephapses and ectopic impulse generation seem reasonable explanations for, particularly, the intermittent neuralgialike pain in conus and cauda and possibly stroke lesions. There do not appear to be convincing data to incriminate sympathetic or hypothalamic involvement. Denervation neuronal hypersensitivity could take the form of bursting cells (a popular notion) or some less obvious alteration of neuronal function. Most of the remaining suggestions are variations on the theme that loss of an ascending pathway damaged by the stroke results not only in loss of the function of that pathway but also in disinhibition of other structures. Regev and colleagues (132) reported a patient with a pontine hematoma without somatosensory deficit but with transient spontaneous pain and allodynia to touch, pinprick, and temperature, attributed to damage to the central tegmental tract, with resulting disinhibition of the thalamus by the reticular formation resulting in the pain. Cassinari and Pagni (5) found central pain rare after medullary spinothalamic tractotomy and attributed this observation to concomitant damage to the reticulospinothalamic tract with resultant lack of disinhibition.

Boivie and Leijon and their colleagues (123,127,133) concluded from their clinical studies that lesions of the spinothalamic cortical pathways or their trigeminal equivalents were necessary for brain central pain to develop, in contradistinction to the older hypothesis that medial lemniscal pathway damage was essential. Bowsher (134) proposed that selective destruction of the spinothalamic tract sparing the spinoreticulothalamic tract fibers that subserve pain was responsible for central pain through disinhibition of the nonsomatotopographic pathway. Craig (135) has collected evidence to support the hypothesis that stroke- induced pain results from selective loss of thermal sensitivity pathways with disinhibition of cold-evoked pain.

Jensen and Lenz (131) suggest that the pain is caused by central sensitization of the third- or higher-order deafferented neurons. They theorize that the deafferented cells in reticular nucleus can generate bursting activity that can cause hyperpolarization and bursting activity of thalamic relay cells projecting to cortex. Corticothalamic axons pass through the reticular nucleus, giving the neurons collaterals on the way. Thus, a cortical lesion could result in reticular nucleus neuronal hyperactivity and pain. They suggest loss of spinothalamic tract function leads to hyperpolarization of thalamic cells and bursting. Because some of such cells are involved in pain processing, they could cause pain. They rationalize the functional imaging studies showing both increased and decreased thalamic activity in chronic pain and hypothesize that pain control might be achieved by manipulating the interplay of glutamatergic, GABAergic, noradrenergic, serotonergic, histaminergic, and cholinergic input to thalamus. They suggest that serotonergic, noradrenergic, and cholinergic input may be responsible for the bursting and that noradrenergic and serotonergic input might modulate thalamic bursting by action on the thalamic reticular and relay nuclei.

Microelectrode Exploration of the Thalamus in Brain Central Pain

Observations made using stereotactic surgery reflect on these theories. In 29 patients operated on to institute DBS, 22 of them with microelectrodes, in whom lesions ranged from brainstem through thalamus to cortex, we correlated receptive fields (RFs) and projected fields (PFs) with clinical features.

Issue of Bursting Cells

A considerable literature suggests that bursting cells may be markers of neuronal denervation hypersensitivity (2,3,4,136,137,138,140,141,142,143,144,145,146 and 147), and it is currently popular to suggest that these bursting cells, which can occur at any level upstream from the site of injury, could trigger pain. We have extensive experience recording bursting cells in lateral thalamus during microelectrode exploration preliminary to making destructive lesions or implanting chronic stimulators for the relief of chronic pain or movement disorders. Bursting cells occur normally in sleep (148) and in the normal waking state in various medial thalamic nuclei including dorsomedian. In the lateral thalamus we have found them only in patients who have deafferenting lesions, such as amputation, other peripheral deafferentation, spinal cord injury, stroke, previous thalamotomy for tremor, and multiple sclerosis, regardless of whether the deafferentation is associated with pain (149,150). Hirayama and colleagues (151) have suggested that regularly bursting cells that have RFs and are located in the tactile relay might be correlated with pain. Lenz and colleagues (152,153) found a series of abnormalities in the tactile relay nucleus of patients with spinal cord central pain: absent RFs below the level, increased numbers of neurons without RFs, replacement of some missing RFs by RFs from parts of the body that border the level of the lesion, resulting in mismatches between RFs and PFs (sites in the contralateral body where the patient experiences paresthesiae during microstimulation), as well as bursting cells with characteristics of calcium spikes in the deafferented thalamic area. It is possible that bursting cells are responsible for central pain. However, careful study (150) of bursting cells in deafferented patients, with and without pain, failed to provide any correlation between pain and bursting cells in the lateral thalamus.

During surgical exploration of the medial thalamus, Rinaldi and colleagues (154) found bursting cells in dorsomedian, centrolateral, centrum medianum, and parafascicular nuclei in 8 of 10 patients with various types of neuropathic pain, including one case of stroke and one of central pain. These bursting cells occurred from the junction between lateral dorsomedian nucleus, centrolateral nucleus, and centrum medianum to the inferior limit of centrum medianum. Jeanmonod and colleagues (155) made similar observations in 39 of 45 patients with pain, 7 of whom had spinal cord lesions, 2 brainstem, 2 thalamic, and 3 parietal lesions. In their patients, bursting cells were clustered around the centrolateral nucleus, and many of them had the characteristics of calcium spikes. Both groups of authors implicate the bursting cells as generators of neuropathic pain, with Jeanmonod's group reporting considerable success in relieving neuropathic (including stroke) pain by medial thalamic lesions aimed at destroying the bursting cells. I suggest caution in interpreting these findings; we have routinely found bursting cells in this region of thalamus in patients who did not have pain.

Somatotopographic Reorganization

It has been suggested that somatotopographic reorganization may lead to central pain. Kiss and colleagues (156) demonstrated that in humans somatotopographic reorganization can occur within minutes in the ventrocaudal nucleus of the thalamus, presumably by synaptic rearrangement, although, in other settings, it could be the result of sprouting. In our thalamic explorations we found various patterns of RFs and PFs with no correlation with the pain syndrome produced: preserved RFs and PFs with good somatotopographic matching, preserved RFs and PFs with somatotopic mismatch, absent RFs with preserved PFs, preserved RFs with absent PFs, and absent PFs and RFs.

Figure 23-2 is a computed tomographic scan of a patient with a small right-sided thalamic infarct that resulted in fluctuating left-sided burning dysesthetic pain with allodynia. When he was explored stereotactically with microelectrodes to identify sites for electrode implantation for DBS, no neurons were recorded and no responses to stimulation up to 160 μA were found in the 14-mm sagittal plane (Fig. 23-3) except for two sites in which deep tactile facial responses were recovered. This plane, which would normally be expected to house responses referable to hand and face, appeared otherwise dead. The responses that would have been expected there were found laterally misplaced in the 17-mm sagittal plane (Fig. 23-4). At some sites RFs and PFs matched; at others mismatch occurred. In keeping with the fact that the patient had allodynia (see following discussion) pain was elicited seven times, and burning was elicited twice where normally paresthesiae would have been expected.

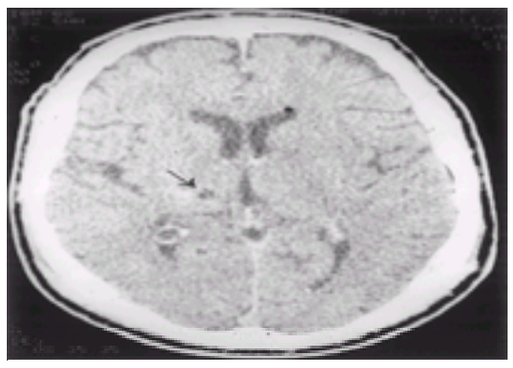

Figure 23-2. Computed tomographic scan of a man who suffered a thrombotic stroke (*arrow*) at the age of 60 years with left hemiplegia. Central pain began 5 to 6 years later. He was studied for 7 years. Pain varied over time, consisting of burning and dysesthesia associated with allodynia relieved by rest and aggravated by activity, affecting chiefly the left upper extremity, face, and head, rarely the trunk or leg. It was associated with dystonia in the left upper limb. There was slight reduction of feeling of pinprick and warmth on the left half of the body; absence of position sense distal to left wrist and ankle; at first, slight reduction of appreciation of touch in left upper and lower extremities, and later no clinically detectable abnormality of appreciation of touch, vibration, or cold. Allodynia was induced by vibration, repeated light touch, and movement in the left upper extremity on some occasions, and by light touch throughout the left side, especially in the cheek at others. There was extinction with simultaneous stimulation bilaterally on the left face and slight reduction of two-point discrimination on the left. A trial of dorsal column stimulation and two trials of paresthesiae-producing deep brain stimulation failed, the latter actually being described as painful. Pentothal, 150 mg intravenously, abolished his pain temporarily.

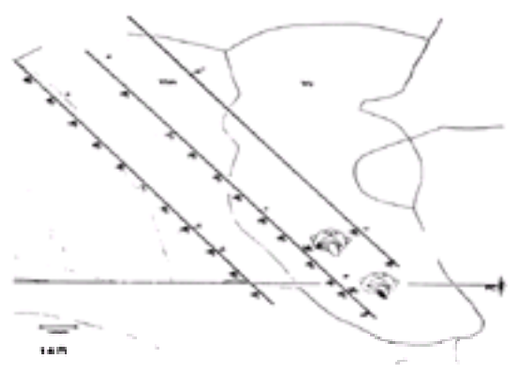

Figure 23-3. Figurine map of the thalamus of the patient seen in Figure 23-2 explored in the 14-mm sagittal plane with microelectrodes. Three trajectories were made with continual recording (receptive fields shown in body diagrams to the right) and microstimulation every 1.0 mm (projected fields shown in body diagrams to the left). *Triangle*, no response to stimulation at the current used. Numbers indicate stimulation strength in microamperes. (M, bursting cells; PC, posterior commissure; SA, slowly adapting; TD, deep tactile; U, unidentified cell; Vc, ventrocaudal nucleus of thalamus; Vim, ventral intermediate.)

Figure 23-4. As in Figure 23-3, but the 17-mm sagittal plane is shown. (B, burning; Do, pain; MR, motor response; P, paresthetic response; SA, slowly adapting; SM, sensory response with motor connotations; TD, deep tactile; TS, superficial tactile stimulus; U, unidentified cell; Vc, ventrocaudal nucleus of thalamus; Vim, ventral intermediate.)

In general, RF/PF match or mismatch as well as sensory changes caused by the stroke did not correlate with the clinical features of the pain. In fact, some patients appeared to have experienced total destruction of the sensory thalamus and its projections [no RFs or PFs on extensive recording (157,158)], but they still showed the same patterns of sensory loss and pain as a patient with a small stroke and preserved RFs and PFs.

Evidence for Ipsilateral Mediation of Stroke Pain

Pain was identical in our patients with absent RFs from proximal tract interruption to that seen in the presence of intact PFs and RFs; the former retained intact PFs, showing that transsynaptic degeneration does not occur in the thalamus and that thalamic neurons and thalamocortical connections can be left intact and apparently isolated after a stroke yet still capable of generating conscious effects and presumably capable of activation by alternate somatosensory input, possibly to generate pain.

Figure 23-5 is a computed tomographic scan of a patient who had a massive right-sided thrombotic stroke causing left homonymous hemianopsia, spastic hemiplegia, and multimodality hemisensory loss with allodynia and hyperpathia. Stereotactic exploration with microelectrodes to treat him with DBS was carried out. However, 14 trajectories explored with microelectrodes and microstimulation and three with macrostimulation from the third ventricle to the 15-mm left sagittal plane failed to reveal any neuronal activity or response to stimulation (Fig. 23-6). Exploration in the 6-mm sagittal plane on the side ipsilateral to the hemiplegia, however, done to implant an electrode in functioning PVG, gave normal responses for that area (Fig. 23-7); stimulation there produced a feeling of warmth in face and chest and reduced his allodynia.

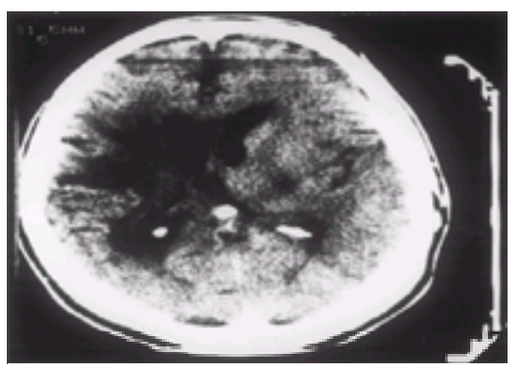

Figure 23-5. Computed tomographic scan of a man who at age 56 years had a thrombotic stroke causing spastic left hemiplegia, left homonymous hemianopsia, and almost immediate onset of central pain. He was followed over 4 years with a somewhat variable pain and sensory picture until he died of bronchogenic carcinoma. Constant sharp pain was felt in the left shoulder, left hip, and left hand, with spontaneous exacerbations every 2 minutes increased by activity. There was burning pain in the left medial thigh, knee, and foot and cramps in the left calf. Appreciation of light touch, pinprick, position, and vibration sense was reduced on the left side, although he was an inconsistent witness and the degree of position and vibration senses varied; there was mild allodynia to light touch, mild hyperpathia, inconsistently localized, to pinprick and severe cold allodynia. He was treated with left deep brain stimulation in periventricular gray inserted December 19, 1990, which reduced his allodynia dramatically at first, less so over the 4 years of follow-up. This induced a warm feeling in the face and chest.

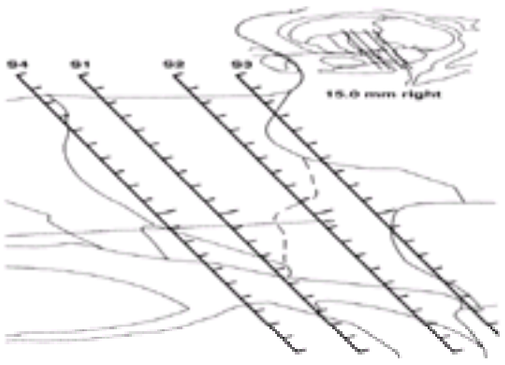

Figure 23-6. Four microelectrode trajectories in the 15-mm sagittal plane of the thalamus of the patient seen in Figure 23-5, showing absence of receptive fields and projected fields.

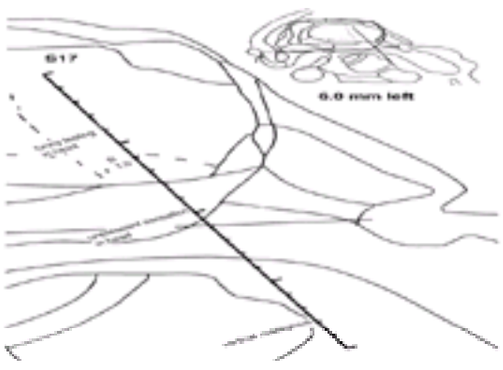

Figure 23-7. Macroelectrode trajectory through the medial (6.0-mm sagittal plane) thalamus of patient in Figure 23-5 that is on the side opposite to the stroke. Responses characteristic of this area occurred. (B, burning; 1.0, stimulation current in milliamperes.)

These observations implicate ipsilateral pathways in the generation of the steady pain and allodynia and hyperpathia that plague such patients. Whatever the ipsilateral paths responsible for the pain, they must be somatotopographically organized to preserve the somatotopographic features of the pain and capable of inducing steady pain and allodynia, incriminating the ipsilateral spinothalamic tract; the method of their activation is unclear. Miller Fisher (159) found two patients with stroke hemiplegia who were beginning to regain motor function when they suffered new strokes on the opposite side of the brain. At that time, the originally paralyzed but recovering side again became paralyzed, implicating ipsilateral mechanisms in the motor recovery.

Implication of the hemisphere opposite to the stroke is demonstrated in one of our patients who had suffered a massive thrombotic stroke (Fig. 23-8) that produced a spastic right hemiplegia, aphasia, right hemibody sensory loss, and right-sided head and neck pain. Microelectrode exploration revealed intact RFs but few PFs. DBS produced paresthesiae in the painful area but failed to lessen the pain. Consequently, a Resume electrode (Medtronic Corporation, Minneapolis, MN) was implanted extradurally over the motor cortex on the side of the head opposite to the stroke and ipsilateral to the hemiplegia (Fig. 23-9). Bipolar stimulation of this electrode produced paresthesiae on the right (paralyzed) head, neck, and arm; and, at higher intensities, the right half of the body. Stimulation reduced the patient's pain, but to a diminishing degree, over 6 years of follow-up. The electrode was repositioned in the subdural space when stimulation no longer produced responses, recapturing for a few months the same effect as before. Suprathreshold stimulation tetanized the right cheek and neck and caused speech arrest for the few words this severely dysphasic patient could utter.

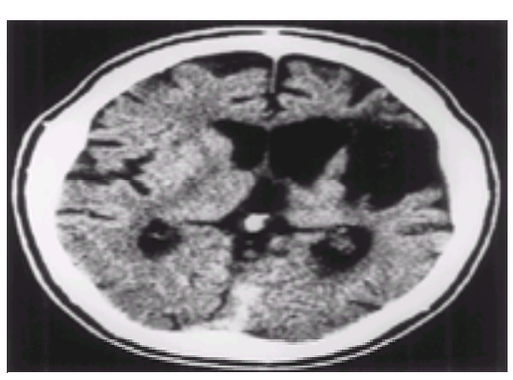

Figure 23-8. Computed tomographic scan of a man who suffered a massive left (dominant hemisphere) thrombotic stroke at age 61 and who has been studied for 6 years. He experienced immediate spastic right hemiplegia and aphasia but regained the ability to walk. He developed steady, aching, pulling pain on the right side of his head, face, and neck, with episodes of shooting pain associated with reduction of appreciation of pinprick, touch, vibration, and cold on the right side of the body, with questionable mild allodynia to cold and touch in the face. There was absence of position sense distal to right wrist and reduction in the right lower extremity. His left thalamus was explored with four microelectrode trajectories, revealing intact receptive fields and absent projected fields. Nevertheless, a site was found in which deep brain stimulation provided paresthesiae in the right side of the head and face. This, however, had no effect on his pain.

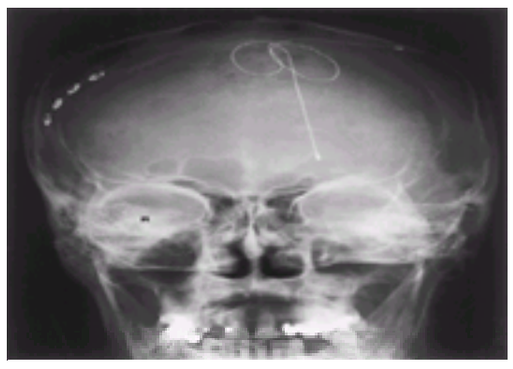

Figure 23-9. Anteroposterior view of plain radiograph of the head of the same patient as in Figure 23-8, showing a Resume electrode (Medtronic Corporation, Minneapolis, MN) implanted over the motor cortex ipsilateral to the hemiplegia and a disconnected unipolar electrode implanted in the tactile relay nucleus of thalamus on the side of the stroke contralateral to the hemiplegia. Stimulation between the two highest poles (2 and 3) produced ipsilateral paresthesiae and reduced his pain on the side ipsilateral to the electrode.

Observations Implicating Particular Brain Structures in the Generation of Pain

Implication of a brain structure in the generation of a patient's pain can be made from various observations: production of pain by stimulating the structure, elimination of pain by destroying or otherwise manipulating it, or physiologic observations within the structure that link the region to the pain.

Induction of Pain by Stimulation of Medial Thalamus and Mesencephalic Tract

Burning and pain are rarely evoked by brain stimulation. However, in stereotactic procedures guided by macrostimulation (160), we induced burning at 162 of approximately 10,000 brain sites, nearly always on the contralateral side of the body. Forty-three percent of these sites occurred in the 89% of patients with movement disorders, usually sporadically, in isolation from other pain sites, and 57% occurred in the 13% of patients operated on for chronic pain. In the latter group, the pain sites were usually clustered. Burning was induced contralaterally without somatotopographic organization. Eighty percent of the sites at which stimulation induced burning occurred in the 41% of pain patients who experienced neuropathic pain; only 20% occurred in the 59% with cancer pain. Finally, these burning responses were clustered in medial mesencephalic tegmentum and medial thalamus, in which stimulation usually evokes no conscious response at all except by volume conduction to adjacent structures. Of the seven patients with neuropathic pain who showed these abnormal burning responses on stimulation, four had brainstem cerebrovascular accidents and one each multiple sclerosis, anesthesia dolorosa, and peripheral neuritis.

In the same study, macrostimulation at 67 points induced nonsomatotopically organized painful rather than burning responses on the opposite side of the body, 39% of them occurring in the 89% of patients with movement disorders, 61% in 8 of the 22 who had intractable pain. Eighty percent of the pain points occurred in patients with deafferentation pain (five brainstem cerebrovascular accidents, one surgical anesthesia dolorosa, one multiple sclerosis, one peripheral neuritis, and one spinal cord vascular accident). When pain was induced in patients with deafferentation pain, the induced pain was always similar to the patient's discomfort; in patients with cancer pain, this was never the case. The induction of pain occurred in the same sites as did the induction of burning. We have not had the opportunity to study these medial sites in similar patients with microelectrodes. The observations implicate the medial structures in the generation of neuropathic pain, but also raise questions as to how structures in which no conscious response is normally elicited by stimulation become sensitive in neuropathic pain states and how their stimulation impinges on consciousness.

Induction of Pain by Stimulation of the Tactile Relay Nucleus of Thalamus

In most patients, macrostimulation or microstimulation of the tactile relay nucleus of thalamus [Hassler's ventrocaudal nucleus (Vc)] even at four times threshold, induces paresthesiae in projected fields that match the RFs of the tactile cells at the same sites. This occurs despite the fact that spinothalamic input is thought to project to all of Vc in a somatotopographic manner as supported by the ability to record cool sensitive neurons (161) in the same area. Surgical lesions in Vc, once practiced in attempts to relieve chronic pain, produce loss of all somatosensory modalities (159,160) and commonly induce central pain (5).

The findings are different, however, in the posterior-inferior rim of Vc, in Hassler's parvocellular Vc. Here, a variety of warm, cold, burning, or painful responses occur with stimulation in the normal state (162,163,164,165 and 166), and nociceptors can be recorded there (167,168).

In patients with stroke-induced pain, microstimulation of the main body of Vc may induce not paresthesiae but pain (169,170,171 and 172). This phenomenon appears to be associated with the presence of allodynia, hyperpathia, or both as in the patients shown in Figure 23-2 and Figure 23-5. It is not usually present in other neuropathic pain syndromes, regardless of whether allodynia or hyperpathia is present (172). When this phenomenon is present, one cannot use paresthesiae-producing DBS to treat the patient's pain. It also has pathophysiologic implications for stroke-induced pain by implicating Vc in the generation of allodynia, hyperpathia, or both, suggesting that normally nonnoxious stimulation of Vc becomes garbled, presumably at the cortex, so that neurons that are normally not nociceptors now signal pain. Moreover, the evoked pain in stroke-induced pain syndromes appears to be relieved by PVG stimulation (173). Whatever the process, it is different from that involved in stroke pain without allodynia or hyperpathia, which is sometimes relieved by paresthesiae-producing DBS (74).

Observations on Surgical Attempts to Relieve Pain

Further insight may be gained by studying the outcomes of different surgical procedures used to treat brain central pain. Table 23-26 summarizes our experience. As in spinal cord central pain, steady pain appears to respond best to paresthesiae-producing DBS, and evoked and neuralgic pain to destructive lesions in the mesencephalic pain tract and medial thalamus. It has been mentioned that PVG stimulation (173) also relieves allodynia and hyperpathia, as in the case of the patient shown in Figure 23-5. Thus, even in the brain, steady pain does not seem to depend on pain pathways, but stimulation of PVG or section of spinoreticulothalamic tracts is useful for the treatment of evoked or intermittent pain. The seven patients relieved of these features by pain tract sections all suffered from brainstem strokes with prominent elements of neuralgialike pain or of allodynia and hyperpathia.

	Steady	Neuralgic	Evoked
Stimulation	53	0	25
Destructive	30	(100)	60

TABLE 23-26. Surgical treatment of 73 cases of brain central pain: percent relieved

Conclusions

In an attempt to synthesize information into a hypothesis explaining stroke central pain, the first question is whether the mechanism is the same in all cases. Possibly

it is not, but because the clinical features are so uniform and the clinical picture appears largely unrelated to the site and degree of neural damage, it would be useful to establish a mechanism applicable in all cases.

Although brain central pain may have a delayed onset, suggesting that, whatever the causative process, it may take time to develop, it can also appear immediately, suggesting that sprouting is not necessary. Brain central pain is idiosyncratic, suggesting that something beside the damaged neurons is required to produce the report of pain. Brain central pain can be reversible, again suggesting that it is not dependent on fixed anatomic changes, but pharmacologic and surgical therapies have yet to clearly identify the essential underlying chemical and anatomic substrates.

Much has been written about the causative lesions, particularly emphasizing selective damage to one structure over another, setting up either irritation or disinhibition in projection pathways responsible for pain. However, brain central pain can result from lesions so minimal that they induce no clinically detectable sensory loss or by lesions so massive that they appear to eliminate all somatosensory function on one side of the brain. Indeed, surgical hemispherectomy can induce brain central pain (5,6). Any hypothesis must account for these observations.

One implication of these observations is that spontaneous pain and evoked pain appear to arise equally readily from brain mechanisms ipsilateral to the causative lesion in the case of milder strokes or contralateral in the most severe strokes. Yet, the pain syndromes are the same in each case. There are no significant interhemispheral connections for somatosensory structures above the brainstem after severe hemispherectomylike strokes, which should eliminate the connections of the corpus callosum or thalamus. Current thinking stresses the importance of damage to the fast conducting spinothalamic system in the origin of brain central pain, but it is difficult to be sure of the importance of this factor. Lesions in the tactile relay nucleus and its projection to cortex, however, cause central pain, but these structures also contain spinothalamic input. Patients with brain central pain may show no detectable sensory loss, selective loss of spinothalamic function, or global loss of all somatosensory modalities. Although some authors deny its presence, selective loss of lemniscal function has also rarely been associated with brain central pain in our experience and in that of others (6). Could the much more common relationship of selective spinothalamic over selective lemniscal lesions in cases of spinal cord and brain central pain simply reflect anatomic curiosities? For example, is the spinothalamic tract more readily exposed to selective iatrogenic or naturally occurring damage than the medial lemniscus? One striking cause of neuropathic pain, tabes dorsalis, is alleged to be the result of damage to the dorsal columns. Thus, although the evidence is impressive, it does not seem inevitable to this author that damage to some component of the spinothalamic is the essential cause of brain central pain.

The primary dilemma, however, is to explain how a small, localized lesion on one side of the brain can result in the same clinical picture as a lesion so massive that spinothalamic tract, medial lemniscus, and lateral and medial thalamus are all eliminated. It is perhaps easier to think in terms of pain caused by stroke hemispherectomy than that caused by a lesser lesion, because one can eliminate mechanisms that depend on the thalamocortex on the side of the stroke and try to imagine what derangement of the normal hemisphere on the opposite side to the stroke can cause the pain. This author dismisses the possibility that bursting cells or somatotopographic reorganization is responsible.

The infrequency of neuralgic pain after strokes makes it difficult to come to conclusions concerning it. Its slightly greater incidence with infratentorial strokes, the observations of Nashold and colleagues (125), and its tendency to be relieved by destructive proximal lesions in the spinoreticulothalamic tract would be in keeping with its generation by ectopic impulse generation at an injury site and propagation in the pain pathways in a similar manner to that described in spinal cord central pain.

Allodynia and hyperpathia appear to be associated with garbled central (cortical?) processing of usually nonnoxious stimuli so as to induce pain in a manner similar to that that occurs at the dorsal horn after peripheral lesions that induce neuropathic pain (57,58). It appears to respond to PVG DBS (173) and to proximal section of pain pathways. It still occurs in patients whose stroke has completely eliminated RFs and PFs on the side of the stroke, so that the undamaged ipsilateral hemisphere must be implicated in its generation. The other clue we have is that it changes the response to stimulation of the tactile relay nucleus of thalamus (Vc) from a paresthetic one to a painful one in the case of strokes with surviving thalamic function on the side of the stroke. If the process is the same in lesser and massive strokes, one must conclude that loss of somatosensory input can sensitize the contralateral damaged or the ipsilateral intact hemisphere so that incoming nonnoxious stimuli are interpreted as painful (i.e., are processed in the pain pathway rather than the nonnoxious pathway between thalamus and cortex). This processing appears to be suppressed by PVG stimulation.

The most common feature of brain central pain (and of all neuropathic pain syndromes) is the steady pain. Only three of our observations reflect on the pathogenesis of steady pain. First, it seems to be associated with a process that activates the medial thalamic and brainstem sensory pathways normally silent to stimulation and whose lesioning normally produces no sensory loss (160) so that macrostimulation in these structures induces a somatotopographically organized conscious experience of contralateral pain. Second, the pain is not relieved by PVG DBS or lesioning pain structures, but only by DBS that produces paresthesiae in the area of the patient's pain. Third, the pain can occur in the absence of identifiable RFs and PFs in the thalamus on the side of the stroke, thereby implicating the normal ipsilateral hemisphere. It would be interesting to explore the ipsilateral hemisphere in such cases; we have, however, demonstrated that stimulation of the sensorimotor cortex on the side opposite to the stroke in one patient with a massive stroke caused ipsilateral paresthesiae, ipsilateral motor twitches, diminished the ipsilateral pain, and caused arrest of the limited speech he had after his dominant hemisphere stroke. The findings would be in keeping with pain resulting from disinhibition of the ipsilateral or contralateral component of the medial nonspecific pain pathway with the somatotopic localization dependent on deficits in the specific somesthetic paths damaged by the stroke. Presumably, chronic paresthesiae-producing stimulation can reverse this process.

Treatment of Brain Central Pain

Figure 23-10 presents an algorithm for treating brain central pain. General principles and medical treatment are similar to those described under Spinal Cord Central Pain, whereas surgical approaches are limited both in choice and success by virtue of the fact that only procedures performed on the brain itself are likely to benefit brain central pain; peripheral procedures, including cordotomy and DCS, are futile (174).

Figure 23-10. Algorithm for the treatment of brain central pain. (DBS, deep brain stimulation.)

Nonsurgical Strategies

Dehen and colleagues (175) concluded that stroke pain was independent of endogenous opioid pathways. Crisologo and colleagues (176) reported lidocaine-induced spinal block relieved poststroke pain accompanied by allodynia in two-thirds of patients; one of the successes and the failure had thalamic lesions. Galer and colleagues (177) found intravenous lidocaine infusion useful, although more so in patients with peripheral than central neuropathic pain. Edmondson and colleagues (178) also found intravenous lidocaine infusion useful, and sometimes mexiletine, an oral cogener of lidocaine, gave good results. Loh and colleagues (179) reported that stellate block or guanethidine infusion relieved or reduced the steady pain and allodynia in eight patients with brain central pain as well as benefiting the accompanying dystonia. Canavero and colleagues (180) found propofol useful in central but not neuropathic pain. Bowsher (181) suggested first a trial of adrenergically active antidepressants, then mexiletine. Strumpf and Zenz (182) suggested opioids. Budd (183) found naloxone useful. Taira and colleagues (48) found that intrathecal baclofen reduced poststroke pain as well as that after spinal cord injury. In our earlier studies of neuropathic pain, we found intravenous

infusions of 50 to 225 mg of sodium pentothal reduced brain central pain in 73% of our patients, whereas 15 to 18 mg of morphine was not effective in any (2,3 and 4).

Surgical Treatment

Our own experience with surgery for brain central pain is summarized in Table 23-26.

Cordotomy. Pagni (6) recounted that Frazier and colleagues alleviated a case of paroxysmal neuralgic pain caused by a stroke, as Nashold and colleagues (125) had done with mesencephalic tractotomy. He quoted Turnbull's success in another case, but stated that there have been no further successful reported cases, although there have been many published unsuccessful cases.

Trigeminal Dorsal Root Entry Zone. Sampson and Nashold (184) have reported one patient with brain central pain caused by a pontine infarct and another with an arteriovenous malformation of the tectum of the mesencephalon who suffered from facial pain that was relieved by a DREZ procedure on the trigeminal nucleus caudalis. The first patient had allodynia and some steady pain; the second had steady pain. In both cases, the DREZ procedure induced mild ipsilateral upper limb dysmetria.

Medial Thalamotomy. In the section on Spinal Cord Central Pain, I pointed out the poor results of medial thalamotomy in neuropathic, including brain central, pain compared with results in cancer pain. It is difficult to obtain specific outcome statistics for brain central pain, because most series quote data from mixed groups of pain patients. Table 23-27 lists outcome data from four surgical series of brain central pain, showing strikingly different outcome figures.

Procedure	No. of patients	% Successful	Reference
Medial thalamotomy	9	89 (recur in 2 yr)	185
	17	Recur in 6 mo	186
	–	25	173
	69	67	154
Mesencephalic tractotomy	28	64	187
	26	62	188
	11	27	93
	–	54	25

TABLE 23-27. Published outcome data for destructive surgery for brain central pain

Mesencephalic Tractotomy. Table 23-27 includes outcome data for mesencephalic tractotomy in brain central pain. Two series (187,188) are surprisingly encouraging. It is hoped that other studies will support these more promising outcomes.

Miscellaneous Procedures. Levin and colleagues (189) reported relief of three cases of stroke pain with intrahypophyseal alcohol injection, but there does not appear to be other published experience with this procedure.

Electrical Stimulation

Trigeminal Stimulation. Seven of the patients on whom we have used trigeminal stimulation (190) for the relief of chronic neuropathic facial pain suffered from brain central pain, three with lateral medullary syndrome, one with a middle cerebral artery area infarct, one with a massive thalamic and suprathalamic infarct, one with an infarct after internal carotid artery ligation, and one with neuropathic pain after a medullary trigeminal tractotomy. Five of these seven patients reported relief during trial stimulation and went on to enjoy more than 50% ongoing pain relief after implantation of a permanent device, a rather surprisingly good result. The chief complication of this procedure was superficial infection at hardware sites.

Dorsal Column Stimulation. Pagni (6) found DCS of no benefit in brain central pain. Of 12 of the author's cases, 6 reported pain relief during trial stimulation and received a permanent stimulator, but only 17% of the original group enjoyed ongoing relief. In four patients, all experiencing allodynia, hyperpathia, or both, DCS was unsuccessful because it was perceived as painful. This observation recalls the experience described previously in which microstimulation of the tactile relay of thalamus is often painful in patients experiencing stroke-induced pain with allodynia, hyperpathia, or both.

Deep Brain Stimulation. The dichotomy between paresthesia-producing and PVG/periaqueductal gray DBS in nociceptive versus neuropathic pain has already been mentioned. Thus, we would suggest that paresthesiae-producing DBS, and not PVG/periaqueductal gray DBS, should be used in attempts to treat most cases of brain central pain. Table 23-28 lists some published outcome data. Anecdotal evidence suggests (203,204 and 205) that stimulating in the internal capsule is preferable to that at other sites, but until larger numbers of patients have been reported it is difficult to draw conclusions (see Chapter 101).

No. of patients	% Relieved	Site stimulated	Reference
—	0	Sensory thalamus	191
6	83	Medial lemniscus	192,193
10	80		194
5	40		195
9	78	Sensory thalamus	196
20	30	Sensory thalamus, internal capsule	79
3	0	Periventricular/peri-aqueductal gray	79
11	36	Internal capsule	192
7	43	Internal capsule	185
17	43	Sensory thalamus, internal capsule	73
—	20		197
—	27	Literature review	197
—	56	North American study	198
—	38	Literature review	198
—	46	—	199
—	52	—	200
10	20 >50% 50 <50% relief	Sensory thalamus	201
23	58 short term 24 long term 0	Sensory thalamus Internal capsule Periventricular gray	80
—	58 group, 2 years	Sensory thalamus	202

TABLE 23-28. Published outcome data for deep brain stimulation for brain central pain

Six of the author's patients (74) treated with paresthesiae-producing DBS, all of whom suffered from allodynia, hyperpathia, or both, found stimulating in the ventrocaudal nucleus painful, preventing use of that treatment modality, whereas patients with neuropathic pain not caused by cerebral lesions who had allodynia or hyperpathia seldom found such stimulation painful. In three patients with stroke-induced allodynia, hyperpathia, or both, PVG stimulation relieved the allodynia and hyperpathia (173). When we reviewed our 18 patients with brain central pain explored stereotactically (not necessarily implanted with electrodes) in whom microstimulation in ventrocaudal nucleus was painful, we found that all suffered from allodynia, hyperpathia, or both, whereas only 5 of 20 patients in whom such stimulation was not painful experienced this feature of pain. The sense of burning was induced equally frequently in the two groups. It is therefore not surprising that 10 of 16 patients with brain central pain who did not have allodynia or hyperpathia reported pain relief with paresthesiae-producing stimulation, but only 2 of 12 who had allodynia, hyperpathia, or both did so.

Motor Cortex Stimulation. Tsubokawa and colleagues (206) described motor cortex stimulation for the treatment of brain central pain, placing paddle-type electrodes designed for DCS extradurally parallel to the central sulcus 3 to 4 cm from the midline for upper limb, and 1 cm from midline for lower limb pain. Ninety percent of 10 cases of brain central pain so treated did well after 1 year of follow-up. In another report (207), 11 patients were described with brain central pain, 73% of whom enjoyed initial, 45% long-term pain relief at 2 years' follow-up. Hosobuchi (208) reported that 50% of six patients were effectively controlled by motor cortex

stimulation. It is to be hoped that more published experience will accumulate to support this simple technique for treating such a refractory problem.

In using motor cortex stimulation, Tsubokawa and colleagues applied stimulation below the threshold for motor events, at which level it usually caused tingling or mild vibration in the area of pain. Pain typically diminished after 5 to 10 minutes of stimulation, and pain relief outlasted a 10-minute period of stimulation by 2 to 6 hours. Thus, patients would typically use five to seven bouts of stimulation daily. They believed that to relieve neural injury pain, it was necessary to stimulate rostral to the causative lesion (explaining the failure of DCS in brain central pain), hypothetically activating the fourth-order sensory neurons whose nonnociceptive impulses induced by cortex stimulation inhibited nociceptive neurons.

Yamamoto and colleagues (209) tried to correlate certain pharmacologic tests with the success of motor cortex stimulation. They concluded in 25 cases of brain central pain with thalamic lesions and 14 with suprathalamic lesions that those patients whose pain was diminished by thiamytal and ketamine administration but not by morphine responded best to motor cortex stimulation.

Septal Stimulation. Schvarcz (210) reported relief of neuropathic pain in 12 of 19 patients by chronic septal stimulation, both spontaneous and evoked elements being diminished. No other case reports of this stimulation site have been reported.

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CHAPTER 24

The Psychophysiology of Pain

C. Richard Chapman

Psychophysiology is a field of study that seeks to relate subjective awareness and behavior to physiologic events (1,2 and 3). As a field of scientific inquiry, it concerns itself with central mechanisms of cognition and behavior, including learning, the emotions, and the relationship of brain activity to consciousness. As a clinical area, psychophysiology has classically addressed somatoform disorders, stress (most recently posttraumatic stress disorders) and affective disorders in general. Psychophysiology is an important resource for the pain field for two primary reasons. On the one hand, it provides valuable resources for addressing the difficult question of how noxious signaling becomes conscious. On the other hand, and more important, it offers a framework for understanding pain as an emotion.

Most physicians think of pain as an unpleasant sensation that originates in traumatized tissues, but pain is more than sensory information about the condition of the body. It has powerful emotional qualities. Any reasonable and unbiased observer studying mammals, particularly humans, would have to conclude that pain's affective features, rather than its sensory properties, govern behavioral responses to injury. People who experience pain do not quietly report the fact; they express negative emotions.

Is the affective dimension of pain as important as its sensory aspect? A contemporary nonmedical writer described pain's characteristics as including extreme aversiveness, an ability to annihilate complex thoughts and other feelings, an ability to destroy language, and a strong resistance to objectification (4). Her perspective resonates with the lessons of everyday life. Although pain has sensory features and lends itself to sensory description, it is above all else a powerful negative feeling. One cannot evaluate and address the suffering of a person in pain without an appreciation of its emotional nature.

The International Association for the Study of Pain acknowledged the central role of emotion in its keystone definition: “Pain [is] an unpleasant sensory and *emotional* experience associated with actual or potential tissue damage, or described in terms of such damage” (5) (italics added). This definition clearly emphasizes the role of affect as an intrinsic component of pain. Emotion is not a consequence of pain sensation that occurs after a noxious sensory message arrives at somatosensory cortex. Rather, it is a fundamental part of the pain experience.

The purposes of this chapter are to describe the psychophysiology of pain and to explore its importance for the care of patients. This involves characterizing the emotional aspect of pain, emphasizing current understanding of the psychophysiologic mechanisms that produce it, and outlining emerging issues associated with the growth of knowledge in this area. In this chapter I show that: (a) pain (awareness of tissue trauma) has emotional properties including negative emotional arousal; (b) the brain creates bodily states and arousal (emotions) in response to threat to biologic integrity; and (c) the affective dimension of pain involves hypervigilance, bodily arousal, and the awareness of altered bodily states.

HISTORIC PERSPECTIVE: MIND-BODY ISSUES

Through most of the twentieth century, our understanding of the relationship between mental processes and the body stemmed directly from Cartesian notions of mind-body dualism. For Descartes, a seventeenth-century philosopher and mathematician, human beings are dualistic: The mind and body are separate entities. Descartes described the life processes of the body as though they were clockwork mechanisms. The actions of the mind were, in his thinking, the workings of the soul.

Descartes believed that the awareness of pain, like awareness of other bodily sensations, must take place in a special location in which the mind observes the body. Dennett (6) termed this hypothetical seat of the mind the *Cartesian theater*. In this theater, the mind observes and interprets the array of multimodality signals that the body produces. The body is a passive environment; the mind is the nonphysical activity of the soul.

Today, most people avow that such a theater of the mind cannot exist. Scientifically, the activity of the brain and the mind is inseparable. And yet, Cartesian dualism is endemic in Western thought and culture. Classical approaches to psychophysiology stemmed from Cartesian thinking, as did psychophysics. Early work on psychosomatic disorders focused on mind-body relationships. Today, much of the popular movement favoring alternative medicine emphasizes the mind-body connection, keeping one's self healthy through right thinking, and the power of the mind to control the immune system. It is hard to avoid Cartesian thinking when the very fabric of our language carries it along as we reason and speak.

Cartesian assumptions are subtle but powerful barriers for someone seeking to understand the affective dimension of pain. Relegating emotions to the realm of the mind and their physiologic consequences to the body is classic Descartes. It prevents us from appreciating the intricate interdependence of subjective feelings and physiology, and it detracts from our ability to comprehend how the efferent properties of autonomic nervous function can contribute causally to the realization of an emotional state. This chapter emphasizes the interdependence of mental processes and physiology. What we call the mind is *consciousness*, and consciousness is an emergent property of the activity of the brain. In a feedback-dependent manner, the brain regulates the physiologic arousal of the body, and emotion is a part of this process.

EMOTIONS: DEFINITION AND MECHANISMS

What Are Emotions?

The first step in understanding pain as an emotion is appreciating the origins and purposes of emotion. Many physicians regard emotions as epiphenomenal feeling states associated with mental activity, subjective in character, and largely irrelevant to the state of a patient's physical health. In fact, emotions are primarily physiologic and only secondarily subjective. Because they can strongly affect cardiovascular function, visceral motility, and genitourinary function, patient emotions can have an important role in health overall and especially in pain management. Simple negative emotional arousal can exacerbate certain pain states, such as sympathetically maintained pain, angina, and tension-type headache. It contributes significantly to musculoskeletal, pelvic, and other pain problems in some patients.

Emotions are complex states of physiologic arousal and awareness that impute positive or negative hedonic qualities to a stimulus (event) in the internal or external environment. The objective aspect of emotion is autonomically and hormonally mediated physiologic arousal. The subjective aspects of emotion, *feelings*, are phenomena of consciousness. Emotion represents in consciousness the biological importance or meaning of an event to the perceiver.

Emotion as a whole has two defining features: valence and arousal. *Valence* refers to the hedonic quality associated with an emotion: the positive or negative feeling attached to perception. *Arousal* refers to the degree of heightened activity in the central nervous system and autonomic nervous system (ANS) associated with perception.

Although emotions as a whole can be positive or negative in valence, pain research addresses only negative emotion. Viewed as an emotion, pain represents threat to the biological, psychological, or social integrity of the person. In this respect, the emotional aspect of pain is a protective response that normally contributes to adaptation and survival. If uncontrolled or poorly managed in patients with severe or prolonged pain, it produces suffering.

Emotion in a Sociobiological Perspective

Psychologists have many frameworks for studying emotion. I favor a sociobiological (evolutionary) framework, because this way of thinking construes feeling states, related physiology, and behavior as mechanisms of adaptation and survival. Nature has equipped us with the capability for negative emotion for a purpose; bad feelings are not simply accidents of human consciousness. They are protective mechanisms that normally serve us well, but, like uncontrolled pain, sustained and uncontrolled negative emotions can become pathologic states that can produce maladaptive behavior and physiologic pathology.

By exploring the emotional dimension of pain from the sociobiological perspective, the reader may gain some insight about how to prevent or control the negative affective aspect of pain, which fosters suffering. Implementing this perspective requires that we change conventional language habits that involve describing pain as a transient sensory event. Pain is a compelling and emotionally negative state of the individual that has as its primary defining feature awareness of, and homeostatic adjustment to, tissue trauma.

Adaptive Functions of Emotion

Emotions, including the emotional dimension of pain, characterize mammals exclusively, and they foster mammalian adaptation by making possible complex behaviors and adaptations. They play a strong role in consciousness and serve the function of producing and summarizing information that is important for selection among alternative behaviors. According to MacLean, emotions “impart subjective information that is instrumental in guiding behavior required for self-preservation and preservation of the species. The subjective awareness that is an affect consists of a sense of bodily pervasiveness or by *feelings localized to certain parts of the body*” (7) (italics added). Because negative emotions such as fear evolved to facilitate adaptation and survival, emotion plays an important defensive role. The ability to experience threat when encountering injurious events protects against life-threatening injury.

The strength of emotional arousal associated with an injury indicates and expresses the magnitude of perceived threat to the biological integrity of the person. Within the contents of consciousness, threat is a strong negative feeling state and not a pure informational appraisal. In humans, threatening events such as injury that are not immediately present can exist as emotionally colored somatosensory images.

Phenomenal awareness consists largely of the production of images. Visual images are familiar to everyone: We can readily imagine seeing things. We can also produce auditory images by imaging a familiar tune, a bird song, or the sound of a friend's voice. Similarly, we can generate somatosensory images. We can, for example, imagine the feeling of a full bladder, the sensation of a particular shoe on a foot, or a familiar muscle tension or ache. Cognition operates largely on images.

Patients can react emotionally to the mental image of a painful event before it happens (e.g., venipuncture), or for that matter they can respond emotionally to the sight of another person's tissue trauma. The emotional intensity of such a feeling marks the adaptive significance of the event that produced the experience for the perceiver. In general, the threat of a minor injury normally provokes less feeling than one that incurs a risk of death. The emotional magnitude of a pain is the internal representation of the threat associated with the event that produced the pain.

Emotions and Behavior

Negative emotions compel action, such as fight or flight, along with expression through vocalization, posture, variations in facial musculature patterns, and alterations of activity. This action represents communication and often elicits social support, thus contributing to survival. Darwin (8), observing animals, noted that emotions enable communication through vocalization, startle, posture, facial expression, and specific behaviors. He held that emotions must be inborn rather than learned tendencies. Darwin pursued this issue by comparing the facial and other emotional expressions of children born blind with those of other children, reasoning that blind children would express emotion differently if emotion is primarily a learned behavior. As others have since confirmed (9), Darwin learned that the basic blueprints for human emotional expression are innate.

Contemporary investigators who study emotions and human or animal social behavior emphasize that communication is a fundamental adaptive function of emotional expression (10,11). Social mammals, including humans, depend on one another or their social group as resources for adaptation and survival. The emotional expression of pain in the presence of supportive persons is socially powerful; it draws on a fundamental sociobiological imperative, communicating threat and summoning assistance.

Central Neuroanatomy of Emotion: Limbic Structures

The limbic brain represents an anatomic common denominator across mammalian species (7), and emotion is a common feature of mammals. Consequently, investigators can learn much about human emotion by studying mammalian laboratory animals.

Early investigators focused on the role of olfaction in limbic function, and this led them to link the limbic brain to emotion. Emotion may have evolutionary roots in olfactory perception. MacLean introduced the somewhat controversial term *limbic system* and characterized its functions (12). He has identified three main subdivisions of the limbic brain—amygdala, septum, and thalamocingulate (7)—that represent sources of afferents to parts of limbic cortex (Fig. 24-1). He also postulated that the limbic brain responds to two basic types of input: interoceptive and exteroceptive. These refer to sensory information from internal and external environments, respectively. Because nociception by definition involves signals of tissue trauma, it excites the limbic brain via interoceptive signaling (13).

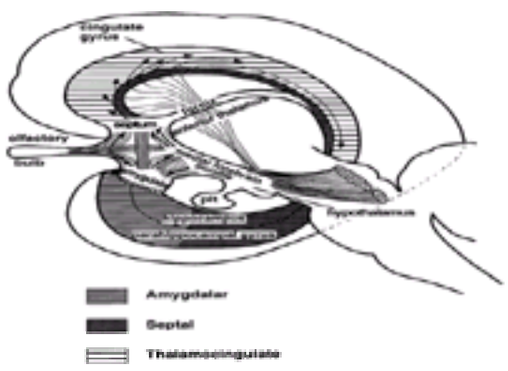

Figure 24-1. Three subdivisions of the limbic brain. MacLean (7) proposed a three-part grouping of limbic structures and functions: amygdalar, septal, and thalamocingulate subdivisions. These groupings appear as shadings. The figure, derived from MacLean's illustration, portrays the hippocampus as an upright arch joining the septum at one end and the amygdala at the other. (Adapted from MacLean PD. The triune brain in evolution: role in paleocerebral functions. New York: Plenum Publishing, 1990.)

Pain research has yet to address definitively the links between nociception and limbic processing. However, anecdotal medical evidence and careful psychometric studies implicate limbic structures in the distress of pain. Cingulumotomy interrupted pathways projected from hypothalamus to cingulate cortex and relieved the suffering of intractable pain without destroying sensory awareness, cognitive functioning, or social interactions (14). Such neurosurgical records help to clarify positron emission tomographic (PET) observations of human subjects undergoing painful cutaneous heat stimulation: Noxious stimulation activates contralateral cingulate cortex and several other limbic areas.

Peripheral Neuroanatomy of Emotion: Autonomic Nervous System

The ANS plays an important role in regulating the constancy of the internal environment, and it does so in a feedback-regulated manner under the direction of the hypothalamus, solitary nucleus (nucleus tractus solitarius), amygdala, and other central nervous system structures (15,16). In general, it regulates activities that are not normally under voluntary control. The hypothalamus is the principal integrator of autonomic activity. Stimulation of the hypothalamus elicits highly integrated patterns of response that involve the limbic system and other structures (17).

Many researchers hold that the ANS comprises three divisions: the sympathetic, parasympathetic, and enteric (18,19). Others subsume the enteric under the other two divisions. Broadly, the sympathetic nervous system makes possible the arousal needed for fight and flight reactions, whereas the parasympathetic system governs basal heart rate, metabolism, and respiration. The enteric nervous system innervates the viscera via a complex network of interconnected plexuses.

The sympathetic and parasympathetic systems are largely mutual physiologic antagonists: If one system inhibits a function, the other typically augments it. However, important exceptions that demonstrate complementary or integratory relationships exist. The mechanism most heavily involved in the affective response to tissue trauma is the sympathetic nervous system.

During emergency or injury to the body, the hypothalamus uses the sympathetic nervous system to increase cardiac output, respiration rate, and blood glucose. It also regulates body temperature, causes piloerection, alters muscle tone, provides compensatory responses to hemorrhage, and dilates pupils. These responses are part of a coordinated, well-orchestrated response pattern called the *defense response* (20,21 and 22). It resembles the better-known orienting response in some respects, but it can only occur after a strong stimulus that is noxious or frankly painful. It sets the stage for escape or confrontation, thus serving to protect the organism from danger. In an awake cat, both electrical stimulation of the hypothalamus and infusion of norepinephrine into the hypothalamus elicit a rage reaction with hissing, snarling, and attack posture with claw exposure, and a pattern of sympathetic nervous system arousal accompanies this reaction (23,24 and 25). Circulating epinephrine produced by the adrenal medulla during activation of the HPA axis accentuates the defense response, fear responses, and aversive emotional arousal in general.

Because the defense response and related changes are involuntary in nature, we generally experience them as something that the environment does to us. We generally describe such physiologic changes not as the bodily responses that they are, but rather as feelings. We might describe a threatening and physiologically arousing event by saying that “It scared me” or “It made me really mad.”

Phenomenologically, feelings seem to happen to us; we do not *do* them in the sense that we think thoughts or choose actions. Emotions are who we are in a given circumstance rather than choices we make, and we commonly interpret events and circumstances in terms of the arousal that they elicit. ANS arousal, therefore, plays a major role in the complex psychological experience of injury and is a part of that experience.

Early views of the ANS followed the lead of Cannon (20) and held that emergency responses and all forms of intense aversive arousal are undifferentiated, diffuse patterns of sympathetic activation. Although this is broadly true, research has shown that definable patterns characterize emotional arousal, and that these are related to the emotion involved, the motor activity required, and perhaps the context (15,16). An investigator attempting to understand how humans experience emotions must remember that the brain not only recognizes patterns of arousal; it also creates them.

One of the primary mechanisms in the creation of emotion is feedback-dependent sympathetic efferent activation. The ANS has afferent and efferent functions. The afferent mechanisms signal changes in the viscera and other organs, whereas efferent activity conveys commands to those organs. Consequently, the ANS can maintain feedback loops related to viscera, muscle, blood flow, and other responses. The visceral feedback system exemplifies this process. In addition, feedback can occur via the endocrine system, which under the control of the ANS releases neurohormones into the systemic circulation. Because feedback involves both autonomic afferents and endocrine responses, and because some feedback occurs at the level of unconscious homeostatic balance and other feedback involves awareness, the issue of how visceral change contributes to the creation of an emotional state is complex. The mechanisms are almost certainly pattern dependent, dynamic, and at least partly specific to the emotion involved. Moreover, they occur in parallel with sensory information processing.

The feedback concept is central to the field of psychophysiology. Awareness of physiologic changes elicited by a stimulus is a primary mechanism of emotion. The psychiatric patient presenting with panic attack, phobia, or anxiety is reporting a subjective state based on patterns of physiologic signals and not an existential crisis that exists somewhere in the domain of the mind, somehow apart from the body. Similarly, the medical patient expressing emotional distress during a painful procedure, or during uncontrolled postoperative pain, is experiencing the sensory features of that pain against the background of a cacophony of sympathetic arousal signals.

Figure 24-2 illustrates some of the general mechanisms of feedback associated with autonomic arousal. It helps to illustrate an essential point: A sensory stimulus does not have purely sensory effects. It undergoes parallel processing at the affective level. When that signal involves threat to biological integrity, it elicits strong patterns of sympathetic and neuroendocrine response. These, in turn, contribute to the awareness of the perceiver. Sensory processing provides information about the environment, but this information exists in awareness against a background of emotional arousal, either positive or negative, and that arousal may vary from mild to extreme.

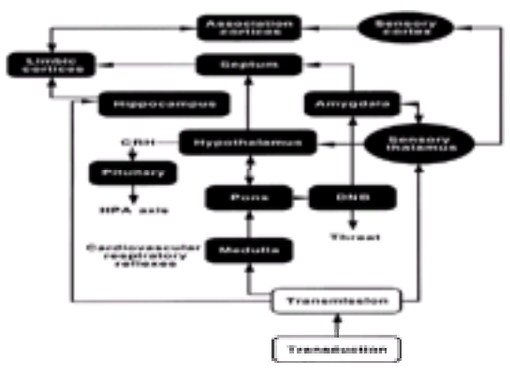

Figure 24-2. Feedback-dependent mechanisms associated with autonomic arousal. A noxious sensory stimulus has both sensory and affective effects. (CRH, corticotropin-releasing hormone; DNB, dorsal noradrenergic bundle; HPA, hypothalamo-pituitary-adrenocortical.)

Nociception and Central Limbic Processing

Central sensory and affective pain processes share common sensory mechanisms in the periphery. As described in Chapter 3, A-d and C fibers serve as tissue trauma transducers (nociceptors) for both processes, the chemical products of inflammation sensitize these nociceptors, and peripheral neuropathic mechanisms such as ectopic firing excite both processes. In some cases, neuropathic mechanisms may substitute for transduction as we classically define it, producing afferent signal volleys that appear, to the central nervous system, like signals originating in nociceptors. Differentiation of sensory and affective processing begins at the dorsal horn of the spinal cord. Sensory transmission follows spinothalamic pathways, and transmission destined for affective processing takes place in spinoreticular pathways. For more detail on the sensory processing of nociception, see Chapter 3, Chapter 4 and Chapter 5 and Willis and Westlund (26).

Nociceptive centripetal transmission engages multiple pathways: spinoreticular, spinomesencephalic, spinolimbic, spinocervical, and spinothalamic tracts (26,27). The spinoreticular tract contains somatosensory and viscerosensory afferent pathways that arrive at different levels of the brainstem. Spinoreticular axons possess receptive fields that resemble those of spinothalamic tract neurons projecting to medial thalamus, and, like their spinothalamic counterparts, they transmit tissue injury information (28,29). Most spinoreticular neurons carry nociceptive signals, and many of them respond preferentially to noxious activity (30,31). The spinomesencephalic tract comprises several projections that terminate in multiple midbrain nuclei, including the periaqueductal gray, red nucleus, nucleus cuneiformis, and Edinger-Westphal nucleus (26). Spinolimbic tracts include the spinohypothalamic tract, which reaches both lateral and medial hypothalamus (32,33) and the spinoamygdalar tract that extends to the central nucleus of the amygdala (34). The spinocervical tract, like the spinothalamic tract, conveys signals to the thalamus. All of these tracts transmit tissue trauma signals rostrally.

Central processing of nociceptive signals to produce affect undoubtedly involves multiple neurotransmitter systems. Four extrathalamic afferent pathways project to neocortex: the dorsal noradrenergic bundle (DNB) originating in the locus ceruleus (LC); the serotonergic fibers that arise in the dorsal and median raphe nuclei; the dopaminergic pathways of the ventral tegmental tract that arise from substantia nigra; and the acetylcholinergic neurons that arise principally from the nucleus basalis of the substantia innominata (35). Of these, the noradrenergic and serotonergic pathways link most closely to negative emotional states (36,37 and 38). The set of structures receiving projections from this complex and extensive network corresponds to the classic definition of the limbic brain (7,37,39,40).

Although other processes governed predominantly by other neurotransmitters almost certainly play important roles in the complex experience of emotion during pain, I emphasize the role of central noradrenergic processing here. This limited perspective offers the advantage of simplicity, and the literature on the role of central noradrenergic pathways in anxiety, panic, stress, and posttraumatic stress disorder provides a strong basis (38,41). This processing involves two central noradrenergic pathways: the dorsal and ventral noradrenergic bundles (VNBs) (Fig. 24-3).

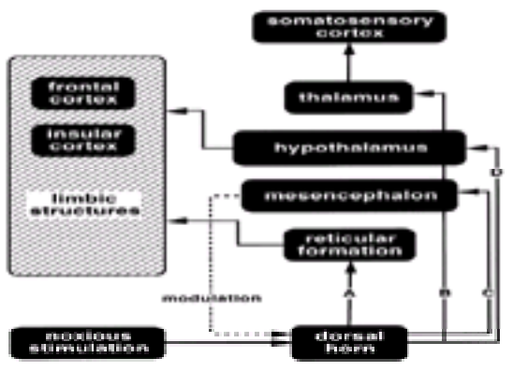

Figure 24-3. Multiple pathways of corticopetal nociceptive transmission. (A, spinoreticular; B, spinothalamic; C, spinomesencephalic; D, spinohypothalamic tracts.)

Locus Ceruleus and the Dorsal Noradrenergic Bundle

Substantial evidence supports the hypothesis that noradrenergic brain pathways are major mechanisms of anxiety and stress (38). The majority of noradrenergic neurons originates in the LC. This pontine nucleus resides bilaterally near the wall of the fourth ventricle. The locus has three major projections: ascending, descending, and cerebellar. The ascending projection, the DNB, is the most extensive and important pathway for our purposes (42). Figure 24-4 illustrates the DNB. Projecting from the LC throughout limbic brain and to all of neocortex, the DNB accounts for approximately 70% of all brain norepinephrine (43). The LC gives rise to most central noradrenergic fibers in spinal cord, hypothalamus, thalamus, hippocampus (44), and in addition it projects to limbic cortex and neocortex. Consequently the LC exerts a powerful influence on higher level brain activity.

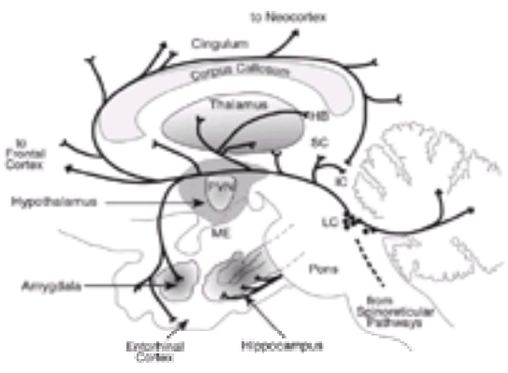

Figure 24-4. The dorsal noradrenergic bundle (parasagittal view). Tissue injury signals from spinoreticular pathways excite the primarily noradrenergic locus ceruleus (LC), activating the dorsal noradrenergic bundle, which extends throughout the limbic brain and to neocortex. (HB, habenula; IC, inferior colliculus; ME, median eminence; PVN, paraventricular nucleus; SC, superior colliculus.)

The *noradrenergic stress response hypothesis* holds that any stimulus that threatens the biological, psychological, or psychosocial integrity of the individual increases the firing rate of the LC, resulting in increased release and turnover of norepinephrine in the brain areas involved in noradrenergic innervation. Studies show that the LC reacts to signaling from sensory stimuli that potentially threaten the biological integrity of the individual or signal damage to that integrity (43). Spinal cord lamina I cells terminate in the LC (29). The major sources of LC afferent input are the paragigantocellularis and prepositus hypoglossi nuclei in the medulla, but destruction of these nuclei does not block LC response to somatosensory stimuli (45). Other sources of afferent input to the locus include the lateral hypothalamus, amygdala, and solitary nucleus. Whether nociception stimulates the LC directly or indirectly is still uncertain.

It is quite clear that nociception inevitably and reliably increases activity in neurons of the LC, and LC excitation appears to be a consistent response to nociception (43,46,47 and 48). Notably, this does not require cognitively mediated attentional control because it occurs in anesthetized animals. Foote and colleagues (49) reported that slow, tonic spontaneous activity at the locus in rats changed under anesthesia in response to noxious stimulation. Experimentally induced phasic LC activation produces alarm and apparent fear in primates (50,51), and lesions of the LC eliminate normal heart rate increases to threatening stimuli (52). In a resting animal, LC neurons discharge in a slow, phasic manner (53).

Although the LC reacts consistently, it does not respond exclusively to nociception. LC firing rates increase after nonpainful but threatening events, such as strong cardiovascular stimulation (47,54), and certain visceral events, such as distension of the bladder, stomach, colon, or rectum (43,55). Highly novel and sudden stimuli that could represent potential threat, such as loud clicks or light flashes, can also excite the LC in experimental animals (53). Thus, the LC responds to biologically threatening or potentially threatening events, of which tissue injury is a significant subset. Amaral and Sinnamon (56) described the LC as a central analogue of the sympathetic ganglia. Viewed in this way, it is an extension of the autonomic protective mechanism described previously.

Invasive studies confirm the link between LC activity and threat. Direct activation of the DNB and associated limbic structures in laboratory animals produces sympathetic nervous system response and elicits emotional behaviors such as defensive threat, fright, enhanced startle, freezing, and vocalization (57). This indicates that enhanced activity in these pathways corresponds to negative emotional arousal and behaviors appropriate to perceived threat. LC firing rates increase two- to threefold during the defense response elicited in a cat that has perceived a dog (25). Moreover, infusion of norepinephrine into the hypothalamus of an awake cat elicits a defensive rage reaction that includes activation of the LC noradrenergic system. In general, the mammalian defense response involves increased regional turnover and release of norepinephrine in the brain regions that the LC innervates. The LC response to threat, therefore, may be a component of the partly *prewired*

patterns associated with the defense response.

Increased alertness is a key element in early stages of the defense response. Normally, activity in the LC increases alertness. Tonically enhanced LC and DNB discharge corresponds to hypervigilance and emotionality (38,49,58). The DNB is the mechanism for vigilance and defensive orientation to affectively relevant and novel stimuli. It also regulates attentional processes and facilitates motor responses (35,37,43,59). In this sense, the LC influences the stream of consciousness on an ongoing basis and readies the individual to respond quickly and effectively to threat when it occurs.

LC and DNB support biological survival by making possible global vigilance for threatening and harmful stimuli. Siegel and Rogawski (60) hypothesized a link between the LC noradrenergic system and vigilance, focusing on rapid eye movement (REM) sleep. They noted that LC noradrenergic neurons maintain continuous activity in both normal waking state and non-REM sleep, but during REM sleep these neurons virtually cease discharge activity. Moreover, an increase in REM sleep ensues after either lesion of the DNB or following administration of clonidine, an a $_2$-adrenoceptor agonist. Because LC inactivation during REM sleep permits rebuilding of noradrenergic stores, REM sleep may be a necessary preparation for sustained periods of high alertness during subsequent waking. Siegel and Rogawski (60) contended that ". . . a principal function of NE in the central nervous system is to facilitate the excitability of target neurons to specific high priority signals." Conversely, reduced LC activity periods (REM sleep) allow time for a suppression of sympathetic tone.

Adaptation and sensitization can alter the LC response to threat. Abercrombie and Jacobs (61,62) demonstrated a noradrenergically mediated increase in heart rate in cats exposed to white noise. Elevated heart rate decreased with repeated exposure as did LC activation and circulating levels of norepinephrine. Libet and Gleason (63) found that stimulation via permanently implanted LC electrodes did not elicit indefinite anxiety. This indicates that the brain either adapts to locus excitation or engages a compensatory response to excessive LC activation under some circumstances. In addition, central noradrenergic responsiveness changes as a function of learning. In the cat, pairing a stimulus with a noxious air puff results in increased LC firing with subsequent presentations of the stimulus, but previous pairing of that stimulus with a food reward produces no alteration in LC firing rates with repeated presentation (53). These studies show that, despite its apparently prewired behavioral subroutines, the noradrenergic brain shows substantial neuroplasticity. The emotional response of animals and people to a painful stimulus can adapt, and it can change as a function of experience.

From a different perspective, Bremner and colleagues (38) postulated that chronic stress can affect regional norepinephrine turnover and thus contribute to the response sensitization evident in panic disorder and posttraumatic stress disorder. Chronic exposure to a stressor (including persevering nociception) could create a situation in which noradrenergic synthesis cannot keep up with demand, thus depleting brain norepinephrine levels. Animals exposed to inescapable shock demonstrate greater LC responsiveness to an excitatory stimulus than animals who have experienced escapable shock (64). In addition, such animals display *learned helplessness* behaviors: They cease trying to adapt to, or cope with, the source of shock (65). From an evolutionary perspective, this is a failure of the defense response as adaptation; it represents surrender to suffering. Extrapolating this and related observations to patients, Bremner and colleagues (38) suggested that persons who have once encountered overwhelming stress and suffered exhaustion of central noradrenergic resources may respond excessively to similar stressors that they encounter at a later time.

Ventral Noradrenergic Bundle and the Hypothalamo-Pituitary-Adrenocortical Axis

The VNB originates in the LC and enters the medial forebrain bundle. Neurons in the medullary reticular formation project to the hypothalamus via the VNB (66). Sawchenko and Swanson (67) identified two VNB-linked noradrenergic and adrenergic pathways to paraventricular hypothalamus in the rat: the A1 region of the ventral medulla (lateral reticular nucleus), and the A2 region of the dorsal vagal complex (the nucleus tractus solitarius, or solitary nucleus) that receives visceral afferents. These medullary neuronal complexes supply 90% of catecholaminergic innervation to the paraventricular hypothalamus via the VNB (68). Regions A5 and A7 contribute in a comparatively minor way to the VNB.

The noradrenergic axons in the VNB respond to noxious stimulation (43), as does the hypothalamus itself (69). Moreover, nociception-transmitting neurons at all segmental levels of the spinal cord project to medial and lateral hypothalamus and several telencephalic regions (26,32,33). These projections link tissue injury and the hypothalamic response, as do hormonal messengers in some circumstances.

The hypothalamic paraventricular nucleus (PVN) coordinates the hypothalamo-pituitary-adrenocortical (HPA) axis (Fig. 24-5). Neurons of the PVN receive afferent information from several reticular areas, including ventrolateral medulla, dorsal raphe nucleus, nucleus raphe magnus, LC, dorsomedial nucleus, and nucleus tractus solitarius (67,70,71). Still other afferents project to the PVN from the hippocampus, septum, and amygdala (72). Nearly all hypothalamic and preoptic nuclei send projections to the PVN. This suggests that limbic connections mediate endocrine responses during stress. Feldman and colleagues note that limbic stimulation always increases adrenocortical activity in rats (72).

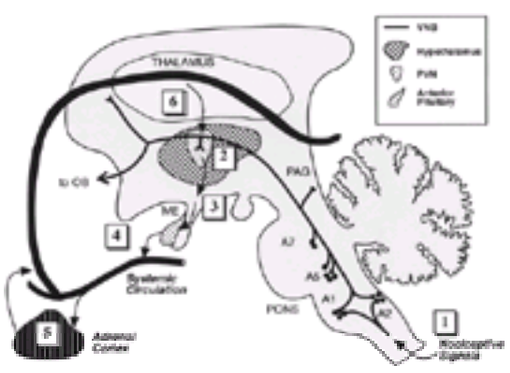

Figure 24-5. Response of the hypothalamo-pituitary-adrenocortical axis to noxious stimulation. Feedback-modulated response is depicted in six steps. In the first step signals of tissue injury excite the ventral noradrenergic bundle (VNB), including several medullary and pontine nuclei (designated A1, A2, A5, and A7). When these signals reach the hypothalamus, they stimulate the paraventricular nucleus (PVN) (step 2). The PVN produces corticotrophin-releasing hormone (CRH). CRH-producing neurons extend from the PVN to the median eminence (ME), from which they release CRH into the portal circulation (step 3). At this point, the tissue-injury signals become neurohumoral rather than neuronal. The anterior pituitary responds to CRH by releasing adrenocorticotropic hormone into the systemic circulation (step 4). The adrenocortex responds to adrenocorticotropic hormone by releasing corticosteroids into the systemic circulation (step 5). In addition to their extensive metabolic effects, the corticosteroids bind to receptors at the PVN (step 6), thus closing the feedback loop. This mechanism provides the physiologic arousal associated with the affective component of pain. (ME, median eminence; OB, olfactory bulb; PAG, periaqueductal gray.)

In responding to potentially or frankly injurious stimuli, the PVN initiates a complex series of events regulated by feedback mechanisms. These processes ready the organism for extraordinary behaviors that will maximize its chances to cope with the threat at hand (73). Although laboratory studies often involve highly controlled and specific noxious stimulation, real-life tissue trauma usually involves a spectrum of afferent activity, and the pattern of activity may be a greater determinant of the stress response than the specific receptor system involved (74). Traumatic injury, for example, might involve complex signaling from the site of injury, including inflammatory mediators, baroreceptor signals from blood volume changes, and hypercapnea. Tissue trauma normally initiates much more than nociception.

Diminished nociceptive transmission during stress or injury helps people and animals to cope with threat without the distraction of pain. The medullary mechanisms involved in this are complex and include the response of the solitary nucleus to baroreceptor stimulation (75). Laboratory studies with rodents indicate that animals placed in restraint or subjected to cold water develop analgesia (76,77 and 78). Lesioning the PVN attenuates such stress-induced analgesia (79).

Some investigators (80,81) emphasize that neuroendocrine arousal mechanisms are not limited to emergency situations, even though most research emphasizes that such situations elicit them. In complex social contexts, submission, dominance, and other transactions can elicit neuroendocrine and autonomic responses, modified perhaps by learning and memory. This suggests that neuroendocrine processes accompany all sorts of emotion-eliciting situations.

The hypothalamic PVN supports stress-related autonomic arousal through neural as well as hormonal pathways. It sends direct projections to the sympathetic intermediolateral cell column in the thoracolumbar spinal cord and the parasympathetic vagal complex, both sources of preganglionic autonomic outflow (82). In

addition, it signals release of epinephrine and norepinephrine from the adrenal medulla. Adrenocorticotropic hormone release, although not instantaneous, is quite rapid: It occurs within approximately 15 seconds (83). These considerations implicate the HPA axis in the neuroendocrinologic and autonomic manifestations of emotion associated with tissue trauma.

In addition to controlling neuroendocrine and ANS reactivity, the HPA axis coordinates emotional arousal with behavior (84). As noted previously, stimulation of the hypothalamus can elicit well-organized action patterns, including defensive threat behaviors and autonomic arousal (85). The existence of demonstrable behavioral subroutines in animals suggests that the hypothalamus plays a key role in matching behavioral reactions and bodily adjustments to challenging circumstances or biologically relevant stimuli. Moreover, stress hormones at high levels, especially glucocorticoids, may affect central emotional arousal, lowering startle thresholds and influencing cognition (83). Saphier (86) observed that cortisol altered the firing rate of neurons in limbic forebrain. Clearly, stress regulation is a complex, feedback-dependent, and coordinated process. The hypothalamus appears to take executive responsibility for coordinating behavioral readiness with physiologic capability, awareness, and cognitive function.

Central Serotonin Pathways

The serotonergic system is the most extensive monoaminergic system in the brain. It originates in the raphe nuclei of the medulla, pons, and mesencephalon (87,88). Descending projections from the raphe nuclei modulate nociceptive traffic at laminae I and II in the spinal cord and also motor neurons. The raphe nuclei of the midbrain and upper pons project via the medial forebrain bundle to multiple limbic sites, such as hypothalamus; septum and hippocampus; cingulate cortex; and cerebral cortex, including frontal cortex.

The potential role of serotonergic mechanisms in affective disorders, particularly depression and panic disorder, continues to receive a great deal of attention (88,89). Currently, the major antidepressant medications are selective serotonin (5-hydroxytryptamine) reuptake inhibitors, often called *selective serotonin reuptake inhibitors* (90). Increased receptor selectivity in the newer drugs helps to maximize benefit and minimize side effects of these medications.

It is now clear that the older assumptions of simple bioamine deficiency are insufficient to account for the role of serotonin in affective disorders. Although a definitive understanding is still at issue, it has become clear that the serotonergic system influences the actions of the HPA axis, particularly by augmenting cortisol-induced feedback inhibition (91,92 and 93). Moreover, it interacts with noradrenergic pathways in complex ways, including attenuation of firing in LC neurons (94). The interdependence of the monoamine systems and the HPA axis makes it clear that we cannot hope to account for complex patterns of brain or behavioral responses by considering these elements individually. They appear to be components of a larger system that we have yet to conceptualize.

Primary and Secondary Features of the Affective Dimension of Pain

The physiology of emotion suggests that the affective dimension of pain involves a two-stage mechanism. The primary mechanism generates an immediate experience akin to hypervigilance or fear. In nature, this rapid response to injury serves to disrupt ongoing attentional and behavioral patterns. At the same time, efferent messages from the hypothalamus, amygdala, and other limbic structures excite the ANS, which in turn alters bodily states. Cardiac function, muscle tension, altered visceral function, respiration rate, and trembling all occur, and awareness of these reactions creates a strong negative subjective experience. This body state awareness is the second mechanism of the affective dimension of pain.

Damasio (95) submits that visceral and other event-related, autonomically mediated body state changes constitute *somatic markers* (i.e., they serve as messengers, delivering affective evaluations of perceptual experiences that either confirm or deny the potential threat inherent in an event). A *somatic marker* is essentially a somatic image. Perceptually, the brain operates on images that are symbolic representations of external and internal objects or events. Just as it is more efficient for a listener to work with words in language as opposed to phonemes, cognition is more efficient when it uses images rather than simple sensations. The somatic marker images associated with tissue trauma are often complex patterns of physiologic arousal. They serve as symbolic representations of threat to the biological (and sometimes the psychological or social) integrity of the person. Like other images, they can enter into complex patterns of association. Because the secondary stage of the affective response involves images and symbols, it represents cognition as well as emotion.

NEUROPLASTICITY AND PSYCHOLOGICAL PROCESSES

Emotion in Learning and Memory

Sociobiologically, species that can learn readily from experience have adaptive advantages over those that cannot. That which promotes learning fosters adaptation. The affective component of pain contributes to both operant (instrumental) learning and classical conditioning (learning by association). One learns to associate threat with certain environments, social encounters, or other experiences and thereby gains the capacity for avoidance or coping. Patients sometimes learn to associate threat with health care providers, as all dentists know, and they can also learn, maladaptively, to attach threat to various somatic messages of muscle tension or visceral distension that do not, as biological facts, signal actual or impending tissue trauma. The role of learning in the experience of pain and the progression of acute pain to chronic pain is therefore substantial.

Classical Conditioning

Classical conditioning is a form of learning that involves the formation of an association between a normally neutral event and the negative emotion associated with the onset of pain (see Chapter 25). Memory of past events, like learning, depends heavily on emotion, and memories of past experience tend to shape expectations for the present and future.

Imagine conducting a study in which we pair the sound of a bell with a stimulus that evokes a response of interest, such as strong sympathetically mediated arousal. We sound a bell a half-second before we deliver a strong but harmless electrical shock to the fingers of a volunteer. The sudden intense shock elicits many physiologic changes, including an increase in heart rate, rapid shallow breathing, increased skin conductance, pupil dilation, and a sense of fear. After several pairings of the two stimuli, the sound of the bell, presented alone, elicits a similar pattern of physiologic arousal.

In the language of classical conditioning, the arousal reaction to the bell alone is the conditioned response. The sound itself is a conditioned stimulus. The intense electrical shock is the unconditioned stimulus, and the physiologic arousal that the unconditioned stimulus elicits is the unconditioned response. The essence of classical conditioning is that a stimulus that heretofore was neutral (the conditioned stimulus) can, after conditioning, elicit a strong response, such as arousal and fear (conditioned response). This is one of the mechanisms by which the environment can alter the emotional responsivity of the brain.

Nonnoxious stimuli can elicit the emotional patterns normally associated with tissue trauma through classical conditioning. The negative emotion that normally accompanies tissue trauma can become associated with normally neutral, nonnoxious stimuli through classical conditioning. In fear conditioning, the repeated pairing of a neutral stimulus with a noxious one can condition the perceiver so that the neutral stimulus, occurring alone, acts as a trigger to elicit fear. The term for a learned negative emotional response (awareness of threat, increased heart rate, shallow respiration, and so forth) to an objectively nonthreatening stimulus is *conditioned emotional response*. Many people develop fear or frank phobia in dentists' offices through classical conditioning.

Biologically, the conditioned emotional response supports survival because it helps an organism to avoid recurring and potentially dangerous situations. Through conditioning, ordinarily neutral stimuli become warning cues for danger (96). It also helps the individual martial a flight or fight response to a challenge after preexposure to it. Osborne and colleagues (97) found that 3-methoxy-4-hydroxyphenylglycol, an indicator of norepinephrine turnover in the brain, can provide a marker of fear conditioning. Exposure to a painful event increases 3-methoxy-4-hydroxyphenylglycol in a manner that tracks the conditioning process.

Conditioned emotional responses are essentially sensory-affective associations. The amygdala is a key structure in the linking of sensory experience to emotional arousal and in the conditioning of negative emotional associations (36,98,99). Aggleton and Mishkin (100) described the amygdala as a gateway to the emotions for stimuli (simple or complex) in all sensory modalities, both conditioned and unconditioned.

Sensory processing (in the case of pain, spinothalamocortical processing) can elicit complex, negative emotional processes through Pavlovian conditioning (the standard model for classical conditioning). This is not a *postsensory* cortical association but rather a by-product of thalamic processing. LeDoux and colleagues (81,98), working with auditory stimuli, determined that projections from acoustic thalamus to the amygdala allow the classical conditioning of emotional responses to normally neutral auditory stimuli in experimental animals. To condition animal subjects, they paired tones with foot shock, evaluating autonomic responses and

emotional behaviors. Their lesion work implicates separate efferent projections from the amygdala in conditioning of autonomic and behavioral responses. Moreover, emotional memories established by conditioning of subcortical systems strongly resist extinction (101). Once we learn to pair a sensory experience with a negative emotion, it is extremely difficult to unlearn the association. These and other observations indicate that the negative emotion associated with a long-standing painful condition is a complex process, probably sustained by several mechanisms.

Fear conditioning, the formation of a conditioned fear response, almost certainly occurs in patients who undergo repeated painful diagnostic or treatment procedures. Fear conditioning can exacerbate the affective dimension of pain in cases in which circumstances pair minor pain and intense affective arousal. Moreover, fear conditioning can link the environment surrounding a painful event and affective processing of that event so that the environment alone could elicit some elements of the affective dimension of pain.

Operant Learning

Operant learning (also called *operant conditioning*) has received substantial attention in the chronic pain literature (102,103; also see Chapter 25). This type of learning requires that patients emit specific behaviors (e.g., grimacing, bracing, and groaning with postures indicating back pain) and that rewarding events (nurturing, social attention, rest) follow the behaviors. Through operant mechanisms, some patients build complex habit patterns of complaining, expressing pain, seeking nurturing, and evading the quotidian responsibilities of everyday life. In short, they learn pain as a social behavior and develop elegant skills for pain expression. Such patients differ markedly in presentation from the deeply distressed and usually stoic cancer patient with pain.

The typical emotion researcher is quick to contend that positive reinforcers are events accompanied by positive emotions. It is not the fact of the reward that counts in shaping behavior patterns, but rather the emotional experience of reward. Because people and animals alike will work for simple tokens and symbols that have no intrinsic value apart from their conditioned association to positive emotion, this seems a compelling argument.

In any setting in which patients are active and others introduce reinforcing (emotionally rewarding) events, operant learning can occur. A reinforcer is an event that alters the likelihood of a behavior's recurring when it follows an instance of that behavior (103). Events that create pleasant feelings function as rewards (positive reinforcers); events that produce negative feelings are punishments (i.e., they suppress behaviors or delay them until a later time). The positive or negative nature of reinforcers and their personal significance occur in conscious awareness as feelings (104). Put another way, the events that shape behavior are those that are emotionally prominent. Emotion-free events have no reinforcing properties and therefore cannot contribute to adaptive (or maladaptive) learning.

Emotion associated with pain probably influences memory. Memory researchers surmise that both limbic and nonlimbic mechanisms contribute to memory processes (105). Emotional significance controls at least some and perhaps much memory formation. Evidence exists that the brain preferentially stores information that has strong emotional loadings (106,107). Heath (108) proposed that learning and memory are “rooted in feeling and emotion” and identified hippocampus, cortical medial amygdala, and cingulate gyrus as key areas involved in negative emotions.

In sum, the emotional component of pain appears to support adaptation and survival by facilitating learning, memory, and related cognitive processes. It provides a bridge by which pain can influence the psychological status of the individual and his or her behavioral tendencies. Inadvertent classical conditioning can cause anticipatory anxiety or exacerbate the emotional distress of a painful event. Operant conditioning can shape patient behavior in the direction of increased pain complaint and disability.

EMOTION AND COGNITION

Negative emotions are much more than reactions to undesirable events; in nature, they help an organism determine which things benefit and which things threaten survival, and they compel behavior consistent with such evaluations. Moreover, emotional expression communicates this judgment to others and thus sets up group approach or avoidance behaviors. As noted previously, MacLean (7) described emotion as a process that imparts subjective information. In these respects, our feelings approximate crude intelligence. How we feel about something is often as important, or more important, than what we know about it. If emotion is a protointelligence, then evolutionarily newer structures—namely, the later stages of cortical development—should have demonstrable links with limbic structures and functions.

Such interconnections exist. Parts of frontal lobe (the dorsal trend) appear to have developed from rudimentary hippocampal formation, whereas other parts (the paleocortical trend) originated in olfactory cortex. Although these two areas interconnect anatomically, the former analyzes sensory information, whereas the latter contributes emotional tone to that sensory information (109). Pribram (110), noting that limbic function involves frontal and temporal cortex, offered a bottom-up concept for how cognition relates to feelings (i.e., emotion determines cognition). However, the multimodal neocortical association areas project corticofugally to limbic structures (111), and this suggests that cognitions may drive emotions.

The debate on whether emotion or cognition is primary may never resolve. For immediate purposes, it seems best to conclude that knowing and feeling are closely interrelated. Still, these processes are not identical. We can know something about our feelings, and we can have emotional responses to what we know. The brain is a complex, dynamic organ, constantly constructing its internal model of reality from sensory input and memory storage. Feeling and thinking are major processes in this construction.

PAIN, STRESS, AND SICKNESS

The defensive response of the central nervous system to injury or disease is complex. We have already seen that it is not limited to simple sensory signaling of tissue trauma, awareness of such signaling, and conscious response. Much of the information processing is unconscious, and physiologic responses are initially unconscious, producing affective changes and subsequent awareness of emotional arousal. The HPA axis plays a strong role in emotional arousal and the defense response, and it helps to govern the immune system (112). The immune system does much more than identifying and destroying foreign substances: It may function as a sense organ that is diffusely distributed throughout the body (113,114).

Some investigators (74,114) contend that the brain and immune system form a bidirectional communication network. First, products of the immune system communicate injury-related events and tissue pathology to the brain. The key products are cytokines, such as interleukin-1 and interleukin-6, released by macrophages and other immune cells. They appear to do this not by functioning as blood-borne messengers, but by activating the vagus nerve. Paraganglia surrounding vagal terminals have dense binding sites for interleukin-1, and they synapse on vagal fibers that terminate in the solitary nucleus. Thus, cytokines appear to excite (albeit indirectly) vagal afferents that terminate in one of the major control centers for the ANS.

Second, the brain controls the immune system via the actions of the sympathetic nervous system and the hypothalamic secretion of releasing factors into the bloodstream that activate the anterior pituitary via the HPA axis (112). The pituitary body releases peptides related to proopiomelanocortin, such as adrenocorticotropic hormone and b-endorphin, and these in turn trigger the release of glucocorticoids. Because the cells and organs of the immune system express receptors for these hormones, they can respond to humoral messenger molecules of central origin. This system is important for pain research because, according to Maier and Watkins (114), activation of these pathways by a stressor such as tissue trauma produces a constellation of adaptive behaviors and physiologic changes that correspond to the *sickness response*.

The sickness response is a negative experience, but it evolved to promote recuperation and survival. It includes fever, increased slow-wave sleep, increased leukocytosis, reduced exploration, diminished sexual interest, reduced activity, depressed mood, and somewhat diminished cognitive abilities. Collectively, these responses conserve energy and foster its redirection to increased body temperature, which suppresses the reproduction of microbial organisms. Sickness tends to occur with both microbial infection and tissue injury because an open wound normally invites infection. Viewed broadly, sickness is an unpleasant motivational state that promotes recuperation.

These considerations suggest that feeling sick is a part of the brain's defense against microbial invasion. Tissue trauma can provoke it, and thus it tends to accompany the experience of pain. Obviously, chronic sickness in the absence of definable injury of pathology serves no biological purpose. The role of the sickness response in chronic pain states merits study.

MODEL FOR THE AFFECTIVE DIMENSION OF PAIN

Figure 24-6 summarizes the concepts covered previously. This is a bottom-up depiction of the fate of nociceptive signals produced by injury or disease. Spinothalamic (sensory thalamus) and spinolimbic processing occurs in response to noxious signaling. In the person with pain, spinothalamic and thalamocortical sensory processing produces sensory information related to the tissue trauma and performs feature extraction on it: intensity, location, duration, and general nature of the injury. Spinolimbic processing, which involves spinohypothalamic pathways and central noradrenergic innervation, provides emotional arousal. Figure 24-5 provides a more detailed description of the interdependence of sensory and limbic processes.

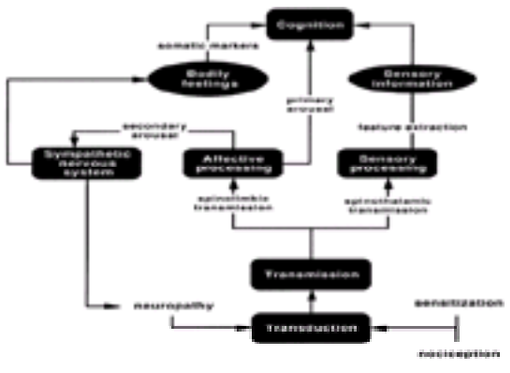

Figure 24-6. A bottom-up model of how nociception produced by tissue pathology or injury enters into cognition. The experience of pain is the product of both spinothalamic and spinolimbic processing.

Spinolimbic processing involves two stages, as Figure 24-6 shows. The first stage, primary arousal, produces a generalized heightened alertness and sense of threat. The perceiver is not directly aware of this state in the way that one is aware of sensory information; rather, it is the emotional coloring against which the perceiver appreciates the sensory information processed via the parallel spinothalamic tract. It is a sense of disquiet and apprehension akin to fear. The key point is that the perceiver is hypervigilant without being concomitantly aware of the hypervigilance.

As this happens, the hypothalamus and ANS initiate a secondary arousal response that involves efferent sympathetic stimulation of visceral organs, skeletal muscle, skin, and the vasculature. Figure 24-7, a top-down model, depicts many central structures contributing to sympathetic arousal and the defense response.

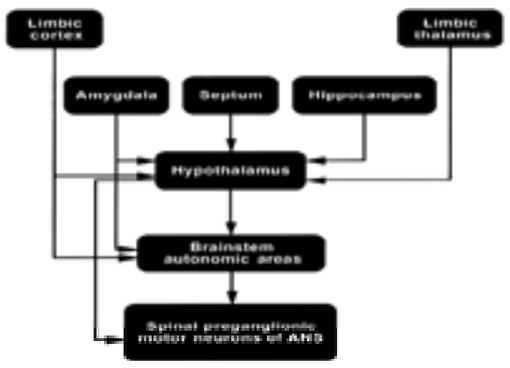

Figure 24-7. A top-down model for how the limbic brain influences autonomic function. Many central structures contribute to the defense response and to sympathetic arousal. (ANS, autonomic nervous system.)

This defense response largely readies the body for flight or fight. Its sudden onset creates a wave of emotion that follows on the heels of the primary negative arousal response. The perceiver is ordinarily quite aware of this arousal because of its dramatic bodily effects. In some cases, such as panic attack, the arousal itself becomes the focus of attention; in others, it simply colors the immediate sensory experience. The essential concept here is that secondary arousal creates and sustains an emotional state.

Both pathways feed forward into cognition. Figure 24-8 illustrates some of the processes that act on sensory and affective input. Primary arousal captures and directs attention. Secondary arousal affects memory, the formation of schemata (perceptual hypotheses), and the retrieval of learned schemata for memory. If the painful stimulus persists, it elicits a sustained stress response that creates a negative mood state.

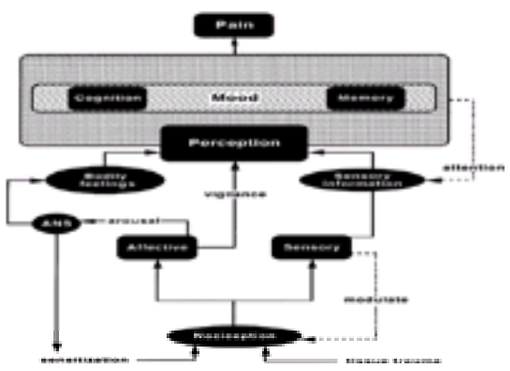

Figure 24-8. Higher-order processes that influence the transmission and processing of sensory and affective input. Negative mood states can bias attention and memory retrieval. (ANS, autonomic nervous system.)

Mood states are extended emotional predispositions that can strongly bias cognition, as Figure 24-8 indicates. A negative mood, such as reactive depression, biases memory by ensuring that only negative, emotionally unpleasant recollections come forward. Similarly, it directs attention toward threatening, aversive, or otherwise unpleasant things, and it fosters the creation of schemata that are inherently negative. In this way, an unchallenged negative mood state can sustain itself indefinitely.

Sensory information feeds forward into thinking (ratiocination), goal-directed efforts (motivation), and awareness of the external and somatic environment. Emotional arousal and mood can distort thinking and foster metacognition: errors in perception and reasoning (115). Metacognition is a major source of erroneous self-report of pain intensity and the effect of pain on lifestyle. Through affective mechanisms, excessive, persistent, or both, pain can extract a substantial toll on the mental and physical health of the individual.

Supporting Findings from Brain Imaging Studies

The model offered in this chapter predicts that noxious stimulation, whether of experimental or pathologic origin, generates massive, parallel distributed processing in the central nervous system. This processing must involve limbic structures as well as sensory pathways.

Studies involving positron emission tomography (PET) of regional cerebral blood flow (rCBF) in volunteers experiencing pain, and similar studies in pain patients, offer strong support for the hypothesis that noxious stimulation activates limbic structures. Changes in rCBF index neuronal activity in specific brain regions.

The partial review that follows targets studies designed to capture the complex central processing associated with pain. Collectively, they have puzzled and challenged pain researchers with classical sensory neurophysiology perspectives. Although not perfectly consistent, they demonstrate beyond any doubt that massive parallel distributed processing occurs in the brain after tissue damage. Processing includes, but is not limited to, sensory pathways. The most striking feature of this massive, parallel distributed processing is that a great deal of it occurs in limbic brain. This provides supporting evidence for the contention that pain has an affective dimension.

Just what does increased rCBF in a brain area mean? Glib interpretation is tempting, but fraught with pitfalls. It seems naïve to presume that the brain works on a rope and bell basis: Pull the rope in the periphery and ring a bell in a specific brain center. It is quite clear that the brain as a whole, and especially the limbic brain, operates as a system with complex feed-forward and feedback mechanisms. Notions of *centers* for one or another function have largely disappeared from the landscape of contemporary brain research. Consequently, attempts to chase nociception-specific messages to nociception-specific centers are probably doomed to fail. Also, little justification exists for assuming that brain activation means that sensory information processing is taking place. Affective processing may involve such processes as arousal and anticipation.

Because of these uncertainties, clear interpretation of massive parallel rCBF indicators of brain activation still eludes us. Moreover, in the end, we have no idea how any of the areas feeds forward into the contents of consciousness. Despite these limitations, the following studies indicate a striking consistency, and they strongly implicate limbic structures in the construction of the pain experience.

Pioneering studies examined healthy subjects and patients. Jones and colleagues (116) applied heat via a Peltier thermode to the hands of six normal volunteers. They contrasted the rCBF findings across three stimulus intensities, ranging from noxious to innocuous. Pain-related changes in rCBF appeared in contralateral thalamus, lenticular nucleus, and cingulate cortex. The same team studied rCBF in five cancer patients with pain before and after percutaneous, ventrolateral cervical cordotomy. They compared patients before pain with healthy subjects and then compared patients with themselves before and after neurosurgical intervention. The comparison of patients with healthy subjects revealed significantly less blood flow in three of four of the individual quadrants of the hemithalamus contralateral to the side of pain in the cancer patients. Cordotomy abolished the differences. Cordotomized patients demonstrated decreased CBF in the dorsal anterior quadrant of the thalamus contralateral to the side of pain, but no changes were evident in either primary somatosensory cortex or prefrontal cortex.

The lenticular nucleus, or lentiform nucleus, resides lateral to the thalamus and within the internal capsule. It comprises two parts, the larger putamen and (medial to it) the smaller globus pallidus, which is separated from the thalamus by the posterior limb of the internal capsule.

Talbot and associates (117) stimulated the forearms of six normal volunteers with noxious heat from a contact thermode. Pain- related rCBF changes appeared in contralateral cingulate gyrus and in primary and secondary somatosensory cortex. Coghill and colleagues (118) followed this with a PET study comparing rCBF changes in normal volunteers during painful heat stimulation and vibrotactile stimulation. With painful stimulation, subjects demonstrated rCBF changes in contralateral thalamus, primary and secondary somatosensory cortices, anterior cingulate cortex, insula, and frontal cortex. With vibrotactile stimulation, changes appeared contralaterally in primary somatosensory cortex and bilaterally in secondary somatosensory cortex and insula. Both types of stimuli activated primary and secondary somatosensory cortical areas, but painful stimuli had a significantly greater effect on insula and produced in general a more widely dispersed effect.

Casey and colleagues (119) delivered noxious and innocuous heat pulses to the forearms of volunteers during PET analysis of rCBF. Significant rCBF increases occurred contralaterally with painful stimulation in thalamus, cingulate cortex, primary and secondary somatosensory cortex, and insula. Ipsilaterally, secondary somatosensory cortex, thalamus, medial dorsal midbrain, and cerebellar vermis also showed increases in rCBF.

In a later study, Casey and colleagues (120) sought to detect rCBF increases in 27 normal humans as they discriminated differences in the intensity of noxious and innocuous thermal stimulation applied to the nondominant (left) arm. They divided subjects into three groups of nine each: repetitive contact heat stimuli (40°C and 50°C of thermode stimuli), cold pressor, and warmth discrimination (36°C and 43°C of thermode stimuli). Significant increases in rCBF to the 43°C stimuli occurred in the contralateral ventral posterior thalamus, lenticular nucleus, medial prefrontal cortex (Brodmann's areas 10 and 32), as well as cerebellar vermis. The painful stimuli elicited more extensive brain activity. Significant rCBF increases to 50°C stimuli appeared contralaterally in the thalamus, anterior cingulate cortex, premotor cortex, and secondary somatosensory (S2) and posterior insular cortices. Significant activity also appeared within the region of the contralateral anterior insula and lenticular nucleus. The ipsilateral premotor cortex and thalamus and the medial dorsal midbrain and cerebellar vermis also showed significant rCBF increases. In the heat pain and cold pain conditions, five areas responded consistently: cerebellar vermis, ipsilateral thalamus, contralateral premotor cortex, contralateral anterior cingulate cortex, and contralateral insula and lenticular nucleus. Cold pain created a greater rCBF increase than did heat pain. These observations are consistent with the interpretation that rCBF increases reflect activity both of the sensory and affective processing of nociceptive signaling.

Vogt and coworkers (121) studied the rCBF responses of seven healthy subjects to noxious and nonnoxious heat stimulation. They used statistical parametric mapping for the group to identify regions of altered relative rCBF. In addition, they fitted the PET data on a subject-by-subject basis to magnetic resonance images of the brain. The mapping analysis of the group showed one site with elevated rCBF in the midcingulate cortex and one in the perigenual cortex predominantly contralateral to the side of stimulation. Bilateral sites of reduced rCBF were in the cingulofrontal transitional cortex and in the posterior cingulate cortex as well. Coregistered PET and magnetic resonance images for individuals showed that only one case had a single, large region of elevated rCBF, whereas the others had a number of smaller regions. This study helps clarify the noteworthy range of individual differences in rCBF responses during pain.

Hsieh and colleagues (122) investigated rCBF in eight patients with neuropathic pain (lateralized mononeuropathy). They compared two conditions: normal ongoing pain experience and a condition in which the experimenters had temporarily blocked the pain via lidocaine block. The ongoing neuropathic pain produced activation of bilateral anterior insula, posterior parietal, lateral inferior prefrontal, and posterior cingulate cortices as well as the posterior sector of the right anterior cingulate cortex. The contralateral posterior thalamus demonstrated reduced rCBF. However, they found no significant change in rCBF in the somatosensory areas SI and SII. The investigators concluded that these findings point to the affective-motivational dimension of chronic ongoing neuropathic pain.

In a later study, Hsieh and colleagues (123) explored the effects of minor dermal injury elicited by intracutaneous injection of a minute amount of ethanol on rCBF in four subjects. A saline injection served as control. The painful condition (ethanol) prominently activated the hypothalamus, periaqueductal gray, prefrontal cortex, insula, anterior cingulate cortex, posterior parietal cortex, primary motor and somatosensory areas, supplementary motor area, and cerebellum.

Silverman and associates (124) looked at pain threshold rCBF in six patients with irritable bowel syndrome, contrasting them to six normal subjects tested under identical conditions of noxious rectal distension. For the healthy subjects, a significant relationship existed between activity of the anterior cingulate cortex and actual or simulated delivery of the painful stimuli, but no response occurred for nonpainful stimuli. In patients, no response occurred in anterior cingulate, and instead they demonstrated a significant activation of left prefrontal cortex during activation and anticipation.

Jones and colleagues (125) examined rheumatoid arthritis patients with chronic inflammatory pain in a test of the hypothesis that such pain alters endogenous opioid binding at receptors in the brain. A high concentration of such receptors exists in periaqueductal gray, medial thalamus, lentiform nucleus, anterior cingulate cortex, and insular cortex. If chronic pain is associated with increased production of endogenous opioids and increased binding at receptors, then an exogenously introduced opioid substance should find fewer binding sites in these areas. The investigators used PET scanning to tracer quantities of ^{11}C diprenorphine after its intravenous injection in four patients, in pain and after pain relief. They observed significant changes in superior and inferior frontal cortex, straight gyrus, anterior and posterior cingulate, and superior and midtemporal cortex.

Derbyshire and coworkers (126) studied rCBF in six patients with atypical facial pain, applying noxious and innocuous heat stimuli to the back of their hands and contrasting their regional blood flow patterns to those of normal controls. Patients and controls showed marked rCBF differences between painful and nonpainful conditions in thalamus, anterior cingulate cortex, lentiform nucleus, insula, and prefrontal cortex. The patient group showed increased blood flow in anterior cingulate cortex but decreased blood flow in prefrontal cortex.

Does chronic and acute pain produce different patterns in rCBF? Mountz and colleagues studied women diagnosed with fibromyalgia syndrome, a disorder characterized by widespread chronic pain and fatigue (127). They examined resting state rCBF in 10 patients and compared their data with those of seven healthy women. Resting regional bilateral blood flow was significantly lower in the fibromyalgia patients than in normal subjects at the thalamus, at the head of the caudate nucleus, and in cortex. The observation of lower rather than higher rCBF levels in the fibromyalgia patients led the authors to speculate that chronic pain may eventually reduce blood flow in certain brain areas. They postulated that a release of C-fiber neuropeptides in response to chronic noxious stimulation, together with diminished rCBF, altered central nervous system sensitivity to normally mildly noxious stimulation in fibromyalgia patients. These findings open new hypotheses about central differences in acute and chronic pain and the role of potential compensatory processes.

Collectively, these brain imaging studies demonstrate massive parallel distributed processing, largely in limbic structures, and thereby support the hypothesis that there is an affective component of pain. Thalamus, anterior cingulate cortex, insula, and frontal cortex emerge with high consistency across studies of normal volunteers and patients with pain. This response pattern corresponds to MacLean's thalamocingulate division of the limbic brain (7). Moreover, the results of the various PET studies are broadly consistent with the hypothesis that noradrenergic activation plays a major role in the affective component of pain.

Can one derive any strong interpretations about pain as a modality? This line of research seems to demonstrate that pain is not limited to a sensory modality. The patterns of central arousal demonstrated thus far are not specific to pain as a sensory modality; whether any of them is specific to threatening stimuli in general remains to be seen. Central activation, not surprisingly, appears to correspond to higher-order psychological processes. As more studies appear in various areas, it becomes increasingly clear that PET studies demonstrate that such processes are a part of the complex experience of pain.

FUTURE DIRECTIONS

Psychophysiology is a rapidly expanding field. To date, its influence on pain research has been minimal, because many pain investigators have favored the classical view of pain as a sensory modality. Now that brain imaging observations are challenging classical models, pain research has to expand its horizons. Psychophysiology has much to contribute in theory as well as in methodology. Integrating the rich knowledge base in psychophysiology with contemporary models of pain at present is difficult, but such integration is inevitable. Pain is a psychophysiologic phenomenon.

As brain imaging research on pain unfolds, it becomes increasingly clear that the brain deals in complex ways with signals of tissue trauma. Highly organized patterns of protective response exist, and they involve the ANS, the HPA axis, and the immune system, as well as subjective awareness. Negative emotion is a major feature of pain and a direct consequence of complex central processing. In light of these findings, it is no longer enough to trace the sensory messages of tissue trauma to somatosensory cortex. The challenge for the twenty-first century is to discover and describe the complex central processes involved in pain. Expanded models of central processing will help substantially in bridging basic science knowledge and theory with clinical care.

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CHAPTER 25

Learned Pain: Pain as Behavior

Wilbert E. Fordyce

Pain is a concept, not a *thing*. People do not *have* pain; they experience the unpleasant effects of nociceptive stimulation or they suffer in ways that they associate with pain. Recognition of this point is basic to understanding pain and suffering. If pain consisted solely of a hard-wired stimulus-response capability, there would be no role for learning or for other cognitive processes. Conversely, if a hard-wired stimulus-response capability were the defining characteristic of pain, neuroanatomic and pathophysiologic parameters would suffice in dealing with clinical pain, which, obviously, they do not (1,2 3) (see Chapter 6, Chapter 7, Chapter 8, Chapter 9 and Chapter 10).

In an intact organism, a nociceptive stimulus virtually always elicits some form of pain behavior, as well as a subjective unpleasant sensation. However, it also commingles with whatever other stimuli are currently active, extant physiologic and mood states, and perceived or anticipated consequences to whatever actions might be taken. Responses emerge from this process. It is those responses that tell us that the person is experiencing what he or she identifies as pain. It is the commingling of the processing of nociceptive stimuli with other cognitive and sensory phenomena that ensures an opportunity for learning. *Learning* is the persistence or inhibition of a response, across time. As a consequence of learning, the response occurs or is inhibited in different contextual circumstances.

Melzack and Wall's gate control theory was first presented in 1965: a pioneering recognition that pain is a complex affair implicating central processing capabilities. It pointed toward the current and changing state of the individual as being capable of exerting major influence on responses to nociception. Clearly, the observed, inferred, or alleged nociceptive stimulus could not encompass the concept of pain alone. It follows that, when confronted with a pain problem, the clinician should not focus solely on the peripheral stimulus and make inferences as to its cause.

Subsequent to the emergence of the gate control theory, behavior modification technology in the form of operant conditioning techniques was applied to selected problems of chronic pain (4,5). This had the effect of extending the range of parameters affecting pain problems to include the residuals of prior experience and, perhaps more important, environmental contingencies. Behavioral-based interventions have proven to have considerable potential for improvement in function, reduction in pain-related health care use, and subjective reports of pain and suffering in appropriately selected cases.

The gate control theory and behavioral interventions pointed to the need for a paradigm shift. Instead of viewing chronic pain as solely a biomedical-based problem, it became apparent that it is a problem having psychological and environmental-relational aspects potentially every bit as important as neuroanatomic ones. To understand a person's pain, one needs to factor in responses or behavior and the factors that influence it.

Persisting noxious stimuli can produce lasting changes in neurophysiologic mechanisms that influence ensuing responses. Those matters are considered in Chapter 3, Chapter 4 and Chapter 5 and Chapter 10. It is not always clear whether nervous system changes are induced by peripheral mechanisms at the injury site or whether they are brought about by environmental factors.

Behavior is a product of prior learning or experience as well as current stimulation. That is why we must consider learning and behavior when we consider pain. Although this concept is now virtually universally understood and accepted by health care professionals, it is far less common that this understanding is translated into how pain is diagnosed or treated. We often do not recognize the extent to which our thinking is guided by often implicit and infrequently articulated conceptual models. These models help us to organize our thoughts and to understand more readily the phenomena with which we are dealing. The lure of a seemingly simpler and more straightforward model of pain, as embodied in a stimulus-response or biomedical-rooted view, is strong both in health care professionals and in the patient consumers of their services. It is all too often the case that the relatively straightforward biomedical perspective is either assumed to be the major force in seeking to understand a pain problem, or, at the least, must be eliminated before equally viable alternatives receive the consideration they deserve. This chapter focuses on one of these alternative major influences on clinical pain: learning. It examines behavior because that is the primary manifestation of learning or experience.

Viewing pain in behavioral terms arose serendipitously. A more detailed account of the origins of this view was related in an earlier edition of this text (2). It is repeated here, although in abbreviated fashion, because it is a particularly graphic illustration of the potential effect of environmental influence in the form of social feedback on pain behavior.

The circumstances were that a pain-ridden patient in an inpatient setting was confronted in the course of events by a treatment team decision to respond to his verbal expressions of pain by looking away instead of maintaining eye contact. This crude and simple-minded action led surprisingly to a marked change in the patient's behavior. Initially, he was bed-bound with complaints of pain; then he began arising and undertaking physical reactivation procedures. The patient made it clear that he knew how the team was reacting to his expressions of suffering, but it made little difference in his ensuing pain behaviors and in his progress toward reactivation. This demonstration that pain behaviors are sensitive to consequences tells us two things: (a) that pain behaviors are an integral part of pain problems and (b) that those pain behaviors are subject to influence by consequences.

BASIC CONSIDERATIONS

Distinctions between a biomedical and a biopsychosocial model of pain are important, for they may lead us to quite different actions when dealing with patients who complain of pain. The biomedical model points to seeking a diagnostic explanation for the observed or inferred nociceptive stimulus. At least a passing attention is paid to personality and motivational considerations, but the initial focus clearly is to seek to understand what is considered to be the initiating event: the nociceptive stimulus.

A biopsychosocial model leads to a different focus. It is no less important to sort out the role, if any, of noxious stimulation from disease or injury. The complaints of pain (i.e., the pain behaviors) may be occurring for a variety of reasons, perhaps a complex mix of neuroanatomic and psychosocial. The two models are not mutually exclusive; their explanatory powers are often intertwined. It is rarely the case that a patient's chronic pain problem should be addressed solely from the perspective of either model (2,6).

This chapter presents conceptual and empiric bases for adding a behavioral science perspective to the medical science perspective in dealing with clinical pain. A

brief description of basic concepts of learning is needed before proceeding.

Classic and Operant Conditioning

Classic conditioning has also been termed *Pavlovian conditioning*. A conditioned stimulus, the bell in the case of Pavlov's dog, is paired with an unconditioned stimulus, the food, which in turn elicits salivation by reflex. After repeated training trials (i.e., experience), that response comes to be elicited successfully by a previously unconditioned but now conditioned stimulus, the bell. Learning has occurred in that classical conditioning paradigm.

Instrumental or operant conditioning works differently. A behavior (e.g., pain behavior) previously in the repertoire, when elicited, acts on the environment; therefore, it is likely to have effects or influence on the environment by eliciting some environmental reaction. If the effect is to evoke a reinforcing consequence, the behavior is likely to be repeated when cues indicating potential reinforcing consequences are again present.

In classic (respondent) conditioning, the behavior is said to occur in response to the antecedent stimulus. In the Pavlovian example, the bell was antecedent to the salivation. The response was automatic and reflexive. In operant conditioning (the term *operant* is used because the response acts on the environment), change or learning occurs because of what follows, or is anticipated to follow, the behavior. Smiling at other people may serve as an illustration. Experience probably has taught us that smiling often leads to approval or emotional support from those exposed to the smile, a reinforcing consequence that is likely to encourage future smiling. Similarly, moaning or rubbing an aching body part may elicit supporting or commiserating responses in observers, thereby potentially encouraging persistence of those pain behaviors.

The ability to *anticipate* consequences is important, as are the effects of the consequences. Anticipation of consequences is a cognitive act. Operant conditioning can never be isolated entirely from cognitions. The term *cognitive-behavioral* is a partial recognition of this, although that term relates to other matters as well. This chapter focuses on operant conditioning. Cognitive factors going beyond operant conditioning are addressed in Chapter 6 and Chapter 89.

Respondent and operant conditioning differ in important ways. The difference most relevant to clinical pain, and the only one to be considered here, is that behavior elicited by antecedent stimuli, as in respondent or Pavlovian conditioning, is unlikely to persist, unless it continues to be systematically exposed to reinforcing consequences. Pavlov's dog did not long persist in salivating to the bell when food no longer followed. Additional conditioning trials with bell and food were necessary to reestablish the conditioned response. An exception to this point is noted below in relation to trauma-induced pain problems.

Pain behaviors under operant control persist or diminish because of persistence of consequences favorable or unfavorable to learning, or the anticipation of such consequences. This means that the behavior may persist even when it receives reinforcing consequences only intermittently. Responses or behavior reinforced on every occasion that it occurs tends to satiate and diminish in strength. Responses reinforced intermittently are persistent. If, however, reinforcement occurs too infrequently, the behavior also is likely to disappear, a process known as *extinction*. A whole technology is concerned with schedule or frequency of reinforcement and receives more consideration in Chapter 88.

The potential for conditioning effects points to a different target for treatment of pain problems. The first objective of treatment for pain problems under control of nociceptive stimuli is usually to diminish or eliminate the nociceptive stimulation. Treat the cause, not the symptom. Pain problems that have come under control of conditioning effects they may have originated, however, should be treated in a different way. The focus of treatment may be to modify consequences to pain behaviors, while also helping the patient to become reactivated. In the practical case, clinical pain problems, particularly if they are chronic, present features relevant to both biomedical and learning-based strategies. To paraphrase, it is often the case that one should seek to treat both the cause and the symptom; to do only one and not the other well may result in needless persistence of the pain problem.

Suffering

Expectations or anticipation of consequences has another type of importance to clinical pain, relating to the ease with which suffering from pain and suffering for other reasons may be confounded. A nociceptive stimulus is perceived. Part of that process is the assignment of a *meaning* (i.e., an interpretation). That interpretation or meaning assigned often reaches beyond the nociceptive stimuli coming from the periphery. Coincidental or contiguous stimuli may be incorporated into the meaning. Expectations as to what might occur, given the context of the situation, play a role, as does anticipation of probable or possible consequences. During the course of a football game, a player expects to receive physically punishing blows that, if received by another person in a different context, would probably produce a highly charged emotional response. For the football player, it may be a relatively inconsequential event because of experience and expectations. Emotional responses often become implicated in meanings assigned to stimulus situations. When the situation is noxious or unpleasant, these emotional responses often elicit feelings that can be thought of as suffering.

Cassell (7) distinguishes suffering from physical distress in this fashion:

> Suffering occurs when an impending destruction of the person is perceived; it continues until the threat of disintegration has passed or until the integrity of the person can be restored in some other manner . . . although suffering often occurs in the presence of acute pain . . . or other bodily symptoms, suffering extends beyond the physical. Most generally suffering can be defined as the state of severe distress associated with events that threaten the wholeness of the person.

Suffering, as defined by Cassell and seen as the emotional component of pain, involves the anticipation of consequences. If the person does not understand the natural course of the pain problem and the timing and character of the outcome, the future is clouded and the suffering will be greater. Suffering, like nociceptive stimulation, produces pain or suffering behaviors. These behaviors may be maintained if the future looks aversive or uncertain.

Suffering behaviors, because they are operant, may also come under the control of conditioning. One of the greatest problems in clinical pain, particularly chronic pain, is the confounding of pain with suffering, both by the patient and the clinician. Pain behavior may reflect nociceptive stimulation at onset of the problem, as in tissue injury, but can continue long after the nociceptive stimulation has ceased and the injury has healed. Suffering behavior can continue as a consequence of learning without substantial ongoing nociceptive input.

One long-term effect of prolonged nociceptive stimulation is that it tends to promote guarding or resting behaviors. Unless the person clearly distinguishes hurt from harm by continuing to move, or to resume moving in a timely fashion, guarding behaviors persist and the effects of disuse (8) replace the effects of nociceptive stimulation associated with the originating injury. Thereafter, movement continues to be painful and the future continues to be clouded with doubts or, much worse, seems to promise continued impairment, both of which produce pain or suffering. Reinforcement derives from the patient's mistaken belief that the pain of movement means that healing is incomplete. Reinforcement may also come from the environment because pain or suffering behaviors meet reinforcing consequences in the patient's milieu.

CLINICAL CONSIDERATIONS

Influence of Learning on Pain Behavior

When a behavior is followed contingently by positive or reinforcing consequences, it tends to persist. The probability of its recurrence or persistence also increases in the presence of cues that signal that reinforcing consequences may be forthcoming (9). Because pain behaviors are behavior, they can be influenced by the same factors that influence any other behavior.

Two patterns of operant conditioning important to clinical pain can be distinguished. One is the case in which a reinforcing consequence is contingently applied after an overt behavior: a *positive reinforcement* paradigm. The consequence is generally something of positive value to the person and is therefore reinforcing. The second is when a consequence is removed as a contingency after an overt behavior: a *negative reinforcement* paradigm. That which is removed is generally an aversive or unpleasant consequence. The negative reinforcement paradigm is also known as *escape* or *avoidance conditioning* in that it tends to establish and maintain behavior designed to escape or avoid the negative consequence (10).

Positive and negative reinforcement is implicated in clinical pain. For example, a muscle is strained in the low back during the course of heavy lifting. Pain behaviors ensue and may meet reinforcing consequences from the environmental milieu in the form of solicitous behavior from a spouse or attention from a highly regarded

physician who may also prescribe rest, itself likely a potent reinforcement. If analgesics are also prescribed, another positive reinforcement may occur in the form of a relatively carefree state induced by the medications. Concomitant to the potentially positive reinforcers just noted, negative reinforcement may also occur. Curtailed activity and avoiding flexing the back may successfully escape anticipated suffering. Medically sanctioned time out from a job already aversive for other reasons may provide additional escape or avoidance conditioning opportunities.

In both examples cited, the learning or conditioning effects occurred as automatic consequences of experience (3,11). They did not occur as a conscious decision by the suffering person to engage in pain behaviors. Thus, these events do not indicate malingering, imagining pain, or some manifestation of mental illness.

In these examples, I have not referred to such mental concepts as inferred underlying motivation, conversion reaction, or personality types. The examples refer to cues, processing of those cues, and anticipation of consequences. They focus on what a person does, not on what a person is alleged to have, as is the case with most psychological approaches.

Operant Conditioning and Reinforcing Consequences

Potential reinforcing consequences to pain behaviors abound. A chronic pain patient may receive special attention, sanctioned rest, or pleasurable effects of a prescribed analgesic. These consequences readily may occur contingent on pain behavior. This is illustrated by prescription of analgesics on an as-needed basis (i.e., the effect of the analgesic depends on the occurrence of pain behaviors). Similarly, a person who moves guardedly thereby conveys to a helpful spouse that movement is painful. The consequences may be solicitous behaviors by the spouse, who offers to complete a half-finished task or provides admonitions to rest. If those consequences are positively reinforcing, the pain behaviors have been rewarded and are more likely to persist. In these illustrations, note that the consequences occurred only if pain behaviors occurred. They were contingent on pain behavior.

Not all consequences of behavior are positively reinforcing to every patient (e.g., not everyone finds attention pleasurable, and some find sedation aversive). For conditioning to occur, the consequences must occur with fair frequency, be positive or reinforcing to the individual, and be contingent on pain behaviors. If they occur irrespective of the occurrence or nonoccurrence of pain behaviors, conditioning is unlikely.

Assessment of the role of operant conditioning in clinical pain requires that one determine which potentially reinforcing consequences are presently contingent on pain behaviors. This is accomplished by detailed interviewing of patient and spouse or significant others around the patient (4,12) (see Chapter 16 and Chapter 18).

Treatment of acute and chronic pain must also take into account whether reinforcing contingencies are being set up systematically by a treatment regimen that persists over time. This is particularly an issue in management by analgesics and rest versus activity when pain is likely to persist for extended periods. In the case of a recent injury in which healing is expected in days or weeks, little need for concern usually exists. Similarly, postoperative pain with an expected course of only a few days probably will not lead to enduring conditioning effects.

Analgesics

Prescription of analgesics, muscle relaxants, and tranquilizers for more than a few days on an as-needed or pain-behavior contingent basis sets up a conditioning paradigm that risks causing pain behaviors to persist long past healing time and perhaps indefinitely (3,5,13). Time-contingent medications are a preferable style of drug delivery for both psychological and pharmacologic reasons.

Rest

Rest often is overprescribed (13). Healing is usually rapid and is often promoted by motion (14). Rest, excessively or carelessly prescribed, may inhibit or interfere with healing while also encouraging deactivation. The problem is compounded if the task of determining whether healing has occurred and activity is now appropriate is assigned to the untrained patient (15), as by saying to the patient, “Let pain be your guide” to determine when to terminate rest and resume activity. Often, the result of this arrangement is that the patient, on moving, experiences some discomfort and interprets it to mean that healing has not occurred and that continued movement may impair healing. The patient then moves less, thereby increasing the adverse effects of disuse and making it more probable that future movement of the involved body part will be painful. Thus begins a vicious circle. Each painful movement interpreted to reaffirm that healing has not occurred encourages greater disuse and more pain. It also pairs movement with events in the environment that, through conditioning, become cues capable of eliciting more discomfort. In sum, the pain problem may persist and worsen despite adequate healing, because the consequences of use and movement were misinterpreted because of ambiguous clinician guidance.

AVOIDANCE LEARNING

Behavior that avoids or postpones an anticipated aversive consequence, known as *avoidance learning*, has been studied in clinical pain (10). The following are the most important points about avoidance learning.

Aversive Consequences to Pain

A person learning that an activity has aversive consequences is likely to avoid that activity. Anticipating that a body position or physical activity will likely result in increased pain usually leads to avoiding or minimizing that activity. A strained back muscle is likely to lead to avoiding flexing forward and lifting heavy objects.

Resistance to Extinction

Once established, avoidance behaviors are highly resistant to extinction, because the behavior to be avoided rarely occurs. Each time it is avoided there appears to be a confirmation of the effectiveness of the avoidance. Conversely, the opportunity to disprove the expectation that a movement leads to pain does not occur. For example, a chronic low back pain patient during the early history of the problem may have experienced great pain on flexing the torso forward. Now the patient may hold him- or herself rigidly erect and studiously avoid flexing forward. The back muscles, of course, soon become tight, ensuring pain on flexing as a consequence of disuse. Although healing may long since have occurred, the patient continues to avoid flexing. Each guarding or avoidance of flexing seems to have confirmed the success of avoidance.

Other Aversive Consequences

An avoidance behavior that successfully minimizes pain may also avoid other aversive consequences and thereby receive additional reinforcement. The avoidance behavior has successfully prevented aversive consequences relating to pain, but also relating to the significant others. To illustrate, a housewife whose back pain is aggravated by vacuuming, who also finds housekeeping generally unpleasant irrespective of pain, receives reinforcement for avoiding pain by not using the vacuum. She is also reinforced by time out from housekeeping. The avoidance behavior may be maintained long after healing by the reinforcement of avoiding the housekeeping chore of vacuuming.

Further Considerations

It is not necessary for nociceptive stimuli to occur for avoidance learning-based pain behaviors to occur. Only an anticipation that an activity will lead to suffering is required. Humans can and do anticipate. A person with leg pain knows from experience that climbing stairs results in increased pain. We return to the back pain patient who avoids flexing forward. The patient need not begin to flex forward, experience pain, and then arrest the motion. Experience causes the patient to anticipate that forward flexing will be be painful, thus the avoidance behavior of holding the torso rigidly upright to occur in circumstances in which the patient might otherwise flex.

TRAUMA-INDUCED CONDITIONING

Stimuli previously unable to produce a given response may, through conditioning, come to have that ability, as in classical conditioning. Classical conditioning in the normal course of events rapidly extinguishes. However, if the originating stimulus event was traumatic, clear evidence exists that there may be persisting and

profound alterations in stress hormone secretion and memory processing that make pain and suffering responses highly resistant to extinction (16,17 and 18). Because of the adverse influence on memory functioning, the person may be unable to relate persisting suffering or pain behaviors to extant stimuli now producing them. Studies reporting persistent pelvic pain in women reporting histories of sexual abuse are an example (16,19). However, the findings as they pertain to chronic pelvic pain, although suggestive, are thus far conclusive (19). As viewed from the perspective of the learning process, studies have failed to search for and delineate specific discriminated stimuli presently capable of evoking previously traumatically conditioned pain behaviors, but related only adventitiously to the site of pain.

IMPLICATIONS FOR THE CLINICIAN

The major implications of learning or conditioning on occurrence and persistence of pain behaviors follow:

- Pain behaviors are not reliable indicators of underlying pathophysiology. Pain behaviors may accompany nociceptive stimuli, but they may also occur and persist in their absence.
- In chronic pain, evaluation of the pain problem requires analysis of possible sources of nociceptive stimuli and of possible learning-conditioning effects. Neither suffices without the other.
- Learning and conditioning may play an important role in treatment as well as diagnosis of chronic pain.

EFFICACY OF BEHAVIORALLY BASED TREATMENT OF CHRONIC PAIN

Numerous studies have appeared in the professional literature regarding the efficacy of behavioral or learning-based treatment for chronic pain (20,21 and 22). Three essential questions should be addressed in outcome studies. First, do the treatment methods produce significant changes in patient performance? Second, do the treatment methods produce results equal to or better than alternative methods? Third, are the methods cost-effective? In the evaluation of treatment outcomes, the array of variables to be considered is broad. These include site and duration of pain, extent of suffering, general health status of patient, activity level, restoration of social role function, pain-related health care use, and employment status. The diversity of these parameters and of studies addressing various aspects of them is too great to warrant detailed analysis and reporting here and is further discussed in Chapter 109. Flor and colleagues (22) have provided comprehensive and exhaustive analyses of the data available. Table 25-1 and Table 25-2 report findings selected to portray the efficacy and effect of treatment programs reflecting the concepts addressed in this chapter (Fig. 25-1).

27 of 100 fewer back surgeries for patients treated at multidisciplinary pain centers (23).

Applying that percentage to patients included in the metaanalysis of multidisciplinary pain centers by Flor et al. (22), we could anticipate 832 fewer back surgeries for patients treated at multidisciplinary pain centers.

The estimated cost of back surgery is $40,000; multiplied by 832 fewer surgeries, this represents a savings of $33,280,000.

From Turk DC. Efficacy of multidisciplinary pain centers in the treatment of chronic pain. In: Cohen M, Campbell J, eds. *Pain treatment centers at a crossroads: a practical and conceptual reappraisal*. Seattle: IASP Press, 1996;7:264–265, with permission.

TABLE 25-1. Reduction in surgical expenditures

Tollison (24) reported that at 1-year follow-up, 18% of patients treated at multidisciplinary pain centers compared with 55% of conventionally treated patients were hospitalized for pain.

Simmons et al. (25) reported a 58% reduction in medical costs following treatment at a multidisciplinary pain center. Average cost of medical care for 1 year before treatment was $15,675; average cost for 1 year after treatment was $6,603.

Extending these figures to the 3,089 patients treated in the studies included in the metaanalysis by Flor et al. (22) leads to the following: 3,089 × $15,675 = $48,420,075 pretreatment versus 3,089 × $6,603 = $20,396,667 posttreatment, for a savings of $28,023,408.

Average cost of multidisciplinary pain center treatment is $5,900 (based on University of Pittsburgh Multidisciplinary Pain Center and corrected for inflation). Cost of treating 3,089 patients included in Flor et al.'s (22) metaanalysis: 3,089 × $5,900 = $18,225,100.

Estimated savings in medical expenditures: $28,023,408 savings minus $18,225,100 cost of multidisciplinary pain center = $9,798,308 savings.

From Turk DC. Efficacy of multidisciplinary pain centers in the treatment of chronic pain. In: Cohen M, Campbell J, eds. *Pain treatment centers at a crossroads: a practical and conceptual reappraisal*. Seattle: IASP Press, 1996;7:264–265, with permission.

TABLE 25-2. Reduction in medical expenditures

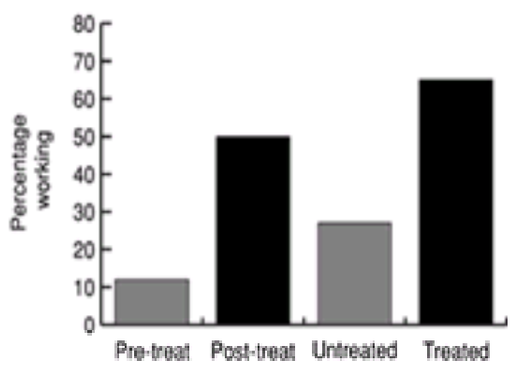

Figure 25-1. Meta-analysis of pain program outcomes. (Adapted from Flor H, Fydrich T, Turk D. Efficacy of multidisciplinary pain treatment centers: a meta-analytic review. *Pain* 1992;49:221–230.)

FUTURE CONSIDERATIONS

The implication of assigning importance to learning factors in conceptualizing clinical pain is great. Conceptual models or perspectives, once adopted and practiced, tend to fade into the background of our thinking. What started as hypotheses or ways of thinking come to be perceived as facts. The commonly expressed dictum *Pain is a symptom of some underlying problem* is only a hypothesis, which is sometimes true and sometimes not, or only partially so, but it has taken on the coloration of a fact. One consequence is that the health care system and training for health care professionals, by failing to distinguish hypothesis from fact, tends to perpetuate the error. Students as well as practitioners accept as fact what is only a hypothesis or extrapolation from a particular theory.

Chronic trauma-induced pain persisting after healing can reasonably be expected to have occurred and, in the absence of a demonstrable residual pathoanatomic defect, often continues to be treated from within the perspective of a biomedical model. That is true despite the absence of demonstrated effectiveness sufficient to contain and diminish the problem and in the presence of data pointing to more favorable outcome from methods derived from alternative models. It is a paradox that has for too long remained unresolved.

As health care and workers' compensation costs soar, most particularly in regard to chronic low back pain, ever-growing pressure exists for change in pain

management methods. Change is needed and will occur, whether from within the health care system or in response to social pressure. One major element of that change appears to this author to reflect a growing awareness of the impact of learning and conditioning and of the influence of social contingencies on human functioning, including illness behavior. Changes in professional training and in allocation of treatment resources should follow greater understanding of this issue.

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CHAPTER 26

Psychiatric Illness, Depression, and Psychogenic Pain

Mark D. Sullivan and Dennis C. Turk

The high rates of psychiatric illness in patients with chronic nonmalignant pain, although well recognized, are still poorly understood. Diagnostic hierarchies taught to physicians in medical school and residency, impairment rating strategies used by compensation systems, and the natural scientific method used by medicine that looks for objective causes for clinical phenomena force us into a mind-body dualism. If we cannot explain pain in terms of objective tissue pathology, we seek to explain it in terms of patients' psychopathology. Although this dichotomy is popular, if not inescapable, in current clinical settings, scientific evidence for it is lacking.

Epidemiologic evidence supports the use of inclusive rather than exclusive models of psychiatric diagnoses in medical settings. Medical illness in no way excludes the possibility of a clinically important psychiatric illness. Medically ill patients are, in fact, much more likely to have psychiatric illness than patients without medical illness. Psychiatric illness in no way precludes the possibility of a clinically important medical illness. Psychiatric illness is, in fact, associated with health behaviors and psychophysiologic changes known to promote medical illness.

The structure of our clinical settings makes the integrated delivery of mental and physical health care difficult. Nowhere is this more important than in the care of the patient with chronic pain. Psychotherapeutic and psychopharmacologic interventions for chronic pain are rarely effective in isolation from somatic treatments. Distress, disuse, and disability are important facets of a chronic pain problem, and all require clinical attention. Neglect of one of these components can result in treatment failure even in the presence of excellent care for the other components.

Any discussion of psychiatric disorders in patients with chronic pain is haunted by the concept of psychogenic pain. We are drawn to the concept of psychogenic pain because it fills the gaps left when our attempts fail to explain clinical pain exclusively in terms of tissue pathology. Psychogenic pain, however, is an empty concept. Positive criteria for the identification of psychogenic pain, mechanisms for the production of psychogenic pain, and specific therapies for psychogenic pain are lacking. Psychiatric diagnosis of many disorders, such as depression, can be helpful to clinician and patient by pointing to specific effective therapies. But the diagnosis of psychogenic pain too often only serves to stigmatize further the patient who experiences chronic pain.

In the discussion that follows, psychiatric disorders as defined in the *Diagnostic and Statistical Manual*, fourth edition, of the American Psychiatric Association (DSM-IV, 1994) are used as an organizing strategy. It is important to note, however, that the categorical model of mental disorder favored by psychiatrists and used in DSM-IV can imply more discontinuity between those with and those without a mental disorder than is actually the case. For example, it is common for patients with chronic pain to partially meet criteria for a number of mental disorders. Therefore, it is sometimes useful to think of these disorders as dimensions rather than categories. The DSM-IV nevertheless provides a well-recognized and systematic template for the discussion of psychiatric disorders in patients with chronic pain.

DEPRESSION

One must begin by distinguishing between depressed mood and the clinical syndrome of major depression. It is important to note, especially when working with chronic pain patients, that depressed mood or dysphoria is not necessary for the diagnosis of major depression. Anhedonia, the inability to enjoy activities or experience pleasure, is an adequate substitute. It is common for patients with chronic pain to deny dysphoria but to acknowledge that enjoyment of all activities has ceased, even those without obvious relation to their pain problem (e.g., watching television for a patient with low back pain).

The DSM-IV criteria for major depressive episodes are listed in Table 26-1. These include psychological symptoms, such as worthlessness, and somatic symptoms, such as insomnia. It is important to note that somatic symptoms count toward a diagnosis of major depression unless they are caused by “the direct physiologic effects of a general medical condition” or medication. The poor sleep, poor concentration, and lack of enjoyment often experienced by patients with chronic pain are frequently attributed to pain rather than depression. However, because they are not a direct physiologic effect of pain, these symptoms should count toward a diagnosis of depression. In fact, studies of depression in medically ill populations have generally found greater sensitivity and reliability with “inclusive models” of depression diagnosis than with models that try to identify the cause of each symptom (1).

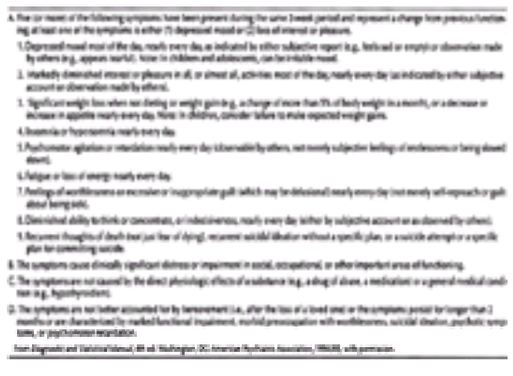


TABLE 26-1. *Diagnostic and Statistical Manual*, Fourth Edition, Criteria for Major Depressive Episode

Patients with chronic pain often dismiss a depression diagnosis, stating that their depression is a direct reaction to their pain problem. Psychiatry has long debated the value of distinguishing a *reactive* form of depression caused by adverse life events from an *endogenous* form of depression caused by biological and genetic factors (2). Life events are important in many depressive episodes, although they play a less important role in recurrent and severe or melancholic or psychotic depressions (3). Only bereavement excludes someone from a depression diagnosis who qualifies on the basis of symptoms. Determining whether a depression is a *reasonable response* to life's stress may be important to patients seeking to decrease the stigma of a depression diagnosis and has been of interest to pain investigators [for a review, see Fishbain and colleagues (4)]. It is not, however, important in deciding that treatment is necessary and appropriate. Indeed, no clinical benefit is gained from debating whether the depression caused the pain or the pain caused the depression, although such information may be useful in psychotherapy. If patients meet the diagnostic criteria outlined previously, it is likely that they can benefit from appropriate treatment. It may be useful when initiating depression treatment to accept that the pain caused the depression because it builds rapport and is consistent with epidemiologic evidence about the current depressive episode.

A variety of biological tests for depression have been investigated (5). These tests have included the dexamethasone-suppression test, thyrotropin-releasing hormone stimulation test, clonidine-induced growth hormone secretion, and rates of imipramine binding to platelet membrane serotonin transporters. Forty percent to 50% of patients with major depression do not show normal suppression of morning plasma cortisol after receiving dexamethasone the night before. However, high false-positive rates for this dexamethasone-suppression test exist in patients who are pregnant; patients with dementia, alcoholism, anorexia nervosa, and other chronic debilitating diseases; and patients who are taking medications that induce microsomal enzymes, including barbiturates and opioids. This has limited the clinical value of this test (6). The serotonin transport mechanism on platelet membranes is similar to that on serotonergic neurons. ^{3}H-imipramine binding to this platelet receptor is reduced in patients with major depression. It appears to be further reduced in patients who have both pain and depression (7). Although patients show significant differences on these tests, when considered as a group, substantial variation between individual patients limits the usefulness of these tests in the clinical setting. In the future, they may be able to provide a better understanding of the biochemical links between pain and depression.

When considering the diagnosis of depression in the patient with chronic pain, important alternatives include bipolar disorder, substance-induced mood disorder, and dysthymic disorder (particularly if accompanied by a severe personality disorder, such as borderline personality disorder). Patients with bipolar disorder have extended periods of abnormally elevated as well as abnormally depressed mood. These periods of elevated mood need to last more than 1 continuous day and include features such as inflated self- esteem, decreased need for sleep, and racing thoughts. A history of manic or hypomanic episodes predicts an atypical response to antidepressant medication and increases the risk of antidepressant-induced mania. Substance-induced mood disorders can also occur in those with pain. Patients with chronic pain may be taking medications such as corticosteroids, dopamine-blocking agents (including antiemetics), or sedatives (including muscle relaxants) that produce a depressive syndrome. Current medication lists should be scrutinized before additional medications are prescribed for any patient.

Dysthymic Disorder

Dysthymic disorder is a chronic form of depression lasting 2 years or longer. Individuals with dysthymia can develop major depression as well. This combined syndrome has often been called *double depression* (8). It is important to note dysthymia, because it is frequently invisible in medical settings, often being dismissed as “just the way that patient is.” Dysthymia has been shown to respond to many antidepressants, including the selective serotonin reuptake inhibitors (SSRIs) (9). Treatment of double depression can be particularly challenging because of treatment resistance and concurrent personality disorders (10). Psychiatric consultation should be considered when dysthymia or double depression is suspected.

Epidemiology

The prevalence of depression is much higher in medical settings and in patients with chronic illnesses than in the general population. It has been shown in studies using structured psychiatric interviews that a linear increase occurs in the prevalence of major depressive disorder when comparing community, primary care, and inpatient medical populations. Although 2% to 4% have major depression in the community, 5% to 9% of ambulatory medical patients and 15% to 20% of medical inpatients meet diagnostic criteria (11). Primary care patients with major depression have been found to have more severe medical illness than those who are not depressed (12). Even among community samples, the risk for depression appears to increase with worse perceived health status, number of chronic medical conditions, and number of medications taken (13).

Prevalence rates of depression among patients in pain clinics have varied widely depending on the method of assessment and the population assessed. Rates as low as 10% and as high as 100% have been reported (14). The reason for the wide variability may be attributable to a number of factors, including the methods used to diagnose depression (e.g., interview, self-report instruments), the criteria used (e.g., DSM-IV, cut-off scores on self-report instruments), the set of disorders included in the diagnosis of depression (e.g., presence of depressive symptoms, major depression), and referral bias (e.g., higher reported prevalence of depression in studies conducted in psychiatry clinics compared with rehabilitation clinics). The majority of studies report depression in more than 50% of chronic pain patients sampled (15).

Studies of primary care populations (in which generalization is less problematic) have revealed a number of factors that appear to increase the likelihood of depression in patients with chronic pain. Dworkin and colleagues (16) reported that patients with two or more pain complaints were much more likely to be depressed than those with a single pain complaint. Number of pain conditions reported was a better predictor of major depression than pain severity or pain persistence (16). Von Korff and colleagues developed a four-level scale for grading chronic pain severity based on pain disability and pain intensity: (a) low disability and low intensity; (b) low disability and high intensity; (c) high disability, moderately limiting; and (d) high disability, severely limiting. Depression, use of opioid analgesics, and doctor visits all increased as chronic pain grade increased (17). Engel and colleagues showed that depression was associated with high total health care costs, but not high back pain costs among health maintenance organization patients with back pain (18). When dysfunctional primary care back pain patients are studied for a year, those whose back pain improves also show improvement of depressive symptoms to normal levels (19).

These epidemiologic studies provide solid evidence for a strong association between chronic pain and depression, but do not address whether chronic pain causes depression or depression causes chronic pain. As indicated previously, this question has more importance in medicolegal contexts than clinical contexts. Because it is a perennial question, however, some attempt to answer it should be made. Prospective studies of patients with chronic musculoskeletal pain have suggested that chronic pain can cause depression (20), that depression can cause chronic pain (21), and that they exist in a mutually reinforcing relationship (22).

One fact often raised to support the idea that pain causes depression is that the current depressive episode often began after the onset of the pain problem. The majority of studies appears to support this contention (23). However, it has been documented that many patients with chronic pain (especially those disabled patients seen in pain clinics) have often had episodes of depression that predated their pain problem by years (24). This has led some investigators to propose that there may exist a common trait of susceptibility to dysphoric physical symptoms (including pain) and to negative psychological symptoms (including anxiety and depression). They conclude that “pain and psychological illness should be viewed as having reciprocal psychological and behavioral effects involving both processes of illness expression and adaptation” (25).

Pain and Depression: Mechanisms of Association

Beyond documenting the association of chronic pain and depression lies the question concerning mechanisms by which they may interact. Biological, psychological, and social mechanisms have been proposed to explain the concurrence of chronic pain and depression.

Biological Theories

Pain Sensitivity. It is well documented that patients with major depression, or even depressive symptoms, have more pain complaints that those without depression. Studies have shown that 30% to 60% of depressed patients complain of pain (26). These findings raise the possibility that depressed patients may have a greater sensitivity to noxious stimuli. In other words, depressed patients may have a reduced pain threshold. Although this theory appeared confirmed in an early study (27), it has been discounted repeatedly in more recent studies. Pain threshold to both thermal and electrical stimuli has been found to be elevated in depressed patients by multiple investigators (28). Sensitivity to nonnoxious thermal stimuli appears unaltered or slightly reduced (29). This diminished sensitivity does not appear to be caused by a general decrease in reaction time in depressed patients. Although depressed patients have been reported to have high plasma and cerebrospinal fluid endorphin levels, this decreased sensitivity to noxious stimuli is not reversed by naloxone (30). Thus, the stoic response of depressed patients to noxious stimuli

remains unexplained by known psychophysiologic mechanisms. It remains an intriguing and well-confirmed anomaly in the research linking pain and depression.

Biogenic Amines. The highly variable relationship between injury severity and pain severity has been known since Henry Beecher's studies of the soldiers at Anzio beach in World War II. Since the 1970s, great strides have been made in identifying the central nervous system mechanisms of endogenous pain modulation. Opioid and nonopioid branches to this system have been identified (see Chapter 4). Stimulation of the rostral ventromedial medulla or the dorsolateral pontine tegmentum produces behavioral analgesia in animals and inhibition of spinal pain transmission. The rostral ventromedial medulla is the principal source of serotonergic neurons that project to the spinal dorsal horn. The dorsolateral pontine tegmentum is the major source of noradrenergic neurons that project to the dorsal horn. Both neurotransmitters inhibit nociceptive dorsal horn neurons when locally applied (31).

Antidepressants Associated with Analgesia Enhance Serotonergic and Noradrenergic Neurotransmission. That antidepressants associated with analgesia enhance serotonergic and noradrenergic neurotransmission has been hypothesized to be responsible for both the antidepressant and analgesic effects of antidepressants (see Chapter 85). The interdependence of the opioid and nonopioid systems has been suggested by studies that show enhanced opioid analgesia in the presence of antidepressant treatment (32) and decreased opioid analgesia after serotonin and norepinephrine depletion (33). Therefore, it appears that biogenic amines play a critical role in endogenous pain modulation. To the extent that depletion or impaired function of amines such as serotonin and norepinephrine occurs in depression, this may contribute to the pain experienced and reported by those with major depression. It is not clear why this is not also manifested as increased sensitivity to external noxious stimuli.

Sleep Disturbance. Depression produces well-documented disturbances to sleep architecture. Polysomnographic recordings have documented reduced slow wave sleep, early onset of the first period of rapid eye movement (REM) sleep, and increased phasic REM sleep in patients with major depression (34). Sleep continuity disturbances and increased phasic REM sleep tend to normalize with depression remission, even with psychotherapeutic treatment. However, reduction of REM latency and decreased slow wave sleep tend to persist despite clinical recovery. Thus, there appear to be *state* and *trait* elements to the sleep disturbance associated with depression.

Some studies have demonstrated that sleep disturbance can cause chronic pain. The best studies have investigated the association of sleep disruption and fibromyalgia. Moldovsky and colleagues produced fibromyalgia-type symptoms in volunteers by depriving them of stage 4 slow wave sleep (35). In another study, however, those deprived of REM sleep did not develop these symptoms (36). Tricyclic antidepressants (alone or in combination with SSRIs) have been shown effective for fibromyalgia, even in the absence of a full depressive syndrome, perhaps because of restoration of sleep continuity.

Psychological Theories

Psychodynamic Theory. In classic psychoanalytic theory (37), depression is postulated to be derived from anger unconsciously turned inward, excessive dependence on others for self-esteem, and feelings of helplessness in achieving one's goals. Some have suggested that the depression in some chronic pain patients is a manifestation of a personality style that draws from early developmental conflicts of guilt, anger, and masochism (38,39). From this perspective, chronic pain may be a symptom of depressive disorder (40).

Psychoanalytic theory stresses the fundamental parallelism between mental and physical pain and the possible displacement from the former to the latter. Intrapsychic links between pain and depression suggest that pain may function as a *hysterical* or conversion symptom that may prevent the breakthrough of more severe depression. These intrapsychic links largely correspond with the dynamics of *pain proneness* that were originally described by Engel (41) and, in a further elaboration, connected with the concept of *masked depression* by Blumer and Heilbronn.

Blumer and Heilbronn (38) proposed a new psychological disorder, the “pain-prone” disorder, building on Engel's (41) notion of the pain-prone patient. In this view, pain should be considered as a variant of depressive disease. The central explanation is unconscious core conflicts. Core issues include “strong needs to be accepted and to depend on others, as well as marked needs to receive affection and to be cared for.”

Pain in the absence of organic pathology is considered by Blumer and Heilbronn (38) to be a *depressive spectrum disorder*. According to this model, pain and depression are viewed as manifestations of a single, common disease process. Specifically, the pain-prone disorder is viewed as a masked “depressive equivalent . . . the prime expression of a muted depressive state.” No empiric research has supported the psychoanalytic formulation as presented by Blumer and Heilbronn (42,43).

Behavioral (Operant Conditioning) Theory. The behavioral model of depression concentrates on the most obvious symptom of depression, the motivational deficit characterized by a reduction in active behavior. A central feature of the behavioral model is response-contingent reinforcement (i.e., the responses from significant others to the individual's behavior). From this perspective, depressive behavior and depression are associated with low rates of positive reinforcement from the environment. Lack of positive reinforcement leads to a decrease in the frequency of the individual engaging in these behaviors and ultimately, they may be extinguished completely. These low rates of reinforcement may occur because (a) positive reinforcers in the environment may become less available, or aversive events in the environment may have become more prevalent; (b) the positive effect of previous reinforcers may have declined, or the negative impact of aversive events may have increased; or (c) the individual may lack the skills either to attain the available positive reinforcers or to cope with aversive aspects of the environment. When individuals experience low rates of positive reinforcement, they reduce the performance of those behaviors, unless they are self-reinforcing. The reduction of behavior decreases further opportunities to receive positive reinforcement.

In the case of chronic pain, the individual may reduce his or her behavior because of physical impairments or because of fear of additional pain or further injury. Thus, by the restriction in behavior and social contacts, chronic pain patients may reduce the opportunity to achieve positive reinforcement and to engage in previously rewarding activities and consequently become depressed.

Cognitive Theory. According to Beck (44), people may be vulnerable to depression because, from an early age, they have possessed negatively biased conceptualizations (schemas) of themselves and their experiences. When they are challenged by stressful life events, these schema become activated, which in turn elicits negative thoughts about themselves, the world, and the future (the *negative cognitive triad*).

In depressed patients, Beck suggests that the cognitive triad serves as a filter for incoming information. This filter creates a negative bias that serves to put a pessimistic light on information and reinforces the depressed state. It also creates low expectations about their ability and thus may lead to lack of effort. Moreover, these people tend to discount their performance, underestimating their accomplishments.

Beck's (44) cognitive theory of depression emphasizes the importance of peoples' appraisal processes. In particular, it is believed that depressed persons show faulty information processing reflected by errors of logic. Through these cognitive errors (collectively referred to as *cognitive distortions*), depressed persons systematically misinterpret or distort the meaning of events so as to consistently construe themselves, their world, and their experiences in a negative way (the negative cognitive triad). According to this perspective, differences in cognitive errors and cognitive distortions, in general, should differentiate depressed and nondepressed patients.

Cognitive-Behavioral Perspective. The cognitive-behavioral perspective is based on five central assumptions: (a) People are active processors of information and not passive reactors. They attempt to make sense of information and determine what constitutes positive reinforcers. (b) Thoughts (e.g., appraisals, expectancies, beliefs) can elicit and influence mood, affect physiologic processes, have social consequences, and serve as impetuses for behavior; conversely, mood, physiology, environmental factors, and behavior can influence the nature and content of thought processes. (c) Behavior is reciprocally determined by both the individual and environmental factors. (d) People can learn more adaptive ways of thinking, feeling, and behaving. (e) Individuals should be active collaborative agents in changing their maladaptive thoughts, feelings, and behaviors (45). From the cognitive-behavioral model, the way in which one thinks about pain and behaves in response to pain affects the extent of depression experienced. Like Beck's cognitive theory, its essential difference from the purely behavioral model is its view of patients as active interpreters of their environment.

Depression in chronic pain patients is postulated to result from patients' interpretations of the meaning and effect of their symptoms and their inability to exert any control over their symptoms. It is only when patients interpret their pain as interfering with important life activities and believe that they (or anyone) can do little to control the symptoms that they become depressed (i.e., they become depressed when they feel helpless and hopeless to exert any control, overwhelmed by the disruption of their lives, and unable to attain significant positive reinforcement from previous activities) (22). Thus, the cognitive-behavioral approach integrates the principles of operant conditioning and behavioral techniques with the emphasis of cognitive theory on the patients' appraisals, beliefs, and attributions (46).

Sociologic Theories

Traditional and industrial societies appear to hold individuals less responsible for somatic symptoms than psychological symptoms. This difference may be especially prominent in modern Western biomedicine, in which symptom complexes are validated or invalidated through their correspondence with objective disease criteria (47). A somatic “idiom of distress” therefore becomes the favored means for communicating distress of any origin that is overwhelming or disabling (48). In many cultures, pain is a more acceptable reason for disability than depression. Therefore, cultural incentives exist for translation of depression into pain. Because depressed patients have many physical symptoms, these can become the focus of clinical communication and concern. Giving patients with chronic pain permission to talk of distress in the clinical setting, using nonsomatic terms, can facilitate treatment as long as they do not feel that somatic elements of their problem are being neglected or discounted.

Depression Treatment

Pharmacologic Agents

Antidepressant medication can effectively treat depression in the presence of chronic pain. When depression accompanies chronic pain, as when it accompanies other chronic medical disorders, there may be some extra hurdles for depression treatment to overcome. These include aversive physical symptoms, severe deactivation, vocational dysfunction, marital conflict, social isolation, and concurrent medications. Comprehensive assessment of these issues and formulation of a treatment plan that takes them into account increase the likelihood of successful depression treatment in the chronic pain patient. When antidepressant treatment is suggested, patients often respond that their depression will resolve when the pain gets better. This may be true. However, depression is often more accessible to treatment than an entrenched and multidetermined pain problem. If depression can be relieved, many other aspects of rehabilitation, such as physical therapy, are often much more easily accomplished. Pain often subsides with improvement in depressive symptoms.

All currently marketed antidepressants are equally effective for the treatment of depression. Whatever differences may exist among antidepressants in efficacy for neuropathic pain do not appear to affect their ability to treat depression. Given the lack of greater efficacy of any one antidepressant compared with another, medications should be selected based on their side effects.

The clinical art of depression treatment for those with chronic pain consists of establishing a solid therapeutic alliance around the problem of depression and finding a medication regimen with a side-effect profile that the patient can tolerate. Because patients with chronic pain can be vigilant and catastrophic thinking about somatic symptoms, care must be taken to educate them about antidepressant side effects. Sometimes it becomes necessary to initiate an antidepressant regimen at the lower doses used for geriatric patients to ease habituation to side effects. The SSRIs (SSRIs available in the United States include fluoxetine, fluvoxamine, sertraline, and paroxetine) have become the most popular antidepressants because of their favorable side-effect profiles. Bupropion and venlafaxine are useful medications for those who do not respond to the SSRIs. Nefazodone is a useful alternative for patients who have problems with agitation or insomnia on the SSRIs. More detailed information is available in one of the standard psychopharmacology manuals (49,50). A number of case reports have described relief of chronic pain in patients with treatment-resistant depression using electroconvulsive therapy (51); however, no carefully controlled studies demonstrate the effectiveness of electroconvulsive therapy for treatment of chronic pain.

Chronic pain is frequently associated with insomnia and anxiety. It is, therefore, common that patients are treated with benzodiazepines or other sedatives (e.g., the muscle relaxers). Some patients begin taking these medications during the acute phase of the pain problem and then continue to take them for many months or years. Assessing chronic pain patients who take benzodiazepines for depression is important. These medications mask some symptoms of depression (e.g., initial insomnia, agitation), but they are not adequate treatments for depression. Indeed, dangerous levels of depression can develop under the cover of benzodiazepines. It has been suggested that benzodiazepines can induce depression with chronic use, but the evidence for this is not strong (52). More important is the masking of depression by benzodiazepines.

Nearly all patients with chronic pain should be tapered off benzodiazepines. Few conditions exist for which chronic benzodiazepines are the treatment of choice (53). The treatment of choice for chronic anxiety disorders, which are almost always accompanied by depressive symptoms, is antidepressant medication (54). Buspirone (a 5-HT_{1a} partial agonist) is marketed as an anxiolytic, but is more similar to the antidepressants in its pharmacology and side-effect profile. It is a reasonable alternative to the benzodiazepines for the treatment of chronic anxiety, particularly for those who experience agitation on the antidepressants.

Psychotherapy

Psychodynamic Psychotherapy. In general, psychodynamic theory emphasizes the long-term predisposition to depression, rather than the losses that occur in the short term. Treatment of depression from the classical psychoanalytic perspective tries to help the patient achieve insights into the repressed conflict and often encourages outward release of hostility turned inward. In the most general terms, the goal of therapy is to uncover latent motivations for the patient's depression. The psychodynamic approach to the depressed individual with chronic pain emphasizes the importance of individual differences in patients based on their developmental history, intrapsychic conflicts, interpersonal difficulties, and the subsequent failure to adapt to chronic illness. Patients' premorbid characteristics are hypothesized to color their adaptation to their current situation and affect their vulnerability to depression.

Psychodynamic therapy emphasizes the need for patients to address unconscious conflicts that may contribute to and maintain the depression and makes use of the therapeutic relationship, assuming that the patient will transfer or project his or her feelings onto the therapist (55). This approach can be contrasted with treatment based on operant conditioning, in which it is assumed that the basic principles of learning apply to all individuals and the environmental contingencies of reinforcement can influence the reports of pain, distress, and suffering (see Chapter 88).

Behavioral Model. As noted, the behavioral model of depression concentrates on the reduction in active behavior that is a central feature of depression. The focus of treatment for depression is on the shaping of behavior through the use of graded task assignments and response-contingent reinforcement. Depressed individuals are encouraged to engage in more activities and to behave in ways that are likely to be regarded more positively by others. In some instances, it is believed that depressed patients are deficient in certain skills necessary to achieve positive reinforcement. Social skills training may also be included when the therapist determines that the patient is deficient in specific skills (e.g., communication skills). Attention may also be given to assisting the patient in planning pleasant events that the patient will find reinforcing.

Cognitive Model. From the cognitive perspective, therapy is based on the rationale that an individual's affect and behavior are largely determined by the ways in which he or she construes the world and the therapeutic techniques were designed to identify, test, and correct distorted conceptualizations and the dysfunctional beliefs (schemas) underlying these cognitions. Beck's (44) therapy for depression is based on the assumption that the affected people engage in faulty information processing and reasoning and subscribe to schema that are self-defeating. In particular, depressed people are subject to the negative cognitive triad, in which they have feelings of pessimistic helplessness about themselves, the world, and their future. The aim of the cognitive therapist is to identify and then help patients to correct these distorted ideas and also to improve their information processing and reasoning. In contrast to psychodynamic therapy, the focus is on the here and now. Thus, attention to the origin of dysfunctional schemas in the cognitive model is limited.

The therapeutic procedures are highly structured and time limited and begin with the recognition of the connections between cognitions and affect, careful recording of these connections, collection of evidence for and against the ideas, followed by substitution of more adaptive and realistic interpretations. The cognitive approach is most frequently combined with behavioral techniques to treat patients with chronic pain, even though some debate exists about the compatibility of these approaches (44,45).

Cognitive-Behavioral Model. No one cognitive-behavioral model exists, but rather sets of models that share a perspective and incorporate some common features, namely: (a) an interest in the nature and modification of patients' thoughts, feelings, and beliefs, as well as behaviors; and (b) some commitment to behavior therapy procedures in promoting change (e.g., graded practice, use of homework, training in relaxation, coping skills training, problem solving, and relapse prevention) (46).

Depressed people may focus attention selectively on and become preoccupied with somatic symptoms and their potentially ominous significance for their health and future. They may view themselves as helpless and their situation as hopeless and beyond their control. To break this vicious circle, the cognitive-behavioral therapist applies a comprehensive approach to treatment that combines physical, psychological, behavioral, and social interventions. Coping skills training, problem-solving strategies, communications skills training, and directing patients to attend to their appraisals, interpretations, and beliefs are commonly used techniques (see Chapter

89).

The cognitive-behavioral therapist attempts to assist patients to try new behaviors and to adopt more adaptive modes of thinking. Alterations in behavior become information that the patients are encouraged to use as the basis for changing their views of their situation and themselves from being helpless, hopeless, and out of their control to being resourceful and capable of exerting at least some control over their plights. Changing the cognitive schema by cognitive and behavioral means is designed to result in different interpretations of information about themselves and their futures. Thus, changing behaviors and thoughts may be reciprocally related and mutually reinforcing. Neither attending exclusively to behavior, as in the behavioral model, nor only attending to patients' thinking, as in the cognitive model, is adequate to alleviate depression (45). The cognitive-behavioral approach has become a central component for treating depression in many multidisciplinary pain rehabilitation and functional restoration programs.

All of the psychological therapies emphasize patients' active role in alleviating depression. In contrast to the psychodynamic model, in which the therapist plays a relatively passive role, in behavioral, cognitive, and cognitive-behavioral therapies, the therapist takes an active, directive role, attempting to guide patients into changing their behavior and reorganizing their thinking and actions. The behavioral, cognitive, and cognitive-behavioral therapies are all centered in the present, compared with psychodynamic therapy, which focuses on the past.

ANXIETY DISORDERS

It is not unusual for patients with symptoms of pain to be anxious and worried. This is especially true when the symptoms are unexplained, as is often the case for chronic pain syndromes. For example, in a large-scale, multicenter study of fibromyalgia patients, between 44% and 51% of patients indicated that they were anxious (56). Anxiety and concern about symptoms, however, are not synonymous with a psychiatric diagnosis of an anxiety disorder. When anxiety is debilitating, it may meet criteria for an anxiety disorder. Anxiety disorders almost always accompany mood disorders, so clinicians should remain alert to the possibility of a mood disorder when patients complain of severe anxiety.

Generalized Anxiety Disorder

When patients with chronic pain do suffer from an anxiety disorder, it is rare that this is their sole psychiatric diagnosis. Most pain patients with chronic anxiety also meet criteria for either major depression or dysthymia. In these cases, treatment should be directed toward the mood disorder. With successful treatment of the mood disorder, the anxiety should be relieved as well. Benzodiazepines should almost always be avoided, as discussed previously.

Panic Disorder

Panic disorder is a common, disabling psychiatric illness associated with high medical service use and multiple medically unexplained symptoms. The diagnosis of panic disorder requires recurrent, unexpected panic attacks (Table 26-2) followed by at least 1 month of worry about having another panic attack, the implications or consequences of the panic attacks, or behavioral changes related to the attacks. These attacks should not be the direct physiologic consequence of a substance or other medical condition. The panic attacks should not be better accounted for by another mental disorder, such as posttraumatic stress disorder (PTSD; see following discussion) or obsessive-compulsive disorder. At least two unexpected attacks are required for the diagnosis, although most patients have many more.

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Depersonalization (feelings of unreality) or derealization (being detached from oneself)
10. Fear of losing control or going crazy
11. Fear of dying
12. Paresthesias (numbness or tingling sensations)
13. Chills or hot flushes
14. Persistent concern about having additional attacks
15. Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
16. A significant change in behavior related to attacks

From *Diagnostic and Statistical Manual*. 4th ed. Washington, DC: American Psychiatric Association, 1994:395, with permission.

TABLE 26-2. *Diagnostic and Statistical Manual*, Fourth Edition, Criteria for Panic Attack

One of the most common problems with panic disorder is the fear of an undiagnosed, life-threatening illness. Patients with panic disorder can receive extensive medical testing and treatment for their somatic symptoms before the diagnosis of panic disorder is made and appropriate treatment initiated.

Epidemiology

Lifetime prevalence of panic disorder throughout the world is estimated to be 1.5% to 3.5%. One-year prevalence rates are from 1% to 2%. Panic disorder is two to three times more common in women than in men. Age of onset is variable, but most patients typically start between late adolescence and the mid-30s. Of all common mental disorders in the primary care setting, panic disorder is most likely to produce moderate to severe occupational dysfunction and physical disability (57). It was also associated with the greatest number of disability days in the past month.

The most common complication of panic disorder is agoraphobia, or fear of public places. Patients with panic disorder learn to fear places where escape might be difficult or help not available in case they have an attack. One-half to two-thirds of patients with panic disorder also suffer from major depression. These patients are the most disabled panic disorder patients. The differential diagnosis of patients presenting with panic symptoms in the medical setting includes thyroid, parathyroid, adrenal, and vestibular dysfunction, seizure disorders, cardiac arrhythmias, and drug intoxication or withdrawal. Patients with panic disorder typically present in the medical setting with cardiologic, gastrointestinal, or neurologic complaints. These include chest pain, abdominal pain, and headaches (58).

Chest pain is one of the most common complaints presented to primary care physicians, but a specific medical etiology is identified in only 10% to 20% of cases. From 43% to 61% of patients who have normal coronary arteries at angiography and 16% to 25% of patients presenting to emergency rooms with chest pain have panic disorder. A number of these patients eventually receive the diagnoses of vasospastic angina, costochondritis, esophageal dysmotility, or mitral valve prolapse. High rates of psychiatric disorders have been found in some of these groups as well (59). Many of these patients remain symptomatic and disabled 1 year later despite reassurance concerning coronary artery disease (60).

Patients with documented coronary disease also have elevated rates of panic disorder. A number of studies have found nearly identical rates of panic disorder in chest pain patients with and without coronary disease. Increased mortality has been noted in those with anxiety and coronary disease. These data point to the importance of remaining alert to both medical and psychiatric diagnoses in those presenting with chest pain. Patients with unexplained chest pain who were given low-dose imipramine (50 mg per day) reported significant reductions in pain regardless of whether they had increased anxiety symptoms or another psychiatric disorder. This has been postulated to be caused by a *visceral analgesic effect* of imipramine (61). It is possible, however, that imipramine was treating subthreshold anxiety and depressive symptoms, because 63% of the sample had a history of these disorders at some point in their lives.

Approximately 11% of primary care patients present the problem of abdominal pain to their physician each year. Less than one- quarter of these complaints are associated with a definite physical diagnosis in the following year. Among the most common reasons for abdominal pain is irritable bowel syndrome. It is estimated that irritable bowel syndrome accounts for 20% to 52% of all referrals to gastroenterologists (see Chapter 66). Various studies have found that 54% to 74% of these patients with irritable bowel syndrome have associated psychiatric disorders. Walker and colleagues determined that patients with irritable bowel syndrome have much higher current (28% versus 3%) and lifetime (41% versus 25%) rates of panic disorder than a comparison group with inflammatory bowel disease (62). This suggests that the psychiatric disorder was not simply a reaction to the abdominal distress.

Among 10,000 persons assessed in a community survey who consulted their physicians for headache, 15% of female and 13% of male subjects had a history of panic

disorder. Further studies have suggested that migraine headache is most strongly associated with panic attacks (63). Often, anxiety symptoms precede the onset of the headaches, whereas depressive symptoms often have their onset after the headaches. Some authors have suggested that a common predisposition exists with headaches (especially migraines and chronic daily headache), anxiety disorders, and major depression.

Treatment

Psychopharmacologic and psychotherapeutic treatments for panic disorder have been proven effective. The American Psychiatric Association has released a *Practice Guideline for the Treatment of Patients with Panic Disorder* (64). Panic-focused cognitive- behavioral therapy and four classes of medications (SSRIs, tricyclic antidepressants, monoamine oxidase inhibitors, and benzodiazepines) have demonstrated effectiveness. These drugs may be used in combination with cognitive-behavioral therapy. Panic-specific cognitive-behavioral therapy includes psychoeducation, continuous panic monitoring, development of anxiety management skills, cognitive restructuring, and *in vivo* exposure. As discussed previously with depression, the SSRIs likely are the easiest antidepressants to use for panic disorder. However, starting doses should be halved to avoid any initial exacerbation of agitation or anxiety. Tricyclic antidepressants and monoamine oxidase inhibitors are now reserved for those patients who do not respond to the SSRIs. Benzodiazepines should only be used for early symptom control in conjunction with one of the other classes of effective medication.

Posttraumatic Stress Disorder

Diagnosis

At the time of initial physical trauma, patients who develop chronic pain may also experience overwhelming psychological trauma. George Crile, a surgeon and experimental physiologist, laid the foundation for our modern concept of psychological trauma. He suggested that fear is the memory of pain. This fear holds an adaptive advantage in directing individuals to anticipate and avoid injury. Freud added anxiety to our modern conceptualization. Anxiety is the capacity to imagine pain and not merely to remember it. In other words, anxiety is memory of pain set loose (65).

After direct personal exposure to an extreme traumatic event, some individuals develop a syndrome that includes reexperiencing the event, avoidance of stimuli associated with the event, and persistent heightened arousal. PTSD was originally described after exposure to military combat, but is now recognized to occur after sexual or physical assault, natural disasters, accidents, life- threatening illnesses, and other events that induce feelings of intense fear, hopelessness, or horror. Persons may develop the disorder after experiencing or just witnessing these events. DSM-IV diagnostic criteria are shown in Table 26-3.

TABLE 26-3. *Diagnostic and Statistical Manual*, Fourth Edition, Diagnostic Criteria for Posttraumatic Stress Disorder

Epidemiology

Up to 80% of Vietnam veterans with PTSD report chronic pain in limbs, back, torso, or head (66). Increased physical symptoms, including muscle aches and back pain, are also more common in Gulf War veterans with PTSD than in those without PTSD (67). The prevalence of PTSD in medical populations has been shown to be quite high. For example, a number of patients presenting at medical clinics with myocardial infarctions (68) and cancer (69,70) often meet the criteria for PTSD. Averaging the prevalence rates of PTSD across a number of studies reveals that after motor vehicle accidents sufficient to require medical attention, 29.5% of patients meet the criteria for PTSD (71). For more than one-half of these patients, the symptoms resolve within 6 months. In one study, 15% of idiopathic facial pain patients seeking treatment were found to have PTSD (72). In another study, 21% of fibromyalgia patients were found to have PTSD (73). Case reports have associated reflex sympathetic dystrophy (complex regional pain syndrome) with PTSD. Other studies suggest that 50% to 100% of patients presenting at pain treatment centers meet the diagnostic criteria for PTSD (73,74). Pain patients with PTSD have been shown to have more pain and affective distress than those without PTSD (75), so it is not surprising that PTSD rates among pain patients increase as treatment settings become more specialized.

Pain and Posttraumatic Stress Disorder: Mechanisms of Association

The relationship between pain and PTSD is multifaceted, as suggested by the early thinking by Crile and Freud discussed previously. Pain and PTSD may result from a traumatic event. Sometimes acute pain can constitute the traumatic event, as described in a case of traumatic eye enucleation (76). PTSD also appears to permit induction of an opioid-mediated stress-induced analgesia. PTSD- related stimuli can result in a naloxone-reversible decreased sensitivity to noxious stimuli in affected individuals (77). Much research remains to be done on the relative contributions of physical trauma and psychological trauma to chronic pain problems.

Treatment

It is best to institute treatment for PTSD as close in time to the trauma as possible. Acute crisis intervention may reduce the development of chronic PTSD and other complications, including, possibly, chronic pain. This treatment should establish support, promote acceptance of what happened, provide education and information about symptoms, and attend to general health needs. Beyond the acute phase, the cognitive-behavioral therapy treatment described for panic disorder earlier has been shown to be effective with PTSD as well. Stress-inoculation training, implosive therapy, and systematic desensitization have also been reported to have some efficacy (71,78). Medications are rarely adequate as the sole treatment for PTSD. Controlled trials of tricyclic antidepressants, SSRIs, and monoamine oxidase inhibitors have demonstrated some benefit by 8 weeks at reducing core intrusive features. These benefits appear to be in addition to the antidepressant and antianxiety effects of these medications (79).

SCHIZOPHRENIA

Schizophrenia is a chronic mental disorder characterized by delusions, hallucinations, disorganized speech and behavior, and negative symptoms (e.g., flattening of affect and lack of volition). At least 6 months of continuous symptoms are required for the diagnosis. Most individuals are affected for many years with exacerbations and partial remissions. Onset typically occurs in late teens to early 30s. Lifetime prevalence is estimated at 0.5% to 1.0% throughout the world.

Patients with schizophrenia appear to complain of pain less frequently than patients with other psychiatric disorders. This can pose problems in the diagnosis of acute medical illnesses that are usually painful, such as peritonitis (80). Numerous studies have demonstrated decreased sensitivity to noxious stimuli in schizophrenic patients, although the precise character of this insensitivity and its mechanism remain to be elucidated (81). Chronic pain problems appear to be rare in schizophrenics. Studies of psychiatric diagnoses in patients with chronic pain have identified few patients with schizophrenia. Two schizophrenic patients were identified in a study of atypical facial pain patients (82). In another study, 78 schizophrenics were documented to have 29 current pain complaints. Sixteen of these were thought to be of likely *psychological origin* (83). How this was determined is not clear. In fact, it is unclear how any pain could be established to be delusional.

Schizophrenics commonly have delusions of persecution, passivity, and somatic damage, but pain is rarely a part of these delusions, even when it is an expected part of the delusional illness (e.g., *dead bowels*). The existence of delusional pain is therefore in doubt. This is important because delusional pain is the prototypical case

of psychogenic pain. If no delusional pain exists, then there may be no purely psychogenic pain.

Dementia

Dementia is characterized by the gradual onset of multiple cognitive deficits, including memory impairment and either aphasia, apraxia, agnosia, or disturbances in executive functioning. The deficits cannot occur exclusively in the course of a delirium. The prevalence of dementia increases exponentially with age, from 1% at age 65 years to 25% by age 85 years. Our understanding of clinical pain in patients with dementia is generally derived from patients with mild to moderate dementia who remain communicative (84). Although it has been hypothesized that demented patients may complain of pain to mask failures caused by dementia, only case reports exist to support this theory. Large studies of institutionalized elderly have generally found an inverse relationship between cognitive impairment and reported level of pain (85). These differences persisted after controlling for functional status and medical illness severity. Dementia appears to be most important in the clinical care of pain because it impairs the ability of patients to communicate pain and therefore the capacity of caregivers to adequately respond to pain.

SUBSTANCE ABUSE

Diagnosis

Diagnosis of substance abuse and substance dependence in patients with chronic pain is controversial because it is difficult to achieve consensus on what constitutes a maladaptive pattern of substance use. DSM-IV distinguishes between substance dependence and substance abuse. The essential feature of substance dependence is continued use of a substance despite a cluster of cognitive, behavioral, and physiologic problems. It is characterized by tolerance, withdrawal, and compulsive drug-taking behavior. DSM-IV diagnostic criteria are presented in Table 26-4.

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. tolerance, as defined by either of the following:
   (a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
   (b) Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
   (a) The characteristic withdrawal syndrome for the substance (refer to criteria A and B of the criteria sets for Withdrawal from the specific substances).
   (b) The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain smoking), or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Specify if:

With physiologic dependence: evidence of tolerance or withdrawal (i.e., either item 1 or 2 is present)

Without physiologic dependence: no evidence of tolerance or withdrawal (i.e., neither item 1 nor 2 is present)

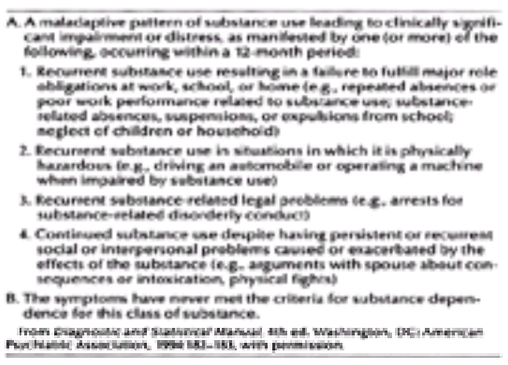
From Diagnostic and Statistical Manual, 4th ed. Washington, DC: American Psychiatric Association, 1994:181, with permission.

TABLE 26-4. *Diagnostic and Statistical Manual*, Fourth Edition, Criteria for Substance Dependence

Traditionally, opioids have been considered appropriate for terminal cancer pain when tolerance, dependence, and dose escalation are limited in their importance by the impending death of the patient. But they have been considered by many who treat chronic pain as problematic for the chronic noncancer pain patient in cases in which long-term function is an essential issue. A large percentage of patients referred to multidisciplinary pain centers report taking opioids at the time of assessment. After treatment, the majority of these patients reports significantly reduced pain concurrent with elimination of opioid medication (86,87). Portenoy and others have argued forcefully that chronic opioid therapy can be appropriate and beneficial in some patients with chronic noncancer pain (88). One of the current unanswered questions is what factors characterize those patients who are likely to benefit from long-term opioids without problems of addiction, tolerance, or increased disability. To date there have been no long- term, double-blind studies that help to select the group for which long-term opioids are beneficial.

In a series of 20 patients with chronic noncancer pain and substance abuse, Dunbar and Katz found that those with alcohol abuse alone, and especially those with a stable family and those active in Alcoholics Anonymous, were least likely to abuse opioids (89). Others have suggested that the label of substance abuse may deny appropriate analgesia to some patients. A study by Breitbart and colleagues of ambulatory patients with acquired immunodeficiency syndrome suggests that a past history of substance abuse may lead to inadequate analgesia for current pain problems (90). These concerns about underuse of opioids must be weighed against the personal and social costs of impaired function caused by substance abuse and dependence in patients with chronic noncancer pain. A number of guidelines have been proposed to assist the physician in prescribing opioids for chronic pain patients (91). In a joint statement, the American Academy of Pain Medicine and the American Pain Society have provided a balanced approach to the issue of prescribing opioids on a long-term basis for chronic, noncancer pain patients (86,87). The issues associated with prescribing opioids are discussed in more detail in Chapter 84.

The essential feature of substance abuse is a maladaptive pattern of substance use characterized by recurrent and significant adverse consequences. These include impaired role function, use in physically hazardous situations, and legal problems. It is distinguished from substance dependence in that it does not require tolerance, dependence, or a compulsive pattern of use. DSM-IV criteria are presented in Table 26-5.



A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for substance dependence for this class of substance.

From Diagnostic and Statistical Manual, 4th ed. Washington, DC: American Psychiatric Association, 1994:183, with permission.

TABLE 26-5. *Diagnostic and Statistical Manual*, Fourth Edition, Criteria for Substance Abuse

Epidemiology

Prevalence rates for substance abuse in chronic pain patients are variable because of differences in definitions used and populations assessed. Studies have used the DSM-III-R criteria that are similar to those listed in Table 26-5. Chabal and colleagues assessed patients attending a pain clinic at a VA Medical Center using five criteria derived from DSM-III-R (92). Nineteen percent of clinic patients were on chronic opiates. Thirty-four percent met one criterion, and 27% met three criteria. They found no differences concerning histories of drug and alcohol abuse between those on opioids who did and who did not meet abuse criteria. Brown and colleagues compared primary care patients making repeated visits for back pain to a random sample of other patients in the clinic (93). Lifetime substance abuse rates were approximately 53% for both groups; current substance abuse rates were 23% for both groups. Substance abuse predated the onset of chronic pain in 77% of patients who met criteria for current substance abuse. Kouyanou and colleagues reported on patients attending pain clinics in South London (94). In this study, 70% of patients were on opioids, but DSM-III-R substance abuse or dependence was diagnosed in only 12%.

The studies cited previously suggest that substance abuse and dependence occur in a minority of chronic pain patients on opioids. They do not answer the more difficult question as to whether opioids are, on balance, beneficial treatment for these patients. Studies involving random assignment of patients with chronic pain to opioid treatment are necessary to answer the question of what patients, with what characteristics are able to obtain benefits (pain reduction and improvement of

function) from long-term opioids without developing deleterious effects.

Treatment

When a patient with chronic pain meets criteria for substance abuse or dependence, treatment for the substance abuse should precede rehabilitative chronic pain treatment. Actively substance-abusing patients do not have the frustration tolerance necessary to succeed at the difficult task of chronic pain rehabilitation. Details concerning substance abuse treatment are beyond the scope of this book. Readers are referred to some of the standard texts in this area (95). However, a few comments about the interface between pain treatment and substance abuse treatment are in order. Laws in the United States strongly distinguish between the prescription of opioids for the treatment of pain and for the treatment of addiction (96). All physicians are allowed to do the former; only specialized methadone centers are allowed to do the latter. Because both groups of patients may be maintained on methadone long term, it can be difficult to distinguish the purposes of the prescription. If a patient with chronic pain has a history of illicit drug use or substance abuse (opioid or otherwise), it is wise to obtain a consultation from an expert in substance abuse before prescribing opioid maintenance therapy.

SOMATOFORM DISORDERS, ILLNESS BEHAVIOR, AND SICK ROLE

Definitions

Sickness is a complicated psychological and social state that has been understood from a variety of perspectives over the years. We consider those of sick role, illness behavior, and somatoform disorder.

The concept of the *sick role* was first introduced by Talcott Parsons in 1951 (97) and was formulated more concretely 12 years later (98). The sick role is granted to an individual provided that he or she regards his or her condition as undesirable, and is not held responsible for it (i.e., under his or her control and able to be reversed voluntarily). If granted, the individual is allowed exemption from his or her usual obligations to a greater or lesser extent and is considered to be deserving of care and attention. Associated with the sick role are the obligations of seeking the advice and assistance of a person regarded as competent to diagnose and treat the condition and of cooperating with that person.

The basic concept of *illness behavior* was introduced by Mechanic and Volkart (99) and later fully formulated by Mechanic (100). Mechanic's concept of illness behavior complements the sick role, because it delineates the contribution of the patient to the role-granting process. Illness behavior was originally defined as the ways in which individuals differentially perceive, evaluate, and respond to their symptoms. This concept proved to be an extremely useful one, because it has facilitated the empiric study of behaviors that are of considerable importance to clinicians and other health care providers, as well as to the individual's family and society.

Although useful as it stands, health care providers find Mechanic's definition restrictive because it refers to *symptoms* as the focus of behavior, and consequently deemphasizes actions directed toward avoidance of the illness. A slightly modified definition describes illness behavior as “the ways in which individuals experience, perceive, evaluate and respond to their own health status.” This definition recognizes the possibility that a person may be concerned about illness in the absence of symptoms.

Illness behavior is a concept more easily applied to individual patients than sick role and has therefore seen more use in clinical settings. However, it is dependent on social definitions of what constitutes legitimate illness. Although medical science determines what qualifies as *disease* based on objective changes in anatomy and physiology, society determines what qualifies as illness. These often follow each other quite closely, but there can be interesting discrepancies. Essential hypertension is a disease usually without symptoms. It has taken a concerted educational effort on the part of the medical profession to convince the public that it is an illness that should be monitored and treated. Chronic fatigue syndrome and fibromyalgia are illnesses increasingly recognized and accepted by the public. Because the medical profession has not been able to identify objective changes in physiology with these illnesses, many physicians question whether they qualify as legitimate diseases. Physicians, insurance companies, and compensation systems can find themselves in disagreement with patients experiencing chronic pain about whether a legitimate disease or illness is causing the pain.

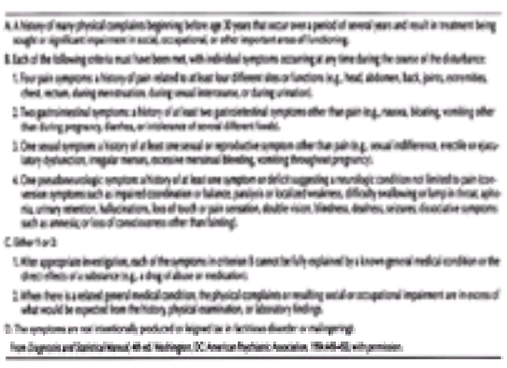
Pilowsky introduced the concept of *abnormal illness behavior* for those situations in which physician and patient disagree about the applicability of the sick role to the patient's condition (101). He contends that patients with truly abnormal illness behavior have extreme difficulty accepting the advice of any physician if it does not agree with their own appraisal of their health status. He cautions that misdiagnoses of abnormal illness behavior can occur when physician and patient do no share a common culture. We might add that it is also important to keep in mind the limitations of current diagnostic tests and disease criteria when diagnosing the patient's disagreement with his or her physician as pathologic.

SOMATIZATION DISORDER

Current psychiatric theory dictates diagnoses of somatoform disorders rather than abnormal illness behavior or misuse of the sick role. The essential feature of the somatoform disorders is the presence of physical symptoms that suggest a general medical condition but are not fully explained by a general medical condition. These symptoms must cause impairment in social and occupational functioning. The somatoform disorders are distinguished from factitious disorders and malingering in that the symptoms are not intentionally or voluntarily produced in the somatoform disorders.

Diagnosis

Somatization disorder is a chronic condition characterized by a pattern of multiple and recurrent somatic complaints resulting in medical treatment and impairment in role functioning, but not explained by a general medical condition. For this particular somatoform diagnosis, the somatic symptoms must be persistent and pervasive. These complaints must begin before 30 years of age and last for a period of years. Diagnostic criteria are displayed in Table 26-6.



A. A history of many physical complaints beginning before age 30 years that occur over a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning.

B. Each of the following criteria must have been met, with individual symptoms occurring at any time during the course of the disturbance:

1. Four pain symptoms: a history of pain related to at least four different sites or functions (e.g., head, abdomen, back, joints, extremities, chest, rectum, during menstruation, during sexual intercourse, or during urination).
2. Two gastrointestinal symptoms: a history of at least two gastrointestinal symptoms other than pain (e.g., nausea, bloating, vomiting other than during pregnancy, diarrhea, or intolerance of several different foods).
3. One sexual symptom: a history of at least one sexual or reproductive symptom other than pain (e.g., sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting throughout pregnancy).
4. One pseudoneurologic symptom: a history of at least one symptom or deficit suggesting a neurologic condition not limited to pain (conversion symptoms such as impaired coordination or balance, paralysis or localized weakness, difficulty swallowing or lump in throat, aphonia, urinary retention, hallucinations, loss of touch or pain sensation, double vision, blindness, deafness, seizures, dissociative symptoms such as amnesia, or loss of consciousness other than fainting).

C. Either 1 or 2:

1. After appropriate investigation, each of the symptoms in criterion B cannot be fully explained by a known general medical condition or the direct effects of a substance (e.g., a drug of abuse or medication).
2. When there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings.

D. The symptoms are not intentionally produced or feigned (as in factitious disorder or malingering).

From *Diagnostic and Statistical Manual*, 4th ed. Washington, DC: American Psychiatric Association, 1994:445–446; with permission.

TABLE 26-6. *Diagnostic and Statistical Manual*, Fourth Edition, Diagnostic Criteria for Somatization Disorder

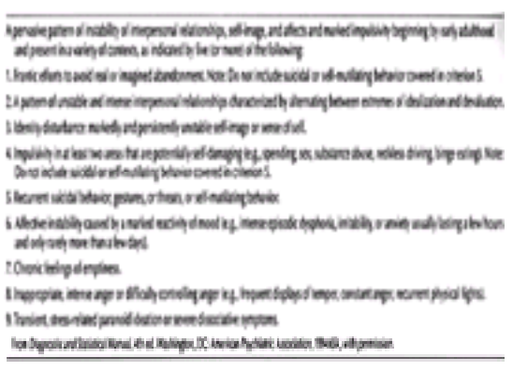
Many of the somatoform diagnoses, including somatization disorder, have their historic roots in the diagnosis of hysteria (102). The Egyptians first ascribed multiple unexplained somatic symptoms to the displacement of other organs by a wandering uterus. In the seventeenth century, Thomas Sydenham dissociated hysteria from the uterus and associated it with psychological disturbances. In 1859, Briquet described the multisymptomatic and protracted course of the illness in 430 Parisian patients. This description was taken up in the 1950s by investigators at Washington University in St. Louis (102). They described *Briquet's syndrome* as a multisymptomatic form of hysteria with 25 symptoms from 10 different symptom groups. By the publication in 1980 of DSM-III, the diagnosis had been streamlined to require 14 of 37 potential symptoms, and the name had been changed to *somatization disorder*. Through these changes, the essential feature of somatization disorder has remained multiple unexplained somatic symptoms producing disability and health care use. Somatization disorder must be distinguished from medical disorders producing multiple and scattered symptoms, such as multiple sclerosis or systemic lupus erythematosus. It must also be distinguished from panic disorder that also

produces multiple somatic symptoms but is a more acute and treatable psychiatric disorder.

Epidemiology

The prevalence of somatization disorder in the community has been reported to be between 0.13% and 0.4%, with the vast majority of cases occurring in women (103). Prevalence estimates in the primary care setting have ranged from 0.2% to 5.0%. Studies of patients referred to pain clinics have produced estimates from 8% to 12%. Although prevalence rates clearly increase when moving from community to primary care to tertiary care settings, somatization disorder patients remain in the clear minority in all settings. Unexplained somatic symptoms are a common problem in medical settings that extend far beyond the bounds of somatization disorder. Various attempts have been made to assess the prevalence of an abridged version of somatization disorder in primary care, requiring four to six unexplained symptoms (4.4% of patients) or three symptoms persistent over a 2-year period (8.2% of patients) (104). Even these abridged forms of somatization disorder are associated with increased rates of disability, health care use, and mood and anxiety disorders. Although the initial emphasis with Briquet's syndrome and somatization disorder was on a discrete, familial, even genetic, disorder, evidence suggests that somatization is a process that exists along a spectrum of severity (105). A large international study confirms that medically unexplained somatic symptoms are common, whereas full somatization disorder is quite rare (106). A great deal of confusion exists between somatization as a process and somatization as a disorder. Somatization as a process, meaning the somatic experience of distress, is ubiquitous (107). It accounts for the majority of symptoms presented to primary care physicians. It is most frequently associated with transient stressors (therefore time limited) or acute psychiatric disorders (which are treatable). Somatization disorder is a rare, chronic, and treatment-resistant condition that characterizes the most severely and chronically distressed individuals. When clinicians use the term *somatizer* to refer to a patient with unexplained symptoms, it is unclear whether they are implying the process or the disorder.

Although somatization disorder frequently occurs within families and has a genetic component, it also appears to have a strong association with childhood physical and sexual abuse (108). A significant percentage of patients who meet criteria for somatization disorder also meet criteria for borderline personality disorder (109). This has led some investigators to question the independence of these diagnoses and others to stress their common origin in severe childhood abuse. Borderline personality disorder is a severe, chronic pattern of chaotic and dysfunctional interpersonal relationships. Diagnostic criteria are presented in Table 26-7.



A pervasive pattern of instability of interpersonal relationships, self-image, and affects and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment. Note: Do not include suicidal or self-mutilating behavior covered in criterion 5.
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). Note: Do not include suicidal or self-mutilating behavior covered in criterion 5.
5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
6. Affective instability caused by a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

From Diagnostic and Statistical Manual, 4th ed. (Washington, DC: American Psychiatric Association, 1994), with permission.

TABLE 26-7. *Diagnostic and Statistical Manual*, Fourth Edition, Diagnostic Criteria for Borderline Personality Disorder

In a study of 200 patients with back pain attending a pain clinic, 51% of patients had some personality disorder and 15% had borderline personality disorder determined by structured psychiatric interview (110). This is a strikingly high prevalence of these disorders compared with other clinical populations. Some controversy exists about the validity of these diagnoses, especially as to whether they constitute a cause or effect of the chronic pain problem (111).

Treatment

Recognizing patients with somatization disorder is important, because they are among the most difficult patients to treat in the entire health care system. Above all, it is important to prevent iatrogenic damage to these patients through overly focused and invasive attempts to treat pain complaints. These patients are typically resistant to standard cognitive-behavioral treatment strategies used in chronic pain. They have extreme problems with trust and do not form therapeutic relationships easily. Any attempt to reframe somatic distress in emotional terms is likely to be experienced as an invalidation until a therapeutic alliance is well established. An adaptation of cognitive-behavioral therapy called *dialectical-behavioral therapy* has been shown effective for patients with borderline personality disorder, but has not been tested in patients with somatization disorder (112).

Psychotropic medications have highly unpredictable effects in this group (113). Any medications associated with tolerance and dependence, such as opioids and benzodiazepines, should be avoided, because they are often associated with clinical deterioration. Antidepressant medications also have unpredictable effects and should be prescribed only in collaboration with a psychiatrist. For patients with soft psychotic symptoms, such as depersonalization and derealization, low-dose antipsychotic medication may be of some benefit.

PAIN DISORDER

Diagnosis

In many prevalent pain syndromes (e.g., low back pain, headache, fibromyalgia), it is difficult to identify the tissue pathology giving rise to symptoms. When a somatic cause for pain cannot be identified, many clinicians begin to seek psychological causes. The identification of psychogenic pain is a difficult and perhaps impossible task. *Pain disorder* is the current psychiatric diagnosis that most closely corresponds to the diagnosis of psychogenic pain.

Because pain disorder is an important but problematic concept at the interface of pain medicine and psychiatry, it is important to understand some of the history of the concept. In DSM-II (published in 1968), no specific diagnoses existed that pertained to pain. Painful conditions caused by emotional factors were considered part of the psychophysiologic disorders. In 1980, DSM-III introduced a new diagnostic category for pain problems, *psychogenic pain disorder* (114). To qualify, a patient needed to have severe and prolonged pain inconsistent with neuroanatomic distribution of nociceptors or without detectable organic etiology or pathophysiologic mechanism. Related organic pathology was allowed, but the pain had to be “grossly in excess” of what was expected on the basis of physical examination. Accepted evidence that psychological factors were involved in the production of the pain were (a) a temporal relationship between pain onset and an environmental event producing psychological conflict, (b) pain appearing to allow avoidance of some noxious event or responsibility, and (c) pain promoting emotional support or attention the individual would not have otherwise received. It is important to note that this kind of evidence never proves that psychological factors have caused a pain complaint.

Difficulties in establishing that pain was psychogenic led to changes in the diagnosis for DSM-III-R, which was published in 1987 (115). In DSM-III-R, the diagnosis was renamed *somatoform pain disorder*, and three major changes were made in the diagnostic criteria. The requirements for etiologic psychological factors and lack of other contributing mental disorders were eliminated, and a requirement for “preoccupation with pain for at least six months” was added. The diagnostic criteria were thus reduced to the following:

1. Preoccupation with pain for at least 6 months
2. Either a or b:
   a. Appropriate evaluation uncovers no organic pathology or pathophysiologic mechanism to account for the pain.
   b. When there is related organic pathology, the complaint of pain or resulting social or occupational impairment is grossly in excess of what would be expected from the findings (116).

In DSM-III-R, therefore, somatoform pain disorder becomes purely a diagnosis of exclusion. The diagnosis is made when medical disorders are excluded in a patient *preoccupied* with pain.

The DSM-IV subcommittee on pain disorders found that, despite these changes, *somatoform pain disorder* was rarely used in research projects or clinical practice. They identified a number of reasons for this: (a) the meaning of “preoccupation with pain” is unclear, (b) whether pain exceeds that expected is difficult to determine, (c) the diagnosis does not apply to many patients disabled by pain in which a medical condition is contributory, (d) the term *somatoform pain disorder* implies that this pain is somehow different from organic pain, and (e) acute pain of less than 6 months' duration was excluded (117). They therefore proposed the DSM-IV category of pain disorder described in Table 26-8.

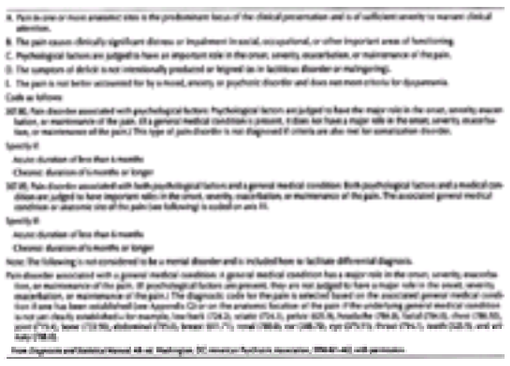


TABLE 26-8. *Diagnostic and Statistical Manual*, Fourth Edition, Diagnostic Criteria for Pain Disorder

The DSM-IV subcommittee has tried to devise a broader diagnostic grouping encompassing both acute and chronic pain problems. They wanted to have all the factors relevant to the onset or maintenance of the pain delineated and also to have a diagnostic category that does not require more training than the majority of DSM-IV users would be expected to have. These two requirements may not be compatible. Furthermore, no guidance is given in determining when psychological factors have a major role in pain or are considered important enough in the presence of a painful medical disorder to be coded as a separate mental disorder. Given the high rates of mood and anxiety disorders among disabled chronic pain patients, many patients most appropriate for the diagnosis would be excluded. Although depression and anxiety diagnoses point toward specific proven therapies, this is not true for pain disorder. The diagnosis thus continues covertly as a diagnosis of exclusion with neither clear inclusion criteria nor implications for therapy.

Epidemiology

Because pain disorder has poor interrater reliability (118) and (as suggested previously) poor validity, there have been few epidemiologic studies of the DSM pain disorders. There have, however, been good studies of pain complaints and unexplained medical symptoms. In a study of adult health maintenance organization members, Von Korff and colleagues found the prevalence of pain over a 6-month period was 41% for back pain, 26% for headache, 17% for abdominal pain, 12% for chest pain, and 12% for facial pain (119). These pain complaints were typically long-standing but nondisabling. However, 9% to 40% reported 1 or more days of disability in the past 6 months. Persons with a pain condition had higher levels of anxiety, depression, and nonpain somatic complaints.

Multiple studies have also demonstrated the association between medically unexplained symptoms (pain and nonpain) and psychiatric disorders. A linear relationship has been demonstrated between the lifetime number of medically unexplained physical symptoms and the lifetime number of depressive and anxiety disorders or the degree of neuroticism or harm avoidance the patient demonstrates on psychological testing (120). Increased psychiatric morbidity has been repeatedly demonstrated for levels of unexplained medical symptoms far below the number required for a DSM diagnosis of somatization disorder (121). This suggests that the somatoform disorders may be less distinct than implied by their separate DSM categories and that they have a strong kinship with the depressive and anxiety disorders. It may be more accurate and productive to think of somatization as a process present in varying degrees throughout the population rather than a set of disorders affecting a small subset of the population (122).

Treatment

Because chronic pain often has multiple causes or contributing factors, it often does not respond to purely somatic or purely psychological modes of treatment. Persistent pain can set a vicious cycle of reinforcing features into motion that then becomes a self-perpetuating problem independent of the initiating illness or injury. Deactivation, depression, disuse, medication misuse, and vocational dysfunction are all common contributing factors to the suffering and disability associated with chronic pain. Although simpler cases of chronic pain may respond to an approach based on the biomedical model, this is not true for the extremely disabled or prolonged cases likely to be referred to psychiatrists or psychologists.

Patients with disabling chronic pain are prone to *doctor shopping*, in which they obtain medications and procedures from a number of physicians unknown to each other. It is not possible to successfully treat a patient with chronic pain who has not formed a solid and honest therapeutic alliance with his or her treating physician. When evidence of doctor shopping becomes apparent, the patient should be confronted immediately and a conversation opened about the doctor–patient relationship. If the patient does not agree to stop unannounced visits to other physicians, he or she should be dismissed from care, as it is impossible to provide appropriate service in this situation.

The needs of patients with disabling chronic pain often outstrip the resources of the most enlightened and eager primary care physician. These patients are most appropriately treated by a multidisciplinary team experienced in the treatment of chronic pain. Members of this team may include a psychiatrist, psychologist, neurologist, neurosurgeon, physical therapist, occupational therapist, nurse, and vocational counselor. Although each case does not require the expertise of each of these disciplines, all of these disciplines have expertise relevant to the management of chronic pain (see Chapter 11).

The treatment of chronic pain is in many ways counterintuitive to the clinician and the patient. Many medications used for acute pain are contraindicated. Relief from pain must often be secondary to reduction in disability and deactivation. Clinical phenomena that seem clearly caused by the pain (e.g., depression must be addressed before pain relief is possible).

Most important, pain is not itself a psychiatric disorder. Chronic pain is frequently complicated by psychiatric disorders, however. The most common of these is depression. Psychiatric treatment of these disorders has an important role to play in the rehabilitation of the chronic pain patient.

CONVERSION DISORDER

The essential feature of conversion disorder is an alteration in voluntary motor or sensory function that suggests a neurologic or general medical disorder. Classic examples include hysterical paralysis, blindness, or mutism. Psychological factors must be associated with the initiation or exacerbation of this deficit. Diagnostic criteria are displayed in Table 26-9.

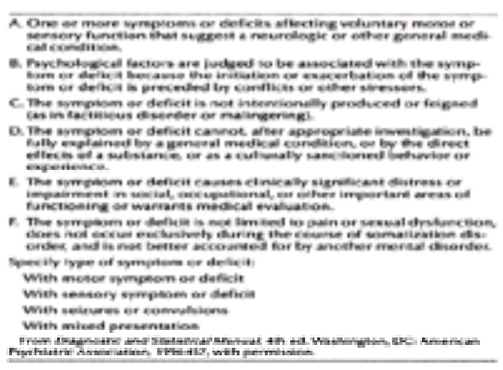


TABLE 26-9. *Diagnostic and Statistical Manual*, Fourth Edition, Diagnostic Criteria for Conversion Disorder

Great caution must be exercised in making the diagnosis of conversion disorder, because the presence of relevant psychological factors does not exclude the possibility of a concurrent organically caused condition.

In “Psychogenic Pain and the Pain-Prone Patient,” George Engel proposed that psychogenic pain arose from guilt and an intolerance of success (41). He indicated that it functioned as a substitute for loss or a replacement for aggression. He furthermore stated that “. . . patients with conversion hysteria constitute the largest percentage of the pain-prone population.” Others have also contended that pain is probably the most common conversion symptom encountered clinically (123). However, only case reports exist to support this contention. Pain is not a classic conversion disorder symptom, and it is controversial whether chronic pain can ever qualify as a conversion disorder by itself. Some, for example, have contended that reflex sympathetic dystrophy (complex regional pain syndrome) can be understood as a conversion reaction; however, this is highly controversial (124). Some elements of conversion disorders appear to be present in reflex sympathetic dystrophy/complex regional pain syndrome patients (e.g., indifference or neglect toward the affected body part), although it is highly unlikely that the condition is entirely psychogenic.

Rather than labeling some chronic pain problems as conversion reactions and others as not, it may be more useful to understand what components of conversion reaction may be present in chronic pain problems. Being ill surely creates problems in living for those affected. Being ill, however, can also solve problems in living. For example, being ill provides an excuse for not being at school or not meeting a deadline at work. These interpersonal advantages of illness were originally recognized by Freud and termed *secondary gain*.

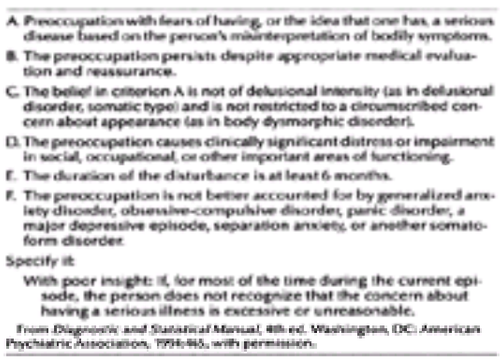
The term *secondary gain* has been distorted and misunderstood in the care of chronic pain, probably because of medicolegal pressures. A number of corrections are in order. First, all illnesses are characterized by some secondary gain, not just illnesses considered to be psychogenic. Being sick always has advantages as well as disadvantages. Second, secondary gain includes all potential interpersonal benefits of illness, not just monetary advantages. Many of the advantages of illness are quite subtle and individualized. Third, secondary gain must be understood in the context of *primary gain*, the intrapersonal advantages of illness. For example, focusing on pain rather than depression may allow patients to avoid self-blame and thereby achieve primary gain. This is a common phenomenon in chronic pain. Indeed, blame avoidance has been hypothesized by some to be one of the main functions of somatization (125). Thus, traditional elements of conversion disorder may be present in many chronic pain problems without many pain problems qualifying as conversion disorders *per se*.

Purely psychogenic or conversion models of chronic pain have some questionable implications for diagnosis and therapy of chronic pain disorders. Interview of the patient with a suspected conversion disorder with the aid of a sodium amobarbital (Amytal) infusion has been a standard tool in psychiatric diagnosis (126). It is more common that motor and sensory deficits than pain resolve under Amytal sedation. Furthermore, some patients have had violent or suicidal reactions to abrupt resolution of their somatic symptoms under Amytal, possibly caused by loss of face-saving primary gain aspects of the illness. Psychodynamic theories of the origin of conversion symptoms imply that psychological treatments alone will be effective.

Psychodynamic treatments for chronic pain, however, have little documented success. The most effective psychological treatments, such as cognitive-behavioral therapy, include a reactivation component that addresses the profound disuse and deconditioning found in many patients with chronic pain.

Hypochondriasis

Many patients with chronic pain resist their physician's reassurance that “nothing is wrong” or that the “tests reveal nothing.” These patients know that they hurt and cannot accept that a bodily cause cannot be identified for their pain. This has been described as *disease conviction* in the chronic pain literature. Disease conviction has been measured with the Illness Behavior Questionnaire, and Hypochondriasis is assessed with the Minnesota Multiphasic Personality Inventory. In DSM-IV there also exists a disorder called *hypochondriasis*. Diagnostic criteria are list in Table 26-10.



A. Preoccupation with fears of having, or the idea that one has, a serious disease based on the person's misinterpretation of bodily symptoms.
B. The preoccupation persists despite appropriate medical evaluation and reassurance.
C. The belief in criterion A is not of delusional intensity (as in delusional disorder, somatic type) and is not restricted to a circumscribed concern about appearance (as in body dysmorphic disorder).
D. The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The duration of the disturbance is at least 6 months.
F. The preoccupation is not better accounted for by generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, a major depressive episode, separation anxiety, or another somatoform disorder.

Specify if:

With poor insight: if, for most of the time during the current episode, the person does not recognize that the concern about having a serious illness is excessive or unreasonable.

From *Diagnostic and Statistical Manual*, 4th ed. Washington, DC: American Psychiatric Association, 1994:465, with permission.

TABLE 26-10. *Diagnostic and Statistical Manual*, Fourth Edition, Diagnostic Criteria for Hypochondriasis

The prevalence of hypochondriasis in primary care has been reported to be 4% to 9% (127). The prevalence of hypochondriasis in pain clinic populations is difficult to determine, but is likely to be high if patients are not excluded by qualifying for pain disorder, because of the likelihood of disagreement between patient and physician about the cause of the pain problem.

Treatments of hypochondriasis have attempted to shift patient focus from cure of the disease causing the symptoms to strategies of symptom management (128). These strategies are common components of multidisciplinary pain treatment programs as well (see Chapter 11). It is indeed critical to achieve early in treatment some agreement with the patient about the cause of the pain that acknowledges the reality of the pain and yet points away from invasive attempts to cure disease or repair broken parts. The task is not to convince the patient that “nothing serious is wrong,” because his or her pain may be severe and persistent. The task is to convince the patient that the appropriate treatment is different than the treatment he or she thought necessary.

CONCLUSION: A BIOPSYCHOSOCIAL MODEL OF PAIN AND SUFFERING

Psychiatric diagnosis and treatment can add an essential and often neglected component to the conceptualization and treatment of chronic pain problems. However, it is absolutely critical to avoid a dualistic model that postulates that pain is either physical or mental in origin. This model alienates patients who feel blamed for their pain. It also is inconsistent with modern models of pain causation. Since the gate control theory of pain, multiple lines of evidence suggest that pain is a product of efferent as well as afferent activity in the nervous system. Tissue damage and nociception are neither necessary nor sufficient for pain. Indeed, it is now widely recognized that the relationship between pain and nociception is highly complex and must be understood in terms of the situation of the organism as a whole.

We are only beginning to understand the complexities of the relationship between pain and suffering. Pain usually, but not always, produces suffering. Suffering can, through somatization, produce pain. We have traditionally understood this suffering, as we have understood nociception, as arising from a form of pathology intrinsic to the sufferer. Hence, the traditional view that pain is caused by either tissue pathology (nociception) or psychopathology (suffering). An alternative model that allows us to escape this dualism is to think of pain as a *transdermal process* with causes outside as well as inside the body. For humans, social pathology can be as painful as tissue pathology. We can investigate the physiology and the psychology of this *sociogenic* pain without losing sight of its origins in relations *between* people.

Psychological care for patients with chronic pain should occur within the medical treatment setting whenever possible. This is the most effective way to reassure

patients that the somatic elements of their problems are not neglected. It also allows integration of somatic and psychological treatments in the most effective manner.

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CHAPTER 27

Arthritis and Periarthritic Disorders

Gregory C. Gardner and Bruce C. Gilliland

This chapter contains a concise discussion of the most painful arthritides encountered in clinical practice. These are osteoarthritis (OA), rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, gout, pseudogout, and infectious arthritis. Tendinitis, bursitis, fibrositis, bone lesions, and soft tissue inflammation are discussed in Chapter 31. More comprehensive discussion of arthritides can be found elsewhere (1,2).

BASIC CONSIDERATIONS

Joint Anatomy

Joints in the extremities are synovial (diarthrodial) joints that permit movement over a wide range (3) (Fig. 27-1). The joint is held together by a capsule of dense fibrous tissue and ligaments and gains further support from overlying muscle and tendons. The inner surface of the joint capsule is covered by synovium, which consists of an intimal layer of specialized cells called *synoviocytes*, and an outer layer of highly vascularized connective tissue. Synoviocytes comprise one to three cell layers and are of two basic types, A and B. Type A synoviocytes are active in phagocytosis, and type B cells synthesize hyaluronate, which is responsible in large part for the high viscosity of normal synovial fluid. Synovial fluid in a normal joint lubricates the surfaces of synovium and cartilage. The synovium is folded along the inside of the joint capsule and does not cover the load-bearing surface of articular cartilage. The connective tissue layer of synovium blends with periosteum, which does not cover the bone within the joint. The synovium has a rich network of capillaries, venules, and lymphatics, and it is innervated by sympathetic nerve fibers. The knee and the sternoclavicular and radiocarpal joints contain disks of fibrocartilage that help to stabilize these joints when they rotate. The intervertebral facet joints are diarthrodial joints and are covered by synovium.

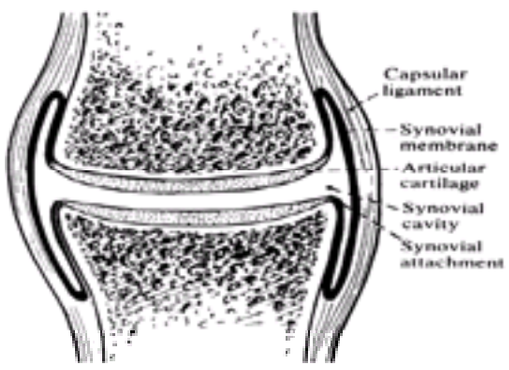

Figure 27-1. Schematic diagram of the anatomic features of a typical synovial joint seen in a section cut across the middle of the joint. The extent of the joint cavity is exaggerated to show the anatomic arrangement of the synovial membrane more clearly. (From Polly HF, Hunder GG. *Rheumatologic interviewing and physical examination of the joints*. Philadelphia: Saunders, 1978, with permission.)

Amphiarthrodial joints are only slightly movable and include the symphysis pubis and the joints between vertebral bodies. The joint surfaces are separated by intervertebral disks. The sacroiliac joint has elements of both a diarthrodial and an amphiarthrodial joint.

Articular cartilage is composed of type 2 collagen and proteoglycans. Type 2 collagen is unique to joints and provides cartilage with form and tensile strength. Proteoglycan molecules are linked noncovalently to a long chain of hyaluronic acid and are interwoven within the network of collagen fibers. Proteoglycan molecules bind most of the water present in cartilage, which represents approximately 70% of the total weight of articular cartilage. The proteoglycan molecules are constrained within the meshwork of collagen fibers and are responsible for the resiliency of cartilage. Chondrocytes secrete collagen, proteoglycans, and enzymes that degrade the cartilaginous matrix. The process of remodeling and degradation is kept in balance unless the microenvironment of these cells is altered. Joints normally contain a small amount of synovial fluid, which is viscous, clear, and does not clot spontaneously. Normal synovial fluid contains fewer than 200 cells per cubic millimeter; most of these cells are mononuclear.

Nerve and Blood Supply

Joints are supplied partly by articular nerves, which are branches of major peripheral nerves, and partly by branches of nerves supplying adjacent muscles, as well as vasomotor sympathetic fibers. Nerve endings are distributed in the interstitial and perivascular tissue located in the subsynovium fibrous capsule, articular fat pads, and in the adventitial sheaths of arteries and arterioles supplying the joints. The periosteum is innervated, but articular cartilage and subchondral bone are not.

Figure 27-2 shows the four types of receptors that supply joints (4). Type I receptors are ovoid corpuscles with a thin connective tissue capsule and each is supplied by a small myelinated nerve fiber (5 to 8 mm in diameter) that arborizes within the capsule. The type I receptor occurs almost exclusively in the fibrous joint capsule, acts as a slowly adapting mechanoreceptor (stretch receptor), and resembles both structurally and functionally the Ruffini endings in the dermis. The type II receptor is approximately twice as large as the type I receptor and is supplied by a somewhat thicker myelinated fiber (8 to 12 mm in diameter) that usually ends as a single terminal within a rather thick laminated capsule. These receptors, which resemble the pacinian corpuscles, occur only in the fibrous joint capsule and have been shown to be rapidly adapting mechanoreceptors (acceleration receptors) that are sensitive to rapid movements. Type III receptors, which are the largest, are supplied by thick myelinated fibers that branch profusely. These receptors, which resemble the Golgi organs, are present in extrinsic and intrinsic ligaments (and not in the joint

capsule) and adapt slowly and at high thresholds. Type IV receptors are represented by plexuses of fine unmyelinated fibers that occur in the fibrous joint capsules, ligaments, and subsynovial capsules and fat pads; they are considered to be the joint nociceptors.

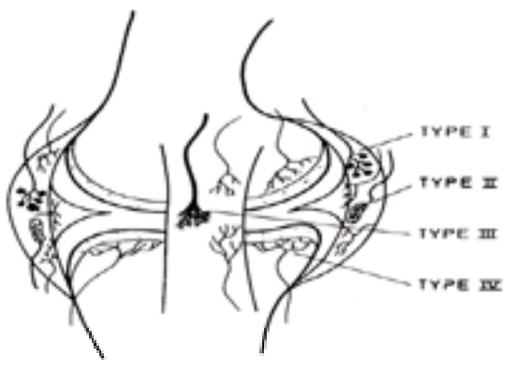

Figure 27-2. Schematic diagram of the knee joint showing the distribution of the various types of receptors in the capsule ligaments of the joint. The menisci are free from nerve fibers except at their attachment to the fibrous capsule. See text for details. (From Brodal A. *Neurological anatomy in relation to clinical medicine*, 3rd ed. New York: Oxford University Press, 1981, with permission.)

An anastomotic plexus of blood vessels called the *periarticular anastomosis*, together with these nerves, surrounds the capsule, and its branches penetrate the capsule. The periarticular anastomosis is fed by branches of arteries passing the joint and is the source of blood to the capillary bed in the synovial membrane and also to the epiphysis (Fig. 27-3).

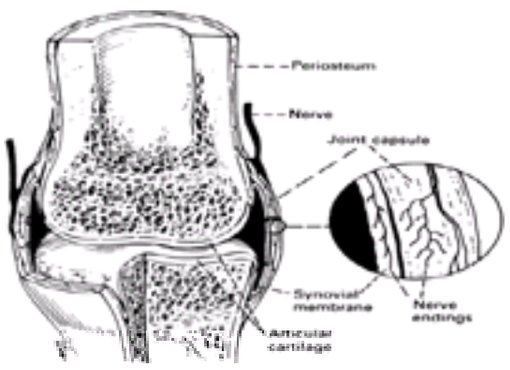

Figure 27-3. Blood and nerve supply to bone and the synovial joint. The upper bone is shown before and the lower bone after obliteration of the growth plate cartilage. The blood vessels that enter the periosteum from the attached muscles have been omitted from the illustration. (Modified from Rosse C, Clawson DK, eds. *The musculoskeletal system in health and disease*. Hagerstown, MD: Harper & Row, 1980.)

MAGNITUDE OF THE PROBLEM

Surveys on the prevalence of a variety of health conditions in the United States, including arthritis, are carried out by the National Center for Health Statistics on an ongoing basis. The data derived from these surveys, known as the *National Health Interview Survey*, estimated in 1976 that 26.2 million people in the United States were affected by arthritis or other musculoskeletal conditions and by 1986 this number had risen to 34.5 million (5). The most recent data from these surveys indicate that currently there are 40 million people in the United States with musculoskeletal conditions and by 2020 it is projected that 60 million will be affected (6). Women are almost twice as likely to report the presence of a musculoskeletal condition as men and are also twice as likely to feel the condition is activity limiting. Twenty percent of people in the lowest income bracket in the United States (less than $10,000 per year) report the presence of a musculoskeletal condition and 6% thought it was limiting. This compares with a 13% prevalence of musculoskeletal conditions in the highest income bracket (more than $50,000 per year), with only 1.6% considering the condition limiting. Moreover, arthritis and rheumatism ranks first as a cause of mobility limitation and second only to heart disease as a cause of activity limitation in the United States. In England, arthritis is the disease most frequently causing severe handicap, and it ranks second only to respiratory infections in number of visits to physicians in that country.

Approximately 23% of people with a musculoskeletal condition have some form of limitation directly related to the underlying musculoskeletal problem (7). Mortality is elevated for most of the major forms of arthritis including OA, in which a slight increase in mortality exists for knee OA, but not hip OA. People with rheumatoid arthritis have 10 to 15 years taken off life expectancy by the disease, with factors such as higher number of joints involved, worse functional status, and less education, all helping to predict mortality (8). Diseases such as scleroderma, systemic lupus erythematosus, and myositis have significant morbidity and mortality both caused by the disease itself and the treatment.

Estimates of the economic impact of arthritic conditions vary widely. Yelin and Callahan estimated that the costs of arthritis in the United States are as high as $149 billion in 1992 dollars with $71 billion attributed to direct costs and the rest attributed to lost wages related to the musculoskeletal condition (9). This figure represents 2.5% of the gross national product of the United States in 1992. A more conservative estimate is offered by Praemer and colleagues, who calculated the direct cost of caring for patients with musculoskeletal conditions at $13 billion and the indirect cost at $55 billion during the same period reported by Yelin and Callahan (10).

CLINICAL APPROACH TO ARTHRITIS

A variety of disorders, both systemic and local, cause joint pain. A thorough history should be taken and a careful physical examination should be performed on each patient, along with appropriate laboratory and radiographic studies (11,12 and 13).

History

The following information should be obtained from the patient. Is the pain localized to one or a few joints, or is it more generalized? Is joint involvement symmetrical? Are peripheral joints primarily involved, or is the axial skeleton the primary site of involvement? What is the pain in the joint like? How rapidly does it appear, how intense is it, how long does it last, what is the quality of the pain, and what is its pattern of radiation? Is the pain produced by physical activity and relieved by rest? Is there morning stiffness, and how long does it last? Morning stiffness of greater than 30 minutes usually suggests an inflammatory arthritis. Symmetric polyarthritis persisting longer than 6 weeks raises the possibility of rheumatoid arthritis.

Migratory polyarthritis is defined as arthritis occurring in one joint and then moving to another joint while inflammation in the previously involved joint subsides. This type of arthritis is more characteristic of a viral infection or rheumatic fever. Arthritis that is additive or progressive continues in the initially involved joints as new joints become affected. Additive arthritis is more likely to occur in inflammatory arthritides such as rheumatoid arthritis.

Development of an acute arthritis involving one or a few joints suggests a crystal-induced arthritis, such as gout or pseudogout or bacterial arthritis. In a young man, low back pain radiating into the buttock and posterior thigh, along with morning stiffness, raises the possibility of ankylosing spondylitis, which can be incorrectly diagnosed as a herniated intervertebral disk. One should search for subcutaneous nodules, which are seen in rheumatoid arthritis or gout. Nodules occur most often over bony prominences such as the elbows. Patients with disorders such as rheumatoid arthritis, psoriatic arthritis, gout, or ankylosing spondylitis often have a

positive family history for that type of arthritis.

The patient should be questioned for constitutional symptoms. Weight loss and fatigue in a patient with polyarthritis and morning stiffness lasting more than 30 minutes point to rheumatoid arthritis. Skin lesions such as those caused by psoriasis should be noted. An acute oligoarthritis in a sexually active young man in association with urethritis, conjunctivitis, or mucocutaneous lesions (or any combination of these symptoms) is most likely Reiter's syndrome. A patient with acute arthritis in one or two joints in the lower extremities and chronic diarrhea should be evaluated for arthritis associated with inflammatory bowel disease.

Physical Examination

When evaluating a patient with musculoskeletal complaints, it is important to distinguish arthritis from soft tissue inflammation and muscle disease. Joints should be examined for evidence of synovial proliferation, fluid, and bony enlargement. Tenderness, warmth, and any limitation of range of motion should be noted. Pain on passive motion of a joint suggests the possibility of inflammation in the joint or periarticular structures.

Muscles should be evaluated for tone, strength, and size. Muscle atrophy and weakness develop in patients with painful chronic joint disease. Proximal muscle weakness is observed in polymyositis, dermatomyositis, and hyperthyroidism. An elderly patient with pain and stiffness in the shoulder and hip girdle should be evaluated for polymyalgia rheumatica. Muscle weakness is usually not prominent, and the erythrocyte sedimentation rate is elevated. Fatigue, persistent aching of the arms, legs, and shoulders throughout the day, and tenderness over specific sites such as the lateral epicondyles, upper shoulders, interscapular region, posterior iliac spines, and medial aspect of the knees are seen in patients with fibromyalgia.

Laboratory Examination

Examination of the joint fluid is essential in patients who have undiagnosed arthritis. Diagnosis of infectious or crystal-induced arthritis is established only by examination of joint fluid. Characteristics of the joint fluid in various rheumatic conditions are shown in Table 27-1. In inflammatory effusions, the cell count is usually elevated, with predominantly polymorphonuclear white cells. The fluid is cloudy, has reduced viscosity, and forms a fibrin clot. Normal joint fluid does not spontaneously clot because it contains no fibrinogen. Viscosity is reduced in inflammatory arthritis because of the breakdown of hyaluronate. A rough assessment of viscosity can be made by forcing a drop of fluid through the end of the syringe. Fluid with poor viscosity drops like water. In normal joint fluid or noninflammatory conditions, a string trails the drop; the longer the string, the higher the viscosity. The mucin clot test has been used for years in the examination of joint fluid. The addition of a drop of synovial fluid from a normal or OA joint to a tube of dilute acetic acid results in the formation of a tight, ropy precipitate of hyaluronate and protein. The mucin clot in inflammatory joint disease is loosely formed, and it fragments readily when shaken gently. A good mucin clot correlates with normal viscosity of joint fluid. The mucin clot test is not essential for the examination of joint fluid because the degree of inflammation can be determined by other methods.

Diagnosis	Appearance	Mucin clot*	White blood count (per mm³ leukocytes)	Polymorphonuclear white cells	Glucose† (%) of blood
Normal	Clear, straw-colored	Good; firm	<200	<25	~100
Osteoarthritis	Straw-colored	Good; firm	<2,000	<25	~100
Rheumatoid arthritis	Yellow	Fair to poor; friable	5,000–25,000 or greater	>65	~75‡
Gout or pseudogout	Yellow, slightly cloudy	Fair to poor; friable	2,000–75,000	>70	[illegible]
Spondyloarthropathies	Yellow, slightly cloudy	Fair to poor; friable	2,000–75,000	>60	[illegible]
Bacterial arthritis	Cloudy to purulent	Poor; friable	10,000, often >100,000	>75	<50
Tuberculous arthritis	Yellow, cloudy	Poor; friable	10,000–20,000§	Variable	[illegible]
Traumatic arthritis	Straw-colored, xanthochromic, bloody	Good; firm	2,000	<25	~100

*Mucin clot correlates with viscosity except with grossly purulent fluid.
†[illegible]
‡May be less than 50%.
§[illegible]
[illegible]

TABLE 27-1. Synovial fluid findings in arthritis

Normal joint fluid usually contains fewer than 200 white cells per cubic millimeter and these cells are predominantly mononuclear. Cell counts greater than 50,000 per cubic millimeter, and in which the cells are predominantly polymorphonuclear, suggest an infectious arthritis, but cell counts of this magnitude are also seen in noninfectious inflammatory joint diseases such as Reiter's syndrome.

The joint fluid glucose approximates the blood glucose when the two compartments are in equilibrium, which is reached 6 hours after a meal. In bacterial arthritis, the glucose in joint fluid is less than 50% of the serum glucose. In rheumatoid arthritis, joint fluid glucose can also be less than 50% of a simultaneously obtained serum glucose because of a defect in glucose transport across the synovium.

Biopsy of the synovium is often needed to diagnose conditions such as tuberculous, sarcoid, or amyloid arthritis. Arthroscopy and arthrography might be required to search for evidence of mechanical derangements such as a torn meniscus, tendon, or ligament. Computed tomography and nuclear magnetic resonance imaging add another dimension to conventional radiography for examination of the musculoskeletal system, especially the spine.

CLINICAL CONSIDERATIONS

Osteoarthritis

OA is characterized by progressive loss of articular cartilage leading to joint pain and limitation of movement. Weight-bearing and frequently used joints are most often affected. The disease is divided into a primary (idiopathic) form, in which no predisposing factors are apparent, and a secondary form, which is associated with trauma, a metabolic disorder, or a congenital abnormality.

Primary OA is the more common form. Pathologically, the two forms are indistinguishable.

Epidemiology and Pathophysiology

OA is the most common form of arthritis worldwide. The disease occurs in all races and geographic areas. Prevalence and severity increase with age. Under age 55 years, the frequency and joint distribution of OA in men and women are approximately the same. After age 55 years, OA of the knee is more common in women and OA of the hip in men (14). OA can be demonstrated radiographically in almost all persons over the age of 75 (15). Weight-bearing joints such as the hips, knees, feet, and cervical and lumbosacral joints are most often affected. The distal and proximal interphalangeal joints of the hands are also commonly involved. Certain occupations have been shown to predispose a person to OA. In coal miners, for example, OA of the shoulders and knees is more frequent, presumably because of the forces placed on these joints during work. Prize fighters are more likely to develop OA of their metatarsophalangeal joints, football players of their knees, and ballet dancers of their ankles. Hereditary factors also exist: Heberden's nodes are twice as frequent in mothers of affected persons and three times more frequent in sisters (16). A single point mutation in the cDNA coding for type II collagen was found in family members with an inherited form of OA associated with a mild chondrodysplasia (17,18). Previous major trauma and repetitive use of a joint increase the risk of developing OA. Age alone is a risk factor, with the prevalence of OA increasing after age 45 years. Obesity has been shown to be a definite risk factor for developing OA of the knees (19).

The process of OA may begin with a decrease in the energy-absorbing property of the subchondral bone (20). This change means that the energy of weight bearing is absorbed mainly by the articular cartilage and chondrocytes. In response to this impact, the chondrocytes multiply and increase their synthesis of degradative enzymes as well as collagen and proteoglycans. Chondrocytes produce a family of metalloproteinases that include stromelysin, collagenase, and gelatinase. These enzymes can degrade all the components of cartilage. Cytokines (interleukin-1 and tumor necrosis factor-a) secreted by mononuclear cells of the synovium and by chondrocytes stimulate the release of metalloproteinases. These enzymes are inhibited by tissue inhibitors of metalloproteinase, which are also made in chondrocytes and serve to protect against excessive degradation of cartilage. Eventually, this protection is lost, resulting in loss of cartilage. In addition, antibodies to proteoglycans

and other degradative products induce an inflammatory response that may further injure the joint.

The cartilage initially shows fissuring and pitting, which eventually progress to erosions and denuded areas. The proteoglycan content of cartilage and the number of chondrocytes decrease in proportion to the degree of disease. Subchondral bone becomes thickened and has an eburnated, or ivorylike, appearance. Cysts appear in the subchondral bone, and the formation of new bone at the joint margins produces osteophytes or spurs. The synovium is thickened and contains a modest infiltration of lymphocytes, plasma cells, and an occasional multinucleated giant cell. The joint capsule and ligaments are hypertrophied.

Symptoms and Signs

OA may be limited to one or two joints or may occur in a generalized form involving many joints. Symptoms usually begin insidiously as a deep aching pain that is poorly localized. Pain occurs during use of the involved joint and is relieved by rest. Involved joints are stiff for 30 minutes or less in the morning and after periods of inactivity. The involved joints often ache at night, and the ache can keep the patient awake. Night pain is caused in part by increased intraosseous venous pressure. As the disease progresses, pain becomes a constant feature of physical activity and can persist for several hours afterward. Eventually, restricted motion and joint deformities develop.

OA most frequently affects the distal interphalangeal joints, the first carpometacarpal joint, and the scaphotrapezoid joint. The proximal interphalangeal joints are less frequently involved. OA of the metacarpal phalangeal joints, especially the second and third joints, is unusual and when present is caused by previous trauma, calcium pyrophosphate deposition disease (CPDD), or hemochromatosis. Patients experience aching pain in the involved joints during and shortly after using their hands. With vigorous activities, such as gardening, golf, or tennis, the joints swell and ache for several hours or even days. Heberden's nodes usually develop after age 40 and are associated with OA of the distal interphalangeal joints. Similar nodes, called *Bouchard's nodes*, appear at the proximal interphalangeal joints. At times, these nodes become red and painful to touch. Bony enlargement, small effusions, restricted motion, and angulation can be seen on physical examination. Radial subluxation of the first carpal metacarpal joint gives a square appearance to this joint (shelf sign).

A form of OA, referred to as *primary generalized OA*, appears most often in middle-aged women and affects the distal interphalangeal and proximal interphalangeal joints of the hand, the first carpal metacarpal joint, knees, hips, and the first metatarsal phalangeal joint. Episodes of inflammation are characterized by warmth, pain, and swelling of these joints.

OA of the hip is usually unilateral, but the opposite side is also affected in approximately 20% of patients (21). Congenital or developmental abnormalities such as slipped capital femoral epiphysis, Legg-Calvé-Perthes syndrome, or hip dysplasia underlie many of the cases. OA follows avascular necrosis, which can be related to deep-water diving, glucocorticosteroid therapy, alcohol, or sickle cell disease. Hip pain is experienced in the groin, over the greater trochanter, in the buttock, or down the anterior and inner thigh. Pain might be referred to the distal thigh and upper knee because the obturator nerve and its branches supply both hip and knee. Hip disease can be mistaken for knee arthritis or trochanteric bursitis because hip pain can be referred to those locations. The pain of hip disease is often described as dull and aching and is initially experienced with physical activity. Later, night pain is also experienced. Patients might limp and have difficulty rising from a sitting position. Functional shortening of the leg caused by adduction and flexion contractures causes the patient to walk with a shuffling gait. Examination of the hip shows initially decreased internal rotation that is followed later by decreased extension, abduction, and flexion, as well as a flexion contracture.

The cause of OA of the knee is not known in most patients. Previous injury such as a torn meniscus or ligament predisposes the knee to secondary OA. The presence of genu varum (bow legs) or genu valgum (knock knees) increases the force directed through either the medial or lateral side of the knee and can lead to OA. These deformities are also acquired in OA as a result of destruction of either the medial or lateral articular cartilage. Obesity predisposes the knees to OA by the additional weight and by the thigh thickness, which places the legs in a genu varus position and increases the pressure on the medial compartment.

The first symptom is usually pain with activity. The pain is dull and aching and usually poorly localized in and around the knee. Pain also can be localized to either the medial or lateral aspect of the joint. Stiffness lasting less than 30 minutes is present in the morning or after prolonged rest during the day. Stiffness improves with activity but might return later in the day. Atrophy and weakness of the quadriceps muscle develop with progression of the arthritis. Crepitus might be noted with bending of the knee. With loss of ligamentous and muscle support, the knee becomes unstable, and the patient may be hesitant to walk on uneven surfaces. The knee might suddenly give way because of a pain reflex. A loose cartilaginous fragment, sometimes referred to as a *joint mouse*, can prevent the joint from being fully extended.

On examination, a small joint effusion might be present. Presence of a large effusion suggests the possibility of associated CPDD or recent trauma. Ligamentous laxity, limitation of motion, and flexion contractures might be present.

Patellofemoral arthritis occurs alone or in conjunction with arthritis of the other knee compartments, especially in older patients. The term *chondromalacia patellae* is often used interchangeably with patellofemoral arthritis, although some restrict this term to a self-limiting disorder occurring in adolescents and young adults. Patellofemoral arthritis is caused in some patients by improper tracking of the patella through the patellofemoral groove (trochlea). The patella is pulled to the lateral margin of the groove by a tight lateral patellar retinaculum or a relative weakness of the vastus medialis compared with the vastus lateralis of the quadriceps muscle. Lateral subluxation of the patella can also be caused by an increased Q angle resulting from rotational malalignment of the femur and tibia.

In the spine, intervertebral disks and apophyseal (facet) joints are sites for OA. Involvement of intervertebral disks is referred to as *spondylosis*, whereas disease in the apophyseal joints is considered true OA. OA also affects the joints of Luschka (uncovertebral joints), which are located in the cervical spine between the superior process of one vertebral body and the inferior process of the vertebral body above it.

Symptoms of spine involvement are localized pain and stiffness, referred or dermatomal pain, and radicular pain from nerve root compression. Nerve root involvement produces paresthesias, decreased sensation, loss of muscle strength, and diminished or absent deep tendon reflexes. OA of the cervical spine causes either localized pain or pain referred to the occiput, shoulder, interscapular area, or arm, depending on the level affected. With upper cervical disease, the pain tends to be referred to the occiput or upper interscapular area, and with lower cervical involvement it is referred to the shoulder and upper arm. Neurologic manifestations are also caused by compression of the spinal cord by posteriorly directed osteophytes and by occlusion of the anterior spinal artery by a herniated disk. Cervical spine diseases are discussed in Chapter 55; lumbar spine in Chapter 75 and Chapter 76.

Secondary Osteoarthritis

OA can develop in joints that have been damaged. A torn knee meniscus or ligament can lead to incongruity of the joint surfaces resulting in OA. OA may follow joint damage produced by infectious arthritis or an inflammatory arthritis such as rheumatoid arthritis. Neuropathic joint disease is a severe form of OA resulting from the loss of pain sensation, proprioception, or both (22). Without these protective mechanisms, joints are subjected to repeated trauma, leading to progressive cartilage damage. Diabetes is the most common cause of neuropathic joint disease. Other causes include tabes dorsalis, syringomyelia, amyloidosis, meningomyelocele in children, and leprosy.

OA occurs in patients with excessively hypermobile joints. Patients with Ehler-Danlos syndrome, a hereditary disorder of connective tissue, develop OA of their hands, shoulders, knees, and ankles usually before age 40 years (23). Debate exists regarding whether patients with idiopathic joint hypermobility are at risk of developing premature OA (24).

Several metabolic disorders are associated with the development of OA. These include hemochromatosis, ochronosis, and acromegaly. Arthritis occurs in 20% to 50% of patients with hemochromatosis and may appear before other overt clinical manifestations (25). Hands, knees, and hips are most commonly affected. A particularly characteristic finding is involvement of the second and third metacarpophalangeal joints, which are rarely affected in primary OA. Ochronosis is a rare disorder caused by a hereditary deficiency of homogentisic acid oxidase, leading to accumulation of homogentisic acid in connective tissue. Deposits of homogentisic acid impart a blue-black hue to the sclerae and external cartilage of the ears. Arthritis appears in middle age and involves most often the knees, shoulders, hips, and spine (26). Approximately 60% of patients with acromegaly develop OA, which most often involves the spine, knees, hips, shoulders, and, occasionally, ankles (27). The increased growth of articular cartilage causes joint surface incongruity and abnormal wear.

Laboratory Findings. Routine laboratory work is normal in patients with primary OA and reflects the underlying metabolic disorder in secondary OA. The synovial fluid is straw colored and has good viscosity. The cell count is usually less than 2,000 white cells per cubic millimeter, and the cells are predominantly mononuclear. Radiographs in early OA are usually normal, but as the disease progresses joint space narrowing, subchondral bone sclerosis, and osteophytes are observed.

Erosive OA is characterized by erosions on the joint surface, sclerosis of subchondral bone, and later by bony ankylosis. Radiographic abnormalities do not always correlate with clinical symptoms.

Treatment. The first-line therapy for OA is over-the-counter analgesics (e.g., acetaminophen, 1,000 mg four times a day, or even less if it is effective). If the patient remains symptomatic after 2 to 4 weeks, low-dose ibuprofen or nonacetylated salicylates are indicated. If the response is still inadequate after 2 to 4 weeks, the patient should be placed on a full dose of a nonsteroidal drug (Table 27- 2). In the patient with risk factors for upper gastrointestinal bleeding or ulcer disease, misoprostol or a proton pump inhibitor should also be taken. Intraarticular corticosteroid injections should be used judiciously in weight-bearing joints and those subjected to vigorous activity because in the absence of pain, the joint may be overused, leading to accelerated joint damage. No more than three injections per year should be placed into a weight-bearing joint. Corticosteroid injection of the first carpal metacarpal joint, a frequently symptomatic joint, often provides significant relief of pain and improvement of function. Injectable hyaluronan is approved for use on OA of the knee, and it has been shown to reduce the level of pain with few side effects in controlled studies (28). Glucosamine sulfate is also reported to be of benefit in OA and at least one animal model of OA suggests disease modification (29,30).

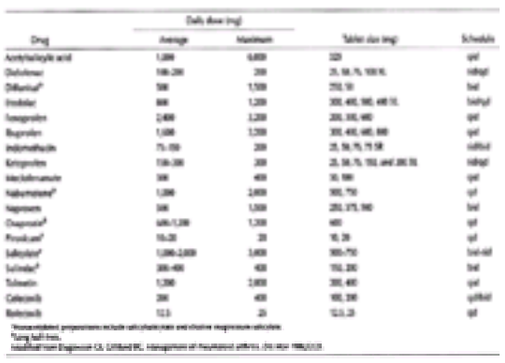

TABLE 27-2. Nonsteroidal antiinflammatory drugs for arthritis

Physical therapy plays an important role in improving muscle strength and range of motion. Affected joints should not be overused, especially in high-impact exercises. It is important to build up the muscles before using a joint that has been injured. Overweight patients benefit from weight reduction. Splinting a painful first carpal metacarpal joint is often quite helpful.

When a joint is severely damaged and painful, joint replacement should be considered. Total hip replacement has provided dramatic relief of pain and improvement of function. Placement of a knee, shoulder, or ankle prosthesis can also be quite helpful. Correction of a valgus or varus deformity by osteotomy of the knee, shoulder, or ankle improves weight distribution and extends the functional life of the joint. A prosthesis at the carpal metacarpal joint of the thumb helps some patients.

Rheumatoid Arthritis

Rheumatoid arthritis is an inflammatory polyarthritis of unknown etiology and typically involves peripheral joints in a symmetric distribution. The worldwide prevalence varies from 0.097 to 2.900 per 1,000 (31). In the United States, the prevalence is 1% to 2% (32). Women are more commonly affected: The average ratio is 3:1. An association also exists with HLA-DR4, the prevalence being 48% to 59% in persons with this genetically determined antigen compared with 8% to 16% in the general white population (33).

Etiology and Pathophysiology

Even though the etiology of rheumatoid arthritis remains unknown, significant advancements have been made in the understanding of the inflammatory events leading to joint injury and extraarticular manifestations. The hallmark of rheumatoid arthritis is the proliferation of synovium, which spreads over the articular surface as a pannus and damages cartilage, bone, and joint capsule. Harris has classified the pathophysiology of rheumatoid arthritis into four phases (34). Stage I is characterized by the presentation of an as yet unknown antigen or antigens to T cells. In stage II, proliferation of T and B cells, as well as synovial angiogenesis, occurs. In stage III, synovial hypertrophy begins and neutrophils accumulate within the joint in response to chemotactic factors produced by the fixing of complement and the production of cytokines by macrophages and synoviocytes such as tissue necrosis factor-a, interleukin-1 and -6, and granulocyte macrophage cell-stimulating factor. Of interest, cytokines from macrophages and synoviocytes are present in abundance in the rheumatoid joint but typical T-cell cytokines such as interleukin-2 and interferon-g are notably absent in established disease. Finally, stage IV is characterized by pannus formation and joint destruction.

B cells in the synovium have been shown to synthesize immunoglobulins, some of which have anti-IgG (rheumatoid factor) activity. Immune complexes consisting of IgG and anti-IgG form in the joint fluid and activate the complement system, which results in the formation of vasoactive and chemotactic factors. Polymorphonuclear white cells attracted to the joint by chemotactic factors phagocytize these immune complexes and secrete proteolytic enzymes within the synovial fluid. The most common form of rheumatoid factor is an IgM molecule directed against the *Fc* portion of IgG. IgG and IgA rheumatoid factors can also be found in patients with rheumatoid arthritis, and IgA rheumatoid factors in particular have been noted to be associated with more severe disease (35).

In addition to the complement system and cytokines, other inflammatory mediators are also involved. These include prostaglandins, leukotrienes, and free oxygen radicals. Prostaglandin E_2 is a potent vasodilator and enhances the action of histamine and bradykinin to produce edema and pain (36). Leukotrienes, another product of arachidonic acid metabolism, produce smooth muscle contraction, neutrophil chemotaxis, and vasodilatation (37). Superoxide anions released from neutrophils and macrophages during phagocytosis and oxygen radicals formed during metabolism of arachidonic acid also produce tissue damage (38).

The etiology of rheumatoid arthritis is uncertain, but research for many years has focused on the possibility of an arthrotropic infectious disease either triggering the inflammatory cascade or persisting in some form in the joint. An interesting piece of evidence in this light is the fact that rheumatoid arthritis was rare in the Old World before European exploration of the New World and seems to have appeared in Europe after this period (39). Rheumatoid arthritis has been diagnosed via skeletal remains in certain Native American population antedating the age of exploration, leading some to speculate that the disease is a New World phenomenon that was transmitted back to the Old World.

Symptoms and Signs

The typical patient with rheumatoid arthritis is a young to middle-aged woman who presents to her physician with a history of 2 to 3 months of joint pain and stiffness in her hands. Constitutional symptoms of fatigue, weight loss, and low-grade fever might also be present. The hands and other involved joints are stiff on arising in the morning. Stiffness might last from 30 minutes to 2 hours or longer. In severe disease, the patient might remain stiff most of the day.

Patients with involvement of the hands and wrists might have difficulty performing tasks such as lifting pots, washing their hair, and opening jars or doors. A firm handshake can be quite painful. Tingling and numbness of the thumb and index and middle fingers, which often occur at night, indicate compression of the median nerve by synovial tissue in the carpal tunnel (carpal tunnel syndrome). At times, the carpal tunnel syndrome produces pain radiating up the forearm and down into the hand. Rheumatoid arthritis can begin in the feet in the metatarsal phalangeal joints. It is not unusual for a patient to attribute metatarsalgia to improperly fitting shoes before seeking medical attention.

On physical examination, the joints are swollen, tender to palpation, and warm but not hot. The combination of synovial proliferation and fluid gives the joint a boggy sensation on palpation. Synovial proliferation in the flexor tendons of the fingers fills in the palm, giving it a flat appearance. The skin over the small joints often has a bluish discoloration resulting from venous engorgement. The hands may be cool and clammy. Hand grips are significantly reduced. Measurement of the hand grip provides a quantitative tool for assessing response to treatment. The range of joint motion is initially limited by pain and later by contractures. Ulnar deviation of the fingers at the metacarpal phalangeal joint is a common deformity in established disease and results from radial deviation of the wrist and slippage of the extensor tendons to the ulnar side of the metacarpal phalangeal joints. Another common deformity of the hand that develops in chronic disease is the swan-neck deformity.

This appearance results from flexion of the distal interphalangeal joint and metacarpal phalangeal joint with hyperextension of the proximal interphalangeal joint. The boutonniere deformity is caused by avulsion of the extensor hood over the proximal interphalangeal joint, leading to a flexion deformity of this joint and hyperextension of the distal interphalangeal joint. In advanced disease, subluxation and flexion deformities are common and involve the knees, ankles, elbows, wrists, shoulders, hands, and feet.

The course of rheumatoid arthritis is highly variable. Fifteen percent of patients have complete remission, whereas 10% or less go on to destructive disease that responds poorly to all forms of therapy. Most patients fall between these two groups with variable periods of remission and relapse. Some patients experience significant disability, whereas others respond to treatment and function quite well throughout their lifetimes. Prognostic factors for more severe disease include the presence of high titers of rheumatoid factor, presence of HLA-DR4, and more joints initially involved.

Laboratory Findings

Patients often have a normocytic normochromic anemia and an elevated erythrocyte sedimentation rate. Approximately 80% of patients have a positive rheumatoid factor test result. Radiography in early disease reveals only juxtaarticular osteopenia and soft tissue swelling. In more advanced disease one finds narrowing of joint spaces, erosions at the margins of the joint, and eventually subluxation. The synovial fluid usually has a white blood cell count that varies from 5,000 to 25,000 cells per cubic millimeter (most of the cells are neutrophils), decreased viscosity, and a low glucose level (see Table 27-1).

Treatment Philosophy. The goal of treatment is to reduce pain and swelling to preserve joint function and activities of daily living. Management of patients with rheumatoid arthritis requires coordinated, comprehensive care involving rheumatologists, the patient's primary care physician, orthopedic surgeons, rehabilitation physicians, occupational therapists, and physical therapists.

Medications remain the mainstay of the treatment of rheumatoid arthritis. Drug treatment can be separated into two broad categories (see Table 27-2). The first consists of drugs that have a rapid onset of action and do not significantly alter the ultimate course of rheumatoid arthritis. These drugs include salicylates and other nonsteroidal antiinflammatory agents. The second category consists of drugs that have a slow onset of action varying from weeks to 6 months or longer. These drugs have been referred to by many descriptions, including remitting drugs, slow-acting drugs, and disease-modifying antirheumatic drugs (DMARDs). These drugs have the potential to bring about complete or substantial improvement in clinical symptoms and signs. These drugs also bring about improvement of the laboratory indices, and roentgenography shows a decreased progression of joint destruction and, in some cases, actual disappearance of erosions. The drugs in this group include antimalarials, sulfasalazine, methotrexate, cyclosporine, and gold salts. The cytotoxic agents azathioprine and cyclophosphamide have also been shown to be remitting, but they are placed in a separate category because of their toxicity and concerns about their long-term safety.

The treatment of rheumatoid arthritis has undergone considerable rethinking over the years. The time-honored approach to the treatment of rheumatoid arthritis has been based on the *pyramid*, in large part because of the philosophy that rheumatoid arthritis was a disabling but otherwise benign disease. Via the treatment pyramid, patients would receive nonsteroidal antiinflammatory drugs (NSAIDs) or salicylates along with education and physical and occupational therapy and, as the disease progressed, more aggressive therapy with DMARDs of increasing toxicity would be used. In 1965, up to 120 months would pass before a DMARD would be started (40). Because a majority of patients with rheumatoid arthritis develop erosions by 2 years of disease and it has been found not to be the benign disease it was once thought to be, it has been suggested that we invert the pyramid (i.e., begin with aggressive therapy up front to prevent erosive changes to joints that are generally not reversible and thus prevent the disability and potentially the mortality caused by unchecked rheumatoid arthritis) (41,42 and 43). Currently, most rheumatologists start a DMARD at approximately 3 months of persistent synovitis, especially in a patient with a positive rheumatoid factor. In addition, combination therapy with more than one DMARD has been shown to be more effective and no more toxic than single-agent therapy (see following discussion).

Current Management of Rheumatoid Arthritis

Nonsteroidal Antiinflammatory Drugs. NSAIDs are usually given to most patients early on in the course of rheumatoid arthritis. NSAIDs are antiinflammatory and analgesic drugs and should be given at least 2 to 3 weeks before their clinical effectiveness can be fully evaluated. It is usually possible to find one of these drugs that will help the patient. Salicylates or NSAIDs usually can be continued when a disease-modifying drug is administered. The currently available NSAIDs, along with their daily doses, are shown in Table 27-2.

The side effects of NSAIDs are somewhat similar (44). These agents can cause gastritis and are associated with peptic ulcer disease. Other gastrointestinal manifestations include flatulence, bloating, and diarrhea, which tend to be more common with indomethacin and sodium meclofenamate. Mild elevations of the liver enzymes occur, but use of these drugs seldom leads to serious liver damage. Asthma can be exacerbated. Many of these drugs also cause urticaria or angioedema and, rarely, an anaphylactic reaction. Interstitial nephritis has also been observed. NSAIDs reduce renal blood flow by inhibiting renal prostaglandin synthesis and can precipitate renal failure. Rashes, including Stevens-Johnson syndrome, have been reported. NSAIDs can be associated with headache, confusion, and dizziness. Aseptic meningitis is a rare complication, reported most often with ibuprofen. NSAIDs interfere with platelet function, which returns to normal within five half-lives after stopping the drug. The anticoagulant effect of warfarin (Coumadin) is also enhanced by several of the NSAIDs.

Disease-Modifying Agents. Patients with early mild synovitis are generally started on hydroxychloroquine (45). This agent takes 8 to 12 weeks before it begins to affect the synovitis and may take up to 6 months in some patients. Its mechanism of action is thought to be on the basis of increasing the pH of the vacuoles in antigen-presenting cells and gently disrupting the interaction of the major histocompatibility complex, with antigen thus affecting the way antigen is presented to T cells (46).

Hydroxychloroquine is dosed by weight at 6.5 mg per kg per day in divided doses. Doses higher than this increase the risk for ocular toxicity. Common side effects include diarrhea, gastrointestinal upset, and rash. Serious side effects are listed in Table 27-3 as well as a monitoring schedule. Improvement in morning stiffness and pain, as well as a decrease in the number of tender and swollen joints, and a reduction in acute-phase reactants (i.e., erythrocyte sedimentation rate or C-reactive protein) are measures of success. Patients with more significant synovitis may be candidates for either sulfasalazine or methotrexate as single agents.

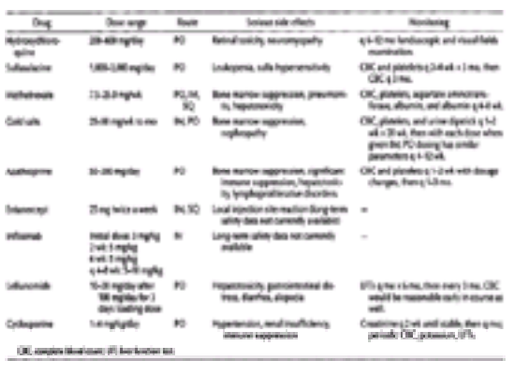

TABLE 27-3. Disease-modifying antirheumatic drugs

Sulfasalazine is a combination of sulfapyridine and 5-aminosalicylic acid, which is cleaved by gut bacteria into two compounds. It is thought that the sulfapyridine moiety is the active one in rheumatoid arthritis. It is dosed generally at 2,000 mg in two divided doses and monitored as noted in Table 27-3. It takes 4 to 8 weeks for an effect to be apparent in most patients and in some may be up to 12 weeks. Common side effects include gastrointestinal upset, diarrhea, and rash. Severe agranulocytosis can occur and is idiosyncratic. Drug cessation resolves the cytopenias in most cases, but there have been a few cases requiring granulocyte colony-stimulating factor therapy. G6PD deficiency may lead to severe anemia in affected patients and should be checked before starting therapy if suspected.

The other commonly used DMARD in single therapy is methotrexate. The dose range and other characteristics are presented in Table 27-3. Methotrexate is a dihyrofolate reductase inhibitor. Its mode of action is uncertain but may be caused by an increase in adenosine, an antiinflammatory compound (47). Methotrexate has the advantage of being given once a week and can be given both orally and intramuscularly. Methotrexate begins to be effective generally in 3 to 8 weeks after

initiation of therapy. Common side effects include stomatitis, nausea, gastrointestinal upset, and mild hair thinning. Stomatitis in particular might respond to the addition of 1 mg of folic acid daily without affecting its activity in rheumatoid arthritis. The response rate in studies is approximately 75% and approximately 50% of patients are still on methotrexate at 5 years of therapy compared with 20% or less for the other DMARDs (48).

For those who have a partial response to a single DMARD, the DMARD is not typically stopped but additional DMARDs are added. Combinations found useful include hydroxychloroquine, sulfasalazine, and methotrexate or cyclosporine added to methotrexate (49,50). Azathioprine is typically used in some form of combination therapy and cyclophosphamide is given to patients with severe unresponsive disease and to those with rheumatoid vasculitis (see following discussion). Most of the combination regimens are given under the direction of a rheumatologist.

Two medications have recently been approved for the treatment of rheumatoid arthritis. Entanercept and infliximab are anti–tumor necrosis factor-a agents that have been shown to be quite effective in reducing joint counts and acute-phase reactants. Etanercept is administered intramuscularly twice weekly, and infliximab is given intravenously at 0, 2, and 6 weeks, and then every 8 weeks thereafter. Both medications reduce joint swelling and pain, and decrease morning stiffness and fatigue. They are usually given to patients on methotrexate who have had only a partial response. Leflunomide is a pyrimidine synthesis inhibitor also shown to be effective in reducing joint counts, acute-phase reactants, and retarding joint erosions. After an initial loading dose of 100 mg for 3 days, the usual daily dose is 20 mg per day.

Glucocorticoids. The antiinflammatory mechanisms of glucocorticoids include altering leukocyte traffic and function, stabilizing lysosomal membranes of neutrophils and monocytes, and inhibiting the secretion of destructive enzymes including collagenase and elastase (51). They also inhibit the products of arachidonic acid metabolism including prostaglandins and leukotrienes.

Studies have shown that low-dose glucocorticoids (defined as 7.5 mg or less of prednisone or the equivalent of another short- acting glucocorticoid) given in the morning by 10 am reduces the progression of joint damage (52). Also, the hypothalamic-pituitary-adrenal axis remains intact when low doses of prednisone are used. Low-dose prednisone treatment can be especially beneficial during initiation of treatment with a DMARD. The prednisone dose can be tapered once the patient has had a response to the remitting agent.

In patients on corticosteroids, it is important to give calcium in the range of 1,000 to 1,500 mg per day, and vitamin D, 400 units a day. Patients should be monitored closely for evidence of hypercalcemia and hypercalcinuria. A bisphosphonate (e.g., alendronate) may also reduce the bone loss of calcium in patients on corticosteroids.

Judicious intraarticular administration of corticosteroids can be quite useful in the treatment of rheumatoid arthritis. It is recommended that an individual joint be injected no more than three times at intervals of 6 months or longer. In a badly damaged joint or one that is soon to be replaced by a prosthetic joint, corticosteroids may be injected more frequently.

Surgery

Indications for orthopedic surgery in rheumatoid arthritis are twofold: pain unresponsive to medical management and loss of function. Synovectomy of selected joints provides alleviation of symptoms and improvement of function in the first year after operation, but may not provide a long-term effect (53). Removal of synovial tissue from the wrist and dorsal tendon sheath and resection of the ulnar head might prevent rupture of the extensor tendon. Patients with severely deformed hands can benefit from metacarpal phalangeal arthroplasty. Patients with severe pain and loss of function can benefit from total joint replacement, especially the knee or hip. Metatarsal head resection can be of tremendous help in patients with painful metatarsal heads. Intermittent splinting of selected joints is beneficial.

Important Complications of Rheumatoid Arthritis Presenting with Pain

Carpal Tunnel Syndrome. Carpal tunnel syndrome is a common problem in rheumatoid arthritis caused by wrist synovitis that can lead to median nerve compression. Therapy is generally directed at the rheumatoid synovitis with DMARDs and antiinflammatory agents. A wrist injection with corticosteroids may be helpful in many cases. Carpal tunnel release may be necessary in some cases.

Rheumatoid Vasculitis. This is a potentially life-threatening complication. Patients with long-standing, seropositive, erosive rheumatoid arthritis are generally at risk for this small to medium vessel vasculitis similar to polyarteritis nodosa. Patients may present with digital gangrene or symptoms of mononeuritis multiplex (i.e., footdrop). More serious complications include intestinal perforation or cardiac involvement. Kidneys are less commonly involved than in polyarteritis nodosa. Treatment is with cyclophosphamide and high-dose prednisone.

Cervical Spine Disease. The synovial portions of the cervical spine can be involved in rheumatoid arthritis. This can lead to C1-2 instability or subaxial instability. Symptoms may be caused by cord or vascular compression and may include neck pain, shocklike sensation up or down the spine, and intermittent loss of consciousness when vertebral artery compression occurs. Before surgery, all patients with long-standing rheumatoid arthritis should have a set of lateral flexion and extension views of the cervical spine taken to evaluate the cervical spine for C1-2 subluxation.

Septic Arthritis. Patients with rheumatoid arthritis are at increased risk of septic arthritis caused by abnormal joint architecture, use of immunosuppressive drugs, and skin breakdown over high-pressure, biomechanically abnormal sites such as the feet. Patients often present with one joint out of proportion to the others in terms of pain or swelling and may have a paucity of systemic symptoms typical in nonrheumatoid patients. Detection is imperative because of the high mortality in such patients (i.e., 20% mortality if a single joint is infected and over 50% in patients with multiple joints involved) (54).

Ankylosing Spondylitis

Ankylosing spondylitis is an inflammatory arthritis involving sacroiliac joints and the spine (55). Inflammation also occurs at sites of tendon and ligament insertions (enthesitis). Hips and shoulders can also be affected. Peripheral arthritis is less common. Onset of disease is usually in the second or third decade, and men are predominantly affected. The histocompatibility antigen HLA-B27 is found in 90% or more of patients, fulfilling clinical criteria for ankylosing spondylitis (56). The normal frequency of HLA-B27 in the white population is approximately 7%.

Pathophysiology

Synovitis in the apophyseal and costovertebral joints of the spine and peripheral joints is characterized by synovial hyperplasia with focal accumulation of lymphoid and plasma cells. Inflammation also involves cartilaginous joints, which include the intervertebral disks, manubriosternal joint, and symphysis pubis. Ossification of the outer layers of annulus fibrosus of the disk and the inner layers of the longitudinal ligaments forms syndesmophytes that eventually interconnect to give the spine the appearance of bamboo.

A common site of inflammation is at the insertion of tendons, ligaments, and joint capsule to bone. New bone formation can occur at these sites, particularly at the greater trochanter, pelvis, and heels. Focal medionecrosis of the proximal aorta leads to dilation of the aortic valve and aortic regurgitation. Inflammation of the atrioventricular bundle produces cardiac conduction abnormalities.

Symptoms and Signs

The onset of the disease is usually in the second and third decades. The patient initially notes low back pain and stiffness, especially on arising in the morning. The stiffness of the back lasts for several hours in the morning and occurs after periods of activity during the day. The pain might radiate into either buttock, extend down the back of the leg to the knee, and can be mistaken for the pain caused by herniated disk. The pain might alternate from side to side. Involvement of the hips and shoulders causes pain, stiffness, and decreased motion. Peripheral joints other than the hips or shoulders are affected relatively infrequently. Costovertebral joint arthritis can cause chest pain similar to that of angina pectoris or pleurisy. The entire spine can become ankylosed. Atlantoaxial subluxation (with the potential danger of spinal cord compression) can occur, but this is observed less often in ankylosing spondylitis than in rheumatoid arthritis. The fused spine, especially the neck, is susceptible to fractures with trauma.

Cardiac abnormalities include aortic regurgitation caused by aortic root dilatation and varying degrees of heart block. Acute iritis occurs in approximately one-third of

the patients. A rare manifestation is fibrosis of the upper lobes of the lung, which occurs late in the course of the disease. Patients occasionally have significant constitutional symptoms of fever and weight loss.

Ankylosis develops over several years, usually 10 years or more. The extent of involvement varies among patients and ranges from bilateral sacroiliitis to complete ankylosis of the spine. The spondylitis sometimes skips segments of the back.

On physical examination, sacroiliac tenderness is elicited by direct palpation or by maneuvers that stress the joint. A loss of normal lumbar lordosis occurs, giving the lumbar area an ironed-out appearance. Flexion is limited. Tenderness can be present over costovertebral joints, iliac crests, greater trochanter, and heels. Chest expansion is limited. In advanced disease the spine becomes rigid, fusing in varying degrees of flexion.

Laboratory Findings

The sedimentation rate can be elevated, and a mild hypoproliferative anemia can occur. The rheumatoid factor test result is negative. The synovial fluid is inflammatory (see Table 27-1). Radiography of the sacroiliac joints in early disease shows blurring and irregularity of the joint margins, followed later by subchondral erosions, sclerosis, and eventually fusion. Bony spurs appear at tendinous insertions such as the sites of attachment of the Achilles tendon and plantar fascia. Radiography shows a straight lumbar spine, squared vertebrae, and syndesmophytes. Syndesmophytes extend along the outer aspect of the intervertebral disk and eventually form a bridge between adjacent vertebrae (bamboo spine).

Treatment

Nonsteroidal Antiinflammatory Drugs. NSAIDs (see Table 27-2) are especially useful in reducing inflammation and relieving pain, but they may not change the course of the disease. It is speculated, but not proven, that NSAIDs may encourage the patient to be more mobile and possibly lessen the chance of spine fusion. Preferred agents include indomethacin or a once-a-day agent such as piroxicam because of their antiinflammatory activity. Any antiinflammatory agent chosen usually needs to be dosed at an antiinflammatory level (i.e., upper limit of dosing range) for benefit.

Disease-Modifying Antirheumatic Drugs. Sulfasalazine has been shown to be beneficial in ankylosing spondylitis, especially when peripheral joints are involved (57,58). It can also lower levels of acute-phase reactants, suggesting disease-modifying activity. Methotrexate has also been used for ankylosing spondylitis, but controlled trails are lacking.

Physical Therapy. Physical therapy is directed at maintaining the erect posture of the patient. Patients should be encouraged to sleep in the prone position and to avoid using a pillow when sleeping on their backs. Anterior uveitis or iritis can be treated with intraocular corticosteroids. Patients with severe destructive hip disease can benefit from total hip replacement.

Important Complications of Ankylosing Spondylitis Presenting with Pain

Cauda Equina Syndrome. Patients with cauda equina syndrome generally have long-standing ankylosing spondylitis. The patient generally presents with progressive lower extremity weakness, pain, and loss of sensation in the lower extremities and perineum. Impotence and overflow incontinence are also frequently occurring problems. Radiographically, large dorsal diverticula are seen on myelography or magnetic resonance imaging (59). Electromyography demonstrates multiroot involvement. Therapy with high-dose corticosteroids and surgery both have been disappointing.

Spondylodiskitis. Spondylodiskitis is a rare complication of long-standing ankylosing spondylitis. Patients have persistent mechanical-type back pain (pain with activity) rather than inflammatory low back pain (pain in the morning or with rest). It is caused by a mobile vertebral segment surrounded by fused segments. The focus of activity at the one segment may lead to significant inflammation and damage to the adjacent vertebral bodies, simulating infection. Infection generally needs to be ruled out and treatment is directed to immobilizing the segment either via brace and allowing it to fuse or refuse; occasionally it may need to be surgically fused (60).

Vertebral Fracture. Vertebral segments connected by syndesmophytes are subject to fracture with even minor trauma (60). The usual location for such fractures are the C-5–7 vertebral segments; the fractures are typically caused by a hyperextension injury. Patients suspected of fracture should be evaluated by computed tomographic scan or bone scan to try to identify a potential fracture site, as plain radiography may not be able to demonstrate the fracture. Patients with such fractures have a relatively high morbidity and mortality even if identified, because of surgery or prolonged immobilization usually required for treatment. Only 40% of such patients return to their former level of activity.

Chronic Enthesitis. Enthesitis of Achilles tendon, plantar fascia, and occasionally the ribs can be a chronic source of pain and may be more resistant than spondylitis to usual therapies (61). In such cases indomethacin at maximum dose, or use of a DMARD such as methotrexate or sulfasalazine may be warranted. Refractory patients may benefit from low-dose radiation to the heel (62).

Reiter's Syndrome

Reiter's syndrome is defined as an asymmetric arthropathy involving predominantly joints of the lower extremities plus one or more of the following: urethritis or cervicitis, dysentery, mucocutaneous lesions, and inflammatory eye disease. It is also defined as an episode of arthritis lasting longer than 1 month that is associated with urethritis or cervicitis (63,64). The histocompatibility antigen HLA-B27 is present in approximately 80% of patients (65).

There appears to be a relationship between certain infections and a specific genetic background. Reiter's syndrome can follow infections with *Shigella*, *Salmonella*, *Campylobacter,* or *Yersinia* (64,66). An association also exists with urethritis associated with *Chlamydia* or *Mycoplasma* infections. In addition, Reiter's syndrome has been associated with human immunodeficiency virus (HIV) infection. Reiter's syndrome develops in patients without these infections, however, and most patients with nonspecific urethritis do not develop this syndrome. The risk of an individual who has a positive result for HLA-B27 with nonspecific urethritis developing Reiter's syndrome is in the range of 20%. Up to 3% of individuals with nonspecific urethritis have been shown to develop a reactive arthritis. Reiter's syndrome has a worldwide distribution and occurs more often in men. In postdysenteric Reiter's syndrome, the gender distribution is equal.

Symptoms and Signs

Arthritis affects several joints in an asymmetric fashion; knees and ankles are most often involved. Patients also experience pain in the feet and ankles secondary to inflammation at the insertion of the Achilles tendon and plantar fascia. Joints can remain swollen for several months. Swelling of two adjacent interphalangeal joints and adjoining tendon sheath results in a sausage digit or dactylitis. In approximately 20% of patients, spinal involvement occurs. Sacroiliitis is usually unilateral and spine involvement mild. Patients can also experience chest pain caused by inflammation at the tendinous insertions of the intercostal muscles.

The mucocutaneous lesions of Reiter's syndrome include oral ulcers, balanitis, and keratoderma blennorrhagica. The oral ulcers are shallow and irregular, and have a slightly erythematous base. These lesions are only present for several days. Balanitis usually begins as small painless vesicles that become hyperkeratotic. These lesions are painless and remain crusted in the circumcised patient. In the uncircumcised patient, lesions are moist and can become secondarily infected. Keratoderma blennorrhagica most commonly involves the feet. Sometimes it involves the hands, but it can be present almost any place on the body.

Conjunctivitis involves one or both eyes. Uveitis also occurs. Urethritis can precede or accompany the arthritis. Prostatitis is present in approximately 80% of patients.

As with ankylosing spondylitis, some patients may develop dilatation of the proximal aorta leading to aortic valve insufficiency.

The course of Reiter's syndrome is recurrent or persistent, with only an occasional patient experiencing transient, self-limited disease. In some patients sexual intercourse with a certain partner appears to lead to an exacerbation of Reiter's syndrome. These patients should be advised to use a condom even though the benefit of this practice is questioned by some. No evidence exists that the use of an antibiotic prevents or alters the course of Reiter's syndrome.

Laboratory Findings

Routine laboratory test results are usually normal. The sedimentation rate is quite variable and does not correlate with disease activity. Synovial fluid shows an elevated white cell count ranging from 5,000 to 50,000 cells per cubic millimeter, predominantly neutrophils. Radiography shows juxtaarticular osteopenia, joint space narrowing, and bone erosions. Periostitis is present adjacent to the involved joints and at the insertion of tendons and fasciae. Erosions, sclerosis, and irregularity of the sacroiliac joint can be present and are usually unilateral. Changes of spondylitis are usually asymmetric, occur at various levels of the spine, and are similar to those seen in psoriatic arthritis. Testing for HLA-B27 is not necessary for diagnosis. This test should be reserved for patients who have asymmetric arthritis without other evidence of Reiter's syndrome.

Treatment

Treatment of Reiter's syndrome is similar to that of ankylosing spondylitis. NSAIDs are first-line therapy followed by sulfasalazine in refractory cases. Methotrexate or azathioprine can be used in more severe disease. Intraarticular corticosteroid can also be useful. Data also exist to suggest that treatment of Reiter's syndrome or reactive arthritis with several weeks of antibiotics useful against *Chlamydia* may affect the course of the subsequent illness (67).

Complications of Reiter's Syndrome Associated with Chronic Pain

Rare patients may have more persistent inflammatory eye disease requiring continuous ophthalmology care.

For a discussion of chronic enthesitis, see Ankylosing Spondylitis.

Psoriatic Arthritis

Arthritis appears in up to 20% of patients with psoriasis (68). Hereditary factors play a role: An increased prevalence of psoriatic arthritis occurs in first-degree relatives. The epidemiology and pathogenesis of psoriatic arthritis are not known. An association with HLA-B27 is seen in psoriatic arthritis with spondylitis, but not in patients with peripheral arthritis. Onset of psoriatic arthritis is usually in the third or fourth decade, and the gender ratio is approximately equal. In most patients, psoriasis precedes the arthritis by several years. Most patients with psoriatic arthritis have only a few joints that are involved, and, overall, the prognosis tends to be better than in rheumatoid arthritis. Psoriatic arthritis has been noted in patients with HIV infection.

Symptoms and Signs

Several patterns of arthritis are observed in patients with psoriasis. The majority of patients have an asymmetric oligoarthritis involving the proximal joints of the hands and feet. In approximately 10% of patients, arthritis affects predominantly the distal interphalangeal joints and is usually accompanied by psoriasis of the adjacent nail. Other patients have a symmetric polyarthritis similar to that seen in rheumatoid arthritis. These patients usually have negative results for rheumatoid factor. If the rheumatoid factor test result is positive, the patient probably has both rheumatoid arthritis and psoriasis. Patients can also manifest sacroiliiitis, usually unilateral, and variable degrees of spondylitis. In some patients the spine becomes ankylosed. A few patients have a severe, destructive, and deforming polyarthritis referred to as *arthritis mutilans*.

Joints are swollen, warm, and tender, and a digit may have the appearance of a sausage. Contractures and ankylosis of joints occur with long periods of persistent joint inflammation. In most cases there appears to be no definite correlation between the degree of skin involvement and joint disease.

Laboratory Findings

Laboratory findings include an elevated sedimentation rate and a hypoproliferative anemia. The rheumatoid factor test result is negative. The synovial fluid shows evidence of inflammation with elevated white cell counts; the cells are predominantly polymorphonuclear. A somewhat characteristic radiographic finding is that of the pencil-in-cup deformity caused by osteolysis, or whittling of the distal end of the middle phalanx, which produces a pencil point that projects into a widened cuplike erosion in the adjacent surface of the distal phalanx. Radiography shows joint space narrowing, erosions, osteolysis, and ankylosis, depending on the degree of clinical severity. The radiographic findings of the spine are similar to those found in patients with Reiter's syndrome.

Treatment

Initial treatment of psoriatic arthritis is aspirin or other NSAIDs (see Table 27-2). In patients with progressive disease, gold, sulfasalazine, and even hydroxychloroquine have been used successfully (69). Methotrexate and cyclosporine have also been used to treat both the arthritis and the skin disease. Low-dose oral corticosteroids as well as intraarticular corticosteroids can also be used. The tapering of corticosteroids in patients who have been on moderate to large doses may exacerbate the skin disease. Recently, statistics have shown that psoriatic arthritis responds well to etanercept, a TNF-a antagonist.

Important Complications of Psoriatic Arthritis Presenting with Pain

See Ankylosing Spondylitis for a discussion of chronic enthesitis. For a discussion of carpal tunnel syndrome, see Rheumatoid Arthritis.

Arthritis Associated with Inflammatory Gastrointestinal Disease

Both ulcerative colitis and regional enteritis (Crohn's disease) are associated with peripheral arthritis and spondylitis (70). Peripheral arthritis occurs in approximately 10% to 20% of patients with inflammatory bowel disease. Onset of peripheral arthritis is usually in the third or fourth decades. Both genders are equally affected. The arthritis usually follows the onset of colitis by months to years and involves only one or two joints. Arthritis is acute, lasts several days to several weeks, and leaves no residual damage. The knees and ankles are most frequently affected.

Ankylosing spondylitis is also associated with inflammatory bowel disease. The gender distribution is equal, in contrast to the male predominance observed in primary ankylosing spondylitis. The majority (70%) of patients with spondylitis associated with inflammatory bowel disease has positive results for HLA-B27. Asymptomatic bilateral sacroiliiitis can be found in up to 15% of patients with inflammatory bowel disease. Frequency of HLA-B27 is not increased in patients with only peripheral arthritis. Synovial fluid analysis shows an inflammatory effusion.

Treatment

Peripheral joint symptoms are managed with salicylates or other NSAIDs (see Table 27-2). NSAIDs, however, may lead to an exacerbation of the inflammatory bowel disease. Peripheral arthritis often disappears after colectomy. Treatment of the spondylitis is similar to that described for ankylosing spondylitis.

Arthritis Caused by Deposition of Calcium Pyrophosphate

Deposition of calcium pyrophosphate dihydrate in the joint produces both an acute and chronic form of joint disease (71,72). The acute or subacute form is referred to as *pseudogout* because of its similarity to gout. *Chondrocalcinosis* refers to calcium pyrophosphate deposits in articular tissue that are detectable radiographically and occurs in the absence of inflammatory arthritis. Pseudogout affects persons over the age of 40, men predominately. The knee is the most frequent site of acute arthritis, but the hip, shoulder, ankle, wrists, and bursae can be affected. Approximately 3% to 5% of the adult population have calcium pyrophosphate deposits in knee joints at the time of death. This disorder is associated with OA.

Three forms of CPDD are recognized: a hereditary form, CPDD associated with metabolic and other diseases, and an idiopathic form. The frequency of OA in CPDD varies from 40% to 70%. CPDD occurs in 41% of patients with hemochromatosis and in 5% to 15% with hyperparathyroidism (73). An association is suspected in patients with diabetes mellitus, hypophosphatemia, Wilson's disease, ochronosis, and hypothyroidism.

Pathophysiology

The initial site of crystal formation is in articular cartilage. In idiopathic CPDD it is not clear whether the primary event is deposition of crystals in cartilage or whether the crystals develop as a consequence of disturbed cartilage metabolism. Increased inorganic pyrophosphate is found in the synovial fluid and probably reflects a local disorder of pyrophosphate metabolism leading to deposition of calcium pyrophosphate crystals in the joint (74,75). Elevated levels are also found in patients with OA. Acute arthritis is brought on by shedding of crystals into the joint space. The mechanism for crystal shedding is the lowering of either calcium or pyrophosphate ions in synovial fluid (76,77). The decreased concentration of ionized calcium results in movement of crystals from cartilage into synovial fluid. Crystals can also be shed into the synovial fluid as a consequence of mechanical disruption of cartilage. Attacks can follow trauma. In addition, crystals can be released as a result of degradation of cartilage by enzymes from polymorphonuclear white cells during episodes of bacterial arthritis or other forms of inflammatory arthritis. Increased enzyme activity is also present in OA.

Calcium pyrophosphate dihydrate crystals are capable of inducing an inflammatory response. Injection of these crystals into a normal joint produces an inflammatory response (78). Crystals bind IgG and are phagocytized by polymorphonuclear white cells, resulting in the release of cytoplasmic and lysosomal enzymes.

Symptoms and Signs

Several patterns of joint disease are recognized (71). In approximately 25% of patients, CPDD presents as an acute arthritis involving a single joint or a few joints at any given time. The clinical picture mimics that of acute gout, which accounts for the term *pseudogout*. The onset of joint swelling and pain is abrupt and severe and usually reaches a peak within 24 to 36 hours. An attack can last up to 14 days. The joint is swollen, red, and tender. The most common site of involvement is the knee, but attacks can involve other large joints such as the ankles, wrists, elbows, or hips. Also, the lumbar and cervical spine can be involved. Trauma, surgery, or severe medical illness can precipitate an attack. The same joint is often involved in subsequent attacks. Radiographic evidence of chondrocalcinosis may be present in affected joints.

Approximately 5% of patients with CPDD have a form of disease that mimics rheumatoid arthritis (*pseudorheumatoid disease*). Involvement of multiple joints, synovial proliferation, limitation of joint motion, and joint deformity can develop. Patients experience fatigue and morning stiffness. To further confuse the issue, calcium pyrophosphate deposition can occur in rheumatoid arthritis.

CPDD also occurs in a chronic form that is similar to OA. Multiple joints are involved and include the knees, wrists, metacarpal phalangeal joints, hips, shoulders, elbows, and ankles. The disease involves middle-aged to elderly patients, predominantly women. CPDD can mimic neuropathic arthropathy and can also occur in patients with neuropathic joint disease.

The diagnosis of calcium pyrophosphate disease is established by identification of calcium pyrophosphate crystals in synovial fluid, both free and in polymorphonuclear white cells. The crystals appear as short rods, rhomboids, and cuboids, and they have a sign of weakly positive birefringence under compensated polarized light. Radiography shows calcification in articular hyaline cartilage that is parallel to and separated from the subchondral bone. Calcifications in fibrocartilage are thick and irregular densities and are found in the menisci of the knee, symphysis pubis, annulus fibrosus, and the triangular cartilage of the wrist. Calcifications also occur in the Achilles, supraspinatus, and triceps tendons, but can involve any tendon. Changes in the joint are similar to those seen in OA with sclerosis of subchondral bone, joint space narrowing, and large subchondral cysts.

Treatment

The NSAIDs (see Table 27-2) are effective in the treatment of acute and chronic joint disease. An NSAID is given for 10 to 14 days in patients with acute pseudogout. The drug can be continued indefinitely in patients with chronic calcium pyrophosphate disease associated with OA. When an NSAID is contraindicated, another method of treatment for an acute attack is prednisone, starting with 40 mg the first day and gradually tapering over a 7-day period. Colchicine, 0.6 mg twice a day, is started on day 3 or 4 and continued for several weeks to avoid a flare of arthritis after prednisone is discontinued. Colchicine, 0.6 mg twice a day, can also be given prophylactically to reduce the number and length of attacks (see colchicine in section on gout). Aspiration of the involved joint followed by an injection of glucocorticoids reduces pain and swelling.

Hydroxyapatite Arthropathy

Arthritis is caused by deposition of calcium hydroxyapatite crystals in the joint (71). Knees and shoulders are most frequently involved. The Milwaukee shoulder, also known as *cuff tear arthropathy*, is an entity observed in elderly women with glenohumeral OA, rotator cuff tears, and joint effusions. Joint fluid from the shoulder has few white cells, but it has elevated levels of collagenase and neutral proteases. Calcium hydroxyapatite and calcium pyrophosphate crystals are often found together in the joint. Hydroxyapatite crystals are extremely small, ranging from 0.1 to 1 mm in length. The calcium components in the synovial fluid can be detected by staining with alizarin red S (79). Definitive diagnosis depends on electron microscopy or x-ray diffraction studies. Radiographically, intraarticular calcifications of hydroxyapatite have a diffuse and amorphous pattern. Treatment of hydroxyapatite disease is with NSAIDs, repeated joint aspirations, and rest of the involved joint.

Gout

Gout is characterized by elevated serum urate levels, recurrent attacks of acute arthritis involving a single joint or a few joints at any given time, and deposition of monosodium urate dihydrate (tophi) in and around joints, leading in some patients to a deforming and crippling arthritis. Renal stones also may form. These features are present in varying combinations (80).

Recognized since ancient times, gout has been depicted in caricatures as affecting well-fed aristocrats overindulging in rich foods and wines. The disease has been referred to as the *king of diseases* and the *disease of kings* (80,81).

The normal serum urate concentration is 5.1 ± 1.0 mg per dL in men and 4.0 ± 1.0 mg per dL in premenopausal women. After menopause, the level in women approximates that of men. The level in young boys is 3 to 4 mg per dL and increases to adult levels at puberty. Serum urate levels show a positive correlation with weight and surface area in various racial groups (82). The prevalence of gout varies from 0.20 to 0.35 per 1,000 (83,84). The prevalence of gout increases with age and increasing levels of serum urate. In one study of men whose ages ranged from 35 to 44 years old, the prevalence was 15 per 1,000 men (85).

The familial incidence of gout varies widely. In one study, approximately 40% of the patients gave a positive family history of gout (86). Serum urate levels appear to be controlled by multiple genes. Both genetic and environmental factors play a role in the expression of hyperuricemia and gout. For example, higher serum urate levels are found in Filipinos living in the United States compared with racially identical persons living in the Philippines. These persons are unable to excrete the greater uric acid load resulting from the higher purine content of the diet eaten in the United States (87).

Etiology and Pathophysiology

Uric acid is a product of purine metabolism (80). The serum urate concentration depends on the rate of uric acid production and excretion. Approximately two-thirds of uric acid is excreted in the urine and one-third into the gastrointestinal tract. Normally, uric acid is completely filtered through the glomeruli and completely reabsorbed in the proximal tubule. Secretion of uric acid occurs in the proximal tubule, followed by a second reabsorption in the proximal tubule.

Primary gout is defined by the absence of other diseases or conditions such as drugs that lead to hyperuricemia and gout. Approximately 90% of patients with primary gout have decreased renal clearance of uric acid resulting from reduced glomerular filtration, increased tubular reabsorption, reduced tubular secretion, or combinations of these factors. Evidence for a molecular renal defect is still lacking in the majority of patients.

Approximately 10% of patients are overproducers of uric acid. Overproduction is defined as the urinary excretion of more than 800 to 1,000 mg of uric acid in 24 hours while the patient is on a regular purine diet.

Two inborn errors of purine metabolism make up a small number of primary gout patients who are overproducers of uric acid. The first disorder is caused by a partial

deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase, which catalyzes conversion of hypoxanthine to inosinic acid and guanine to guanylic acid (80). These patients usually experience the onset of gouty arthritis in the second or third decade and have a high frequency of uric acid stones. The disease is inherited as an X-linked disorder, therefore affecting male subjects, with women as carriers. Some of these patients also have dysarthria, hyperreflexia, lack of coordination, and mental retardation. A severe form of this disorder with almost a complete deficiency of this enzyme, referred to as the Lesch-Nyhan syndrome, is characterized by self-mutilation, choreoathetosis, and mental retardation (88,89). This disorder is classified under secondary hyperuricemia or gout because the neurologic disorder is predominant.

The second disorder is caused by increased 5-phosphoribosyl-1-pyrophosphate synthetase activity leading to elevated levels of intracellular 5-phosphoribosyl-1-pyrophosphate and overproduction of uric acid (80,90). This disorder is also genetically X- linked. The onset of gouty arthritis is in the second or third decade, and a high frequency of uric acid stones occurs.

Secondary gout is defined as gout or hyperuricemia occurring in patients with other disorders. Overproduction of uric acid results in hyperuricemia in patients with disorders associated with increased cell proliferation and turnover of nucleic acids. These disorders include myeloproliferative and lymphoproliferative diseases, multiple myeloma, polycythemia, pernicious anemia, hemoglobinopathies, and some carcinomas. The hereditary disorder glucose 6-phosphatase deficiency (von Gierke's glycogen storage disease) is also manifested by overproduction of uric acid.

Secondary hyperuricemia can also result from renal failure or the effects of drugs or toxins on renal clearance of uric acid. Diuretic agents, low doses of aspirin (less than 2 g per day), alcohol, ethambutol, cyclosporine, and lead are some of the agents that decrease the clearance of uric acid and thereby raise the serum urate level.

Pathophysiology of Acute Gouty Arthritis

Acute gouty arthritis results from the inflammatory reaction to urate crystals that form in the joint space or are released into the joint from synovium or articular cartilage. Plasma becomes supersaturated with urate at concentrations of approximately 7 mg per dL (91). Factors in addition to supersaturation of plasma urate are necessary for crystal precipitation because most patients with hyperuricemia do not develop gout. The lower temperatures found in peripheral joints or tissues might contribute to urate precipitation at these sites. Urate is less soluble at 32°C, which is the temperature observed in a normal knee, compared with the core body temperature of 37°C (92). Another mechanism for urate precipitation might be the faster reabsorption of extracellular fluid than urate from the joint space, resulting in a transient increased urate concentration and crystal formation (93). Trauma or impact loading of a joint that breaks crystals loose from the joint surface is yet another possible mechanism and might explain the high frequency of gout at the base of the great toe, which is a joint subjected to great stress.

Urate crystals induce inflammation by several mechanisms (80). Urate crystals activate Hageman's factor in joint fluid, leading to the formation of kinins that induce vasodilatation and increased vascular permeability. Urate crystals activate the complement system with the generation of leukocyte chemotactic factors and also stimulate the formation of leukotrienes from arachidonic acid. Furthermore, urate crystals can activate platelets, which secrete several inflammatory mediators including prostaglandins. Urate crystals can also stimulate synovial lining cells and macrophages that secrete prostaglandins and collagenase.

The key to urate-induced inflammation is the polymorphonuclear white cell. Urate crystals bind IgG, leading to their attachment to and phagocytosis by polymorphonuclear white cells. This process mediates the production of superoxide anions, which damage tissue (94). In addition, ingestion of crystals results in the release of chemotactic factors from the polymorphonuclear white cells, thus attracting more polymorphonuclear white cells (95). On ingestion by polymorphonuclear white cells, crystals are incorporated into phagosomes, which fuse with lysosomes. The rupture of phagolysosomes inside polymorphonuclear white cells damages these cells. Lysosomal and cytoplasmic enzymes are released into the joint space, resulting in tissue inflammation and injury.

Gouty arthritis often develops with fluctuation of serum urate levels. A rapid increase in serum uric acid results in precipitation of crystals in tissue or fluid. A rapid decrease in serum urate brings about release of urate from the joint surface into the joint space.

Drinking of alcohol is also associated with the precipitation of gouty attacks. Metabolism of ethanol results in an increased concentration of blood lactate, which blocks the renal excretion of uric acid by inhibiting tubular secretion and raising the serum urate level. Alcohol consumption also leads to accelerated degradation of adenosine triphosphate to adenosine monophosphate with accumulation of adenine nucleotides that are degraded to uric acid and other purine metabolites (96). The drinking of moonshine whiskey is associated with gouty arthritis and is referred to as *saturnine gout* (97). Moonshine whiskey is often distilled in automobile radiators containing a lead core. Lead reduces the excretion of urate and decreases its solubility. In addition, lead may affect renal mechanisms for handling urate, leading to elevated levels.

Gout follows periods of fasting. During fasting the increased plasma level of acetoacetate and b-hydroxybutyrate interferes with renal excretion of urate (98). Overindulgence of food and wine has often been associated with gout. When a large protein- and purine-rich diet is ingested along with copious amounts of wine or other liquor, the uric acid serum concentration rises because of increased formation and decreased excretion of sodium urate. Acute gouty arthritis attacks occur when drugs increase or lower the serum uric acid level. Attacks are precipitated by allopurinol, which lowers the uric acid concentrations, and thiazides or low doses of aspirin, which raise the level. Cyclosporine interferes with the renal excretion of uric acid and induces hyperuricemia and gout (99). An increased frequency of gout is seen in transplant recipients receiving cyclosporine and may affect atypical joints such as the hips, sacroiliac joints, or shoulders.

Symptoms and Signs. Gouty arthritis occurs mainly in middle-aged and older men and after menopause in women. Approximately one-fourth of the patients have a family history of gout. Nephrolithiasis precedes the first attack of arthritis in approximately 10% of patients. The first attack occurs most often in the metatarsal phalangeal joint of the great toe (podagra). Subsequent attacks might be separated by several months or even years. The involved joint usually returns to normal between attacks. In untreated cases, the attacks become more frequent and involve other joints, such as wrists, elbows, olecranon bursae, and the small joints of the hand. Gouty arthritis can occur in distal interphalangeal joints already involved with OA and Heberden's nodes (100). Gout can be overlooked in these joints because acute inflammation can also occur with Heberden's nodes. Gouty arthritis of intervertebral joints, sacroiliac joints, and shoulders and hips is uncommon.

The typical attack of gout comes on acutely, often during the early hours of morning. Attacks also occur after surgery. Pain and swelling reach a peak within 24 hours. The joint is exquisitely tender, and overlying soft tissue is swollen and erythematous even to the degree that it could be mistaken for cellulitis. Pain is intense and throbbing. Patients are unable to tolerate even a light sheet touching the involved great toe. Jarring of the bed can make the patient wince with pain. The patient might even dread the landing of a fly on the involved toe. Both a low-grade fever and leukocytosis can accompany the attack, especially in polyarticular gout. An untreated attack of gout usually lasts for 1 to 2 weeks. Less severe attacks also occur that last only a few days.

Chronic tophaceous gout develops in some patients. Before the effective control of hyperuricemia, approximately one-half of the patients with episodes of gouty arthritis eventually developed deposits of monosodium urate dihydrate in and around joints as well as in other tissues. These deposits, referred to as *tophi*, usually become apparent at least 10 years after the onset of gouty arthritis. They develop in the olecranon, infrapatellar and prepatellar bursae, Achilles tendons, synovium, subchondral bone, and, infrequently, in the cartilage of the ear. Tophi can ulcerate and drain material that contains microscopic needle-shaped crystals of monosodium urate. Patients with tophaceous gout have frequent episodes of acute gouty arthritis. Joint deformity and disability can be quite severe in the untreated patient.

Significant renal disease secondary to gouty nephropathy is rare. Proteinuria, decreased concentrating capacity, and a decrease in creatinine clearance might be present. Small deposits of urate are observed in the interstitium of the renal medulla. Nephrosclerosis and hypertension are frequently associated with gout.

Treatment of patients with underlying myeloproliferative or lymphoproliferative disorder results in extremely high levels of serum urate that can precipitate in the renal tubules, producing obstruction and oliguria. Patients should be treated with allopurinol and colchicine before treatment of the blood dyscrasia.

Renal calculi develop in approximately 20% of patients with gout (101). Hypertension, diabetes mellitus, and hypertriglyceridemia occur more frequently in patients with gout.

Laboratory Findings. Radiography of the affected joint in acute gouty arthritis is usually normal. When the first metatarsal phalangeal joint is involved, radiography might show underlying changes of OA. The typical erosion caused by urate deposition is sharply defined and has a thin shell-like overhanging edge at the margins of the erosion. The diagnosis of gout is established by demonstration of the characteristic crystal of monosodium urate monohydrate in the synovial fluid or from tissue deposits. Crystals are found both in the polymorphonuclear white cells and free in fluid. The crystals in joint fluid are usually rod shaped and 7 to 10 µm in length. They are identified by use of polarized microscopy. With use of a first-order red compensator, crystals have a sign of strongly negative birefringence (102). Crystals

from tophi are long and needle shaped and are not usually found in white cells.

Treatment. Treatment of a patient with gout has two components: treatment of the acute gouty arthritis and treatment of hyperuricemia (80). Each is treated independently. Even though they are closely interrelated, the drugs used for each are different. In fact, the indiscriminate use of a drug to lower the uric acid can exacerbate or prolong an attack of gouty arthritis.

Antiinflammatory Drugs. For the acute attack of gouty arthritis, the patient is given indomethacin, 200 mg in four divided doses (50 mg every 6 hours) the first 24 hours, followed by 150 mg every day for 7 to 10 days. Other NSAIDs (see Table 27-2) can also be used. NSAIDs for the treatment of acute gout should be avoided or used with caution in patients with symptomatic heart failure, renal failure, oliguria, or peptic ulcer disease. Glucocorticoids are also quite effective in treatment of acute gout. Prednisone is given over a 7-day period with an initial dose of 40 mg as a single dose and then gradually tapered over a 7-day period. To avoid a flare of arthritis when prednisone is discontinued, the patient is started on 0.6 mg of colchicine or an NSAID beginning on day 3 or 4 of prednisone therapy and continuing for several weeks. Methylprednisolone can be given intravenously to patients unable to take oral medications. The dose schedule for oral prednisone is followed. Intraarticular corticosteroids can also be used to treat gout in a large joint such as the knee.

In patients who experience frequent attacks of acute gouty arthritis, colchicine, 0.6 mg once or twice a day, is quite effective in preventing attacks. Patients on this prophylactic regimen can abort an acute attack by taking colchicine, 0.6 mg every hour for four to six doses, when they experience the first twinge of joint pain.

Myopathy and polyneuropathy may occur on maintenance doses of colchicine in patients who have renal insufficiency (103). Myositis manifests as proximal muscle weakness and serum creatine kinase becomes elevated. These abnormalities return to normal 3 to 4 weeks after stopping the drug. Polyneuropathy also disappears on discontinuing colchicine. In addition, agranulocytosis or aplastic anemia can occur in patients with renal insufficiency who are on regular doses of colchicine because the plasma drug levels in these patients greatly increase.

Antihyperuricemic Drugs. Treatment of hyperuricemia in patients with gout is directed at preventing the formation of tophaceous deposits. It is not uniformly agreed that all patients with elevated uric acids and gouty arthritis require medications to lower their uric acid. If the patient already has tophaceous deposits in joints or subcutaneous tissue, then the uric acid should be lowered. On the other hand, an elevated uric acid of less than 10 mg per dL in a patient without tophi or frequent gouty attacks might not require treatment. Whether they have gout or not, persons with uric acid levels above 10 mg per dL are usually treated because of their higher risk of developing gout.

The uric acid concentration can be lowered by probenecid, which is a uricosuric agent (104). In patients with normal renal function and no renal stones, probenecid is an effective agent. The dose of probenecid is 1 to 3 g per day given twice a day. The urine should be alkalinized to prevent precipitation of urate in the urinary tract. Sulfinpyrazone is another uricosuric drug. The usual daily dose is 300 to 400 mg per day, administered in 3 or 4 divided doses.

Serum uric acid level is effectively reduced by allopurinol, which is a potent inhibitor of xanthine oxidase (104). This drug blocks the conversion of hypoxanthine to xanthine and xanthine to uric acid. This leads to the accumulation of other oxypurines in the blood. The daily dose of allopurinol is 300 to 800 mg per day, which is regulated to reduce uric acid to a concentration below 6 mg per dL. Allopurinol administration can precipitate an acute attack of gout, presumably because of fluctuation of sodium urate between tissue and blood. To prevent an acute gouty attack, allopurinol is started in a low dose and gradually increased. Colchicine, 0.6 mg twice a day, is given along with the allopurinol to prevent an acute attack.

The most significant side effect of allopurinol is a rash that occasionally progresses to a severe life-threatening exfoliative dermatitis. Transient leukopenia and abnormalities of liver function are observed in some patients. In patients treated for many years, xanthine stones may occur. These tend to occur in patients who are overproducers and hyperexcretors of uric acid.

Allopurinol is the drug of choice in patients with renal insufficiency who are unable to excrete a uric acid load. This drug is also indicated in patients with uric acid renal calculi. Allopurinol is more effective than probenecid in reducing tophi in patients with severe tophaceous gout. The addition of probenecid, however, further enhances the lowering of serum acid level.

Allopurinol is also indicated in patients with gout who are overproducers and hyperexcretors of urate (urine acid excretion greater than 1,000 mg for 24 hours) because these patients are at greater risk for developing renal stones. No clear evidence exists that treatment of asymptomatic hyperuricemia in a person who is not a hyperexcretor is beneficial.

Allopurinol potentiates the action of 6-mercaptopurine and azathioprine (104). The dose of the cytotoxic agent is usually reduced by at least one-third in patients on allopurinol.

Infectious Arthritis

Nongonococcal Bacterial Arthritis

Acute bacterial or septic arthritis is a serious problem that requires prompt treatment to avoid joint damage (105,106). Bacteria usually reach the joint by hematogenous spread from a primary infection elsewhere. Often, however, no primary source of infection is found. An infection in the adjacent bone or soft tissue can extend directly into the joint. Acute bacterial arthritis is most often caused by *Neisseria gonorrhea*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Staphylococcus pyogenes*, or *Haemophilus influenzae*, with *Staphylococcus* spp. being the most common causative organisms. Gram-negative organisms include *Escherichia coli*, *Salmonella*, and *Pseudomonas* and are usually seen in patients who are immunosuppressed or use intravenous drugs.

Patients with diabetes mellitus or blood dyscrasias or those receiving glucocorticoids or immunosuppressive drugs are more susceptible to joint infection. Septic arthritis is more likely to occur in joints previously damaged by trauma or inflammatory arthritis (e.g., rheumatoid arthritis).

Pathophysiology. The synovium is edematous and infiltrated by neutrophils. As the disease progresses, small abscesses are present in the synovium and subchondral bone. Proteolytic enzymes from neutrophils damage the cartilage, bone, and joint capsule. Healing is manifested by proliferation of fibroblasts, which can lead to ankylosis.

Symptoms and Signs. The onset of bacterial arthritis is usually abrupt and associated with severe pain and fever. A shaking chill occasionally accompanies the onset. Any motion of the joint causes excruciating pain. The overlying skin is usually erythematous. In elderly patients and those who are on glucocorticoids, the symptoms can be less severe.

The joint affected most frequently by septic arthritis is the knee, which is involved in at least one-half of the cases. Other commonly involved joints are hips, shoulders, wrists, ankles, elbows, and sternoclavicular and sacroiliac joints. Involvement of the latter two joints has been noted in intravenous drug abusers. In the spine, the intervertebral disk space and adjacent vertebral bodies are infected. Infection in the hip is more difficult to recognize because swelling is less evident. Patients with hip infection might hold the thigh in adduction, flexion, and internal rotation. Pain is felt in the groin or thigh and is also referred to the anterior surface of the knee.

An overlying infected bursa or cellulitis can be mistaken for septic arthritis. It is important in aspirating a joint not to insert the needle through an infected bursa or cellulitis and possibly infect a normal joint.

Laboratory Findings. Joint fluid usually shows increased numbers of neutrophils ranging from 10,000 to greater than 100,000 per cubic millimeter. The white cell count in infected bursa fluid is not as high as observed in the joint. A peripheral blood leukocytosis might also be present. The synovial fluid glucose is usually less than 20% of a simultaneously drawn blood glucose when these two compartments are in equilibrium. Equilibrium is usually reached 6 hours after a meal. In gonococcal arthritis, however, the synovial fluid glucose is not significantly reduced. Gram's stain performed on synovial fluid often shows bacteria except in gonococcal infections. Culture results of synovial fluid as well as blood are also often positive.

Radiography of the joint initially shows soft tissue swelling and distension of the joint capsule, followed later by juxtaarticular osteoporosis and periosteal elevation. As the process continues, destruction of articular cartilage leads to joint space narrowing followed by bony erosions. Juxtaarticular bone destruction might indicate

osteomyelitis. In the spine, the initial change consists of narrowing of the disk space and proliferation of bone at vertebral margins. Osteolytic lesions in adjacent vertebrae are seen later. Radioisotope scans can be helpful in identifying infection in certain joints such as the hip, shoulder, spine, and sacroiliac joints, but inflammatory arthritides and degenerative joint disease also give a positive scan result.

Treatment. An infected joint requires immediate aspiration and rapid initiation of parenteral antibiotic therapy. It has been reported that joint outcome is best when patients are seen within 7 days of initial symptoms (107). Joint fluid should be immediately cultured and a Gram's stain performed. When organisms are seen on Gram's stain, a penicillinase-resistant penicillin or cephalosporin plus aminoglycan should be given immediately and adjusted appropriately when the organism is identified and antibiotic sensitivities are determined. Antibiotics should be given intravenously for at least the first 2 weeks. A total of 6 weeks of antibiotic therapy is indicated. Antibiotics do not need to be infused into the joint. The joint should be adequately drained to prevent damage. Usually drainage can be accomplished with a large-gauge needle. Drainage reduces intraarticular pressure and removes pus, which is a source of proteolytic enzymes. Repeated aspirations are only necessary during the first few days of treatment. Surgical drainage is required when the joint cannot be adequately aspirated and irrigated by needle or when the cell count in the synovial fluid does not decline in spite of what appears to be adequate drainage. Surgical drainage via arthroscopy should also be considered in patients with underlying arthritis and those with prolonged symptoms (i.e., longer than 7 days) (54). During the first few days of treatment, splinting of the involved joint in extension makes the patient more comfortable and reduces the possibility of a flexion contracture. Daily physical therapy, once the acute process has resolved, improves the range of motion. In a severely damaged joint, bony fusion might be required.

Gonococcal Arthritis

Gonococcal arthritis is a frequent cause of bacterial arthritis in young adults (105,106). Women are more susceptible to gonococcal arthritis during menses and pregnancy. Persons who have a homozygous deficiency of complement component C5, C6, C7, or C8 are also susceptible to disseminated neisserial infections (108). Patients with low complement levels caused by consumption of complement might also be more susceptible to disseminated neisserial infections (108).

Symptoms and Signs

Patients typically present with fever and migratory arthritis or arthralgias that evolve in several days into a monoarticular arthritis. Patients also directly present with monoarticular arthritis. Wrists and knees are common sites of involvement, but any joint can be affected. Arthritis is manifested by swelling, erythema, and severe pain as in other bacterial arthritides. Skin lesions can accompany gonococcal arthritis. These lesions can be pustular, vesicular, or hemorrhagic and can ulcerate.

Laboratory Findings

Joint fluid shows increased numbers of polymorphonuclear white cells, but the white cell count might not be as high as in other bacterial infections. The joint fluid glucose is also not decreased to the low levels found in other bacterial joint infections.

Diagnosis

Gonococcal arthritis is suspected in a patient presenting with fever, typical skin lesions, and polyarthralgias or arthritis that evolves into a monoarticular arthritis. Diagnosis is confirmed by positive culture results from synovial fluid or from blood, but culture results from these sites are positive in fewer than 50% of cases. Cultures from skin lesions are also usually negative. Gram's stain or culture results from cervix, urethra, or rectum might be positive when joint, skin, and blood culture results are negative.

Treatment

The patient should be admitted to the hospital and receive parenteral antibiotics. Currently, the recommendation is to start a third-generation cephalosporin such as ceftriaxone until susceptibilities are determined, as 5% of strains are penicillin resistant (109). Most patients are still candidates for aqueous crystalline penicillin G, 10 million U per day given intravenously for 3 to 4 days. If substantial improvement has occurred, the patient can be discharged on oral ampicillin or amoxicillin, 500 mg 4 times daily for an additional 7 days. In most patients this regimen is adequate, but in some patients with severer joint involvement, treatment is continued for 3 to 4 weeks. Unlike other bacterial infections, gonococcal infection seldom requires that antibiotics be given for 6 weeks.

The patient is placed at bed rest for the first 2 days. Splinting of the affected joint provides pain relief. The infected joint should be immediately aspirated. The frequency of aspirations depends on the degree of inflammation. In most patients residual joint damage does not occur.

Tuberculous Arthritis

Pathophysiology

Infection of a joint with *Mycobacterium tuberculosis* causes a destructive arthritis (110). Arthritis and tenosynovitis can also be caused by atypical mycobacteria such as *M. kansasii*, *M. marinum*, and *M. intracellulare*. Approximately 1% of patients with tuberculosis have arthritis. Patients with arthritis might have no evidence for active or even inactive pulmonary involvement. Joints are infected by direct hematogenous spread or by extension from a tuberculous process in adjacent bone. As the disease evolves, the cartilage is destroyed and erosions appear in the subchondral bone. Infection can extend from the joint to soft tissues, producing cold abscesses and draining sinus tracts. Tendon sheaths are also involved.

Tuberculosis of the spine (Pott's disease) involves the margins of the vertebral bodies and spreads into the adjacent disk space. Collapse of vertebral bodies in the thoracic spine results in kyphosis or a gibbus. Infection can also spread into the adjacent paraspinal muscles, extend up and down the spine, and eventually emerge as a cold abscess in the groin. Extension into the meninges results in tuberculous meningitis or, into the spinal cord, cord compression and paraplegia.

Symptoms and Signs

The patient with tuberculous arthritis might have low-grade fevers and night sweats. The involved joint is warm, swollen, and painful. An effusion is usually present. Tuberculous tenosynovitis of the flexor tendons in the wrist can compress the median nerve and produce a carpal tunnel syndrome. Tuberculous tenosynovitis should be excluded in patients presenting with unilateral carpal tunnel syndrome and low-grade fevers. Symptoms of spine involvement depend on the level of involvement.

Laboratory Findings

The white cell count in synovial fluid is usually greater than 10,000 per cubic milliliter, with approximately 50% to 60% polymorphonuclear white cells. The synovial fluid glucose is low. The tubercle bacilli might be seen on smear, but the diagnosis often requires biopsy and culture of synovial tissue.

Treatment

The antibiotic treatment of tuberculous arthritis is the same as for pulmonary tuberculosis except that a longer duration of therapy may be necessary, depending on the clinical and radiographic response. For adults, isoniazid, 300 mg per day (5 mg per kg), and rifampin, 600 mg per day (10 mg per kg), are given for at least 9 months (110). Some patients with tuberculous arthritis may require 12 to 18 months of therapy. When isoniazid resistance is documented, ethambutol, 15 to 25 mg per kg per day, is given with rifampin for a minimum of 12 months. In these patients, pyrazinamide, 15 to 30 mg per kg per day, can be added for the initial 2 months of therapy.

The joint should be placed at rest and adequately drained. In severe destructive disease, debridement and fusion of the joint might be required.

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CHAPTER 28

Neuropathic Myofascial Pain Syndromes

C. Chan Gunn

Myofascial pain syndromes are a large and diverse group of painful conditions that occur in the musculoskeletal system. They affect muscles and their connective tissue attachments in any part of the body, and are therefore customarily named according to the location of the painful part (e.g., lateral epicondylitis, Achilles tendonitis, frozen shoulder, bicipital tendonitis, and even low back pain) (Table 28-1). They are puzzling because they seem to arise and persist in the absence of any detectable injury or inflammation. Myofascial pain syndromes are often difficult to treat because medications and the commonly available physical therapies give only temporary relief. Innumerable patients, therefore, wander from provider to provider in a vain search for relief.

TABLE 28-1. Common myofascial pain syndromes caused by shortened muscles[a]

The term *myofascial pain syndrome* is presently used in a vague and indeterminate way to denote any regional musculoskeletal pain syndrome without regard to its source or cause. However, careful examination of these syndromes often reveals them to be the effects of neuropathy appearing in the musculoskeletal system. The initial and underlying problem is malfunction of the peripheral nervous system, and pain is just one possible although not inevitable downstream product of the neuropathy. The key to successful management of this important and widespread category of chronic pain is to understand neuropathy, how it can cause pain, and recognize it in its many guises.

PERIPHERAL NEUROPATHY AND PAIN

Medical diagnosis traditionally presumes that pain is a signal of tissue injury conveyed to the central nervous system via a healthy nervous system. The definition of pain, as given by the International Association for the Study of Pain, underscores this: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described by the patient in terms of such damage” (see Chapter 2). The traditional model, however, fails to explain many pain syndromes associated with damage to the peripheral nerve, or to the pathways coursing through the dorsal horn and spinal cord. Although pain may be linked causally to tissue injury, it is not necessarily so. Injury does not always generate pain, nor does pain always signal injury. Persistent pain can occur in the presence of the following conditions: (a) ongoing nociception (e.g., an unhealed fracture) or persistent inflammation (e.g., rheumatoid arthritis). Inflammation results in the local release of algogenic substances such as bradykinin, serotonin, histamine, H^+, K^+, prostaglandins, leukotrines, nerve growth factors, and neuropeptides; (b) psychological factors such as somatization disorders, depression, or adverse operant learning processes; (c) abnormal functioning in the nervous system. Pain can arise from nonnoxious input, or from within the body when there is some functional disturbance in the nervous system (e.g., peripheral neuropathy). *Neuropathic* pain is generally used to refer to any acute or chronic pain syndrome in which the mechanism that sustains the pain is inferred to involve aberrant somatosensory processing in the peripheral nervous system or central nervous system. In neuropathic myofascial pain, structural factors exist as well, such as muscle shortening, degraded and weakened collagen, and trophic changes that contribute to the pain.

How the Concept of Neuropathic Pain Originated

It is well accepted that pain can follow gross nerve injury, but the many and varied effects of dysfunction in the peripheral nervous system are recent concerns. I proposed the concept of neuropathic pain when it became evident from clinical observations and research carried out at the Workers' Compensation Board of British Columbia that pain is not always a signal of injury, but can be a product of abnormal nerve function (1).

In 1970, my examination of patients who had back pain, but no signs of injury, showed that those who were disabled for long periods had tenderness over muscle motor points in affected myotomes. Tender motor points, I found, are sensitive indicators of radicular involvement or irritation at the nerve root. Tender points differentiate a simple mechanical low back strain, which usually heals quickly, from one that is slow to improve (2). Next, a study of patients with *tennis elbow* showed that tender points at the elbow were secondary to cervical spondylosis and radiculopathy (i.e., neuropathy originating at the nerve root). Treating the neck, but not the elbow, was able to provide relief (3). A study of pain in the shoulder likewise implicated neuropathy at the cervical spine (4).

A pattern began to emerge: Patients who have pain, but no signs of injury, generally have sensory, motor, and autonomic manifestations of peripheral neuropathy. Peripheral neuropathy may be defined as a disease that causes disordered function in the peripheral nerve. Although sometimes associated with structural changes in the nerve, a neuropathic nerve can, deceptively, appear normal. It still conducts nerve impulses, synthesizes and releases transmitted substances, and evokes

action potentials and muscle contraction.

In 1978, I presented a paper to the Royal College of Physicians and Surgeons of Canada reporting that following neuropathy and denervation, “many diverse pain syndromes of apparently unrelated causation may be attributed to supersensitive receptors (nociceptors) and hyperreactive control systems at internuncial pools.” The concept of neuropathic pain is well accepted today, but at that time, not all physicians were familiar with peripheral neuropathy, and some vigorously denied its existence (Merskey H, *personal communication*, 1986).

The following attributes generally are associated with neuropathic pain (5,6):

- Pain when no ongoing tissue-damaging process exists.
- Delay in onset after precipitating injury. It generally takes approximately 5 days for supersensitivity to develop (7).
- Dysesthesia, unpleasant burning or searing sensations, or deep, aching pain that is more common than dysesthetic pain in musculoskeletal pain syndromes.
- Pain felt in a region of sensory deficit.
- Neuralgic pain, paroxysmal brief shooting or stabbing pain.
- Severe pain in response to a noxious stimulus (hyperalgesia).
- Severe pain in response to a stimulus that is not normally noxious (allodynia).
- Pronounced summation and afterreaction with repetitive stimuli.

Peripheral Mechanisms in Neuropathic Pain

Neuropathic pain is customarily perceived as beginning with peripheral sensitization. In peripheral sensitization, increased transduction sensitivity of nociceptors is associated with alteration of ionic conductances in the peripheral terminal (see Chapter 3). Sensitization can occur following tissue inflammation or damage to a peripheral nerve. Inflammatory cells also produce growth factors and cytokines that contribute to the increased sensitivity of nociceptors. However, damage to the peripheral nerve is most commonly caused by spondylosis at the root level (i.e., *radiculopathic* pain) when all fibers of the peripheral nerve can be damaged and can lead to any or all of the following effects:

- Motor: Muscle shortening is the most significant feature of radiculopathy; pain caused by the mechanical effects of muscle shortening.
- Autonomic: Increased vasoconstriction; hyperhidrosis; trophedema; and causalgic pain, reflex sympathetic dystrophy, or now, better labeled c *omplex regional pain syndrome*.
- Trophic: Dermatomal hair loss; collagen degradation and frailty leading to enthesopathic tendons.

Inflammation is clinically obvious, but minor damage to the nerve root is not. Early radiculopathy is universal, but it is usually unsuspected in prespondylosis when painless muscle shortening precedes peripheral sensitization. Damaged primary afferent fibers demonstrate three electrophysiologic features: (a) spontaneous activity; (b) exaggerated response to stimulus; and (c) sensitivity to catecholamines. These can be explained by a fundamental physiologic law.

Cannon and Rosenblueth's Law of Denervation

This law is seldom cited to explain neuropathic pain; it deserves to be better known. It points out that the normal physiology and integrity of all innervated structures are dependent on the arrival of nerve impulses via the intact nerve to provide a regulatory or *trophic* effect. When this flow, which is probably a combination of axoplasmic flow and electrical input, is blocked, innervated structures are deprived of the trophic factor, which is vital for the control and maintenance of cellular function. *A-trophic* structures become highly irritable and develop abnormal sensitivity or supersensitivity according to Cannon and Rosenblueth's Law of Denervation (7): “When a unit is destroyed in a series of efferent neurons, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated.”

All denervated structures develop supersensitivity (including skeletal muscle, smooth muscle, spinal neurons, sympathetic ganglia, adrenal glands, sweat glands, and brain cells). Cannon and Rosenblueth's original work was based on total denervation or decentralization for supersensitivity to develop; accordingly, they named the phenomenon *denervation supersensitivity*. But it is now known that physical interruption and total denervation are not necessary. Any circumstance that impedes the flow of motor impulses for a period of time can rob the effector organ of its excitatory input and cause disuse supersensitivity in that organ and, significantly, in associated spinal reflexes (8).

The importance of disuse supersensitivity cannot be overemphasized. When a nerve malfunctions, the structures it supplies become supersensitive and behave abnormally. These structures overreact to many forms of input, not only chemical, but physical inputs as well, including stretch and pressure. Supersensitive muscle cells can generate spontaneous electrical impulses that trigger false pain signals or provoke involuntary muscle activity (9). Supersensitive nerve fibers become receptive to chemical transmitters at every point along their length instead of only at their terminals. Sprouting may occur, and denervated nerves are prone to accept contacts from other types of nerves including autonomic and sensory nerve fibers (10). Short circuits are possible between sensory and autonomic (vasomotor) nerves and may contribute to complex regional pain syndrome.

Disuse supersensitivity is basic and universal, yet not at all well known or credited. The important role of supersensitive structures after neuropathy or denervation was previously neglected. Many diverse pain syndromes of apparently unknown causation may be attributed to the development of hypersensitive receptor organs and supersensitivity in pain sensory pathways. Instead of nociception, there can be severe pain in response to a noxious stimulus (hyperalgesia) or severe pain in response to a stimulus that is not normally noxious (allodynia).

RADICULOPATHY: ITS FREQUENT RELATIONSHIP TO SPONDYLOSIS

It is not unusual for the flow of nerve impulses to be obstructed. Peripheral neuropathy, often accompanied by partial denervation, is not exceptional in adults. Of the innumerable causes of nerve damage, such as trauma, metabolic, degenerative, toxic, and other conditions, chronic attrition from spondylosis (the structural disintegration and morphologic alterations that occur in the intervertebral disk, with pathoanatomic changes in surrounding structures) is by far the most common. The spinal nerve root, because of its vulnerable position, is notably prone to injury from pressure, stretch, angulation, and friction. Other causes of radiculopathy (i.e., neuropathy at the nerve root), such as arachnoiditis, neuroma, and intraspinal tumors, are much less common. Spondylosis increases with age; therefore, spondylotic pain is more common in middle-aged individuals who have accumulated an *injury pool*, an accumulation of repeated major and minor injuries to a segment leading to unresolved clinical residuals that may, or may not, produce pain (11).

Ordinarily, spondylosis follows a gradual, relapsing, and remitting course that is silent, unless and until symptoms are precipitated by an incident often so minor that it passes unnoticed by the patient. All gradations of spondylosis can exist, but early or incipient spondylotic changes, even when unsuspected, can nevertheless irritate and upset function in the segmental nerve. The emphasis on radiculopathy is not without reason. With an acute injury to a healthy nerve, there is no prolonged discharge of pain signals, whereas the same injury to a neuropathic nerve can cause a sustained discharge (12). In other words, for pain to become a persistent symptom, the affected fibers must be previously irritated or defective. That is why some people develop severe pain after an apparently minor injury, and why that pain can continue beyond a *reasonable* period.

The manifestations of neuropathic dysfunction are motor, sensory, and autonomic. In our studies, early and subtle signs of peripheral neuropathy were found in a significant number of young (under 30 years), apparently normal, and asymptomatic individuals (13). Brief and transient motor manifestations are the first to appear, and radiculopathy can occur without pain. Muscle shortening is an early and regular feature of radiculopathy, because large diameter nerve fibers at the nerve root—axons of motoneurons and myelinated primary afferents (muscle proprioceptors)—are the first to suffer physically. Painless, reversible, tight muscle knots can be felt in most individuals; not uncommonly, even in toddlers. Pain is not therefore a feature of radiculopathy unless nociceptive pathways are involved. Many neuropathies are pain free, such as sudomotor hyperactivity in hyperhidrosis, and muscle weakness in ventral root disease.

Degradation of Collagen

Ironically, neuropathy itself contributes to degenerative conditions (including spondylosis). Neuropathy degrades the quality of collagen, causing it to have fewer cross-links; it is, therefore, more frail than normal collagen (14). The amount of collagen in soft and skeletal tissues is also reduced. Because collagen lends strength to ligament, tendon, cartilage, and bone, neuropathy can expedite degeneration in weight-bearing and activity-stressed parts of the body, which include the spine and

joints, and become a source of pain. Enthesopathic thickening in a tendon is possibly a compensation for this weakness.

CENTRAL MECHANISMS IN NEUROPATHIC PAIN

Interactions between peripheral and central mechanisms occur to produce postinjury hypersensitivity and neuropathic pain. The spinal cord is not simply a passive conveyer of peripheral sensation to the brain. It can modify or amplify incoming signals. Central sensitization, a state of hyperexcitability of the dorsal horn neuron, can occur after damage to a peripheral nerve (e.g., irritation of a nerve root by spondylosis) or after low-frequency repetitive C fiber nociceptor input (e.g., from peripheral tissue inflammation, as in arthritis). Central sensitization has several aspects: increased spontaneous activity of dorsal horn neurons, increased response to afferent input, expansion of receptive field size, reduction in threshold, and prolonged afterdischarges. Central sensitization leads to a cascade of molecular events, such as activation of the *N*-methyl-d-aspartate (NMDA) channel, increase in intracellular Ca^{2+}, wind-up/wide dynamic range (WDR) neuron sensitization, and other phenomena (15,16,17,18,19,20 and 21).

Altered Sensitivity in the Dorsal Horn

Central sensitization may be maintained by ongoing primary afferent input, by altered central neural circuitry, or both. Woolf has identified four stimulus-processing states (22,23):

1. Normal state: In this state, low-intensity A-b stimulation, such as touch, is perceived as innocuous, but high-intensity A-d and C noxious stimulation is perceived as pain.
2. Suppressed state: High-intensity stimulation is not painful because of inhibition from segmental inhibition or descending inhibition from higher centers.
3. Sensitized state: Low-intensity stimulation is perceived as painful mechanical allodynia, and high-intensity stimulation, which is normally painful, leads to hyperalgesia.
4. Reorganized state: There may be structural changes and reorganization of the dorsal horn circuitry. Inappropriate synapses may form. A-b fibers from layer 3 can sprout into layers 1 and 2, causing low-threshold afferent input to be misinterpreted as pain. A-b afferents acquire the capacity, after inflammation, to produce central excitability, something they cannot normally do.

Expansion of Receptive Field Size

The clinical observation that pain radiates several segments above and below the level of nociceptive stimulation may be explained by dispersion of the primary afferent input through propriospinal connections in adjacent layers 5 and 6 of the dorsal horn. This area also contains WDR neurons (so called because they can encode a range of stimuli from light touch to intense pain). The WDR receptive field is immense compared with that of the primary afferent neuron; therefore, any increase in nociceptive stimulation can lead to the recruitment of many more WDR neurons.

Prolonged Afterdischarges

Perceived pain often outlasts the stimulus. In neuropathy, a brief discharge from A-d or C fibers generates prolonged activity of WDR neurons because the normal inhibitory effects of A-b fibers on A-d and C activity is lost.

Wind-Up

Wind-up is a frequency-dependent phenomenon. Low-frequency (0.1-Hz) C fiber input gives a constant response from dorsal horn neurons. But frequencies greater than 0.5 Hz can give rise to hyperexcitability lasting for many minutes after the stimulus. In wind-up, C fibers release substance P, neurokinin A, and excitatory amino acids (glutamate and aspartate) onto dorsal horn neurons. There are two types of receptors at the dorsal horn, a neurokinin receptor and an NMDA receptor for amino acids. The binding of amino acids to the NMDA receptor depends on its prior activation by the binding of substance P to the neurokinin receptor. Thus, the release of substance P may lead to the recruitment of a second receptor type (NMDA) and an exaggerated response to further stimulation. The sensitized cell undergoes other biochemical changes, as indicated by the expression of the gene c-*fos*. Products of c-*fos* expression are involved in the regulation of neurotransmitter and nerve growth factor synthesis.

CHALLENGES IN DIAGNOSIS AND TREATMENT

Diagnosis

Diagnosing pain and dysfunction caused by radiculopathy depends almost entirely on the examiner's clinical experience and acumen. The history gives little assistance. Pain often arises spontaneously with no history of trauma, or else the degree of reported pain far exceeds that consistent with the injury. Laboratory and radiologic investigations are generally not helpful. Thermography reveals decreased skin temperature in affected dermatomes and this can be an indication of neuropathy, but does not necessarily signify pain. Radiculopathies are difficult to document with routine nerve conduction studies, which measure only the few fastest conducting and largest fibers and take no account of the majority of smaller fibers. In focal neuropathy, nerve conduction velocities remain within the wide range of normal values, but F-wave latency may be prolonged. Electromyography is not specific either.

The physical signs of neuropathy are distinctive and different from the well-known ones of outright denervation, such as loss of sensation and reflexes. They are important to look for because they indicate early neural dysfunction for which no satisfactory laboratory or imaging test exists. A careful inspection for signs of motor, sensory, and autonomic (vasomotor, sudomotor, and pilomotor) dysfunction in the skin and affected muscles is necessary. Vasoconstriction differentiates neuropathic pain from inflammatory pain: In neuropathic pain, affected parts are perceptibly colder. There may be increased sudomotor activity and the pilomotor reflex is often hyperactive and visible in affected dermatomes as goose bumps (Fig. 28-1). There can be interaction between pain and autonomic phenomena. A stimulus such as chilling, which excites the pilomotor response, can precipitate pain; conversely, pressure on a tender motor point can provoke the pilomotor and sudomotor reflexes.

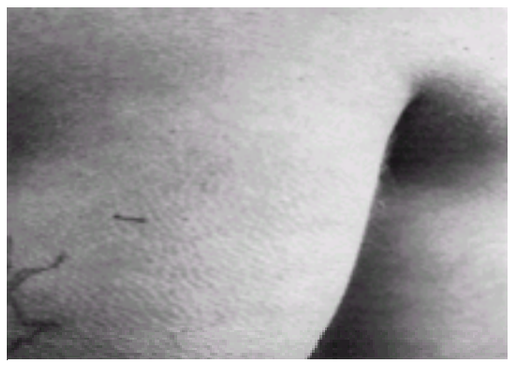

Figure 28-1. A readily seen signal of neuropathy affecting the autonomic system is an isolated patch of *goose bumps* created by a super-sensitive pilomotor reflex responding to exposure while undressing. Here it appears locally at the shoulder and arm, indicating trouble related to segments C-5 and C-6.

Increased permeability in blood vessels can lead to local subcutaneous tissue edema (neurogenic edema or trophedema). This can be seen as *peau d'orange* skin (Fig. 28-2) and confirmed by the match stick test. Trophedema is nonpitting to digital pressure, but when a blunt instrument such as the end of a match stick is used, the indentation produced is clear-cut and persists for many minutes (Fig. 28-3). This quick and simple test can demonstrate neuropathy earlier than electromyography. Trophic changes such as dermatomal hair loss may also accompany neuropathy.

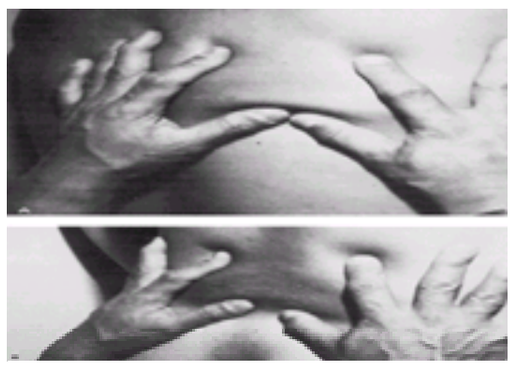

Figure 28-2. **A:**Wrinkling of normal skin when gently squeezed together. **B:** Trophedematous skin when gently squeezed together, the *peau d'orange* effect. (From Gunn CC, Milbrandt E. Early and subtle signs in low-back sprain. *Spine* 1978;3:267 –281.)

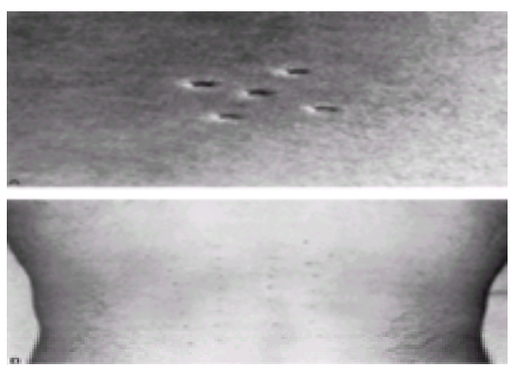

Figure 28-3. **A:** The matchstick test. Trophedema may be found by pressing on the suspected area using the end of a matchstick. The deeper the indentations, and the longer they last (up to many minutes), the more severe the neuropathy. **B:** In low back pain, the matchstick test result is often positive over an area that is more widespread than the painful area. This patient had symptoms only in the low lumbar back, but indentations are seen at all lumbar levels, which indicates that even though pain is limited to one level the neuropathy is more extensive. (**A** from Gunn CC, Milbrandt E. Early and subtle signs in low-back sprain. *Spine* 1978;3:267–281.)

Knowledge of the Segmental Nerve Supply to Muscles Is a Clue to Diagnosis

Neuropathic changes are primarily in muscle. Even when symptoms appear to be in joints or tendons, signs in the muscles are the most consistent and relevant: increased muscle tone; tenderness over motor points; and taut and tender, palpable contracture bands and restricted joint range. Each constituent muscle must be palpated and its condition noted. Palpation requires detailed knowledge of anatomy, and clinical skill comes only with practice. Moreover, because many paraspinal muscles are compound (e.g., the longissimus) and extend throughout most of the length of the vertebral column, the entire spine must be examined even when symptoms are localized to one region.

Muscle Shortening from Contracture

Muscle contracture is a fundamental feature of musculoskeletal pain (Fig. 28-4). Of all structures that can develop supersensitivity, the most widespread is striated muscle. Contracture can physically give rise to pain by its relentless pull on sensitive structures (24) (Fig. 28-5). *Classic contracture* refers to the evoked shortening of a muscle fiber in the absence of action potentials. According to Cannon and Rosenblueth (7), skeletal muscle can become supersensitive in several ways: (a) by increased susceptibility; lessened stimuli, which do not have to exceed a threshold, can produce responses of normal amplitude; (b) by hyperexcitability; the threshold of the stimulating agent is lower than normal; (c) by superreactivity; the capacity of the muscle to respond is augmented; and (d) by superduration of response; the amplitude of response is unchanged but its time course is prolonged.

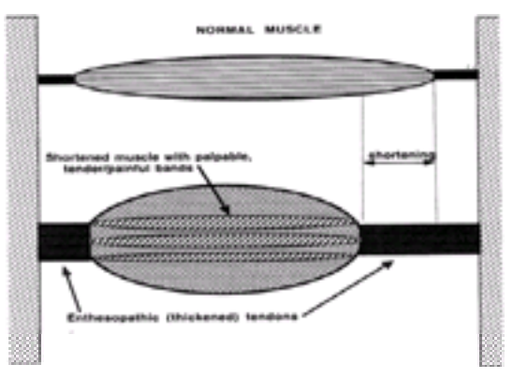

Figure 28-4. Neuropathy can cause muscle contracture and shortening. (From Gunn CC. *The Gunn approach to the treatment of chronic pain.* New York: Churchill Livingstone, 1996, with permission.)

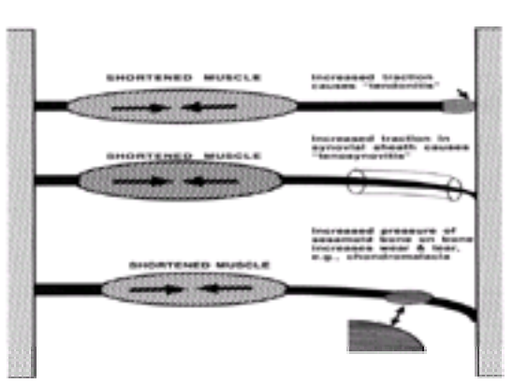

Figure 28-5. Shortening creats tension in tendons and their attachments and can cause syndromes as epicondylitis, tendonitis, or chondromalacia patellae. (From Gunn CC. *The Gunn approach to the treatment of chronic pain.* New York: Churchill Livingstone, 1996, with permission.)

Supersensitive skeletal muscle fibers, furthermore, overreact to a wide variety of chemical and physical inputs, including stretch and pressure. Furthermore, they have a lowered threshold to acetylcholine, which is itself increased from reduced levels of acetylcholinesterase. Acetylcholine slowly depolarizes supersensitive muscle

membrane, inducing an electromechanical coupling in which tension develops slowly without generating action potentials. In normal muscle, acetylcholine acts only at receptors that are situated in the narrow zone of innervation, but in neuropathy, it acts at newly formed extrajunctional receptors (*hot spots*) that appear throughout the muscle (Fig. 28-6).

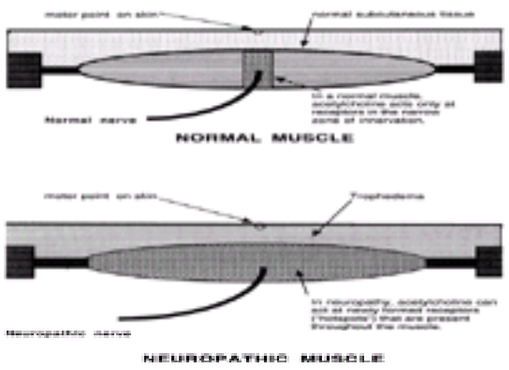

Figure 28-6. In comparison to normal muscle, widespread newly formed acetylcholine receptors are present throughout neuropathic muscle. (From Gunn CC. *The Gunn approach to the treatment of chronic pain.* New York: Churchill Livingstone, 1996, with permission.)

TREATMENT

Pharmacologic Management Is Difficult

A critical review of controlled clinical trials for peripheral neuropathic pain concluded that the pharmacologic management of neuropathic pain is difficult (25). Further trials are needed to establish the efficacy for all treatments currently in use. The review gave support to corticosteroids, which had long-term effectiveness, and limited support to tricyclic antidepressants, intravenous and topical lidocaine, intravenous ketamine, carbamazepine, and topical aspirin. There was also limited support for oral, topical, and epidural clonidine and for subcutaneous ketamine. Data were contradictory for mexiletine, phenytoin, topical capsaicin, oral nonsteroidal antiinflammatory medication, and intravenous morphine. Codeine, magnesium chloride, propanol, lorazepam, and intravenous phentolamine all failed to provide pain relief. There was also limited support for the effectiveness of topical dimethyl sulfoxide, epidural clonidine, and intravenous regional blocks with bretylium and ketanserin. Data were contradictory for intranasal calcitonin and intravenous phentolamine. Guanethidine, reserpine, and droperidol intravenous regional blocks were ineffective. No data were available to evaluate sympathetic ganglion blocks with local anesthetics. Regional and systemic adrenergic blockages gave limited success. Overall, there were no long-term data to support the effectiveness of any drug in treating this condition.

Physical Therapy and Stimulation-Induced Analgesia

Physical therapy is widely used as a first-line treatment for peripheral neuropathic pain. Early physical treatment is advocated, because earlier treatment is said to correlate with better outcome. Neuropathic pain is a supersensitivity phenomenon, and its treatment requires desensitization. Lomo has shown in animal experiments that supersensitivity and other features of denervated muscle can be reversed by electric stimulation (26). Physical therapy also achieves its effect by stimulation. Local therapy excites receptors (in skin and muscle); for example, massage activates tactile and pressure receptors; exercise, manipulation, and dry needling stimulate muscle spindles and Golgi organs; heat and cold act on thermal receptors. These stimuli are sensed by their specific receptors, transduced into nerve impulses, and relayed to the dorsal horn. All forms of physical therapy, including dry needling, are effective only when the nerve to the painful part is still intact. A dry needling technique called *intramuscular stimulation* (see Chapter 97) is often effective. In intramuscular stimulation, diagnosis, treatment, as well as progress during therapy are determined according to physical signs of neuropathy. The effective application of intramuscular stimulation therefore requires a sound background both in anatomy and neurophysiology (27).

Stimulation also can be applied directly to the spinal cord (28) (see Chapter 100). Cui and colleagues have reported that neuropathic pain may be effectively relieved by electric stimulation of the spinal cord. Stimulation of the spinal cord has been shown to normalize withdrawal response thresholds in a rat model. The effect of stimulation of the spinal cord on neuropathic pain and allodynia is believed to be caused by inhibition of glutamate and aspartate release at NMDA receptor sites, and activation of local GABAergic mechanisms.

Removing the Cause of Neuropathy Is Key to Treatment

Spondylosis is, by far, the most common cause of radiculopathy, and treatment should be aimed at relieving the cause of impingement or entrapment of the nerve root. Local treatment (starting with simple measures such as massage, and, if necessary, escalating to more effective modalities such as dry needling) should be given to all tender and shortened muscles in the affected myotome(s), including paraspinal muscles. The outcome of treatment depends on the modality used and the skill of the therapist.

The fine, flexible, acupuncture needle used in intramuscular stimulation is a unique tool for finding and releasing contractures. Contracture is invisible to radiography, computed tomographic scans, or magnetic resonance imaging, and in deep muscles beyond the finger's reach. Deep contracture can only be discovered by probing with a needle. The needle transmits feedback information on the nature and consistency of the tissues it is penetrating. When penetrating normal muscle, it meets with little hindrance; when penetrating a contracture, there is firm resistance, and the needle is grasped by the muscle. This causes the patient to feel a peculiar cramplike or grabbing sensation, which is referred to in acupuncture literature as the *Deqi* or *Teh Ch'i response*. The *Deqi* response is an important finding: It is a sign of muscle contracture and confirms the status of neuropathy.

Myofascial muscle pain is not merely dull and aching. It has a peculiar cramplike quality that is associated with muscle tenderness and shortening. Any experienced dry-needling therapist or acupuncturist would be aware of this distinctive sensation produced by needling a contracture. The classic acupuncturist painstakingly differentiates between pain that has the *Deqi* response (therefore, the muscle is shortened and neuropathic), and pain that does not (nociceptive). This distinction is important because of the difference in the nature and treatment of the two pains. According to Fields, the strange quality of neuropathic pain probably results from disruption of the sensory apparatus so that a normal pattern of neural activity is no longer transmitted to the perceptual centers. He allows that neuropathic pain probably activates nociceptive neurons, because the message that gets through to the perceptual centers is clearly unpleasant, but he astutely notes that patients distinguish the peculiar sensations from *normal* pain sensations (29).

Chronic myofascial pain is not ordinary nociception. *Deqi* pain sensations are not normal because they are associated with receptors that sense muscle shortening (proprioceptors). The classic acupuncturist demonstrates this by the needle grasp occurring at the site of penetration when a neuropathic muscle is needled. Needling is usually pain free when an acupuncture needle enters a normal muscle, but when the needle pierces a shortened muscle, it produces a cramp, and the needle is observed to be firmly grasped by the shortened muscle. The intensity of the needle grasp parallels the degree of muscle shortening, and it gradually eases off during treatment as muscle shortening is released: Release frequently occurs in minutes. Because muscle pain eases concurrently with the release of the needle grasp, patients soon become aware of the importance of eliciting the *Deqi* sensation and releasing needle grasp during treatment.

Progressive Tactile Hypersensitivity

Laboratory investigators presently pursue A-d and C fiber nociceptive pathways but give little consideration to large-diameter fibers. However, Ma and Woolf have described a noteworthy phenomenon, *progressive tactile hypersensitivity* (30). They have found that repeated light touch to an inflamed paw produced cumulative allodynia. Progressive tactile hypersensitivity can only be induced in inflamed tissue and persists for several hours. It is different from central sensitization induced by C fiber stimulation, which can be induced in noninflamed tissue and lasts only for minutes. Progressive tactile hypersensitivity demonstrates that A-b afferents have the capacity to produce wind-up of spinal cord neurons, normally a C fiber–mediated effect.

Myofascial pain is not solely A-d and C fiber nociceptive pain. Muscle shortening is an essential component; by simply releasing a shortened muscle, pain is

banished. If large-diameter A-b primary afferents from the cutaneous nerve can contribute to hyperalgesia, is it possible for large-diameter proprioceptor fibers from the muscle nerve to likewise contribute to myofascial pain? Fibers from muscle fascia and other deep tissues must now be studied, in particular group I and II fibers, which sense muscle length and tension, and group III and IV fibers, which sense muscle pain.

In chronic pain, fibrosis eventually becomes a major feature of the contracture; response to dry-needle treatment is then much less dramatic. The extent of fibrosis does not correlate with chronologic age. Scarring can occur after injury or surgery, and many older individuals have sustained less wear and tear than younger ones who have subjected their musculature to repeated physical stress. The treatment of extensive fibrotic contractures necessitates more frequent and extensive needling. To relieve pain in such a muscle, it is necessary to needle all tender bands. It is uncommon to encounter a muscle that is totally fibrotic and cannot be released by vigorous needling.

For long-lasting pain relief and restoration of function, it is essential to release shortened paraspinal muscles that may be compressing a disk and disperse fibrotic tissue that may be entrapping a nerve root (Fig. 28-7). Surgical release is rarely necessary as the needle can reach deeply located shortened muscles.

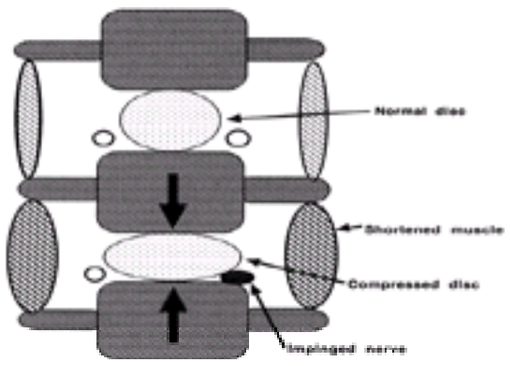

Figure 28-7. Shortened paraspinal muscles across an intervertebral disk space can compress the disk. (From Gunn CC. *The Gunn approach to the treatment of chronic pain.* New York: Churchill Livingstone, 1996, with permission.)

DISCUSSION

Myofascial pain syndromes frequently become medical riddles when they are not recognized as the effects of neuropathy presenting primarily in the musculoskeletal system. The primary problem is peripheral neuropathy, and pain is just one of its many possible presentations. Pain is not a feature unless nociceptive pathways are involved. Many neuropathic conditions are pain free. It is helpful to remember the following points:

- Because pain is a manifestation of neuropathy, therapy should aim at the cause of the neuropathic condition.
- Spondylosis is, by far, the most common cause of radiculopathy. Myofascial pain syndromes are almost invariably segmental; symptoms are found in dermatomes, myotomes, and sclerotomes. Examination and treatment must always include the spine.
- Establish that neuropathy is present. Signs of neuropathy are subtle and differ from those of outright denervation. Look for vasoconstriction and trophedema.
- Neuropathic pain has a proprioceptive component; it cannot exist without muscle shortening. Look for tender, shortened muscles in myotomes.
- Neuropathic pain is often the unsuspected cause of many other conditions (e.g., tension headache, frozen shoulder, tennis elbow, and even low back pain). Muscle shortening upsets joint alignment and increases pressure on articular surfaces. Neuropathy degrades the quality of collagen and contributes to degeneration in weight-bearing and activity-stressed parts of the body.
- Radiculopathy is perpetuated when shortened paraspinal muscles draw adjacent vertebrae together to compress the disk and irritate the nerve root. The vicious circle must be treated at the spine.

CONCLUSIONS

It is only through hands-on examination of patients, explicitly searching for neuropathic signs, that one is able to understand and treat neuropathic myofascial pain. Drug treatment is difficult, and physical therapy is the first approach. The efficacy of intramuscular stimulation for chronic low back pain has been demonstrated by a randomized clinical trial involving a large group of Workers' Compensation Board patients. At their 7-month follow-up, the treated group was clearly and significantly better than the control group (27). It is a most convincing experience to diagnose neuropathic pain by finding its unmistakable physical signs and then to treat the patient with intramuscular stimulation and witness the signs disappear, often within minutes.

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CHAPTER 29

Myofascial Pain Syndromes

Anders E. Sola and John J. Bonica

Myofascial pain syndromes constitute a large group of muscle disorders characterized by the presence of hypersensitive points, called *trigger points* (TPs), within one or more muscles, the investing connective tissue, or both, together with a syndrome of pain, muscle spasm, tenderness, stiffness, limitation of motion, weakness, and occasionally autonomic dysfunction. The symptoms are usually referred to an area distant from the TPs, although local pain may also be present. These syndromes have been previously described as, among other terms, *myalgia*, *myositis*, *fibrositis*, *myofascitis*, *fibromyositis* (or *myofibrositis*), *muscular rheumatism*, and *muscular strains*.

Management of patients with myofascial pain syndromes constitutes one of the most important problems encountered in clinical practice. This importance stems from several interrelated factors. First, they are the most common musculoskeletal disabilities of the shoulder girdle, neck, low back, and, to a lesser extent, the chest and ribs. They are certainly among the most frequent causes of severe disabling pain. Moreover, because of the peculiar symptoms associated with these syndromes, they were not generally recognized until recently. Consequently, they were often misdiagnosed and treated as bursitis, arthritis, or visceral disease.

Once recognized, however, these disorders are relatively simple to manage. Most of the therapeutic procedures can be carried out in the physician's office, and in many cases, a short series of treatments can relieve conditions that might otherwise result in continued pain and disability.

In this chapter we present the epidemiology, etiology, pathophysiology, symptoms and signs, diagnosis, and treatment of these syndromes. A more detailed discussion of syndromes affecting each part of the body is presented in the various sections of Part IV of this book. Comprehensive discussions of this subject can be found in an excellent monograph by Travell and Simons (1) and in a number of review articles (2,3,4,5,6,7,8,9,10 and 11).

BASIC CONSIDERATIONS

The TP phenomenon was first recognized in the mid–nineteenth century by physicians in Germany, Sweden, and Britain (1,2,3,4,5,6,7,8,9,10 and 11). The early German writers referred to conditions with symptoms and signs characteristic of myofascial syndromes as *myogelosis* (*myogelosen*) and as *muscular rheumatism* and later as *muscle hardenings* or *muskel schmerzen* and noted the presence of tender spots in various muscle groups. Swedish writers used the term *myositis* for myofascial syndromes, whereas British writers used a number of terms, including *myalgic spots*, *myalgia*, *myofascitis*, *myositis*, and especially *fibrositis*. Unfortunately the term has been used interchangeably with such terms as *nonarticular rheumatism*, *muscular rheumatism*, *fibromyositis*, *fibrofascitis*, and *muscular strain*.

A number of writers, especially Good (12), in Britain, and Kelly (13), in Australia, have used the term *fibrositis* for symptoms that describe myofascial pain syndromes. At about the same time, Travell (14), who has made immeasurable contributions to this field, published her first paper on the subject and used the terms *idiopathic myalgia* and *myalgia*. Later, she began to call these conditions *myofascial pain syndromes* (15).

In the first edition of this book, Bonica, in conformance with the widespread literature of the 1940s, considered fibrositis separate from myofascial pain syndromes. For a number of years he continued to consider these two conditions separately, although he emphasized the importance of myofascial syndromes (16). At about the same time, Sola, following his experience with Bonica, also published reports on myofascial pain syndromes (17,18). In recent years some authorities (19) have come to believe that fibrositis is similar to myofascial pain syndromes and have suggested that the term be abandoned. Others, however, have continued to insist and have provided evidence that fibrositis, now commonly known as *primary fibromyalgia syndrome* (PFS), can be differentiated from myofascial pain syndromes. The difference is based on the fact that myofascial pain syndromes are characterized by presence of specific TPs in one or several muscles, whereas PFS is characterized by local tenderness in more than 11 specified sites, with widespread aching of more than 3 months' duration. This difference has been recognized by the Committee on Taxonomy of the International Association for the Study of Pain and therefore will be respected here. PFS is discussed in Chapter 30.

Epidemiology

As in most other acute and chronic painful disorders, there are no data from national epidemiologic studies on the incidence and prevalence of myofascial pain syndromes. These syndromes, with their characteristic TPs, exist as primary conditions and also as secondary conditions, in conjunction with musculoskeletal injuries, arthritis, nerve injuries, and visceral diseases. Further complicating the data is the fact that TPs, which can develop in any muscle of the body, can be active or latent. An active TP is associated with spontaneous pain at rest or with motion that stretches or overloads the muscle. A latent TP does not cause spontaneous pain, but it can be diagnosed by applying discrete pressure on the TP, which is likely to cause pain locally and in the area of reference. Consequently, we must rely on local surveys to estimate the incidence and prevalence of TPs in the population.

In a survey of 200 unselected young adults, Sola and associates (20) found latent TPs in the muscles of the shoulder girdle in 54% of the females and 45% of the males. In a survey of 1,000 ambulatory patients, Sola (unpublished data, 1985) found hyperactive TPs with classic myofascial syndromes in 32%. The prevalence was 36% among the 598 women and 26% among the 402 men seen. Table 29-1 lists the distribution of the pain syndromes according to the age group of female and male patients. As may be noted, the highest prevalence was in patients who were between 30 and 49 years of age. Table 29-2 lists the location of the TPs in 214 female and 103 male patients. A significantly greater incidence of myofascial syndromes among female patients has also been reported by others (1). Moreover, Sola's personal observations confirmed the impression of many clinicians that myofascial pain syndromes affect the head and neck, the shoulder girdle, and the lumbar and low back regions more frequently than other regions.

	Females (n = 214)		Males (n = 103)	
Age (yr)	Number	Percent*	Number	Percent*
≤19	2	1	3	3
20–29	34	16	14	14
30–39	48	22	21	21
40–49	40	19	22	22
50–59	30	14	17	17
60–69	33	15	12	12
70–79	22	10	14	14
≥80	5	2	0	0

*Percentage of patients by age group.

TABLE 29-1. Distribution of cases of myofascial syndromes by age and gender

Location	Females (n = 214)		Males (n = 103)	
	Number	Percent*	Number	Percent*
Cervical (approximately one-third with torticollis)	72	34	30	29
Hip(s)	60	28	52	51
Shoulder	44	21	36	35
Lumbar region	34	16	23	22
Generalized	11	5	4	4
Low back	6	3	9	9
Ipsilateral	6	3	0	0
Leg, thigh, knee	5	2	6	6
Upper extremity	3	1	4	4
Thoracic region	2	0.9	3	3
Back	0	0	2	2
Abdominal region	0	0	2	2
Groin	0	0	1	1
Upper and lower trunk	23	11	9	9

*Percentages total more than 100% because several areas may have been noted for each patient.

TABLE 29-2. Locations of sensitive trigger points

In another survey, Sola (*unpublished data*, 1954) found that laborers who exercise their muscles heavily every day are less likely to develop active TPs than sedentary workers who tend to indulge in occasional sessions of vigorous physical exercise. Similar observations have been made by Travell and Simons (1,2 and 3).

The most comprehensive and most revealing overview of the incidence and prevalence of muscle pain can be found in the Nuprin Report (21). This publication contains data derived from the first nationwide survey on the prevalence of pain, which was carried out in 1985 by Lou Harris Associates under the sponsorship of Bristol Myers Company. The survey suggests that 53% of the American population experiences muscle pain. Among the respondents with muscle pain, approximately one-third had pain for 11 or more days and 10% had pain for 100 or more days. The data do not indicate what percentage of these respondents had myofascial pain syndromes, but it is likely that these conditions were present in a significant percent of this population.

Etiology

The most easily identified causes of myofascial pain syndromes are trauma to myofascial structures and acute overload of muscles (Fig. 29-1). After acute injury, TPs (small, circumscribed, hypersensitive regions in muscles or connective tissue) can be identified in some individuals. These TPs are also known as *trigger areas*, *trigger zones*, and *myalgic spots* (1,4,9,18). Impulses arise from these points and bombard the central nervous system to produce local or referred pain, or both, and associated phenomena in the area of reference. The TP is so named because its stimulation, with pressure or activation of the muscle, is like pulling the trigger of a gun, producing effects at another place (a target), called the *reference zone* or *area of reference*. The term, then, implies the existence of a relationship between two different topographic areas, the trigger and the target.

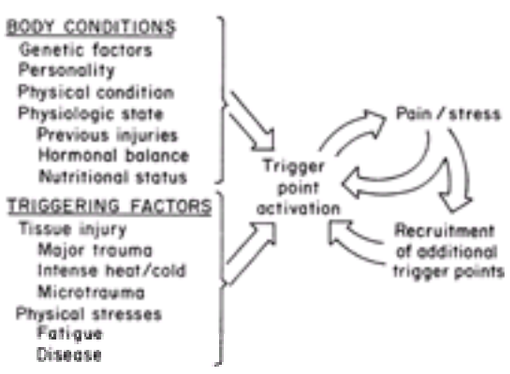

Figure 29-1. Stress and body conditions. A variety of stress-inducing stimuli have been implicated in the onset of myofascial pain. The power of these stimuli to induce pain in an individual is moderated by the genetics, personality, conditioning, and physiologic state of that individual. Once established, however, a painful event may sustain itself in spite of control or elimination of the initiating stimuli. (Modified from Sola AE. Myofascial trigger point therapy. *Med Times* 1982;110:70–75.)

TPs often remain in muscle in a latent form for many years after an injury, contributing to an “injury pool” (6,7 and 8). The only manifestation may be minimal loss of range of motion (ROM), coolness, quick fatigability, slight loss of dexterity in the upper extremities, or a combination of these. Residual clinical stigmata are seen most often in conjunction with injuries to the extremities in association with cervical or lumbar/sacral pathology. In the presence of an injury pool, any additional injury or stress involving the same segment can cause a flare-up of latent TPs. Under these conditions, an insignificant event can initiate bizarre responses, including intense severe pain, prolonged edema, loss of ROM, and slow recovery—many of which could be construed as psychosomatic.

Latent TPs can also be activated by intense heat or cold or by prolonged chilling, as occurs with air conditioning or chilly, damp weather. In these cases, the precipitating factor is not readily identified, or the relationship might be overlooked because the painfulness of the myofascial syndrome is disproportionate to the significance of the incident. A third etiologic pattern for myofascial syndrome is slow onset, in which the microtraumas of daily activities or repetitive movements while working, such as prolonged typing, result in overload fatigue.

In addition to these precipitating factors, a number of factors can make a person vulnerable to development or activation of latent TPs. These include mechanical stresses that overload muscles, such as occurs with a short leg, small hemipelvis, poor posture, and prolonged immobility. Travell and Simons (1) also mention that a variety of nutritional and metabolic and endocrine factors, including vitamin deficiencies, mineral inadequacy, hypometabolism, and endocrine dysfunction (particularly estrogen deficiency and hypothyroidism) are important predisposing and perpetuating factors. They also list chronic infection due to viral or bacterial disease and parasitic infestation as predisposing or perpetuating factors.

An acute episode of myofascial pain often follows overuse of unconditioned muscles (the weekend athlete); excessive zeal in fitness programs; prolonged stresses on musculoskeletal structures due to poor posture during activities such as computer-oriented work or television watching; sports injuries; automobile accidents involving cervical or lumbar sprain, or both; or a period of intense emotional stress. Travell and Simons (1) point out that there is a difference between soreness after exercise and the TP phenomenon. They note that muscles that are stiff and sore from exercise do contain tender points, but the tenderness is not similarly referred to other areas and it is distributed “as if it were caused by sensitization with a different noxious agent, or by the sensitization of a different neural structure than that responsible for the trigger point phenomenon.”

The precipitating factor for primary myofascial pain is often a seemingly innocent activity (1,8). Among the more common of these is a change in heel height from high heels worn during the day to slippers in the evening. Other examples are working at a table or counter that is too low, sitting in an overstuffed chair, and riding in an airplane or car (in these instances, vibration is added to the postural and environmental stressors, which include the handling of heavy luggage).

An afternoon of shopping can be the precipitating event, particularly when the person has been walking in leather-soled shoes on highly waxed floors, which are common in shopping malls and many other public areas and institutions (e.g., nursing homes, convention centers, schools). The muscular accommodation necessary to maintain balance in these conditions, plus abnormal adjustment of gait, can aggravate muscles with existing TPs, causing acute onset of pain in hips, knees, ankles, feet, low back, head, or neck.

Frequently, more than one TP area is found in pain syndromes, each having a site of reference comprising a portion of the pain pattern. A prolonged barrage of noxious impulses from a TP area is conducive to the creation of secondary tender areas in the zone of reference. In such instances, the more recent secondary foci can be a major source of pain, and it is not until these are eliminated that the primary focus becomes evident. Although trigger areas can develop anywhere in the

body, they occur most frequently in the neck, shoulder girdle, low back, and extremities.

Pathophysiology

Present knowledge of myofascial pain syndromes and TP phenomena depends heavily on clinical observations and theories that relate limited physiologic data to physical findings. Although TPs can sometimes be palpated, their presence is more commonly established by the pain response of the patient when pressure is applied to them—Travell calls this response the “jump” sign (1,2). By probing and observing pain responses, Travell and Simons (1) have estimated the size of a single TP to be between 3 mm and 6 mm.

Hypersensitive TPs have been studied histologically, but there is little experimental evidence to substantiate their role in causing or perpetuating pain. Henriksson and associates (19) reported that muscle tissue biopsied from tender areas in patients with primary “fibromyalgia” had a “moth-eaten” appearance. In these patients, adenosine triphosphate and phosphocreatine levels were reduced, lactate values were normal, and glycogen concentrations were below normal. These findings led Henriksson et al. to conclude that the TP phenomenon could be caused either by a primary metabolic disturbance or by overload secondary to muscle tension.

There is little doubt as to the reality of TPs, but there is great diversity of opinion as to how these points become hypersensitive and how they produce pain. Cailliet (22) suggested that TPs are caused by the presence of blood and extracellular material that are not reabsorbed after damage of any type to soft tissue. The resulting adhesions limit the gliding action of muscles, resulting in tension, spasm, and further development of irritants. Travell and Simons maintain that the principal causes of TPs are microtrauma and overload (1).

According to Gunn (23), the cause of TP hypersensitivity is neuropathy of the nerve serving the affected muscle (see Chapter 28). Cannon's law of denervation states that any structure affected by denervation responds with supersensitivity, which is translated as hyperactivity of its normal function (24). Neurologic deficit to the muscle therefore results in supersensitivity of the muscle to biochemical agents and to impulses to contract (25,26,27,28 and 29). Supersensitivity associated with neuropathy has been supported by studies of Lomo (30), which show increased sensitivity of muscle to acetylcholine and a broadened distribution of acetylcholine receptors—a condition that was reversible in laboratory animals.

Clinical findings confirm that TP formation, with the associated potential for pain, occurs subsequent to injury or stress (1). The muscle fibers “hosting” the TP are contracted for an extended period of time, and muscle fatigue develops. Local ischemia occurs, leading to changes in the extracellular environment of the affected cells, including release of such algogenic agents as histamine, kinins, and prostaglandins (27). These changes feed into a cycle of increasing motor or sympathetic activity, or both, which leads to increased pain (Fig. 29-2), with the TP as the focus of distress signals to the central nervous system. Once established as a cycle, a painful event can sustain itself in this way after the initial stimulus has been controlled or treated.

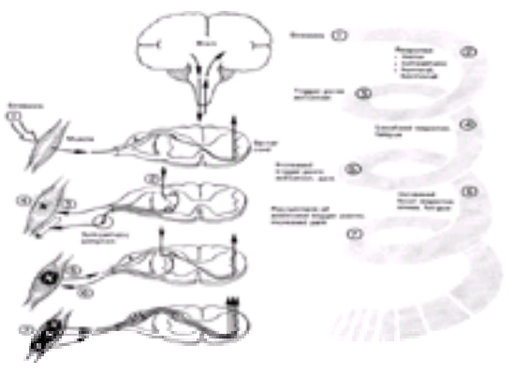

Figure 29-2. Mechanisms in myofascial pain syndrome. (*1*) The individual, subjected to the physical and emotional stresses of daily living, responds with defense mechanisms that include various physiologic changes, such as splinting and bracing of muscles, vasomotor changes, increased sympathetic discharge, and hormonal and other humoral changes in the plasma and extracellular fluids. (*2,3*) A particular point in a braced, stressed muscle or fascia that is more sensitive than the surrounding tissue—perhaps due to previous injury or genetic mandate—fatigues and begins to signal its distress to the central nervous system. (*4*) A number of responses are possible. The most readily understood involves the motor reflexes. Various muscles associated with the trigger point become more tense and begin to fatigue. Sympathetic responses lead to vasomotor changes within and around the trigger point. Local ischemia following vasoconstriction or increased vascular permeability following vasodilation can lead to changes in the extracellular environment of the affected cells, release of algesic agents (bradykinins, prostaglandins), osmotic changes, and pH changes, all of which can increase the sensitivity or activity of nociceptors in the area. Sympathetic activity can also cause smooth muscle contraction in the vicinity of nociceptors, thus increasing their activity. (*5,6*) Increased nociceptor input contributes to the cycle by increasing motor and sympathetic activity, which in turn leads to increased pain. The pain is shadowed by growing fatigue, which adds an overall mood of distress to the patient's situation and feeds back to the cycle. (*7*) As tense muscles in the affected area begin to fatigue in an environment of sympathetic stimulation and local biochemical change, latent trigger points within these muscles also begin to fire, thus adding to the positive feedback cycle and spreading the pain to these adjacent muscle groups. Finally, the stress of pain and fatigue, coupled with both increased muscle tension and sympathetic tone throughout the body (conceivably with ipsilateral emphasis through the sympathetic chain), leads to flare-ups or trigger points in other muscles remote from the initial area of pain. (Modified from Sola AE. Myofascial trigger point therapy. *Med Times* 1982;110:70–75.)

An important characteristic of a TP is that stimulating it with dry needling or injecting it with a local anesthetic that has only transitory pharmacologic action (1,4,16,31), or with a cooling spray (1,2), can render it nonexcitable, and the pain cycle can be terminated for a period of time or even permanently.

In many cases the hyperactivity of TPs remains at a subclinical level, particularly after minor or moderate injuries to the shoulder girdle and upper extremities. In these instances the TPs remain undiagnosed and untreated. These points remain as latent, or “weak,” points, with increased sensitivity of slow nerve fibers, associated vasoconstriction, and low-grade hypersympathetic activity, resulting in the “injury pool” phenomenon (6,23,32). The significance of the injury pool is that subsequent injury, stress, or fatigue can initiate an accrued response that is vastly disproportionate to the immediate circumstances, because latent points throughout the body can easily be activated by subsequent sympathetic nervous system activity.

CLINICAL CONSIDERATIONS

Symptoms and Signs

Patients with myofascial disorders usually present with persistent pain, tight or aching muscles, limited ROM, general fatigue, or a combination of these. The patient might not be aware of the muscular involvement, however, and might complain instead of headache, neck pain, joint pain, backache, or sciaticalike pain in the buttocks or lower extremities (5,7,33,34).

The intensity of myofascial pain ranges from a low level, felt as a mild ache, to excruciating aching or burning pain, or both. The pain can be either continuous or periodic, but it is usually persistent, debilitating, and limiting. It is usually elicited explosively and spontaneously as soon as the trigger area is touched. The extent of the area of focal and referred pain apparently depends on the sensitivity of the trigger areas: If the trigger area is very sensitive, there is a wide radiation of pain to include the essential zone of reference as well as a spillover zone (Fig. 29-3), whereas if the trigger area is not sensitive, pain is present only in the essential zone. Associated with pain are deep hyperalgesia or tenderness in the reference zone, often continuous hyperalgesia, and, as previously mentioned, limited ROM, general fatigue, or both.

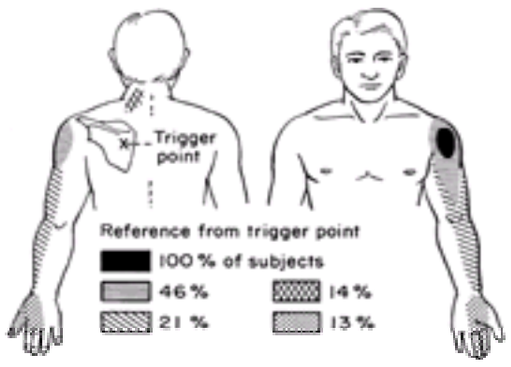

Figure 29-3. Pain reference pattern of trigger area in the upper portion of infraspinatus muscle as mapped in 193 patients with shoulder pain. The black area is called the *essential reference zone* because 100% of the subjects felt pain there; the shaded and stippled areas are collectively labeled the *spillover reference zone* because not all patients felt pain in these areas. (Modified from Travell JG. Basis for the multiple uses of local block of somatic trigger areas. *Miss Valley Med J* 1949;71:13–22.)

The pattern of this referred pain and associated phenomena is relatively constant and predictable, which indicates that impulses concerned in the unfamiliar reference of somatic pain, like that of visceral pain, follow fixed anatomic pathways (1,2,3,4,5,6,7,8 and 9,16). This predictability of pain patterns enables one to use a known reference pattern by which to locate the myofascial source of the pain. It must be added, however, that the distribution of referred somatic pain, although remarkably constant for the structure stimulated, does not follow a dermatomal pattern or nerve root distribution. This lack of neurotomal distribution of symptoms and signs has been perhaps the most important factor delaying recognition of this group of disorders as clinical entities and has misled physicians to misdiagnose them as bursitis, tendinitis, or arthritis or as functional. Figure 29-4 shows some of the common myofascial pain syndromes in different parts of the body.

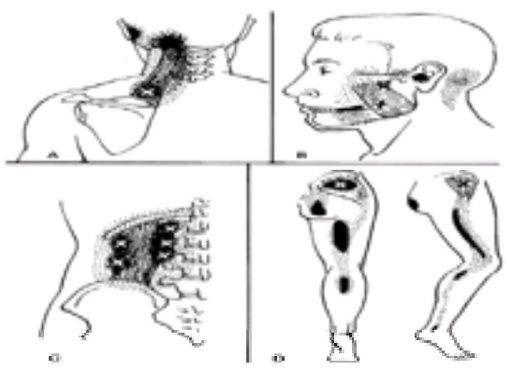

Figure 29-4. **A:** Pain pattern and trigger points of the levator scapulae muscle. **B:** Masseter muscle with some of its characteristic pain reference sites. **C:** Quadratus lumborum muscle with common trigger points and local pain reference pattern. **D:** Gluteus medius trigger point (one of the most powerful trigger points in the body, with its local pain and reference referral patterns to the thigh and legs), and tensor fascia lata trigger point and characteristic hip pain and lateral thigh and leg reference zones.

In a minority of patients, the presenting complaint is not pain but limited ROM or conditions associated with shortened or guarded muscles. One example of this is short-leg syndrome, in which the shortening of the leg can be attributed to extreme muscle tightness involving hyperactive TPs, particularly in the ipsilateral quadratus lumborum and into the ipsilateral extremity. Compensation for the shortened leg then creates another set of symptoms that bring the patient in for treatment. Another common example is patients who have limited ROM in one shoulder, for which they have compensated to the extent that they are no longer aware of the condition as a source of pain. Their presenting complaint might be muscle weakness in the forearm or hand. On examination, affected muscles do not extend to full range and resistance is exquisitely painful. Maximum contractile force is weakened, and muscle strength is unreliable.

Severe hip pain associated with pregnancy is often myofascial in origin. In a study by Sola (unpublished data, 1986) of 32 gravidas referred for treatment because of moderate to severe hip and low back pain, 29 had symptoms and signs characteristic of myofascial pain syndromes. All 29 responded positively to treatment, and follow-up revealed that pain relief persisted during the remainder of the pregnancy. In most cases relief occurred after one or two treatments consisting of TP injections with normal saline and hot packs.

When the pain is of long duration, it is extremely common for patients to indicate involvement of several areas—for example, pain and ache in one upper extremity, associated with edema in the hand or wrist, might be associated with stiffness or discomfort in the hip and lower limb on the ipsilateral side (4,7,16). Both active and latent TPs are hypersensitive to pressure on examination, but only active TPs cause pain. Latent TPs can result in involuntary guarding of muscles, including involuntary limitation of ROM. Such patterns of guarding and disuse contribute to arousal of the latent TP to a level of activity resulting in achiness in the ipsilateral limb.

Secondary myofascial syndromes are usually associated with a known condition. A reliable indicator of secondary myofascial involvement is a history of pain that is disproportionate to what might be expected or pain that persists after the normal treatment period for the primary clinical disorder. In some instances of severe, generalized pain, treatment for myofascial syndrome can accomplish sufficient pain relief to reveal and permit localization of the primary pain source, thereby assisting in the diagnosis. (TPs, both in the upper and lower body, are also frequently found in association with herpes zoster and in stress-related disorders.)

Myofascial syndromes may complicate recovery from surgical procedures, causing intense pain near the incision (Sola, unpublished data, 1975). Latent points can also be activated by adjunct therapies after surgery or injury, such as physical therapy, massage, exercise, and, particularly, ultrasound or electrical stimulation. If any of these treatments increases patient suffering, it should be discontinued until a thorough evaluation has been made for myofascial supersensitivity.

Undiagnosed and untreated, myofascial syndromes can delay recovery from uncomplicated stressful incidents and injuries and can perpetuate a state of disability with chronic pain as the primary symptom. In a study of workers disabled by low back pain, Gunn and Milbrandt (34) found that patients with “low back sprains” without tender myofascial points were disabled an average of 6.9 weeks. In contrast, those with “low back sprains” who also had tender myofascial points were disabled for an average of 22.4 weeks, almost as long as those who had signs of radiculopathy, who were disabled for an average of 25.7 weeks.

Most of the current pain literature associates prolonged symptoms and disability with abnormal illness behaviors caused by emotional, psychological, or environmental factors (35). As mentioned in Chapter 10 and Chapter 18, this conclusion is neither surprising nor inaccurate because most of the reports on chronic pain originate in major comprehensive multidisciplinary referral pain programs. Clinical studies have demonstrated that the psychological profiles of patients in such programs are different from those of the general population (36,37). In one study in which 200 patients from the university clinical population were compared with 200 patients from a private pain management practice, there were significant differences in illness behaviors and personality factors between the two populations (37). These data suggest that there is potential danger in generalizing knowledge about the psychological profiles of tertiary referral clinic patients to private-practice settings. Physicians in private practice are much more likely to encounter patients with medical causes of their pains and less likely to encounter moderate or severe depression in association with chronic pain (see Chapter 10). Evaluation of the patient for myofascial syndromes will frequently provide the practitioner with the medical explanation for persistent pain.

Of course, it is possible that TPs are a physiologic mechanism through which a psychophysiologic process manifests and perpetuates itself. Regardless of the causative factor—that is, whether a TP is the result of injury, psychological stress, or environmental factors—once it has formed its own hypersensitivity it is sufficient to generate progressively greater responses that are painful and physically limiting. Although the family physician or the average clinical specialist might not be able

to treat the psychopathologic processes that might account for some of the symptoms, the myofascial syndrome can be readily relieved through TP therapy.

Diagnosis

Diagnosis of myofascial syndrome requires a detailed history of the pain problem, the patient's personal and family history, a general physical examination (which might include neurologic and orthopedic evaluation), and a systematic search for the TP (see Chapter 12).

A detailed history of the pain problems should be taken. Briefly, this entails eliciting a history of the cause and characteristics of the pain at onset, subsequently, and at the time of interview. As previously mentioned, myofascial syndromes caused by sudden trauma are usually easily remembered so that the patient can describe what activity was associated with the onset of pain. In the absence of recent trauma and when onset of pain has been gradual, the physician must inquire about daily activities that might involve repeated movements of muscle groups that could result in chronic overload of muscles.

Physical examination should focus on observation of abnormalities of gait, postural deviation, body asymmetries, and any protective and restricted movements as the patient moves about or disrobes. Normal ROM does not preclude the presence of TPs, but TPs are invariably present if ROM is limited. The involved muscles, as identified by screening for restricted motion and by palpation, usually reveal no sensory deficit or changes in reflexes. Areas distal to the affected muscle, however, might show subtle signs of denervation (26).

To systematically search for the trigger zones, it is essential to know the reference pattern of various myofascial pain syndromes, or at least to have a source to consult to refresh one's memory. As an example, pain in the head and face is often associated with TPs in the cervical muscles (Fig. 29-5). The area of pain reported by the patient can be helpful in attempting to ascertain the pain pattern and tentatively identifying the TPs. The examiner then palpates the suspected muscle for tender TPs and tight bands. The search for TPs is best accomplished by palpating the area with the tip of the finger.

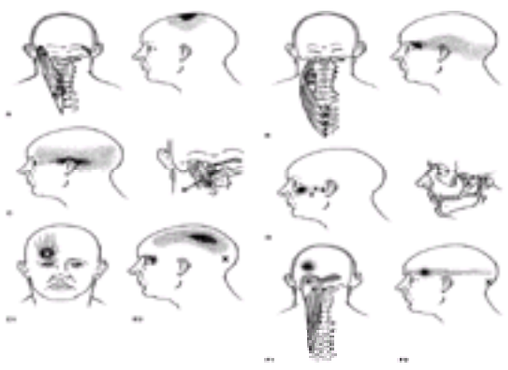

Figure 29-5. Patterns of pain related to trigger points in the head and neck. **A:** Splenius capitis. **B:** Cervicis. **C:** Suboccipital muscles. **D:** Lateral pterygoid muscles. **E:** Occipitofrontalis muscles: 1. frontalis, 2. occipital. **F:** Medial posterior cervical muscles: 1. semispinalis cervicis, 2. semispinalis capitis. *Note: These regions must be approached with extreme caution due to the proximity of underlying nerves and vessels.* (Modified from Travell JG, Simons DG. *Myofascial pain and dysfunction: the trigger point manual*. Baltimore: Williams & Wilkins, 1983.)

The palpation should be systematic so that every square centimeter of the surface overlying the suspected sensitive zone or site from which the pain arises is palpated. The patient is instructed to indicate when the point of exquisite tenderness is not only locally painful, but also aggravates or reproduces the pain in the reference zone. The patient is observed closely during the palpation, because pressure on the exquisitely tender TP usually causes the patient to jump, wince, or cry out. Often seemingly remote TPs contribute to the problems in reported painful areas. Thus, the search for hypersensitive areas should extend to large ipsilateral muscles, particularly in the gluteal region (Fig. 29-6).

Figure 29-6. Ipsilateral pain, a diagnostic key to treatment of refractory local pain. An ipsilateral pattern of pain is very common, with simultaneously active painful trigger points (TPs) in the neck and shoulder, quadratus lumborum, and gluteal muscles (m.) and frequently in the calf muscles. The patient may not be aware of pain in the lumbar gluteal region or lower extremity but may confirm achiness or stiffness in the hip area, sciaticalike pain, or fatigue in the lower back and extremities. Hyperactive TPs in the lumbar gluteal muscles must be treated before positive results can be expected from treatment of TPs in the head, neck, or extremities.

Once the suspected TP has been found and marked with a skin pencil, the palpation is varied so that the patient is required to assist in identifying the particular spot. Uncertainty on the part of the patient suggests that a spot is not a true TP. When several areas of exquisite tenderness are found, it is important to initiate treatment at the most sensitive point.

Search for Tight Bands

To examine the suspected muscle for the objective sign of a tight band, it is placed on stretch. This maneuver places the fibers in a tight band under increased tension, while uninvolved adjacent fibers remain slack. This tight band can be felt most readily by rubbing the tip of the finger (rather than the flat pad) across (perpendicular to) the direction of the fibers (Fig. 29-7). As the fingertip passes over the tight muscle, it feels tense as a nodule. Another technique of palpating the tight muscle and the TP is to grasp the belly of the muscle between thumb and forefinger and squeeze the fibers with a back-and-forth rolling motion to locate taut bands. Tense nodules promptly disappear after effective treatment of the TP.

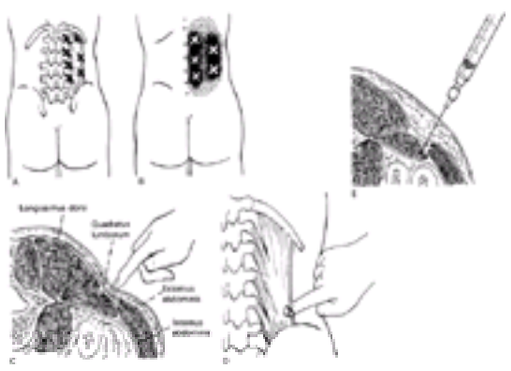

Figure 29-7. Quadratus lumborum myofascial pain syndrome. **A:** Anatomy of the quadratus lumborum and its attachment. Trigger points (TPs) are shown by *X*. **B:** Pattern of pain caused by TPs in the lateral part of the muscle and in its attachment to the transverse processes of the lumbar vertebrae. In the black areas (the essential zones) the pain is most intense and is felt by all patients; in the stippled areas (the spillover zones) not all patients experience pain, and if they do, it is of lesser intensity. **C,D:** Palpation of the area to locate the TP. **E:** Techniques of injecting the TP.

Local Twitch Response

Another objective sign recommended by Travell and Simons (1) is the local twitch response (LTR), which is readily observed in superficial muscles when rapidly changing pressure is applied to the TP by snapping palpation. They cite electromyographic studies showing that this response represents a transient (usually less than 1 second) contraction of a circumscribed group of fibers that correspond closely to the palpable band. The greatest LTR is observed when the TP itself is stimulated, and generally, the more active (hyperirritable) the TP, the stronger its LTR. As one moves further from the TP, stronger pressure is required and the LTR becomes less and less vigorous.

Although the LTR can be useful, the most reliable technique is to systematically search for the TP, and once the point is found, apply sustained pressure sufficient to cause mild local pain that invokes the referred pain pattern in 5 to 10 seconds. If very strong pressure is applied, the local pain can overshadow the referred pain. The referred pain pattern caused by stimulation of a TP is also invoked when a needle penetrates a TP during injection.

TPs are most commonly found in the mid-portion of the muscle belly, coinciding with the motor point in many cases. They are also found at the attachment to the bone, however, and they can develop at other points along the muscle. The size or significance of the host muscle is unrelated to the amount of pain generated by activation of the TP. Once a TP is identified, its sensitivity should be determined by comparing the affected muscle with contralateral muscles in the same segment.

The patient's report of pain should never limit the area of search for TPs. Some patients are acutely aware of pain in only one portion of the body (head, neck, extremity). Examination might reveal hyperactive points in the lower trunk or shoulder girdle that are more important in achieving pain relief. The search should proceed to include the predicted patterns discussed below, with particular emphasis on the erector spinae and the gluteal muscle.

Segmental Clusters

We have found that several different muscles supplied by a specific nerve or nerves frequently contain clusters of hypersensitive TPs. The spread from a single point of stress into clusters is assumed to be associated with local pain response and muscle fatigue. Clusters of myofascial syndromes are common in the neck and shoulder area and include most frequently the trapezius, levator scapula, and infraspinatus. As the severity and duration of pain increase, so do clinical findings of progressively greater involvement of all other muscles innervated by the same spinal segment(s). Hypersensitivity at one level readily involves other muscles with overlapping segmental innervation. For example, the innervation of the splenius capitis muscle starts at the C-2 level and reaches the mid-thoracic level. Therefore, progressive involvement of TPs can be anticipated in all of the muscles with the common spinal nerve supply.

If a TP with referred pain is found in a muscle innervated by the anterior division of the spinal nerve, palpation of the muscles innervated by the posterior division of the same nerve frequently reveals latent TPs that are hypersensitive to pressure and can cause muscle tightness with pain. Thus, TPs in the posterior abdominal muscles may be accompanied by somatic-visceral symptoms related to anterior abdominal muscles in the same segment(s) (38,39). Effective treatment would then involve both the muscles of the lower back and the anterior abdominal muscles, including the rectus abdominis. Contralateral muscles as well as muscles in neighboring segments can also be involved, although usually to a lesser extent.

Multiple Segmental Clusters

As the self-perpetuating myofascial disturbance continues and progresses, TPs develop further and further from the initial area of stress or injury. Although it is generally appreciated that there can be contralateral involvement along segmental lines, it is not generally realized that TPs tend to develop with a higher frequency in ipsilateral muscle groups. Careful examination is likely to reveal that at least 50% more hypersensitive points are found in muscles of the same side as compared with muscles of the contralateral side. Thus, TPs in the upper trunk or shoulder area are likely to be accompanied by TPs in ipsilateral gluteal or lumbar muscles, or both. Activation of TPs in these lumbar and gluteal muscles can adversely affect TPs involving the shoulder, neck, and head or those in the lower limb.

Treatment

General Considerations

Treatment of myofascial pain syndromes revolves around interruption of the pain cycle by eliminating the TP. This may be accomplished by penetrating the TP with a needle; injecting a local anesthetic, a weak steroid solution (38), or saline alone; or spraying the skin overlying the muscle containing the trigger area with a vapocoolant (preferably chlorofluoromethane, although some clinicians use ethyl chloride). In addition, stretch of the muscle is used after TP therapy. Indeed, some clinicians (1,9) believe that stretch of the muscle is as important as the injection or spray. Although we use passive stretch alone in mild cases of myofascial syndromes and we use it in combination with needle penetration of the trigger area in a number of patients, we do not use it routinely, as advocated by Travell and Simons (1,9). Although the latter clinicians consider “stretch and spray” the “workhorse of myofascial therapy,” extensive experience with thousands of patients suggests that penetration of the TP with a needle or injection of a local anesthetic, a weak steroid solution, or saline remains the most effective therapy (4,6,7,16,31). The limited use of low- dose steroids [0.05% dexamethasone (DMSO) in saline] is a more recent approach that shows particular promise in older patients or in those with an extended history of myofascial pain.

Although good results have been reported with injections of saline or with dry needling (1,9,33,40,41), the use of local anesthetics diminishes the local discomfort associated with the injection. In my experience, the optimal concentrations of local anesthetics for injections of TPs are 0.5% procaine, 0.25% to 0.5% lidocaine, and 0.125% or 0.25% bupivacaine in 2 mL. Using these concentrations and volumes virtually eliminates the risk of systemic toxic reactions and local damage to muscle. Thus, injection of 20 mL to treat 10 TPs involves a maximum of 100 mg of procaine, 50 to 100 mg of lidocaine, or 25 to 50 mg of bupivacaine. It is of interest to note that lidocaine, in doses of 50 to 100 mg injected as a bolus, is frequently used for the treatment of cardiac arrhythmia without systemic toxicity. Although procaine was long considered the standard of reference as the best drug, lidocaine has the advantage of more rapid and longer action; bupivacaine produces analgesia that lasts four to six times longer than procaine and two to three times longer than lidocaine.

The theory underlying treatment is that the entire symptom complex is an expression of reflex mechanisms, provoked by the TP, and that once it is initiated, it is self-sustaining by implication of closed, self-exciting chains of internuncial neurons in the central nervous system. Interruption of this pain cycle by eliminating the TP, using dry needling; injection with local anesthetic, a weak steroid solution, or saline alone; or stretch and spray, interrupts the reflex and can produce prolonged relief.

Treatment of myofascial syndromes secondary to ligamentous injuries is somewhat difficult. Injuries associated with physical labor (impact, heavy lifting, twisting) and automobile accidents might not respond to the initial course of TP therapy. If no response is apparent, attention should be turned to the adjunctive therapies and TPs should be reevaluated periodically over the course of treatment.

Trigger Point Injection Technique

To apply the injection technique successfully, it is necessary to have knowledge of the patterns of various myofascial syndromes and the locations of the trigger areas. Application of this knowledge requires a thorough history and physical examination. Treatment must be directed primarily toward the trigger area and not to the zone of reference. Although infiltration of the spastic muscle and application of heat and other physical therapeutic procedures that produce spasmolysis are of benefit, blocking of the TP or trigger area is more efficacious because it eliminates the cause of the referred pain and the associated phenomena. It is also important to remember that more than one trigger may be, and usually is, present. Therefore, for optimal results, it is necessary to examine all of the muscles for TPs that could be producing the pain pattern so that all of the abnormal foci of pain can be interrupted. Finally, it is important to recognize sites that include crucial underlying structures such as nerves or vessels that must be avoided. Great care must be taken when treating the head and neck (see Fig. 29-5); the inguinal, axillary, or

popliteal areas; and the scapular region (apex of lung).

Preparation of the Patient. Before the first treatment, whether by penetration of TPs or by stretch and spray, it is important to provide the patient with information about the purpose of the treatment, a detailed description of the procedure, and what is expected to be accomplished. The patient must understand clearly why the therapy is directed toward the TP rather than the area of pain reference. This understanding can be enhanced by again exerting pressure on the TP and reminding the patient that the pain provoked by the pressure is referred to another area. Because in many instances the period of relief produced by the treatment is followed by pain that may be even greater than the original complaint, the patient should be informed that such a reaction is not uncommon. Unless this information is provided in advance of the therapy, the patient might become discouraged and not return for a second treatment. The patient's full cooperation is required if optimal results are to be obtained.

For needle preparation, the patient is placed in the recumbent position to prevent or minimize attacks of psychogenically induced arterial hypotension and syncope, which are likely to occur in apprehensive patients who are upright. The patient should be repeatedly reassured and informed of each maneuver before treatment. It is essential to have a source of oxygen in the office to treat vasovagal or psychogenic reactions. This need not be a complicated piece of equipment, but merely a tank, regulator, and mask.

Technique of Injection. Just before initiating the treatment, the precise site is marked with a skin pencil or gentian violet and the skin is washed with soap and water and then with antiseptic solution. Sterility must be strictly maintained to preclude infection. Immediately before insertion of the needle, the TP is again identified with the finger (Fig. 29-8). Penetration is accomplished with a 25-gauge, 5-cm needle for deep muscles or a 27-gauge, 2-cm needle for superficial muscles. The use of such fine needles makes preliminary intracutaneous injection of the local anesthetic unnecessary and even undesirable because the pain caused during injection is usually more than that caused by the deliberate insertion of a fine needle through the skin. Although some clinicians advocate the use of 22-gauge needles for fear of breaking finer needles, we believe that proper insertion of a good needle virtually eliminates the danger of breakage and has the advantages of making insertions almost painless and avoiding trauma to tissues.

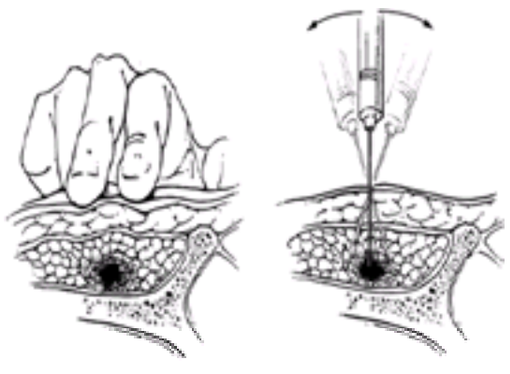

Figure 29-8. **A:** Technique of locating trigger point for injection. **B:** Fanning technique for injection.

The needle is attached to a 10-mL Luer-Lok control syringe filled with a local anesthetic solution, saline, or a weak solution of saline and 0.05% DMSO. Although some clinicians use a smaller syringe (3 or 5 mL), the larger syringe acts as a reservoir and avoids the necessity of refilling the syringe several times if many TPs are to be injected. Saline only is very effective and preferable in young patients and is the only choice for pregnant patients. Local anesthetic or the DMSO solutions should *not* be used with pregnant patients. The DMSO solution should also be avoided in patients who are diabetic, have clotting disorders, or have other contraindications to steroid use.

The needle is directed at the most sensitive TP identified and is advanced until the TP is penetrated. Penetration of the TP elicits exquisite tenderness and pain, not only locally but also at the zone of reference. The depth of the injection depends on the region involved and on the site of the TP. Once the TP is penetrated, a total of 0.5 to 2 mL of solution is injected under some pressure. This process usually causes further exaggeration of the local or referred pain and tenderness and, not infrequently, local spasm.

The needle is then withdrawn slightly and redirected two or three times to cover the immediate area of the TP with a fanning technique depicted in Figure 29-8. Exaggeration of pain and tenderness and local spasms is presumptive evidence that the injection has been properly executed. Confirmation is obtained if the procedure effects relief of pain and muscle spasm, which is usually dramatic. If no relief is obtained, it is most likely that the TP was not injected, indicating another trial. It is essential to eliminate the TP or points completely by repeated infiltration because incomplete blockade is not only partially ineffective, but it is followed by increased pain after disappearance of the effects of the local anesthetic.

Although some physicians have reported injection of as much as 10 to 15 mL of solution at a given TP, we have found this amount to be unnecessarily excessive, and it carries the risk of systemic toxicity if multiple TPs are injected.

Treatment of the neck and head muscles can be done with a very short 27-gauge or 30-gauge needle. Use of a fine needle precludes most of the bleeding and subsequent discomfort associated with TP injections (4,5,16). When a fine needle is used in large muscle mass, however, there is always the possibility that it might break off.

Several TPs can be treated, provided the patient is monitored closely during and immediately after treatment. If the patient manifests signs of pallor, sweating, or faintness, treatment should be promptly discontinued. Immediately after the injection therapy, a warm, moist pack is applied to the area to relieve temporary discomfort. This also extends the time the patient is quiet after treatment, and patients report that they find this aspect of treatment soothing.

TPs in the extremities are slightly more difficult to locate precisely. When they have been identified, however, injection is generally safe and uncomplicated. If bleeding into tissue occurs, such as might be anticipated in the tight compartments of the forearm, the treatment is followed with applications of cold packs and compression rather than the warm, moist packs otherwise recommended.

The dominant role of the larger muscles of the lower torso requires that TPs identified in these areas be treated on the first visit. They are usually involved in a myofascial syndrome that has been well established. Failure to treat TPs in the lower trunk concurrent with or before treatment of points in other parts of the body is likely to result in greater discomfort for the patient. We have seen many patients in whom TPs in the neck and shoulder areas were treated by injection without a full clinical evaluation of TPs in other locations. The result for many of these patients was painful activation of TPs in the lumbar and gluteal muscles. In addition, treatment of the cervical and shoulder areas was not effective.

In patients who have severely limited ROM, it is recommended that muscles supplied by both anterior and posterior divisions of the nerve on ipsilateral and contralateral sides be examined for latent TPs. Obviously, if TPs are present they should be treated.

Relief of pain, tenderness, muscle spasm, and associated phenomena persists for several hours after treatment, and sometimes for a day or two. In patients with acute myofascial syndromes (i.e., the symptoms are of recent onset and caused by major trauma), two or three treatments are often sufficient to provide permanent relief. In general, young patients tend to respond more quickly and positively than older patients; however, a series of two to five treatments is usually sufficient either to provide prolonged relief or to establish that the patient is responding to the therapy. Patients with severe pain associated with activation of latent TPs might require 3 to 6 weeks of intensive therapy consisting of TP injections and physical therapy (4,5,7,16).

Patients who have had a history of severe pain for several years before treatment may not respond to treatments for many months. Persistence with the treatment is indicated in these cases, however, by the clear finding of numerous hyperactive TPs with either an ipsilateral tendency or general distribution throughout the body. Release of muscle tension for these patients has usually been dramatic, and it has been described as “tight armor suddenly falling off the whole body.”

Technique of Stretch and Spray

As previously mentioned, Travell and Simons (1,9) and Kraus (42), among others, prefer the technique of spraying the skin overlying the muscle of the trigger areas and subsequent stretch of the muscle to injection therapy. The advantages claimed for this technique are that it is simple, relatively painless, and a rapid way to relieve a single muscle syndrome. Moreover, they believe that it is more effective in deactivating all TPs in the affected muscles, some of which might be missed by palpation. They also believe that it is useful immediately after injection to ensure deactivation of any remaining active or latent TPs in a group of muscles. Although they claim that this technique provides a more rapid way to relieve myofascial syndromes, our extensive experience with both techniques suggests that beneficial results from the spray and stretch technique are slower in occurring.

Travell and Simons (1,9) emphasize that they use the term “stretch and spray,” not “spray and stretch” because they consider “stretch” the essential component, whereas the spray facilitates the stretch. Gentle, persistent stretch without spray is more likely to inactivate deep TPs than spray without stretch. They find the best results are obtained by spraying first and then stretching and spraying. They believe that the spraying reduces the painfulness of the stretch tension, helping the patient to achieve complete relaxation, and that it helps to block reflex muscle spasm initiated by autogenous stretch reflexes.

For this procedure, the patient is prepared as discussed above, but the position used for the technique differs depending on the target muscles to be sprayed and stretched. For myofascial syndromes in the head and neck, and for some in the upper limbs, the patient should be in a sitting position; for syndromes involving most of the muscles in the upper extremity, trunk, and lower extremity, the patient is placed recumbent either in the supine or lateral position, to permit the most appropriate spray and stretch.

Technique. The patient is made comfortable, and the part to be sprayed is well supported so that the involved muscles are relaxed. One end of the muscle must be anchored so that the pressure can be applied at the other end to passively stretch it. With the patient in the position for stretch, the bottle containing Flouri-Methane (Gebauer Chemical Company, Cleveland, OH) is held 18 inches away from the patient and the spray applied at an angle of 30 degree with the skin as illustrated in Figure 29-9. A jet or stream (not a diffuse mist) of the vapocoolant spray is applied to the skin overlying the trigger area and moved slowly in one direction, rather than to and fro. The direction is determined by the pain reference pattern of the specific TPs to be sprayed; the sweep should be started on the skin over the trigger area and made to travel toward the area of referred pain, and then over the referred pain pattern.

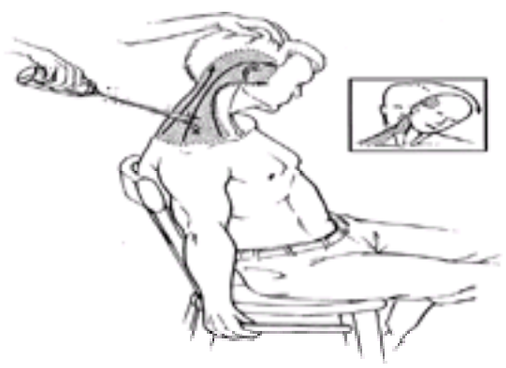

Figure 29-9. Stretch and spray technique.

The spray is applied in parallel sweeps to cover the entire muscle involved, as well as the area of reference, to achieve full muscle length. A given area of skin is sprayed only two or three times before rewarming. A moist hot pack is applied to rewarm the skin and help further relax the muscle. After the skin has rewarmed, stretch and spray can be repeated. Several cycles of full ROM and complete stretch and spray treatment of the muscle may be required. The patient is cautioned to avoid overloading the muscle after treatment.

Travell and Simons (1,9) believe that the stretch and spray technique inactivates myofascial TPs, with consequent release of the abnormal muscle tension and disappearance of the sensitive point and the referred pain and associated phenomena. We believe that the spray facilitates the stretching by inhibiting the pain and stretch reflexes, perhaps by provoking spinal inhibition, descending inhibition, and/or inhibition of TPs.

Adjunctive Therapies

For optimal results it is necessary to use other therapeutic measures in addition to deactivation of the TP. If severe autonomic (sympathetic) dysfunctions are prominent, a sympathetic block might be useful in addition to the infiltration or spray and stretch. Immediately after these procedures we frequently have the patient receive physical therapy in the form of massage (especially gentle deep friction) and, as previously mentioned, heat applied to the affected muscle. Passive and active motion of the part is an essential adjunct to treatment. The physician should impress on the patient the importance of his or her active participation in treatment and encourage the patient to undertake specific, appropriate forms of exercise. It is essential that the involved muscles not be activated too rapidly or moved to a painful degree, especially in the early phases of treatment, because severe pain itself is deleterious and provokes reflex muscle spasm.

Drugs should be used only as an adjunct to a comprehensive therapy program. In patients who are likely to have moderate to severe pain after the injection therapy, it is best to prescribe nonnarcotic analgesics such as aspirin or nonsteroidal antiinflammatory drugs to be taken between treatments. If muscle spasm is diffuse throughout the body, a short course of muscle relaxants may be prescribed during a trial therapy period. If the patient experiences severe intractable pain, small doses of a narcotic may be prescribed for 3 to 5 days, but not longer, lest the patient develop physical dependence. Patients with chronic, persistent pain often consult several physicians, with the consequent possibility of having had several prescriptions for medication.

In place of TP therapy, a number of clinicians have used other modalities, including massage (especially deep friction); electrical stimulation; ice massage; cervical or lumbar traction, or both; compression; ultrasound; and biofeedback (1). Because there is little conclusive research on how these various treatments act to modify myofascial pain syndromes, all can be considered on a case-by-case basis as either treatment or pain management adjuncts.

Pressure and Massage. Pressure over TPs and massage of muscles have been reported to be effective in treating myofascial syndromes. From a medical viewpoint, however, when these methods are used inappropriately they can exacerbate the conditions that perpetuate pain through the TP locus, resulting in more severe symptoms. Our observations led to the conclusion that pressure and massage must be used with caution when the small muscles of the head and neck have flared up with TP hyperactivity. When pressure, massage, or both are used in a controlled situation by a clinician who is prepared to follow through with alternate therapies, these noninvasive methods have the advantage of being an initial approach that does not increase the patient's anxiety.

Ice Massage. Report on the use of ice massage for pain relief shows that it might be comparable to transcutaneous electrical stimulation and acupuncture, mediating pain relief with similar neural mechanisms (beta afferent fibers). In a study by Melzack et al. (43), ice massage provided pain relief among patients with chronic low back pain, the majority of whom had undergone diskectomy, spinal fusion, or both or with radiologic evidence of degenerative disk disease. The efficacy of ice massage for TP desensitization has not been documented.

Electrical Stimulation. Transcutaneous electrical stimulation (TENS) as a therapeutic method is discussed in Chapter 98. This treatment has been demonstrated as a useful tool in reduction of myofascial pain as well as pain of nonmuscular etiology. Kaada (44), in a review of research on physiologic and biochemical mediators of pain, pointed out that neither the spinal gate mechanisms nor the analgesic effect of endorphins can explain the “widespread cutaneous vasodilation evoked by low frequency TENS and acupuncture.” He suggested that different mechanisms are working as pain mediators in response to these treatment methods. The three possibilities presented were reduction of vasoconstrictor tone, active vasodilation via sympathetic nerves by inhibiting the release of norepinephrine at the neuromuscular junction and vasoactive peptides, and an axon reflex. The axon reflex differs from the other mechanisms mediated over the sympathetic nerves in that it is local and “rather immediate.” Much of the confusion in the literature about the effectiveness of TENS is now being cleared; recent work illustrates the importance

of different stimulation parameters for specific painful conditions (see Chapter 98).

CONCLUSIONS

Myofascial syndromes affect virtually everyone at some time, either as a primary source of pain or in association with other painful conditions. The syndromes should be recognized by clinicians to prevent their attribution to normal aging or degenerative processes. They should be suspected in all chronic pain cases and in all cases in which pain exceeds expected duration or intensity. When myofascial pain is secondary to another painful condition, treatment of TPs can reduce the patient's pain level and aid in diagnosis of the underlying condition.

Creditable clinicians and investigators for the treatment of these conditions have recommended many treatment methods. At present, it is difficult to evaluate the relative efficacy of these methods or to determine the most appropriate applications. Much of the confusion can be attributed to differences in the patient populations that are served and in the wide range of pathology treated under the “myofascial pain syndromes” classification. The variations range from a single TP of recent activation to broadly generalized TP hypersensitivity of many years' duration accompanied by high levels of sympathetic nervous system involvement. All of these can be secondary to an underlying pathology, with or without neuropathy.

Myofascial syndromes are most effectively treated by penetration of the TPs and injection of a local anesthetic, low-dose steroids, or saline alone. The use of local anesthetics in conjunction with needling has the obvious advantage of eliminating patient discomfort during and after treatment. This highly effective therapy is sufficient to relieve pain without need for adjunct therapies when the patient is seen before the myofascial syndrome has been well established. Therefore, the optimal approach is for clinicians in all specialties to be alert to myofascial pain syndromes as primary and secondary sources of pain and to incorporate the basic techniques of TP desensitization into any comprehensive patient management program.

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CHAPTER 30

Fibromyalgia Syndrome

I. J. Russell

Fibromyalgia syndrome (FMS) is a controversial disorder of unknown etiology. It is characterized by the history of chronic, bilateral, upper and lower body, “musculoskeletal” pain combined with typical examination findings of painful tenderness at 11 or more of 18 anatomically defined soft tissue tender points (TePs).

Even though the joints of FMS patients are apparently normal, the severity of the discomfort they experience and the extent to which they are limited physically are comparable to those reported by patients with rheumatoid arthritis (RA). Other clinical manifestations that are common but less consistently associated with FMS include lightheadedness, memory loss, insomnia, depression, fatigue, irritable bowel syndrome, and urodynia. The situation is further complicated by the apparent comorbidity of FMS with a variety of rheumatic, inflammatory, infectious, and endocrine disorders.

Despite many attempts to identify a histologic abnormality in the painful soft tissues, none has been confirmed. The widespread pain and low pain threshold of FMS patients has led to a suspicion that a neurochemical mechanism may be involved. Broad experimental support for that concept has led us to propose FMS as “chronic, widespread allodynia.”

In animal studies, a variety of manipulations of nerves and transmitters can induce allodynia. The findings from such studies may be relevant to humans with FMS. Serotonin is a recognized mediator in the regulation of deep sleep and of pain perception. Its production appears to be compromised in many tissues of FMS patients. One of the functions of serotonin is to regulate the release of substance P in the central nervous system (CNS) and thereby alter the perception of tissue damage. Substance P concentration appears to be elevated in the spinal fluid of most FMS patients. There also appear to be abnormalities in several neuroendocrine systems and in high-energy phosphate stores. The major challenges for the coming years will be to better characterize FMS with respect to its etiology (predisposing, initiating, and perpetuating factors). Such information should lead to the development of interventions that are more effective than those currently available.

This chapter first examines the basic considerations pertaining to FMS and then turns to clinical considerations. Under the basic considerations section, issues relating to diagnosis, epidemiology, natural history, and proposed pathogenesis of FMS are discussed. The section dealing with clinical considerations is intended to help the clinician deal compassionately with the many problems presented by individual FMS patients. A compendium of review articles contains up-to-date information about FMS (1).

BASIC CONSIDERATIONS

History

It seems unlikely that FMS is a new condition, but there is very little information available from antiquity to shed light on its history. Aches and pains are so common to the human condition that it is easy to argue that disorders like FMS have always been present.

An early use of the term *fibrositis* dates back to the turn of the century, when Sir Edward Gowers attempted to characterize lumbago (Table 30-1).

Dates	Persons	Events
1500s	Spa Balneotherapists	Rest and hydrotherapy for aches and pains prescribed
1900	Sir Edward Gowers	Published the term *fibrositis*
1950s	Philip Hench	Used fibrositis in clinical diagnosis
1970s	Smythe et al.	Fourteen tender points diagnosis criteria developed
1970s	Moldofsky et al.	Insomnia, alpha-delta sleep dysfunction noted
1980s	Yunus et al.	Two-stage criteria developed, *fibromyalgia* term first used
1988	Vaeroy et al.	Substance P concentration noted to be elevated in FMS spinal fluid
1990	Wolfe et al.	1990 ACR classification criteria developed
1992	Bennett et al.	Low concentration of growth hormone noted in FMS
1992	Russell et al.	Low concentration of serotonin noted in FMS
1993	Pillemer et al.	First NIH conference on FMS
1994	Crofford et al.	Abnormal HPA axis noted in FMS
1995	Mountz et al.	Low regional brain blood flow noted in FMS
1997	Buskila et al.	Increased rates of FMS after cervical spine trauma

ACR, American College of Rheumatology; FMS, fibromyalgia syndrome; HPA, hypothalamic-pituitary axis; NIH, National Institutes of Health.

TABLE 30-1. Key events in the history of fibromyalgia (FMS)

For many years, FMS was considered to be a subjective disorder of vague musculoskeletal pain that the physician could not objectively document on examination nor confirm by laboratory testing. The diagnosis was usually made by exclusion, but only after an extensive (and expensive) clinical evaluation had failed to disclose any other explanation for the patient's symptoms.

A dramatic milestone in the modern thinking about fibrositis was the insight provided by Smythe (2), who recognized that there was a group of patients whose widespread pain was accompanied by remarkably consistent tenderness to palpation at soft tissue body sites referred to as “tender points.” In a collaboration with Moldofsky (3), the concept of disrupted slow-wave sleep became associated with the fibrositis pattern of widespread pain and TePs. The diagnostic criteria developed by Smythe and Moldofsky were modified by Yunus and colleagues (4) to require less TePs but to include a variety of constitutional manifestations.

The prolonged morning stiffness reported by fibrositis patients resembled that of the inflammatory disorders, such as RA, but the erythrocyte sedimentation rate was usually normal in fibrositis and no other objective inflammatory features were found. For that reason, it was argued that the disorder was poorly named (the suffix *-itis*, inferring inflammation). The name was changed to *fibromyalgia syndrome*, but that name is similarly troublesome. It is not clear, for example, that either fibrous tissue (*fibro*) or muscle (*my*) is pathologically involved in this disorder. It seems wise to delay any further change in terminology until more information is known about the pathogenesis of this disorder.

In FMS, the clinical symptoms of widespread body pain, multiple TePs, long-duration morning stiffness, and inefficient sleep are characteristically and distinctly different from healthy normal controls. Despite clinical similarities of individuals with FMS, it is still possible that FMS is the ultimate manifestation of several distinct physiologic processes that involve genetic predispositions, age, chronic insomnia, neurochemical dysfunctions, endocrinopathies, spinal stenosis, and perhaps even physical trauma. It is possible that new findings from biochemical measures or genetic markers will allow identification of clinical or etiological subsets of FMS that should be viewed or managed differently. There may also be different modes of prevention.

From the early 1970s until approximately 1990, the numbers of publications about FMS (including those using the term *fibrositis*) numbered between 10 and 20 annually. After 1990, those numbers increased dramatically to more than 100 annually. A probable explanation for the dramatic change was a research study prospectively designed in collaboration with the American College of Rheumatology (ACR) (5). Investigators from approximately 20 clinical centers in the United States and Canada followed the same protocol to evaluate systematically the symptoms and signs found in people with the diagnosis of FMS. Healthy controls and disease control groups with early RA, systemic lupus erythematosus (SLE), and other painful conditions were assessed similarly. Analysis of these data led to classification criteria that have been endorsed by the ACR. The ACR criteria for the classification of FMS (Table 30-2) exhibited a moderately high sensitivity (88.4%) and specificity (81.1%), clarifying the clinical distinction between FMS and other painful conditions. Although these criteria have been criticized because they are subjective, they have facilitated research on FMS. They probably will not be effectively replaced until the pathogenesis of this condition is better understood and some form of laboratory test or histochemical lesion can objectively support the diagnosis and guide effective treatment.

From history: Widespread musculoskeletal pain.

Definition: For the past 3 months, pain has been experienced in four quadrants; the locations are counted as follows: both sides of the body, above and below the waist, in the trunk (e.g., cervical spine, anterior chest, thoracic spine, low back areas). Shoulder and buttock involvement count for either side of the body. "Low back" counts as lower segment.

From examination: Pain induced by palpation of tender points.

Definition: Pain must be inducible at 11 or more of the following 18 (9 bilateral) tender point sites:

Anatomic location of tender point sites:

1, 2. Occiput: at the suboccipital muscle insertion
3, 4. Low cervical: at the anterior aspects of the intertransverse spaces at C5–C7
5, 6. Trapezius: at the midpoint of the upper muscle border
7, 8. Supraspinatus: near the origins, above the spine of the scapula
9, 10. Second rib: upper surface just lateral to the second costochondral junction
11, 12. Lateral epicondyle: extensor muscle, 2 cm distal to the epicondyle
13, 14. Gluteal: in upper-outer quadrants of buttocks in anterior fold of muscle
15, 16. Greater trochanter: posterior to the trochanteric prominence
17, 18. Knees: at the medial fat pad proximal to the joint line and condyle

Adapted from Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33:160–172.

TABLE 30-2. The 1990 American College of Rheumatology criteria for the classification of fibromyalgia syndrome

In the wake of successful diagnostic criteria, a number of important new findings regarding the epidemiology of FMS have been identified. FMS has been found to be common in most Western countries. It has been shown to be present in approximately 2% of the adult general population in the United States (6), with a similar distribution in other countries where valid epidemiologic studies had been conducted. Adult women were affected five to seven times more commonly than men. In children, the gender distribution was approximately equal for boys and girls (7).

In the absence of observable tissue pathology, some have thought of FMS as a psychosocial disorder. Dissatisfaction with this approach as an explanation for FMS led to an ongoing deliberation referred to as the “central versus peripheral” pathogenesis debate. In the absence of a histologic basis for peripheral disease, the focus shifted heavily toward involvement of the CNS. As a result, findings in the neurochemical mechanisms of nociception and in the neuroendocrine system have taken center stage. Abnormal levels of biochemicals such as tryptophan, serotonin, substance P, growth hormone, and abnormal diurnal regulation of cortisol production all have been reported. Exactly how CNS alterations lead to FMS remains unclear.

Debate continues as to whether FMS should be considered a psychosocial disorder or a disabling condition on a par with RA, osteoarthritis, compression myelopathies, myasthenia gravis, multiple sclerosis, and diabetic neuropathy. This controversy is important because of its impact on social welfare eligibility and the role of health care in the relief of symptoms (8,9).

Classification

FMS is not a form of arthritis. Joint range of motion usually remains normal throughout the course of FMS, although there may be some limitation of active range of motion due to the discomfort experienced. Joint swelling, inflammation, effusions, or heat are not expected components of FMS. Occasionally FMS may antedate or follow the onset of a rheumatic disease, but in the majority of cases, FMS is not simply the early stage of another medical condition.

Soft Tissue Pain Syndromes

FMS can be classified as a soft tissue pain syndrome characterized by widespread pain emanating from periarticular structures located outside the joint capsule and periosteum. The soft tissue pain syndromes differ from arthritic disorders in that the synovial joints are not directly involved. The anatomic structures that appear to be symptomatic can include ligaments, tendons, fascia, bursae, and muscles. All of these soft tissue structures are known to facilitate mechanical functions of the diarthrodial joints. Any of these structures can become painful and dysfunctional alone or in association with distinct inflammatory, autoimmune, arthritic, or endocrine disorders.

Table 30-3 shows a contemporary classification of soft tissue pain syndromes. The main subheadings divide the syndromes into localized, regionalized, and generalized categories. Most of the “localized” conditions are believed to result from repetitive mechanical injury to inadequately conditioned tissues. They are often named anatomically and are disclosed by a typical history plus the exquisite tenderness elicited by digital palpation of the affected structures.

Localized	Regionalized	Generalized
Entrapment syndrome (e.g., carpal tunnel syndrome)	Myofascial pain syndrome	Fibromyalgia syndrome
Tenosynovitis (e.g., biceps tendinitis)	Masticatory myofascial pain syndrome	Chronic fatigue syndrome
Bursitis (e.g., trochanteric bursitis)	Complex regional pain syndrome	Polymyalgia rheumatica
Enthesopathies (e.g., tennis elbow)	Referred visceral pain (e.g., left shoulder pain due to angina)	Hypermobility syndrome

Adapted from Russell IJ. A new journal [Editorial]. J Musculoske Pain 1993;1:1–7.

TABLE 30-3. Soft tissue pain disorders

The “regionalized” syndromes can also result from “overuse” and may involve more than one type of body structure but are still limited in anatomic scope to a region or body quadrant. The myofascial pain syndrome (MPS) is characterized by trigger points (TrPs) (contrasted with the TePs of FMS) and has traditionally been managed by physiatrists. The masticatory MPS involves the temporomandibular joint or TrPs, or both, in the muscles of mastication that are typically treated by dentists. Several types of visceral pain can be referred to a musculoskeletal structure (e.g., angina felt in the shoulder or jaw), and the recently renamed complex regional pain syndrome would be classified in this category.

The “generalized” category implies a systemic process that affects the musculoskeletal system in a more global manner. Chronic fatigue syndrome has been

characterized by persistent fatigue and a number of other constitutional symptoms. It initially presented in epidemics but more recent applications of that diagnosis have emphasized sporadic cases and current criteria no longer exclude FMS (10). An overlap between FMS and chronic fatigue syndrome has led to speculation that they are identical, but there are important historical and clinical differences, suggesting that they are separate family members of an overlapping soft tissue pain spectrum.

Symptoms and Signs

Widespread Pain

The most prominent symptom of FMS is chronic, widespread pain in soft tissue regions such as the muscles, ligaments, bursae, and tendons. The pain has been described as a persistent, diffuse, deep, aching, throbbing, sometimes stabbing, pain associated with distal extremity dysesthesias. Patients with FMS typically exhibit high pain severity scores on the *McGill Pain Questionnaire*. They choose dramatic words to describe their symptoms, and the veracity of the FMS patient has often been questioned, due to their dramatic verbal and facial portrayal of the pain they experience.

When patients were asked to indicate the locations of their pains on a body diagram they usually indicated bilateral body sites involving the upper and lower extremities, the neck posteriorly, the anterior chest, and the low back (Fig. 30-1). Monitoring of a patient's course with serial quantitative (percent-shaded) pain diagrams may provide a reliable method for research outcome studies (11).

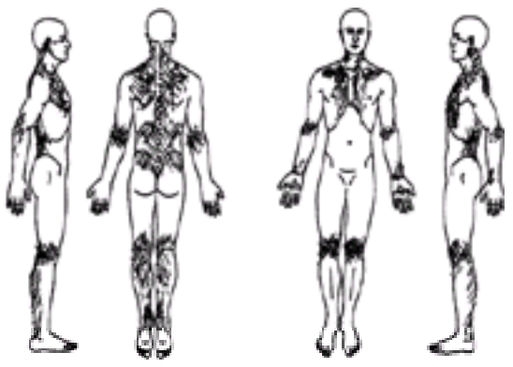


Figure 30-1. Fibromyalgia pain diagrams. The shaded areas on the set of four diagrams were marked by a patient with fibromyalgia to indicate the locations of her painful symptoms on the occasion of her entry into a clinical research study. The pattern of widespread pain is typical of pain diagrams by other fibromyalgia patients. Using the rule of nines, numeric values can be derived to indicate the proportion of the entire figure affected. That number provides an estimate of the pain severity.

Tender Points

The characteristic physical finding of multiple TePs in FMS can be elicited by pressing firmly (approximately 4 kg of pressure on an area of approximately 1 square cm) over each of 18 anatomically defined soft tissue sites called TePs. At least 11 of the 18 TePs must exhibit painful sensitivity from such pressure to meet the ACR TePs criteria for the diagnosis of FMS.

The tenderness in FMS is apparently located in the deep soft tissues because topical anesthesia has no effect on the severity of pain induced by deep-pressure stimuli (12). Despite this apparently unique sensitivity of the TePs to palpation pressure, there is no convincing evidence that the tissues that hurt are histologically or functionally abnormal.

Control Points

As investigators explored the application of the TeP examination to people with FMS, it was observed that there were body sites at which people with FMS exhibited very little tenderness to deep palpation pressure. These so-called control points (CPs) were at first expected to provide a resource for checking the specificity of tenderness at the TePs. According to the original theory, if a patient reported pain after deep palpation pressure at a CP, there must have been some psychological augmentation of the symptoms at the true TePs for the purpose of secondary gain. This concept was discounted when it was recognized that the consistently lower severity of tenderness at the CPs actually correlated quite closely with the severity of tenderness at the TePs (13). This provided substantial support for the hypothesis of a CNS rather than a peripheral muscle tissue pathogenesis of FMS.

Allodynia

Healthy individuals generally do not perceive a 4-kg digital pressure stimulus to be painful. Therefore, this finding in FMS seems to represent a lower-than-normal pain threshold and meets the clinical definition of allodynia. For that reason it was proposed that FMS could be viewed mechanistically as “chronic, widespread allodynia.” Allodynia is defined as a situation in which pain is perceived from a stimulus that is not normally painful (see Chapter 2).

Several methods have been explored to quantify pain and tenderness at TePs. These include

1. Counting the number of TeP sites (total TeP count) that are tender at a given time in a specific individual.
2. Documenting the relative severity of tenderness to digital palpation at 18 TePs [herein called the *tender point index* (TPI); some authors call it the *myalgic score*].
3. Reporting the average pain threshold (APT) from algometric (dolorimetric) examination of the 18 TePs. The TPI and APT correlate with each other, but the APT exhibits a higher reliability. The TPI bears some correlation to the patient's level of anxiety and depression that is not exhibited by the APT.
4. Documenting the extent of the pain distribution using a quantified pain diagram.

Epidemiology

Epidemiologic studies have provided valuable information about FMS. The frequency with which FMS is found in a number of subpopulations permits increasingly sophisticated estimates of the actual prevalence of the disorder. There is very little information about the incidence of FMS. Equally important is an improved understanding of the natural history of FMS.

Prevalence

FMS occurs in all ages, ethnic groups, and cultures studied to date. Its gender distribution is nearly equal in childhood but in adults, it is fourfold to sevenfold more common in females. Most of the epidemiologic studies conducted to determine the prevalence of FMS in the community have consisted of a screening questionnaire followed by confirmatory examination of those who reported widespread body pain. FMS does not seem to be a disorder limited to affluent peoples nor to the industrialized nations.

Two studies conducted in Canada and the United States found that approximately 65% of the general population are free of pain, 5% have transient pain, 20% have regional pain, and 10% have widespread pain (the group most likely to include people with FMS) (6,14). Examination of those with widespread pain has established that approximately 2% of the general population have FMS sufficient to meet ACR criteria. The overall adult population average of 2% was composed of approximately 0.5% males and 3.5% females. The gender distributions varied with age by decade, exhibiting the highest prevalence in women 50 to 60 years of age (6) (Fig. 30-2).

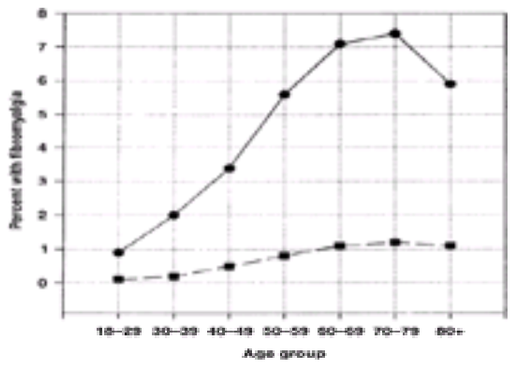


Figure 30-2. Age distribution of fibromyalgia syndrome by gender in the general population. Although the prevalence of fibromyalgia was consistently higher among females (*circles*) than males (*squares*), it increased with age in both sexes to approximately age 70. The explanation for the decline thereafter is elusive. (From Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19–28, with permission.)

It has been observed that 6% to 10% of patients in a typical physician's waiting room (15) and 15% of those evaluated by a rheumatologist meet criteria for FMS. The implication is that for every 10 patients examined, at least one will have FMS.

Incidence

A group of Israeli investigators enrolled subjects who had recently suffered a whiplash injury in a rear-end automobile accident and a control group that had just suffered a lower extremity fracture in an industrial accident (16). At 18-month follow-up, more than 22% of the whiplash injury subjects had developed FMS, compared with less than 2% of the control group. In most cases, the diagnostic symptoms had developed within 3 months of the whiplash injury. From a separate magnetic resonance imaging study (17) comes the observation that the size of the cervical canal is an important risk factor for the development of chronic pain symptoms after a whiplash injury. Based on these independent observations, there is reason to believe that monitoring whiplash injury subjects, especially those with narrow cervical canals, will prospectively allow the development of FMS to be observed and characterized.

Natural History

Extended follow-up (7+ years) studies have shown that FMS is not a disorder in transition to another medical condition (8). Although FMS commonly accompanies RA, SLE, and Sjögren's syndrome, the associated condition is usually apparent at the time of diagnosis of FMS or shortly thereafter.

There is a growing awareness that the impact of FMS on an individual's quality of life and physical function is substantial and may be comparable to that of RA (18). Although there is considerable variation across the United States, it appears that approximately 30% of FMS patients accept shorter work hours or less physically taxing work to maintain employment and that approximately 15% currently receive disability funding because of their symptoms (9). The annual direct medical costs incurred by each FMS patient averaged $2,274 (8). As a result of this and other estimates, the calculated direct cost of FMS to the United States economy is in excess of $16 billion annually. There is currently no cure for FMS, so people who develop FMS will be affected for the rest of their lives. There is no information to suggest that FMS contributes to a shortening of life span, but longer follow-up studies will be needed to be certain that mild limitation is not present or even that drug therapy may have some effect on longevity.

Pathogenesis

The cause of FMS is still unknown. Theories regarding its etiology have undergone a transition from a psychiatric process, as some still view it, to a muscle disorder, as it is currently classified in the Medline Index, to a genetically determined CNS disorder of nociception and neuroendocrine dysfunction, as it probably should now be considered. In the following paragraphs, this historically relevant transition is briefly summarized.

Psychopathology

One of the most prevalent clinical myths about FMS has been that it is a somatic manifestation of an affective disorder. Some physicians have perceived it to be a sign of masked depression or merely an aberrant expression of anxiety in neurotic individuals. That concept has persisted, in part, because there has been no specific laboratory test for FMS. It is interesting to reflect on the history of RA by comparison. No one currently doubts that RA was an objective, painful disorder with inflammatory, destructive synovitis, but 20 to 30 years ago, before the roles of rheumatoid factors, inflammatory cells, and lymphokines were recognized as objective factors in the pathogenesis of RA, it was common for clinicians and investigators to view RA as an emotively driven disorder (19,20).

Payne et al. (21) studied 30 individuals in each of three groups: FMS, RA, and “other forms of chronic arthritis.” Responses by the FMS patients to questions on a *Minnesota Multiphasic Personality Inventory* (MMPI) resulted in variably higher scores on many of the scales (hypochondriasis, hysteria, psychosis, paranoia, schizophrenia) than were seen with either of the arthritic groups. These findings were echoed and expanded by another study reported in 1985 (22). The authors found a higher lifetime rate of major affective disorder among the FMS patients (70% versus 13%). In 64% of the FMS patients with major depression, the affective symptoms anteceded the onset of the FMS by at least 1 year. Only approximately 30% were depressed at the time of the study, which raised a question regarding the relevance of the depression to the patient's current somatic symptoms. Perhaps the most interesting observation was a higher prevalence (10% versus 3%) of major affective disorder in the first-degree relatives of the FMS patients.

Many of the psychological studies comparing FMS with RA involved interview methods in which the investigator was required to make subjective judgments. That is potentially critical because the interviewer in most of the studies was not blinded to the group designation. One study (23), which made a concerted point of blinding the evaluator to the prestudy diagnosis, found no difference in the prevalence of depression between FMS and RA.

In retrospect, the original study by Payne et al. (21) had several limitations. It is likely that there was some selection bias due to referral patterns, especially because their subjects were hospital inpatients. Moreover, the fact that the original MMPI had been developed and validated with psychiatric patients suggests that the questions used to identify somatization were not adequately validated against medical conditions in which people would be *expected to exhibit* a somatic symptom like pain. Thus, MMPI testing of patients with chronic pain was more likely to reflect the nature of the painful condition than to indicate a true psychological disturbance. Indeed, patients with RA have exhibited similarly elevated MMPI scores for hypochondriasis, depression, and hysteria (24).

Generalizations from a variety of sources would suggest that 30% to 40% of FMS patients are depressed. This frequency is higher than expected for healthy controls (less than 10%) and higher than expected for persons hospitalized with a variety of medical illness (20%) but is not consistently greater than observed with RA patients. Despite their continuing pain and morning stiffness, between 40% and 60% of FMS patients fail to meet criteria for any current affective disorder.

Another view has been that the pain and fatigue of FMS might be inappropriately amplified by the presence of depression or anxiety. A study described by Ward (25) was designed to evaluate the roles of mood or depression in modifying the perception of painful stimuli administered to RA patients. Depression explained less than 1% of the changes in pain and global arthritis status. It was concluded that depression was an unlikely cause for the pain of RA. It seems reasonable to extrapolate that conclusion to patients with FMS and suggest that depression in both conditions is reactive and is a consequence of daily chronic pain, insomnia, physical limitation, and compromised quality of life (26,27).

Muscle Physiology and Pathology

The perception of many FMS patients is that they experience deep muscle or even bone pain. An important minority of the TePs are located over muscle masses such as the lateral border of the trapezius, the supraspinatus, the lateral epicondyle, the upper gluteal, and the medial knee. Adding these observations to the perception of fatigue and exercise-induced pain in FMS logically led to the concept that there may be some form of energy deficit or anatomic abnormality in the skeletal muscles of people with FMS. However, a controlled, electron microscopic study has failed to identify any histologic abnormality specific for FMS (28). It has been convincingly

argued (29) that the abnormal findings in FMS skeletal muscle disclosed by nuclear magnetic resonance spectroscopy were actually due to chronic deconditioning, which is very prevalent among patients with FMS.

Central Nervous System Dysfunction

Having failed to find a histologic basis for FMS, the focus of research has shifted heavily toward a search for involvement of the CNS. As a result, abnormalities have now been found in the neurochemical process of nociception and in the neuroendocrine system. Abnormal levels of biochemicals, such as tryptophan, serotonin, substance P, and growth hormone, have been reported. The diurnal regulation of cortisol production appears to be distorted, potentially contributing to insomnia and to difficulty in managing physiologic stress.

Genetic Predisposition

It is quite common for a patient with FMS to report that a relative, usually a female, has had similar symptoms. There is growing evidence for an autosomal dominant mode of inheritance for FMS (30). In a study, Yunus et al. (31) found probable linkage of FMS with the histocompatibility locus examined by the sibship method. To date no abnormal genes have been identified, but several candidate genes have been proposed to explain metabolic abnormalities observed in the patients.

Neuroendocrine Model

Many of the symptoms of FMS resemble those observed in patients with hormone deficiencies. That observation has led to the study of neuroendocrine function in FMS (32). Subsets of people with FMS exhibit functional abnormalities in the hypothalamic-pituitary-adrenal axis, in the sympathoadrenal system, in the hypothalamic-pituitary-thyroid axis, or in the hypothalamic- pituitary-growth hormone axis. It appears that there may be diurnal rhythm abnormalities in cortisol production and that the epinephrine response to physiologic stress may be blunted.

Growth hormone was studied because it was known to be produced during delta-wave sleep that many FMS patients fail to achieve normally. Growth hormone is difficult to measure because its release is pulsatile and its plasma half-life is short. An alternative means of monitoring growth hormone production has been to measure the plasma levels of insulin-like growth factor-1 (IGF-1) (previously called *somatomedin C*), which has a long half-life. An age-adjusted deficiency of IGF-1 has been documented in a large number of FMS patients (33).

The reasons why these endocrinopathies would be associated with a chronic pain syndrome is not clear. It may be that CNS abnormalities in the availability of biogenic amines such as norepinephrine or serotonin are responsible for the abnormal regulation of the neuroendocrine system (34). These systems interact and are interdependent, so in susceptible individuals, a partial failure of one system may lead to subtle malfunction of others.

Administration of glucocorticosteroid medications to people with primary FMS does not seem to improve their symptoms (35). Conversely, substantial improvement of FMS symptoms may result from otherwise indicated corticosteroid treatment of patients with RA or SLE. FMS-like symptoms in such inflammatory disorders may be exacerbated by tapering the corticosteroid dose too rapidly. Whether that happens only when there is already an underlying predisposition to develop FMS is unknown. The administration of mineralocorticoids can reduce the severity of the neurally mediated hypotension that occurs in some FMS patients (36). Parenteral therapy with human growth hormone was effective in reducing the severity of FMS symptoms (37) but regular injection therapy with this hormone is not universally appealing to FMS patients and the cost of such therapy is prohibitive.

Gender Model

The much higher prevalence of FMS among females than among males has led to speculation regarding gender-specific causes. For example, in an epidemiologic study of a Midwest community (6), the curves representing pain thresholds (sensitivity to a pressure stimulus) in men and women consistently showed lower values for women. Because the examination component of the ACR criteria for FMS involves the response to a fixed pressure stimulus of 4 kg, it is not surprising that the ACR criteria have identified more women than men with FMS.

Understanding of the mechanisms responsible for this gender-related difference in pain thresholds is incomplete. Measurements of female hormones have not been very fruitful. A possible explanation for gender-related differences in pain perception has come from a positron emission tomography study of the brain that suggested that the metabolism of indoles was distinctly different in males and females (38). Gender-related differences in pain sensitivity and FMS prevalence could be explained by such differences.

Low-Energy Model

There is evidence (39) to suggest that adenosine triphosphate (ATP) levels may be lower than normal in FMS patients' red blood cells. The significance of that finding is still uncertain because the low levels do not correlate with the subject's perception of fatigue. If ATP is also low in FMS platelets, it could explain the low platelet serotonin level because energy is required for serotonin uptake and serotonin complexes with ATP would help to retain it internally. The role of peripheral platelet serotonin in central pain perception is still unclear.

Nociceptive Pain Model

The nociceptive pain model for FMS relates to central amplification of pain. It combines information available from animal systems and data collected from FMS studies to predict that central sensitization has resulted in an increase in the effects of afferent stimulae on pain perception. This model also predicts that chronic sensitization to pain might adversely alter the mechanisms involved in signal transmission.

Neurochemicals and Neurotransmitters

The roles of neurochemicals as neurotransmitters in the process of nociception and allodynia have been studied extensively in animals (40) and the findings are now at least theoretically relevant to human FMS (41). This line of reasoning has led to the measurement of neurotransmitter levels in biological fluids obtained from FMS patients. Two biochemical participants in the nociceptive process that appear to be important to FMS are serotonin and substance P.

Serotonin in Fibromyalgia Syndrome. Moldofsky and colleagues (42) were the first to suggest that serotonin might be involved in the pathogenesis of FMS, both in failing to attenuate persistent pain and to correct insomnia. They found a clinical correlate between FMS pain and the plasma concentration of tryptophan (TRP). More recently, the serum and cerebrospinal fluid (CSF) of FMS patients were found to exhibit low concentrations of TRP. Early findings of a low serum concentration of serotonin (43) have been supported by other investigators (44). It is now apparent that the low serum concentration of serotonin in FMS patients is due to low levels of serotonin in their peripheral platelets (45).

The levels of serotonin have not yet been reported in FMS CSF, but the levels of its immediate precursor, 5-hydroxy-TRP, and its metabolic product, 5-hydroxyindole acetic acid, have been. Both were found to exhibit lower-than-normal concentrations in FMS CSF relative to the CSF of healthy individuals (34,46). In addition, 5-hydroxyindole acetic acid was measured in the 24-hour samples of patients with FMS and compared with the results from normals (47). The rate of 5-hydroxyindole acetic acid excretion was significantly lower in FMS patients than in normals.

Klein et al. (48) proposed a novel and rather appealing hypothetical explanation for both the low serum TRP and serotonin concentrations in people with FMS. They reported finding high titers of antibodies (immunoglobulin G or immunoglobulin M classes of antiserotonin antibodies that cross-reacted with TRP) in the serum of FMS patients relative to normal controls and in controls with rheumatic conditions. Their data raised the possibility that an autoimmune process might be responsible for the low levels of serotonin in FMS sera and platelets.

Substance P in Fibromyalgia Syndrome. Substance P is a neuropeptide that has several important roles in the process of nociception (49). The concentration of substance P is normal in both the serum and the urine of people with FMS. Recent evidence (50) suggests, however, that substance P levels correlate inversely with TRP levels and 5-hydroxyindole acetic acid levels in FMS serum.

Vaeroy et al. (51) were the first to show that the concentration of substance P was elevated (approximately threefold) in the CSF of FMS patients compared with normal subjects. Their findings have now been reproduced in three other clinical studies (52,53 and 54). In each case, the average CSF substance P level in FMS was twofold to threefold higher than in the healthy controls.

In the author's first study of CSF substance P in FMS patients (Fig. 30-3), 87.5% of FMS exhibited CSF substance P concentrations greater than the highest normal value (52). Age and sex had no influence on the measured CSF SP levels, but minor differences were related to ethnicity. In an attempt to further characterize the nature of the CSF SP abnormality, a number of lumbar- level CSF samples were collected in three sequential numbered fractions. The CSF substance P concentrations in these samples failed to define a cranial to caudal gradient of CSF substance P concentration. Another experiment involved inducing noxious pressure on the lower-body TePs to see if it would have any effect on the lumbar-level CSF substance P concentration. There was no significant increase in the levels of CSF substance P as might have been expected if the substance P were coming primarily from local afferent dorsal horn neurons.

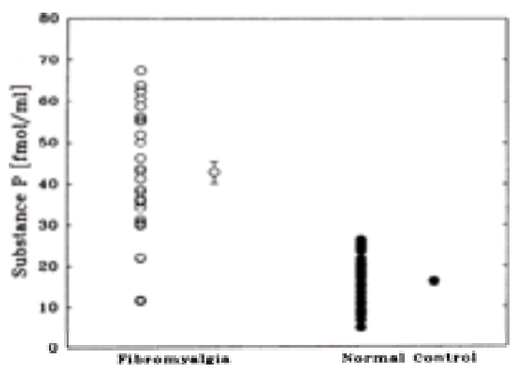


Figure 30-3. Substance P concentrations in cerebrospinal fluid samples. Fibromyalgia syndrome patients (*open dots*) exhibited significantly (p <.001) higher mean levels (*open dots with standard error bars*) than healthy normal controls (*closed dots*). Each dot represents an individual patient or a normal control. There was very little overlap of values between the two groups. Eighty-seven percent of fibromyalgia patients exhibited spinal fluid substance P levels higher than the highest normal control value. (From Russell IJ, Orr MD, Littman B, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis Rheum* 1994;37:1593–1601, with permission.)

Clinical Relevance of Elevated Cerebrospinal Fluid Substance P in Fibromyalgia Syndrome. In each of the four studies on CSF substance P discussed above, the conclusions were based on only a single sample of CSF from each subject. It was not possible from such data to know whether the abnormal CSF levels of substance P were stable or fluctuated with the patients' symptoms. To answer that question, lumbar level CSF samples were collected from the same 28 medication-free patients an average of 12 months after the first medication-free sample had been obtained (55). By medication-free it is meant that the FMS patients discontinued for 2 weeks all medications believed to be helpful in treatment of FMS symptoms. There was, on average, a slight increase in the concentration of CSF substance P over time that correlated directly with a small clinical change in pain and tenderness occurring over the same period of time. These findings imply that CSF substance P may be integrally related to changes in the severity of the symptomatic pain of FMS.

An important question that must eventually be settled is whether elevated CSF substance P concentration is unique to FMS. An earlier report (56) indicated that substance P was lower than normal in a variety of chronic painful conditions. Finally, both CSF substance P and CSF met-enkephalin have been reported to be normal in chronic pain patients. Patients with pain from herniated disks had normal CSF substance P levels, but CSF substance P levels were mildly elevated in patients with severely painful osteoarthritis of the hip and normalized in those subjects after most of the pain had been relieved by total hip arthroplasty (57).

Experience with spinal fluid neuropeptides includes analysis of substance P in CSF collected from more than 300 clinical subjects, including more than 150 primary FMS patients and more than 50 healthy controls (I.J. Russell, *unpublished data*, 1998). Disease control groups included more than 30 subjects with FMS associated with another painful condition (secondary FMS). A smaller group of 14 subjects had other painful conditions but lacked FMS. Only the healthy individuals' CSF substance P values were significantly different from those found in the primary FMS patients.

The FMS study group at the University of Alabama at Birmingham (54) has shown that the higher CSF substance P levels in FMS correlated with a decrease in regional cerebral blood flow within the caudate nucleus and thalamus of the same FMS patients. The reason for this relationship is not yet clear. It is possible that the decrease in blood flow could have been caused by neuropeptide Y (32) or dynorphin-A (58), as both are known to be potent vasoconstrictors and both are elevated in FMS. One could speculate, then, that the excess substance P is produced in response to tissue hypoxia, as an attempt on the part of the CNS to restore more normal blood flow. That explanation seems unlikely, however, because major brain hypoxic injury (ligation of an internal carotid artery in rats) causes a substantial decrease in brain tissue levels of substance P.

Nerve Growth Factor. An exciting development in the study of CSF substance P in FMS was the finding of elevated levels of nerve growth factor in the CSF of primary FMS patients, but not in FMS with an associated painful condition (secondary FMS) (59). This peptide neurotransmitter is believed to facilitate the growth of substance-containing neurons and to be involved in the process of neuroplasticity. For these reasons, nerve growth factor could be critical to the initiation or perpetuation of the painful symptoms of FMS (60,61).

Conclusions Regarding Pathogenesis

In contrast with the situation just a few years ago, when FMS patients were often viewed as healthy complainers without any examination findings, there are now classification criteria to aid in making the diagnosis. The purely psychiatric model appears to be inadequate in the face of widespread metabolic changes. Where the pathogenesis was once diligently sought in “painful muscles,” the symptoms now appear to better fit a CNS model. Abnormalities in neurochemical mediators of CNS nociceptive function (Fig. 30-4) have been demonstrated and may be relevant to FMS (62,63,64 and 65).

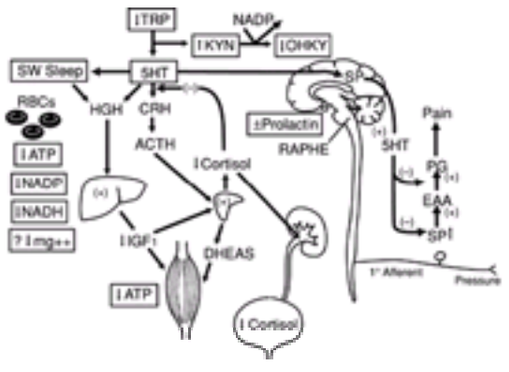


Figure 30-4. Laboratory abnormalities in fibromyalgia syndrome. They are reported to include lower-than-normal serum and cerebrospinal fluid (CSF) tryptophan (TRP) concentrations; increased CSF kynurenine (KYN) levels; decreased CSF 3- hydroxykynurenine (OHKY) levels; lower-than-normal red blood cell (RBC) adenine nucleotides such as adenosine triphosphate (ATP), and a functionally abnormal RBC transketolase enzyme that can be partially corrected by an increased concentration of thiamine pyrophosphate *in vitro*; decreased production of hypothalamic/ pituitary hormones such as human growth hormone (HGH), corticotropin-releasing hormone (CRH), and adrenal corticotropic hormone (ACTH); decreased production of liver insulinlike growth factor-1 (IGF-1); decreased production of dehydroepiandrosterone sulfate (DHEAS), and cortisol from the adrenal gland; decreased ATP levels in certain areas of skeletal muscle; and finally, increased levels of CSF substance P (SP). (5-HT, 5-hydroxytryptamine or serotonin; EAA, excitatory amino acids such as glutamine or asparagine; mg, magnesium; NADH, reduced form of nicotinamide adenine dinucleotide; NADP, nicotinamide-adenine dinucleotide phosphate; PG, prostaglandin synthesis step involving a cyclooxygenase type-2 enzyme; SW, delta slow wave, non–rapid eye movement, deep sleep.) (Adapted from Russell IJ. Neurochemical pathogenesis of fibromyalgia

syndrome. *J Musculoske Pain* 1996;1:61–92.)

The recognition of allodynia as a manifestation of abnormal central nociceptive processing has changed the perspective of FMS. It has led research in a new direction, toward the study of nociceptive neurotransmission in FMS. Some of the abnormalities found in FMS, namely low serotonin levels and the elevated substance P levels, are logically consistent with a pain-amplification syndrome. The extent to which these mechanisms are unique to FMS will be critical in determining the direction that future research should take. Certainly, a better understanding of the cause of FMS will be an important step toward the development of more effective therapy.

CLINICAL CONSIDERATIONS

Clinical Presentation

The typical patient with FMS is a middle-aged female who says to her physician, “Doctor, I hurt all over.” She may look fatigued, a little bewildered or even agitated, but usually does not appear chronically ill. The symptoms have usually been for more than 3 months. The pain is most pronounced in the regions of soft tissues such as the muscles, ligaments, bursae, and tendons, near the diarthrodial joints but not in them. Two graphic, actual, descriptions of the pain associated with FMS are as follows: “I feel as if I fell out of a car traveling at 30 miles per hour”; or “I feel just like the time I played volleyball in the hot sun all day at the beach. I had a terrible sunburn and every muscle was sore. No position was comfortable and I couldn't sleep.”

Some patients present quite differently. The initial complaint can mimic some other well-known medical condition, such as the substernal chest pain of angina pectoris, the throbbing occipital head pain of recurrent muscle contraction headache, the mechanical lumbar area pain of a degenerative disk syndrome, or even the radiating lower extremity pain of sciatica. Other common symptoms are listed in Table 30-4.

Depression, anxiety
Cognitive deficits, short-term memory loss
Throbbing occipital pain of muscle contraction headache
Lightheadedness, dizziness, syncope
Chronic insomnia, nocturnal myoclonus, nocturnal bruxism
Daytime tiredness resembling physical fatigue
Prolonged morning stiffness as in rheumatoid arthritis
Chest wall pain mimicking angina pectoris, breast area pain
Mechanical low back pain or sciaticalike radiation of pain
Bursitis, tendinitis, myalgias, arthralgias, piriformis syndrome
Numbness, tingling, dysesthesias in hands and feet
Irritable bowel, abdominal pain, diarrhea, constipation
Interstitial cystitis, frequency, urgency, sterile dysuria

These symptoms may be present at different times in a given patient, but none of them is required for classifying a patient as having fibromyalgia syndrome.

Adapted from Russell IJ. Fibromyalgia syndrome: approaches to management. Bull Rheum Dis 1994;43:1–4.

TABLE 30-4. Clinical symptoms associated with fibromyalgia syndrome

The patient's physical response to palpation of a TeP can be viewed as a semiobjective clinical sign similar to a deep tendon reflex. The designated sites do not appear to represent a single type of anatomic structure but can include skeletal muscles, ligaments, and bursae (see Table 30-2).

Testing for FMS TePs is not difficult, but it helps to learn the method from an experienced examiner and then to practice the examination with a patient known to have FMS. The procedure can be accomplished on a clinic patient in approximately 30 seconds. Three of the variables that can influence the reliability of this examination are the amount of digital palpation pressure applied, the rate at which it is applied, and whether it is applied singly or as a series of brief pulses of pressure. A clinical estimate of the correct amount of pressure can be achieved by pressing the examining thumb or finger against a soft tissue resistance (e.g., the mid-thigh) until the distal portion of the nail blanches. The more accurate means of standardizing the examining finger is to press it against a pediatric scale (4 kg is approximately 1.6 lb). Pressure gauges (dolorimeter or algometer, mechanical or electronic) are available to help standardize the amount of digital pressure to be applied. One type of electronic algometer is a pressure transducer that can be worn on the distal phalanx of the examiner. It will indicate the amount of pressure exerted by the examining digit at the time of withdrawal from the skin.

The pattern of the TeP distribution in a given FMS individual is not known to have any pathogenic significance. Approximately one-third of FMS patients will exhibit a preponderance of painful TeP sites on one side of the body. Some patients seem to be more affected in the upper half of the body than in the lower half. Early in the study of FMS, it was believed that “CPs” must fail to be tender in order to validate the presence of true TePs. Now, it is accepted that the pain thresholds at the control sites are similarly and diffusely lower than normal in FMS.

Sequential pressure on one TeP after another will often induce an involuntary writhing withdrawal on the part of the patient or even an unintended burst of tears. That should not be viewed as a hysterical response any more than would involuntary guarding of an acutely inflammed abdomen to deep palpation. After a patient has been examined at each of 18 TePs, he or she will often experience a residual deep ache described as bonelike pain that can continue to hurt for 1 to 3 days. A bruise may appear at some TeP sites after examination.

A TeP is defined differently than a TrP, so the two should not be used as synonyms (see Chapter 28 and Chapter 29). A TeP hurts locally when pressed but does not refer pain. In FMS, there are multiple, symmetric TePs. By contrast, a TrP is a regional phenomenon, which may be sensitive to pressure as a TeP is but also refers pain to a symptomatic zone of reference, which is usually more distal. The complex of symptoms and signs associated with a TrPs characterizes MPSs (as discussed in Chapter 29).

There is evidence of some overlap between MPS and FMS (66). At least one TrP may be found in 20% of healthy controls and in 68% of FMS patients in addition to a full complement of 11 or more TePs. If a typical TrP is present in an FMS patient, a concomitant diagnosis of MPS should be made. The two conditions should be treated separately, with the knowledge that TrPs in the setting of FMS are more resistant to treatment than when they present alone in isolated MPS (67).

The clinical recognition of FMS using the ACR criteria is not adequate to document the syndrome's severity in a given patient at a specific point in time. Although the TeP count is critical for diagnosis of FMS, it has not proven very useful as a measure of treatment efficacy. The TPI is easily determined clinically and provides an objective measure to follow. As shown in Table 30-5, a tenderness scale is applied to the tenderness at each site examined (nontender = 0; tender without physical response = 1; tender plus wince or withdrawal = 2; exaggerated withdrawal = 3; too painful to touch = 4). The sum of the tenderness severities at all 18 sites is the TPI. This value can be calculated and reported on clinical records as a measure of severity at time of the visit. The reliability and validity of TPI have not yet been established.

A.	Apply 4 kg of digital pressure at each tender point.	
B.	Observe body language, especially the face, for response.	
C.	Use the following scale to quantify each response:	
	Not painful:	0
	Feels painful, no physical response:	1+
	Feels painful, wince or withdrawal:	2+
	Feels painful, exaggerated withdrawal:	3+
	Area deemed too painful to allow pressure:	4+
D.	Add the individual tenderness severities for all 18 sites.	
E.	The sum is the tender point index.	
F.	The expected range for normal controls:	0–5
G.	The expected range for fibromyalgia:	11–72
H.	Typical finding in research study:	Tender point index of (mean ± SD) 35.7 ± 9.7

Adapted from Russell IJ, Fletcher EM, Michalek JE, et al. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam: A double-blind, placebo-controlled study. Arthritis Rheum 1991;34:552–560.

TABLE 30-5. Clinical determination of tenderness severity calculating the tender point index

Comorbidities

The clinical manifestations of FMS are often more complex than body pain alone. For example, patients experience great frustration with their inability to achieve normal, restorative sleep. They awaken feeling unrefreshed and are stiff for an extended period of time (often hours) each morning. During the day, they are tired but have difficulty napping. They have chronic muscle contraction–type headaches with pain in the occipital region extending over the scalp and leaving it sensitive to touch. Temporary relief can often be achieved by taking a hot bath, massaging the neck, and then sleeping with the neck supported by a small pillow. Depression is common, as seen in many chronic illnesses (23).

Considering the sleep loss and chronic headache associated with FMS, it is not surprising that patients complain of changes in cognitive functions. They have difficulty remembering events, patterns of behavior, task-related protocols, and numbers that had been second nature to them before the onset of FMS. This is a very inadequately studied aspect of FMS, so it is not known whether it results from loss of sleep, the distraction of head and body pain, or even from the myriad of medications taken in the hope of achieving relief.

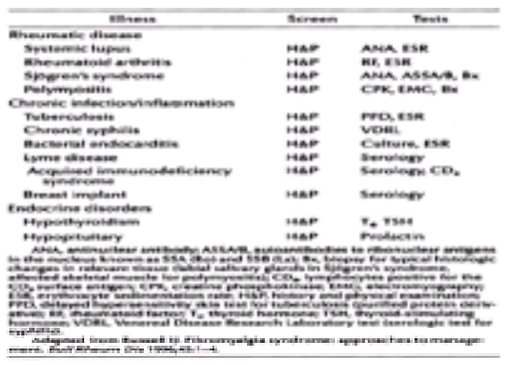
People with FMS often describe numbness or tingling of their hands or lips and a sense of hand or finger swelling. On questioning, however, they will usually acknowledge that the fingers do not really look swollen. This phenomenon sometimes resembles the symptoms of hyperventilation syndrome but the respiratory component is usually lacking.

Irritable bowel–like symptoms are seen in approximately 40% of patients with FMS. Patients may complain of troublesome constipation interspersed with painful cramping and diarrhea. Clinical examination often discloses tenderness to palpation in the left upper quadrant of the abdomen.

The bladder can also be involved, with complaints of urgency, frequency, a sense of incomplete voiding, and sometimes culture- negative dysuria. These symptoms mimic the syndrome of interstitial cystitis, but it is not yet clear whether the bladder is structurally involved.

Secondary Fibromyalgia Syndrome

A curious finding is that FMS may be associated with a number of other medical conditions. In the past, such an association was assumed to be governed by the other condition, so FMS was assumed to be somehow secondary to the other disorder (“secondary FMS”). Table 30-6 lists a classification of such associated conditions, divided into three headings: rheumatic diseases, infectious/inflammatory disorders, and endocrine disorders. The current belief is that these conditions have not developed from FMS and that FMS is not due to them. In fact, data suggest that the FMS that occurs in association with other conditions is clinically identical to “primary FMS” (5). It appears that CSF nerve growth factor concentrations are elevated only in persons with primary FMS; this may be a clue to the potential heterogenicity of factors leading to FMS.



Illness	Screen	Tests
Rheumatic disease		
Systemic lupus	H&P	ANA, ESR
Rheumatoid arthritis	H&P	RF, ESR
Sjögren's syndrome	H&P	ANA, ASSA/B, Bx
Polymyositis	H&P	CPK, EMG, Bx
Chronic infection/inflammation		
Tuberculosis	H&P	PPD, ESR
Chronic syphilis	H&P	VDRL
Bacterial endocarditis	H&P	Culture, ESR
Lyme disease	H&P	Serology
Acquired immunodeficiency syndrome	H&P	Serology, CD_4
Breast implant	H&P	Serology
Endocrine disorders		
Hypothyroidism	H&P	T_4, TSH
Hypopituitary	H&P	Prolactin

ANA, antinuclear antibody; ASSA/B, autoantibodies to ribonuclear antigens in the nucleus known as SSA (Ro) and SSB (La); Bx, biopsy for typical histologic changes in relevant tissue (labial salivary glands in Sjögren's syndrome, affected skeletal muscle for polymyositis); CD_4, lymphocytes positive for the CD_4 surface antigen; CPK, creatine phosphokinase; EMG, electromyography; ESR, erythrocyte sedimentation rate; H&P, history and physical examination; PPD, delayed hypersensitivity skin test to tuberculosis (purified protein derivative); RF, Rheumatoid factor; T_4, thyroid hormone; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory test (serologic test for syphilis).

(Adapted from Russell IJ. Fibromyalgia syndrome: approaches to management. Bull Rheum Dis 1996;45:1–4.)

TABLE 30-6. Clinical conditions that may accompany fibromyalgia and screening evaluation for them

Nearly one-third of patients with RA will be found to have FMS. A clinical observation is that the RA patients with concomitant FMS seem to have pain in and around their joints that is out of proportion to the amount of synovitis. This must be taken into account in treating the patient, because increasing the methotrexate dosage is not likely to reduce the pain severity amplified out of proportion by FMS. In fact, the best results are obtained by treating each of the conditions separately in the same patient.

The prevalence of FMS in people with SLE may approach 40%. Shin tenderness is thought to be more prevalent in SLE patients with concomitant FMS than in either condition alone. The SLE patients who met the criteria for FMS exhibited more severe symptoms and were more likely to be unable to perform daily activities. They were less likely to be employed, more likely to be divorced, and more likely to receive welfare or medical disability benefits (68,69). However, SLE patients with and those without FMS do not differ with respect to the severity of SLE activity, as evidenced by laboratory testing or progressive organ injury.

An important observation has been that the FMS symptoms may become more clearly apparent as the SLE symptoms resolve with treatment. The FMS symptoms seem particularly to emerge with too rapid a taper of the corticosteroid dosage. If not recognized as distinct from the SLE, the remaining or emerging FMS symptoms could prompt inappropriate immunosuppressive therapy. To reduce the severity of FMS symptoms with a steroid taper, it is best to decrease the dosage in graduated steps at approximately 2-week intervals. A suggested tapering protocol is based on the current dosage (from prednisone equivalent dose of 30 to 60 mg per day, each step would reduce the daily dose by 10 to 20 mg; between 15 and 30 mg per day, reduce by 2.5 to 5.0 mg per dose; between 1 and 15 mg per day, reduce by 1 to 2 mg per dose).

Approximately 50% of patients with Sjögren's syndrome also meet clinical criteria for FMS. Any association there might be between FMS and polymyositis, dermatomyositis, or polymyalgia rheumatica is less well defined.

Infectious and inflammatory conditions that seem to be associated with FMS include tuberculosis, syphilis, and Lyme disease. The prevalence of overlapping conditions depends on the community prevalence of the infectious disorder. There are no formal studies with tuberculosis and syphilis, but there may be more than a chance association between Lyme disease and FMS. A Lyme- endemic area monitored 287 patients with apparent infection for a mean of 2.5 years (range, 1 to 4 years). Eight percent met classification criteria for FMS, clearly more than would be expected by chance, based on a population prevalence of 2% for FMS. The symptoms of FMS tended to develop within 1 to 4 months after infection, often in association with Lyme arthritis. Most of the Lyme/FMS patients had typical serology, but a subset were seronegative, while exhibiting cellular immune responses to borrelial antigens, CSF pleocytosis, or even specific antibody formation in the CSF. The signs of Lyme disease generally resolved with antibiotic therapy (e.g., intravenous ceftriaxone, 2 g per day for 2 to 4 weeks), but the FMS symptoms persisted. Rheumatologists who practice in Lyme-endemic areas indicate that they diagnose many more patients with FMS alone than with concomitant Lyme/FMS. The extent of the clinical search for infection and whether or not to administer antibiotic therapy to a new FMS patient should depend on the regional prevalence of Lyme disease and clinical judgment.

An ongoing controversy has surrounded the issue of silicone breast implants. In one study (70), soft tissue pain was substantially more common among patients with implants than in persons who had reduction mammoplasty or breast cancer without implantation, but FMS was not specifically identified. When women with implants are troubled by musculoskeletal pain symptoms, consideration of FMS is warranted.

An association between subacute bacterial endocarditis and FMS has not really been proved using the current ACR criteria for classification of FMS, but the

description of the characteristic musculoskeletal symptoms (arthralgias, myalgias) associated with subacute bacterial endocarditis certainly suggests the possibility of an overlap of the two conditions. The most serious consequence of misdiagnosis would be a delay in antibiotic therapy for the endocarditis.

Mention was made earlier of the hypothalamic-pituitary-adrenal axis abnormalities in FMS. There is some evidence for abnormal production of cortisol, growth hormone, thyroid, and prolactin. The only generalization from this information at present is that careful clinical assessment of people with FMS is warranted, with intent to correct neuroendocrine abnormalities when they are important contributors to the clinical symptoms.

Disability

Pain is a troublesome symptom in many clinical settings; perhaps the most perplexing relates to decisions regarding certification for disability support. In the United States, FMS is not specifically listed as a disabling condition, whereas RA and osteoarthritis are included. Yet, it is clear that some people with FMS are physically or emotionally incapable of daily physical work. Not only does the constant pain nag at the affected person's attention but also morning stiffness can interfere with preparation for work and cognitive difficulties (probably due to insomnia and medication effects) can impair concentration. These are most likely problems of degree and probably are not incapacitatingly severe in most patients.

The problem for any society is to determine who is deserving of compensatory support and who should be expected to function in spite of his or her symptoms. This decision is particularly difficult when it is clear from research evidence that people with FMS should be involved in an active exercise program to maintain aerobic fitness and to increase their whole blood (platelet) serotonin levels (S.E. Geel, I.J. Russell, et al., *unpublished data*, 1998).

It is easy to believe that a person with a bleeding comminuted fracture is experiencing discomfort. On the other hand, there is natural skepticism when an apparently healthy individual dramatically complains of unbearable pain. Several sets of circumstances tend to support that measure of doubt. In FMS, routine laboratory tests have usually been normal, failing to implicate inflammation or dysfunction of a major organ system. Affective pathology, such as depression and anxiety, is present in a substantial proportion of FMS patients, raising the specter of psychic distortion of the perceived physical symptoms. Finally, some FMS patients have observed a temporal relationship between a physical injury and the onset of their symptoms. A common legal implication is that “someone should pay.” Naturally, the accused will mount a defense, which often takes the form of a counter offense. Disproportionate resources available to such a defender can prove formidable. Legal attempts to discredit both the person and the disorder reverberate widely, whether or not they bear scientific merit.

The task of the health care provider in the clinical setting is different from what is called for in the highly charged atmosphere of the courtroom. The objective should be to guide the patient on a path toward better health and function. No matter how obtuse the complaint, *illness is evidenced by virtue of presentation.* It is therefore incumbent on medicine to find solutions and to make them available to the patient. The search for solutions requires a knowledge base and an open mind on the part of both the clinician and the patient. Management of the condition must then proceed despite a substantial measure of remaining uncertainty.

On the other hand, it must be acknowledged that there is a rapidly growing, significant mass of information about the pathogenesis, natural history, and management of FMS. Objective measures of the FMS diagnosis will likely be available soon and severity measures may follow. Certainly, the best solution for any physical limitations of FMS would be a cure. Short of that, effective therapy should be offered to all who exhibit its symptoms. Because neither of those is now possible, clinicians in all fields who evaluate patients with pain must use their best judgment in relating to the issue of disability.

Therapeutic Approaches

There is no single treatment that is effective in controlling the symptoms of FMS, and no published management program has achieved universal acceptance. The management approach I recommend begins with an accepting attitude toward the disorder; progresses to a comprehensive clinical evaluation to establish accurate diagnoses; requires concerted education of affected individuals to involve them directly in the care process; and then enters the realm of psychological, physical, and pharmacologic interventions, whose benefits are maintained by close follow-up. Multidisciplinary pain management is useful in FMS patients (see Chapter 10, Chapter 18, and Chapter 109) (71).

Diagnosis

When a clinician evaluates an individual with a history of pain, the examination should include both a careful assessment of joints for evidence of arthritis and soft tissues around the joints for sites of painful tenderness. In most patients with FMS, nearly all of the TeP sites will be symptomatic and painful to palpation at the first clinical presentation. Occasionally, a patient will present with a single area of symptomatic pain (“chest pain” and “sciatica”) but on examination will be found to exhibit tenderness of which they were unaware at most of the other TePs. At times the generalized pain presentation can be so dramatic that it has been referred to as a “flair” or as “fibromyalgia storm.”

Tests

Despite the research recognition of reproducible biochemical abnormalities in FMS, none of those measures is yet indicated for routine use in clinical diagnosis. The diagnosis of FMS is adequately made by a typical history and TeP examination. The value of laboratory screening (e.g., blood cell counts; sedimentation rate; chemistry panel; creatine kinase; antinuclear antibody; rheumatoid factor; thyroid function tests; skin test for tuberculosis; and perhaps serologic tests for syphilis, the Lyme spirochete, or acquired immunodeficiency syndrome virus in individuals at risk) is to help screen for other clinical disorders that would require separate treatment (see Table 30-6). There is no diagnostic dependence of FMS on x-rays, electromyography, computerized tomography, magnetic resonance imaging, or radioisotope scans, so those tests should be used only if otherwise clinically indicated.

Education

Making a confident diagnosis of FMS usually has the effect of reducing the patient's use of medical resources such as emergency visits and expensive imaging tests. That benefit results principally from the patient's better understanding of his or her symptoms. Education may not reduce the severity of the pain experienced but can decrease the patient's concern that another condition such as cancer has been missed. Accurate reading materials, video programs, and support group interaction resources are increasingly available to assist the health care provider in this area (Table 30-7), but there is no substitute for quality physician time. The first visits should be used to instill confidence in the diagnosis and to directly involve the patient in responsibility for the outcome of the FMS care program. It is important to inform the patient up front that a cure is not available but that teamwork between clinician and patient can usually result in substantial and sustained benefit. Psychologists are helpful in the management of many patients with FMS.

TABLE 30-7. Materials available for patient education

For patients with very troublesome fatigue, especially toward the end of the day, an alternating work and rest program for daytime has been helpful. The actual details of the program are determined by trial and error. Patients begin by setting a timer in the morning for perhaps 1 hour of work. When the timer rings, they rest for a

period of time, perhaps 10 minutes. The timer would then be reset for the next cycle. No matter what is happening at the end of the work period, patients should stop and rest. At the end of the day, the results should be assessed and adjusted for the next day until a workable program has been found. Many women with FMS who do their work at home have found that 20 to 30 minutes of work followed by 10 minutes of rest is an effective schedule for them. Adapting this to a workplace setting is obviously more problematic but can sometimes be arranged.

Physical Modalities

Physical exercise is important to the maintenance of physical functions in patients with FMS. The problem is that unaccustomed physical exertion can induce severe body pain for an FMS patient, which will result in near incapacitation for several days thereafter. Gradual adaptation to a routine progressive exercise program such as alternate-day bicycle ergometry, walking, or water exercise will usually be well tolerated. Most patients report benefit from heat in the form of a hot bath or a professional modality. Use of the operant principles described in Chapter 89 can facilitate increases in physical activities.

Medications

Even though most patients with FMS regularly use one or more oral medications, none of those in common use can be said to be specific for FMS, and none is dramatically effective. The development of specific pharmacologic therapy requires a better understanding of the underlying biochemical abnormalities. Perhaps future medications will be found to increase platelet serotonin levels, increase serum IGF-1 concentrations, or decrease spinal fluid substance P concentrations, and in so doing, effect greater symptomatic benefit. Nevertheless, there is some biochemical logic to the medications that have proven beneficial to some patients with FMS.

The most commonly advocated medication programs involve the use of low-dose, tricyclic antidepressants, sedative-hypnotic medications, and analgesic dosages of nonsteroidal antiinflammatory drugs (NSAIDs) (Fig. 30-5). There has been anecdotal evidence of benefit from amitriptyline, cyclobenzaprine, tramadol, and alprazolam: All theoretically increase serotonin availability and have been studied in placebo-controlled trials. Marginal additional reduction in pain severity may be achieved by adding an NSAID, if well tolerated. A typical maintenance regimen might include amitriptyline (10 to 35 mg at bedtime) or cyclobenzaprine (2.5 to 10.0 mg at bedtime), along with ibuprofen (400 to 800 mg bid) or another NSAID. Our experience has suggested that the propionic acid NSAIDs are more useful than other classes of NSAIDs but that has not been proven by comparative study. Tricyclics have common side effects that limit their use (see Chapter 85). A drug holiday may be useful (Table 30-8).

Three to 4 months of serotonin reuptake inhibition:
Amitriptyline, 10–25 mg hs (cyclobenzaprine 5–10 mg hs)
Possibly fluoxetine, 10–20 mg, in the morning
Possibly ibuprofen, 800 mg bid, or nonnarcotic analgesic
Possibly tramadol, 50–300 mg, in divided dosages
One month of serotonin reuptake inhibitor holiday:
Alprazolam, 0.5–1.0 mg hs, or clonazepam, 1.0 mg hs
Resume serotonin reuptake inhibition for another cycle

Adapted from Russell IJ. Fibromyalgia syndrome: approaches to management. Bull Rheum Dis 1996;45:1–4.

TABLE 30-8. Drug holiday concept for use of low-dose serotonin reuptake inhibitors

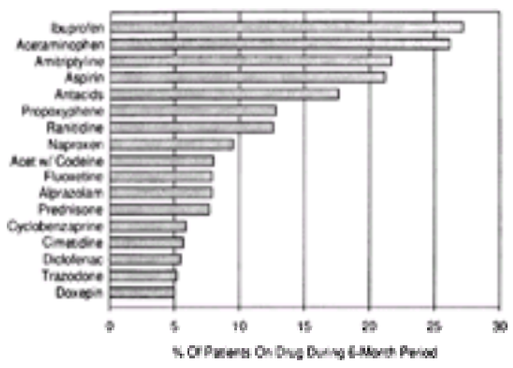


Figure 30-5. Drugs most commonly used by patients with fibromyalgia syndrome. According to a multicenter, 8-year follow-up study, which monitored medication usage, the nonsteroidal antiinflammatory drug most commonly used by fibromyalgia patients was ibuprofen, and the most commonly used psychoactive drug was amitriptyline. Note that "propoxyphene" includes various propoxyphene compounds. (Acet, acetaminophen.) (From Wolfe F, Anderson J, Harkness D, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis Rheum* 1997;40:1560–1570, with permission.)

In one study (72), tramadol was used in divided dose ranging from 50 mg to 400 mg per day. It was tolerated poorly by approximately 20% of FMS patients, who experienced nausea, somnolence, dizziness, pruritis, constipation, or headache. For those who tolerated at least 50 mg per day, relief from pain was quite uniform and persisted for at least 6 weeks. It is likely that this drug will find considerable use in the management of FMS. Many issues about its use in FMS remain to be resolved. Will it be subject to tachyphylaxis and thus benefit from periodic "holidays," as is seen with the more typical tricyclic drugs? Will it prove to be synergistic with other analgesic medications? Will concomitant sleep medications still be needed?

Because one of the theoretical goals with the tricyclic drugs was to increase the availability of serotonin, it seemed likely that the new, highly selective serotonin reuptake inhibitors might also be useful. To date, only the first approved in this class [fluoxetine (Prozac)] has been tested, but most have been tried clinically. Fluoxetine reduced the overall severity of depression in the treatment group but did not significantly alter the painful symptoms (73). One hypothetical explanation was that the muscarinic, histaminergic, or a_1-adrenergic receptors, which are more substantially influenced by the tricyclic drugs than by fluoxetine, may be important to the mechanism of benefit. When given to patients with FMS, fluoxetine should be given in the morning to avoid worsening the insomnia. There is evidence to suggest that a combination of fluoxetine (10 to 20 mg) in the morning followed by amitriptyline (10 to 35 mg) in the evening provides more relief from pain than either agent alone, while avoiding the nighttime insomnia or daytime grogginess that can characterize each separately.

In FMS patients, two glycolytic pathway enzymes that depend on thiamine pyrophosphate (vitamin B_1) as a cofactor appear to require higher than normal levels of the vitamin for optimal activity. It is not clear that administration of large doses of the vitamin will correct that problem but a trial (thiamine, 100 mg per day) might be reasonable, considering its safety profile.

A proprietary combination of malic acid and magnesium (Super Malic, 200/50 mg per tablet) was tested in FMS and was found useful in fairly high doses (600 to 1,200 mg bid). The dose-limiting factor may be loose stools due to the magnesium. Caution is also advised when administering magnesium to any patient with renal insufficiency because the levels of magnesium can rise and cause severe skeletal muscle (including diaphragmatic) weakness.

Topical capsaicin cream appears to be beneficial in FMS and can be used on locally painful areas in addition to a regimen of oral agents. The limiting factor may be the cutaneous burning sensation, which tends to decrease with use and may respond to topical lidocaine or a eutectic mixture of local anesthetic cream.

Opioid analgesics, including codeine admixtures with nonnarcotic analgesics, are currently not recommended in the treatment of FMS because of the perceived risk of

habituation in patients with chronic pain. Adequate assessment of the risks of efficacy of opioids has not yet been undertaken.

Follow-Up

It is difficult to extrapolate what may be optimal follow-up in a variety of physician-patient relationships and in other health care delivery settings. It is generally observed that FMS patients appreciate access to the physician at fairly frequent intervals (perhaps every 1 to 2 months for 3 visits) immediately after diagnosis and then do well with less frequent visits (perhaps every 3 to 4 months) thereafter. Visits can be used to document the severity of the TeP pain and to supportively monitor the patient's progress with the exercise program, the use of medications, the quality of sleep, and efforts toward self-education. The tone of the interaction should not be as follows: Patient: “I'm not better; what are you going to do about it?” Rather, it should be as follows: Physician: “You are still having quite a bit of trouble; let's see how we can work together more effectively to optimize the limited numbers of useful treatment options available.” The management of patients with FMS can be beneficial to the patient and satisfying for the physician.

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CHAPTER 31

Treatment of Acute Musculoskeletal Pain

David R. Clawson

This chapter addresses acute musculoskeletal pain, defined as pain occurring from recent local tissue injury to ligament, joint capsule, fascia, tendon, muscle, or bone. The chapter does not address chronic musculoskeletal pain or musculoskeletal pain syndromes without clear local tissue damage. These are covered in Chapter 10, Chapter 28, Chapter 29, and Chapter 30. The chapter is subdivided into basic considerations, musculoskeletal system injuries and pain control, selected clinical examples, general management principles, and concluding remarks.

EPIDEMIOLOGY

The Centers for Disease Control and Prevention National Center for Health Statistics, Vital and Health Statistics Report for the year 1994 estimated in the U.S. general population approximately 8 million fractures and dislocations, 14 million sprains and strains, and 12 million contusions and other superficial injuries annually (1) (Table 31-1). These led annually to 137 million restricted activity days for fractures and dislocations, 115 million days for sprains and strains, and 48 million days for contusions and superficial injuries. There were 40 million bed-rest days for fractures and dislocations, 31 million bed-rest days for sprains and strains, and 12 million bed-rest days for contusions and superficial injuries annually. The number of lost workdays is approximately 40 million from fractures and dislocations, 39 million from sprains and strains, and 17 million from contusions and superficial injuries.

Type of injury	No. (millions)	Days of restricted activity (millions)	Days of bed disability (millions)	Days off lost work (millions)
Fractures and dislocations	7.8	137	40.6	65.3
Sprains and strains	14.3	115.1	31.5	38.3
Open wounds and lacerations	11.8	30.1	4.4	7.6
Contusions and superficial injuries	12.2	48.6	11.7	16.3
Other musculoskeletal injuries	16.5	122.4	31.5	40.3
All types	61.8	453.3	127.9	168.1

Reprinted from: NCHS, Current estimates from the National Health Interview Survey, US 1994. DHHS Pub. No. (PHS) 96-1521. Hyattsville, MD: National Center for Health Statistics, 1995.
[a] In 1,000 millions.

TABLE 31-1. Epidemiology and effect of musculoskeletal injuries; 1994 [a]

Only respiratory conditions rank higher than injuries in the incidence of acute conditions. It is estimated that approximately 92% of these injuries will be medically attended. Acute musculoskeletal injuries and their sequelae represent a substantial medical and social problem with enormous costs. Optimal outcomes are dependent on early medical, surgical, and rehabilitation efforts. Early activation can minimize the deleterious effects of inactivity and bed rest. These effects include contractures, muscle weakness and atrophy, immobilization osteoporosis, orthostatic hypotension, reduction in total plasma volume, reduction in cardiovascular performance, thromboembolic phenomena, cardiovascular deconditioning, skin atrophy and pressure sores, reduced respiratory efficiency, pneumonia, pulmonary embolism, urinary stasis and stones, negative nitrogen and mineral balance, decreased insulin sensitivity, constipation, anxiety and depression, impaired intellectual capacity, and impaired balance and coordination (2). Adequate pain management is essential for remobilization, prevention of these complications, and return to normal activities of daily living.

PHYSIOLOGY

Tissue injury results in stimulation of nociceptors and transmission of impulses along afferent nociceptive axons to the central nervous system (see Chapter 9). It is at the level of the supraspinal central nervous system that the nociceptive input is given meaning. The perception of the nociceptive input is modulated by past experiences, current emotional state, level of awareness, and other stimuli. Acute pain signals tissue damage and is identified by the organism as a form of stress. Acute pain is usually associated with an increase in autonomic activity such as hypertension, tachycardia, sweating, and vasoconstriction. In opposition, chronic pain conditions are not associated with ongoing tissue injury but are frequently described in terms of such damage. Tissue injury is a trigger for a complex cascade of events involving the inflammatory, immunologic, metabolic, neurologic, endocrinologic, and psychological systems. Nociception can be produced by a wide variety of stimuli including pressure, tension, heat, cold, chemical changes, and hydrogen ion concentration, histamine, serotonin, bradykinin, and other polypeptides, such as substance P.

These physiologic responses have evolved to prevent further tissue injury, maintain homeostasis, and prevent mortality. However, the evolution of the response to trauma and tissue injury may not have resulted in a system that is ideal for the modern person living in an industrial, cognitive society with the technologies of modern medicine. In some cases the immunologic, inflammatory, neurologic, endocrinologic, metabolic, and psychological responses to trauma and tissue injury may be excessive or maladaptive, and, in fact, increase morbidity and mortality. Human physiology, with respect to its response to trauma, is probably best designed to fight contaminated wounds and injuries inflicted by a predator, as evidenced by the intensity of the inflammatory cascade and the prolonged adrenergic and catabolic states after injury (Fig. 31-1).

Figure 31-1. Acute pain.

INFLAMMATORY RESPONSE

In 1888, Sir John Scott Burden-Sanderson wrote, “The process of inflammation is a succession of changes which occurs in the living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy its structure and vitality” (3). This statement indicates that inflammation is a succession of events. The inflammatory response starts at a local level but is a multimodality, systemic process with events running both in sequence and also concurrently (see Chapter 3). At the time of tissue injury and the release of local chemical stimulants, the inflammatory pathway commences. Through local nociceptors and ascending afferent impulses, the inflammatory response perpetuates the pain response to the initial tissue trauma. Chemical mediators of inflammation can be exogenous mediators (i.e., venom, bacteria, and bacterial products), or endogenous mediators. Endogenous mediators come from plasma or from the local tissues. Injury to a cell changes the cellular membrane and membrane permeability, allowing the leakage of intracellular substances and exposing the phospholipids in the cell membrane. Hydrolysis occurs, and arachidonic acid is formed; it is then converted into prostaglandins and leukotrienes, the key mediators of the inflammatory cascade.

Stimulation of nociceptors results in an increase in the inflammatory response by reflex activation of the sympathetic nervous system, with local tissue release of axonal catecholamines, increased hypothalamic activity with release of pituitary hormones, and adrenomedullary release of circulating catecholamines. A change in blood vessel permeability and the activation of cells occurs, including leukocytes, fibroblasts, endothelial cells, and the production of cytokines. Lysosomal enzymes, vasoactive amines, and prostaglandins are released. Plasma leaks into the local tissues, either by direct vascular injury or through neural hormonal alterations in vascular permeability. In addition to the chemicals that directly stimulate nociceptors (bradykinin, serotonin, histamines, potassium, leukotrienes, and hydrogen ions), chemical mediators are released in the tissues that sensitize nociceptors or augment the response of local nociceptors (prostaglandins and thromboxanes) (see Chapter 3).

As a result of this cascade at the site of tissue injury, initially heavy edema, low oxygen tension, and aggressive immunologic response are seen. This environment may be advantageous for controlling bacterial contamination and preventing infection in a wound. However, it may also result in increased tissue damage, increased pain, and delayed tissue healing. Therefore, in aseptic tissue trauma (a clean wound) or in a world with multiple antibiotics, it may be beneficial to the organism to modulate this intense inflammatory response.

STRESS RESPONSE

Beyond the inflammatory pathway, tissue trauma and nociception interweave the immunologic, metabolic, endocrinologic, and psychological systems in the stress response. The pain response and the closely integrated stress response are part reflex and part learned behavior. The organism responds by a hard-wired reflex to noxious stimuli. This reflex response, however, may be variable from individual to individual. This system is modulated by the current physiologic state as well as conscious and subconscious learned behavior. From an evolutionary and survival standpoint, it is clearly advantageous for the organism to learn to avoid noxious stimuli and injury.

The stress response can be stimulated by decreasing circulating volume, changes in O_2, CO_2, or hydrogen ion concentrations, nociception, temperature, tissue injury, and adversive emotional states. These result in increased sympathetic activity with increased release of norepinephrine from postganglionic neural terminal axons as well as release (of epinephrine) from the adrenal medulla into the plasma. Peak concentration of circulating systemic catecholamines occurs 24 to 48 hours after tissue injury. The pain response begins with the stimulation of nociceptors with a signal traveling up the neural afferents to the central nervous system and then retrograde over the afferent pathways. Nociceptive primary afferents exist in the skin, subcutaneous tissue, periosteum, joint capsules, muscle, and viscera. The peripheral, spinal, and brain pathways for nociception and their transmitter substances are discussed in Chapter 3, Chapter 4 and Chapter 5.

In the management of musculoskeletal injury and pain, it is essential to keep the complexity of the nervous system in mind and to contemplate the emotional and cognitive aspects of pain and pain management. The psychological or emotional status of the organism, by affecting the outflow of the supraspinal centers, can affect the perception of pain and the total response to localized tissue injury. This may explain the phenomenon seen in athletic competition in which athletes may experience tremendous tissue impact and experience little pain and little fear (and may in fact experience rage). There may be relatively little residual tissue damage; edema and inflammation and the injury can heal relatively rapidly. However, for that same individual, tissue trauma in an entirely different setting, such as a motor vehicle accident, may evoke an entirely different emotional and physiologic response with excessive fear and anxiety that can, in the worst case scenario, lead to a chronic pain syndrome and chronic disability.

It must be remembered that the pain experience is in part reflex, an autonomic and automatic response, and also is part primitive or primal emotional and endocrinologic response, and is only in part a cognitive processing response. Emotional status and mental activities can influence the pain response through cortical and subcortical descending tracts. The outflow from these supraspinal centers in response to trauma, tissue injury, or stress results in increased cardiac output, increased peripheral vascular resistance, increased blood pressure, and increased oxygen consumption. From the pituitary there is release of adrenocorticotropic hormone and stimulation of the adrenal glands for the release of cortisol, increased release of glucagon, decreased insulin release, decreased insulin sensitivity, activation of plasma cyclic adenosine monophosphate, release of arginine vasopressin, and decreased free water excretion from the kidneys. This process results in mobilization of substrates or a catabolic state in an effort to sustain the organism. This catabolic state can last for hours to weeks.

The neuroendocrinologic response producing a catabolic state was probably at one point advantageous, in that it allowed the organism while incapable of hunting and gathering to mobilize substrates to nourish vital organ systems and the damaged tissues. It is interesting that the length of this catabolic state corresponds well with the level of tissue injury and theoretically the level of incapacitation. No clear benefit exists for a catabolic state when the organism has a safe harbor and adequate nutrition can be provided. Nutritional support and modulation of the catabolic state are beneficial to the patient.

The limbic system may also act disproportionately in certain circumstances (see Chapter 5). At a primitive level, it is advantageous for an organism to recognize threat from an instinctive standpoint as well as to be able to learn from previous experiences with threatening stimuli. It is important to be able to determine when to appropriately choose fight or choose flight and, if one survives, postinjury maintenance of a high level of arousal and vigilance for the likely return of a predator is beneficial. It is interesting that peak catecholamine levels do not occur until 24 to 48 hours after injury, sustaining the adrenergic state. However, in modern society with our current medical system, this level of sympathetic response is probably not beneficial and can be detrimental.

The patient may have an elevation in the pain response mediated by the somatomotor reflex system and muscle spasm, the sympathetic nervous system via vasoconstriction and release of norepinephrine and epinephrine, and by increased local ischemia or an enhanced inflammatory response. The central nervous system does exert a descending inhibition system, mediated by cortical diencephalic and mesencephalic tracts, periaqueductal gray matter and other opioid-receptor-rich tracts, and the dorsolateral funiculus from the locus ceruleus and the nucleus raphe magnus, sending noradrenergic and serotonergic transmission to the dorsal horn.

Gamma-aminobutyric acid (GABA) receptor–specific medications act presynaptically in the large primary afferents, 1-A afferents for muscle, to decrease somatomotor reflex activity, thus the rationale for the use of GABA-specific receptor medications such as the benzodiazepines for decreasing reflex muscle spasm in response to pain. Some a-adrenergic agonist receptors, when stimulated, inhibit pain transmission and possibly somatomotor reflex activity. This is the rationale for the use of medications such as clonidine and tizanidine in the management of pain, spasticity, and spasm. Endogenous opioids, enkephalins, and endorphins can inhibit

nociceptive transmission. The pituitary adrenal axis also exerts effects on stress, pain perception, and pain behaviors.

It is interesting to note that mood and emotional state are modulated by norepinephrine, serotonin, and GABA, as are the descending pain inhibitory pathways. Dopamine may have a small role in pain modulation, primarily through the arousal matrix.

Summary

The stress response appears to work best for preventing excessive morbidity or mortality in response to the physical assault of predators. However, hypercoagulability, catabolism, and hypervigilance are not adaptive when no physical threat exists, or the threat has been removed. The stress response can lead to multiple negative physical and psychological complications of trauma. Because the inflammatory and stress response systems can be exuberant and prolonged, medical modulation can be beneficial to the patient to relieve physical and emotional pain, promote healing, and prevent the development of chronic pain syndromes and the potential negative psychological sequelae of trauma.

TISSUE INJURIES

Connective tissue functions to support or contain other tissues or organs and to transmit mechanical forces. Components of connective tissue include collagen, ground substance (proteoglycans and water), and cells. The collagen fiber type and arrangement designate the classification of soft tissues. In general terms there are *loose* and *dense* connective tissues. Because of the high density and organization of the collagen in tendons and ligaments, these are referred to as dense connective tissue. The strength of connective tissue is a result of the triple helical structure protein, collagen. The ground substance is relatively amorphous. Proteoglycans and water are the main elements of the ground substance. Glycosaminoglycans, chondroitin sulfate, keratin sulfate, and hyaluronate make up the carbohydrate component of the proteoglycans. The main cellular component of connective tissue is fibroblasts. The collagen fibers give the tissue a high tensile strength. The ground substance allows diffusion of nutrients to the tissue. As well, it helps to minimize friction within the tissue and gives the tissue its compressive properties. Fibroblasts are responsible for the production of the collagen and the ground substance.

Tendons and ligaments have a high volume of type I collagen and a relatively low quantity of proteoglycan. They are particularly tolerant to tensile loads. Articular cartilage is composed of type II collagen and a large amount of proteoglycan-laden ground substance, making this a better tissue to handle compressive forces and associated frictional forces seen with weight-bearing activities. Also seen within connective tissue are circulating blood cells, including microphages acting as scavengers of dead cells, bacteria, and foreign particles and mediators of the inflammatory response; and mast cells (containing vasoactive substances) including histamine, serotonin, and possibly other kinins playing a key role in the control of blood flow and the inflammatory process. Lymphocytes and polymorphonuclear neutrophils can be seen within connective tissues.

The mechanical properties of soft tissues are not only determined by their structural components but also by temperature, activity, and age. Tendons and ligaments are stiffer when cold and become less viscous and more extensible with elevating temperature. Stretching results in creeping of the collagen fibers and change in the viscoelastic properties of that tissue, changes that can protect tissues from injury. In sports medicine, stretching has been recommended to prevent injury (4,5). In rehabilitation, stretching is used as a method to regain range of motion and improve function (6,7). Static stretching is the preferred technique for gaining sustained tissue elongation with minimal risk of injury. Ballistic stretching should be avoided. To get an adequate sustained elongation of soft tissues (i.e., stretch), it is helpful if the tissues are warm before stretching (8,9 and 10).

In sports medicine, active warming up with low-resistance, high-frequency exercise until a light perspiration has broken out on the skin (indicating an elevated body temperature and tissue temperature) should be performed before stretching. It may in fact be this warm-up procedure that is most responsible for injury prevention during the athletic activity that immediately follows. Stretching and resultant increased flexibility not only help prevent injury in the athletic activity immediately after, but if done on a consistent basis over time, also leads to a further reduction in soft tissue injuries and improved performance over time, as the athlete's baseline level of flexibility improves (11,12). An injury prevention program should include routine stretching five to seven times per week with warm- up and stretching before and stretching after any strenuous activity.

It should be noted that warming up not only improves the viscous properties of tissue, leading to increased flexibility and increased range of motion, but also leads to increased enzymatic activity, increased force production, perhaps secondary to increased enzymatic activity, an increase in the dissociation of oxygen from hemoglobin and myoglobin, increase in muscle blood flow, increase in the sensitivity of nerve receptors, and increase in the speed of nerve conduction velocities. The improvement in nerve conduction times leads to improved proprioception, coordination, and reaction times as well as pain response times. All of these can lead to further reduction in injury rates (13).

The changes in tissues discussed previously can also be achieved with passive warming of these tissues. These passive methods are used in the rehabilitation process and therapeutically use the multiple benefits of warming soft tissues to promote healing of injured tissue and reverse the tissue changes that may have resulted from immobilization (14,15).

The old adage that an ounce of prevention is worth a pound of cure holds for acute and chronic musculoskeletal injury and pain. In many cases it is as simple as warming up and stretching. These should be done in this temporal sequence: warming up and then stretching before any strenuous activity, whether that strain is cumulative, based on the volume of repetitive activity or from relatively low repetition activity but with high force production in the musculotendinous unit. Stronger muscles are also less likely to be injured than weaker muscles. This is an argument for strength training, not only to be used for performance enhancement but also for injury prevention (16).

The pathophysiology of tendon, ligament, and muscle injury and pain is similar. Soft tissue injuries can be classified in terms of etiology: (a) direct injuries, usually caused by blunt trauma; and (b) indirect injuries, which include the following types: Acute injuries occur with the sudden overloading of musculotendinous units. Chronic or overuse injuries are caused by repetitive overloading, frictional resistance, which occurs in highly repetitive activities, or both. Acute or chronic injuries are caused by sudden rupture of a persistent lesion (e.g., rupture of Achilles tendon with chronic tendinitis).

Collagen fibers are the major building blocks of the soft tissues. Normal physiologic loading may produce 2% to 5% strain in collagen fibers and still result in return to resting length after removal of the load. Strain equals the increase in length divided by the original length multiplied by 100. This is characterized as the elastic deformation property of the tissue. At 7% or 8% strain, collagen fiber failure begins. Beyond this one sees plastic deformation, or failure to resume original length after removal of the load. Microscopically collagen failure occurs. Healing of soft tissue injuries occurs by fibrous repair (scar tissue).

Okes and van der Muelen have described the phases of healing postinjury (17,18). An early phase is associated with the sympathetic response or early stress response to tissue injury, vasoconstriction, which may last up to 10 minutes. Beyond this early phase, there is phase 1, described as the acute inflammatory phase (Okes) or the reaction phase (van der Muelen). Phase 2 has been described as the repair phase by Okes, and the regeneration phase by van der Muelen. Phase 3 has been described by both as the remodeling phase.

Phase 1

This phase may last for up to 72 hours, depending on the severity of the injury. It has both cellular and humeral components. Disruption of the cells and surrounding connective tissue occurs. The injury to the small vessels and capillaries results in leaking or bleeding. The local cellular damage also leads to extravasation of intracellular substances. The inflammatory cascade is initiated with further edema formation. Within 24 hours macrophages are present in the tissue, releasing antibacterial and antiinflammatory substances and enzymes for the breakdown of damaged tissues and subsequently the phagocytosis of the residual debris. The complement system is also activated, resulting in antigen–antibody complexes, stimulating chemotaxis and phagocytosis. Degranulation of mast cells occurs with release of histamine and serotonin. Granulocytes release prostaglandin, further increasing vasodilatation and chemotaxis. Phase 1 is characterized by inflammation, swelling, redness, warmth, and acute pain.

Phase 2

Phase 2 may last from 48 hours to 6 weeks. As early as 24 hours postinjury, macrophages are present in the tissue, releasing antibacterial and antiinflammatory substances as well as enzymes for the breakdown of damaged tissue, and subsequently allowing phagocytosis of the residual debris. The repair of tissue only takes place when the site has become clean with the removal of cellular debris. Phagocytosis by the granulocytes of devitalized tissue and bacteria is the essential first step

in the healing process.

Early postinjury low oxygen tension occurs in the tissues because of blood vessel injury and poor perfusion, as well as the hypoxia created from the tissue edema. Aerobic bacteria do poorly in this environment; however, macrophages and granulocytes are able to perform their functions in a hypoxic environment, because of their capacity for anaerobic metabolism (i.e., glycolysis). The low oxygen tensions serve to stimulate vascular budding in the repair phase. There is usually relative immobilization and collagen contraction, which can help to protect the injured tissue, but also leads to a loss of flexibility and range of motion.

Phase 3

Phase 3, the remodeling phase, may last from 3 weeks to 12 months or possibly more, depending on the severity of the injury. This phase primarily involves the remodeling of collagen to increase the functional capabilities of the tendon or ligament to withstand the stresses of routine activities. The tensile strength of the collagen is related to the forces imposed on it during the remodeling phase. To fully rehabilitate the patient and prevent future injury, the rehabilitation program must incorporate highly specific but controlled exercises.

The collagen tissues in phase 2 are relatively disorganized. In phase 3 a higher level of organization occurs with appropriate orientation and improvement in the tensile strength of the tissues. Normal ligaments are composed of type I collagen. In a damaged, healing, or healed ligament a higher level of type III collagen is seen, having a fewer number of cross-linkages between and within the tropocollagen subunits. The quality of the tissue improves over time, but may never obtain the same tensile strength as an undamaged ligament (19).

Repair Processes

Phagocytosis by the granulocytes of devitalized tissue and bacteria is an essential first step in the healing process. Excessive edema can inhibit cellular migration to the devitalized tissues. Therefore, it makes sense to try to control this initial response to tissue damage, minimizing the extravasation of fluid and the amount of devitalized cellular material, both of which increase the workload for the phagocytes. In the early stage after injury it is important to control the exuberant inflammatory response and minimize bleeding and edema formation. This facilitates macrophage migration and expedites the removal of debris, enabling earlier pain relief and healing.

For the first 42 to 72 hours after injury, relative rest is important. Gentle nonpainful range of motion is useful. In lower extremity injuries, ambulating with assistive devices and limited weight bearing may be indicated. Complete immobilization and non– weight bearing are sometimes indicated. Ice and nonsteroidal antiinflammatory agents also help control inflammation and edema.

Connective tissue disruption is associated with stimulation of the pain pathways and inflammatory response. Vasodilatation, exudation of tissue fluids, extravasation of blood, and reactive edema are present. An exaggerated inflammatory response results in increased pain and delay in tissue healing. An excessive early inflammatory response associated with bleeding in the soft tissues and edema results in increased pain, prolonged pain, and delay in tissue healing. Ice, elevation, compression, nonsteroidal antiinflammatory drugs, and analgesics are indicated to reduce this response. With the removal of debris and resolution of edema, healing can take place. Initially, revascularization is followed by fibroblast proliferation and production of collagen. Early regeneration is characterized by disorganization and poor mechanical properties of the connective tissues. Remodeling is characterized by orientation and organization of the collagen fibers and stable bonds of the ground substance and takes place over many months after injury.

MUSCULOSKELETAL SYSTEM INJURIES

A general approach to acute musculoskeletal injuries is depicted in Figure 31-2.

Figure 31-2. An algorithm for the management of acute injuries.

Muscle Injury

Delayed Muscle Soreness

The most common form of muscle injury is delayed muscle soreness. High force eccentric loading of the muscle beyond its familiar capacity leads to injury of the muscle fibers and associated inflammatory response (20). Peak soreness is usually 24 to 48 hours after the stimulus and is usually substantially improved at 72 hours poststimulus. Icing after activity is helpful for prevention of symptoms. However, the patient is frequently unaware that symptoms are going to occur until 12 to 24 hours after exercise. Stretching has been shown to be effective in alleviating symptoms of delayed muscle soreness (21). Heat and a light workout when tolerable are beneficial and can hasten symptom resolution. In severe cases nonsteroidal antiinflammatory drugs may be indicated for inflammation and analgesia (22). Acetaminophen is also helpful for symptom management. Narcotics and antispasm medications are seldom indicated. Delayed muscle soreness has a benign course and is rarely associated with a long-term problem.

Compartmental Syndrome

Exercise-induced compartmental syndrome is a much more worrisome condition. Occasionally, with prolonged, repetitive exercise, excessive muscle damage can result in enough inflammation and edema within a muscle compartment to cause neurovascular compromise (23,24 and 25). The patient complains of pain with activation or stretch of the muscle; the most worrisome sign is the complaint of sensory changes within the extremity. The most commonly affected compartments include the anterior and deep posterior compartments of the leg (Fig. 31-3). On palpation, a compromised compartment is tense and painful. Immediate referral should be made to an orthopedic surgeon for compartment pressure measurements, sequential neurovascular examinations, and evaluation of the need for urgent surgical decompression.

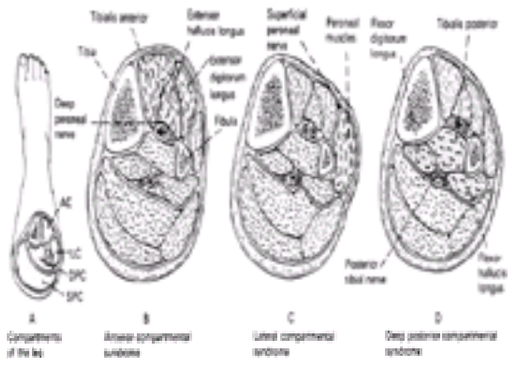

Figure 31-3. **A–D:** The leg contains four compartments bounded by bone and semirigid fascia. The anterior (AC), deep posterior (DPC), and lateral compartments (LC) each contain a major peripheral nerve having both sensory and motor components, as well as a group of muscles. (SPC, superficial posterior compartment.)

Muscle Strain

Muscle strains, as with ligament sprains, are categorized. First degree indicates a mild injury occurring at a microscopic level. Second degree indicates a moderate strain or partial tear, and third degree indicates severe complete tear of the muscle. These injuries occur when the tension elicited within the musculotendinous unit exceeds the biomechanical strength of a component part. Muscle strains can occur at the mid substance of the muscle or, more commonly, at the weak link in the chain, the musculotendinous junction (26). Typical sites for these injuries are depicted in Figure 31-4.

Figure 31-4. Gastrocnemius-Achilles junction separation. Medial head of the gastrocnemius tear occurring at the musculotendinous junction. Muscle strains most commonly occur at the musculotendinous junction during an eccentric contraction of the muscle.

Most of these injuries result from an eccentric muscle contraction that exceeds the capacity of the musculotendinous unit. Resistance to such forces is from both the intrinsic and the eccentric components of the musculotendinous unit. The system is designed for energy absorption. Contracted muscle is capable of storing more energy before failure than noncontracted muscle. Eccentric strength of a musculotendinous unit increases the tolerance for strain and lessens the risk for injury. As discussed earlier, warming of the tissue also has a protective effect (27). Histology after muscle strain initially shows hemorrhage. After 24 hours, distal fiber necrosis and infiltration of inflammatory cells occurs with an intense inflammatory reaction by 48 hours postinjury.

Early treatment consists of rest, ice, compression, and elevation. The goal is to minimize the inflammatory response, bleeding, and edema formation. Nonsteroidal antiinflammatory agents may be useful in this condition. Early intervention may result in a faster healing time as well as prevent the complications of prolific scarring, contracture, and loss of normal viscoelastic properties.

Muscle Contusion

Another form of muscle injury is the muscle contusion, which can result in a large distribution of muscle fiber damage (contusions are from direct injury; strains are from high-intensity contraction of the muscle against resistance). Complications of muscle contusion are bleeding and the formation of a hematoma. Hematomas can be intermuscular, spreading through the fascial planes, or more worrisome, intramuscular, occurring within the belly of the muscle. This can lead to increased local muscle cell injury, and because the blood cannot drain through the fascial planes, intramuscular hematomas take longer to resolve and have the potential of significant scar formation, muscle shortening, contracture, and, most worrisome, the development of myositis ossificans traumatica. Myositis ossificans traumatica is the formation of an osteoid matrix that goes on to mineralization within the substance of the muscle (28). This process can lead to prolonged and at times permanent impairment caused by pain and contracture.

Early intervention is key to preventing long-term morbidity. Rest, aggressive icing, compression, and elevation to minimize bleeding, inflammation, and edema formation are the cornerstones of early treatment. Nonsteroidal antiinflammatory medications may help control inflammation and provide analgesia. Acetaminophen may also be helpful for symptom control. In severe cases, oral narcotics and muscle relaxant medications may be indicated.

Ligament Injuries

Trauma to a ligament is classified as either first, second, or third degree, or grade I, II, or III. A grade I or first-degree sprain is considered mild, with microscopic stretching and minimal tearing of ligament fibers. There is mild pain at the time of injury or within 24 hours from injury. There is pain with stress of the ligaments. There may or may not be local tenderness. Recovery can be expected in 10 to 14 days. The pain response is typically mild and can be managed with ice, acetaminophen, or nonsteroidal antiinflammatory medications.

A grade II or second-degree ligament sprain is characterized by moderate tearing of the ligament fibers, loss of structural integrity, and instability. Pain occurs during activity, pain with stress, and local tenderness on palpation. One can expect adequate healing and rehabilitation to be complete within 4 to 6 weeks of injury. A slightly increased risk exists of developing chronic instability, altered joint mechanics, posttraumatic arthritis, and chronic pain. In addition to ice, acetaminophen, nonsteroidal antiinflammatory agents, or all three, early pain management may require low-dose narcotic analgesia and muscle relaxant medications.

A grade III or third-degree ligament sprain indicates complete disruption of the ligament on a macroscopic level (Fig. 31-5). Severe pain or loss of function occurs. Pain is felt with palpation, but paradoxically, at times there can be less pain with stress of the ligament than when the ligament is still partially intact.

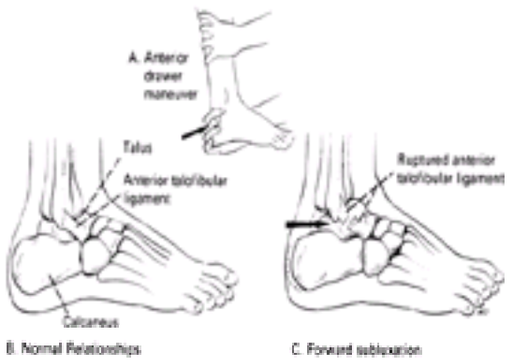

Figure 31-5. **A–C:** Positive anterior drawer sign: When the anterior talofibular ligament is ruptured, the talus can be subluxed forward in the ankle mortise.

Whole ligament strain levels can be as high as 20% to 40% before failure becomes apparent. After injury there may be the appearance of continuity of the ligaments macroscopically; however, microscopically there may be such failure that complete loss of the load- carrying capacity of the ligament occurs. Ligament failure occurs diffusely throughout the length of the ligament or at the site of ligament attachment to bone. Treatment varies from protected mobilization, modified immobilization to complete immobilization, to surgical correction. The period for healing, rehabilitation, and return to activities is variable, depending on the structure involved. Inadequate treatment carries the risk of developing chronic instability, posttraumatic arthritis and chronic pain, impairment, and disability. In addition to ice, acetaminophen, and nonsteroidal antiinflammatory medications, treatment may require small to moderate doses of narcotic analgesics and muscle relaxant medications.

Apophyseal Injuries

In the pubescent and adolescent population, because of hormonal changes, rapid growth, relative shortening of muscles, and increased strength (force production) of muscles, the apophyses can be at greater risk for injury than the musculotendinous units. What may appear as a tendinitis or muscle strain may in fact be an apophysitis or apophyseal avulsion. Common sites of apophyseal injury are the origin of the sartorius, at the anterior superior iliac spine, the origin of the rectus femoris at the anterior inferior iliac spine, the origin of the hamstrings at the ischial tuberosity, the insertion of the quadriceps mechanism through the patellar tendon at the tibial tuberosity, and the insertion of the gastroc-soleus mechanism at the calcaneus (Fig. 31-6). Treatment for apophyseal injuries is similar to the treatment for tendinitis or muscle strain. However, if gross displacement of the fragment occurs, referral to an orthopedic surgeon is recommended for consideration of surgical reduction and fixation.

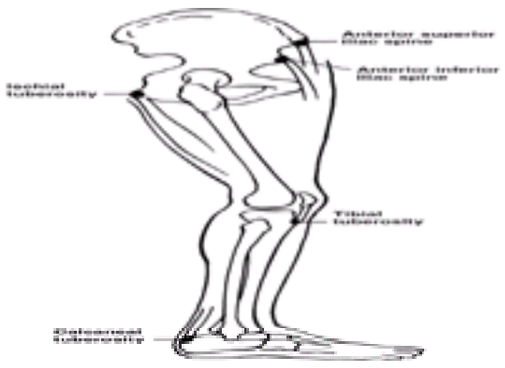

Figure 31-6. Apophyseal injuries. Common sites of apophyseal injuries. In the prepubescent and adolescent population, the apophyses can be the weakest link in the osseomusculotendinous unit, resulting in apophysitis or apophyseal avulsion.

Tendon Injury

The breaking point of human tendon is estimated at around several hundred kilograms per square centimeter. Tendon injury can be divided into three classifications: inflammatory (acute versus chronic), degenerative, or rupture, and these classifications can coexist (Fig. 31-7). Tendinitis or inflammation of the tendon is commonly an overuse injury. Repetitive loading leads to microinjury that results in an inflammatory cascade with increased permeability of cell membranes, leaking of intracellular substances into the extracellular spaces, edema, and pain. This can result from inadequate warm-up, insufficient flexibility, or insufficient strength (too much too soon).

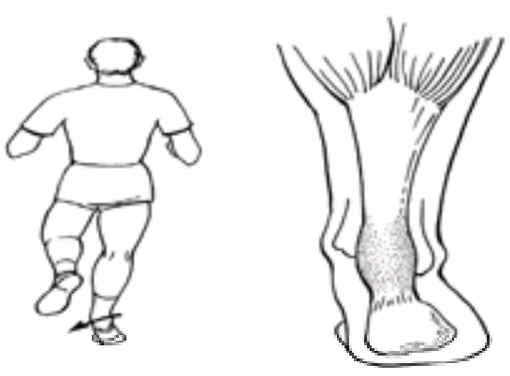

Figure 31-7. Achilles tendinitis. Overuse of a tendon can lead to inflammation and pain.

In the acute phase, relative rest, ice, and compression are indicated. Nonsteroidal antiinflammatory medications are frequently helpful, both to block the inflammatory response and for analgesia. Acetaminophen may also be helpful for pain relief. When the acute inflammatory phase resolves, ultrasound that provides deep heat to the tissues, gentle stretch to restore functional length, and gradual strengthening are indicated before returning to routine use of the tendon.

The term *tendinitis* indicates an acute or active inflammatory condition. Clinical examples are presented in Table 31-2. The term *tendinosis* should be used when the problem is predominantly degenerative. Some tendons become chronically painful, particularly the rotator cuff and the tendon of origin to the extensors of the wrist. Histologic examination of these chronically painful tendons are more consistent with tendinosis, revealing angiofibroblastic hyperplasia and fibrinoid necrosis with few or no inflammatory cells. In these cases the early response to antiinflammatory drugs may be based solely on their analgesic properties and may not constitute an actual antiinflammatory response (29). It is important to adequately treat acute tendinitis to prevent chronic changes within the tendon. Chronic edema leads to secondary changes in the peritendon tissue and the tendon itself. Fibrin deposits from chronic edema organize in the subperitendon space, forming thick nonelastic scarring and adhesions. Chronic changes of mucoid degeneration and calcification can also be seen. Complete rupture often requires surgical repair, and chronic changes also may benefit from debridement and surgical repair (Fig. 31-8).

Tendon	Site of pain	Associated findings
Extensor carpi radialis brevis/extensor carpi radialis longus/extensor digitorum communis	Lateral epicondyle of elbow	Pain/↓ in active wrist dorsiflexion
Extensor pollicis brevis/abductor pollicis longus (De Quervain's syndrome)	Snuffbox of wrist	Painful grip when thumb is inside fist and fist is deviated in palmar and medial directions
Iliotibial	Lateral condyle of knee	Pain increased by climbing stairs or running up a hill
Patellar (jumper's knee)	Patellar tendon distal to patella	Pain increased by jumping
Posterior tibial	Medial border of tibia or behind medial malleolus	Excessive pronation, pain increased by running or exercise
Flexor hallucis longus (trigger toe)	Behind medial malleolus	Found in dancers, pain increased by dancing

TABLE 31-2. Types of tendinitis

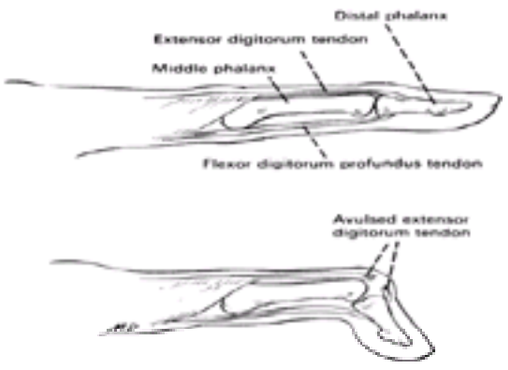

Figure 31-8. Normal and *mallet* finger: In mallet finger, the distal phalanx is flexed and the patient is unable to actively extend it.

Dislocations

Joint dislocations occur when a joint undergoes excessive range of motion with a force applied that results in tearing of the ligamentous, capsular, or both kinds of restraints of the joint. Fracture should be ruled out before attempts at relocating the joint. The patient also requires a complete assessment for neurovascular compromise. Initial treatment should include immobilization and ice. Relocation of the joint frequently results in dramatic pain relief. Effective analgesia is required to relocate the joint. Narcotics in combination with sedative-hypnotics or muscle relaxants frequently provide adequate analgesia and relaxation for reduction of the joint. The intravenous route for relaxants and opiates has distinct advantages in this setting. Regional anesthesia is sometimes required. Regional anesthesia has the benefit of not only providing pain relief but also relaxation of the musculature. Regional anesthesia may also provide early postreduction pain relief and block the endocrine and metabolic reflexes associated with trauma. After successful relocation, immobilization, ice, compression and elevation are indicated. For small joints, nonsteroidal antiinflammatory medications and acetaminophen may be adequate for pain management. In larger joints, oral narcotic and muscle relaxant medications are appropriate.

Bone Injury

Bone injury occurs when excessive loading occurs or energy is applied beyond what can be absorbed, followed by structural failure (Fig. 31-9). The greater the volume of bone, the more energy that can be absorbed before fracture. Also, the greater the elasticity of the bone, the more energy can be absorbed before frank fracture. The higher the rate of application of force, the lower the energy that can be absorbed before injury. Fracture and associated tissue injury are characterized by disruption of small vessels and capillary beds, bleeding, and the formation of a fracture hematoma. Local cell death occurs, with bone necrosis and tissue debris resulting in the release of lysosomal enzymes, thus the inflammatory cascade begins. As with all tissue healing, an inflammatory response is essential to this process. After macrophageal migration and removal of tissue debris, rapid vascular and cellular proliferation occurs. Increased periosteal capillary formation occurs. Despite the high capillary density, the high cellular volume results in relative low oxygen tension and low pH, which is a favorable environment for the growth of bone callus. Early callus formation begins when swelling has subsided and can take up to 3 weeks to form in fractures of major long bones. The callus results in fracture splinting and decreasing pain caused by immobilization. The bone now reorganizes to its normal or near normal architecture and healing is completed. Reduction and immobilization of the fracture is essential to promote adequate and early healing and pain management. Ice and elevation are indicated acutely. Adequate pain management frequently requires the use of oral, intramuscular, or intravenous narcotics as well as muscle relaxant medications. Acetaminophen and nonsteroidal antiinflammatory medications are helpful supplements.

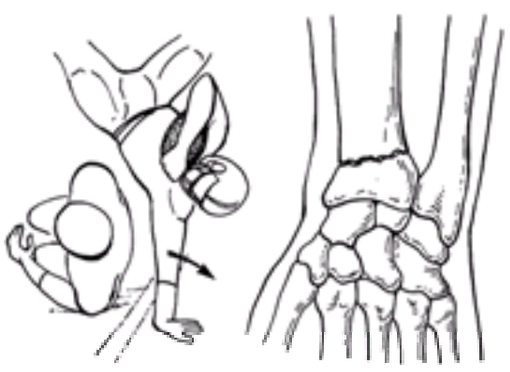

Figure 31-9. Colles' fracture of the radius. A common mechanism of wrist injuries is landing on an extended hand and wrist, in this case resulting in a distal radius fracture, or Colles' fracture.

Stress Fractures

Repetitive use injury can also occur to bones, in the form of stress reactions or stress fractures. Failure results from repetitive loading, which when applied as an individual instance of force would not cause the bone to fail. However, a cumulative fatigue results in failure. As with any tissue, bone is dynamic and constantly remodeling. Mechanical stress accelerates adaptive remodeling to strengthen the bone. However, a high volume of repetitive stress results in weakened trabeculae and, eventually, microfracture.

Common sites for stress fractures, in declining order of incidence, include tibia, tarsal bones, metatarsal bones, femoral neck, fibula, pelvis, hallux, sesamoids, and the spine. However, stress fractures can occur in other areas, particularly in athletes who may place excessive demands on other structures in their sport-specific training. Throwing athletes may present with clavicle fractures; tennis players with humeral fractures; wheelchair athletes, weight trainers, and gymnasts with radius and ulna fractures; rowers with rib fractures; football players, weight lifters, and gymnasts with vertebral or pars interarticularis fractures; and runners with pelvis fractures. Usually, relative rest is adequate treatment. Average times to recovery from common stress fractures are listed in Table 31-3. Occasionally, in a severe case, immobilization and non–weight-bearing status are indicated. With femoral neck stress fractures, open reduction and internal fixation may be indicated. Ice and nonsteroidal antiinflammatory medications are appropriate acutely. Pain management is usually adequate with acetaminophen or nonsteroidal antiinflammatory drugs.

Narcotics and muscle relaxant medications are seldom indicated for stress fractures.

Bone	Average recovery time (wk)
Femur	4–6
Tibia	4–6
Fibula	4
Metatarsals	3–4
Tarsals	8–12

TABLE 31-3. Average length of recovery from stress fracture

Clinical Examples

Rotator Cuff Tendinitis. Rotator cuff tendinitis is seen in upper extremity overhead athletes, such as swimmers, wrestlers, throwing athletes, and tennis players (30). It involves impingement of the rotator cuff musculature against the undersurface of the acromial arch (Fig. 31-10). As the arm moves overhead, the rotator cuff and subacromial bursa glide underneath the acromion and the coracoacromial ligament. This can cause impingement and chronic irritation resulting in inflammation of the tendon and the bursa and potentially tissue tearing. The shoulder capsule needs sufficient flexibility to allow normal humeral inferior gliding, and the rotator cuff needs adequate strength and control of the humeral head to prevent upward gliding and pinching of the soft tissues between the humeral head and acromion (see Chapter 58).

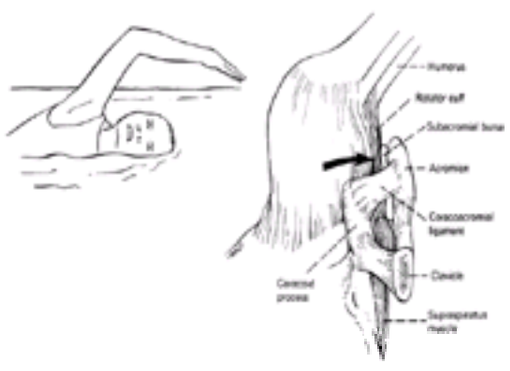

Figure 31-10. Rotator cuff impingement. As the arm moves overhead, the rotator cuff muscles and subacromial bursa slide underneath the acromion and the coracoacromial ligament. The arrow points to the area of impingement.

Patients present with complaints of aching in the shoulder region, frequently radiating down to the midlateral deltoid or even as far as the lateral elbow or forearm. Symptoms are aggravated by attempted forward flexion or abduction, particularly with the shoulder in internal rotation. The insertion of the supraspinatus into the humeral head area is frequently tender to palpation. The supraspinatus is the most commonly affected tendon in this process. Inflammation and degenerative tears usually occur approximately 1 cm from the insertion into the humeral head. Initial treatment requires eliminating or decreasing the frequency of the range of motion or activity that is aggravating the inflammatory condition. Nonsteroidal antiinflammatory medications and ice are indicated early in the course. These should be followed by ultrasound of the capsule, capsular stretching, strengthening of the rotator cuff and shoulder girdle musculature, restoration of normal movement, and gradual return to activity. If treatment fails, rotator cuff tear should be ruled out.

Acromioclavicular Dislocation. Acromioclavicular dislocation occurs when a high-velocity, high-force injury occurs to the tip of the shoulder (31). The acromion is forced downward, injuring the bridging ligaments between the acromion and the clavicle and between the clavicle and the coracoid process (Fig. 31-11). If only the acromioclavicular ligament is torn, an incomplete separation exists. The acromioclavicular ligament is tender to palpation, but no significant deformity is present. When both the acromioclavicular and the coracoclavicular ligaments have been torn, a complete acromioclavicular dislocation occurs and the untethered clavicle protrudes upward, giving the classic deformity of this injury. Both ligaments are tender on palpation. The patient has pain with attempted movement of the arm and chooses to support the arm. Initial treatment is with ice and analgesics. Oral narcotic medications frequently are needed, as well as support of the upper extremity in a sling for 7 to 10 days. If the clavicle has torn through overlying soft tissues it should be treated with open reduction and internal fixation.

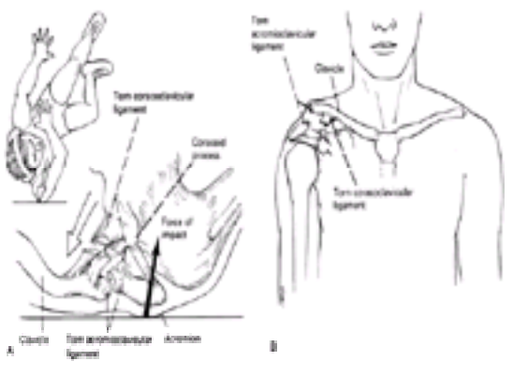

Figure 31-11. Acromioclavicular dislocation. **A:** A fall on the top of the shoulder forces the acromion downward, putting great tension on the ligaments joining the acromion to the clavicle and the clavicle to the coracoid process. The resulting tear of these ligaments produces an acromioclavicular separation or dislocation. **B:** When both the acromioclavicular and the coracoclavicular ligaments have torn, a complete acromioclavicular dislocation occurs, and the untethered clavicle rides up, giving a squared-off appearance to the shoulder.

Ankle Sprain

The most frequent form of ankle sprain is one of an inversion mechanism (32). The patient usually says that he or she rolled over the lateral side of the foot and had sudden onset of pain in the lateral anterior ankle. Swelling can be quite profound. The injured ligaments are tender to palpation. Most often the greatest tenderness starts at the anterolateral ankle. Usually the most severely injured ligament is the anterior talofibular ligament. Ecchymosis develops around the malleolus. On stress testing there may be some increased anterior subluxation of the talus or sideways shifting of the talus in the mortise. Radiography is useful to rule out bony injury.

Initial treatment is with a compressive and supportive dressing. Multiple types include elastic wraps, air orthoses, plastic and foam orthoses, and simple plaster splints. Usually reduction in weight bearing, elevation, and ice are adequate for pain management. In some cases acetaminophen, nonsteroidal antiinflammatory

medications, or mild narcotic analgesia are indicated. Clinical judgment determines the length of immobilization indicated, depending on the severity of the sprain.

Blood flow decreases proportionately as temperature decreases to a tissue temperature of 25°C. Therefore, the deeper the tissue injury, the longer the period of icing should be, as it takes longer to get cooling in the deeper tissues. Ice, ice chips, bags of frozen vegetables, ice baths, and whirlpools provide better cooling in terms of decreased intramuscular temperatures than products such as frozen gel packs, chemical ice, and freon-injected bladders (33). Studies have shown both physiologically and functionally the benefits of cryotherapy. Not only is there decreased inflammation and better pain management, but also the period of disability is substantially reduced with early cryotherapy after soft tissue injury (34,35). Cryotherapy is an effective form of analgesia and, in fact, anesthesia, but declines rapidly after removal of the modality (36). In many cases early mobilization can be initiated. This is best done in hot and cold bath contrast therapy. Immobilization may be indicated for up to 3 to 6 weeks. Surgical reconstruction is seldom required.

Metatarsal Stress Fracture

The most frequent stress fracture of the foot is to the second metatarsal (Fig. 31-12). Typically there has been a rapid increase in the patient's activity level, a change in footwear, or a change in activity surface before the onset of symptoms. A short first metatarsal is also a risk factor for this stress fracture. The patient complains of a dull ache in the foot that is present and worsens with activity. The site of the fracture is tender to palpation. Radiography may be unremarkable early on. Three to 4 weeks from onset of the symptoms a stress line may become visible and fracture callus may be present. Technetium dyphosphinate bone scans are more sensitive than radiography and may be helpful in the early diagnosis of stress fractures. Analgesia with nonsteroidal antiinflammatory drugs or acetaminophen may be indicated. Management of this injury is focused on the reduction or elimination of aggravating activities. It is infrequent that the patient needs to be made non–weight bearing. When the tenderness disappears, the patient can gradually return to previous activities.

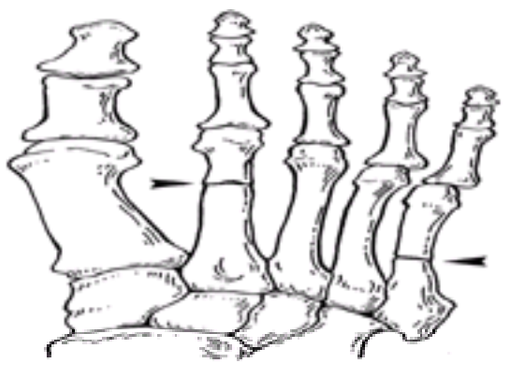

Figure 31-12. Metatarsal stress fracture. Second and fifth metatarsal stress fractures (*arrowheads*). High volume of repetitive stress results in weakening of the bone trabeculi; without adequate rest to remodel, a microfracture or stress fracture results.

Tibial Fracture

A tibial fracture frequently occurs when a sudden deceleration occurs across the midtibia, such as in athletic events when a player with his or her foot firmly planted on the ground falls into the leg of a competitor, or in the case of a skier in which the anterior aspect of the ski boot acts as a restraint against the distal to midtibia and the long lever arm of the ski produces sufficient force to fracture the tibia (Fig. 31-13). Examination shows the patient to have well-localized severe pain, inability to bear weight on the limb, and tenderness at the site with swelling. Deformity may or may not be present. Radiography is used to determine the severity of the injury and the need for surgical treatment. Immobilization is usually with a circumferential cast. The limb should be elevated for 48 to 72 hours. The patient is made non–weight bearing. Narcotic oral analgesia is usually adequate. These fractures typically heal within 12 weeks.

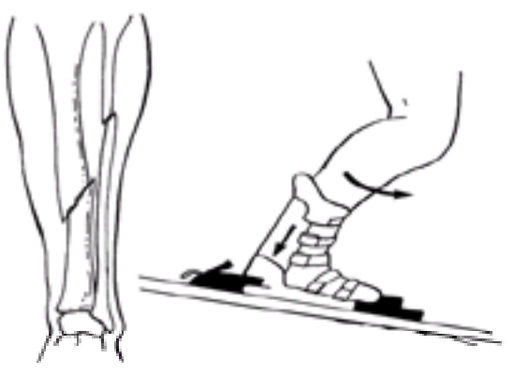

Figure 31-13. Rotational tibial fracture. Ski boot fracture of the tibia. Maximum force occurs as the tibia pivots across the superior margin of the ski boot (*arrows*), resulting in failure and fracture.

General Management Principles

A systematic approach can be developed for the management of an acute musculoskeletal pain problem. As discussed in the beginning of this chapter, musculoskeletal trauma and pain are associated with the stress response and release of stress hormones. The response results in breakdown of body tissue, increased metabolic rate, blood clotting, water retention, impaired immune function, increased sympathetic outflow, fight-or-flight response, and frequently an emotional change in the organism. Pain can be controlled peripherally by the elimination of the stimuli or by inhibition of chemical pain mediators including prostaglandins, a chief component of the inflammatory pathway, or more centrally by modulation of the analgesic pathways in the spinal cord and brain.

Tissue Level

At the tissue level the key to controlling pain is relieving abnormal forces on the injured tissues. With fractures and dislocations, reduction followed by a method of immobilization (sling, splint, cast, internal or external fixation) is indicated. With muscle, tendon, or ligament strains and sprains, a form of immobilization may be indicated as well. With all of these injuries it may be necessary to limit weight bearing through the extremity. The type of assistive device chosen depends on the severity of the injury; the patient's strength, balance, and neuromuscular coordination; and the patient's environmental needs.

Peripheral modification of pain can also be achieved by the use of locally injected anesthetic agents. Anesthetic agents are frequently required for the reduction of fractures and dislocations and provide the benefit of relaxing muscular activity including reflex spasm, blocking the reflex neuroendocrine and metabolic responses, and prompt pain relief. If the patient has severe pain lasting for days from extensive musculoskeletal injury that requires hospitalization, regional or local anesthetics may also be used for more prolonged pain management (see Chapter 102). In patients with rib fractures, local anesthetics may provide better pain relief than narcotics with no respiratory drive suppression, allowing better ventilation, oxygenation, and clearing of secretions (37).

The inflammatory response occurring at the site of the tissue injury is a primitive response, probably once necessary to fight contaminated wounds inflicted by a predator but now excessive in our world of modern medicine. Although the response is necessary for tissue healing, some modulation is appropriate to help minimize pain and minimize the excesses of this response, which can in fact slow tissue healing. Inflammation and edema increase nociception by the formation of chemical nociception stimulants and nociception sensitizers as well as increased tissue pressure. Edema interferes with tissue nutrition, oxygenation, and the cellular migration necessary for healing. Elevation and compression increase the hydrostatic gradient from the tissues to the lymphatic and venous circulation and help to prevent,

control, and dissipate edema.

Cryotherapy is also indicated in acute musculoskeletal trauma. Cold minimizes the inflammatory reaction to trauma, slows enzymatic activity, stimulates vasoconstriction and decreases blood flow (thus decreasing edema and hemorrhage), slows nerve conduction and nociceptive volleys, and decreases muscle spindle activity (inhibiting reflex muscle spasm) (38,39). The earlier the application of the cold, the better.

However, when bleeding and the acute phase of inflammation and edema production have passed, the benefits of ice decline. The vasoconstriction induced by ice may decrease the delivery of oxygen and nutrients to healing tissues. However, the analgesic and antispasm effect of ice without the potential toxicity of medications may warrant continued use of this modality. In acute injury ice should be used every 20 minutes for 20 to 30 minutes out of every hour for the first 4 hours, and then 20 to 30 minutes at least every 6 hours for 24 to 48 hours, depending on the severity of the injury. Rest, compression, and elevation are also part of therapy.

A risk exists of tissue damage with ice. Cloth can be placed on the skin before the application of ice. As well, petroleum jelly or a similar product can be placed on the skin for protection. Superficial nerves, such as the ulnar nerve as it crosses the elbow and the peroneal nerve as it crosses the fibular head, should be protected to prevent cold injury. Contraindications to the use of ice include Raynaud's disease, cold allergy, cryoglobulinemia, and paroxysmal cold hemoglobinuria. Relative contraindications are arterial insufficiency and impaired sensation.

After a musculoskeletal injury occurring in an athletic event, ice should be applied immediately for 10 to 20 minutes. Afterward the player may be reassessed for the ability to return to play. The evaluator needs to be aware that the cooling effect causes changes in the viscoelastic properties of the tissues, causing them to stiffen. As well, axonal cooling and slowing of nerve conduction velocity and potential blocking of nociceptive volleys may be beneficial for analgesia; but ice causes slowing of axons responsible for neuromuscular control and force production. Therefore, icing can lead to a decrease in performance and flexibility, potentially placing the athlete at risk for further injury (40).

The inflammatory response can also be controlled pharmacologically. The antiprostaglandins or nonsteroidal antiinflammatory drugs are the most commonly used drugs for the management of acute soft tissue injury.

The nonsteroidal antiinflammatory drugs not only have an antiinflammatory effect, but also have mild antipyretic and analgesic properties. In general, they are effective in the management of mild to moderate pain and can be used as adjuvant therapies for more severe pain. Nonsteroidal antiinflammatory drugs are discussed in Chapter 83. Current nonsteroidal antiinflammatory medications are known for causing gastrointestinal intolerance, gastrointestinal bleeding, and rarely bone marrow suppression. These medications are relatively nonspecific and inhibit the production of not only the prostaglandins that result in inflammation but also inhibit production of prostaglandins that appear to be more beneficial to overall homeostasis and health. The cyclooxygenase-2 inhibitors generation of nonsteroidal antiinflammatory drugs may minimize the unwanted effects of the nonsteroidal antiinflammatory drugs.

There have been numerous studies done to evaluate the efficacy of nonsteroidal antiinflammatory agents in reducing the severity and duration of pain as well as the disability after acute musculoskeletal injury. Efficacy has been mixed (41). If these medications are to be used, they should be used immediately, as antiprostaglandin pain relief is at maximum within the first 24 hours after injury (42). The use of these medications should be no longer than 5 to 7 days' duration. Beyond this point, their actions could be detrimental to the repair mechanism (43).

Corticosteroids are potent antiinflammatory medications. They are only briefly mentioned here, because they are not indicated in the management of acute musculoskeletal pain. However, they may be useful in the management of subacute musculoskeletal pain with a heavy inflammatory component, such as a bursitis or tendinitis. Side effects of the corticosteroids include induction of a catabolic state and reduction in the production of collagen and ground substance in connective tissues, thereby weakening the structures and potentially contributing to further tear, complete rupture, or tissue degeneration (44). Corticosteroid injections need to be used judiciously and may be ill-advised in and around major weight-bearing structures, as they lead to the decrease in synthesis of the matrix of articular cartilage and may result in destructive changes in the articular cartilaginous surface (45). The ability of corticosteroids to retard fibroblastic activity may also delay healing.

Corticosteroids should not be used as a sole form of treatment for these painful conditions. The biomechanical abnormality or irritant must be addressed before or in parallel with the use of a corticosteroid. Oral corticosteroid with tapering dose can also be used. Methylprednisolone or a Medrol Dosepak taper begins at 24 mg per day, tapering down to 4 mg over 6 days. A disadvantage of oral corticosteroids is systemic distribution of the corticosteroid and lower dosing delivered to the inflamed tissue. An advantage is a noninvasive method of administration. Adverse effects of injected corticosteroids include subcutaneous atrophy, depigmentation, and telangiectasias.

Opioids probably also work at the level of local tissue damage. There are opioid receptors on the peripheral nerve terminals, and stimulation of these results in inhibition of substance P release (46). Opioids also work both peripherally, at the level of the cord, and at the supraspinal level (47). Opioids are discussed in detail in Chapter 84. Tramadol (Ultram) has been demonstrated to be effective in the management of acute pain (48). However, in one study of postoperative orthopedic patients, tramadol was found no better than placebo (49).

Other muscle relaxant medications such as carisoprodol (Soma), hydroxyzine (Vistaril), metaxalone (Skelaxin), methocarbamol (Robaxin), and orphenadrine (Norflex) do not appear to act at the level of the spinal cord but more centrally and primarily work as sedatives, possibly depressing polysynaptic spinal reflexes (50). Carisoprodol (Soma) is a precursor of meprobamate and there is a risk of the development of dependency and substance abuse (51). This drug should be used with caution on a time-limited basis. Hydroxyzine is also thought to potentiate the effects of narcotic analgesia. Dantrolene sodium (Dantrium) is used in the management of spasticity, but is not indicated for use in reflex spasm associated with musculoskeletal injury. Dantrium probably interferes with the release of calcium from the sarcoplasm reticulum, thus decreasing the contractile response of skeletal muscle at the level of the muscle itself.

Tizanidine (Zanaflex) is an a_2-adrenergic agonist being used for treatment of spasticity. The effects of tizanidine appear to be on the polysynaptic reflex pathways; therefore, there may be a role for this medication in the management of muscle spasm and acute musculoskeletal injury. Hypotension and hepatotoxicity are the major concerns with this medication.

Other Treatments for Acute Musculoskeletal Pain

Acupuncture is widely used in musculoskeletal pain management (see Chapter 97). The mechanism of effectiveness of acupuncture is not known. However, reports exist of increased levels of endogenous opioids and other possible antinociceptive effects after treatment with acupuncture. Alternative medicine proponents have found acupuncture to be helpful in the management of acute pain, although controlled studies are sparse.

Ultrasound is capable of decreasing swelling by producing heat in the tissues, resulting in hyperemia and increased capillary permeability and promoting the absorption of inflammatory exudates (52). Ultrasound is contraindicated in the presence of growing bone and healing fractures, prosthetic implants, tumor, and viscous spaces. It should not be used in the first 48 hours after injury.

Transcutaneous electrical nerve stimulation has been shown to be effective postoperatively in decreasing immobilization time, decreasing dosages of narcotics, and decreasing hospital stay (53,54). Transcutaneous electrical nerve stimulation units have been proposed to provide analgesia by either stimulating light touch and proprioceptive axons and blocking or gating sensation at the spinal level, or increasing endorphins in the body.

Biofeedback, relaxation, and imagery can also be helpful in the management of muscle tension and anxiety (55,56). At the physiologic level, emotional arousal is accompanied by sympathetic excitation and increased muscle tone. This can establish a vicious cycle with increasing activation of the stress response and persistence or growth of the pain response. Benson first described the relaxation response, the antagonist of the fight-or-flight or stress response, in the 1970s (57). Focused attention, breathing, relaxation, repetitive motion, and visualization techniques are the cornerstones of this type of treatment (see Chapter 89, Chapter 90, Chapter 91 and Chapter 92).

Education of the patient also helps with acute pain management. Studies have shown that patients provided with information related to physiologic coping (i.e., instruction in coughing, deep breathing, and training in ambulation) reported less pain, required fewer medications, and had shorter lengths of stay (58,59 and 60). Also, patients provided with education on procedures and expected sensations complain of less pain and use less analgesic medication (61).

Other Sequelae of Trauma

Spasm

Spasm is defined as an involuntary and abnormal muscle contraction. It therefore encompasses multiple different subtypes of involuntary muscle activity. After acute musculoskeletal injury, the most common type of involuntary muscle activity found is spasm from segmental reflex activity resulting in increased muscle contraction in an effort to splint and protect injured tissues.

This activity needs to be differentiated from spasm caused by spasticity. *Spasticity* is defined as the presence of uncontrolled or disinhibited spinal and brainstem reflexes with hyperactive tendon jerks, clonus, increased muscle tone, and involuntary movements. Spasticity has been differentiated into gamma spasticity and alpha spasticity. The gamma motor neurons innervate small muscle fibers within the muscle spindles and set the sensitivity of the muscle spindles to stretch. Loss of gamma motor inhibition causes increased spindle sensitivity, resulting in increased activity of the stretch reflex. Afferent input traveling along the 1-A afferents synapse with the alpha motor neurons, resulting in muscle contraction.

Alpha spasticity is from long loop, multisegmental reflex activity. These loops lie within the brainstem and the spinal cord. Spasticity is an indication of an upper motor neuron lesion and must not be confused with muscle spasm from local tissue injury. In acute musculoskeletal injury the identification of hyperreflexia is a worrisome sign and an upper motor neuron lesion must be investigated and appropriately treated.

Treatment of spasticity includes range of motion and stretch, which results in a reduction in stretch reflex hyperactivity, and cryotherapy, which results in cooling of the muscle spindle as well as blocking or slowing of nerve conductions and dampening of the stretch reflex. Because this requires deep tissue heating, the ice must be left on for 20 to 30 minutes to see a significant effect. Warming the tissues is also effective. Increasing the temperature of the muscle spindles also decreases their activity and results in decreased reflex muscle spasm (62).

Medications such as baclofen and diazepam (GABA neurotransmitterlike medications), dantrolene sodium (which blocks calcium ion release from the sarcoplasm reticulum of the muscle fibers, thus inhibiting contraction), and tizanidine and clonidine (centrally acting a_2-agonists) are helpful in the management of spasticity.

Spasms from segmental reflex activity can be treated with principles similar to those applied to spasticity from upper motor neuron injury, as the final pathway is the segmental reflex arc. The benzodiazepines and Baclofen have an inhibitory effect at the level of the spinal cord, thus dampening this reflex activity. Sedation is the major side effect of concern. Dantrium works systemically throughout the muscle to decrease excitation contraction coupling muscle contraction and spasm. Hepatotoxicity is the major concern with this medication. Tizanidine and clonidine, with their a_2-agonist activity, probably enhance presynaptic inhibition or modulate polysynaptic reflex circuits. It seems that these medications would be less helpful in the management of peripheral injury and segmental muscle spasm. However, they may be able to decrease the segmental reflex activity through their action on descending supraspinal pathways. Hypotension is the greatest side effect with these medications. Tizanidine also has a history of inducing reversible elevation in liver enzymes. Epidural morphine and fentanyl have been effective in the management of muscle spasm but are not recommended as first-line interventions (63).

As in the spasms of spasticity, heat and cold therapy are efficacious for treating spasm from musculoskeletal injury. Ice is most effective and is recommended during the first 72 hours postinjury. Ice can be used after this 72-hour window; however, heat is preferred, as it helps to promote healing of the injured tissues.

Cramping is another form of involuntary muscle contraction. The precise etiology for muscle cramps is not known. Theoretic causes include electrolyte or mineral depletion, ischemia, acidosis, and fatigue with associated inability to completely relax a muscle. Near maximal or maximal contraction of a muscle while in a shortened position also induces a cramp (64). Treatment of cramps is with rest; restoration of normal fluid, electrolyte, and pH balance; stretching and avoiding placing the muscle in a shortened position; and ice. In cramping and spasticity, stretching is indicated. However, in acute musculoskeletal trauma, stretching for relief of spasm is contraindicated, as it may increase tissue damage. Immobilization of the injured tissues, joint, or limb with various wraps, orthotics, or simply bed rest may decrease segmental nociceptive input and reflex muscle spasm. Immobilization of the muscle in a shortened position should be avoided.

Unfortunately, muscle spasm appears to have at times a cyclical and self-propagating pattern. As muscles fatigue, they show a concomitant decreased ability to relax completely. Tonic muscle contraction can also lead to a degree of ischemia in the active muscle. Associated with this fatigue and ischemia are chemical and metabolic changes within the muscle. These changes result in muscle pain. Precisely what is responsible for this muscle pain is not clear. There are theories that the pain is due to one of the metabolic by- products or transfer of one of these by-products across the muscle cell membrane into the tissue fluid where it stimulates nociception. This was proposed by Lewis and described as factor P, also known as the substance P of Lewis (65). Psychological stress may also result in an increase in muscle pain and spasm, particularly along the axial skeleton. Biofeedback, relaxation, transcutaneous electrical nerve stimulation unit, anxiolytics, counseling, and education may be beneficial for these patients. In any case, early intervention in the treatment of spasm is prudent to prevent the sequelae of propagating the causes of local tissue pain and psychological stress response resulting in an exacerbation of pain and delayed healing.

Insomnia

Insomnia needs to be well managed. Lack of restorative sleep can lead to central nervous system neurochemical imbalance, increased nociceptor transmission, anxiety, and depression. In a patient who complains of acute insomnia, it is important to evaluate whether pain and anxiety management is adequate. For patients who have difficulty falling asleep, a short-acting sedative hypnotic such as triazolam, prazolam (Halcion), temazepam (Restoril), and zolpidem (Ambien), or an antihistamine such as diphenhydramine (Benadryl) or hydroxyzine (Vistaril) may be beneficial. For patients who have difficulty maintaining sleep, one needs to review that the patient has adequate pain management through the night. A long-acting narcotic or continuous infusion may allow the patient to sleep through the night. The tricylic antidepressant agents are also helpful for patients who have difficulty sleeping through the night.

Psychological Sequelae

After trauma it is important not only to assess the patient's level of nociception and pain but also the patient's emotional status and level of anxiety. It is critical that early management of both pain and anxiety is adequate. Ongoing assessment of pain and anxiety is imperative. Adequate control may necessitate the use of a combination of medications such as narcotics and benzodiazepines. Assessment can be facilitated by self-reporting pain and anxiety scales such as the Visual Analog scales. The emotional response to trauma can vary widely from patient to patient, and what would appear to be a relatively minor trauma may have a deep emotional significance with exaggerated stress response and suffering in some patients. It is essential to control all suffering associated with musculoskeletal trauma. It is important to remember that pain is dynamic. Studies have demonstrated long-lasting changes in cells within the spinal cord pathways after painful stimulus. It seems logical that such changes may also occur at supraspinal levels.

As well, it is important to remember that established pain is more difficult to suppress. Early intervention with medication, relaxation, and patient education can be the key to a successful outcome in preventing long-term morbidity and chronic pain conditions. Severe accidental injuries including musculoskeletal trauma can produce long-term psychological effects in the form of posttraumatic stress disorders (*Diagnostic and Statistical Manual*, third edition, of the American Psychiatric Association: 309.81). Muse has described a stress-related chronic pain syndrome (66). These patients are faced with not only functional restrictions but chronic pain and terrifying phobic reactions. When psychological conditions appear poorly controlled in both acute and chronic pain conditions, expert consultation should be sought expeditiously. Denying or ignoring the affective dimensions of acute pain and its concomitant stress is not acceptable in modern pain management.

CONCLUSIONS

Acute musculoskeletal pain is a complex, multisystem response involving the inflammatory and immunologic, neuroendocrinologic, and neuropsychological systems, as well as the stress response. The management of acute musculoskeletal pain must take an equally broad multisystem approach for optimal management and outcome. When developing the treatment plan for the management of acute pain, one needs to look both at the severity of the local tissue injury and the patient's psychological response to injury. The prudent physician looks at the appropriate level of intervention (i.e., local tissue, spinal cord, or supraspinal levels), modalities, and medications that best fit the needs of the patient and ensure an optimal outcome.

Options for acute musculoskeletal pain management include ice, intermittent or continuous local neural blockade, spinal analgesia via epidural opioid or anesthetic,

patient-controlled analgesia (usually with intravenous opioid), systemic administration of medications (including nonsteroidal antiinflammatory drugs, opioid agonists, serotonin, and norepinephrine reuptake inhibitors, GABA medications, and sedative hypnotics), and cognitive and behavioral interventions including biofeedback, relaxation, distraction, and imagery. In general, mild to moderate musculoskeletal pain can be managed with acetaminophen or a nonsteroidal antiinflammatory agent. Moderate to severe pain may require opioid therapy. Nonsteroidal agents and acetaminophen can have significant opioid dose–sparing effects and are useful in reducing the opioid side effects including sedation, respiratory depression, orthostasis, and bowel and bladder dysfunction. When additional symptoms are identified, such as muscle spasm, anxiety, and insomnia, additional medications may be indicated. To accurately determine a patient's pain management needs, it is important to consider the entire person's response to injury and to develop a holistic treatment plan that directly addresses the physical and psychological issues related to the patient's injury.

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CHAPTER 32

Pain of Dermatologic Disorders

Joseph C. Langlois and John E. Olerud

Pain is not as distinctive a feature of dermatologic disorders as is the related disorder of pruritus, which is beyond the scope of this discussion. It is well known that pruritus appears to be so intolerable that the act of scratching inflicts a transient pain with attendant structural damage to the skin. It is generally considered that the induced pain is subjectively more tolerable than the itching. Nonetheless, pain is a distinctive feature of certain dermatologic disorders and merits attention simply because of the great prevalence of skin disorders. Dermatologic disease of sufficient significance that it should be seen by a physician is present in 30% of the population in the United States. Half of all problems related to skin present to primary care physicians other than dermatologists. Of the 12 most common disorders of skin disease, only herpes simplex is attended by pain symptoms. Herpes simplex has a prevalence rate of 4.2 to 1,000 in the United States (1). The effects of pain on the patient are best demonstrated by the impact of the persisting pain that sometimes follows herpes zoster, postherpetic neuralgia, which occasionally leads to suicide. This disease is discussed in Chapter 22, but this chapter focuses attention not only on the impact of pain but also on the need for appropriate recognition of the antecedent viral disease and on the value of immediate and appropriate treatment.

The diseases discussed in this chapter can be grouped into the categories of vasculitis, infections of viral and bacterial origin, inflammatory diseases of the subcutaneous space, and neoplasms. Some neoplasms, although benign, are specifically painful based on their neurovascular components. We discuss the causes and pathogenesis of the selected pain-related skin diseases, paying attention to symptoms and signs, methods of diagnosis, and preferred methods of treatment. For more comprehensive discussions of the individual diseases, refer to selected general textbooks of skin disease (2,3,4 and 5). Because of space limitations, vasculitides and tumors are described in Table 32-1 and Table 32-2.

TABLE 32-1. Characteristics of cutaneous vasculitides

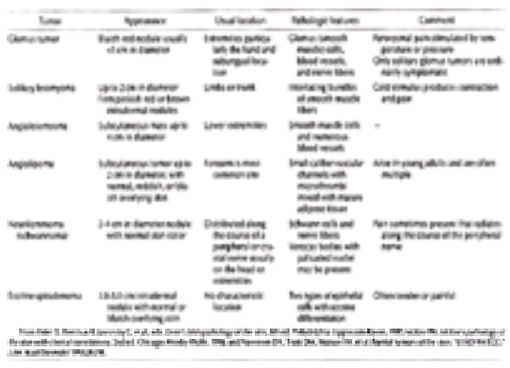

TABLE 32-2. Characteristics of benign painful cutaneous neoplasms

BASIC CONSIDERATIONS: ANATOMY AND PHYSIOLOGY OF THE SKIN

Human skin is a vast, sheetlike interface for the organism with its environment. It is adapted to the dryness of the atmosphere, resisting mechanical shearing and puncturing forces as well as the invasion of chemical and infective agents. This organ, which in aggregate covers an area of more than 2 m^2, has a mass greater than that of any other organ. It contains an extensive vascular and sweat gland system, essential for thermal regulation, and an even more extensive and finely attuned neuroreceptor network, including the varied transducers of pain and other sensations (Fig. 32-1).

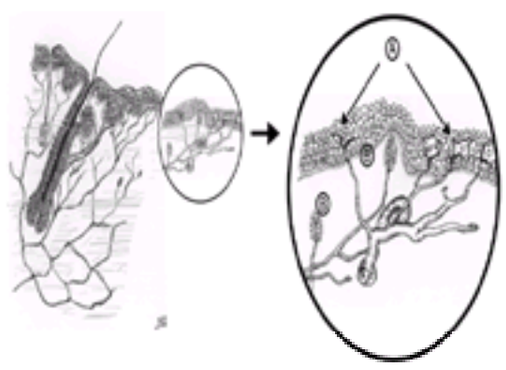

Figure 32-1. Schematic representations of sensory nerve formations (SNFs) for the cutaneous sensory nervous system. The SNFs depicted are the free nerve endings in the epidermis (*A*) and mechanosensors (*B*) in the dermis. Although nociception in the skin is mainly a function of free nerve endings composed of unmyelinated C fibers, more specialized SNFs for mechano- (baro-, preso-, osmo-) sensors, thermosensors, electrosensors, chemosensors, and nociosensors are also present. (Modified from Malinovsky L. Sensory nerve formations in the skin and their classification. *Microsc Res Tech* 1996;34:283–301.)

The skin is covered by a thin, stratified epithelium, the epidermis, which is only 75 to 100 micrometers thick except on the palms and soles, where it is four to five times thicker. The bulk of the skin is fibroelastic dense connective tissue known as the *dermis*, which supports the extensive network of vessels and nerves as well as the specialized glandular structure of the sweat apparatus and keratinizing appendages, such as hair and nail. The subcutaneous space is a variably fatty connective tissue perforated by collagenous septa, continuous on the outermost aspects with the fibers of the dermis and continuous beneath the skin with fascial or periosteal attachments to the skeleton.

It is generally believed that the peripheral pain receptors are the finely arborized (penicillate) free nerve endings that ramify in the superficial aspects of the dermis. This network of fine C fibers has been shown to innervate the epidermis as well (see Fig. 32-1) (6,7 and 8) and has been referred to as the *cutaneous sensory nervous system* (9). These fibers convey information from the skin to the central nervous system and thus have a sensory role. They also have an effector function in the skin, mediated by locally releasing neuropeptides. Sensory neurons express at least 17 different neuropeptides, including substance P and calcitonin generelated peptide (10). The cutaneous sensory nervous system appears to play an important role in the “communication” between the nervous system and the immune system, the vascular system, and the cells of the epidermis. Neuropeptides appear to participate in vital functions such as neuroinflammation and tissue repair (8,11). They have important biological effects on a variety of cells in the skin, including keratinocytes, endothelial cells, fibroblasts, Langerhans cells, mast cells, macrophages, and smooth muscle cells (9). It is easy to imagine how these effector functions may participate in the perpetuation of chronic skin conditions characterized by pain or itch.

The diagnosis of skin disease depends less on deductive logic than on direct observation. One should distinguish localized nodules resulting from small tumors of the skin from the large plaquelike swellings associated with acute edema and redness that mark inflammatory processes, and umbilicated small vesicles occurring in clusters on inflammatory bases that are characteristic of the herpetic viral infections. Subtle or marked defects in the integrity of the protective epidermal sheet should be noted, as manifested by denuded sites of bullae (erosions). Also to be noted are deeper defects in the integrity of the protective barrier that involve loss of the epidermis as well as of some dermis, leading to ulcer formation. Such lesions are inevitably attended by pain, unless associated with a neuropathy, that can best be explained by exposure of free nerve endings.

CLINICAL CONSIDERATIONS

Vasculitis

Characteristics of vasculitis are compared in Table 32-1.

Leukocytoclastic Vasculitis

Leukocytoclastic vasculitis is a common form of vasculitis affecting postcapillary venules (12,13,14 and 15). The clinical hallmarks of leukocytoclastic vasculitis are palpable purpuric lesions occurring in dependent areas such as the lower extremities in ambulatory patients or sacral area in bedridden patients. Other clinical lesions include purpuric macules, nodules, and bullous and ulcerative lesions. Less commonly, one may see urticaria, angioedema, pustules, vesicles, and livedo reticularis. Smaller lesions may be asymptomatic. Pruritus and burning may occur. Larger papules, nodules, or ulcerative lesions are frequently painful. The pain may be very debilitating in patients with chronic vasculitis.

Etiology and Pathophysiology

Leukocytoclastic vasculitis has a number of causes, including infectious agents (e.g., *Streptococcus*; tuberculosis; hepatitis A, B, and C; influenza), drugs (e.g., aspirin, phenacetin, sulfonamides, penicillin, iodides, phenothiazines), chemicals (e.g., insecticides, weed killers, petroleum products, fumes from heat-activated photocopy paper), foreign proteins (e.g., serum sickness, hyposensitization antigen), autoimmune disease (e.g., systemic lupus erythematosus, Sjögren's, ulcerative colitis, hemolytic anemia), and malignancies [e.g., Hodgkin's disease, acute and chronic leukemias, mycosis fungoides, immunoglobulin (Ig) A myeloma and carcinomas]. Leukocytoclastic vasculitis may also occur as a manifestation of C2 deficiency.

Evidence supports the concept that leukocytoclastic vasculitis is mediated by immune complexes being circulated in slight antigen excess and deposited in vessel walls, which leads to activation of the classic complement cascade, release of chemoattractants, infiltration of polymorphonuclear cells, and destruction of vessel walls by lysosomal enzymes. Lymphocytes and mast cells are also reported to play a role. Most recently, adhesion molecule expression and endothelial cell activation have been found to be involved in the pathogenesis (14). Direct immunofluorescence is typically positive for immunoglobulins and complement if the lesion is less than 24 hours old (preferably less than 4 hours).

Histologically there is infiltration of the vessel wall with polymorphonuclear cells, nuclear dust (leukocytoclasis), thickened vessel walls, fibrinoid necrosis, and hemorrhage. Extracutaneous involvement can occur with leukocytoclastic vasculitis, particularly in the kidney, but the joints, gastrointestinal tract, and pulmonary and nervous systems can be involved.

Variants of leukocytoclastic vasculitis include Henoch-Schönlein purpura, urticarial vasculitis, hypergammaglobulinemic purpura, and cryoglobulinemia. Hepatitis C has emerged as an important cause of cryoglobulinemic vasculitis (16). In addition, leukocytoclastic vasculitis can be a part of systemic lupus erythematosus and rheumatoid vasculitis.

Treatment

Suspected etiologic agents should be stopped and avoided in the future and infectious agents treated. Underlying diseases associated with antibody production should be treated and controlled. For some cases of leukocytoclastic vasculitis, no therapy is necessary. For mild cases, antihistamines or nonsteroidal antiinflammatory drugs can be used. Dapsone and colchicine sometimes are helpful. For severe cases involving other organs, cyclophosphamide and systemic prednisone should be considered. Pulse therapy for prednisone and cyclophosphamide has been reported to be successful, with fewer side effects for such inflammatory conditions. No good evidence exists that any form of therapy alters the course of the disease.

Polyarteritis Nodosa

Polyarteritis nodosa is an uncommon form of vasculitis affecting small- and medium-sized arteries. Two forms of cutaneous involvement can occur: benign cutaneous and systemic.

Symptoms and Signs

In benign cutaneous polyarteritis nodosa, tender nodules, livedo reticularis, and ulcers are characteristic. Systemic involvement rarely occurs (17).

In systemic polyarteritis nodosa, cutaneous involvement occurs in up to 50% of cases and consists of palpable purpura and ulcerations. Painful nodules occur only rarely. Small nodules might be palpable along the course of arteries. Histologically, both forms of polyarteritis nodosa show leukocytoclastic vasculitis in the small vessels of the skin. IgM, C3, and fibrin have been found in vessel walls on direct immunofluorescence, suggesting immune complex deposition in vessel walls. Hepatitis B infection, streptococcal infection, Crohn's disease, and relapsing polychondritis are reported associations.

Treatment

The benign cutaneous form of polyarteritis nodosa responds well to systemic steroids. Salicylates and other nonsteroidal antiinflammatory drugs can also be helpful in relieving pain. Sulfapyridine has been reported to induce remissions. Penicillin G is indicated in streptococcal-induced cases and prophylactic therapy may be needed. Low-dose methotrexate has also been reported to be effective (18).

Systemic polyarteritis nodosa is best treated with prednisone (1 mg per kg daily) plus cyclophosphamide (2 mg per kg daily) (19). Prednisone should be continued on a daily regimen for 1 month and then gradually converted to an alternate-day regimen, with the ultimate goal of discontinuation after approximately 6 months. Cyclophosphamide is then tapered if the disease is in remission, with the goal of ultimate discontinuation. Patients must be carefully monitored to keep the total leukocyte count above 3,000 per µL and the absolute neutrophil count at approximately 1,500 per µL. More recently, the use of monthly cyclophosphamide as a pulse dose has been shown to be effective (20). Patients who have hepatitis B–related polyarteritis nodosa respond to plasma exchange plus vidarabine or interferon-alpha-2b (21).

Wegener's Granulomatosis

Wegener's granulomatosis is an uncommon disease of unknown cause characterized by necrotizing vasculitis and granulomatous inflammation involving the upper and lower respiratory tracts, together with glomerulonephritis (22,23). It is thought to be the result of an allergic or hypersensitivity reaction to an as yet unknown antigen, with the tissue injury perhaps mediated by immune complexes. Approximately 90% of patients have antineutrophilic cytoplasmic antibodies (ANCA) usually of the cytoplasmic ANCA type (cANCA) directed at proteinase 3. Although this test may be useful diagnostically, it is uncertain whether this antibody plays a significant role in the pathogenesis of the disease.

Symptoms and Signs

In the limited form of Wegener's granulomatosis, renal involvement does not occur, but involvement of the joints and eyes may develop. Cutaneous lesions occur in approximately 45% of patients and include palpable purpura, papules, subcutaneous nodules, papulonecrotic lesions, nodules with ulceration, ulcers, vesicles, and pustules (23,24). Papules, nodules, and ulcerative lesions may be tender or painful. Most patients present with symptoms related to those of upper airway illness. Mucous membrane lesions are frequent and include oral ulcerations and friable gingival hyperplasia with petechiae. The latter is said to be pathognomonic of Wegener's granulomatosis (25). Saddle nose deformity may result from upper airway involvement. Histologically, there is necrotizing vasculitis involving small arteries and veins, necrotizing palisading granulomas, or granulomatous vasculitis.

Treatment

The treatment of choice for Wegener's granulomatosis is cyclophosphamide, 2 mg per kg daily, plus prednisone, 1 mg per kg daily. Patients with more severe disease may be given higher initial doses (22,23). The prednisone should be continued on a daily dosage for 2 to 4 weeks and then converted to an alternate-day regimen, 60 mg every other day, over 1 to 2 months. The patient is gradually tapered off the prednisone over a period of months until maintenance on cyclophosphamide alone is achieved. Cyclophosphamide is continued for 1 year after the patient is in remission and then tapered in 25-mg decrements every 2 to 3 months. If the patient is in remission and cannot tolerate further cyclophosphamide, an equal dose (in milligrams) of azathioprine can be substituted. Careful monitoring of leukocyte counts is essential to maintain the total leukocyte count above 3,000 to 3,500 per µL and the absolute neutrophil count above 1,000 to 1,500 per µL. Potential complications from cyclophosphamide include severe neutropenia, sepsis, hemorrhagic cystitis, hair loss, gonadal dysfunction, and neoplasia. The complications of prolonged corticosteroid use can also occur. Pulsed cyclophosphamide has been used in place of daily oral cyclophosphamide to lower the total dose and decrease complications but there is a higher frequency of relapses (26,27). Pulsed methotrexate has also been advocated in place of cyclophosphamide as a safer alternative (28). Trimethoprim-sulfamethoxazole has been used successfully for prevention of relapse in recent years (29).

Microscopic Polyangiitis

Microscopic polyangiitis is a systemic small-vessel vasculitis that affects the skin (40%) and typically is associated with necrotizing glomerulonephritis (90%) and pulmonary capillaritis (50%) (22,30). Histologically, a necrotizing vasculitis is seen that affects arterioles, capillaries, and venules, although small- and medium-sized arteries may be affected as well. Immune deposits are notably absent (pauciimmune) on direct immunofluorescence. More than 80% of patients have positive ANCA, usually of the perinuclear type (pANCA) directed at myeloperoxidase. Some patients have cANCA antibodies. It is unclear what role, if any, these antibodies play in the pathogenesis of the disease.

Microscopic polyangiitis has received more attention in the literature since it was newly redefined at the Chapel Hill Consensus Conference (31). Patients previously reported as having leukocytoclastic vasculitis or hypersensitivity vasculitis with systemic involvement were defined as having microscopic polyangiitis. As Braverman (32) points out in his discussion of this topic, the diagnosis of microscopic polyangiitis is based on the absence of immune deposits (pauciimmune) in the skin or visceral organs. Demonstration of the immune deposits can be difficult because they are greatly dependent on the age of the lesion. Whether microscopic polyangiitis proves to be a different disease with a different pathogenesis compared with hypersensitivity vasculitis and leukocytoclastic vasculitis remains to be seen.

Symptoms and Signs

The cutaneous lesions of microscopic polyangiitis are typical of those of a small-vessel vasculitis—that is, palpable purpura and ulcers, often painful.

Treatment

Serious internal organ involvement, such as pulmonary or renal disease, is treated aggressively with high-dose steroids and cyclophosphamide. Remission is achieved in 80% of patients.

Allergic Granulomatosis of Churg-Strauss

The rare syndrome allergic granulomatosis of Churg-Strauss is characterized by allergic rhinitis, asthma, eosinophilia, and systemic vasculitis. Other features include pulmonary infiltrates and cardiac involvement. In contrast to Wegener's granulomatosis, renal involvement is infrequent. Histologically, one sees a necrotizing vasculitis affecting small- to medium-sized vessels. Extravascular granulomas are the most common finding. Tissue infiltration with eosinophils is also a feature. Vascular immune deposits on direct immunofluorescence are typically absent. Approximately 70% of patients have positive ANCA, usually of the perinuclear type (pANCA), directed at myeloperoxidase (22,33,34).

Symptoms and Signs

Cutaneous lesions occur in approximately 70% of patients. Cutaneous nodules, usually tender, are the most frequent lesions and tend to occur on the scalp and extremities. Other types of cutaneous lesions include papules, vesicles, purpura or petechiae, infarctions, livedo reticularis, facial edema, urticaria, erythema, and ulcers. Pain can result from ischemia related to vasculitis or painful granulomas in the skin.

Treatment

The treatment of choice for allergic granulomatosis is systemic steroids, which has reduced the mortality rate from 100% to 38%. Prednisone in a dosage of 1 mg per kg daily is usually sufficient to control the disease. Occasionally 1.5 to 2.0 mg per kg daily might need to be used. Consideration should be given to adding cyclophosphamide, 2 mg per kg daily, for patients who do not respond to high-dose corticosteroids. Azathioprine, 1 to 2 mg per kg daily, can be useful for maintenance therapy in refractory disease (35). The number of patients treated to date with cytotoxic agents is too small to make any definitive conclusion about the cytotoxic agent of choice in patients refractory to corticosteroids. Cyclophosphamide might be preferable, based on successful experience with this agent in treating other serious forms of vasculitis, such as polyarteritis nodosa and Wegener's granulomatosis. Careful monitoring of these patients for complications of therapy is essential. Pulsed monthly cyclophosphamide was recommended by one study over daily oral cyclophosphamide to diminish adverse effects and lower the total amount of cyclophosphamide given (20).

Rheumatoid Vasculitis

Vasculitis associated with rheumatoid arthritis tends to occur in patients with more severe forms of arthritis. Vasculitis can affect vessels of varying size, including venules, capillaries, arterioles, and small- and medium-sized arteries.

Symptoms, Signs, and Pathophysiology

Clinically petechiae, palpable purpura, leg ulcerations, and nail fold, subungual, and digital infarcts are seen (36). These lesions can be painful on an ischemic basis. A variety of nonpainful skin manifestations of rheumatoid arthritis may be seen in these patients, including rheumatoid nodules, rheumatoid papules, rheumatoid neutrophilic dermatosis, and palmar erythema and livedo reticularis (37). Vasculitis can result in visceral infarction, coronary arteritis, cerebral vasculitis, and peripheral neuropathy. Mortality may be as high as 40%. Rarely, pyoderma gangrenosum and erythema elevatum diutinum have been reported with rheumatoid arthritis. Laboratory abnormalities with rheumatoid arthritis include positive rheumatoid factor, elevated sedimentation rate, leukocytosis, anemia, and hypergammaglobulinemia. High-titer IgG rheumatoid factor, anticomplementary activity, and low levels of complement, especially C4, are most indicative of rheumatoid vasculitis.

Treatment

Patients with rheumatoid vasculitis have been treated with various therapeutic agents. The only placebo-controlled study to date was conducted with azathioprine, in which no clinical benefit was demonstrated (38). Patients with asymptomatic cutaneous lesions of venulitis and no internal involvement may need no treatment.

Patients with severe disease may be treated with pulse cyclophosphamide every 2 weeks and steroids used only as supporting therapy (39). High-dose steroids combined with azathioprine are recommended by others (40). Patients must be monitored closely, particularly for severe neutropenia, sepsis, or both.

Livedoid Vasculitis

Livedoid vasculitis is an uncommon disease characterized by livedo reticularis and purpuric papules leading to exquisitely painful ulcerations on the lower extremities that heal with white atrophic scars referred to as *atrophy blanche* (41,42). Hyperpigmentation and telangiectasias are also characteristic. Some patients have associated disease such as systemic lupus erythematosus, polyarteritis nodosa, or Raynaud's phenomenon, but most do not. Other reported associations include hepatitis C infection, cryoglobulinemia, and gammopathies (42).

The histologic changes seen on biopsy have been referred to as a hyalinizing segmental vasculitis with endothelial proliferation, hyaline degeneration, and thrombosis of small vessels of the middle and lower levels of the dermis. Leukocytoclasis as seen in leukocytoclastic vasculitis is absent. Direct immunofluorescence commonly reveals fibrin, C3, and IgM in vessel walls, suggesting an immunologic basis for the disease.

Pathogenesis

Livedoid vasculitis has been referred to as livedoid vasculopathy rather than a vasculitis (43). The basis for this has been a number of observations suggesting an important role of the coagulation system. Patients have responded to fibrinolytic therapy, anticoagulants, antiplatelet drugs, pentoxifylline, and tissue plasminogen activator. Concentrations of fibrinopeptide A, a marker of thrombin generation, have been reported to be elevated in patients during exacerbations of their disease. Activated expression of platelet P-selectin and lymphocyte activation have been reported (44). A vasculopathy with hypercoagulable state and platelet activation may be the underlying pathogenic mechanism.

Treatment

Therapeutic agents of reported value for livedoid vasculitis include aspirin plus dipyridamole (46), phenformin plus ethylestrenol, nicotinamide, and low-dose heparin (47). Other reported treatments of benefit include tissue plasminogen activator, pentoxifylline (48), prostaglandin E1, ticlopidine (49), nifedipine, and low-dose danazol (45). Phenformin may be obtained through the Food and Drug Administration. Patients should avoid smoking. Antibiotics such as dicloxacillin or erythromycin for secondary infection, wet dressings (e.g., Burow's solution), and rest are important. Pain control is a significant problem and physical dependence on narcotics may occur. A methadone-containing pain cocktail can be helpful in selected cases.

OTHER VASCULAR DISORDERS

Antiphospholipid Syndrome

Antiphospholipid syndrome is characterized by a biologic false-positive test for syphilis; lupus anticoagulant or antiphospholipid antibodies associated with thrombosis of major arteries and veins, or both; fetal wastage in pregnant women; and sometimes thrombocytopenia (50,51,52 and 53). It may occur as an idiopathic disorder, associated with systemic lupus erythematosus, or as Sneddon's syndrome. The antiphospholipid antibodies are necessary but not sufficient for the syndrome because not all patients with antiphospholipid antibodies are symptomatic. Histologically one sees noninflammatory thrombosis of vessels in the skin. The pathogenesis of the disorder is poorly understood.

Symptoms and Signs

Patients suffer painful infarcts and ischemia from occlusion of major arteries and veins. Painful cutaneous lesions may occur as part of the syndrome, including painful skin ulcers (usually on the lower extremities), thrombophlebitis, cutaneous gangrene and necrosis (e.g., gangrene of digits or widespread cutaneous necrosis), painful

or tender skin nodules, livedoid vasculitis, and necrotizing vasculitis. Other cutaneous lesions include erythematous macules, purpura, ecchymosis, and subungual splinter hemorrhages. Livedo reticularis is the most common cutaneous manifestation of the syndrome. Sneddon's syndrome (livedo reticularis and recurrent strokes) may occur as part of the antiphospholipid syndrome but also may occur without antiphospholipid antibodies. Diagnosis requires correlation of clinical signs, with tests for antiphospholipid antibodies—enzyme-linked immunosorbent assay antiphospholipid antibody and lupus anticoagulant (partial thromboplastin time). Both tests should be ordered because individuals may have one test positive without the other being positive. Tests positive 6 to 8 weeks apart are useful in excluding transiently positive tests.

Treatment

Any associated risk factors for vascular events should be treated or eliminated, such as stopping smoking, treatment of hypertension or hyperlipidemia, and avoidance of oral contraceptives. Low-dose aspirin or low-dose heparin has been recommended for prevention of vascular events in patients who are at risk. Some patients have resistance to the usual doses of subcutaneous heparin (10,000 to 15,000 units daily) and may need higher doses of subcutaneous heparin (25,000 units daily) or intravenous heparin (40,000 units daily) to achieve the equivalent effect. In patients who have already had a vascular occlusive complication, warfarin is recommended. Low-dose warfarin plus low-dose aspirin has been recommended in patients with intracranial vascular thrombosis. Warfarin resistance may be encountered, and patients may need up to 20 mg per day. It is recommended that the international normalized ratio be maintained between 3 and 4 (54). Patients are maintained on anticoagulation for life.

Patients who have widespread vascular occlusive events or catastrophic antiphospholipid syndrome are candidates for treatment with immunosuppressive agents and immunotherapy with high-dose steroids, cyclophosphamide, plasmapheresis, and gammaglobulin therapy. There have been no prospective trials for any of the therapies for antiphospholipid syndrome.

Treatment of women to prevent fetal loss is indicated only in those women who have had a previous fetal loss. Depending on the level of risk, three regimens have been recommended—low-dose aspirin alone, aspirin plus prednisone, and a sequential regimen of aspirin followed by low-dose heparin and then a return to aspirin. If the patient is already taking warfarin for previous vascular occlusion, this should be changed to heparin (52,53).

Coumarin Necrosis

Coumarin necrosis is a rare reaction to coumarin congeners that typically occurs on the breast, thigh, abdomen, or buttocks of middle-aged and elderly obese women (55,56 and 57).

Pathophysiology

Histologically, one sees occlusion of vessels with fibrin thrombi and a paucity of inflammatory cells. Many patients are heterozygous for protein C deficiency (an autosomal dominant condition). Acquired protein C deficiency and an abnormally functioning protein C have also been reported. Protein C is a vitamin K–dependent factor, along with factors II, VII, IX, and X. Protein C acts as an inhibitor of coagulation through its inactivation of factors VIIIa and Va. Protein C and factor VII have relatively short half-lives compared with factors II, IX, and X. The relatively rapid fall in protein C levels with initiation of warfarin therapy leads to a transient hypercoagulable state.

Symptoms and Signs

Reaction occurs between the third and tenth days of therapy and is manifested by painful erythematous, indurated purpuric lesions that can progress to blistering, necrosis, and scarring. Pain is presumably present on an ischemic basis.

Treatment

Coumarin therapy should be discontinued. Patients are treated with heparin and vitamin K. Protein C concentrates may be helpful for the protein C deficiency. In patients who already have a history of warfarin-induced skin necrosis and need further anticoagulation, initiation of coumarin at low doses under the cover of full heparinization and administration of protein C has been suggested (57). Pentoxifylline, a tumor necrosis factor-alpha antagonist, was recommended after the study of one patient demonstrated upregulation of tumor necrosis factor-alpha on endothelial and infiltrating cells within an area of coumarin necrosis (58). The patient, however, did not receive the medication.

Calciphylaxis

Calciphylaxis is a rare, life-threatening disorder that causes painful ulcerations. It occurs most commonly in patients with chronic renal failure on dialysis with secondary hyperparathyroidism, although it has also been rarely reported in primary hyperparathyroidism and also in patients with normal parathyroid and calcium levels (59,60 and 61).

Pathophysiology

Based on an experimental model by Selye et al., calciphylaxis is believed to be a condition in which patients are “sensitized” by parathyroid hormone, and calcification subsequently occurs when patients are exposed to a “challenging” agent such as corticosteroids, albumin, and immunosuppressants (62,63). Most patients have secondary hyperparathyroidism with an elevated parathyroid hormone level and calcium X phosphate ion product of 70 or higher. Calcification occurs in small- and medium-sized arteries. The calcification can be seen on x-rays, which is helpful diagnostically. Histologically, one can see calcification of vessels and intimal proliferation. Intraluminal debris and fibrin thrombi are seen histologically and sometimes fat necrosis and a sparse lymphohistiocytic infiltrate are seen. Incisional biopsy is needed to obtain sufficient tissue for histologic examination.

Symptoms and Signs

Calciphylaxis begins as a painful mottling of the skin resembling livedo reticularis that evolves to ulceration and necrosis. It occurs most commonly on the distal extremities and lower legs, but it is also often seen on the pannus, thighs, and other areas of excess subcutaneous fat. Gangrene and amputation of digits may occur. Sepsis and amputation are serious complications that can occur and account for the high mortality of the disease.

Treatment

Lowering the calcium X phosphate product is initially indicated. This can be done with phosphate binders and low phosphate diet. Vitamin D_3 [1,25-(OH) 2-vitamin D_3] may be helpful in treating the secondary hyperparathyroidism, although vitamin D has also been reported to be a “sensitizer.”

Hyperparathyroidism is treated with parathyroidectomy (64). Often, one parathyroid gland is transplanted to the forearm and removed later only if necessary. Results are better if surgery is done early. Corticosteroids, immunosuppressants and other “challenging” agents should be avoided if possible.

Supportive care, wound care, and antibiotics for secondary infection are important as well. Amputation may be needed in some instances.

ULCERS

Ischemic Ulcers

Ischemic ulcers are painful ulcerations most commonly caused by arteriosclerosis and located on the distal lower extremities at sites of trauma and pressure, particularly on the toes, over bony prominences, the pretibial area, or the lateral malleolus (65,66). Atrophy of the skin and absence of hair may be associated skin findings. The pain is typically relieved by dependency and aggravated by elevation of the extremity. Ischemic ulcers may be preceded by intermittent claudication with

exercise. If the occlusion is severe patients may have rest pain.

In most instances, the pathology of the condition is an atherosclerotic plaque affecting large- and medium-sized vessels. Histologically, one sees accumulation of lipids, smooth muscle proliferation, collagen deposition, ulceration of the endothelial surface, and thrombosis of the surface. Diabetics may have small-vessel disease complicating their large-vessel disease. Diabetic peripheral neuropathy may diminish the pain and contribute to further injury by inadvertent trauma. Ischemic neuritis may occur as a complication as well. The differential diagnosis includes cholesterol and other arterial emboli, thromboangiitis obliterans (Buerger's disease), trauma to arteries, neurovascular compression, arteriovenous malformation, and hypertensive ischemic ulcer.

Evaluation of the patient should include examination of all pulses and auscultation for bruits. A Doppler flowmeter may be helpful in detecting pulses. Measurement of the ratio of systolic blood pressure in the ankle compared with the arm [ankle brachial index (ABI)] using a Doppler device is a sensitive indicator of disease. The ABI is normally greater than one. An ABI ratio of less than 0.5 indicates severe ischemia. The ABI may be falsely elevated in patients with noncompressible vessels because of significant calcification (e.g., seen in diabetes). The ABI ratio can also be measured after exercise and tends to fall immediately after exercise with occlusive disease. Arteriography is important if surgery is contemplated.

Treatment

General supportive measures include cessation of smoking, treatment of hyperlipidemia, control of blood pressure, and proper foot care to prevent trauma. Elevation of the extremity and compression stockings should be avoided. Patients with claudication benefit from exercise to promote collateral circulation. Sheepskins and foot cradles are helpful in local care to relieve pressure. Bypass surgery or transluminal dilation of arteries may be indicated in individual cases when conservative measures fail. Laser angioplasty, atherectomy, and stent placements are other nonoperative interventions that may be used besides percutaneous transluminal angioplasty.

Stasis Ulcers

Stasis ulcers are painful ulcerations that are usually located on the medial malleoli in patients with chronic venous insufficiency (67,68). Other clinical features include varicosities, hyperpigmentation secondary to hemosiderin deposition in tissues, induration of tissue secondary to fibrosis, and pitting edema. Complicating dermatitis can occur as a result of stasis or sensitization to topically applied medications, especially neomycin. Chronic venous insufficiency can arise from a familial tendency, on an idiopathic basis, or because of single or multiple bouts of thrombophlebitis, leading to destruction and incompetence of venous valves (postphlebitic limb). Obesity and medical conditions causing peripheral edema such as pulmonary, cardiac, renal, and liver disease may also be contributory. Pain and ulceration are presumably on an ischemic basis because of increased venous pressure, with resultant diminished capillary flow.

Treatment

Management should emphasize elevation of legs, when possible, to decrease hydrostatic pressure; wearing of support stockings; or optimal compression wraps. Measures to treat the ulcerations include wet dressings, synthetic dressings (e.g., hydrocolloids, hydrogels, calcium alginates, biological dressings), Unna boots, and antibiotics for secondary infection. Dermatitis related to stasis or sensitization to topical medication responds to topical steroids as well as to avoidance of the sensitizing agents. Weight reduction and diuretics may be helpful in individual cases. Stasis ulcers sometimes require skin grafting.

PAINFUL INFECTIONS

Many skin infections are painful; some are so rare that they are not covered in this chapter. Some of the more common painful infections of the skin are discussed.

Herpes Zoster

Herpes zoster is a painful eruption of varicella zoster virus in a dermatomal distribution (69). It is presented in detail in Chapter 22.

Symptoms and Signs

A prodrome of paresthesias, pain, or both in the involved dermatome is often experienced 1 to 2 days before onset of the skin eruption. Some patients may have pain without an eruption (zoster sine herpete). The individual lesions are clear vesicles on an erythematous base that are clustered within the involved dermatome. The vesicles become cloudy and often hemorrhagic over 3 to 4 days and then become dry and crusted. Healing takes place in 2 to 4 weeks.

Diagnosis

When necessary, the diagnosis can be confirmed by culture, although culture of this virus is somewhat difficult. At many centers, direct immunofluorescence on cells from the culture swab is used to rapidly identify herpes zoster. Pain usually subsides with healing of the lesions. Some patients, especially the elderly, have persistent pain in the involved dermatome. The pain is confined to the involved dermatome and is sharp, often burning, and ranges in intensity from mild to excruciating. Postherpetic neuralgia is discussed in Chapter 22.

Treatment

Local treatment of herpes zoster includes evaporative wet-to-wet Burow's compresses, as well as oral aspirin (0.6 g four times a day), with or without narcotic analgesics, depending on the severity of symptoms. In patients older than age 60 years or in those who are immunoincompetent, systemic corticosteroids and antiviral therapy are indicated. A course of famciclovir, 500 mg PO three times daily (70), with or without prednisone, 40 to 60 mg PO daily for 14 to 21 days, should be started within the first 3 days of the eruption. Chapter 22 is devoted to the description of herpes zoster and postherpetic neuralgia (71).

Herpes Simplex

Herpes simplex infection of the skin is often a painful eruption of clustered vesicular lesions on an erythematous base that may be preceded by burning or tingling 1 to 2 days before onset of the eruption (72,73 and 74).

Symptoms and Signs

The vesicles of herpes simplex can be mildly painful and are often described as sore when touched. The pain is rarely as severe or protracted as that experienced in herpes zoster infections and neither the vesicles nor the pain is in a dermatomal distribution. With primary infections, fever, malaise, and tender lymphadenopathy can also be present. The virus lies latent in sensory nerve ganglia and can periodically reactivate to produce recurrent episodes of herpes simplex infection, which tend to be milder and briefer than the primary infection. Herpes labialis and genital herpes infections are the most common clinical forms of the disease. Other clinical variants include gingivostomatitis, keratoconjunctivitis, herpetic whitlow, eczema herpeticum, and recurrent lumbosacral herpes simplex. Recurrent episodes of erythema multiforme can be triggered by recurrent episodes of herpes simplex. Immunosuppressed patients, such as those with human immunodeficiency virus, may have more frequent and severe infections that are slow in healing. Large, deep, painful ulcerations may develop and last for months if not treated.

Diagnosis

Finding multinucleated giant cells on a Tzanck preparation can permit a presumptive diagnosis of herpes simplex, although herpes zoster gives a similar positive result. Culturing the virus, which grows out readily within 72 hours, establishes a definitive diagnosis. Identification of herpes simplex virus (HSV) antigens or HSV-DNA in skin scrapings is a more rapid method of diagnosis.

Treatment

Treatment of herpes simplex infection includes wet compresses with Burow's solution and analgesics for pain if needed. Occasionally, herpes simplex infection is

complicated by bacterial infection with *Staphylococcus aureus* or group A streptococcus, and an antibacterial agent such as dicloxacillin or cephalexin is indicated.

Antiviral therapy with acyclovir (ACV) is effective for treatment and suppression of the virus, although it does not eliminate latent virus. First episodes of genital or oral-labial herpes simplex infection may be treated with oral ACV, 200 mg five times per day. Intravenous ACV (5 mg per kg every 8 hours for 5 days) is used for patients with severe disease or neurologic complications. Recurrent genital herpes is treated with ACV, 200 mg five times per day for 5 days. Suppression of recurrent disease is managed with ACV, 200 mg two to three times a day. Immunosuppressed patients may need intravenous ACV (5 mg per kg every 8 hours) for treatment of first or recurrent episodes as well as for suppression during high-risk periods. Patients with ACV-resistant HSV may be treated with intravenous foscarnet (40 mg per kg IV every 8 or 12 hours). Valacyclovir and famciclovir are alternative oral agents for HSV that have the advantage of less frequent oral dosing compared with ACV.

Erysipelas and Cellulitis

Erysipelas is a type of superficial skin infection caused by streptococcus pyogenes; it has a characteristic clinical appearance. Group A streptococci may also cause cellulitis (75). In erysipelas and cellulitis, the organism usually gains access by direct transcutaneous inoculation. Infection spreads within the superficial dermis as bacterial enzymes lyse mature proteoglycans.

Erysipelas usually appears on acral skin in adults as one or more painful, bright red, hot, edematous plaques within the skin that advance peripherally and are distinguishable by their sharply demarcated palpable edges. Lesions are painful and attended by high fever, malaise, and headache. Diagnosis depends on the recognition of this complex composed of sharply marginated painful red plaques with attendant systemic signs. Cellulitis is commonly a streptococcal infection of the skin and the subcutaneous tissue as well, with more marked and less clearly marginated redness than erysipelas. It is usually attended by fever. It is difficult to recover the organism for culture and recognition of the clinical syndrome.

Group A streptococcus is typically sensitive to and responds to treatment with oral penicillin VK (250 to 500 mg four times a day) for 10 days. However, it is often not possible to distinguish clinically cellulitis from *S. aureus* with certainty before culture results are known. For this reason, it is prudent to treat these patients with antibiotics effective for both group A streptococcus and *S. aureus*, such as dicloxacillin, 250 to 500 mg four times a day, or cephalexin, 250 to 500 mg four times a day, for 10 days or more depending on the clinical response. More seriously ill patients may need to be hospitalized and treated with intravenous antibiotics. Serious cutaneous infections with a similar clinical presentation have been reported with group B streptococcus, particularly in patients with diabetes (76).

Furunculosis and Carbuncle

Furuncles and carbuncles are painful staphylococcal abscesses of one or more hair follicles in any hair-bearing area of skin. The furuncle may commence as a superficial follicular centered pustule. The process extends down the hair follicle to produce a painful, red, swollen lesion surrounding a deeper abscess and surmounted by a central pustule. A carbuncle results from the dissection of a furuncle in the subcutaneous space to adjacent follicles and the ultimate development of abscesses in a number of adjacent follicles, leading to a more edematous, larger, much more painful, red lesion surmounted by numerous follicular pustules. Cultures should be made of the superficial pustules to determine the antibiotic sensitivities of the staphylococcal agent (77).

Deep abscesses should be surgically incised and drained, as well as cultured. Treatment should be given with an antibiotic effective for penicillin-resistant *S. aureus* such as dicloxacillin or cephalexin, 250 to 500 mg four times a day for 7 to 10 days. Patients with methicillin-resistant *S. aureus* may need intravenous vancomycin, 2.0 g per day in divided doses and adjusted for renal function. In patients with recurrent furunculosis, measures to reduce nasal carriage of *S. aureus* may be helpful. These include local application of mupirocin ointment and a combination of oral rifampin, 600 mg per day for 10 days, plus dicloxacillin, 250 to 500 mg four times a day for 10 days.

Erysipeloid

Erysipeloid is an acute infection with *Erysipelothrix rhusiopathiae*, the causal agent of swine erysipelas. It occurs most commonly as an occupational disease of butchers, fish handlers, and crab fisherman but may also occur in the domestic setting with handling of fish, poultry, and meat products.

The clinical lesion occurs after a prick or scratch when handling meats or fish and results in a hot, painful, swollen, violaceous red edema of the skin that spreads peripherally with central clearing of the rash. There is no scaling or desquamation. It may resemble erysipelas but constitutional symptoms are usually absent.

Erysipeloid responds to penicillin in doses of 2 to 3 million units daily, orally or intramuscularly, for 7 to 10 days. Higher doses are recommended if there is systemic involvement (78).

INFLAMMATIONS

Panniculitis

Erythema Nodosum

Erythema nodosum is a fairly common painful symptom complex characterized by erythematous, tender, slightly raised nodules typically located on the anterior tibial surfaces and sometimes associated with mild, constitutional symptoms of fever, malaise, myalgias, and arthralgias (79). The individual lesions can last for a few weeks, but new lesions can continue to appear.

The causes of erythema nodosum include infections (bacterial, viral, fungal, and protozoan), medications, malignant diseases, and a variety of other causes. Among the more common causes and causes important to keep in mind are streptococcal infections, tuberculosis, systemic fungal infections (e.g., coccidiomycosis, histoplasmosis, blastomycosis), drugs (e.g., sulfonamides, oral contraceptives, aspirin, iodides), sarcoidosis, and inflammatory bowel disease.

The pathogenesis of erythema nodosum is not understood but probably involves hypersensitive immunologic mechanisms. Histologically, an inflammatory process involves the septa between fat lobules.

Management includes treating any underlying disease as well as stopping any potential medications that might be the cause for erythema nodosum. Patients often respond to conservative measures, such as bed rest and salicylates (aspirin, 600 mg every 4 hours). It should be kept in mind that salicylates could also cause erythema nodosum. Iodides (potassium iodide, 300 to 900 mg daily) are also sometimes effective, as are short courses of systemic steroids.

Weber-Christian Disease

Weber-Christian disease typically occurs in middle-aged women and is characterized by recurrent episodes of fever in association with tender, at times aching, painful nodules on the trunk and extremities, particularly the thighs (80,81 and 82). The nodules may be erythematous, sometimes heal with atrophy, and, rarely, break down and discharge oily material. Visceral involvement can occur with involvement of omentum, bone, and joints. Histologically, the diagnosis depends on finding lipid-laden histiocytes or foam cells with lobular panniculitis. Weber-Christian disease bears similarities to cytophagic histiocytic panniculitis and some early reported cases of Weber-Christian disease were cases of alpha $_1$-antitrypsin deficiency. It remains a useful clinicopathologic diagnosis until methods that are more definitive are available to subdivide the panniculitides further.

Patients have been reported to respond to tetracycline, sulfapyridine, dapsone, antimalarials, corticosteroids, cyclophosphamide, and thalidomide. The more benign forms of therapy should be tried first, although corticosteroids are the most predictably effective. Antimalarials or corticosteroids appeared to be the most effective in studies by Panush and colleagues (82).

Dercum's Disease

Also known as *adiposis dolorosa*, Dercum's disease is a rare condition. It occurs most frequently in obese menopausal women and is characterized by painful, diffuse,

or nodular deposits of fat, most commonly on the trunk, arms, and periarticular soft tissue (83).

Histologically, the fatty deposits usually resemble those of ordinary lipomas. Angiolipomas, often painful tumors (Table 32-2), and granulomatous changes are reported (84).

Excision of individual tumors can sometimes be helpful, along with analgesics and weight reduction. Intravenous lidocaine has been reported to be of value.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic, painful, suppurative inflammatory disease of the apocrine glands in the axillae, genitocrural areas, and mammary region (85).

Etiology

The cause of hidradenitis suppurativa is thought to be occlusion of the apocrine duct, leading to an inflammatory foreign body-type reaction, leading to recurrent mixed secondary bacterial infection.

Symptoms and Signs

Hidradenitis suppurativa begins as one or more firm, subcutaneous nodules coalescing in weeks to become deep, painful abscesses surmounted by plaques of redness and heat. The deep abscesses dissect, with scarring and suppuration to adjacent follicles and apocrine glands, ultimately forming sinus tracts. The disease process waxes and wanes for years, causing scarring and gradually extending to involve larger and larger areas of skin in the regions noted.

Diagnosis

The important distinction of hidradenitis suppurativa from ordinary furuncles in the axillae or groin comes with the recognition of the chronic course, the formation of sinuses, and particularly the retracted scars and chronic intermittent suppuration.

Treatment

Oral antibiotics are often helpful in either short courses or long-term maintenance therapy if needed. Tetracycline in doses of 250 to 500 mg four times a day is usually prescribed. Equivalent full doses of erythromycin, cephalexin, and minocycline may be helpful. Individual lesions respond to intralesional steroids in concentrations of 2.5 to 5.0 mg per mL of triamcinolone acetonide solution. Short courses of systemic steroids (prednisone, 40 to 60 mg per day) for 1 to 2 weeks are useful if lesions are widespread and numerous.

Topical antibiotics and weight reduction, if needed, are helpful. Excision of the area with primary closure, a rotation flap, or grafting is the most definitive treatment available. Liposuction in early disease to remove the underlying apocrine glands and hair follicles has been reported to be helpful. This should be done before severe scarring has occurred.

Inflamed Epidermal Cyst

Epidermal cysts are very common, and most are asymptomatic. When traumatized or manipulated, the contents of the cyst may extrude into the surrounding dermis and incite an intense foreign body reaction. This produces a painful, warm, erythematous, and edematous lesion. Treatment consists of hot compresses, incision, and drainage, as well as antibiotics if secondary infection is suspected. When the inflammation subsides, the cyst is excised.

Bullous Dermatoses with Erosions

Pemphigus Vulgaris

Pemphigus refers to a rare group of blistering skin diseases that are painful when blisters rupture, leaving raw, denuded surfaces. Pemphigus vulgaris is the most common type (86). Other variants include pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus, and paraneoplastic pemphigus.

Pemphigus vulgaris typically begins with oral blisters that easily rupture and leave constantly painful oral erosions that, when extensive, preclude eating and swallowing. The disease inevitably progresses to involve the skin with flaccid blisters that easily rupture, leaving raw denuded surfaces. The scalp, chest, and intertriginous areas are commonly affected. Untreated, the disease progressively involves larger surfaces of the body and may be fatal. Histologically, the blistering is seen to occur in the lower part of the epidermis through a process known as *acantholysis*. Almost all patients with pemphigus vulgaris have deposits of IgG in the perilesional skin in the intercellular area of the epidermis, detected by direct immunofluorescence. Approximately 75% of patients have circulating antibodies to desmoplakin or desmoglein on indirect immunofluorescence.

Pemphigus vulgaris is an autoimmune disease mediated by antibodies directed against desmoplakin and desmoglein in the desmosome. The pemphigus vulgaris antigen is a member of the family of adhesion molecules called *cadherins* (calcium-dependent adhesion molecules). A 130-kd glycoprotein is complexed to an 85-kd plakoglobin. The gene for the 130-kd pemphigus antigen has been cloned.

Paraneoplastic pemphigus is a variant of pemphigus associated with benign and malignant tumors. It is characterized by painful oral erosions and a polymorphous, blistering skin eruption that can leave painful raw denuded surfaces. Histologically, one sees acantholysis as in pemphigus vulgaris but also necrotic keratinocytes and interface dermatitis. Direct immunofluorescence demonstrates intercellular IgG and complement and often linear or granular deposition along the basement membrane. The circulating autoantibodies recognize a high-molecular-weight complex of polypeptides: 250, 230, 210, 190, and 170 kd. These have been characterized as desmoplakin I (250 kd), bullous pemphigoid antigen (230 kd), desmoplakin II (210 kd), and not fully characterized 190- and 170-kd polypeptides. The associated tumors are usually malignant and typically one of the following: non- Hodgkin's lymphoma (42%), chronic lymphocytic leukemia (29%), Castleman's tumor (10%), thymoma (6%), spindle cell neoplasms (6%), or Waldenström's macroglobulinemia (6%) (87,88).

Treatment of pemphigus vulgaris is primarily high-dose corticosteroids (80 to 120 mg daily of prednisone), or pulse doses of prednisone are used initially to bring the disease under control. Later, steroid-sparing agents, such as azathioprine, methotrexate, cyclophosphamide, or gold, are added to enable tapering of the corticosteroids. Cyclosporine A has had limited effectiveness. The mortality rate remains at approximately 5%, related primarily to complications of treatment.

In paraneoplastic pemphigus, search for the underlying tumor is essential. Treatment of paraneoplastic pemphigus is most straightforward if the tumor is benign. Excision of the tumor usually results in resolution or marked improvement in the rash. If the patient has an underlying malignancy, the paraneoplastic pemphigus is often refractory to treatment, especially the stomatitis, and it does not parallel the activity of the underlying malignancy. A subset of patients has responded to a combination of prednisone (1 to 2 mg per kg per day) and cyclosporine (5 mg per kg per day).

Bullous Pemphigoid

Bullous pemphigoid is an uncommon subepidermal blistering disease that usually affects elderly patients (89). Pruritus is sometimes present. When blisters rupture, they leave raw, painful surfaces that can be exquisitely sensitive for several days until healed. Lesions typically occur on the thighs, abdomen, forearms, and axillae. Oral lesions occur in approximately one-third of cases.

The blister occurs between the epidermis and dermis, producing tense bullae as opposed to the flaccid bullae and early erosions of pemphigus vulgaris. Although the condition tends to be chronic with exacerbations and remissions, the disease is self-limited, and with treatment, the overall prognosis is good.

Deposits of IgG, C3, or both are found on direct immunofluorescence at the basement membrane zone of the epidermis in almost all patients. Approximately two-thirds of patients have circulating antibodies to the basement membrane zone on indirect immunofluorescence. Bullous pemphigoid is an autoimmune disease

with autoantibodies directed against the bullous pemphigoid antigen. The bullous pemphigoid antigen is associated with the lamina lucida portion of the basement membrane zone and the hemidesmosomes. The antigen has two components: a 230-kd polypeptide reactive with most patients' sera and a 180-kd polypeptide reactive with a smaller percentage of patients' sera.

Potent topical steroids such as fluocinonide 0.05% cream or clobetasol 0.05% cream and wet dressings are usually sufficient for limited disease. Systemic steroids, such as prednisone in daily dosages of 60 to 80 mg, are indicated for widespread disease. Tapering the prednisone and using steroid-sparing agents such as azathioprine, methotrexate, or cyclophosphamide are recommended if difficulty is encountered. In those patients who receive azathioprine, measurement of thiopurine methyltransferase has been recommended to provide a guideline in dosing because thiopurine methyltransferase metabolizes the drug (90). Dapsone is helpful in approximately 15% of cases, especially in cases with a neutrophil-rich infiltrate histologically. Erythromycin alone or tetracycline (500 mg four times a day) plus niacinamide (1.5 to 2.5 g per day) have been effective in some patients and may be particularly helpful in patients unable to tolerate systemic steroids.

Epidermolysis Bullosa

Epidermolysis bullosa refers to a group of uncommon diseases in which minor trauma results in detachment of the epidermis from the dermis, causing painful blistering of the skin. Hereditary and acquired forms exist that are both scarring and nonscarring (91,92). Mucous membranes and skin can be involved. Milia formation and dystrophic nails are helpful clinical clues that indicate the scarring type.

Blisters lie within or beneath the epidermis, depending on the type of epidermolysis bullosa. Little, if any, inflammatory infiltrate is usually present, but dense infiltrates may be seen in the acquired form of the disease. Electron microscopy and immunohistochemical mapping with antibodies to type VII collagen, laminin, or bullous pemphigoid antibodies are often necessary in classifying the hereditary forms of the disease. Immunofluorescence on 1 molar sodium chloride (1 M NaCl) split skin is needed to confirm the diagnosis of acquired epidermolysis bullosa. Acquired epidermolysis bullosa has been reported in association with various systemic diseases, including diabetes mellitus, inflammatory bowel disease, systemic lupus erythematosus, lung carcinoma, chronic lymphocytic leukemia, multiple myeloma, and amyloidosis. In acquired epidermolysis bullosa, search for an underlying systemic illness is indicated.

Pathogenesis. Molecular biological techniques have been extremely helpful in understanding the specific gene defects that occur in the hereditary forms of the disease. Point mutations in keratin genes have been found in epidermolysis bullosa simplex and the type VII collagen gene in recessive dystrophic epidermolysis bullosa (88). Molecular biological and monoclonal antibody techniques suggest mutations in the anchoring filament–associated proteins in junctional epidermolysis bullosa. Acquired epidermolysis bullosa is an immune-mediated subepidermal bullous disease with autoantibodies to type VII collagen. Four different regions within the noncollagenous portion of amino-terminus of the alpha chain of type VII collagen have been found to be antigenic sites.

Treatment. Measures should be taken to avoid trauma, friction, and heat to skin and mucous membranes. Nutritional support and topical antibiotics and dressings are useful. Skin grafts may be needed in some instances. Esophageal dilation and surgical correction of scarring may also be needed at times. Acquired epidermolysis bullosa is treated with prednisone (1 to 2 mg per kg). Dapsone, colchicine, and plasmapheresis have been reported to be helpful. Cyclosporine in doses of 6 mg per kg may also be helpful.

Cutaneous Endometriosis

In cutaneous endometriosis, endometrial tissue deposits in skin are often tender and painful, especially at the time of menstruation (93). The lesion is usually solitary, varying from 0.5 to 6.0 cm in diameter, and appears usually as a brownish or bluish nodule. This rare condition most often arises in surgical scars, such as those from cesarean sections or episiotomies. The disease can also arise spontaneously, especially in the umbilicus. Treatment is either with hormones (estrogen, progesterone, or androgen) or excision.

DISORDERS OF CONNECTIVE TISSUE STRUCTURE (CARTILAGE DISORDERS)

Relapsing Polychondritis

Relapsing polychondritis is a systemic inflammatory disease characterized by inflammation and often pain in cartilaginous structures (94). The cause of the disease is unknown. An autoimmune basis is suggested by a variety of autoimmune phenomena associated with the disorder.

Recurrent bouts of pain, erythema, and edema of the external ears are the most constant features of the disease. The earlobes are spared. The ears ultimately may become “cauliflower” or “floppy” in appearance due to loss of cartilaginous support. Painful skin lesions (palpable purpura) related to a systemic vasculitis may also occur. Other reported cutaneous manifestations include urticaria, angioedema, livedo reticularis, panniculitis, erythema multiforme and erythema nodosumlike lesions. The other major features of the disease include nasal involvement with saddle nose deformity, ocular involvement (scleritis, episcleritis, and uveitis), oligo- or polyarthritis, vestibular damage, respiratory tract involvement, and involvement of cardiac valves and the aorta. Serious complications may occur from respiratory tract involvement producing respiratory obstruction. Cardiac involvement leads to valvular dysfunction; aortic aneurysms may also occur.

Detection of autoantibodies to type II collagen, circulating immune complexes, deposition of immunoglobulins, and complement at the chondrofibrous junction support an autoimmune pathogenesis. The association with other preceding or coexistent autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Behçet's disease has been reported.

Milder features of the disease may be controlled with nonsteroidal antiinflammatory drugs and dapsone. Dapsone is typically started at a dosage of 50 mg per day and increased if needed, with careful monitoring for side effects. Hemolysis occurs in a dose- dependent fashion. Systemic steroids are needed for any serious internal organ involvement. Immunosuppressive agents such as azathioprine and cyclophosphamide may be needed in some instances. Methotrexate was found to be the most effective immunosuppressive agent in one reported series of patients (95). Anti-CO_4 monoclonal antibody as well as oral minocycline have also been reported to be effective.

Chondrodermatitis Nodularis Chronica Helicis

Chondrodermatitis nodularis chronica helicis is a chronic, painful condition of the ear characterized by 2 to 4 mm of erythematous, very tender papules on the rim of the outer helix of the external ear. The lesions often have a slight scale, crust, or erosion (96). Although there is no tendency to malignant change, squamous cell cancer and basal cell cancer are in the differential diagnosis, and biopsy may be needed to exclude these possibilities.

Histologically, one sees degenerative changes in the dermis and cartilage; chronic inflammatory changes at the periphery and epidermal ulceration with an edematous and thickened epidermis are observed. Vascular insufficiency may be the underlying cause, whether induced by trauma, pressure, cold, or chronic actinic damage (97).

Treatment with intralesional steroids (0.1 mL of triamcinolone, 2.5 mg per mL) may be helpful, but repeated injections at monthly intervals may be needed. Excision of the entire lesion is also helpful. A pillow with a hole in it for the ear is commercially available and helps some patients by relieving pressure on the lesion.

NEUROVASCULAR CUTANEOUS DISEASE

Sensory Mononeuropathies

A variety of sensory mononeuropathies affect the skin (98). They may involve cranial nerves, the extremities, or the trunk (see Chapter 19). Patients may experience numbness, burning, tingling, pruritus, or other paresthesias in the distribution of the affected nerve. Most commonly this is related to trauma or mechanical irritation of the affected nerve, but diabetes, vasculitis, and benign and malignant tumors are in the differential diagnosis. Electrodiagnostic studies can be confirmatory. Among the more common sensory neuropathies are meralgia paresthetica (lateral femoral cutaneous nerve), cheiralgia paresthetica (superficial branch of the radial nerve), gonyalgia paresthetica (infrapatellar branch of saphenous nerve), digitalgia paresthetica (digital nerve), notalgia paresthetica (posterior rami to T-2 to T-6), intercostal neuropathy, and mental nerve neuropathy. The mental nerve neuropathy with numbness on the side of the chin is the most ominous because it is more likely to be associated with malignancy than the extremity lesions. The malignancy may be a solid tumor or reticuloendothelial malignancy and usually is proximal to the mental

foramen. Thorough evaluation is indicated (see Chapter 47).

Notalgia paresthetica is the variant most commonly seen by dermatologists, probably because pruritus is the predominant symptom; however, tingling, pain, and other paresthesias may be present. It has been postulated that spinal nerves emerging at right angles through the multifidus spinae muscles are subjected to trauma or entrapment. A hereditary form has been reported and also association with multiple endocrine neoplasia type 2a (99).

Clinically, one sees a hyperpigmented patch in the affected area. Histologically, there may be hyperpigmentation of the basal layer, melanophages, and macular amyloidosis. These changes are believed to be secondary to scratching.

Treatment usually consists of topical and intralesional steroids, which afford only partial relief. Treatment with a topical local anesthetic lidocaine/prilocaine or topical capsaicin may be helpful for some patients. A paravertebral nerve block with bupivacaine plus methylprednisolone was helpful for one patient (100) and an epidural steroid injection (101) was helpful for another.

Fabry's Disease

Fabry's disease is a rare X-linked genodermatosis with deficiency of the enzyme alpha-galactosidase A, which produces accumulation of neutral glycosphingolipids in tissues. These glycosphingolipids accumulate in vascular endothelium, resulting in vascular occlusion, ischemia, and pain (102,103 and 104).

Symptoms and Signs

The characteristic cutaneous lesions of Fabry's are dark reddish macules and papules (angiokeratomas) that are 3 to 4 mm in diameter. They may or may not have epidermal changes with hyperkeratosis and scaling. They occur most commonly between the umbilicus and the knees but may be widespread, sparing only the face, scalp, and ears. They typically occur between 7 and 13 years of age and are nonpainful. Hypohidrosis and peripheral edema are other cutaneous features of the disease.

A painful and incapacitating peripheral neuropathy occurs in Fabry's disease (see Chapter 19). The pain typically occurs in crises affecting the fingers and toes and occasionally radiating proximally. Attacks of abdominal and flank pain may occur, simulating an acute abdomen and renal stones. The attacks of pain may last from minutes to several days and be associated with low-grade fever and elevated erythrocyte sedimentation rate. The attacks may be brought on by exertion, fatigue, fever, heat, and cold. Between attacks, patients may be left with burning, tingling paresthesias in the hands and feet.

Characteristic eye findings include corneal opacities, tortuous conjunctival and retinal vessels, and a unique posterior capsular cataract termed the *Fabry cataract*.

The cardiac, renal, and central nervous system manifestations account for the major morbidity and mortality of the disease, with death usually by age 41 before hemodialysis and renal transplantation became available. Other manifestations include bronchitis, arthropathy, diarrhea, and hypogonadism.

The glycosphingolipid is demonstrable in the skin with Sudan black-B and periodic acid-Schiff stains and appears under the electron microscope as inclusions with a concentric, lamellar, and myelinlike appearance. The glycolipid is demonstrable in cells in the urine as birefringent inclusions, with the appearance of a Maltese cross under polarized light. The diagnosis is biochemically confirmed by finding deficient alpha-galactosidase activity in plasma or serum, leukocytes, tears, biopsied tissues, or cultured skin fibroblasts. Alternatively, trihexosyl ceramide levels can be demonstrated to be increased in urinary sediment, plasma, or cultured skin fibroblasts.

The differential diagnosis of Fabry's disease includes other unusual lysosomal storage diseases in which angiokeratomas have been reported. These include fucosidosis, aspartylglycosaminuria, adult-onset GM1-gangliosidosis, sialidosis, galactosialidosis, alpha- *N*-acetylgalactosaminidase deficiency, and Schindler's disease (infantile and adult forms). There have been a few cases in which diffuse angiokeratomas similar to Fabry's have occurred with no detectable underlying enzyme abnormality and no detectable cellular inclusions on electron microscopy.

Treatment

Treatment consists of supportive therapy for renal and cardiac disease. Paresthesias may respond to conventional doses of anticonvulsant medications (see Chapter 86). The role of organ transplantation and administration of alpha-galactosidase A in restoring normal enzyme levels is being explored. Genetic counseling is also indicated.

NEOPLASMS

A number of benign cutaneous neoplasms of the skin have pain as a characteristic feature, which may be a helpful clue as to their diagnosis at the time of their initial presentation. The diagnosis may be suspected beforehand but needs to be confirmed histologically. Because the lesions are symptomatic, most patients will want the entire lesion excised, which is usually curative. Table 32-2 lists characteristic features of these tumors. Other benign or malignant tumors of the skin may on occasion be painful, especially if ulcerated, if expanding in closed spaces, or if occurring on weight-bearing surfaces.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contributions of Dr. George F. Odland to this chapter. He was the original primary author, and many of his touches and words remain part of the fabric of the chapter.

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CHAPTER 33

Pain Due to Vascular Disease

Kaj H. Johansen

Pain is a common and, frequently, diagnostic feature of many vascular diseases (1). Although the precise etiology of these diseases is multifactorial, it is probable that pain caused primarily by vascular disease may afflict up to 10% of all Americans at some time. This group includes patients with coronary artery disease, aortic disease, disease of the major vessels to the viscera and to the head and neck, and disease of the vessels to the limbs (see Chapter 61 for additional information on coronary and aortic disease).

This chapter contains a general discussion of most important vascular diseases that produce pain. Because the management of vascular disease is a vast subject, the focus is on the mechanisms and pathophysiology of vascular pain and its control. Because pain of cardiac and aortic origin is discussed in Chapter 61 and pain associated with other visceral vascular disease is considered in various chapters of Part IV, this chapter is devoted to peripheral vascular disease (PVD). The material is presented in three major sections: (a) basic considerations, including a brief review of the anatomy and nerve supply of the peripheral vessels, the general characteristics of pain and its mechanisms and other symptomatology of vascular diseases, and diagnosis of these disorders; (b) diseases of the arteries; and (c) diseases of the veins and the lymphatic system. Detailed discussion of all aspects of vascular disease can be found in comprehensive textbooks on this subject (2,3,4 and 5).

BASIC CONSIDERATIONS

Anatomic Aspects

In discussing vascular disease, some authorities classify the vessels as follows: (a) large arteries, restricted to the aorta and to the major arteries of the thorax, abdomen, and neck; (b) medium-sized arteries (i.e., those with proper names that arise as the first branches of the large arteries or are located outside of the thorax or abdomen); (c) “small arteries” (those unnamed vessels of macroscopic size that are branches of the medium-sized arteries); and (d) the microcirculation, used for the array of vessels from the level of arterioles to and including the venules (6). On the venous side of the circulation, there are large veins, again within the confines of the thorax, chest, and neck. Other veins are classified as deep or superficial, depending on whether they are inside or outside of the fascial envelopes that encase the deeper structures of the extremities and neck. The extensive intercommunications between the superficial and deep venous systems, which are functionally very important, are called the *perforating veins*.

The innervation of these blood vessels includes afferent (sensory) fibers, some of which transmit nociceptive impulses and are components of spinal nerves for the body below the head and of cranial nerves in the head. These fibers have their cell bodies in sensory ganglia; their proximal axonal branches that contact the second-order neurons are in the neuraxis, and their distal axonal branches are part of the somatic nerves that supply these structures. The efferent fibers are sympathetic nerves with a predominance of vasoconstrictors, but also some vasodilator fibers and fibers that supply sweat glands and erector pili muscles. The origin, course, and distribution of these nerves to the blood vessels of the upper limb are discussed in detail in Chapter 54 and depicted in Figure 54-22; those that supply the lower limb are considered in Chapter 75. The sensory and sympathetic supply to the aorta and the large arteries and veins in the thoracic and abdominal cavity is discussed in Chapter 60 and Chapter 65, and the nerve supply to the vessels of the head is discussed in Chapter 46.

Mechanisms of Pain of Vascular Disease

Pain resulting from vascular disease is produced by one or more of the following pathophysiologic factors: (a) inadequate perfusion of tissues, with consequent transient or continuous ischemia such as occurs in the muscles of the limb during exercise, ischemia of the skin that produces rest pain, and ischemia of an organ such as the heart or gastrointestinal tract; (b) secondary changes, such as ulcerations or gangrene in the skin or abdominal viscera; (c) sudden or accelerated changes in the vascular dimension of large vessels, such as occurs with expanding aneurysm; (d) rupture of the aorta or other intracavitary arteries, with consequent spillage of blood that stimulates nociceptive fibers in the parietal peritoneum or parietal pleura; (e) intense spasm consequent to the intraarterial injection of materials that irritate the endothelium of the artery; and (f) impairment of venous return, with consequent massive edema that rapidly stretches fascial compartments. The location, distribution, intensity, quality, duration, and temporal characteristics of the pain that results are determined by the pathology of the disease, its location, the rapidity with which tissue ischemia develops, and most important, the extent of the involvement of the pathologic process.

Classification of Peripheral Vascular Disease

The most important painful diseases of the peripheral vessels are listed in Table 33-1. The order of the listing is according to the aforementioned classification of arteries and veins and in the order of frequency and general importance of each disease.

TABLE 33-1. Classification of peripheral vascular diseases

Evaluation of the Patient

The diagnosis of peripheral vascular disorders that cause pain always starts with a detailed history and complete physical examination. With regard to the history, background data such as occupation, family and social history, prior illness, and surgery can provide insight into what otherwise appears to be a complex or confusing type of problem. For example, machine operators, mechanics, farmers, and others who work with their hands a great deal can develop occupational occlusive arterial disease or Raynaud's phenomenon from vibrating tools. Handling of cold products or entering walk-in freezers can aggravate any type of occlusive arterial disease. A strong family history of arterial disease (cerebral, coronary, or peripheral) can signify a familial lipid disorder and indicate that other poorly understood factors related to inheritance are at play. It is important to find out if previous illness or operations were of vascular nature or if they were accompanied or complicated by vascular problems such as thrombophlebitis, pulmonary embolism, or acute arterial occlusion. Smoking and diabetes are two crucial comorbidities contributing to arterial disease.

The physical examination consists of inspection, palpation, and Doppler interrogation of the vessels of the involved limb and other extremities. The physician should note the quality of the arterial pulsations and the color and temperature of the skin. Using the Doppler ultrasonic flow detector, the blood pressure should be compared with that in the arm: A value of less than 0.9 signifies the presence of arterial occlusive disease in the lower extremities (7). In the diabetic, ankle Doppler pressures may be falsely elevated because of those patients' lower extremity arterial medial calcification. Other tests such as transcutaneous oximetry must be used to quantitate blood supply.

Because PVD is frequently only a part of a more widespread problem, the patient's general vascular status should be determined, including a general physical and neurologic examination to search for lesions of the central and peripheral nervous system. In addition, a radiologic study of the chest and an electrocardiogram may aid diagnosis (see below).

The most prominent symptoms and signs of PVD are (a) pain; (b) decreased or absent pulses, indicating a decrease in or total obstruction of the arterial supply to the limb; (c) prominent veins that develop with venous obstruction; (d) abnormal skin color; (e) diminished (rarely elevated) skin temperature; (f) swelling; and (g) trophic changes of the skin and its appendages.

Pain

Although pain is the most common symptom in PVD, its nature varies with the disease. Therefore, a fairly accurate assessment of the disease can usually be made by a careful evaluation of the pain. It is important to ascertain the history of onset, the localization and distribution, the intensity, the duration and other temporal characteristics, the circumstances that precipitate or aggravate it, and the factors that ameliorate or relieve the pain (see Chapter 12). It is particularly important to know where the pain occurs in its distribution (e.g., the calf, thigh, hip or back, toes or foot), whether the pain is continuous or intermittent, and the duration of the painful experience.

Continuous pain is produced by sudden arterial occlusion; by ulceration and gangrene; by ischemic neuropathy caused by arterial insufficiency; by inflammation of arteries, veins, or lymphatics; and by venous or (occasionally) lymphatic congestion of a limb. *Intermittent pain* (intermittent claudication, from Latin *claudicare*, to limp) is precipitated or aggravated by exercise of contracting muscles and occurs solely in the anatomic distribution of chronic occlusive arterial disease such as arteriosclerosis obliterans (ASO), thromboangiitis obliterans (TAO) (Buerger's disease) and other types of vasculitis, and entrapment syndromes.

The *intensity* of the pain varies according to the etiology and degree of circulatory imbalance and whether the imbalance occurs gradually or suddenly. The *quality* of the pain also varies with the disease process and mechanism of the pain. The pain of intermittent claudication is usually sharp and often burning in character and is promptly relieved by cessation of the activity that precipitates the pain. The pain of ischemic neuropathy is usually aching in character, often associated with paresthesia, but at times the patient complains of a pulling, tearing, or agonizing sensation. The pain of sudden arterial occlusion is usually sharp when the lesion involves the limbs and is dull and sickening in character when the occlusion involves the aorta or vessels to the abdominal viscera. The pain of erythromelalgia is usually burning and is aggravated by heat and relieved by cold.

Associated Phenomena (Signs of Peripheral Vascular Disease)

Table 33-2 summarizes the signs of PVD. Careful observation of changes in skin color, palpation of the pulses, and skin temperature and trophic changes correlated with the characteristics of the pain usually permit the physician to make an accurate diagnosis of the specific type of PVD present.

TABLE 33-2. Signs of peripheral vascular disease

Laboratory Studies

Laboratory studies that should be included as part of the evaluation of patients with PVD include a complete blood count; urinalysis; blood urea nitrogen, and creatinine evaluations; multiphasic screening biochemical profile; and a glucose tolerance test to eliminate overt or subclinical diabetes. Patients with arteriosclerosis should have plasma lipids measured, including fasting cholesterol, triglycerides, and lipoprotein levels. Homocysteine levels may be valuable. In thromboembolic disorders, a coagulation profile should be obtained.

Special Diagnostic Studies

To confirm and document the arterial insufficiency found or suspected by clinical evaluation and to determine the degree of functional impairment, a variety of noninvasive instruments, primarily based on pioneering work in medical ultrasound by Strandness and colleagues (6,7), are now available in peripheral vascular laboratories. Because these instruments are capable of producing objective information on hard copy, they are useful for following the progress of the patient during the course of conservative treatment and for evaluation before, during, and after surgical therapy. Even more sophisticated instruments are used by the vascular surgeon to select the site of amputation and to predict healing of ischemic lesions or the success of an operation.

Pressure Measurements

As noted above, the simplest pressure measurement method available is to determine the ankle systolic pressure with a handheld Doppler ultrasound instrument and compare it with the brachial systolic pressure (2,3,4,5,6,7,8 and 9). These instruments are accurate, simple to use, relatively inexpensive, and ideal to use in the office or at the bedside to confirm the diagnosis of arterial insufficiency or to follow the course of the disease. Normally, the ankle systolic pressure should be equal to or greater than the brachial systolic pressure [ankle brachial index (ABI) of more than 0.9] (7). With arterial insufficiency in the lower limb, however, the ABI is less than 0.9, depending on the degree of insufficiency. With mild insufficiency the ABI is between 0.7 and 0.9, with moderate disease it is between 0.5 and 0.7, and with severe disease it is less than 0.5 (8). Ischemic skin lesions would not be expected to heal with an ABI of less than 0.4.

The sensitivity of tests using pressure measurements can be increased by augmenting blood flow through the stenotic segment. This can be accomplished by exercise on a treadmill or on an exercise bicycle to the point of claudication. Postexercise ankle blood pressure falls, often to unrecognizable levels, requiring several minutes to return to the preexercise level (Fig. 33-1). The explanation of this phenomenon is that with exercise there is a marked fall in arterial resistance in the muscles; blood flow is fixed through the arterial stenosis, and the amount of inflow available through the collateral arteries is inadequate because of their high resistance to flow. As a consequence, distal arterial pressure falls, explaining the pallor in the foot observed during and immediately after exercise. This test is most useful in following the progress of the disease with or without therapy.

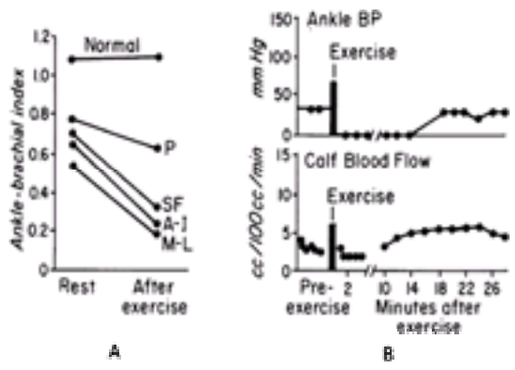

Figure 33-1. **A:** Mean ankle-brachial indexes (ankle systolic blood pressure divided by brachial systolic blood pressure) at rest and after exercise in normal subjects and patients with arteriosclerosis obliterans. Location of occlusion is indicated by letters: P, popliteal below the knee; SF, superficial femoral; AI, aortal iliac; ML, multilevel. **B:** Ankle pressure and calf blood flow before and after exercise in a patient with occlusion of the iliac, common femoral, and superficial femoral arteries. This patient had severe claudication and moderate rest pain. (BP, blood pressure.) (Modified from Sumner DS. Practical approach to vascular laboratory testing in occlusive arterial disease. In: Rutherford RB, ed. *Vascular surgery*, 2nd ed. Philadelphia: WB Saunders, 1984:45–56.)

If more detailed information is desired, the patient can be studied in the vascular laboratory using duplex ultrasound techniques. The specific capabilities of duplex ultrasound relate to its ability not only to localize arterial (and venous) obstructions, but also to make detailed hemodynamic assessments of flow within the normal and affected vessels. Arteriography is rarely indicated unless the patient is to be considered for revascularization. Arteriography documents the exact location of arterial occlusion, length of the occlusion, condition of the vessels above and below the occlusion, the location of other occlusions, and extent of the collateral circulation.

PERIPHERAL DISEASE OF LARGE AND MEDIUM ARTERIES

Arteriosclerosis Obliterans

ASO, also known as obliterative arteriosclerosis, atherosclerotic occlusive disease, and chronic occlusive arterial disease, is the peripheral arterial manifestation of generalized atherosclerosis. Most commonly it affects the lower abdominal aorta; the iliac arteries and the arteries supplying the lower limbs; and the femoral, popliteal, and tibial arteries (Fig. 33-2). Although much less commonly symptomatic, ASO of the upper limbs is not rare and can cause disabling ischemic symptoms or even loss of digits, most commonly in diabetics.

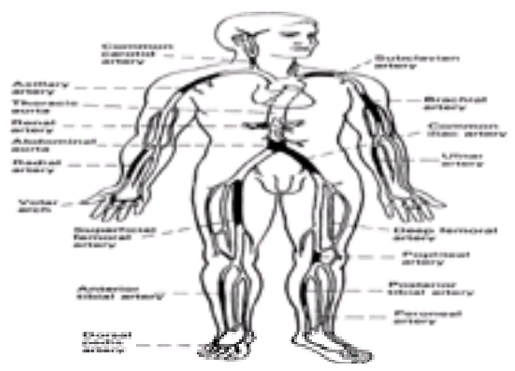

Figure 33-2. The most common sites of arteriosclerosis obliterans in the peripheral arteries. The extent, degree, and pattern of the obstructive lesion vary considerably in each site.

ASO is responsible for 95% of the cases of chronic occlusive arterial disease (3,8). It is a degenerative disease of the peripheral arteries that usually develops slowly and insidiously, most commonly in persons older than age 50 years, although it may occur sporadically in younger persons. Men are affected more often than women, in ratios varying between 5 to 1 and 10 to 1 (8,10). In approximately one-third of patients, ASO is associated with coronary artery disease, and in some 20% to 30% it is associated with diabetes mellitus (8,11).

Etiology

No single factor has been identified as the specific cause of ASO. In addition to age, sex, and its association with diabetes, important risk factors include smoking, hyperlipidemia, and hypertension, and these clearly accelerate the progression of ASO. Ninety percent of patients have a current or past smoking history when first examined, and progression of the disease and failure of arterial bypass grafts are much higher in patients who continue to smoke (11,12). Limb circulation is further compromised by the increase in viscosity of blood in patients with the secondary polycythemia of smoking and the reduced cardiac output associated with heart disease. Alterations in fibrinogen, fibrinolytic activity, and platelet adhesiveness and aggregation due to smoking may also contribute to the progression of

arteriosclerosis or promote thrombosis of already diseased vessels (13). Although diet, focal infections, occupation, heredity, genetic factors, and endocrine imbalance have been implicated in arteriosclerosis in general, their roles as etiologic agents for peripheral ASO remain uncertain (2,8,13).

Pathophysiology

Lesions of arteriosclerosis have three components: atheromas, medial changes, and thrombosis. Usually all three are present in the same area, but one component may be most prominent. The earliest lesion is an atheromatous plaque that develops in the intima. Progression is manifested by enlargement and confluence of atheromatous lesions, which can contain large amounts of lipids, and fibrous tissue. Calcification of the base of the atheroma may occur. The media is thin, and the arterial smooth muscle and elastic tissue are replaced by fibrous tissue. Hemorrhage can also occur via the vasa vasorum. The intimal surface degenerates and liquefies, leaving a rugged irregular ulcer as a starting point for a thrombus to develop. Thrombosis can occur several times with partial organization and recanalization.

The basic pathophysiologic defect produced by ASO is ischemia of the tissue supplied by the obstructed artery or arteries. The disease develops slowly and insidiously and is probably present for 5 to 10 years before symptoms develop (8,13). As the artery becomes progressively stenotic and finally occludes, a collateral circulation develops, probably in response to ischemia in muscles during exercise (Fig. 33-3). The severity of the ischemia depends on the site and extent of the arterial lesion and on the adequacy of the collateral circulation. During the early course of the disease, the flow through the collateral vessels is usually adequate to maintain the viability of the affected extremity but is not sufficient to prevent symptoms, especially during exercise, and the patient experiences the pathophysiologic symptom of intermittent claudication. If the disease progresses, flow through the collateral vessels might become inadequate, causing more ischemia, and the patient might experience pain at rest (8). Further progression can result in skin ulceration and gangrene.

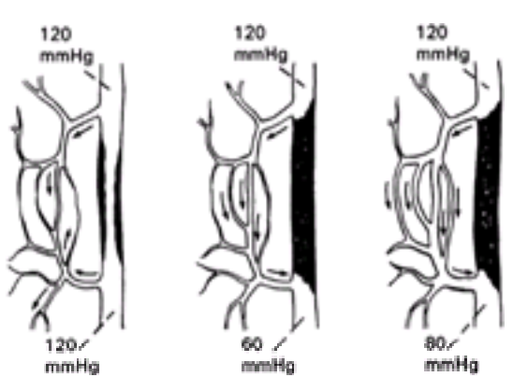

Figure 33-3. Hemodynamic theory of collateral formation. **A:** A developing stenosis in the main artery without a drop in pressure across it. The arrows indicate direction and volume of blood flow in the side branches. **B:** The lesion has progressed to acute thrombosis with a consequent pressure drop of 60 mm Hg and reversal of blood flow in the reentry artery below the obstruction. **C:** Over the course of several weeks the blood flow through the collateral increases in response to the pressure differential, and the gradient across the lesion decreases. (Modified from Kempczinski RF, Bernhard VM. Introduction and general considerations of management of chronic ischemia of the lower extremities. In: Rutherford RB, ed. *Vascular surgery*, 2nd ed. Philadelphia: WB Saunders, 1984:547–558.)

Symptoms and Signs

The earliest symptom is *intermittent claudication*, as noted previously, characterized by extreme fatigue, cramping, and tightening of calf or thigh muscle that progresses to a sharp pain (and occasionally numbness) brought on by walking and relieved within a few minutes by rest. It is not necessary to sit down to obtain relief, but merely to stop walking (8). The distance the patient can walk varies with the degree and extent of arterial occlusion but remains constant for a given time. With mild degrees of occlusion the patient can walk several blocks, but as the disease progresses there is a decrease in the claudication distance. The pain is more severe and occurs earlier when the patient walks rapidly or uphill or upstairs (13).

The location of intermittent claudication depends on the muscle group most severely affected by the arterial insufficiency. Because the femoral-popliteal artery segment is most often involved in ASO, intermittent claudication occurs most often in the calf muscles. The close correlation between the site of intermittent claudication and location of the occlusive disease is characteristic of ASO. Thus, aortoiliac disease causes intermittent claudication in the buttocks, hips, thighs, as well as the calf (Leriche syndrome) (Fig. 33-4). Tandem areas of occlusion such as the iliac and superficial femoral or superficial femoral and tibial artery produce severe, incapacitating intermittent claudication that often is associated with or progresses to rest pain and tissue necrosis. Patients who have involvement of the popliteal-tibial segment, such as in TAO (see below) develop intermittent claudication involving the muscles in the foot (13). Occlusive disease confined only to the tibial arteries or the peroneal artery often does not produce claudication.

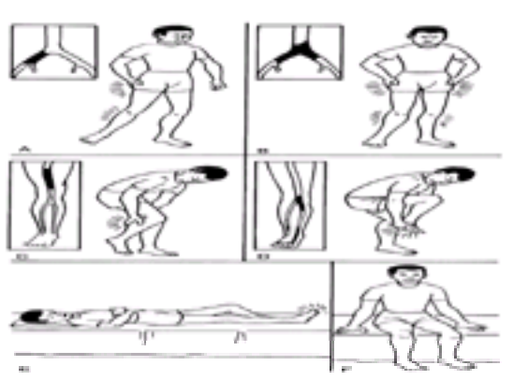

Figure 33-4. Sites of pain (*radiating lines*) caused by arteriosclerosis obliterans in different parts of the arteries of the lower limb. **A:** Obstruction in the right common iliac artery. **B:** Obstruction in both common iliacs and lower aorta, which produces pain in the buttocks, hips, thighs, and calf—the so-called Leriche syndrome. **C:** Obstruction of the superficial femoral artery, which produces severe incapacitating intermittent claudication in the calf. **D:** Obstruction of the popliteal and tibial arteries (and dorsal pedis arterial arch), with pain in the foot. **E:** Rest pain in the digits and distal part of the foot (when the patient lies in bed), as indicated by the facial expression. **F:** Relief of rest pain when the limb is dependent.

Rest pain develops if the disease progresses to multiple levels of occlusion of arteries, including those supplying the collateral vessels. The condition becomes so extensive that arterial flow to the distal limb and foot is insufficient even at rest. Rest pain has the following distinguishing characteristic features (6): (a) It always involves the toes and distal foot and occasionally the heel; (b) the pain is burning in quality, constant and severe, and always worse at night when the patient is in bed because of the loss of beneficial effects of gravity in carrying the blood distally; (c) pain can be partially or completely relieved by dependency and is aggravated by elevating the foot; (d) it is frequently associated with trophic changes in the foot and toes and with ulceration or gangrene; and (e) it rarely improves unless perfusion to the ischemic area can be increased. Occasional patients may note numbness, rather than pain, in the toes or heel; such “rest numbness” has the same morbid implications regarding limb salvage as does rest pain.

At this stage of severe ischemia, ischemic neuropathy can develop and produce severe lancinating shooting or sharp pain in the leg and foot. This pain, similar to diabetic neuropathy, may not completely be mitigated by revascularization but is usually relieved by amputation.

Diminished or *absent pulses* in the affected extremity are the most important physical sign of ASO. Just as the anatomic site of the intermittent claudication is a clue as to which artery is obstructed, so too is the location of the diminished or absent pulses an accurate guideline as to the site of the occlusion (12). When the

aortic-iliac vessels are involved, the femoral pulse is diminished or absent. In superficial femoral artery disease, the femoral pulse is present in the groin, but the popliteal and foot pulses are diminished or absent. In popliteal-tibial disease (common in diabetic patients), the femoral and popliteal pulses are present but the foot pulses are absent. Although the dorsalis pedis pulse is developmentally absent in approximately 6% of persons with otherwise normal pulses, absence of the posterior tibial pulse always indicates occlusive disease (8).

Color changes that occur when the foot is elevated or dependent are a confirmatory physical sign of severe arterial insufficiency. Elevation of the legs causes pallor of the skin of the affected foot because pressure and flow in the collateral circulation are inadequate to overcome the effect of gravity. When the legs are placed in dependency after the period of elevation, a reddish-purple color (rubor) slowly appears. If the venous filling time is delayed beyond 15 seconds, arterial insufficiency is present (8).

Trophic changes do not occur with mild to moderate ASO, and the foot maintains normal color, temperature, and skin nutrition. When ischemia becomes severe, however, trophic changes occur and the foot becomes cool with loss of hair, thickened nails, and dry scaly skin. During this stage, the skin is chronically ruborous due to maximal small vessel dilatation and retention of desaturated blood—the body's attempt to nourish the severely ischemic tissue. Ischemic ulcers in the toes and other parts of the foot can appear spontaneously, but more often they are the result of trauma with nonhealing because of inadequate arterial perfusion to effect healing of otherwise trivial skin lesions.

Arteriosclerosis Obliterans in the Upper Extremity. Although ASO most frequently involves the arteries of the lower limbs, the presence of this condition in the upper limb can cause disabling ischemic symptoms or even loss of digits (2,3 and 4,14). As with ASO in the lower limbs, the symptoms vary according to the degree of ischemia, ranging from no symptoms to fatigue and pain with active use of the muscles of the limb (“arm claudication”). With more severe occlusion the patient has dysesthesia or coldness and eventually develops severe pain of ischemic ulceration. In addition, chronic occlusive arterial disease in the upper extremity can cause intermittent color changes of the fingers on exposure to cold or with emotional unrest, which may be considered as a secondary Raynaud's phenomenon.

Examination of the arterial circulation of the upper extremity should include measurement of blood pressure in both arms, and the pulsation of the subclavian, axillary, brachial, radial, and ulnar arteries should be evaluated and graded. Simultaneous palpation of both radial arteries at the wrist may be a valuable addition to the examination because delay of one radial artery pulse is a useful sign of unilateral subclavian artery occlusion proximal to the origin of the vertebral artery with resultant rerouting of the arterial circulation to the involved arm via retrograde flow in the vertebral artery (commonly although incorrectly known as the “subclavian steal syndrome”) (15). As for the lower extremities the handheld Doppler probe can be used to quantitate limb or digit blood pressures. In addition, Allen's test (Fig. 33-5) provides a method for evaluating the patency of the radial and ulnar arteries and of the superficial palmar arch by observing not only the rate of color return, but also its distribution to the palm of the hand and fingers.

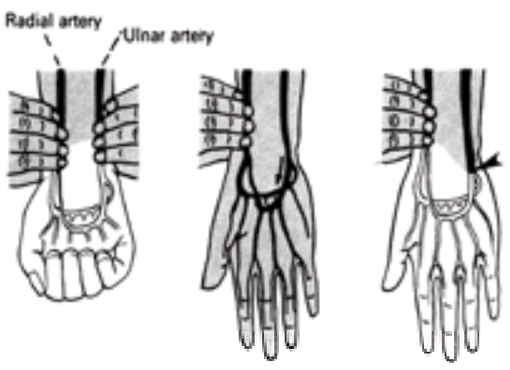

Figure 33-5. Allen's test for determination of patency or occlusion of the vessels to the hand. **A:** Compression of both ulnar and radial arteries produces ischemia and paleness of the closed hand; the hand remains pale when it is opened. **B:** If the ulnar artery is patent, color promptly returns to the palm while the radial artery is still compressed by the examiner. **C:** If the artery is occluded, the skin remains pale as long as the radial artery inflow is blocked by the examiner. The patency of the radial artery is tested by maintaining pressure on the ulnar artery. (Modified from Spittell JA Jr. Occlusive arterial disease in the upper extremities. In: Spittell JA Jr, ed. *Clinical vascular disease*. Philadelphia: FA Davis, 1983:61.)

Arteriosclerosis Obliterans in Patients with Diabetes Mellitus. Patients with ASO associated with diabetes mellitus pre–sent certain differences in the site, pattern, and location of their arterial obstructive lesions, and they often develop a peripheral neuropathy that not only modifies the pain pattern, but also greatly influences available therapy and its outcome (16,17 and 18). With regard to location and extent of the pathology, the following differences are noted: (a) The diabetic patient with ASO has more occlusions involving the tibial and peroneal arteries than the nondiabetic with ASO; (b) the incidence of occlusion in the femoral-popliteal segment is essentially the same between the two groups; and (c) diabetic patients with ASO have a lower incidence of aortoiliac involvement.

A peripheral neuropathy that frequently develops in patients with diabetes produces a bilateral symmetric hypesthesia, with loss of pain sensation, proprioception, and sympathetic tone (16,17). Decrease or loss of pain sensation prevents the patient from recognizing minor trauma and frequently results in the development of painless, nonhealing ulcers at sites of injury or over pressure points such as the metatarsal heads. Because the neuropathy involves the sympathetic fibers, which are, of course, component parts of the peripheral nerves, loss of vasoconstrictor tone results in dry skin, which may crack or fissure, thereby permitting invasion of skin bacteria. Neurologic examination may reveal absent ankle reflexes, loss of proprioception, and a diminished vibratory sense.

When ulcers or areas of necrosis develop they are often deep, extending along tissue planes to involve the underlying tendons, joints, or phalangeal and metatarsal bones. Osteomyelitis is a common sequel and greatly complicates management (19). The fact that the ulcers are painless confirms the diagnosis of diabetic peripheral neuropathy because few other conditions can produce the same picture (6,18).

Diagnosis

Presence of the characteristic symptoms and physical findings mentioned above should be sufficient to diagnose ASO in all but the mildest cases. Special diagnostic studies mentioned in the preceding section are useful for confirming and quantitating the degree of the arterial insufficiency, but the physician often can select the appropriate treatment or refer the patient to a vascular surgeon based solely on a careful history and physical examination.

ASO must be differentiated from other arterial obstructive diseases, including thromboangiitis obliterans, arterial embolism or thrombosis, arterial entrapment syndromes certain neurospinal disorders that produce pseudoclaudication, and myofascial pain syndromes of the limb. The differential diagnosis between ASO and Raynaud's disease, Raynaud's phenomenon, and other vasospastic disorders should not be difficult because the arterial pulses are usually present in these latter conditions. The most important diagnostic features of chronic obstructive arterial occlusive disease are summarized in Table 33-3.

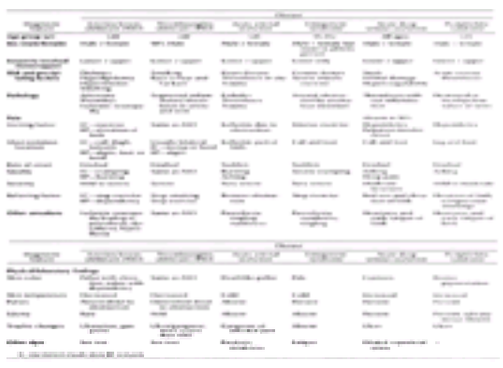

TABLE 33-3. Differential diagnostic features of occlusive peripheral vascular diseases

Treatment

Treatment for patients with ASO is determined by the severity of the disease and the patient's general condition, occupation, and lifestyle. The development of mild to moderate intermittent claudication poses no threat of limb loss. Generally speaking, most patients remain symptomatically stable or may occasionally show some improvement (20). Only 5% become worse, and only 5% to 7% ultimately require extremity amputation (21,22). This is in striking contrast to patients who present with ischemic ulceration or rest pain, virtually all of whom face amputation unless successful limb revascularization is accomplished (23).

Progression of ASO occurs more frequently and rapidly in patients who have diabetes mellitus, who smoke, and who have other risk factors. Unfortunately, these risk factors are additive—for example, the prognosis is geometrically worse in diabetics who smoke (24). Progression of ASO is also more likely to occur when the lesion involves the femoral-popliteal-tibial arterial segments than when it involves the aortoiliac segment (8). The life expectancy of patients with ASO is compromised because of the high incidence of concomitant atherosclerotic complications in other areas, particularly in the coronary arteries.

In view of these considerations, it is obvious that the type of therapy for patients with ASO is determined primarily by the degree and severity of their symptoms and physical findings. Mild to moderate disease is treated conservatively and its course followed closely, whereas incapacitated patients who are unable to work or to function normally in retirement require intervention when possible. Conservative therapy consists of prompt cessation of cigarette smoking, control of hypertension, elimination of hyperlipoproteinemia, changes of patterns of activity and stress, weight loss, a structured exercise program, and, importantly, the regulation of diabetes mellitus if present. These produce major changes in lifestyle and require close and extensive follow-up for successful application (25).

General Measures. General measures include thorough discussion with patients, emphasizing to them that intermittent claudication *per se* is not life-threatening and reassurance that the disease is usually not progressive; however, if worsening of symptoms should occur, intervention might be considered (12,13). Factors that decrease walking time to onset of claudication, such as walking uphill, climbing stairs, and carrying excess body weight or bundles, should be avoided. Obese patients should be placed on a weight-reduction diet. Tobacco smoking has been shown to be highly correlated with intermittent claudication in many epidemiologic studies, and in the Framingham study cigarette smoking was second to no other risk factor as a cause of intermittent claudication (26). The rate of occurrence of intermittent claudication was twice as great among smokers than nonsmokers, and the risk tended to increase with the intensity of the habit. Other clinical studies provide impressive evidence that patients must stop smoking to decrease the risk of amputation and that unless patients stop smoking the results of surgical therapy will be markedly compromised (8,27). Studies have shown that there are more occlusions of bypass grafts or of endoarterectomies if patients continue smoking compared with patients who stopped smoking after surgery.

There is also general agreement in the literature that exercise regimens increase walking distance in patients with intermittent claudication. Successful exercise regimens should include a supervised program done daily, every other day, or weekly, but it is important that the patient exercise daily for periods of 30 to 60 minutes (8,28,29).

The diabetic patient offers special challenges. The patient should be instructed to take protective and prophylactic measures aimed primarily at elimination of foot or toe trauma, which is the chief cause of gangrene. Of paramount importance is the establishment and maintenance of good foot hygiene, including keeping the feet clean, warm, and dry at all times; wearing only correctly fitting shoes; and taking other measures to prevent skin abrasion, contusion, pressure points, corns, calluses, and fungus infection. Toenails should be cut straight across to avoid ingrown nails and infections. Exposure to cold should be avoided. A change of occupation to one of a sedentary nature or one in which the possibility of trauma to the feet is minimal might be advisable. A randomized trial has demonstrated that a simple, repetitive educational program directed at diabetic patients and their families can significantly reduce hospitalizations, amputations, and mortality associated with diabetic foot infection.

Other Medical Measures. Fibrinolytic, anticoagulant, and antiplatelet therapy; vasodilator drugs; and hemorrheologic agents have been used as medical therapy for ASO. Lytic or anticoagulant agents have not been shown to delay or prevent the progression of ASO. Vasodilator drugs that have been subjected to experimental trials include tolazoline (an alpha-receptor blocker), nylidrin (a beta-receptor stimulant), isoxsuprine, papaverine and its derivatives, and niacin and its derivatives. There is no substantive evidence that vasodilator drugs are effective in treatment of obstructive arterial disease, either for intermittent claudication or for ischemic rest symptoms.

Various agents that alter blood viscosity or other flow characteristics have been demonstrated in prospective randomized trials to improve walking distance in patients with intermittent claudication. These include pentoxifylline, which exerts its influence on the red cell cytoskeleton, and cilastozol, which appears to be both a vasodilator as well as a platelet antiaggregant. Experience has suggested that patient compliance and absence of smoking predict beneficial therapeutic results with these agents.

Pain Control. In patients with mild to moderate rest pain, discomfort can sometimes be controlled with nonsteroidal antiinflammatory drugs, such as aspirin or acetaminophen, combined with codeine. The dose of the nonsteroidal antiinflammatory drug can be gradually increased to 1 g every 4 hours, and codeine can be increased to 128 mg every 4 hours. This combination can be used for long periods of time with insignificant risk of physical dependence and little risk of addiction or tolerance. Side effects of both drugs should be treated (see Chapter 83 and Chapter 84). For severe rest pain, narcotics can be used for several weeks, but such patients require surgical intervention—either revascularization or amputation.

Surgery. In the event that the vascular patient remains miserable despite maximal medical therapy or the underlying condition progresses to limb-threatening ischemia (characterized by rest pain, ulcers, or gangrene), surgical therapy is indicated either in the form of transcatheter angioplasty (balloon dilatation or stenting) or operative revascularization (Fig. 33-6). In some settings, amputation may be the most rational option. Selection of the patient for revascularization of the lower extremity should be based on a realistic assessment of risk, expected long-term patency of the reconstruction, likelihood of complications, and the relative risk of limb loss without surgery (8,30). In carefully selected patients, relief of symptoms and salvage of the lower extremities are readily accomplished by adequate revascularization. Satisfactory results require careful delineation of the scope of the occlusive process and meticulous attention to procedural technical details.

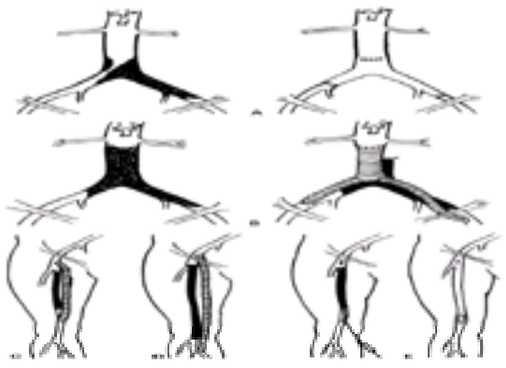

Figure 33-6. Various types of surgical procedures to achieve arterial revascularization. **A:** Aortoiliac endarterectomy, which is especially useful in younger individuals with minimal deterioration of the arterial wall. This is accomplished through transverse incision in the aortic and iliac arteries, removing the atheromatous and thrombotic cast, with subsequent reanastomosis of the iliac arteries and closure of the transverse incision in the aorta. **B:** Endarterectomy of the proximal aorta, end-to-end aorta-graft anastomosis with oversewing of the distal aorta and bypass graft to right external iliac artery and to the left common femoral artery. **C:** A prosthetic bypass connecting the external iliac with the lower portion of the femoral artery. **D:** The lower end of the prosthesis in **C** is grafted to the posterior tibial artery. **E:** Endoluminal endarterectomy with vein patch arterioplasty. (Modified from Hollier LH. Principles and techniques of surgical treatment of occlusive arterial disease of the lower extremities. In: Spittell JA Jr, ed. *Clinical vascular disease*. Philadelphia: FA Davis, 1983:37–48.)

In general arterial stents have been found to be more effective and more durable than balloon dilatation. Iliac artery stents have a primary patency rate of 70% to 80% at 5 years, whereas stents placed in the superficial femoral artery fare much less well, with a patency rate of approximately 40% to 50% at 1 year. Early patency rates for aortofemoral bypass grafts are greater than 98%, and 5- and 10-year patency rates in excess of 90% have been reported (see Fig. 33-6). Femoral-popliteal bypass using the greater saphenous vein (for which patency is far better than with prosthetic materials) provides a 5-year patency rate of 70% to 80%, whereas femoral-tibial vein bypass can provide a 5-year patency rate of 50% in situations with good runoff. In some patients who have superficial femoral artery occlusive disease and profunda stenosis with good collateral circulation between the profunda femoris tributaries and the popliteal-tibial system, a simple profundoplasty may be sufficient to relieve mild to moderate rest pain. Femoral-femoral bypass to treat unilateral iliac occlusive disease has a 5-year patency of only about 50%, which can be improved with donor iliac artery stenting. Axillofemoral bypass grafting may approach the 5-year patency rate of aortofemoral bypass.

Interventional or surgical revascularization is required less often for patients with ASO in the upper limb, partly because ASO occurs less frequently in the upper extremity and also because the collateral arterial supply around the shoulder and elbow, usually robust, tends to minimize the more distal ischemic effects of any occlusive disease located proximal to these collateral beds. Obviously, if segmental occlusive disease is found, stenting or bypass is indicated and should produce excellent results.

Lumbar Sympathectomy. Previous to the advent of vascular surgery, sympathetic denervation of the affected extremity, achieved either surgically or chemically, was used widely for the treatment of various PVDs, including ASO.

Recently acquired information has brought into question the efficacy of sympathectomy in the treatment of most types of peripheral arterial occlusive disease. Sympathectomy does not improve muscular blood flow, and some have even questioned whether it improves nutritive skin blood flow. The clinical improvement in many well-documented cases of intermittent claudication and ischemic pain following sympathectomy reported might be attributable in part to afferent denervation, reduction of vasomotor tone, and perhaps change in the threshold of sensory receptors. In current practice, although the technique remains valuable diagnostically and as treatment for certain nonvascular conditions such as hyperhidrosis or complex regional pain syndrome, little credible evidence supports the use of surgical or chemical sympathectomy for the treatment of ASO.

Thromboangiitis Obliterans

In 1908, Buerger (31) first described a disease entity that caused a specific nonatherosclerotic lesion involving arteries, veins, and nerves of the extremity that frequently led to the development of gangrene. The existence of this disease remained unchallenged for approximately 50 years until Wessler and associates (32) published a provocative article that was critical of the original publication and seriously questioned the existence of this disease. Since 1960, the problem has been reexamined in several excellent clinical reviews and reports, and practically without exception the conclusion has been reached that the disease does exist and can be recognized if rigid diagnostic criteria are followed (33,34).

TAO is an occlusive disease of medium-sized and small arteries and veins affecting chiefly the distal parts of the lower and upper limbs of young adult male smokers. The arterial lesions are often associated with recurrent episodes of segmental superficial thrombophlebitis. Originally thought to occur exclusively in Jews, it is now known to affect all races, and reports in recent decades have indicated its prevalence in the Orient and the Middle East; it is an uncommon PVD in the United States (8,34).

Etiology

The cause of TAO is not known. It occurs nearly exclusively in young male smokers, and striking relationships have been noted between exacerbations and continued use of tobacco and between remissions and cessations of smoking. A slight increase in the proportion of women in TAO populations has been noted—perhaps reflecting women's increasing incidence of smoking (35).

Pathophysiology

The acute pathologic lesions in TAO consist of segmental inflammation of all layers of the walls of medium-sized and small arteries and veins, although the architecture of the wall is preserved. The distal arteries of the lower extremity are more commonly involved, and the lesions are usually more severe here than in the upper extremity (36). The vessels commonly involved are the tibial, radial and ulnar plantar, palmar, and digital arteries. Larger arteries such as the femoral and brachial are affected later and only when the disease is severe and progressive. Thrombosis occurs in the inflamed segment, producing occlusion of the lumen. Fibroblastic proliferation occurs early, with rapid organization of overlying thrombosis. Later there is prominent fibrous tissue throughout the artery and vein, frequently including nearby nerves and binding them together in a dense mass. Recanalization is common, but the multiple new lumina do not approach the original size of the vessel. The lesions are not diffuse but are distinctly focal or segmental, with relatively normal segments of vessels situated between them and distinct lines of demarcation between adjacent normal and pathologic segments. Occlusion of the arteries is followed by development of collateral and anastomotic vessels that are demonstrable by arteriography. The secondary pathologic effects of the disease are the result of severe distal ischemia and inadequate collateral vessel development.

Symptoms and Signs

In addition to the fact that TAO occurs in primarily young male cigarette smokers, the following are other distinguishing clinical features of TAO: (a) There is usually bilateral symmetrical involvement; (b) the distal location of the occlusion in the leg leads to development of instep claudication, a unique feature of the disease; (c) involvement of the distal arteries of the arm, palm, and digit can lead to hand claudication; and (d) cold sensitivity of the Raynaud's type is often present (6,35).

The most common and most bothersome problem in TAO is ischemic rest pain, usually in the toes or distal feet. When intermittent claudication occurs it might be an ache, a sense of fatigue or a persistent cramp, or a severe aching, squeezing pain that is typical in its relationship to the usual walk-pain-rest-relief cycle. If the disease involves the upper extremities, the patient develops intermittent claudication in both hands or forearms when these parts are used actively in doing certain tasks. The ischemic rest pain usually involves the toes and feet or hands and fingers, is often very severe, has a burning quality, is unrelenting, is aggravated by elevation of the extremity, and in late stages may not be relieved by dependency.

Late in the course of progressive TAO, the patient might experience pain of ischemic neuropathy, which is severe and widespread in the extremity. It is usually paroxysmal, often associated with paresthesia and dysesthesia, and may be characterized by bouts of lancinating pain. If ulceration and gangrene develop, the patient experiences pain that is localized to the region adjacent to the ulcers or gangrenous tissue and has the characteristics of rest pain. The pain is severe, persistent, and usually worse at night.

The clinical course of TAO is markedly influenced by whether the patient stops smoking. If smoking continues, episodic progression of occlusive lesions occurs and there is progressively worsening arterial insufficiency. However, after smoking cessation new occlusions do not occur and collateral anastomotic channels develop with time, providing slow improvement in circulation (8,35,36). If the disease has progressed to such an extent that severe digital ischemia has occurred, gangrene is likely to develop after even minor trauma, even if the patient has stopped smoking. The risks of digit or limb loss are vastly greater in TAO than in ASO; patients with TAO can expect a near-normal life span, however, in contrast to patients with ASO, in whom there is decreased survival because of concomitant coronary and/or cerebral arterial disease.

Diagnosis

The diagnosis of TAO is readily made on the history and physical examination, particularly palpation of pulses in distal parts of the limbs. The posterior tibial or dorsalis pedis pulsations, or both, will be greatly diminished or absent. When the disease involves the upper limbs, a positive (unfavorable) Allen test indicates occlusion of the radial and/or ulnar artery distal to the wrist (35,36). A Doppler flow detector is useful in confirming the clinical assessment of the occlusive arterial process. Although not pathognomonic, arteriographic findings showing multiple segmental occlusions in the forearm, hand, or lower leg and foot are typical enough to be confirmative evidence of the diagnosis. Collateral arteries, when present, are usually tortuous and have a “corkscrew” appearance (8) (Fig. 33-7). TAO must be differentiated from other occlusive diseases, including ASO, scleroderma associated with secondary Raynaud's phenomenon, and occlusive arterial disease due to

chronic occupational trauma.

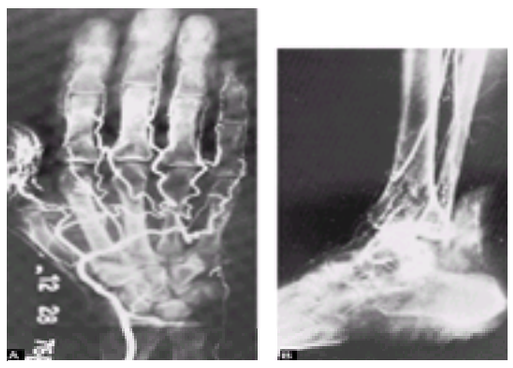

Figure 33-7. Angiograms of patients with thromboangiitis obliterans. **A:** Angiogram of a hand of a patient with disease, showing lack of filling of the ulnar artery, the tortuous corkscrewlike arteries in the hand, and the “skipped” areas of nonfilling in the digital arteries. **B:** Angiogram of the distal part of the leg of a patient with thromboangiitis obliterans. The anterior tibial and posterior tibial arteries appear normal until their abrupt occlusion at the ankle. (From deWolfe VG. Chronic occlusive arterial disease of the lower extremities. In: Spittell JA Jr, ed. *Clinical vascular disease*. Philadelphia: FA Davis, 1983:15–135, with permission.)

Treatment

The cornerstone of therapy of TAO is complete and permanent cessation of tobacco use in any form. The patient must be provided a thorough description of the disease and it should be impressed in the strongest possible terms that there is no option to stopping smoking promptly and permanently if disease progression and amputation are to be avoided.

Mild to moderate pain should be controlled with systemic nonnarcotic analgesics, used alone or combined with codeine. Potent narcotics can be used for short periods of time to control severe pain; in certain cases they may be used for prolonged periods, provided the patient can be monitored closely. Because the arteries involved are small and in most instances located distal to the knee or elbow, often with the involvement of the digital arteries, and because of the multiplicity of the involved segments, interventional radiologic techniques or bypass surgery is rarely feasible in patients with TAO (8,36). Amputation is generally curative, and wound-healing problems are rare because arterial inflow is good.

Acute Arterial Occlusion

The medium-sized arteries of the upper and lower limbs are the most frequently acutely occluded vessels from a variety of causes, but the three most important etiologic factors are embolism, acute thrombosis, and direct injury to the vessel (37,38,39,40 and 41). The clinical picture that results is variable, depending on such factors as the location of the obstruction, the functional capability of the existing collateral circulation, and the general condition of the patient, particularly with regard to cardiac function.

Etiology

An aortic dissection can cause acute arterial occlusion by mechanical blockage of the arterial channel (or of branch vessels) with subsequent thrombosis. Aneurysm of the popliteal or subclavian artery can result in limb-threatening acute arterial occlusion, either by acute thrombosis or by distant embolization.

The incidence of arterial embolism appears to be increasing as a result of an aging population, longer survival of cardiac patients, and the common use of invasive techniques and prosthetic devices. The heart is the chief source of emboli (Fig. 33-8). A thrombus in a fibrillating atrium remained until recently the most common source of emboli, but now has been supplanted by mural clot associated with recent myocardial infarction (40). Recent cardioversion, known valvular disease, history of prior cardiac surgery, or a normal rhythm in a patient with known previous arrhythmia should make the examining physician suspicious about the diagnosis of cardiogenic embolism (40).

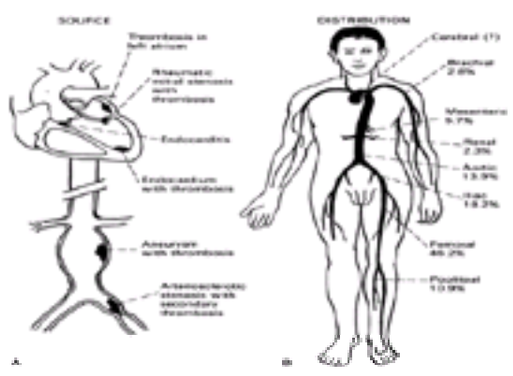

Figure 33-8. The source and distribution of arterial emboli in a series of 338 patients. **A:** More than 90% of the emboli originated in the left atrium or left ventricle; the rest originated from thrombi associated with arteriosclerosis or aneurysm. **B:** More than 90% of the emboli impacted in the distal aorta or in the lower extremities. (From Gordon RD, Fogarty TJ. Peripheral arterial embolism. In: Rutherford RB, ed. *Vascular surgery*, 2nd ed. Philadelphia: WB Saunders, 1984: 449–459, with permission.)

Although arterial thrombosis is less frequent than embolism as a cause of acute ischemia, it remains as an important etiologic factor. Acute arterial thrombosis almost invariably occurs in the area of preexisting atherosclerotic intimal lesion (38). Popliteal aneurysms are frequently complicated by *in situ* thrombosis *or* embolization, which can often result in severe ischemia. The role of vascular trauma in producing acute arterial occlusion is discussed in the next subsection.

Pathophysiology

The severity of the ischemia is partly related to the site and degree of the occlusion. The abrupt cessation of blood to an extremity initiates a chain of events that affects not only the limb but also the entire body. Occlusion of a major artery usually results in propagation of the thrombus proximally and distally, with progressive obliteration of collateral pathways (Fig. 33-9). As the degree and extent of ischemia worsen and tissue destruction ensues, metabolic waste products accumulate and their release into the central circulation produces deleterious systemic effects. Moreover, severe ischemia of a limb may result in massive ischemic myopathy, with consequent cellular disintegration and release of high concentrations of potassium and myoglobin. The systemic effects include acidosis, hyperkalemia, and myoglobinemia. As the myoglobin is filtered through the kidney, crystallization can occur in the tubules, resulting in the “metabolic-myonephropathic” syndrome, myoglobinuric nephrosis and rapidly progressive renal failure.

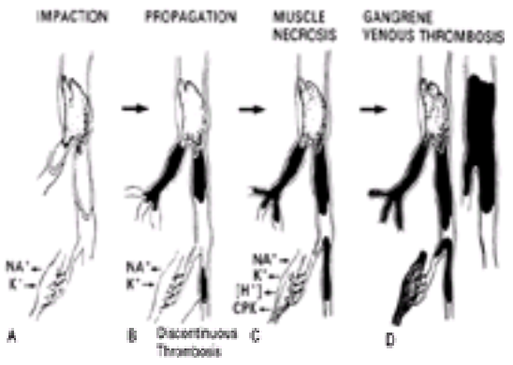

Figure 33-9. Pathophysiology of embolism. **A:** Impaction of the embolus at bifurcation of the artery. **B:** Propagation of the embolus distally with obliteration of the collaterals. **C:** Myopathy and cellular disintegration consequent to severe ischemia, with release of potassium and myoglobin. **D:** Progression to gangrene and venous thrombosis. The interval from impaction to necrosis is variable, but some necrosis is usually present after 6 hours. (CPK, creatine phosphokinase; H^+, hydrogen; K^+, potassium; NA^+, sodium.) (From Gordon RD, Fogarty TJ. Peripheral arterial embolism. In: Rutherford RB, ed. *Vascular surgery*, 2nd ed. Philadelphia: WB Saunders, 1984:449–459.)

Symptoms and Signs

The site and degree of occlusion, the extent of collateral blood flow, and the duration of ischemia all affect the severity and extent of the symptoms and the outcome of therapy. With mild occlusion there may be few or no symptoms, whereas with moderate degrees of obstruction there may be gradual development of symptoms over several hours or merely a change in the distance a patient can walk before claudication occurs. Major (severe) obstruction of blood flow to an extremity is generally heralded by the well-recognized syndrome of the six Ps: pain, pallor, loss of pulses, polar or poikilothermia (coolness), paresthesia, and paralysis (37). In more than half of such patients, the pain is rapid in onset and with a swift progression in severity that reaches a peak in minutes to hours (38,40). If the collateral circulation is able to provide sufficient blood flow to the ischemic area, the pain gradually decreases in severity after a period of initial vasospasm. Unless the collaterals are unusually abundant, however, some degree of pain persists.

The pallor that occurs in acute arterial occlusion is often a deathlike paleness that persists despite attempts by the patient to improve circulation by walking or massage of the limb (40). The extremity might stay pale for hours or even days or rapidly change to a bluish, mottled discoloration due to arterial flow stagnation that extends to the capillaries and venous circulation. Fixed staining of the skin is ominous, signifying progressive tissue ischemia and cellular necrosis.

The loss of a pulse in an extremity in which it was previously present is the hallmark of acute arterial occlusion (40). As the ischemia worsens, nerve function becomes compromised and paresthesia develops, followed by the loss of fine touch and proprioception. These changes are rapidly followed by loss of motor function and complete loss of all sensation, with irrevocable loss of tissue. If the circulation is not restored within 6 to 8 hours of the onset of symptoms, the chance of salvage of the extremity is greatly diminished (40).

Diagnosis

Assessment of acute arterial occlusion and its critical precipitating factors is accomplished by a competent history recording, physical examination, and vascular laboratory studies. Arteriography, if performed, will demonstrate the characteristic sudden interruption in dye flow in the embolized artery, perhaps with a “meniscus sign,” and the feeble collateral development that has resulted in the patient's severe acute ischemia.

Treatment

Treatment, of course, aims to restore normal blood flow. In the case of arterial embolism, treatment consists of thrombolytic disobliteration by the use of urokinase or similar agents or surgical embolectomy. Anticoagulant administration is crucial and should be started as soon as the diagnosis is made. Patients who develop arterial thrombosis usually can be treated by transcatheter thrombolysis (Fig. 33-10). Because the pathogenesis of this lesion is usually a roughened or lacerated intima, reocclusion is common and systemic heparinization at the time of removal, then warfarin administration, can help prevent further clot formation. Heparin is given in full doses (75 to 100 units per kg body weight) even though the patient is to undergo arteriography or surgery. Administration of a vasodilating agent such as papaverine or tolazoline at the time of embolectomy or thrombectomy may interrupt reflex vasospasm of the distal circulation.

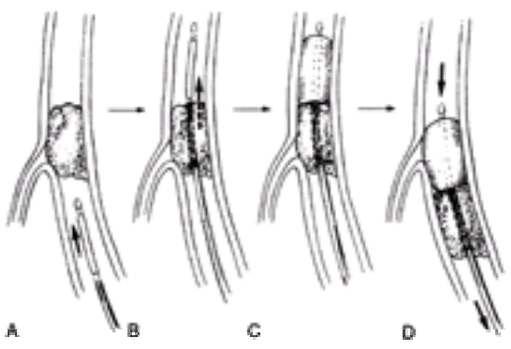

Figure 33-10. Extraction of an embolus lodged at the iliac artery bifurcation with a Fogarty catheter. The catheter is introduced through a transverse arteriotomy **(A)** and very gently passed through the embolus to prevent intimal damage **(B)**. The balloon is then inflated **(C)**, and the catheter (with the embolus) is withdrawn **(D)**. After removal of the thrombotic material, irrigation of the distal arterial system is carried out with heparinized saline solution. (From Gordon RD, Fogarty TJ. Peripheral arterial embolism. In: Rutherford RB, ed. *Vascular surgery*, 2nd ed. Philadelphia: WB Saunders, 1984:449–459, with permission.)

Vascular Trauma

The treatment of vascular injuries improved markedly during the Korean War, when therapy changed from ligation to attempts at repair and amputation risk fell from 50% to 13% (42). More recent surgical advances, both in diagnosis and in treatment, can be considered among the most important encouraging trends in the care of peripheral vascular disorders. Nevertheless, vascular trauma remains a challenge for the physician and the vascular surgeon because of the increasing frequency of these cases (43).

Etiology

The most common cause of peripheral vascular injuries is penetrating trauma, which includes the spectrum between simple puncture wounds to wounds from high-velocity missiles. Penetrating trauma also includes iatrogenic injuries such as those following percutaneous catheterization of peripheral arteries for diagnostic procedures or access for monitoring. Blunt trauma—contusion or crush injuries—can produce transmural or partial destruction of the arterial wall, resulting in elevation of the intima and formation of intramural hematoma. The frequency of chemical injury to blood vessels has increased with inadvertent iatrogenic intraarterial injection of drugs and with the widespread drug-abuse problem.

Pathophysiology

Primary pathology of acute vascular injury includes hemorrhage, arterial disruption, and ischemia. Arterial injury can be obvious when there is pulsatile external hemorrhage, but bleeding can occur also in body cavities and in deeper tissue contained by fascial compartments. Until proved otherwise, ischemia of an extremity must be treated as though it were primarily due to vascular injury. Although extremity ischemia can be tolerated for 6 to 8 hours, occlusion of the carotid artery may result in brain damage within minutes of the injury in approximately 20% of patients (42). Delay in restoring perfusion to an extremity causes a vicious cycle, called the *ischemia-reperfusion syndrome* and characterized by the generation of oxygen radicals, damage to vascular endothelium, activation of platelets and leukocytes, microvascular occlusion, and cellular damage. The primary pathophysiologic changes associated with acute venous injuries include venous hypertension and consequent edema and compression of tissue in closed compartments. Other changes associated with major vascular injuries include false aneurysms and traumatic arteriovenous fistulae.

Symptoms and Signs

Symptoms and signs of arterial injury are similar to those of acute arterial occlusion. The commonly described sudden excruciating pain occurs only in approximately half of the patients with sudden arterial catastrophes. Numbness, marked coldness, tingling, pallor, weakness, and pain are associated in various combinations. Variations in symptoms probably depend on the suddenness of the organic lesion and the degree of vasospasm. Signs of vascular injury include an expanding or pulsatile hematoma, a false aneurysm, continuous murmurs of an arteriovenous fistula, loss of pulses, progressive swelling of an extremity, unexplained ischemic dysfunction, and a unilateral cool, pulseless extremity.

Diagnosis

Vascular injury must be assumed with any wound in the vicinity of a major blood vessel. Unless markedly unstable, all trauma patients should have a complete vascular examination, including palpation of the carotids and all peripheral pulses. It is important to note that normal pulses do not rule out vascular injuries; indeed, 10% of significant major vascular injuries result in no physical findings (44). Neurologic function must also be assessed, and auscultation must be carried out over the area of the obvious or suspected injury. The Doppler flow probe can be useful in detecting diminished pulse and determining whether there is flow in an artery in which injury is suspected. Because a significant percent of these patients have no physical findings suggesting vascular trauma, routine use of duplex sonography or arteriography is necessary (42). For example, posterior dislocation of the knee causes injury to the popliteal artery in 50% of the cases; arteriography or duplex scanning is mandatory in all such instances (45).

Treatment

Treatment of serious vascular injury requires prompt direct repair or bypass surgery. Success is based on timeliness and completeness of therapy, including balloon catheter removal of distal thrombus, appropriate soft tissue coverage of the reconstruction, and a low threshold for performing fasciotomy to prevent a postreperfusion compartment syndrome.

Aneurysm

Saccular or fusiform aneurysm of medium-sized vessels of the extremities can occur, but much less commonly than abdominal aortic or iliac aneurysm. When it occurs, aneurysm can involve the common femoral, superficial femoral, or popliteal arteries (46). Aneurysms of the arteries of the upper extremity are less frequent than those in the lower extremity and usually involve the subclavian, axillary, or brachial arteries. Femoral and popliteal aneurysms are often bilateral and are associated with aneurysm in the aorta or its primary branches in a majority of cases (6,46).

Etiology

The cause of aneurysm in the lower limb is usually degenerative processes, although mycotic arteritis and trauma also play a role in a small percentage of patients. Pseudoaneurysms due to prior diagnostic or therapeutic interventions are increasingly common. The most common cause of aneurysm in the upper limb is arterial trauma; less common causes include mycotic arteritis.

Pathophysiology

The sequelae and pathophysiology of aneurysm of peripheral vessels are quite different from those of aortic aneurysm in that, at these levels of the circulation, the vessels are prone to thrombosis or peripheral embolization, or both. Rupture can occur, but it is much less frequent than with aneurysm of the large arteries.

Symptoms and Signs

The symptoms depend on the site and size of the aneurysm and its sequelae. Femoral artery aneurysms are usually symptomless except for local mass or distal limb swelling. However, a majority of patients with popliteal aneurysm ultimately present with claudication, rest pain, and even gangrene. Limb loss occurs in 10% to 20% of patients (46). Some patients will present because of a painful swollen calf and demonstrate a prominent superficial venous pattern, suggesting deep venous thrombosis (DVT). In most cases the latter is caused by compression of the popliteal vein by the adjacent aneurysmal mass and clears with aneurysm repair, although a few patients are left with secondary venous thromboses.

When thrombosis of the aneurysm occurs gradually, the collateral circulation might have time to develop sufficiently so that the patient experiences pain only with exercise or rest pain. When the thrombosis occurs quickly, however, severe ischemia often develops, leading to tissue necrosis and limb loss. Surgical intervention is not always successful even if timely.

Therapy

Treatment consists of resection and replacement with either prosthesis or vein graft. Before surgery, arteriography is deemed advisable to demonstrate the arterial circulation bilaterally plus the runoff on the involved side. In some instances, particularly with popliteal aneurysm, the sac is isolated by proximal and distal ligation and distal blood flow is maintained by a bypass graft (6).

Popliteal Entrapment Syndrome

Etiology

Muscular entrapment of the popliteal artery can occur as the vessel courses medial to an anomalous head of the gastrocnemius muscle at the knee or beneath an enlarged plantaris or popliteal muscle (Fig. 33-11) (47,48). This entity characteristically affects young adults, usually males in the third or fourth decade of life, and occurs more frequently than previously thought.

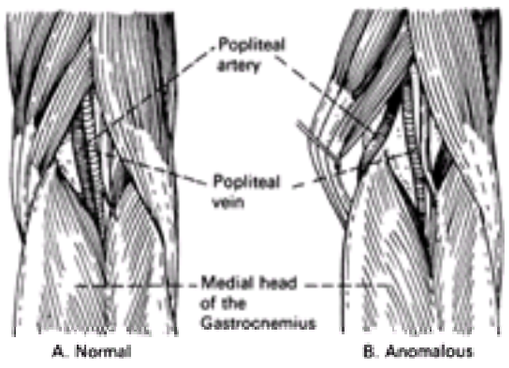

Figure 33-11. **A:** The normal relationship of the popliteal artery and the two heads of the gastrocnemius muscle. **B:** The most common (type 1) anomaly, which causes entrapment syndrome. The popliteal artery is looped medially around and then under the normally arising medial head of the gastrocnemius. Medial hamstring muscles have been retracted for clarity. During strenuous exercise of the leg, the muscle compresses the artery, with consequent ischemia and intermittent claudication. (Modified from Haimovici H. *Vascular surgery*. New York: McGraw-Hill, 1976:498.)

Symptoms and Signs

Onset of symptoms is often sudden, occurring during an episode of intense lower extremity activity. The symptoms are described as cramping in the calf or foot and coldness, blanching, paresthesia, and numbness of the foot associated with walking and relieved by resting the leg. Symptoms are usually unilateral despite subsequent demonstration of bilateral involvement (48). The symptoms may be correlated with the development of thrombosis and segmental occlusion of the mid-portion of the popliteal artery. If the popliteal artery becomes occluded acute ischemia can occur, but limb loss is rare because of the collateral circulation, which usually develops in response to the chronic compression and narrowing.

Diagnosis

Diagnosis is usually made from the patient's history and confirmed by physical findings, especially the presence of normal pulses at rest and in a position of relaxation of calf muscles. In patients with an occluding thrombus of recent origin, popliteal and pedal pulses are absent. In cases of partial chronic occlusion of the popliteal artery by thrombus, the popliteal artery pulse is absent but pedal pulses may be present, although they are diminutive and disappear with exercise. Approximately one-third of the patients have characteristic symptoms but palpable popliteal and pedal pulses (48). Passive dorsiflexion of the foot with active plantar flexion against resistance, which causes the contracted gastrocnemius to compress the abnormally positioned artery, causes loss of the pedal pulse. Auscultation of the popliteal artery can reveal a systolic bruit if the artery is sufficiently suppressed. Duplex scanning of the popliteal artery, demonstrating normalcy at rest but partial or complete extrinsic compression with calf muscle contraction, is diagnostic. Bilateral femoral arteriography is a critical part of the examination to rule out contralateral entrapment.

Treatment

All cases of popliteal artery entrapment, whether the artery is occluded or not, should be treated surgically (48). This applies not only to symptomatic limbs but also to asymptomatic limbs in which the anomaly is incidentally identified by routine bilateral arteriography. To temporize and risk ischemic changes in such young, healthy individuals is inappropriate (48). The procedure is myotomy, complete transection of the compressing muscle or fascial band. In addition, thrombectomy is required when the popliteal artery is occluded by fresh thrombus. If organized thrombus with a poor line of cleavage between thrombus and vessel wall is present or if the vessel is narrowed owing to fibrosis, arterial resection and vein bypass are indicated (48). Results are generally good because of those patients' youth and otherwise normal vasculature.

Compartmental Syndromes

Swelling within a compartment of the arm or leg can lead to severe acute pain and irreversible neuromuscular damage, with loss of function related to the contents of the involved space (49). The most frequent, and indeed the classic, form of this problem is the anterior tibial compartmental syndrome (49). Compartmental syndrome can be a chronic recurrent problem, associated with lower extremity exercise, often in young athletes. Acute compartmental syndrome usually follows extremity trauma or acute ischemia exercise and is manifested by the following symptoms: (a) Within a few hours excruciating pain occurs in the compartment; (b) the muscle within the compartment becomes tense and diffusely tender; (c) there is weakness of dorsiflexion; and (d) sensation is diminished in the distribution of the deep peroneal nerve, particularly in the first web space of the foot. Unless the compartment is promptly decompressed by fasciotomy, there is extensive muscle necrosis and permanent damage to the deep peroneal nerve. This condition is discussed in more detail in Chapter 79.

An equivalent course of events can involve the other three compartments in the leg or the three compartments of the forearm; the etiology might differ, but the outcome is the same unless the problem is promptly recognized and treatment is instituted immediately. Other causes of swelling within compartments bounded by fascial envelopes and bone include trauma, acute arterial obstruction, and restoration of normal perfusion to an extremity that has been ischemic for prolonged periods of time. The association between severe pain in a tight, very tender compartment, and the possibility of subsequent development of myoneural ischemia and necrosis must be kept in mind and readily recognized and treated. The same urgency must be applied to the compartmental syndrome as to any other acute vascular problem because time is of the essence. This urgency is best exemplified by the high incidence of extensive muscle necrosis in the involved compartment when fasciotomy is delayed for more than a few hours (49).

DISEASES OF THE SMALL ARTERIES

The most important diseases of the small arteries that produce pain include embolism, collagen vascular disease, and local cold injuries. Although the latter also involve the microcirculation, they are discussed in this section.

Embolism

Etiology and Pathophysiology

The complicated plaque of arteriosclerosis converts the normal arterial intima from a smooth surface to one with an irregular surface with areas of ulceration. These areas can harbor small thrombi interspersed with cholesterol crystals that can be released and produce occlusion of small arteries of the foot (or occasionally the hand), leading to the development of severe ischemia that can ultimately result in digital, foot, or limb amputation (50). Alternatively the mural thrombus lining an arterial aneurysm may be shed into the distal circulation with similar results. The phenomenon has been given the descriptive terms of “blue toe” or “trash foot” syndrome.

Symptoms and Signs

The clinical picture is dramatic, and the patient usually notes the sudden onset of pain is confined to the digits, often of both feet. The pain is of the ischemic type and is relieved to varying degrees by dependency. The toes are cold, with interspersed areas of erythema and cyanosis. Livedo reticularis of the foot is common and is a clue to the underlying pathology.

Treatment

Treatment is expectant, with attention directed at keeping the patient comfortable. Pain should be controlled with nonnarcotic analgesics; potent narcotics may be used for a short period if the pain is severe. The ultimate outcome depends entirely on the extent of the occlusion and collateral circulation and the degree of reflex

spasm. In the event that conservative measures are not effective and there is obvious gangrene of the toes, amputation at the digital or transmetatarsal level will be required. In some cases it is necessary to bypass or endarterectomize the proximal arterial site responsible for the emboli to prevent recurrences (6).

Vasculitis

Inflammatory and proliferative changes of the small arteries and arterioles occur in diverse diseases, the most important of which are periarteritis nodosa, systemic lupus erythematosus, scleroderma, dermatomyositis, rheumatoid arthritis, rheumatic fever, and systemic giant cell arteritis (temporal arteritis). TAO (Buerger's disease) is classified by some as a vasculitis and is discussed earlier in this chapter. Histologic changes with the vasculitides vary in both extent and severity and range from acute necrotizing arteritis to a proliferative endarteritis. These changes in themselves are often nonspecific and can be seen in varying degrees in all of these diseases. Most of these conditions are discussed in Chapter 27.

Disorders Due to Cold Injuries

Exposure to cold can alter both cells and extravascular fluid (direct effects) and can disrupt the integrity of peripheral circulation and the function of organized tissues (indirect effects) (51). The mildest form of cold injury is called *frostnip* and tends to occur in organs farthest away from the core of the body, such as the fingers, toes, hands and feet, ear lobes, nose, and cheeks. More severe cold injury can be divided into freezing injuries (e.g., frostbite) and nonfreezing injuries (e.g., immersion foot, trench foot, pernio).

Pernio (Chilblain)

Pernio, or chilblain, is the mildest form of disorders due to local cold injuries. This condition occurs most frequently in patients who live in moist, cool, or temperate climates and is seen more frequently in England than in the United States (52). Pernio was long considered a purely dermatologic lesion, but recent work has emphasized the vascular nature of the disease. Acute pernio, or chilblain, has been experienced by many children who go out in the snow or in cold, wet weather without adequate protection for their feet and by women who wear short skirts in cold weather. A chronic form develops after repeated exposure to cold by susceptible individuals.

Symptoms and Signs. In the acute phase the skin is reddish, cyanotic, and slightly edematous. Occasionally small blebs appear that can become hemorrhagic, or small purpuric spots develop that can persist for a long time (52). The patient experiences itching and burning sensations after exposure to cold. When the condition occurs in the legs it is almost always bilateral and symmetric.

In the chronic stage, which develops from persistent exposure to cold and dampness, the blisters break down and produce superficial ulcers with a hemorrhagic, pigmented base. These ulcers persist throughout the exposure or even for the entire winter. Severe pain can accompany the ulcer, and the skin can be cold and cyanotic. Healing produces a pigmented scar, which can break down on further exposure. Pigmentation persists after healing.

Treatment. Pernio can be minimized by avoiding exposure to cold and providing adequate protection from cold when it cannot be avoided completely. When the condition occurs, the limb should be warmed gradually, but the affected region should be kept away from extremely elevated temperatures because excessive heat can easily produce a burn. The lesion should not be rubbed with snow or placed in excessive cold water, because these measures can further damage the skin and add to the vasoconstriction already present. The blisters should be debrided and sterile dressing applied without any salves or antiseptic. Further exposure to cold should be avoided. A recent prospective randomized trial has demonstrated substantial benefit from administration of calcium channel blocker drugs, thus underscoring the vasospastic nature of the condition (53).

Trench Foot and Immersion Foot

Immersion foot and trench foot are similar entities, observed originally during wartime in personnel whose feet have been wet for prolonged periods but not frozen, but now seen in urban destitute or homeless populations as well. Most authorities consider both of these conditions similar entities, and, indeed, some believe that they represent a form of the pernio syndrome (52).

Pathophysiology. The pathophysiology can be divided into three phases: (a) an initial vasospastic ischemic phase characterized by cold-induced vasoconstriction, increased blood viscosity, and impaired oxygen transport; (b) an intermediate hyperemic phase characterized by a bounding pulse, pulsatile circulation, and red, swollen, and painful feet; and (c) a late ischemic vasospastic phase.

Symptoms and Signs. In the initial vasospastic ischemic phase, the extremities are pale or cyanotic and cold; arterial pulsations are reduced; edema appears; and if the exposure is prolonged there are petechial lesions, shallow ulcerations, and patchy areas of anesthesia.

The intermediate hyperemic phase begins when the patient is removed from the cold and is placed in a warm environment, and it usually lasts approximately 2 weeks. During this phase the feet become red and hot, arterial pulsations are full and bounding, and edema supervenes. The edema increases rapidly unless the extremities are placed in a cool environment. Frequently blebs appear and become filled with hemorrhagic fluid. After several days the numbness disappears and the patient experiences burning paresthesia and pain, which can be intense and of a shooting character. Lymphangitis, phlebitis, and cellulitis can complicate the condition.

The late vasospastic ischemic phase does not occur if the initial lesion is of a mild degree and proper treatment is instituted early. In severe cases recovery is slow, and coldness, pain, hyperhidrosis, paresthesia, and stiffness persist for weeks, months, or even years. The sensitivity to cold, manifested by a typical Raynaud's syndrome, can persist for a long period of time.

Treatment. The problem of rewarming is critical in these patients during the stage of ischemia, when overheating of tissue can lead to thermal injury (51). Avoidance of trauma and maintenance of asepsis are extremely important. In patients who have persistence of sensitivity to cold and develop pain on weight bearing (which can cause discomfort for many years), sympathectomy may be considered if prognostic sympathetic blockade produces effective relief.

Frostbite

The degree of cold necessary to produce frostbite is influenced by a number of factors, but primarily the environmental temperature. Exposure to a temperature of –30°C will shortly result in freezing of the extremities of most normal individuals. In the presence of a strong wind, frostbite can occur up to a temperature of –4°C, due to rapid evaporation of sweat and dissipation of the layer of radiant heat around the skin (54). Frostbite can occur at temperatures above 4°C in individuals who have occlusive arterial diseases. Severe hypoxia, anemia, malnutrition, and hypoproteinia with edema are definite contributing factors in the development of frostbite. Wetting of the extremity, such as occurs with perspiration or immersion in water, greatly increases the tendency to freezing because water dissipates heat much more rapidly than air (55). The metabolic effects of physical activity reduce the hazard from thermal cold injuries, but enforced immobility predisposes to development of lesions. Smoking, through its peripheral vasoconstricting action, can be a contributing factor.

Pathophysiology. The pathophysiology of frostbite involves two major mechanisms: (a) vasoconstriction with subsequent stasis and thrombus formation and (b) formation of ice crystals in the tissues and extracellular fluid (56,57 and 58). Exposure to freezing temperatures produces local and reflex arterial and venous constriction that results in increased venous pressure and decreased capillary perfusion (Fig. 33-12). At the same time, ice crystals form in the extravascular space and solutes in the residual nonfrozen interstitial fluid become concentrated and thus produce a localized hypertonic area. As extracellular water passes along this induced osmotic gradient into the extracellular solution, it too is incorporated into ice crystals (51,52). Eventually all intracellular water not directly bound to cellular constituents can be appropriated into this gradient and the cell converted into a shrunken mass of solute surrounded by ice crystals. Final crystallization of the plasma volume completely arrests blood flow, and cells themselves can freeze as lower temperatures are approached. With prolonged exposure to cold and with reduced or absent circulation, there develop swelling; vacuolization; and other inflammatory reactions of the intima of small arteries, arterioles, and capillaries, together with low-grade inflammation of all affected tissue.

Figure 33-12. Pathophysiology of frostbite. See text for details. (Modified from MacLean D, Emslie-Smith D. *Accidental hypothermia.* Boston: Blackwell Scientific, 1977:237–246, with permission.)

With thawing, an initial hyperemic vascular phase intervenes that results from prior capillary and arteriolar damage followed by microcirculatory sludging and subsequent thrombus formation (52,57,58 and 59). Arteriovenous shunting then aggravates the overall insult and converts a hypoperfused area into a nearly avascular one. Moreover, on resumption of the circulation, the damaged endothelium allows pathologic permeability, extravasation, and further intravascular clumping so that the vascular bed of the frozen tissue is occluded by thrombi. Early on, the intravascular clumping is reversible, but with the passage of time, clumped red blood cells within vessels in injured tissue lose their morphologic identity and take on the appearance of a homogeneous hyaline plug (51) (see Fig. 33-12).

The course of most cases of frostbite and other injuries from cold is usually of three phases: (a) the acute phase, characterized by freezing, which produces vasoconstriction and ice-crystal formation, followed by thawing with consequent vasodilation, blistering, and beginning necrosis; (b) the subacute phase, during which necrosis is resolved and vasospasm starts; and (c) the chronic phase, during which the vasospasm continues and pain and recurrent ulceration can occur.

Symptoms and Signs. Frostbite is conventionally classified into degrees according to severity of tissue changes (60). In *first- degree frostbite* the outer layer of the skin is involved, appearing waxy and firm. The patient experiences aching pain, numbness, and paresthesia, but there is no blistering or peeling. Prompt return to a normal environment results in complete recovery, with no demonstrable damage to the tissues.

Second-degree frostbite occurs when exposure is sufficient to produce damage to the superficial layers of the skin. The skin is waxy white and firm, and the involved digits become stiff. As the extremity is thawed, reactive hyperemia develops around the frozen area and gradually spreads to include the entire involved area. The skin is now red and tender, and the patient might complain of burning pain. Edema and blisters develop, and portions of the superficial skin can become necrotic and peel off. In 2 to 3 weeks the superficial layers of the skin peel off, leaving a complete layer of healed skin.

Third-degree frostbite occurs with more severe or prolonged exposure, resulting in damage involving the full thickness of the skin and subcutaneous tissue. The symptoms are the same as with second-degree frostbite, but the pain is more severe and the healing phase is more prolonged. In the deeper necrotic areas the skin becomes darker and adherent to form a hard, dry eschar over the necrotic area. Secondary infection around and under this eschar is common.

Fourth-degree frostbite is caused by very severe and prolonged cold exposure resulting in gangrene of the deep tissue, including bone, with consequent loss of an extremity or portion thereof. Early symptoms are the same except that with rewarming the pain after thawing is severe. The hyperemia does not extend over the dead area, however, and blisters do not occur. The tissues, generally the distal portions of the digits, become gradually darker and shriveled. Spontaneous amputation eventually ensues.

The late sequelae of moderate to severe frostbite include (a) persistent hypersensitivity to cold; (b) pain at rest and in phantom limb fashion if spontaneous amputation has occurred; (c) hypesthesia and subjective numbness alone or in combination with hyperesthesia and allodynia; (d) hyperhidrosis and decrease in hair; (e) persistent skin changes; and (f) such signs of sympathetically mediated pain syndromes as osteoporosis and rigid nails. These late symptoms are generally worse in the winter and after exposure to cold (51).

Diagnosis. The diagnosis of cold injuries is easily made with the history of exposure to cold and the signs of freezing of tissues. The presence of underlying organic vascular disease should always be considered and sought for, especially in circumstances in which others are exposed equally with the patient but developed milder or no frostbite.

Treatment. Most instances of frostbite can be prevented by adequate prophylactic measures. Particular care should be taken to prevent exposure to cold by those known to have occlusive or vasospastic arterial disease. Warm, loose-fitting clothing should be worn during necessary exposure (52,57,58 and 59). Every effort should be made to keep the body and extremities dry. Special foot care is important in those necessarily exposed to cold. This includes daily washing, careful drying, gentle rubbing with oil, and careful attention to the nails, avoiding even minor trauma.

Frostbite should be considered a medical emergency (52). In first-degree frostbite, restoring the normal temperature of the skin is all that is required. The best source of heat for this is the warm skin of the patient's own body. Great care should be taken to avoid trauma, especially from extrinsic heat sources or from vigorous rubbing of the part. Measures to raise core temperature are important. At high altitudes the administration of oxygen is definitely indicated. Persons whose feet are frozen should not be allowed to walk even short distances if it is possible to arrange for other means of transportation, because walking can severely injure the frostbitten foot (52,57). The long controversy of whether rapid or slow thawing should be carried out has been resolved in favor of rapid thawing, achieved by exposing the involved tissue to a warm bath of no more than 40°C to 42°C (104°F to 107.6°F) for 15 to 20 minutes (52,57,58 and 59). If the local damage is extensive, an antibiotic should be administered. Although heparin, fibrinolytic agents, steroids, vasodilators, antiplatelet agents, and other materials have been found useful in experimental models, similar data in humans are less convincing—a fact that might be related to the long interval from the time of injury until treatment. Sympathectomy may be considered but data supporting its human use are unconvincing. In patients with severe injury seen later in the disease and in whom symptoms persist, sympathetic blocks are used for diagnostic purposes. If the results are positive, the patients may have a sympathetically mediated pain syndrome and surgical or chemical sympathectomy should be entertained. Amputation is obligatory in severe cases with extensive gangrene or unremitting pain.

DISEASES OF THE MICROCIRCULATION

The most important painful diseases that involve the microvasculature can be divided into two major categories: (a) vasospastic diseases, which include Raynaud's disease, Raynaud's phenomenon, acrocyanosis, and livedo reticularis and (b) vasodilating disorders, of which erythromelalgia is the most important.

Raynaud's Disease

In 1862, Maurice Raynaud described a disease entity characterized by symmetric impairment of the circulation in the digits of the extremities manifested by pain and phasic color changes, sometimes progressing to ulceration of the fingertips and even gangrene (61). The larger arteries seemed uninvolved. Subsequently it was pointed out that Raynaud had not discovered a separate disease entity but had described a symptom complex that could be either primary or secondary. Consequently, writers have labeled these conditions as *Raynaud's disease*, *Raynaud's phenomenon*, *Raynaud's syndrome*, and other names (see 62 for references). Although controversy remains about terminology, many authorities agree that the term *Raynaud's disease* should be reserved for the relatively common circumstance of benign episodic digital vasospasm in response to cold or emotional stimuli and that the term *Raynaud's phenomenon* should be used for cases in which an underlying pathologic process is responsible for the symptoms.

Raynaud's disease is the benign form of cold sensitivity, and the criteria for establishing this diagnosis have not changed since the original description by Allen and Brown in 1932 (63). These are as follows: (a) The attacks can be precipitated either by exposure to cold or by emotional stimuli; (b) involvement is bilateral and symmetric; (c) there is no evidence of occlusive disease involving the digital arteries; (d) trophic change or gangrene is rare; (e) the disease must have been present for a minimal period of 2 years; and (f) there must be no evidence of an underlying disease that could cause the symptoms. All other cases that exhibit episodic digital

ischemia but do not meet the above criteria and for which an organic basis can be found should be labeled Raynaud's phenomenon.

Etiology and Pathophysiology

The exact cause of Raynaud's disease is unknown, although gender, age, and constitutional factors probably play a role in its development (62,64). Up to 90% of cases are in women and onset of the disease occurs before the age of 30 in approximately 60% of the cases, before 40 years in 80%, and before 55 years in all cases (see 62 for references).

Exposure of the extremity to cold is the most important factor that initiates either Raynaud's disease or Raynaud's phenomenon (65). The threshold for the abnormal vascular response appears to be lowered by anything that activates the sympathetic outflow or release of catecholamines. Patients note that on exposure to cold the fingers turn white, then blue, and finally red during the attack (the so-called tricolor changes).

The color changes in the skin depend on the tone of the capillaries and blood flow through them, whereas temperature changes are related to the condition of the arterioles. The pallor is due to arteriolar spasm and during this stage the capillary microscope will reveal that blood is not entering the capillaries (62). The subsequent hypoxia causes loss of tone, first in the capillary walls, resulting in capillary vasodilation. Stagnant capillary blood becomes increasingly deoxygenated and the fingers become both cold and cyanotic. Increasing anoxia ultimately produces paralysis of the arteriolar walls, which relax; then flush appears, first producing a reddish-blue color and finally a profound hyperemia with fingers that are red and slightly swollen.

Symptoms and Signs

The patient, often a young woman of asthenic build, complains of typical attacks of numb fingers (occasionally the toes as well) on exposure to cold. Usually such color changes begin gradually, although occasionally there is a severe sudden attack (62). Onset of symptoms is precipitated by cold, but as the patient becomes anxious about the condition emotional stress may contribute significantly. At first only the tips of the fingers of both hands are involved, but later more proximal parts of the fingers are also involved, and in the late stages the color changes can extend back to the rest of the hands. Complaints of various paresthesias can accompany the color changes, including numbness, tingling, a feeling of tightness, “pins and needles,” stiffness, aching, and burning. During the attack the fingers are cold and sensory acuity is often diminished. Slight swelling of the involved fingers can occur, but only during and after the attacks. During the initial phase of the disease, pain occurs but is not a prominent symptom. In the advanced stages of Raynaud's disease the attacks become so severe and so frequent as to be disabling. Exposure to a slightly cool environment and almost any emotional stress can precipitate a bout; consequently, the warmer weather of the summer season might afford little relief.

Diagnosis

The diagnosis of Raynaud's disease is relatively easy in cases in which the aforementioned criteria are met. In addition to taking a detailed history and carrying out a complete physical examination, it is essential to exclude the possibility of occlusive arterial disease, which can be done if both the radial and ulnar pulses are present. It is essential to differentiate Raynaud's disease from Raynaud's phenomenon by searching for possible causes of the latter disease. The information that the patients are usually young at time of onset, are predominantly female, and have bilateral symmetric involvement of the upper extremities points to the diagnosis of Raynaud's disease. The differential diagnostic features of the most important vasospastic diseases of the extremities are summarized in Table 33-4. These features can be compared with those in Table 33-3, pertaining to occlusive disease. Importantly, the development of digital trophic changes such as ulceration or frank gangrene generally signifies the presence of Raynaud's phenomenon, resulting from an underlying rheumatologic or other disease.

TABLE 33-4. Differential diagnosis of various vasospastic disorders

The diagnosis of Raynaud's disease and differentiation from Raynaud's phenomenon can be accomplished by the performance of digital arteriography, which will show vasoconstriction of otherwise normal arteries in the former, but segmental digital arterial occlusions and arterial collateral formation in the latter.

Treatment

The type of therapy selected for managing patients with Raynaud's disease depends on the severity of signs and symptoms. In milder cases, certain basic general measures are sufficient. First, it is important to offer reassurance because many patients have considerable anxiety about the development of gangrene, amputation of digits, and other complications as a result of misinformation from relatives, friends, and lay literature (62,64). Patients can be reassured that the condition generally remains stable and ultimately regresses. Second, patients should be carefully instructed to avoid exposure to cold and to protect the extremities by wearing fur-lined gloves and, in some instances, lined boots, and also to keep the body as well as the extremities warm.

In mild to moderate cases, vasodilators such as calcium channel–blocking medications given by mouth have beneficial effects (62). Other agents that have been reported to be useful include (a) prazosin (Minipress) in doses of 1 mg once or twice a day, (b) tolazoline hydrochloride given orally in doses of 25 to 50 mg three or four times daily, (c) griseofulvin in oral doses of 500 to 1,000 mg daily, and (d) phenoxybenzamine hydrochloride (Dibenzyline) in oral doses of 10 to 20 mg 4 times a day (see 62 for references). In moderate to advanced stages of the disease, patients should be advised to move to a warm climate because this in itself can be sufficient to avoid progression of the disease.

In patients who are disabled by severe disease, regional sympathetic denervation should be given serious consideration, especially for lower extremity digital vasospasm. Although it is less effective for the upper limb, it can provide satisfactory results. Palmar digital sympathectomy is probably more effective than cervical sympathectomy, which can have excellent initial results but is unpredictably durable.

Raynaud's Phenomenon

Raynaud's phenomenon by definition is digital ischemia secondary to other pathologic processes. The most important conditions that can cause secondary Raynaud's phenomenon are listed in Table 33-5 (62,64).

TABLE 33-5. Raynaud's phenomenon

Etiology

Microtrauma to the small vessels of the hand and fingers caused by the continued use of a pneumatic hammer or other vibrating tools, such as a chain saw, are frequent causes of Raynaud's phenomenon in both hands. Similarly, the frequent use of tools that require squeezing action of the hand, as seen among farmers, creamery workers, and laborers whose hands are subjected to repeated blunt trauma can also result in bilateral Raynaud's phenomenon. These patients will complain of cold, discoloration, and pain in one or more fingers. Pianists, typists, and other keyboard workers who use their hands for long periods every day may develop vasospastic disease of one or two digits, and the vasospasm is evoked only on exposure to cold (62).

Patients who have thoracic outlet compression syndrome, caused by a cervical rib or hypertrophic scalene muscles or other anatomic abnormality, may develop Raynaud's phenomenon in the affected limb. Patients also may develop Raynaud's phenomenon consequent to carpal tunnel syndrome. In patients with Raynaud's phenomenon the symptoms are frequently more severe and are often associated with areas of digital gangrene and necrosis. The prognosis for loss of digits for those with many of the diseases listed under “miscellaneous conditions” of Table 33-5 is poor.

Symptoms and Signs

The symptoms are similar to those described for Raynaud's disease but more severe, and more constant and ultimately associated with digital trophic changes. The extent of pain experienced by patients is extremely variable. Fingertip ulcers or areas of gangrene are extremely painful, sometimes refractory even to narcotic analgesics. Patients with intact skin will note pain only during the attack, when the digits are profoundly ischemic.

Diagnosis

Raynaud's phenomenon is readily diagnosed on the basis of the age and sex of the patient, on the history of the underlying connective tissue or other disease, and occasionally on information of the occupation of the individual. Whereas Raynaud's disease occurs predominantly in females younger than age 40 years, secondary Raynaud's phenomenon occurs in a more equal gender distribution: Young women more commonly suffer from collagen vascular diseases, whereas young and middle-aged men more often demonstrate occupational Raynaud's phenomenon. Details about the digits involved at onset and subsequently can be useful points in differentiating primary from secondary Raynaud's symptoms. Limitation of the disease to one limb, particularly an upper limb, suggests Raynaud's phenomenon (Table 33-6).

TABLE 33-6. Differential diagnosis of Raynaud's disease and Raynaud's phenomenon

Some diagnostic features	Raynaud's disease	Raynaud's phenomenon
Sex	Female	Male = female
Age at onset (yr)	<40	>40
Bilateral involvement	Usually	Not usually
Ischemic changes	–	+
Underlying systemic disorder	–	+

The physical examination should include complete examination of pulses and elevation and dependency tests of the hands to determine any digital ischemia caused by occlusive arterial disease. Use of the handheld Doppler flow detector can be used to identify palmar and digital arterial occlusion as well as ulnar or radial occlusion. Tests for thoracic outlet compression are particularly indicated in the examination of patients with unilateral upper extremity Raynaud's phenomenon. Skin temperature measurements of the digits before and 30 seconds after immersion of the hands in ice (cold immersion test) is a useful procedure in diagnosing both Raynaud's disease and Raynaud's phenomenon. Whereas the normal response to cold immersion is recovery of digital skin temperature to preimmersion values in 10 minutes or less, it might take 20 minutes or longer for the digital temperature of patients with Raynaud's disease or phenomenon to return to preimmersion levels. Digital strain-gauge plethysmography will display wave forms of digital arteries blunted by vasoconstriction associated with cold immersion: Digital vessels with obstruction will be abnormal in the control setting before cold immersion.

Treatment

Management of patients with Raynaud's phenomenon is the same as for Raynaud's disease regarding protection from cold and trauma, avoidance of tobacco, and the use of vasodilators. In patients with secondary Raynaud's phenomenon, therapy directed toward the underlying condition such as carpal tunnel syndrome or thoracic outlet syndrome, ergotism, and myxedema may relieve the Raynaud's phenomenon. In the patient in whom the condition is caused by repeated trauma, cessation of the causative factor not only stops the progression of any occlusive arterial disease but can ameliorate the Raynaud's phenomenon as well. With recurrent or refractory digital ulceration, local therapy with soaks, protection of the limb, administration of antibiotics, and, occasionally, topical nitroglycerin administration may be successful. Debridement of ulcerations often helps, but healing is commonly slow.

Regional sympathetic denervation may be considered in intractable cases of secondary Raynaud's phenomenon if the underlying cause cannot be eliminated and the disease progresses. Before considering surgery, at least three or four prognostic sympathetic blocks should be carried out with long-acting local anesthetics. As noted previously, palmar periarterial sympathectomy may be more effective than cervical sympathectomy. Fingertip or digital amputation may be required.

Acrocyanosis

Acrocyanosis is a peripheral vasospastic disorder manifested by coldness, intense diffuse cyanosis, and occasionally edema and hyperhidrosis. Although it is frequently confused with Raynaud's disease, the symptoms are sufficiently different to make it a separate entity (6,62,64).

Etiology

The cause of acrocyanosis is obscure, but it is apparent that those with this disorder have an underlying susceptibility to cold. Some authorities attribute it to a dysfunction (hyperactivity) of the sympathetic vasomotor nerves, and others are of the opinion that the fault lies in the smaller vessels of the affected extremity (62,64). The condition occurs predominantly in young women.

Pathophysiology

The mechanism of acrocyanosis has not been clearly defined. The evidence suggests that there is arteriolar spasm followed by secondary dilatation of the capillaries and venules. In chronic cases there can be hypertrophy of the media layer of the affected arterioles (62).

Symptoms and Signs

The clinical picture of acrocyanosis is that of a constant coldness and bluish-purple discoloration of the extremities, particularly the hands and fingers, and, to a lesser degree, the feet and toes, which are aggravated by exposure to cold temperatures. Edema and hyperhidrosis are sometimes present. The symptoms are most marked during the winter, but they can be present (although to a lesser extent) in warmer weather (64). During the summer the extremities are warmer and the color of the skin changes from deep purple, when the skin is extremely cold, to red, when it is warmer. There are no episodes of blanching. In contrast to Raynaud's disease and Raynaud's phenomenon, trophic changes, ulceration, and gangrene do not occur. Examination of the peripheral arteries does not reveal any evidence of occlusive arterial disease.

Diagnosis

Diagnosis is made by the history and clinical manifestations, and the condition is differentiated from Raynaud's disease by the fact that cutaneous discoloration in acrocyanosis is constant without periods of pallor or hyperemia. Acrocyanosis can be differentiated from the cyanosis that occurs with occlusive diseases by the fact that pulses are present. The presence of pulmonary or cardiac diseases that might produce cyanosis should be ruled out.

Treatment

The patient should be reassured about the benign nature of the disease and instructed to avoid exposure to cold. In patients who are disabled, a trial of vasodilators such as calcium channel blockers may be given.

Livedo Reticularis

Livedo reticularis is characterized by a local prominent mottling, or reticular (“fishnet”) reddish-blue discoloration of the skin of the extremities (6,62,64). Although the condition was long considered a primary dermatologic disorder, in recent years the underlying vascular nature of the condition has become recognized (62).

Etiology

The cause of idiopathic livedo reticularis is unknown, although there is unquestionably some inherent vasomotor instability in these patients, most of whom are women. Secondary livedo reticularis can be the initial manifestation of one of the conditions listed below and can affect both men and women (64):

- Connective tissue diseases
- Vasculitis
- Myeloproliferative disorders
- Dysproteinemias
- Atheroembolism (cholesterol embolization)
- After cold injury
- Use of amantadine hydrochloride
- Complex regional pain syndrome

Pathophysiology

The changes occurring with livedo reticularis are similar to those of acrocyanosis—a narrowing, either organic or functional, of arterioles, with dilatation of the capillaries and venules (62,64). The obstruction of the arterioles, which can be either spastic or organic, occurs principally in the peripheral portion and therefore affects only the peripheral subdermal capillary arborization, thus accounting for the peculiar reticular nature of the discoloration. Histologic studies reveal proliferation of the intima in isolated arterioles and small arteries in advanced cases. Although some of these arteries are occluded completely, in most instances no changes are noted in the arterioles of the skin underlying the discolored parts.

Symptoms and Signs

Idiopathic livedo reticularis begins early, typically in the late teens or early 20s, and the patient complains of persistent bluish to bluish-red mottling of the skin of both legs and feet that can extend to the thighs. It can also involve the hands and arms and occasionally the trunk (62,64). Some patients complain of coldness, numbness, dull aching pain, and paresthesia of the affected limb. In most patients the condition is mild and causes no other symptoms or signs. Some patients, primarily women, develop recurrent ulcerations (usually during the winter) about the ankles and feet that have the appearance of typical ischemic ulcers. These ulcers are painful, slow to heal, and located in the distal lateral or posterior leg or dorsum of the foot. The large arteries such as dorsalis pedis, posterior tibial, and popliteal are not involved, although thrombosis of the digital arteries may occur.

Diagnosis

Diagnosis of livedo reticularis can be made readily from the appearance of the extremity. The condition can be confused with acrocyanosis, Raynaud's disease, pernio, scleroderma, and even with some of the chronic arterial occlusive diseases.

Treatment

Patients with idiopathic livedo reticularis should be thoroughly informed about the condition and given reassurance as well as instructions on protecting the involved parts and the body as a whole from exposure to cold. When patients are distressed by the cosmetic effects, a trial of vasodilators, such as prazosin (Minipress) in a dosage of 1 mg twice daily, is given. If ulceration is present, local care, rest in bed and elevation of the extremity, and elastic supportive bandage are used. In secondary livedo reticularis, treatment of the underlying condition is indicated (62,64).

For patients in whom these conservative measures fail and have marked disability from the condition, sympathectomy should be considered because it may make the livedo pattern less prominent and helps to heal the ulcers.

Erythromelalgia (Erythmelalgia)

Erythromelalgia is a term first used by Weir Mitchell to describe a condition manifested by hot, red, and painful extremities due to abnormal arteriolar vasodilatation (66). The more descriptive term “erythmelalgia” is more appropriate for the condition, because it emphasizes the fact that the painful, red skin on the extremity also exhibits an increase in temperature (67).

Etiology

Weir Mitchell divided the condition into a primary (idiopathic) form and a secondary form (66). The cause of the primary form is unknown and the condition occurs in

persons who do not have any demonstrable organic disease of the nervous or vascular systems. Secondary erythmelalgia is usually a symptom of myeloproliferative disorders, but it can also occur with hypertension, venous insufficiency, diabetes, systemic lupus erythematosus, and rheumatoid arthritis (62).

Pathophysiology

The basic mechanism of the vasodilation and the cause of the burning pain are unknown. The temperature at which distress can be produced varies with different persons and in different parts of the extremity of the same person. It usually lies within the range of 32° to 36°C; the temperature at which it occurs in a specific patient was designated by Lewis as the “critical point” (68). If the temperature is higher than this critical point the distress persists, and with temperature lower than this critical point the distress disappears. In the past, vasodilatation was considered the direct cause of this attack of burning pain, but studies in which the blood flow to the limb was terminated by inflation of a cuff and plethysmographic studies have demonstrated that the condition is not due to increased blood flow.

Symptoms and Signs

The primary form of erythromelalgia is relatively rare. It is often bilateral, and middle-aged men are more often affected, although women and children can also be affected. The condition is characterized by severe burning pain and red discoloration. The skin temperature is often raised, the skin is flushed, and venous engorgement is present. The skin is also hyperalgesic and hyperesthetic. The attacks of severe burning pain last from a few minutes to many hours. The distress can be noticeably greater during the summer months and when the patient has fever. Relief often will have been obtained by exposing the affected extremity or extremities to cool air or by immersing them in cool or iced water.

Trophic changes, ulceration, and gangrene are not seen in primary erythromelalgia but may be encountered in the secondary type. Some swelling and puffiness might be present in the localized burning region, or the whole extremity might be slightly swollen. Examination of the peripheral arteries does not reveal evidence of occlusive disease in the primary type, whereas in the secondary type, particularly that associated with polycythemia vera, there might be evidence of occlusive arterial disease.

Diagnosis

A diagnosis of primary erythromelalgia is justified when the patient complains of severe burning pain associated with increased temperature of the skin and no secondary cause for the syndrome is found. To make the diagnosis, it is essential to demonstrate that the skin temperature and the burning pain are related, and this can be achieved by production of reflex vasodilatation, or more commonly, by direct application of heat. Relief of the burning pain by exposure of the limb to cold or ice water confirms the diagnosis.

It is important to differentiate true erythromelalgia from the painful, red, but cold extremities noted in patients with TAO or ASO by measuring the skin temperature and assessing the pulses.

Treatment

Medical treatment consists of making the patient comfortable by avoiding heat and any other conditions that produce vasodilatation in the extremities. When erythromelalgia is secondary to other conditions, treatment of the syndrome would encompass the treatment of the underlying condition. As little as 650 mg of acetylsalicylic acid (aspirin) produces striking and persistent relief, sometimes for days (62). Although the mechanism by which aspirin works is not known, the response is so common that erythromelalgia should be suspected when a patient mentions that substantial and prolonged relief of burning pain in the extremities is experienced with this drug. Others have reported phenoxybenzamine (Dibenzyline) as effective, and still others have used methysergide, a serotonin-blocking agent, providing some dramatic relief with primary erythromelalgia (62). Because the continued use of methysergide can cause vascular complications and retroperitoneal fibrosis, it should be used as a last resort.

DISEASES OF THE PERIPHERAL VEINS AND LYMPHATICS

The most important painful disorders of the peripheral veins are (a) acute venous occlusion, which can present as thrombophlebitis or as acute DVT; (b) chronic venous occlusion, often referred to as *postphlebitic* or *postthrombotic syndrome*; and (c) varicose veins. Disorders of the lymphatics rarely produce pain; lymphedema is briefly mentioned at the end of this section for the sake of completeness in considering all PVD.

Acute Venous Occlusion

As already implied, obstruction of superficial or deep veins occurs in two forms: One is associated with an intense inflammatory component, as usually observed with involvement of superficial veins, and the other, which is more common and potentially lethal, is thrombosis of the deep veins, in which inflammation as the inciting event or clinical manifestation is less common. Although some authorities discuss these two types together, others believe it is appropriate to discuss them separately because the clinical courses, treatments, and prognoses of each are different (6,69,70).

Thrombophlebitis

Thrombophlebitis consists of partial or complete occlusion of a vein by thrombus, associated with inflammatory changes in the vein and adjacent structures. The inflammatory reaction promotes adherence of the thrombus to the venous walls, so thromboembolism occurs infrequently.

Etiology and Pathophysiology. Despite numerous studies, the cause of thrombophlebitis (other than chemical phlebitis secondary to direct intimal injury) remains unclear. In most patients, the following are considered to be contributing factors: (a) slowing or stasis of the venous blood flow, which allows cellular constituents to adhere to the vessel wall, with consequent clotting and subsequent inflammation; (b) alteration of blood constituents and activation of coagulation factors that enhance platelet aggregation, with consequent thrombus formation; and (c) development of venous endothelial damage, which further promotes adherence of blood constituents, development of a thrombus, and an inflammatory reaction. The last factor is particularly important in thrombophlebitis that follows injection of drugs or substances that irritate and produce microscopic lesions of the intima of the vein. A significant percentage of cases of thrombophlebitis occur as perioperative or postpartum complications—a subject discussed in the next subsection (Acute Deep Venous Thrombosis).

Symptoms and Signs. The symptoms and signs of superficial thrombophlebitis include pain and exquisite tenderness along the course of the involved vein, perivenous erythema and edema, and, in some instances, edema involving the limb. Patients with deep thrombophlebitis may manifest moderate to severe calf or thigh pain, exquisite tenderness, Homans' sign (calf pain on dorsiflexion of the foot), dilated superficial veins, and diffuse edema and pallor of the involved extremity. Such symptoms and signs are inconstant, however, and the diagnosis rarely can be made on clinical grounds. Patients with severe superficial thrombophlebitis manifest systemic symptoms including fever, tachycardia, tachypnea, and general malaise: This may be particularly evident when bacterial infection and actual venous suppuration take place—so-called septic phlebitis.

Diagnosis. The diagnosis is readily made by the history and presenting symptoms and signs. This condition must be differentiated from bacterial cellulitis and lymphangitis. The Doppler velocity detector helps to distinguish these, as thrombophlebitis is always associated with thrombosis of the involved segments, whereas the others are not (6).

Therapy. The therapy for superficial thrombophlebitis is largely supportive, with application of heat, elevation of the foot, administration of antiinflammatory drugs such as ibuprofen, administration of antibiotics, and elastic compression (6). The pain is controlled with various types of nonsteroidal antiinflammatory agents, but if these prove ineffective, opioids are given by mouth. Therapy is discussed in more detail in the section that follows.

Acute Deep Venous Thrombosis

Deep venous thrombosis (DVT) is one of the more common painful vascular disorders. Together with its sequelae, DVT is often associated with significant morbidity, prolonged hospitalization, decreased productivity, and lifelong disability (71). As a result of increased interest in venous disorders and because of increased availability of diagnostic procedures such as duplex sonography and photo- or impedance plethysmography scans to establish diagnosis, increased numbers of cases

are being diagnosed and treated. Recent estimates suggest that there are 200,000 deaths annually in the United States from pulmonary embolism (71).

Etiology and Pathophysiology. Most authorities agree that components of Virchow's classic triads of stasis, intimal damage, and hypercoagulability continue to be responsible for most cases of DVT (71). Because these contributing factors have already been mentioned in connection with thrombophlebitis, only a few additional comments are made here. Stasis of venous blood in the extremities, caused by prolonged immobilization or inactivity consequent to a medical or surgical illness, contributes to local accumulation of thrombogenic factors by preventing flow-induced dilution and by decreasing the flow of naturally circulating anticoagulants such as antithrombin III (71). These cause prolonged contact of the platelets and activate coagulation factors such as serotonin, catecholamines, and other catalysts that enhance platelet aggregation. After intimal damage, subintimal collagen and base membranes are exposed, and this promotes platelet adherence and activation of factor XII. Factor XIIa can initiate the intrinsic coagulation cascade: Platelet adherence leads to platelet aggregation, which leads to release of platelet granule contents resulting in thrombus formation. It has been demonstrated that once a venous thrombus is formed, one-third of such thromboses undergo spontaneous lysis, one-third persist, and the remaining thromboses propagate into more proximal veins, with associated increased risk of embolization (71). Such a sequence is much more common for the large veins of the thighs and pelvis.

Stasis and the consequent hypercoagulability undoubtedly play a critical role in postoperative thromboembolism. Because no antecedent disease or injury of the veins of the lower limb (where most of the lesions occur) is present in most cases of postoperative thromboembolism, the causes of the pathophysiology must relate to the anesthetic method, the operative procedure, and postoperative immobilization. As discussed in Chapter 102, the incidence of postoperative thromboembolism in the lower limbs is greater with general anesthesia than with regional anesthesia. The risk of postoperative DVT is particularly elevated after reconstructive orthopedic procedures of the knee and hip (69).

Other risk factors that play an important role in DVT include advanced age, congestive heart failure, atrial fibrillation, estrogen therapy, previous DVT, and the presence of malignancy (69,70 and 71). In pregnant patients, the incidence of venous thromboembolism after delivery is several times higher than before delivery, and the incidence is increased in those who have had obstetric complications (69).

Symptoms and Signs. The presence or absence of symptoms and signs with DVT depends on the location and extent of the thrombus, the degree of occlusion induced, the presence of collaterals, and the effect of gravity (69). The usual signs and symptoms of DVT of the lower extremity include pain and exquisite tenderness of the calf, increased tissue turgor (or resistance, particularly in the calf), edema, and increased skin temperature of the affected limb (due to diversion of blood to superficial veins). Features of limited diagnostic value include Homans' sign, dilated superficial veins, suffusion and cyanosis of the skin, and the presence of fever and tachycardia. Unfortunately, DVT is clinically “silent” in up to half of all patients; pulmonary embolism may be the first indication of the disease.

Acute thrombosis involving the axillary or the subclavian vein produces edema that includes the entire upper limb, prominent venous collaterals over the shoulder and chest, pain and discomfort, and tenderness over the axillary vein. Complicating pulmonary embolism is uncommon in acute upper extremity DVT, although it does occur (69).

A special type of massive venous thrombosis of the leg that produces a painful, edematous, cool, cyanotic lower limb is called *phlegmasia cerulea dolens.* The massive edema causes the skin to be taut and shiny (69). Cutaneous blebs and superficial gangrene, followed by more extensive necrosis of tissue, are part of the clinical picture. The disorder results from severe (not infrequently global) obstruction of all the venous channels draining the extremity, producing an extremely high venous pressure. This may be associated both with inadequate lymphatic flow, edema, and compartmental hypertension, and ultimately cessation of arterial inflow and the onset of tissue necrosis.

Diagnosis. DVT should be differentiated from a number of other conditions that produce similar symptoms and signs, including congestive heart failure, cellulitis, chronic venous insufficiency, lymphedema, edema of pregnancy, hepatic and renal insufficiency, and rupture of the plantaris tendon (71). A complete history and comprehensive physical examination, together with confirmative vascular laboratory studies, are essential to make a correct diagnosis and to develop the most appropriate therapeutic strategy. Objective techniques to diagnose DVT include both noninvasive tests such as duplex ultrasound examination of the peripheral veins and venous plethysmography. Invasive tests such as phlebography are now rarely used, although when noninvasive diagnostic techniques are negative or equivocal and clinical suspicion remains high, ascending phlebography should be used to settle the issue. This test, done with the patient in a semi-upright position, involves injection of a contrast medium through a small needle placed in a dorsal vein of the foot and permits visualization of both the superficial and deep systems.

Treatment. The goals of therapy of DVT are to (a) abort ongoing thrombotic process, (b) restore venous patency, (c) prevent pulmonary embolism, and (d) minimize the sequelae of peripheral venous hypertension. All patients should be hospitalized and placed on bed rest with elevation of the involved extremity above the level of the right atrium. Because extensive thrombosis can cause sequestration of large amounts of fluids, patients with phlegmasia syndromes should be carefully monitored and effective fluid replacement therapy should be given to maintain satisfactory cardiac output and peripheral perfusion.

Pain should be controlled with systemic analgesics. Usually nonsteroidal antiinflammatory agents in effective analgesic doses are sufficient. Patients who experience severe pain should be given opioids, preferably by mouth, at fixed intervals (see Chapter 84). The initial dose depends on the severity of pain, but a dose of 30 mg of morphine by mouth should be tried; if insufficient, it should be increased to 60 mg every 4 hours by the clock. If available, patient-controlled analgesia is preferable because it permits the patient to self-administer the drug to produce more sustained and even pain relief and usually requires lesser amounts of the opioids per 24 hours than when they are given intermittently (see Chapter 84).

Anticoagulant therapy should be started immediately to initiate inhibition of coagulation and permit thrombolysis to occur unopposed. Heparin remains the agent of choice, starting with a “priming dose” of 5,000 to 10,000 units, and this dose is immediately followed by a heparin infusion, usually 1,000 to 1,500 units per hour (6,70). After approximately 18 hours the infusion is regulated to maintain the activated partial thromboplastin time at two to three times the initial level control value. Warfarin is started orally after 2 to 3 days, and heparin infusion is continued until the international normalized ratio is more than 2.5. Edema, inflammation, and pain should have subsided by this point, and ambulation is started with the extremities wrapped in elastic bandages. The duration of oral anticoagulation depends on the severity of the problem: For femoral, popliteal, or iliofemoral thrombosis with or without pulmonary embolism, anticoagulation should be continued for 3 to 6 months (6). Anticoagulation should be maintained indefinitely in those with a chronic underlying risk factor for DVT (e.g., cancer, paraplegia, congestive heart failure). Obviously, the patient should be monitored carefully to promptly diagnose any complication associated with anticoagulant therapy such as hemorrhage, allergic manifestation, osteoporosis, and other adverse conditions.

Fibrinolytic agents such as streptokinase, urokinase, and tissue activator plasminogen have been extensively evaluated in the treatment of DVT in an attempt to preserve patency and normal valve function (71). These agents' benefits, although real, are present only when therapy can be initiated soon (less than 48 to 72 hours) after onset of clotting and must be balanced against an increased risk of hemorrhagic complications.

After the acute phase of therapy, most patients are managed by the use of elastic support, which has been demonstrated to reduce the incidence and severity of later postphlebitic syndrome.

Surgical treatment is rarely indicated in venous thrombosis (2,6,69,71). Patients with an acute iliofemoral thrombosis with compromised arterial perfusion of the limbs who fail to respond to elevation and heparin and who have not had a previous episode of DVT can be considered for iliofemoral thrombectomy and postoperative heparin therapy (71). When thrombolysis and anticoagulation are contraindicated, as in cases of trauma, recent surgery, or bleeding diatheses, vena cava filter placement may be lifesaving.

Postphlebitic (Postthrombotic) Syndrome

Second to pulmonary embolism, the most serious complication of DVT is the postthrombotic (postphlebitic) syndrome, which is characterized by chronic swelling, pain, hyperpigmentation, secondary varicose veins, and cutaneous perimalleolar ulcers (71,72). Although other conditions produce edema of the lower extremity (inferior vena cava obstruction, arteriovenous fistula, lymphedema, congestive heart failure, hepatic failure, and renal failure), postthrombotic syndrome is the most frequent cause of lower limb edema (71). Moreover, postphlebitic syndrome is the most common cause of ulceration of the lower limb (71).

Pathophysiology

Normally, direction of blood in the leg is from the superficial veins to the deep veins by means of the communicating or perforating veins, and the valves situated in these three systems of veins ensures this directional flow pattern. When the patient is erect, the venous pressure at the ankle can exceed 120 mm Hg, but during

walking or other forms of exercise, the normal ankle venous pressure is reduced by the pumping action of the calf muscles (71). When the valves are destroyed or become incompetent secondary to venous thrombosis, the directional flow pattern is altered, and with each contraction of the calf muscles blood flows antegrade, retrograde, and out through the perforating veins so that the venous pressure at the ankle actually increases (6). Increased venous and capillary pressure results in edema, and as the blood is forced outward through the perforators, a high-pressure “leak” develops from rupture of the small veins in the vicinity of the perforators and consequent microscopic hemorrhages. Repeated microhemorrhages lead to deposition of hemosiderin (pigment), producing a tannish-bronze pigmentation, subcutaneous fibrosis, and lymphatic obstruction. The venous hypertension, edema, and fibrosis reduce the cutaneous perfusion sufficiently so that the skin's response to even minor trauma or infection is impaired and nonhealing ulcerations occur.

Symptoms and Signs

Most patients complain of pain, heaviness, and early fatigability of the legs and manifest edema, the aforementioned pigmentation, and nonhealing ulcers that develop secondary to trauma. The pain is always relieved by elevation of the limb, and the edema decreases. If an ulcer is present there may be local pain and tenderness of varying severity.

Diagnosis

In addition to a thorough history and physical examination, including circumferential measurement of the two calves, a duplex ultrasound examination is used to determine the patency and valvular competence of the deep, perforating, and superficial venous systems (6,71).

Treatment

Nonoperative management suffices in the vast majority of patients with postphlebitic syndrome. Such therapy includes reduction or elimination of edema, correction of any associated medical problems, and continued patient education to ensure long-term compliance with management principles (71,72). The edema generally resolves quickly when the venous hypertension is reduced or eliminated by bed rest, with the extremity elevated above the level of the heart, and calf exercise (repetitive dorsiflexion of the ankle) is continued while at bed rest. When the edema has subsided or has become substantially reduced, the patient is fitted for elastic compression stockings, which tend to minimize the edema and keep the superficial veins collapsed (6). The stockings are applied before arising in the morning and are removed in the evening when the patient retires. The patient is encouraged to remain active when erect and to elevate the legs when sitting and to avoid sitting with the knees flexed.

When ulcers are present, they should be cleansed by frequent dressing changes; a zinc oxide–impregnated dressing may be used but is effective only when an elastic bandage holds it in place (6). If the ulcers persist after 6 to 8 weeks of nonoperative management, split-thickness skin grafts may be carried out with or without concomitant ligation and removal of the nearby incompetent superficial and perforating veins (73). Cross-femoral transposition of the saphenous vein has also been found useful in selected individuals with unilateral obstruction of the iliofemoral venous system. This procedure, which entails transposition of the competent greater saphenous vein from the uninvolved extremity across the pubis and anastomosing it end to side to the drainage system of the involved extremity, may be effective in approximately 70% of *selected* patients (74). Ipsilateral saphenous vein bypass of an obstructed superficial femoral vein is also occasionally effective. Other procedures include repair of incompetent femoral valves and vein segment transposition, which entails anastomosing a vein containing competent valves to an adjacent vein in which the proximal valves are incompetent (74).

Varicose Veins

Varicose veins are the most common disorder of the venous system of the lower extremity; they are said to afflict up to 10% of all Americans (75). The greater and lesser saphenous systems are most commonly the cause, but it is the secondary branches of these veins that become varicose. Varicosity usually appears after the age of 20 years, but it can develop in women in relation to puberty and during pregnancy (6). In men the onset of the disorder is evenly distributed by decades up to age 70 years.

Pathophysiology

It is important to classify varicose veins as either primary or secondary (6,73). Primary varicose veins occur in the absence of deep venous disease and generally have a benign course: They often appear in a familial pattern. Varicosities that occur secondary to obstruction and valvular incompetence of the deep venous system are a much more serious problem.

Symptoms and Signs

The disability that occurs with primary varicose veins is usually minimal, but with prolonged dependency, patients complain of heaviness and mild, dull, aching pain that is occasionally associated with minimal swelling. The symptoms and the swelling are promptly relieved by elevation or elastic support. When the varicose veins are secondary to prior DVT, loss of valves, and incompetent perforating veins, the symptoms are much more serious and are accompanied by swelling, stasis pigmentation, and cutaneous ulceration, as discussed in connection with the postphlebitic syndrome.

Diagnosis

The diagnosis of primary varicose veins is easily established by inspection of the legs in the upright position, which causes the dilated tortuous veins to become readily apparent. When isolated clusters are observed in atypical locations, the possibility of an underlying incompetent perforating vein should be considered (6). Duplex scanning can be used to assess whether incompetent perforating veins are contributing factors.

Therapy

Most patients with symptomatic primary varicose veins should be reassured and treated initially with compression stockings (6). If the deep veins and perforating veins are patent and competent (primary varicose veins), it is unusual to see stasis, pigmentation, or ulceration. In those unusual instances in which treatment with compression stockings is inadequate, high ligation and selective stripping of the long and short saphenous system will likely be successful (6).

Lymphedema

Lymphedema, an abnormal accumulation of lymph in the extremity, occurs from multiple causes, including infection, trauma, allergy, and malignancy (76). It is most commonly idiopathic. Painless swelling of the involved extremity is the earliest and most common symptom and sign with most types of lymphedema. Initially, the swelling tends to subside somewhat at night, but as the process progresses, the swelling becomes permanent, due to fibrosis of both the skin and subcutaneous tissues. Pain is rarely a problem in these patients, except for those who develop cellulitis or ulceration. In such instances, pain is relieved when antibiotic therapy results in resolution of cellulitis, or local ulcer therapy produces skin healing.

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CHAPTER 34

Pain in Spinal Cord Injury Patients

John D. Loeser

HISTORICAL OVERVIEW

A particularly difficult group of chronic pain patients to manage are those who have sustained an injury to the spinal cord or cauda equina. These patients usually have devastating neurologic deficits such as paraplegia or quadriplegia. A significant fraction of such individuals also are plagued by refractory chronic pain; estimates of the prevalence of pain have varied from 7% to 75% (1). Some of this variation is caused by the lack of an agreed-on classification scheme for the pains that occur in patients with spinal cord injury; some of it may be because of the vigor with which questions about pain were pursued or answered. These pain syndromes, which are described in detail in this chapter, are clearly directly related to the spinal cord injury. The type of pain associated with the spinal cord injury itself has been considered in detail in Chapter 23 as one of the central pain syndromes.

Severe pain is likely to interfere with the rehabilitation potential of patients who have sustained a spinal cord injury (2,3). Attempts to alleviate pain after spinal cord injury consume significant amounts of health care but have often been unsuccessful. In the past two decades, there has been increased interest in the physiologic mechanisms underlying pain after spinal cord injury and in the development of useful classification schemes. Some types of pain in spinal cord injury patients can be treated with widely accepted standardized forms of therapy when their etiology has been carefully identified. New treatments may offer the promise of pain relief in specific types of pain after spinal cord injury.

Most patients who sustain an injury to the spinal cord have also received massive trauma to the vertebral column and its supporting structures. This typically leads to acute pain similar to that seen with musculoskeletal trauma anywhere in the body. The principles of posttraumatic pain management as discussed in Chapter 43 are applicable to patients with spinal trauma; this chapter does not discuss the management of acute pain seen in such injuries.

The problem of pain after spinal cord injury was addressed by Riddoch (4) in his 1917 paper. I cannot find an earlier paper that focused on this problem. Munro's classic paper on spinal cord injuries in 1943 did not even mention the issue of chronic pain (5). After World War II, Botterell and colleagues described chronic pain in 12 of 103 spinal cord injury patients; 11 of these 12 had cauda equina injuries (6). Kuhn reported that 0.234% of the injuries in World War II involved the spinal cord and that 22.5% of 113 patients with spinal cord injury had chronic pain (7). Davis reported an incidence of 27% in 471 spinal cord injury patients (8). In 1962, Kaplan and colleagues attempted to classify spinal cord injury pains and stated that 37% of 52 spinal cord injury patients had chronic pain 1 year after injury; this increased to 50% by 5 years later (9). Richards and colleagues claimed that 77% of 88 spinal cord injury patients had chronic pain and that psychosocial variables predicted approximately one-half of the variance (10). Waisbrod and colleagues believed that there were three types of pain after spinal cord injury on the basis of their study of 27 patients (11). Woolsey identified less than a 20% incidence of chronic pain in a group of 100 spinal cord injury patients (12). Stormer and colleagues reported on a multicenter study of 901 spinal cord injury patients, 66% of whom had chronic pain (13). Lamid and colleagues, Levi and colleagues, New and colleagues, Beric, Demirel and colleagues, and Rose and colleagues have all contributed data on the incidence of pain after spinal cord injury (14,15,16,17,18 and 19). The methodology and the patient population being studied appear to greatly influence the incidence of spinal cord injury pain. Collating these reports leads me to guess that more than one-half of patients who sustain a spinal cord injury suffer from chronic pain severe enough to interfere with rehabilitation and the activities of daily living and therefore reduce quality of life.

Burke and Woodward constructed a simple classification of pains seen after spinal cord injury and discussed their relationship to phantom phenomena (20). Donovan and colleagues designed a classification scheme for spinal cord injury pain in 1982, but subsequent case series either have used parochial classifications without the attempt to integrate concepts or did not even attempt to classify types of pain (21). Frisbie, Beric, and Siddall and colleagues have published classification schemes for pain after spinal cord injury (22,23 and 24). No attempts have been made to validate any classification system either on the basis of clinical findings, response to treatments, or putative mechanisms. We do not yet have animal models of spinal cord injury that replicate the varied pain phenomena seen in humans.

BASIC CONSIDERATIONS

Experimental Models

Developing animal models for the pain after spinal cord injury is important for the development of successful treatment strategies. Valid models would appear to be those that mimic the histologic effects of human spinal cord injury. Three are currently used: the spinal cord contusion model, the ischemic model, and the excitotoxic model. The spinal contusion model, usually evoked by dropping a weight on the exposed spinal cord, has not been directly used in the study of pain. However, it produces changes in the excitability of neurons that could be relevant to the development of pain after spinal cord injury (25). The ischemic model developed by Wiesenfeld-Hallin and her colleagues uses a photochemical method to produce graduated ischemia in the spinal cord (26). This group of studies has shown that neurochemical changes occur after spinal cord injury that may be responsible for both an acute allodynia syndrome that is not seen in humans and a chronic pain syndrome that may replicate some of the features of central pain after human spinal cord injury. Interactions between opiate and cholecystokinin segmental modulatory systems may play a role in the development of pain, but this model has not ruled out the effects of altered downstream modulation on damaged spinal cord segments.

The excitotoxic model has been described by Yezierski, who has also been one of the more active scientists in this area (27). Substantial evidence has accrued that glutamate was responsible for much of the damage seen after spinal cord injury. This has led to a series of studies using agonists and antagonists of glutamate and *N*-methyl-d-aspartate receptors injected directly into the spinal cord in the absence of trauma. Cavitation within the cord is noted, and the animals manifest allodynia and other signs of chronic pain. It is believed that the effects of excitotoxic substances may lead to cell death and altered synaptic connectivity as well as imbalances between different functional systems. Exactly how this produces pain that persists even when the involved cord segments are removed (as in distal cordectomy in humans) is not clear. The abnormal behaviors seen in animals whose spinal cords had been injected with quisqualic acid (an

alpha-amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid metabotropic receptor agonist) were reversed by intrathecal adrenal medullary transplants (28).

Eide has proposed that upregulation of neuronal activity is the cause of both spontaneous and evoked pain after spinal cord injury (29). He stated that increased glutaminergic excitatory activity involving *N*-methyl-d-aspartate receptor activation is the primary cause. This can lead to changes in voltage-sensitive Na^+ channels. Other mechanisms may be the loss of endogenous inhibition contributed by opioids, monoamines, and gamma-aminobutyric acid. In short, so many changes occur in the spinal cord after injury that it is difficult to ascertain which ones are specifically relevant to the development of pain.

Plasticity

It is now well established that the central nervous system undergoes dramatic changes in response to either peripheral nerve or spinal cord injury. Existing axons sprout and develop connections to new populations of neurons. Second-order neurons lose their synaptic input and enter into new structural relations with glia. Trophic substances play a large role in modulating this type of plasticity, which could underlie some of the pain syndromes that follow spinal cord injury. Damage to neurons from excitatory amino acids has also been proposed as a mechanism for the development of pain (27).

Research studies have generally focused on the effects of deafferentation via dorsal rhizotomy or direct spinal cord injury by cordotomy or trauma to the spinal cord. They are, therefore, relevant only to transitional zone or spinal cord injury pain and do not have much relevance to the other types of pain described in the following sections. Indeed, those models that lead to alterations in, but not the compete loss of, sensation are really suitable only for transitional zone pain or partial spinal cord injury.

A large body of literature exists on the effects of spinal cord lesions on the development of behaviors that suggest chronic pain (30). Among the early studies of the effects of spinal cord lesions on neuronal activity were those of Loeser (31). Although all animals who have sustained a spinal cord injury manifest neuronal hyperactivity in the dorsal horn, only a small fraction develop any detectable pain behaviors. A species effect occurs on the genesis of pain behaviors after spinal cord injury; in addition, within the human species only a fraction of patients report chronic pain. Of course, the ambiguity of what an animal feels that causes it to chew on or to withdraw an extremity is always present. It remains fairly well demonstrated, however, that lesions of the peripheral nerves and spinal cord can lead to behaviors that suggest both spontaneous and evoked pains such as thermal and mechanical allodynia.

Christensen and Hulsebosch have described a model for either transitional zone pains (see Classification of Pain Syndromes, later in this chapter) or pains seen after partial spinal cord injury (32, 33). Their rats developed mechanical and thermal allodynia after a cord hemisection. Dorsal horn neurons were shown to be hyperexcitable in this preparation, suggesting that central sensitization played a role in the development of a pain state after spinal cord injury. The same authors also demonstrated that calcitonin gene-related peptide, which is normally confined to lamina I and II of the dorsal horn, can be found in lamina III and IV after spinal cord hemisection. This suggests ingrowth of fine primary afferent fibers into nuclear regions where they do not normally occur. The intensity of this response to injury was modulated by levels of nerve growth factor; this suggested a potential strategy for prevention of spinal cord changes after injury that could be related to the genesis of pain. This research suggests that plasticity in the spinal cord is responsible for the development of pain.

Central Pattern Generation

Another concept for spinal cord injury pain was proposed by Melzack and Loeser (34). Based on the clinical evidence that cordotomy and cordectomy were usually not effective for the relief of spinal cord injury pain (see Classification of Pain Syndromes, later in this chapter), they proposed that structures rostral to the level of injury were essential for the genesis of this type of pain. Melzack has carried this theme forward to develop the concept of the neuromatrix: The brain contains widely distributed parallel processing neural networks that create an image of self through genetic programs and memories of past experience (35). Afferent inputs act on this neuromatrix and produce output patterns that lead to the report of pain. This concept points to an unresolved issue about pain after spinal cord injury: Is the apparatus essential to produce the report of pain located at or near the site of injury, or does it lie in more rostral structures? The presence of spinal cord injury pain in patients who have high cervical spinal cord lesions seems to indicate that suprasegmental structures may play a critical role. There have been few, if any, experimental studies that address this issue. This concept does not negate the role of neural changes at the level of injury, but it does state that the genesis of the pain is from suprasegmental structures, not the injury site.

PATIENT EVALUATION

The assessment of every patient with spinal cord injury and chronic pain requires a detailed history that describes the onset of the pain and its quality, distribution, and the factors that make it better or worse. It is also important to ascertain how intervening surgeries and treatments have influenced the pain. The physical examination must precisely describe the patient's neurologic status; if this is changing, the relationship to the pain complaint must also be determined. The stability of the traumatized spine must be ascertained through history, physical examination, and imaging studies. Electrodiagnostic studies may be useful in determining the exact levels of injury to the nervous system and specific peripheral nerve function when indicated (see Chapter 13). Diagnostic nerve blocks can also help delineate the level of a painful lesion (see Chapter 102). On the basis of the history, physical examination, and appropriate imaging and electrical studies, it should be possible to classify the pain syndrome as described in the following sections and illustrated in Figure 34-1. The assignment of the patient to one of these pain classes permits optimal treatment planning and implementation. More than one type of pain can be present in the spinal cord injury patient.

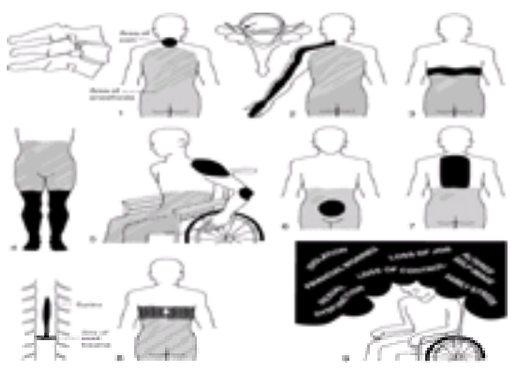

Figure 34-1. Types of pain observed in patients after spinal cord injury. See Table 34-1 and text for explanation.

1. Mechanical instability of the spine
2. Nerve root entrapment
3. Segmental deafferentation
4. Spinal cord injury pain
5. Secondary overuse or pressure syndromes
6. Visceral pain
7. Muscle spasm pain
8. Syringomyelia pain

TABLE 34-1. Classification of spinal cord injury pains

CLASSIFICATION OF PAIN SYNDROMES

Mechanical Instability of the Spine

This type of pain is most common after cervical spine injury and is rarer after thoracic or lumbar injury (Table 34-1). It may be present from the time of injury or, rarely, it may develop later. This is a type of musculoskeletal pain that is caused by the disruption of ligaments or fracture of bones with resultant instability of adjacent structures. It is characterized by the movement of osseous structures in abnormal planes or in abnormal amounts.

Pain usually commences soon after injury and is related to activity or position. The pain is in the region of the spine, although it may radiate around the trunk or toward an extremity; but it is not radicular. This type of pain can be seen after spine injury without an associated spinal cord injury. Radiography, computed tomographic scan, or magnetic resonance imaging (MRI) show instability by manifesting abnormal movement.

This type of pain is relieved by immobilization; it is also usually sensitive to opiate and nonsteroidal antiinflammatory drugs. Immobilization until spontaneous healing has occurred and surgical fusion are both effective treatments in almost all patients. The pain secondary to mechanical instability is almost always alleviated by surgical fusion across a region of instability. Sved and colleagues found that early surgery to stabilize the spine did not lead to any alteration in the incidence of chronic pain after spinal cord injury (36).

Nerve Root Entrapment

Nerve root entrapment leads to radicular pain in the distribution of a single nerve root. It may, rarely, be bilateral. This type of pain occurs at the level of spinal trauma, and the pain usually is present from the time of injury. Nerve root entrapment may be associated with mechanical instability, but this is not a necessary concomitant. This pain is usually described as lancinating, burning, or stabbing. If the involved root contributes to the brachial or lumbosacral plexus, there may be electromyographic or somatosensory-evoked potential abnormalities. Radiographic, computed tomographic or MRI evidence of compression of the nerve root in the foramen by bone or disk is correlated with the location of the pain.

This radiculopathic pain may be relieved by opiates or by neuropathic pain-relieving drugs such as anticonvulsants or tricyclic antidepressants (see Chapter 85 and Chapter 86). If it is associated with instability, stabilization provides relief. If it is associated with bone or disk in the neural foramen, surgical decompression is usually effective.

An important variant of this type of pain is seen after injury to the cauda equina. Several potential etiologies exist for pain after such an injury. First, the spinal cord may be significantly deafferented, leading to changes in central connectivity and neuronal activity that could cause pain. Second, the damaged roots of the cauda equina could be spontaneously active and generate signals that are interpreted as pain. The arachnoiditis that follows major injury to the cauda equina may limit the normal movement of the nerve roots and lead to mechanical irritation of the roots with slight movements (37). Third, peripheral stimuli could lead to abnormal activity at the site of axonal injury.

The pain is reported in the lower lumbar and sacral dermatomes; it is constant but may fluctuate with activity or autonomic activation. It is usually described as burning, stabbing, and hot. Most authors have commented on the refractory nature of pain after cauda equina injury. Spinal cord stimulation has sometimes been successful (see Chapter 100).

Segmental Deafferentation

Segmental deafferentation pain has also been labeled *girdle zone* or *transitional zone* pain. It occurs at the border of normal sensation and anesthetic skin. Transitional zone pain is described as burning and aching and is often associated with allodynia and hyperpathia in the painful region. The pain is located in a two- to four-segment band that is bilateral and circumferential. As many as one- third of spinal cord injury patients who have pain have the segmental deafferentation type, although Beric lumped together radicular pains and transitional zone pains in his report (23). This type of pain usually develops in the first few months after injury.

Transitional zone pain does not usually respond to opiates, but it may respond to neuropathic pain-relieving medications such as anticonvulsants and antidepressants (see Chapter 85 and Chapter 86). Epidural or somatic nerve root blocks that make the painful area anesthetic may relieve the pain. Dorsal root entry zone lesions usually relieve this pain, perhaps by their dorsal rhizotomy effect or perhaps by being an analogue of distal cordectomy that raises the sensory level above the painful region (see Chapter 106). Some have reported pain relief by spinal cord stimulation (see Chapter 100). If the type of pain was not delineated in a clinical report, it is highly likely that this was the type of pain relieved by whatever treatment is being advocated.

Spinal Cord Injury Pain

Spinal cord injury pain is the most difficult to manage of the spinal cord injury pain syndromes. It is perceived in anesthetic regions below the level of injury, although it has also been reported by some patients who do not have a complete cord transection and have some preserved functions. It may be visceral, dysesthetic, superficial, or chronic regional pain syndrome–like. Patients use various descriptors such as tingling, numbness, aching, throbbing, squeezing, and sickening. Sometimes a lancinating component also exists. The pain is always ascribed to specific body regions and is usually bilateral. Patients often provide bizarre descriptions. It is constant, but may fluctuate with mood or activity. It is not related to position or activity. The pain usually starts soon after injury and is found in approximately one-third of spinal cord injury patients who complain of chronic pain. Other terms used for this type of pain include *central pain*, *phantom pain*, *central dysesthesia syndrome*, and *dysesthetic pain* (38,39 and 40). Beric and colleagues described a double lesion phenomenon occurring in patients with cervical or thoracic cord injuries who developed lower motor neuron signs in the lumbosacral segments (41).

Concurrent infections or other illnesses may aggravate this central pain state. It responds poorly to oral opioids or any other medications. It may respond to intrathecal opioids, or to a combination of bupivacaine, clonidine, and opioid when systemic routes are ineffective. Surgical procedures such as cordectomy or any other ablative procedure are rarely successful (see Chapter 106), and it is unlikely to respond to spinal cord or brain stimulation (see Chapter 100 and Chapter 101). Most patients with this type of pain do not get significant relief from any of the currently available therapies.

Beric and colleagues found that 13 of 102 consecutive traumatic spinal cord injury patients with pain had this type of pain (23). Beric and colleagues suggested that this type of pain was caused by loss of spinothalamic systems with the relative preservation of dorsal column function (38).

Secondary Overuse or Pressure Syndromes

Secondary overuse or pressure syndromes are common in paraplegics and much less common in quadriplegics. The pain occurs in normally innervated regions rostral to the level of the spinal cord injury. The onset is delayed months or even years after the cord injury. The pain is described as aching in the area of pressure or overuse and is worse with use of involved joints or pressure on the part. It is typically seen in the shoulders and carpal tunnels of those who propel themselves in wheelchairs and therefore use their shoulders as hips (42). Lal in 1998 reported on shoulder joint degenerative changes in 72% of a sample of paraplegics (43). If the pain is caused by nerve compression, abnormal electrophysiologic studies as well as MRI neurography can aid in diagnosis.

Resting the painful part or protecting it from trauma can alleviate this type of pain. Nonsteroidal antiinflammatory drugs or, when needed, opioids are also helpful. This is not a neuropathic pain and it is not alleviated by anticonvulsants or antidepressants. Peripheral nerve compression can, when necessary, be alleviated by surgical decompression.

Visceral Pain

It is not at all clear that this is a distinct category of chronic pain in patients with spinal cord injury. The patient describes burning, cramping, bloating, and constant but often fluctuating pain. Some patients seem to have intermittent attacks of this type of pain. The onset is usually delayed for months or years after the spinal cord trauma. Visceral pain may be caused by normal afferent input via the sympathetic and vagus nerves in paraplegics and the vagus nerves alone in those who are quadriplegic. This pain could be stimulus driven from abdominal myoneural dysfunction, it could result from imbalance of afferent input, or it could be a form of spinal

cord injury pain as described previously. Davis and Martin believed that this was a pain associated with autonomic phenomena (40). It was described by Kuhn in 1950 in patients with visually inspected cord transections who had preserved recognition of noxious genital stimulation (44). Komisaruk and colleagues reported that women with high spinal cord transections could still perceive genital stimulation (45).

Virtually no information exists on the treatment of this type of pain after spinal cord injury.

Muscle Spasm Pain

Muscle spasm pain is found only in patients with partial spinal cord injuries in whom some sensation is preserved but severe muscle spasm develops. The patient reports pain associated with visible and palpable muscle spasm at or below the level of spinal cord injury. The pain usually starts well after the spinal cord injury. This pain is best relieved by alleviating the muscle spasms; analgesics may be helpful but rarely are adequate. Hence, oral or intrathecal antispasticity medications are the primary treatment for this type of pain.

Syringomyelia

Chronic pain may occur in association with the development of a posttraumatic syrinx in the spinal cord (46). This pain always has a delayed onset, perhaps even years after the spinal cord injury. The development of a syrinx is characterized by new neurologic deficits at a higher level than the original injury. The loss of pain and temperature sensation is typical, but all sensory and motor functions can be affected. Patients describe a constant, burning pain that may be associated with allodynia.

Diagnosis is established by MRI scan (Fig. 34-2). The most effective treatment for the syrinx is surgical decompression of the arachnoid scar at the level of injury so that there is free flow of spinal fluid around the spinal cord. Treating the syrinx by inserting a drainage tube that goes either to the subarachnoid space or the peritoneal cavity does not provide as good long-term results. Even though the syrinx may collapse, it is not always the case that pain relief will be obtained. The medications used for neuropathic pain (see following discussion) may be helpful when syringomyelic pain persists after collapse of the syrinx.

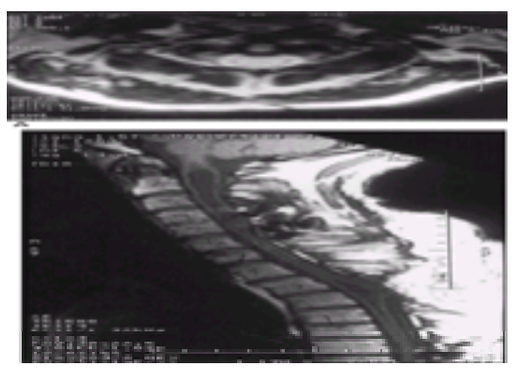

Figure 34-2. **A:** Sagittal magnetic resonance scan of cervical spinal cord demonstrating posttraumatic syringomyelia. **B:** Axial magnetic resonance scan through cervical syringomyelia. Note thin rim of spinal cord tissue surrounding the central cavity.

Cognitive, Affective, and Environmental Pain Syndromes

Any pain syndrome can be modified by cognitive and affective factors as well as environmental influences on the patient. The eight types of pain described are certainly no exceptions to this general rule. Indeed, the disability ascribed to chronic pain is highly likely to be primarily related to these three confounders. It is also possible that the entirety of a patient's pain behaviors can be related to affective or environmental factors, but this is certainly not common. All pain syndromes related to spinal cord injury can benefit from the application of psychological management strategies (47).

Patients who have sustained a spinal cord injury are often physically and psychologically devastated. Suffering may be caused by pain; alternatively, it can be engendered by other effects of spinal cord injury. Lundqvist and colleagues found that pain was the only complication of spinal cord injury that lowered quality of life scores (48). Westgren and Levi reported that pain had more effect on quality of life scores than the extent of spinal cord injury (49). Biomedically focused physicians tend to ignore the psychological factors that may be leading to pain behaviors. The literature contains repeated references to the role of factors other than spinal cord injury itself in the genesis of pain behaviors and disability ascribed to pain (50).

TREATMENT

Pharmacologic

Few properly conducted clinical trials adequately describe the nature of the patients' pains and use effective clinical study techniques. Drewes and colleagues in a double-blind, placebo-controlled study found that valproate was not effective for spinal cord injury pain (51). Small sample size, uncontrolled, unblinded studies characterize the literature in this area. Extrapolation from other types of pain related to central or peripheral nervous system injury has led to the widespread use of anticonvulsant and antidepressant medications with some successes (52,53) (see Chapter 85 and Chapter 86). Some patients may respond to systemic opioids, but this appears to be the exception rather than the rule. All of the medications used for any type of chronic pain have been tried in uncontrolled fashions for the variety of pain syndromes that occur after spinal cord injury (54). Overuse and pressure syndromes may respond to nonsteroidal antiinflammatory drugs.

The advent of intrathecal drug administration systems has led to the delivery of opioids and other pain-relieving drugs directly to the spinal cord (see Chapter 103). Some patients with pain after spinal cord injury have been reported to respond to a variety of drugs delivered by this route. My own experience with opioids for central pain states is not favorable; the addition of local anesthetics or clonidine to opioids may prove to be more effective (55).

Psychological

Patients with a major spinal cord injury usually have significant psychological distress (56,57). The superimposition of chronic pain is a major factor that prevents expected rehabilitation and return to employment and function in domestic life. Psychological assessment should be part of the evaluation of every spinal cord injury patient with chronic pain of any type (see Chapter 16) (58). Use of the strategies described in Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92, Chapter 93 and Chapter 94 can facilitate both pain management and return to maximal functional status (59). Association with groups of spinal cord injury patients is also a positive step for most patients.

Physical

Those pain syndromes that are associated with overuse or pressure can often be managed by physical measures alone. Physicians who specialize in the management of spinal cord injury patients are familiar with the problems engendered by paraplegia and quadriplegia and can design prosthetic devices, orthotics, and exercise routines that aid in the management of these problems. Physical therapies are not useful for the pains related to spinal cord injury itself. Transcutaneous nerve stimulation has not been very effective (60). Stimulating anesthetic skin never provides pain relief; some patients with transitional zone pain may get some relief from stimulation in the area of pain and partial sensation.

Surgical

Orthopedic and neurosurgical procedures designed to stabilize the spine immediately after trauma and to decompress impinged nerve roots can be effective at

eliminating the pains of instability or nerve root compression (61). On the other hand, Burke reported that patients who had spinal surgery were more likely to have chronic pain than those who were treated conservatively; this was not congruent with the observations made by Sved (36,62). Decompressive surgery with lysis of adhesions at the site of spinal cord injury is also effective in the treatment of syringomyelia, although the pain associated with this condition may not remit even though the syrinx is collapsed.

Ablative neurosurgical procedures need to be tailored to the type of pain syndrome if they are to be successful (see Chapter 105 and Chapter 106). When it is impossible to decompress a mechanically compromised nerve root, dorsal rhizotomy may be useful. For transitional zone pains, dorsal root entry zone lesions are often effective (63). The transition zone pains may also be alleviated in some patients by transecting the spinal cord at a higher level (64). For spinal cord injury pain, ablative surgery, including cordotomy, distal cordectomy, and thalamotomy, has a low chance of success.

Electrical stimulation of the spinal cord may be effective for transitional zone or radicular pains, but it does not help spinal cord injury pain (65) (see Chapter 100). Deep brain stimulation has some utility when all else has failed (1,66) (see Chapter 23 and Chapter 101).

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CHAPTER 35

Cancer Pain: Assessment and Diagnosis

Dermot R. Fitzgibbon and C. Richard Chapman

Cancer currently afflicts an estimated 1,382,400 new patients annually and causes 560,000 deaths per year, making it the second leading cause of death in the United States (1).* Among women, the three most commonly diagnosed cancers, breast, lung and bronchus, and colon and rectum, account for over one-half of all cancer deaths. Lung is the leading cancer site, accounting for 25% of all cancer deaths. Breast cancer alone accounts for 30% of new cancer cases, and estimates predict approximately 180,200 new cases for 1997. Breast cancer accounted for 17% of female cancer deaths in 1997. Among men, the most common cancers are prostate, lung and bronchus, and colon and rectum. Prostate is the leading cancer site, accounting for 43% of new cancer cases. Men are more likely to die of lung cancer than from cancer at any other site. Data for 1995 suggest that overall cancer mortality has begun to decline (2). Figure 35-1 and Figure 35-2 show estimated new cancer cases for the 10 leading sites and estimated cancer deaths by sex in the United States for 1997.

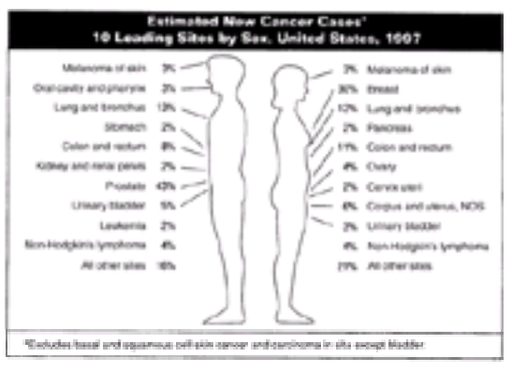

Figure 35-1. Estimated new cancer cases. (NOS, not otherwise specified.) (From Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5–27, with permission.)

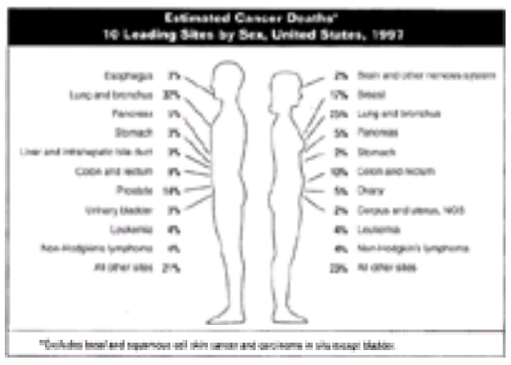

Figure 35-2. Estimated cancer deaths. (From Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5–27, with permission.)

Cancer is one of the medical conditions patients fear most (3). In addition to anxiety about cancer as a potentially lethal disease, patient and family expectancies that pain is an inevitable and untreatable consequence are major sources of distress (3). Cancer pain elevates psychological distress (4,5 and 6), alters social life (7), disturbs sleep (8), and compromises enjoyment of life (9).

End-of-life considerations and palliative care are rarely major issues for acute and chronic nonmalignant pain conditions, but these concerns become extremely important for the cancer pain patient with advanced disease (see Chapter 40). The complexities that emerge from the medical and psychosocial aspects of the situation necessitate a multidisciplinary or interdisciplinary approach to care. The changing nature of cancer pain, either in response to treatments directed at the tumor or progression of the tumor, mandates vigilance and potential frequent alteration of treatment strategies for pain. Many health care professionals may become involved with the cancer pain patient at any one time (Fig. 35-3). Successful pain management requires that the person or persons responsible for pain management adopt, or at least become familiar with, an interdisciplinary approach. In addition, the humanitarian nature of cancer pain management, the focus on suffering and comfort, and the associated effects on patients' relatives all contribute to the uniqueness of this form of pain control.

Figure 35-3. Interdisciplinary care teams of the cancer patient with pain.

Controlling pain associated with cancer is a major health care problem (10,11). Thirty percent of patients with cancer have pain at the time of diagnosis, and 65% to 85% have pain when their disease is advanced (10,11,12,13 and 14). The interaction of pain and its treatment with other common cancer symptoms such as fatigue, weakness, dyspnea, nausea, constipation, and impaired cognition magnifies the negative effect of cancer pain (12,14). Cancer patients treated on an outpatient basis frequently have pain that is inadequately controlled (11,15,16). Cleeland and colleagues (11) reported that 67% of outpatients (871 of 1,308 patients) indicated that they had pain or had taken analgesic drugs daily during the preceding week, whereas 36% had pain severe enough to impair their ability to function. Patients seen at centers that treated predominantly minorities were three times more likely than those treated elsewhere to have inadequate pain management. A discrepancy between patient and physician in judging the severity of the patient's pain was predictive of inadequate pain management (odds ratio, 2.3). Other factors in this study that predicted inadequate pain management included pain that physicians did not attribute to cancer (odds ratio, 1.9), better performance status (odds ratio, 1.8), age of 70 years or older (odds ratio, 2.4), and female sex (odds ratio, 1.5).

DEFICIENCIES IN ASSESSMENT AND DIAGNOSIS OF CANCER PAIN

Experienced physicians now recognize a need for significant improvement in cancer pain assessment and treatment in their practice (17). Lack of expertise by clinicians in assessing and managing cancer pain has been listed as an important cause of poor pain control (18). Interviews of practicing physicians demonstrate knowledge deficits in the basic principles of cancer pain management (19). Similar findings are demonstrated in nurses and nursing students (20,21 and 22).

Assessment of resident physician clinical performance has traditionally comprised limited subjective faculty evaluations and multiple choice tests appropriate only for measuring knowledge. Performance-based testing is a form of evaluation that objectively measures clinical ability (23). It tests what a trainee does in a simulated or real clinical situation. Sloan and colleagues (24) used a standardized assessment protocol called an *objective structured clinical examination*, designed to use performance-based testing to evaluate the skills of 33 resident physicians in assessing and managing severe chronic pain of a cancer patient. The case evolves in a standard manner and students must reassess the patient, formulate treatment, and justify their choices, in a manner similar to an oral board examination. The investigators found many fundamental deficiencies in both assessment and treatment of cancer pain. Only 45% of physicians correctly assessed pain intensity and only 33% adequately assessed the pain description. In addition, most residents assessed pain-relieving factors, previous pain history, and psychosocial history poorly or not at all. In all, only 58% of the trainees were judged to be competent in cancer pain assessment and treatment. These deficiencies were equally evident at both junior and senior levels.

Pain management requires a variety of assessment skills and the integration of knowledge about pharmacology, pharmacokinetics and pharmacodynamics, patient characteristics such as individual variability and compliance with medications, side effects and quality of life determinants, and disease specifics. These skills must contribute to clinical judgment and decision making, often requiring substantial individual experience. Computer simulation software may create a tool that embraces the principles and ideals of cancer pain assessment and management as outlined at professional society meetings, and in clinical guidelines, journal articles, and editorials. Such tools, which are currently in development, may provide convenient platforms to move that learning into the working environment of the student, health care provider, and institution. Although the potential of such tools is still under development, the software may provide the ability to efficiently assist in the identification of specific errors in knowledge, judgment, and practice patterns of the individual.

PAIN AND THE CANCER PATIENT

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (25). The sensory features and subjective qualities of pain vary, depending on its origin. Its emotional features depend in part on the social and physical context in which pain occurs, associated cognition, and the meaning of tissue trauma for the individual, but they are almost always negative.

Sensory Component of Cancer Pain

From a sensory perspective, tumor-associated pain may be classified as nociceptive (somatic or visceral) and neuropathic. Somatic nociceptive pain may be grouped into superficial (cutaneous) and deep. Most cutaneous pain is well localized, sharp, pricking, or burning. Deep tissue pain usually seems diffuse and dull or aching in quality. Visceral pain is diffuse, often referred to the body surface, perseverating, and frequently associated with a queasy quality that patients describe as *sickening*.

Compression and invasion of nerves by tumor result in the destruction of myelinated and unmyelinated fibers and of supporting tissue.

The process of tumor compression and invasion of nerves entails several degenerative, regenerative, and other pathophysiologic processes. The whole afferent neuron is affected and goes through reactive, presumably reparative, biochemical changes. The neuron loses its neuropeptides (26), atrophies, and may finally degenerate. This applies particularly to unmyelinated afferent neurons. The conditions in a nerve, when invaded or compressed by cancerous tissue, are probably similar to those after lesions of nerves induced by mechanical or other events. The process induces changes in the discharge properties of neurons (resting activity, response to mechanical and chemical stimulation).

Affective Processing and Suffering

The emotional mechanisms of cancer pain, and not its sensory features, are the reasons that it generates suffering. Of course, most cancer patients suffer from a complex array of problems and not only pain. Nonetheless, sustained nociception in and of itself can produce suffering because of its ability to create negative emotional arousal and elicit associated stress responses (see Chapter 6).

Suffering is a complex negative emotional and cognitive state characterized by perceived threat to the integrity of the self, perceived helplessness in the face of that threat, and exhaustion of psychosocial and personal resources for coping with that threat (27). The perceived threat to the self may encompass the body, the psychosocial self, or both. Suffering related to cancer is inherently emotional, unpleasant, complex, and enduring. The physician should recognize that, although suffering may be a consequence of pain, it is separate from pain and not a synonym for it. It differs from pain in that it entails additional cognitive affective states. For example, perceived helplessness (inability to cope, bankruptcy of physical, psychological, or social resources) is a key element in the suffering of most patients with incurable disease. Similarly, grief can ensue when a cancer patient perceives the loss of a psychological or social resource, a body part or desired personal appearance, a prized employment status, or a physical capability for a treasured activity. Loss often equates with perceived threat to self. In addition, suffering in the cancer patient sometimes involves a sense of separation from social support or alienation. These factors, combined with the emotional distress, fatigue, and stress associated with prolonged pain produce a complex state that differs from pain itself.

Psychological Factors and the Complexities of Cancer Pain

Health care providers frequently view pain reported by cancer patients as primarily somatogenic, whereas they regard pain of chronic nonmalignant pain patients, who lack adequate objective physical pathology, as psychogenic (28). Consequently, providers tend to treat cancer pain with pharmacologic, medical, or surgical modalities. Psychological factors are considered to be of secondary importance (29).

As stated previously, pain is a complex experience entailing physiologic, sensory, affective, cognitive, and behavioral components. The final individual perception of pain is dependent on nociceptive input and psychological modifiers such as fear, anxiety, anger, and depression (Fig. 35-4).

Figure 35-4. Individual perception of pain. Noxious stimuli are modified at the supraspinal level by emotions such as anxiety, fear, and anger.

Turk and colleagues (28) classified the multidimensional nature of cancer pain. They compared the adaptation of cancer patients and chronic noncancer patients to persisting pain. The majority of the cancer patients, both with (81%) and without (84%) metastatic disease, as well as the noncancer chronic pain patients (85%), fit one of three psychosocial subgroups: dysfunctional (high levels of pain, perceived interference, affective distress, and low levels of perceived control and activity), interpersonally distressed (high levels of affective distress, negative responses from significant others, and low levels of perceived support), and adaptive copers (low levels of interference and affective distress, high levels of perceived control and activity).

Substantial evidence suggests that psychological factors play an important role in exacerbating pain with clear origins of disease (see Chapter 24, Chapter 25 and Chapter 26). For example, the belief that pain signifies disease, a commonly held belief among cancer patients (4), is associated with elevated pain intensity (9,30). Spiegel and Bloom (30) also reported that the affective states of cancer patients, the belief that pain is an indicator for disease progression, and medication use all predict pain severity. Patients who attribute their pain to a warning of underlying disease report greater pain than patients with more benign interpretations, despite comparable levels of disease progression.

Because of psychological factors, the relationship between pain severity and the extent of disease is rarely as linear as one might assume (31). Research investigating the relationships between physical pathology and pain in cancer has shown conflicting results. First, not all patients with advanced cancer report pain. Twycross and Fairfield (32) reported that only 41 of 100 terminal- stage cancer patients reported pain caused by disease. Front and colleagues (33) demonstrated that for many cancer patients, pain reports did not correspond to the presence or location of bone metastases. Turk and colleagues (28) found that patients with cancer-related pain reported a significantly higher level of perceived disability and inactivity caused by pain than did those with pain of nonmalignant origin. Because the level of pain severity was comparable for the two patient groups, elevated disability may have been a consequence of the meanings patients attributed to their pain. The progression of disease means further deterioration of health and impending death. Indeed, the patients with cancer-related pain appeared to be more fearful of pain and reported significantly higher levels of cognitive and behavioral fear responses than did the patients with chronic pain not associated with cancer. These patients appeared to think and worry more about pain and avoid activities to prevent initiation of pain, and they generally felt more hopeless than the patients with noncancer-related pain.

DEPRESSION IN CANCER PATIENTS

Broadly speaking, depressed persons complain of a pervasive dysphoric mood, anhedonia, apathy and disinterest in normal activities, sleep problems, low energy, and in severe cases suicidal ideation (see Chapter 26). Approximately 25% of cancer patients meet criteria for major depressive syndrome at some point during their illness (34), whereas the prevalence of depression in the patient population at large approximates 6% for outpatients and 11% for inpatients (35,36). Craig and Abeloff (37) estimated an overall prevalence of depression at 53% for hospitalized cancer patients with varying primary sites and stages. Passik and Breitbart (36) noted that depression is more often comorbid with certain tumor types, such as pancreas and lung, than with others.

Depression is a complex family of mood disorders, as the evolving *Diagnostic and Statistical Manual* classifications of the American Psychiatric Association indicate, and any global statement about it risks provoking contention (see Chapter 26). To address this complexity, much of the classical thinking on depression attempted to force depressive syndromes (and patients) onto one or another continuum characterized by extremes at the poles (38,39). Two common continua are reactive versus endogenous and neurotic versus psychotic depression. The various continua differ less than one might expect in basic characterizations of depression, and for our purposes, they are almost equivalent. For simplicity, and because its language fits the cancer patient more readily, we describe the reactive-endogenous continuum.

Patients at the reactive pole tend to link their depression to an event, a stressful situation, or a loss. In the cancer patient, the cancer diagnosis itself can serve as the precipitating event, as can the failure of an antineoplastic intervention, the loss of ability to work, or a mutilating or debilitating surgery. When asked, depressed cancer patients may admit anxiety, restlessness, irritability, problems falling asleep, and sometimes obsessional thinking or other obsessional problems. Often, they do not present depressive symptoms to the physician because they assume that the physician is concerned only with the cancer itself. Those patients at the

endogenous pole seemingly develop depression without a precipitating cause. They tend to show marked slowing in motor responses, early morning wakening with the most severe mood disturbance in the morning, weight loss, and feelings of hopelessness. One form of endogenous depression is bipolar mood disorder, in which patients shift between the extremes of depression and mania. A genetic predisposition for unipolar and bipolar depression clearly exists (40). In these patients, a history of depressive disorder is the best indicator of current endogenous depression. Of course, many and perhaps most patients fall between the extremes of reactive and endogenous depression.

Detecting and Assessing Depression in the Cancer Patient

It is important for the physician treating cancer pain to recognize and address depression (Table 35-1). All too often, depression goes unnoticed or unaddressed in the cancer patient (41). Most physicians focus on somatic rather than psychological problems in patients with life-threatening illness, and some erroneously regard reactive depression in a patient who has received a diagnosis of cancer to be a normal response. Few oncologists or supporting consultants feel qualified to address depression, and for those who do, time limits on patient contact time make it difficult to engage in extensive questioning about psychological well-being. Patients and family members may add to the problem by assuming that care providers concern themselves solely with controlling the disease and wish to avoid the distractions that psychological management entails.

Effect	Comment
Suffering	Significant contribution, particularly when major organic disease is present.
Medical evaluation and decision making	Depressive symptoms can complicate.
Outcome and survival	Depressive disorders can adversely affect.
Recovery and compliance	Depressed medically ill patients tend to have slower recovery and poorer compliance.
Suicide	Undetected and untreated depression can lead to suicide.
Pain	Poorly managed pain is a common cause of reactive depression in patients with severe, life-threatening disease.

TABLE 35-1. Consequences of pain and depression in cancer patients

Diagnosing depression in the cancer patient is not straightforward because symptom overlap exists between the psychiatric disorder, the toxicities of treatment, and the effects of the primary disease. Chemotherapeutic agents (e.g., vincristine, vinblastine, l- asparaginase, procarbazine, or cytoxin), biological interventions such as interferon or interleukin, the antifungal agent amphotericin B, the toxic sequelae of whole-brain irradiation, and paraneoplastic syndromes can all produce symptoms that resemble depression. Consequently, many of the physical symptoms of depression such as fatigue, diminished appetite, and weight loss also occur in emotionally healthy cancer patients (42).

Screening for depression should focus primarily on the cognitive and affective features of depression, because these are not confounded with treatment-associated toxicities. Cognitive and behavioral signs of depression include observable sadness; statements of pervasive despair, hopelessness, or despondency; comments about being an unfair burden to others; expression of guilt or low self-esteem; and statements that life is and has been devoid of worth. Depressed patients also resist reassurances; for example, they tend to reject statements that a pain problem may not signal the progression of the disease.

SOURCES OF PAIN IN THE CANCER PATIENT

Most cancer pain results from one or more of three fundamental causes (Table 35-2):

Cause	Example
As a direct consequence of tumor	Involvement of bones; obstruction of hollow organs; compression of nerves
As an indirect consequence of tumors	By infections; by metabolic imbalances; by venous/lymphatic occlusion
As a consequence of tumor therapy	After surgical intervention; after chemotherapy; after radiation therapy
Without relation to cancer	Migraine; diabetic neuropathy; myofascial pain problems

TABLE 35-2. Causes of pain in patients with cancer

- direct tumor involvement,
- cancer-directed therapy, and
- mechanisms unrelated to cancer or its treatment.

Patients may present with complex patterns of pain that result from combinations of these categories, thus complicating the diagnosis. Factors influencing the pain complaint include the primary tumor type, stage of disease, tumor site, and mood factors (anxiety and depression) (6,43,44). Vainio and colleagues (44) estimated the prevalence of pain in 1,840 patients with advanced cancer from seven hospices in Europe, the United States, and Australia. Twenty-four percent of the patients surveyed had no pain, 24% had mild pain, 30% moderate pain, and 21% severe pain. In addition, the prevalence of moderate or severe pain was highest in gynecologic cancer and in head and neck cancer. Severe pain was most common in prostate cancer (Table 35-3).

Primary site	None	Mild	Moderate	Severe	No.
Prostate	17	22	30	41	41
Esophagus	29	21	13	38	24
Gynecologic	10	10	47	33	30
Colorectal	21	21	27	32	63
Lymphohematologic	13	29	26	32	38
Head and neck	17	11	43	29	35
Lung	26	23	30	21	241
Breast	22	25	31	21	118
Stomach	26	30	26	17	53
Other or unknown	26	27	32	15	417
Total	24	24	30	21	1,060

From Vainio A, Auvinen A. Prevalence of symptoms among patients with advanced cancer: an international collaborative study. Symptom Prevalence Group. J Pain Symptom Manage 1996;12:3–10 with permission. Copyright 1996 by the U.S. Cancer Pain Relief Committee.

TABLE 35-3. Prevalence of pain (percentage of patients) by primary site among palliative care cancer patients

Many patients with advanced disease frequently have multiple pains at different sites. Multiple pain complaints were more common in patients with breast, lung, and prostate cancer compared with gastrointestinal cancers (43). In a prospective study of 2,266 cancer patients, Grond and colleagues (45) assessed localization, etiology, and pathophysiologic mechanisms of pain syndromes associated with cancer. Thirty percent of the patients presented with one, 39% with two, and 31% with three or more distinct pain syndromes. The majority of patients had pain caused by cancer (85%) or antineoplastic treatment (17%); 9% had pain related to cancer disease and 9% caused by etiologies unrelated to cancer. These investigations classified pain as originating from nociceptors in bone (35%), soft tissue (45%), or visceral structures (33%), or of neuropathic origin (34%). Patients localized pain syndromes in the lower back (36%), abdominal region (27%), thoracic region (23%), lower limbs (21%), head (17%), and pelvic region (15%). Regions and systems affected by the main pain syndrome varied widely depending on the site of cancer origin, whereas the cancer site did not markedly influence the pain's temporal characteristics, intensity, or etiology.

Although a significant association exists between most cancer pain and the presence of metastases, certain tumor types are exceptions, notably breast and prostate cancers. Neither the prevalence nor the severity of pain among breast cancer patients varies directly as a function of metastatic sites of disease (30,33). Palmer and colleagues (46) evaluated the sensitivity of pain as an indicator of bone metastases in patients with breast or prostate cancer. Pain was a common finding, whether or not metastatic disease was present, and it occurred in over one-half of the patients. Although most patients with bone metastases reported bone pain, significant numbers (21% of breast and 22% of prostate patients) were asymptomatic.

These findings indicate that cancer pain poses a substantial management challenge for the physician. Pain can change over time, involve multiple sites, stem from several origins, involve several causes simultaneously, and may correspond loosely or not at all to the tumor.

CLASSIFICATION OF CANCER PAIN BY FEATURE

Several schemata exist for classifying pain in the cancer patient and are potentially useful for diagnosis and management. One such scheme is presented in Table 35-4.

Chronicity
Intensity and severity
Pathophysiology and mechanism
Individual type and stage of disease
Pattern of pain
Syndrome

TABLE 35-4. Methods used for classifying pain in the cancer patient

Chronicity

Acute pain can occur during and after certain diagnostic procedures and various anticancer therapies, particularly postoperative pain after surgical intervention (47) and pain during chemotherapy (48) or radiation therapy (49) (Table 35-5). The course of acute pain is usually predictable and self-limiting, and the pain does not represent a difficult diagnostic problem. In contrast, assessment of patients with chronic pain tends to be much more difficult and complex.

Procedure	Problem
Diagnostic procedures	Blood samples
	Lumbar puncture
	Angiography
	Endoscopy
	Biopsy
Chemotherapy	Mucositis
	Myalgia
	Arthralgia
	Pancreatitis
	Gastrointestinal distress
	Cardiomyopathy
	Extravasation of drug into tissues
Radiation treatment	Skin burns
	Mucositis
	Pharyngitis
	Esophagitis
	Proctitis
	Itching
	Painful fractures
Surgical therapy	Postoperative pain
	Ileus, colitis
	Urinary retention distress

TABLE 35-5. Acute pain associated with cancer management

Intensity and Severity

Health care workers commonly underestimate the severity of a patient's pain (50,51), particularly when relying on their own observations. This tendency is problematic because pain is often undertreated when patients and physicians differ in their judgment of the pain's severity (11). Although both severity and the degree of interference with function are crucial to the adequate assessment of pain, severity is the primary factor determining the effect of pain on the patient, and it drives the urgency and energy of the treatment process (52). Thus, the consistent measurement of pain intensity helps assess patients' progress, provides outcome measures for research purposes, and may guide therapy (53) (see Chapter 15).

Patient self-report is always the primary source of information for the measurement of symptoms. Observer ratings of symptom severity correlate poorly with patient ratings and are generally inadequate substitutes for patient reporting. Grossman and colleagues (50) found a low correlation between patients' visual analog scores for pain and those of health care providers. The discrepancies were most pronounced in those patients reporting severe pain. Although one can monitor some objective signs to clarify the manifestations and effect of certain symptoms, these signs only complement subjective assessment. An assessment of pain intensity should include an evaluation of not only the present pain intensity but also pain at its least and worst.

The three most commonly used instruments for assessing cancer pain intensity are mentioned here:

- Visual Analog Scale (VAS): A slash mark corresponding to intensity of pain is placed on a 100-mm line ranging at one end from “no pain,” to the other end, “pain as bad as it could possibly be.”
- Numeric Rating Scale: A number is assigned to the intensity of pain on a scale of 0 to 10; 0 reflecting “no pain” and 10 reflecting the “worst pain possible.”
- Verbal Descriptor Scale: The patient chooses one of the following selections that best describes pain: no pain, mild pain, moderate pain, severe pain, or worst possible pain.

All three measures correlate highly with one another. For pain assessment in clinical settings, the VAS, Verbal Descriptor Scale, and Numeric Rating Scale approach equivalency (54) so that clarity, ease of administration, and simplicity of scoring become justifiable criteria in response scale selection. In clinical trials, the Numeric Rating Scale has proven more reliable than the VAS, especially with less educated patients (55). Numeric scales work well as cancer clinical trial instruments because

they are easier to understand and easier to score (56).

Several studies have shown that differences between categorical pain severity items are not linear (57,58). For instance, when pain severity is rated at the midpoint or higher on numeric rating scales, patients report disproportionately more interference with daily function (59). Many people, both with and without cancer, function quite effectively with a background level of mild pain that does not seriously impair or distract them. As pain severity increases to moderate intensity, pain passes a threshold beyond which it is hard for the patient to ignore. At this point, it disrupts many aspects of the patient's life. When pain is severe, it becomes a primary focus of attention and prohibits most activities. Pain severity and the degree to which the patient's function is impaired are highly associated. As a way of delineating different levels of cancer pain severity, Serlin and colleagues (31) explored the relationship between numeric ratings of pain severity and ratings of pain's interference with such functions as activity, mood, and sleep. Based on the degree of interference with function, ratings of 1 to 4 correspond to mild pain, 5 to 6 to moderate pain, and 7 to 10 to severe pain.

Pathophysiology and Mechanisms

A general classification by pathophysiology distinguishes nociceptive (somatic and visceral) from neuropathic pain. This distinction is fundamental in assessment because it determines therapy. In principle, pain results from stimulation of nociceptors or by lesions of afferent nerve fibers. Pain is nociceptive if the sustaining mechanisms are related to ongoing tissue pathology. Pain is neuropathic when evidence suggests that the pain stems from injury to neural tissues and aberrant somatosensory processing in the periphery or in the central nervous system (CNS). Physical influences such as pressure, traction, compression, and tumor infiltration, as well as metabolic or chemical disturbances, produce pain. Obviously, classification by a physiologic mechanism would be an improvement, but sufficient information to do this is not available.

Tumor Involvement of Encapsulated Organs

Primary or secondary tumors of the liver are the most frequent examples of tumors of encapsulated organs. These can enlarge the organ to several times the normal size. Because the organ capsule of connective tissue grows less rapidly than the tumor, the intracapsular pressure increases as capsular distension develops. In addition, tumor infiltrates the capsule locally, producing dull and, rarely, also stabbing pains. The massive growth of the organ not only stimulates intracapsular nociceptors, but it also irritates larger nerves by pressure or traction on the tissue suspending the organ. Similar organ-enlarging processes in the spleen and kidneys do not lead to pain to the same extent as in the liver, perhaps because of the more stable suspension or embedding of these organs, which are farther away from the midline with its abundant nerve pathways. Kidney tumors produce pain only when the kidney has been almost completely destroyed and the tumor has invaded the pararenal tissue, or when it destroys the renal pelvis.

The brain is also an encapsulated organ. Its special feature is that the bony skull capsule prevents any enlargement. Pain arises here, not by destruction of parenchyma, but by the increase of intracranial pressure with stimulation of the meningeal nociceptors. Such an increase of intracranial pressure occurs in space-occupying tumor growth or in focal or generalized brain edema. Focally, edema can develop around isolated tumors. Generalized edema develops in diffuse metastatic invasion of the meninges caused by disturbance of the circulation of cerebrospinal fluid (CSF). Such a tumor invasion of the leptomeninges is frequent in malignant lymphomas. However, metastatic invasion of the leptomeninges occurs in patients with solid tumors (e.g., bronchial carcinoma and malignant melanoma), with the predominant symptom being headache. In such cases, tumor infiltration of cranial nerves may also occur.

Tumor Infiltration of Peripheral Nerves

Because peripheral nerves can usually evade pressure from a tumor on one side, infiltration by tumor tissue is the quintessential tissue trauma stimulus. In addition, indirect damage of unknown pathogenesis might also occur to peripheral nerves in the context of tumor conditions (e.g., paraneoplastic syndromes). Tumor tissue often infiltrates the perineural cleft, but this does not regularly cause pain. A massive and then painful entrapment of the nerve plexus or individual nerves sometimes occurs, especially in extensive breast carcinomas and their recurrences or in chest wall metastases of bronchial carcinomas. The perineural cleft widens with tumor infiltration, and infiltration of the tumor into the nerve itself is common. Degenerative changes of the axis cylinders are sometimes visible with conventional screening methods. Primary tumors of the peripheral nerves themselves lead to painful destruction. Tumor compression regularly elicits pain when the affected nerve cannot give way (e.g., a spinal nerve).

Tumor Infiltration of Soft Tissues

On the one hand, tumor infiltration of soft tissues causes pain via the mechanisms described previously, as with massive infiltrations of the retroperitoneum. On the other hand, infiltration and destruction of mobile structures (e.g., of the skeletal musculature) can lead to pain via disturbance of function. Here, the tumor spreads in the interstitium and destroys blood vessels, lymphatics, and nerves.

Tumor Infiltration of Bone

The most frequent cause of pain in tumor patients is infiltration of bone. This applies to primary and secondary neoplasias originating from the bone marrow as well as to neoplasias of the bone itself. Such tumors always cause pain when they lead to an elevation of the intraosseous pressure, to loss of stability, or to a lesion of the periosteum resulting in periosteal elevation, or with the release of chemical mediators of nociception. The neural structures that generate nociception reside in the bone marrow, in the bone, and in the periosteum.

In metastatic processes, the degree of bone destruction is often extensive. Vertebral spread of tumor may involve intervertebral foramina, where it can compress nerve roots (Fig. 35-5). Further spread posteriorly leads to encroachment of the spinal cord and the spinal nerves. In bone, the metastases primarily localized in the bone marrow result in osteolysis or osteosclerosis. Necroses and hemorrhages occur frequently in bone metastases and doubtless play a role in the etiology of pain. The hemorrhages probably result from microfractures. Metastatic bone disease is discussed in detail later in this chapter.

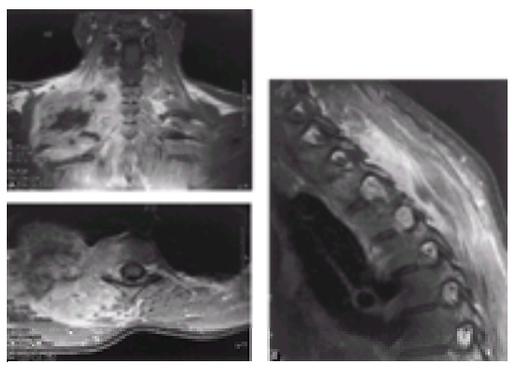

Figure 35-5. **A:** Coronal T1-weighted magnetic resonance imaging scan showing a right apical lung mass with invasion into the spinal canal. **B:** Sagittal T1-weighted magnetic resonance imaging scan (postgadolinium) showing tumor spread into right T-2 and T-3 vertebral foramina with mass infiltration of posterior spinal elements. **C:** Axial T1-weighted magnetic resonance imaging scan showing mass in apex of right lung and right paravertebral muscles extending into T-2 vertebral body and foramen.

Tumor Infiltration of Abdominal Hollow Organs

In general, tumors and their sequelae in the bronchial tree are indolent, whereas those in abdominal hollow organs cause pain. This applies to all primary and secondary intestinal tumors. However, their pain-eliciting potency differs widely from individual to individual. The pain results from ulcerations, motility disorders, dilatations, and disorders of blood flow. In accordance with the extent of the lymphatic tissue, large tumors with extensive ulceration and hemorrhage occur in malignant lymphomas of the gastrointestinal tract. Perineural tumor infiltration, arteritis, or perineural inflammatory reactions are common in tumors of the abdominal

and urogenital hollow organs.

Tumor Infiltration and Inflammation of Serous Mucosa

Normally, pleural carcinosis does not cause pain, probably because of the development of pleural effusion, which prevents the pleurae from rubbing together. In peritoneal carcinosis, pain occurs more frequently, and it may be the first symptom of tumor disease. It stems from either direct contact of the metastases with peripheral nerves or an inflammatory reaction elicited by the carcinosis with disorders of visceral motility. Acute inflammatory reactions of the peritoneum with the clinical picture of *acute abdomen* and possibly with empyema appear after tumor-induced perforation or penetration of hollow viscera.

Tumor-Induced Necroses in Solid Organs

Specific necroses produce typical pain symptoms in the pancreas. Such necroses, with the clinical picture of autodigestive pancreatitis, can occur with pancreatic metastases of a bronchial carcinoma. The autodigestion probably results from tumorous destruction of the parenchyma together with tumor infiltration and stenoses of the excretory ducts.

Tumor-Induced Occlusions of Blood Vessels

Invasion of the lymphatics and blood vessels is part of the biology of malignant neoplasias and is the precondition for metastasis. Generally, small and peripheral vessels are involved, obstruction of which does not result in any appreciable disorder of the circulation. Larger veins occasionally become infiltrated and occluded. Infiltration of larger arteries is rare.

Tumor Type and Stage of Disease

Factors influencing the pain complaint include the primary tumor type, stage of disease, tumor site, and mood factors such as anxiety and depression (6,43,44). When metastatic disease appears, approximately one in three patients reports significant pain. As discussed previously, although pain tends to reflect the presence of metastases, this may not always be the case for certain tumor types, particularly for patients with breast or prostate cancers. The prevalence and severity of pain among breast cancer patients do not appear to vary directly as a function of metastatic sites of disease (30,33).

Pain caused by tumor may occur at the onset of disease or at an advanced stage. Although rarely one of the early indicators of the onset of disease, pain is not a significant problem for the majority of patients in the early stages of disease, with 5% to 10% of patients with solid tumors reporting pain at a level that interferes with mood and activity. However, pain is obviously a major concern that often prompts the patient to seek medical consultation. Vuorinen and colleagues (60) found that 28% of newly diagnosed unselected cancer patients reported pain. Cleeland and colleagues (61) reported that the majority of patients with end-stage disease have pain of a severity that interferes with several aspects of the patient's quality of life. Daut and Cleeland (9) found that pain was an early symptom of cancer in 40% to 50% of patients with cancer of the breast, ovary, prostate, colon, and rectum, and in approximately 20% of patients with cancer of the uterus and cervix.

Knowledge of the natural history of the disease facilitates an understanding of the pain process and is important in determining the nature and timing of treatment. Examples of the more common disease processes follow.

Pancreatic Cancer Pain Syndromes

Over the past 20 years, the incidence of pancreatic carcinoma in Europe and North America has remained unchanged, with an estimated 9 to 10 cases per 100,000 and slightly increased male to female and black to white ratios. Pancreatic cancer currently ranks as the fifth most common cause of cancer-related deaths in Western countries (62). Approximately 90% of pancreatic tumors are adenocarcinomas with a ductal phenotype. Neuroendocrine tumors and acinar cell carcinomas represent approximately 2% to 5% of all pancreatic tumors. Local tumor extension almost invariably involves the peripancreatic fat tissue through direct invasion of lymphatic channels and perineural spaces. Duodenum, stomach, gallbladder, and peritoneum are infiltrated by tumors located in the pancreatic head; body and tail tumors can invade liver, spleen, and left adrenal gland. Lymphatic spread to adjacent and distant lymph nodes seems to precede hematogenous spread, which affects, in descending order, liver, peritoneum, lungs, adrenals, kidneys, bones, and brain. Thirty percent to 60% of patients experience pain with early, relatively limited disease, and over 80% of those with advanced disease have pain (63,64).

Singh and colleagues (65) reported that 60% of patients undergoing pancreatic resections and 84% of those not resected have moderate to severe pain. Pain caused by pancreatic cancer is usually abdominal, typically referred to the epigastric region or the upper abdominal quadrants, but it can also involve the lower quadrants or be diffuse (64). Back pain is associated with abdominal pain in 50% to 65% of cases, but only 5% to 10% of patients report it as their only complaint (66). In one series, 67% of patients could not describe their pain location better than as over their “diffuse abdomen” (66). Direct infiltration of pancreatic afferent nerves, pancreatic duct obstruction with retention pancreatitis, biliary obstruction, or duodenal infiltration resulting in bowel obstruction can generate pain. Eating often aggravates the pain. Tumors of the head of the pancreas may cause epigastric pain with right flank radiation more often, whereas pain from tumors in the tail has left-sided radiation (67). Back pain in the region of T-10– L-2 is common and is the first symptom in 10% to 30% of cases. Lying flat typically exacerbates it and sitting relieves it. This pain probably comes from retroperitoneal tumor involvement, and it may not respond to celiac plexus block. It often merges with similar syndromes caused by nodal or other soft tissue tumor involvement in the retroperitoneal region (Table 35-6). The effect of pancreatic pain can be profound. It is commonly associated with depressed mood, and contributes to the rapid decline in function that characterizes this disease (36,66).

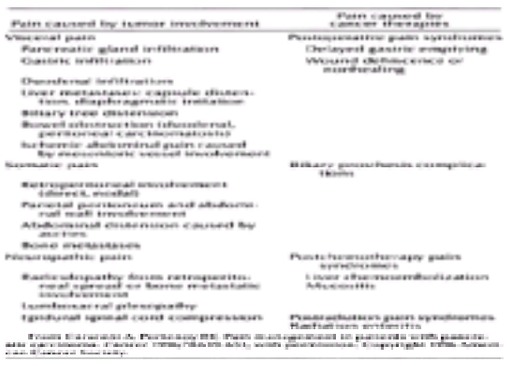

TABLE 35-6. Pancreatic cancer pain syndromes

Ovarian Cancer

The prevalence of pain associated with ovarian cancer resembles the prevalence rates in populations with other solid tumors (68). Ovarian cancer spreads by intraperitoneal, lymphatic, and locally invasive pathways. Lymphatic pathways may extend from the abdominal retroperitoneum to the groin via the inguinal and femoral canals or across the diaphragm to the pleural space. Intraperitoneal spread of tumor begins with extension of tumor through the ovarian capsule, allowing implantation of tumor throughout the abdomen. Intraperitoneal metastases show a predilection for the omentum and diaphragm, but no organ is spared, and concomitant ascites is frequent. Portenoy and colleagues (68) noted that pain, fatigue, and psychological distress were the most prevalent symptoms in patients with advanced (stage III or IV) ovarian cancer. Patients generally describe pain as occurring in the abdominopelvic or lower back region, as being frequent or almost constant, and moderate to severe in intensity. Patients with advanced disease may experience pain in the lower extremities either from invasion of the lumbosacral plexus by tumor or by lymphedema secondary to iliac vessel occlusion.

Cervical Cancer

Cancer of the cervix is a frequent cancer in women worldwide. There are several histologic subtypes of cervical carcinoma. Squamous cell carcinoma is the most

frequently seen and accounts for 80% to 90% of invasive cervical cancers. The next most frequent subtype is adenocarcinoma. The cervix drains by preureteral, postureteral, and uterosacral routes into the following regional lymph nodes: parametrial, paracervical, hypogastric (obturator), common iliac, external iliac, internal iliac, sacral, and presacral. The common sites of distant spread include the aortic (paraaortic, periaortic), lateral aortic and mediastinal nodes, lungs, and skeleton. In patients with locally advanced disease (stages IIB to IVA), 24% have paraaortic disease (69). Identification of paraaortic nodal status allows modification of therapy (usually extended field radiation therapy) with improved survival (70,71). Detection of paraaortic lymph node metastases may be difficult using standard imaging techniques such as abdominopelvic computed tomography (CT) scanning. The sensitivity of CT scanning for identifying paraaortic nodal metastasis may be only 34% (69). Rose and colleagues (72) demonstrated that positron emission tomography (PET) scanning accurately predicts both the presence and absence of pelvic and paraaortic nodal metastatic disease. Identification of sensitive and specific imaging modalities is a useful adjunct in this disease.

Prostate Cancer

These cancers are generally adenocarcinomas. The two most frequent staging systems used for prostate cancer are the American Urologic Association Cancer Staging (A through D) and the TNM classification (0 through IV) of the International Union against Cancer. Approximately 40% of patients with prostate cancer have stage D (IV) disease on presentation, and most of these have bone metastases, with a median survival of 2.4 years. Because of the predilection of prostate cancer to spread to bony sites, a significant proportion of patients with metastatic disease have bone pain. Prostate cancer rarely spreads to vital organs, and the disease tends to progress slowly. The only exceptions are spinal cord compression or ureteral obstruction secondary to retroperitoneal lymph node metastases.

Tumors of the prostate gland may produce local rectal, urethral, suprapubic, and penile pain as a result of expansion and inflammation of the prostate; pain referred to the back, lower extremities, and abdominal area resulting from tumor growth within the pelvis; and distant bone pain with associated neurologic dysfunction associated with long bone, vertebral, and skull metastases (Table 35-7). The regional lymph nodes of the prostate are the nodes of the true pelvis, which are the pelvic nodes below the bifurcation of the common iliac arteries. Distant lymph nodes are outside the confines of the true pelvis. They are the aortic (paraaortic, periaortic, lumbar), common iliac, inguinal, superficial inguinal (femoral), supraclavicular, cervical, scalene, and retroperitoneal nodes. Ultrasound, CT, magnetic resonance imaging (MRI), or lymphangiography can image them. In prostate cancer, preliminary studies using 2-[F-18] fluoro-2-deoxy-d-glucose (FDG) tracer demonstrated that PET cannot reliably differentiate between primary prostate cancer and benign prostatic hyperplasia, and that PET is not as sensitive as bone scintigraphy for the detection of osseous metastases. However, PET may have a role in the detection of lymph node metastases in patients with prostate-specific antigen relapse after primary local therapy (73).

Causes of pain	Examples and clinical syndromes
Bone metastasis	Single metastasis of pelvis or long bone
	Vertebral body metastasis, spinal cord compression
	Base of skull metastasis, cranial nerve palsies
	Perineal pain syndromes
Soft tissue metastasis	Lumbosacral plexopathy
	Pelvic tension "myalgia"
Pelvic visceral pain	"Prostatitis" pain

From Payne R. Pain management in the patient with prostate cancer. Cancer 1993;71:1131-1137, with permission. Copyright 1996 American Cancer Society.

TABLE 35-7. Causes of pain in prostate cancer

One can identify clinical syndromes by the site of bony involvement, the coexistence of mechanical instability secondary to fractures, and the neurologic dysfunction caused by tumor infiltration of contiguous neurologic structures. Bone metastases to the hip and pelvis often produce local pain that is exacerbated by movement, especially during weight bearing. Local invasion of tumor from the pelvis into the sacrum may produce the syndrome of perineal pain. Patients with this syndrome complain of local and perirectal pain that is accentuated by pressure on the perineal region, such as that caused by sitting or lying prone. In its most extreme form, the patient cannot sit or lie flat. Dysfunction of the parasympathetic sacral innervation to bladder and bowel impairs continence early in the course of this syndrome. Local spread of tumor from the prostate into other pelvic and abdominal structures often produces visceral and neuropathic pain. Tumor invasion of the lumbosacral plexus may occur.

Prostate-specific antigen (PSA) is useful in the diagnosis and staging of men with prostate cancer and in monitoring men after all forms of treatment for prostate cancer (74). Serial measurements may more closely reflect actual disease status than single measurements. For example, changes in PSA after radiation therapy or androgen ablation therapy for prostate cancer reflect progression of disease, and add additional information with respect to disease status over that obtained with a single PSA measurement (75,76). In untreated patients, PSA correlates with clinical stage, increasing with increasing tumor stage (77).

Breast Cancer

Breast cancer consists of the following histologic types: carcinoma, ductal, lobular, nipple, and other (undifferentiated). Therapeutic strategies for individual patients with breast cancer frequently depend on the following prognostic variables: size of the primary neoplasm, the presence and extent of axillary lymph node metastases, pathologic stage of disease after primary therapy, and the presence or absence of receptor (estrogen, progesterone) activity. The breast lymphatics drain via three major routes: axillary, transpectoral, and internal mammary. Intramammary lymph nodes are considered with, and coded as, axillary lymph nodes for staging purposes. Metastasis to any other lymph node is distant.

PET scanning can be used to evaluate primary lesions, regionally metastatic, and systemic metastases of breast cancer. Combined FDG-PET and MRI provide useful treatment-planning data for patients clinically suspected of having recurrent axillary or supraclavicular breast cancer. FDG-PET help confirm metastases in patients with indeterminate MRI findings and depicted unsuspected metastases outside the axilla (78). FDG-PET is also superior to bone scintigraphy in the detection of osteolytic breast cancer metastases (79).

Breast cancer can metastasize to any organ in the body: Bone, lung, liver, and brain are frequent sites. Metastases usually appear within a few years, but recurrence may occur, particularly in bone, many years later. Although metastatic disease may be asymptomatic, the most common site of metastases, bone, typically hurts. Between 40% and 60% of patients with metastatic breast cancer have bone disease, and in many of these patients, the involved bones (vertebrae, femoral and humoral shafts, the acetabular area) are those that are involved with motion. Moreover, patients with metastatic breast cancer and bone involvement as their only site of metastatic disease may have median survival expectations of 27 to 29 months, during which time pain may be the chief manifestation of disease. Even patients with pulmonary metastases have median survivals of the order of 18 to 23 months (80), and patients with only unilateral pleural involvement on the order of 44 months (81).

The clinician most likely will have a long relationship with the patient with metastatic breast cancer, and will have the opportunity to follow the course and progression of disease. The course of disease in patients with metastatic breast cancer fits one of two patterns: an indolent course or disease not immediately life-threatening, and that which is rapidly progressing or with extensive vital organ disease. Knowledge of the natural history of the disease is important in determining the nature and timing of treatment.

Table 35-8 lists some of the common causes of pain in patients with breast cancer.

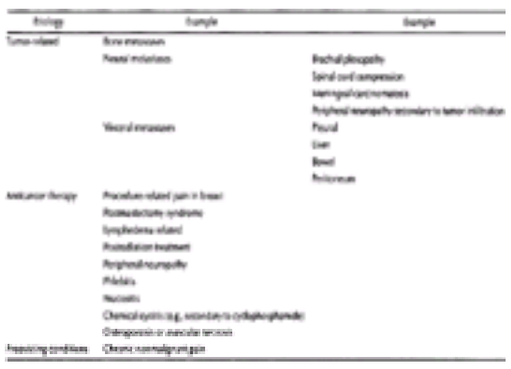

TABLE 35-8. Causes of pain in patients with breast cancer

Lung Cancer

Bronchogenic cancers comprise two groups that reflect their biology and management: small cell lung cancers (SCLC) and non–small cell lung cancers. Each of these further divides into subtypes, but these categories often blend into each other or coexist. SCLCs are relatively sensitive to cytotoxic chemotherapy and radiation therapy. They account for approximately 25% of lung tumors and although usually centrally located, these can arise peripherally. Clinically, these tumors demonstrate a rapid growth rate and early metastatic dissemination.

Before the advent of systemic therapy, local surgical or radiation therapy alone produced poor median survivals, ranging from 8 to 17 weeks and 5-year survivals of less than 1% (82). Effective chemotherapy has allowed the control of disseminated disease and improved the median survival of patients to 1 year or more, increasing the number of long-term disease-free survivors to between 5% and 10% (83).

SCLC tumors express many neuroendocrine markers. Individual tumors may secrete up to 10 discrete hormones (84). Histologically, SCLCs include small cell anaplastic carcinoma, which includes the oat cell type. Small cell anaplastic carcinoma is an aggressive and rapidly growing neoplasm and is limited to the thorax at presentation in only 25% of patients. Metastases occur in regional lymph nodes, lung, abdominal lymph nodes, liver, adrenal gland, bone, CNS, and also bone marrow.

Non–small cell lung cancers are a morphologically diverse group that includes squamous cell carcinoma, adenocarcinoma, and large cell anaplastic carcinoma. Squamous cell carcinoma is less likely to metastasize early. Adenocarcinomas have become the most frequent form of lung cancer in the United States (85). Adenocarcinoma metastasizes widely and frequently to the other lung, liver, bone, kidney, and the CNS. Large cell anaplastic carcinoma metastasizes in a pattern similar to adenocarcinoma, with a predilection for mediastinal lymph nodes, pleura, adrenals, CNS, and bone.

For the purposes of prognosis and for analyzing data from clinical studies, we divide small cell lung cancer into limited and extensive disease categories. Limited disease is characterized by tumor that is clinically confined to the chest, mediastinum, and ipsilateral supraclavicular lymph nodes. Ipsilateral pleural effusion represents limited disease. All other sites of metastases are defined as extensive disease (86). The median survival for patients with limited disease is approximately 12 to 18 months; for extensive disease it approximates 9 months (87).

Lung cancers, particularly SCLC, often entail clinical paraneoplastic syndromes. Malignancy-associated hyponatremia is commonly associated with excessive production of arginine vasopressin by tumor cells, and a large fraction of new cases of the syndrome of inappropriate antidiuretic hormone secretion in elderly smokers are caused by SCLC. Approximately 10% of all lung cancer patients have hypercalcemia, and of these 10% to 15% do not have evident bone metastases. Humoral hypercalcemia of malignancy is more common in non–small cell lung cancer, and especially squamous cell carcinoma. The neurologic syndromes associated with lung cancer are rare disorders such as subacute cerebellar degeneration, optic neuritis and retinopathy, subacute necrotizing myelopathy, and peripheral neuropathy.

Pain is a major symptom in patients with all types of advanced lung cancer (88,89). Chest pain is the most common site of pain in patients with small cell cancer. The pain is often poorly localized, dull in character, may radiate to the neck or back, and exacerbates with coughing. Mercadante and colleagues (89) reported that patients with advanced lung cancer commonly reported chest wall (including ribs and shoulder blade) pain, followed by pain in the lower extremities and lumbar regions, then abdomen and upper extremities, and the head area.

Renal Cell Cancers

Renal cell carcinoma accounts for 2% of all cancers (1). Twenty-five percent to 30% of patients have overt metastases at presentation. Frequent sites include the lung (50% to 60% of patients with metastases), bone (30% to 40%), liver (30% to 40%), and brain (5%). Unusual sites of metastases characterize renal cancer, however, and may involve virtually any organ site, including the thyroid, pancreas, skeletal muscle, and skin or underlying soft tissue. Common metastatic sites include bone, liver, lung, brain, and distant lymph nodes. The regional lymph nodes of the kidney are renal hilar, paracaval, aortic (paraaortic, periaortic, lateral aortic), and retroperitoneal.

Surgical resection remains the cornerstone of treatment for renal cell carcinomas. Radical nephrectomy involves resection of kidney, perirenal fat, and ipsilateral adrenal gland. The extent and benefit of lymphadenectomy is controversial. In 10% to 20% of patients, nodal involvement is found at surgery without clinically evident distant metastases (90,91). Virtually all such patients later relapse with distant metastases despite lymphadenectomy (91). Although an occasional patient may be cured by resection of a lymph node metastasis, in most patients the benefit of lymphadenectomy is limited to the prognostic information it provides.

The most important determinant of survival is the anatomic extent of the tumor (i.e., the pathologic stage). Patients with organ- confined disease that is resected completely generally have better outcomes than those with nodal involvement or distant metastases. Twenty percent to 30% of patients with localized tumors relapse after radical nephrectomy. Less than 5% have local recurrences, whereas lung metastases are the most common sites of distant relapse, occurring in 50% to 60% of patients (92,93). The median time before a relapse after nephrectomy is 15 to 18 months, and 85% of relapses occur within 3 years (92,93).

Colorectal Cancer

The vast majority of these tumors are adenocarcinoma (more than 90%) and, to a lesser degree, carcinoid tumors, leiomyosarcomas, and lymphoma. Spread to regional lymph nodes generally correlates to depth of invasion by the primary tumor and the grade of differentiation. Nodal spread occurs in 10% to 20% of tumors confined to the bowel wall. Hematogenous spread is usually to the liver via portal venous transmission.

The liver is the prime organ for metastatic spread (65%); extraabdominal metastases in lung (25%) and brain and bone (10%) are much less common. Most recurrences appear within 2 years (approximately 70%) and almost all (90%) within 5 years.

Surgery is the primary modality of treatment. There is no well-defined role for radiation treatment in colon cancer. The response rates to chemotherapy (usually 5-fluorouracil) in recurrent and metastatic cancer remain poor and of limited duration. Ulander and colleagues (94) reported on the quality of life in 86 patients who underwent surgery for colorectal cancer. Patients with colon cancer (n = 39) had significantly less pain and less constipation at follow-up compared with preoperatively than did patients with rectal cancer (n = 47). Patients with rectal cancer, having undergone preoperative radiotherapy treatment, had significantly lower confidence intervals for means (95%) on the physical functioning and role functioning scales at follow-up versus preoperatively.

In addition to staging systems, independent prognostic factors include histologic type, histologic grade, serum carcinoembryonic antigen level, and extramural venous invasion.

Patterns of Cancer Pain

Cancer patients may have constant or intermittent pain, as discussed previously. *Breakthrough pain* refers to sudden increases in the base level of pain or different but recurring pains (95).

The majority of breakthrough pains are usually associated with tumor, but Portenoy and colleagues (95) reported that tumor therapy was the cause in 14% of cases and 4% were unrelated to either the cancer or its treatment. There are three types of breakthrough pain:

- *Incident pain* is pain directly related to an event or activity, such as turning in bed, weight bearing, a bowel movement, swallowing meals, and so forth. Often, incident pain is well defined and predictable, so that physicians can anticipate and treat the problem prophylactically.
- *End of dose failure* is pain that emerges because of too much time between doses of medication. One can predict this pattern for the individual patient and readily prevent it by using time-contingent dosing at an appropriate interval. The key is monitoring symptoms in relation to the dosing schedule.
- *Spontaneous pain* occurs spontaneously without relationship to particular events or procedures. These pains are more difficult because of their unpredictable nature and their often fleeting character. In some cases adjunctive analgesics effectively provide relief. Longer lasting pains require rapid-onset analgesics. Increasing the dose of the time-contingent opioids often increases the overall side effects of these medications.

Cancer Pain Syndromes

Table 35-9, Table 35-10, Table 35-11 and Table 35-12 list the common pain syndromes in the patient with cancer. Table 35-13 lists the prevalence of painful manifestations of cancer and their common etiologies. Bone, viscera, and nerve are the most common sites of metastases associated with chronic cancer pain. Each of these sites is discussed separately.

TABLE 35-9. Pain syndromes caused by tumor involvement

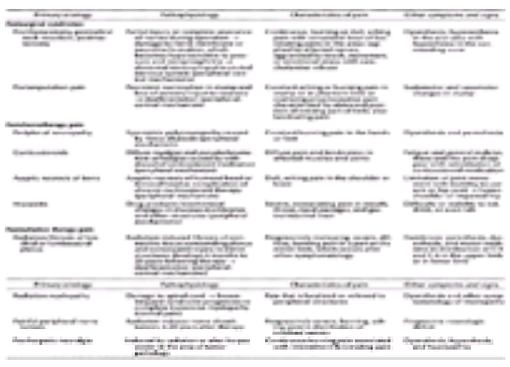

TABLE 35-10. Pain syndromes associated with cancer therapy

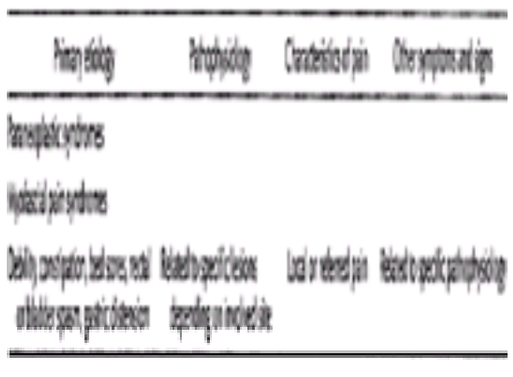

TABLE 35-11. Pain syndromes caused by cancer-induced pathophysiologic changes

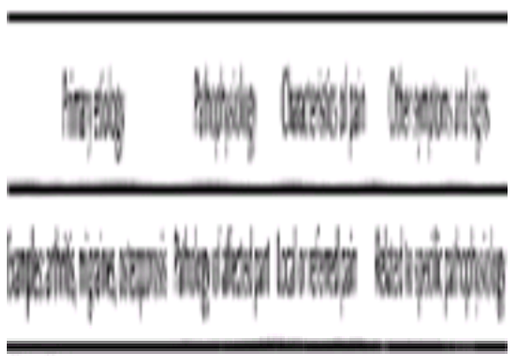

TABLE 35-12. Pain syndromes unrelated to cancer

TABLE 35-13. Prevalence of painful manifestations of cancer and common etiologies

BONE METASTASES

Skeletal involvement, a frequent and troublesome complication affecting many patients with neoplastic disease, is the third most common metastatic site after the lung and liver (96). Metastatic cancer may invade bone in 30% to 70% of patients (97). Up to 85% of patients dying from breast, prostate, or lung cancer demonstrate bone involvement at autopsy (98). Bone pain is the most common kind of pain caused by cancer (32,99,100). Pain from bone metastases affects 28% of hospice inpatients, 34% of patients in a cancer pain clinic (101), and 45% of advanced cancer patients at home. Bone disease frequently gives rise to complications that have a significant effect on a patient's quality of life because osteolytic bone disease is a major source of pain and causes problems such as difficulty in ambulation, neurologic deficits, and pathologic fractures. Fractures are common in patients with myeloma and breast cancer, and long bones are more frequently involved (102).

Bone metastases from carcinomas of the breast, lung, prostate, kidney, and thyroid are the most frequent (Table 35-14). The prevalence of skeletal disease is greatest in breast and prostate carcinoma, reflecting both the high incidence and the relatively long clinical course of these tumors. These two cancers alone probably account for more than 80% of cases of metastatic bone disease. In breast carcinoma, the incidence of bone metastases is significantly higher for tumors that produce parathyroid hormone-related peptide (PTHrP) (103) and are either steroid-receptor positive (104) or well differentiated (105), whereas in prostate carcinoma, bone metastases are more often associated with poorly differentiated tumors (106).

Primary site	Bone metastases (%)
Breast	50-85
Prostate	50-75
Lung	30-50
Kidney	30-50
Thyroid	39
Pancreas	5-10
Colon and rectum	5-10
Stomach	5-10
Liver	8
Ovary	2-6

Adapted from Nystrom JS, Weiner JM, Heilelinger-Juttner J, et al. Metastatic and histologic presentations in unknown primary cancer. *Semin Oncol* 1977;453–58.

TABLE 35-14. Frequency of bone metastases in cancer

Bone metastases most commonly affect the axial skeleton, where the red marrow is located in adults. Bone metastases are typically termed *lytic*, *sclerotic*, or *mixed*, according to the radiographic appearances of the lesions. Where bone resorption predominates, with little new bone formation, focal bone destruction occurs and the metastases have a lytic appearance. Lytic lesions are most common in multiple myeloma, melanoma, breast, lung, thyroid, renal, and gastrointestinal malignancies. Conversely, in bone metastases characterized by increased osteoblastic activity, the lesions appear sclerotic. Metastases from prostate carcinoma especially, but also those of breast, lung, carcinoid, and medullablastoma tumors, produce sclerotic lesions. Some tumors characteristically demonstrate a purely lytic radiographic appearance, such as multiple myeloma, lung cancer, and renal carcinoma, and these are more prone to pathologic fracture. Other tumors have a blastic radiographic appearance. Prostate cancer cells produce osteoblast stimulatory factors, probably specific growth factors or acid phosphatase (107). In this case, new bone forms directly on trabecular bone surface before osteoclastic resorption (108). The resulting sclerotic metastases are less prone to fracture because of locally increased bony mass. Breast cancer cells metastatic to bone promote osteoclastic activity. However, this upsets the normal balance of bone resorption and new formation. Breast metastases exhibit a mixed picture of both lytic and sclerotic areas (109). These different mechanisms correspond to typical radiologic features showing mixed lytic and sclerotic metastases, osteolytic metastases, or sclerotic metastases, respectively.

Metastases may reach the skeleton by direct invasion from the primary tumor or by extension from a secondary site, such as a lymph node. True lymphatic spread to the skeleton is rare. Direct invasion is usually accompanied by a detectable soft tissue mass, an unusual feature of metastases that occur by hematogenous spread. The left sides of the vertebral bodies are more frequently affected by direct invasion from local lymph nodes because the left-sided lymph nodes are closer to bone than the right-sided ones (110). Hematogenous spread is far more frequent than lymphatic spread or direct invasion. The venous route, especially Batson's paravertebral plexus, appears to be more important for hematogenous spread than the arterial route. The distribution of Batson's venous plexus, as well as the overall skeletal vascularity, results in a predilection for hematogenous spread to the axial skeleton and the proximal long bones.

Pathophysiology of Metastases

To develop rational therapies for inhibiting or reversing bone alterations, one must understand the mechanisms involved in the pathogenesis of a bone metastasis and its complication. When cancer cells establish in bone because of chemotaxis of membrane receptor affinity for bone marrow cells, they disturb the normal process of bone turnover. Skeletal imbalance and uncoupled resorption destroy bone architecture, with consequent implications for skeletal strength. Bone destruction results from interactions between tumor cells and bone cells normally responsible for the maintenance of skeletal integrity. The disruption of continuity weakens the connective structure, decreasing the resistance of the skeleton to both compressive and bending forces (107).

Mechanisms of Bone Destruction

Tumor-mediated bone disease has two classifications: focal bone disease associated with metastases, and generalized bone disease (e.g., in myelomatosis). In turn, metastatic disease is either osteolytic or osteosclerotic. In practice, the distinction is difficult because the features are commonly associated. In all these contexts, however, bone disease arises from three principal disturbances in the bone remodeling sequence.

Increased Turnover. Metastatic bone disease involves increased resorption, and biochemical and histomorphometric evidence exists for increased bone formation (111). This suggests that all the elements of bone turnover increase. An increment in bone turnover alone reduces skeletal mass because resorption precedes formation. A fivefold increase in bone turnover diminishes bone mass by approximately 20% at cancellous bone sites.

Imbalance. The amount of bone deposited in a resorption cavity may not equal the volume of bone removed. This leads to skeletal imbalance without necessarily implying a disorder of coupling. Skeletal imbalance contributes to bone loss that occurs in myeloma and the generalized increase in bone resorption associated with some solid tumors. When bone turnover increases, skeletal losses accelerate. Why imbalance occurs at remodeling sites is still unknown. Possible mediators include decreased circulating levels of parathyroid hormone and calcitriol, which have trophic effects on osteoblasts. Inhibitors of bone resorption, including chemotherapy, bisphosphonates, and mithramycin (plicamycin), increase circulating levels of calcitriol and alkaline phosphatase in hypercalcemic patients, suggesting a decrease in the inhibition of osteoblast activity (112). Also, the production of cytokines such as tumor necrosis factor and interleukins may directly suppress osteoblastic activity

(113).

Uncoupling. High tumor cell burdens are associated with a lack of coupling in that bone resorption occurs at a locus that is not the subsequent site for new bone formation. This, in turn, accelerates skeletal losses. Repeated waves of bone resorption without repair lead to the destruction of bone architecture and osteolytic foci. Osteosclerotic metastases are commonly caused by uncoupled bone formation, namely, the deposition of new bone, not at sites of prior bone resorption, but on quiescent bone surfaces or arising from stromal condensations within the marrow cavity. As in the case of osteolytic disease, bone formation is mediated by osteoblasts rather than directly by tumor cells. Most sclerotic lesions are mixed lesions in which uncoupled bone resorption and formation occur together but at different sites. Conversely, many osteolytic lesions seen radiographically are mixed lesions in which uncoupled osteolysis predominates (114).

Determinants of Skeletal Disease and Osteoclast Activation

Skeletal Metastases. Bone is the preferential site for metastases for some cancers but not for others. For example, skeletal disease affects more than 70% of women with breast cancer but only 5% of patients with gastric cancer. However, this may reflect only the duration of disease (the time from diagnosis to death) rather than differences in predilection for skeletal sites. Predictors of skeletal disease include estrogen receptor status. Breast cancers expressing high concentrations of estrogen receptors are more likely to metastasize to skeletal rather than soft tissue sites. Receptor status alone, however, does not predict metastatic disease. Other factors, such as circulating glycoproteins, fetal proteins, indices of proliferation, and the presence of cancer cells in marrow, predict metastatic disease with various degrees of accuracy. These variables do not influence the likelihood of skeletal disease. The expression of PTHrP is more common in skeletal metastases than in soft tissue metastases. The same distribution occurs in patients with both types of metastases when the primary tumor does not express PTHrP. This suggests that PTHrP expression occurs after the metastatic event. Because estrogen receptor status and PTHrP expression are unrelated, PTHrP expression may occur preferentially in the skeletal environment. The attachment of tumor cells to distant sites may require large numbers of laminin receptors, which are important for attachment to basement membrane collagen. Laminin antagonists inhibit the formation of osteolytic metastases of melanoma cells in nude mice, whereas laminin potentiates the process (115). The effect is unlikely to be skeleton specific, because these drugs have similar effects on pulmonary metastases. Other proteins affecting cell adhesion include the glycoprotein E-cadherin, and its expression in breast cancer cells is associated with decreased numbers of skeletal metastases (116,117).

Osteoclast Activation. Histologic specimens obtained from patients with solid tumors reveal unusually large numbers of osteoclasts near tumor cells (114). The mechanism for osteoclast activation differs across different tumor types. More knowledge exists about the mechanisms for osteoclast activation in myelomatosis than for solid tumors. At least three cytokines activate bone resorption, including tumor necrosis factor-b or lymphotoxin, interleukin-1, and interleukin-6. Candidates for osteoclast activation in solid tumors include prostaglandins, procathepsin D, tumor-necrosis factor, PTHrP, and the transforming growth factors. Most histologic evidence suggests the hypothesis that increased bone resorption in breast cancer patients depends on increased numbers of osteoclasts (114). Tumor cell–mediated bone resorption may supervene in the late stages of the disorder. Many squamous cell tumors, particularly of the lung and breast, express PTHrP. High PTHrP values also occur in some patients with renal cell, transitional cell, and liver carcinoma, all of which may be associated with “humoral hypercalcemia” in the absence of skeletal metastases. The division of hypercalcemia patients with solid tumors according to the presence or absence of metastatic bone disease is an oversimplification because humoral mechanisms increasing bone resorption and renal tubular reabsorption of calcium also occur in patients with evidence of metastatic bone disease.

Enhanced osteoclastic bone resorption, stimulated by bone-resorbing factors, is a major factor in the development of bone metastases. Osteoclasts are activated either directly by tumor products or indirectly through an influence on other cells (118). Tumor cells frequently produce factors that can activate immune cells, which release osteoclastic stimulating substances such as tumor necrosis factor and interleukin-1 (119). Tumor products may also act directly on bone cells.

In the late stages of metastatic disease, malignant cells appear to cause bone destruction directly. The role of prostaglandins in osteolysis is moot. They may stimulate osteoclastic cells, thus mediating osteolytic metastases. However, no demonstrated relationship exists between subsequent bony recurrence and tumor prostaglandin production (120). Moreover, prostaglandins may cause a transient inhibition of osteoclastic activity or potentiate other mediators of osteolysis. The mechanisms responsible for osteoclast activation differ across malignancies. In myeloma, bone resorption predominates because of secretion of osteoclast-activating substances with low osteoblastic activity.

Bone resorption caused by increased osteoclastic activation decreases bone density and disrupts skeletal architecture, either at focal sites or generally throughout the skeleton. The periosteum is densely innervated and nerves enter bones via the blood vessels. Microfractures occur in bony trabeculae at the site of metastases, causing bone distortion. Periosteal stretching by tumor expansion, mechanical stress of weakened bone, nerve entrapment by tumor, or direct bone destruction with consequent collapse are possibly associated mechanisms (121,122). Weakening of bone trabeculate and cytokines, which mediate osteoclastic bone destruction, may activate nociceptors. The release of algesic chemicals within the marrow probably accounts for the observation that pain produced by tumors is often disproportionate to their size or degree of bone involvement. Reactive muscle spasm may produce further nociception. Nerve root infiltration and nerve compression are other sources of pain.

Characteristics of Metastatic Bone Pain

Nociception from bony metastases can produce a variety of symptoms, such as muscle spasms or paroxysms of stabbing pain. Hematologic malignancies (especially acute leukemias) may produce a syndrome of generalized and migrating bone pain as a result of marrow infiltration (123). Limb pain is the most common presentation, and local bone tenderness (especially on long bone diaphyses) is a frequent finding. The vertebrae are the most common sites of bone metastases. The thoracic spine is affected in more than 66% of cases, the lumbosacral spine in 20%, and the cervical spine in 10%. Multiple vertebral lesions are common. Pain from metastases involving T-12 and L-1 often is referred to the iliac crest or sacroiliac joint unilaterally or bilaterally. Patients with tumor invasion of the upper cervical vertebrae may present with pain in the neck that is referred to the occipital region and skull vertex. Neck flexion typically exacerbates the pain.

Patients with osteolytic bone metastases commonly present with bone pain, pathologic fractures, hypercalcemia, or more rarely, with swelling or neurologic complaints. The vertebrae, pelvis, ribs, femur, and skull are the sites most frequently involved (96). Pain gradually develops during a period of weeks or months, becoming progressively more severe. The pain is usually well localized in a particular area and is often strongest at night or on weight bearing. Patients describe the pain as dull in character, constant in presentation, and gradually progressive in intensity. Pain increases with pressure on the involved area. Continuous pain may be moderate on resting and then increase with different movements or positions, such as standing, walking, or sitting. Breakthrough pain can result from weight bearing or instability because of incipient or actual pathologic fractures. Although the locus of bone pain usually corresponds to the site of the underlying lesion, characteristic patterns of referral to noncontiguous cutaneous areas occur (e.g., hip pain caused by a hip lesion referred to the knee).

Clinical Consequences

Bone metastases lead to significant morbidity: pain, impaired mobility, hypercalcemia, pathologic fracture, spinal cord or nerve root compression, and bone marrow infiltration. Spinal instability is the cause of back pain in 10% of cancer patients (124). Metastatic destruction of bone reduces its load-bearing capabilities, initially producing trabecular disruption and microfractures and subsequently total loss of bony integrity. Rib fractures and vertebral collapse are most common, resulting in loss of height, kyphoscoliosis, and a degree of restrictive lung disease. However, the fracture of a long bone or epidural extension of tumor into the spine causes the most disability. The probability of developing a pathologic fracture increases with the duration of metastatic involvement. It is therefore paradoxically more common in patients with disease confined to bone who have a relatively good prognosis. Because a fracture is so devastating to a cancer patient, it is important to predict which metastatic sites are at risk of fracture for a particular patient, to use surgery prophylactically, and to administer long-term bisphosphonates (125).

Patients with osteolytic metastases have a high baseline serum calcium level. Hypercalcemia affects 10% to 40% of the oncology population during the course of their illnesses (126). The extent of metastatic bone disease does not correlate with hypercalcemia (119). The pathophysiologic mechanisms of pain in patients with bone metastases in the absence of a fracture are still unclear. The presence or intensity of pain does not correlate with the type of tumor, location, number and size of metastases, gender, or age of patients (127). Although approximately 80% of patients with breast cancer develop osteolytic or osteoblastic metastases, approximately two-thirds of demonstrated sites of bone metastases are painless (33).

The main complications of vertebral metastases are vertebral collapse, radiculopathy, and epidural spinal cord compression. Collapse of vertebral bodies is particularly frequent in the thoracic spine. Radiculopathies can occur at any level; patients feel the pain in the spine, deep in the muscles innervated by the affected nerve root, and in the corresponding dermatome.

Metastatic spinal cord compression is a serious complication of vertebral metastases (see Back Pain and Metastatic Epidural Spinal Cord Compression, later in this

chapter).

Clinical Imaging

The frequency of detection of metastatic disease varies considerably with the type of primary tumor and with the methodology used for detection. For some types of tumors, such as breast carcinoma, skeletal metastases are readily identifiable by imaging studies. For other conditions, such as chordoma, disseminated skeletal metastases are often evident at autopsy but rarely apparent during the patient's life.

Four clinical imaging methods are commonly used to help identify and characterize skeletal metastases: plain film radiography, CT scanning, radioisotope scanning, and MRI (see Chapter 14). FDG-PET scanning is currently an area of intense clinical research.

Radiography has proven useful for evaluating symptomatic sites and for confirming findings on other imaging studies. It is poorly suited for screening because of its low sensitivity. A positive radiograph result confirms the presence of metastasis, but a negative radiograph result does not rule it out. For patients with multiple myeloma, a radiographic survey is still valuable because of the relatively poor sensitivity of the radioisotope scan. The appearance of a radiograph may help distinguish metastases from other conditions and also help identify the primary tumor. Bone density must change by approximately 40% before plain radiography can identify bone metastases.

In contrast to plain radiography, bone scintigraphy can detect change of 5% to 10% in bone density. Bone scintigraphy results are positive in 14% to 34% of patients who have no radiographic evidence of bone metastases. However, the method is less sensitive for the detection of purely osteolytic metastases.

For approximately 25 years, the radioisotope bone scan has been the standard initial imaging method for detection of skeletal metastases. Tracer accumulates in the reactive new bone formed in response to the lesion. The amount of accumulation depends on the level of blood flow. Thus, although most metastatic lesions are *hot*, some, particularly aggressive metastases, are *cold* because of the complete absence of reactive bone or poor blood flow. Tracer may accumulate diffusely throughout the skeleton (super scan). This occasionally occurs in disseminated skeletal disease, leading to the false impression of a normal scan result.

Tracer accumulation may occur at any skeletal site with an elevated rate of bone turnover. It is thus nonspecific and may accompany trauma (even remote trauma), infection, arthropathy, or even acute osteopenia of disuse. In a patient with a known primary tumor, a scan showing multiple lesions strongly suggests metastases. However, only 50% of solitary foci represent metastases, even in patients with cancer. Because of this lack of specificity, positive scan results require radiographic correlation.

Advances in isotope scanning methods have improved the detection of metastases. One of the most important of these is single photon emission computed tomography (SPECT) scanning. SPECT imaging has improved both the sensitivity and the specificity of bone scanning (128). SPECT proves useful in such an evaluation because it allows for precise localization of a lesion to the vertebral body, disk space, or vertebral arch (129). This anatomic distinction is necessary for accurate diagnosis of the underlying condition detected by the bone scan. Most bony abnormalities result in focal areas of abnormal tracer activity, but do not affect all components of a vertebra with equal frequency, or do not have a random pattern of involvement. Vertebral diseases tend to conform to predictable patterns that can be more readily identified by SPECT than planar imaging. Other isotope scanning techniques have shown varying degrees of promise. Quantitation of whole body diphosphonate uptake has been disappointing. FDG-PET scanning detects abnormal areas of glucose metabolism. FDG-PET can detect prostate carcinoma metastases to bone with moderate sensitivity (65%) and high specificity (98%) and may have some value in lesion detection (130). However, FDG does not accumulate in Paget's disease and thus may prove useful for separating Paget's disease and other benign conditions from metastases or sarcomatous degeneration (131). Currently, no established clinical role exists for bone PET scanning.

Bone marrow scanning is more sensitive than conventional bone scanning for the detection of metastases from prostate carcinoma (132). In one study, bone marrow imaging with technetium 99m anti–non-specific cross-reacting antigen–95 monoclonal antibody detected almost twice the number of lesions observed on conventional methylene diphosphonate scans; however, the number of patients identified as having metastases was the same (13 in both instances) (133).

For certain types of primary tumors, especially lymphomas and soft tissue sarcomas, gallium scanning may be a useful staging tool, detecting metastases that would not otherwise be observed (134). It may also be helpful in following the effects of treatment in these patients (135).

CT scanning has proven minimally useful for the detection of skeletal metastases. Although CT is more sensitive than conventional radiography for the detection of destructive bone lesions, it is a cumbersome tool for screening the entire skeleton. It may help confirm suspicions raised by bone scans and aid in clarifying which anatomic sites are affected. CT can detect metastases within bone marrow before bone destruction has occurred. The lesion manifests as an increase in attenuation of the normally fatty bone marrow. CT is superior for diagnosing early metastatic involvement of bone, particularly of the spine (118).

MRI is highly sensitive to skeletal metastases, in large part because of its ability to demonstrate abnormalities in bone marrow. Because bone marrow (including hematopoietic or *red* marrow) contains a high percentage of fat, T1-weighted MRIs generally reveal metastases as focal areas of low signal intensity. Lesions differ from normal deposits of red marrow on T1-weighted images because they are more localized. Other advantages of MRI scanning include delineation of the whole spine, identification of multiple sites of cord and vertebral involvement, the paravertebral epidural extension, and integrity of the spinal cord. It also allows for differentiation between traumatic, osteoporotic, or pathologic fractures and compressions without the invasive techniques. Unfortunately, MRI often cannot distinguish among changes that are caused by treatment, fracture, and tumor. MRI can demonstrate metastases that are not apparent on radioisotope bone scans (136), and it is well suited to detecting spinal metastases. Planar scintigraphy detects approximately one-third to two-thirds of the lesions revealed by MRI. Some authors contend that SPECT makes the two techniques comparable, with MRI better for vertebral body lesions and SPECT better for the posterior elements (137).

Advantages of the isotope scan include a large field of view, inexpensive radiopharmaceuticals, low morbidity, and the ability to provide functional and vascular information. MRI may be a simpler and faster method for evaluating the axial skeleton, but is less well suited to screening the long bones. MRI, like bone scan, can be problematic for the *super scan* of diffuse bone marrow replacement. A number of specific categories exist of patients for whom bone scanning is superior to MRI. They include patients with contraindications to MRI, such as claustrophobia and pacemakers, and patients with thyroid cancer who receive iodine for scanning. MRI is preferred for patients with bone marrow diseases, such as myeloma and Waldenström's macroglobulinemia (138).

The factors that influence the choice of imaging modalities continue to evolve. Progress in MRI is rapid, and practical, cost-effective methods for evaluation of the entire skeleton probably are forthcoming. Until this happens, isotope scanning, especially with SPECT imaging, continues to have an important role.

The integration of multiple imaging modalities in the assessment of musculoskeletal neoplasia is complex (139). A combination of conventional radiography and MRI is the best way to assess most soft tissue masses. Initial bone scintigraphy is optimal for skeletal screening without localizing symptomatology that includes axial and appendicular skeleton. Optimal screening of the axial skeleton in the presence of clinical symptomatology or with a strong suspicion of axial skeletal metastases or pathology requires a total spine screening examination with MRI and specialized pulsing sequences. CT is reserved primarily for assessment of cortical and juxtacortical lesions, fracture fragment positioning and configuration, and characterization of lesion matrix calcification or ossification when conventional radiographic results are indeterminate.

Radionuclide bone scintigraphy still is the first choice in routine follow-up of asymptomatic patients with metastatic disease of the skeleton. A negative scan result requires reevaluation with other findings, with emphasis on the possibility of a false-negative result. The best approach for screening for metastases in patients with local symptoms or pain is a combination of radiography and MRI. Approximately 30% of patients with known cancer have benign causes of radiographic abnormalities (140). Most of these are related to degenerative diseases and are usually easy to diagnose.

Prognosis

In general, the prognosis for patients presenting with bone metastases is poor (Table 35-15). Patients with fewer metastases or solitary lesions appear to have a better outlook than those with multiple metastatic deposits. Once tumor cells spread to the skeleton, the disease is usually incurable and it may be best to shift the focus of treatment to palliation. Patients suffering from metastatic breast disease survive 34 months on average after detection of the first metastasis, with a range of 1 to 90 months (141). Survival with metastatic prostate cancer averages 24 months, and lung cancer patients have a prognosis less than 1 year (98).

	Incidence in advanced disease (%)	Median survival (mo)	5-Yr survival (%)
Myeloma	95–100	20	10
Breast	65–75	24	20
Prostate	65–75	40	25
Lung	30–40	<6	<5
Kidney	20–25	6	10
Thyroid	60	48	40
Melanoma	14–45	<6	<5

Data from Rubens RD, Coleman RE. Bone metastases. In: Abeloff MD, Armitage JO, Lichter AS, et al., eds. *Clinical oncology*. New York: Churchill Livingstone, 1995:461–465.

TABLE 35-15. Incidence and prognosis of bone metastases

Factors that influence prognosis in patients with metastatic disease include the interval between primary diagnosis and the development of metastases, and the Karnofsky performance status (Table 35-16). The Karnofsky score after palliative irradiation reliably predicts survival (142). Other factors that predict survival include the site of the primary disease and whether single or multiple bone metastases are present (143,144,145,146,147 and 148). No one as yet has developed a classification system, such as a staging system, that can predict the overall prognosis and subsequent patterns of metastatic spread from multiple factors. Staging systems currently in use predict probability of disease control and patterns of failure.

Grade	Performance level
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his or her needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated; death not imminent
20	Very sick, hospitalization necessary, active supportive treatment necessary
10	Moribund, fatal processes, progressing rapidly
0	Dead

TABLE 35-16. Karnofsky performance status

The incidence of distant metastases in patients with prostate carcinoma increases with the presenting stage of disease, occurring in 21% of patients with stage A $_2$ (T_{1b}) and B (T_2) disease, 40% of patients with stage C (T_3) disease, and 62% of patients with stage D_1 (T_4) disease presentations (145). The risk for the subsequent development of distant metastases diminishes significantly when the primary tumor is controlled. Survival rates after an isolated recurrence of disease in the prostate depend on the initial stage of the disease and the disease-free interval from initial treatment. With or without associated local recurrence of the prostate carcinoma, the survival rate is significantly worse when distant metastases are present. The survival rates at 5 and 10 years after pelvic recurrence alone equal 50% and 22%, respectively; with distant metastases, the survival rate at 5 years is 20% and less than 5% at 10 years (145,146). Age significantly influences the 5-year survival rate for patients with prostate carcinoma, independent of race and extent of disease. Five-year survival rates are only 74% with localized disease, 55% with regional disease, and 29% with distant metastases in prostate carcinoma patients older than 75 years. In contrast, the 5-year survival rates are 86% (p <.01), 73% (p <.01), and 31% (p <.05), respectively, in patients 65 to 74 years of age (147,149).

The distribution of metastases on bone scans also has prognostic significance. Patients with metastatic carcinoma survive significantly longer if their metastases respond to salvage hormone therapy and do not spread beyond the pelvis or lumbar spine (146). Diffuse bone metastases tend to occur in patterns of anaplastic histologic features, visceral metastases, and lymph node metastases (146).

After bone metastases diagnosis, the median survivals are 12 months for patients with breast carcinoma, 6 months for patients with prostate carcinoma, and 3 months for patients with lung carcinoma. The median survival rate is 48 months when metastases are confined to the skeletal system in patients with breast carcinoma, but it decreases to only 9 months if visceral metastases also are present (148,150).

VISCERAL PAIN

Visceral infiltration is a common cause of pain in cancer patients. Table 35-17 lists the common pain syndromes associated with tumor infiltration.

Esophageal mediastinal pain
Shoulder pain from diaphragmatic infiltration
Epigastric pain from pancreatic or other upper abdominal tumor
Right upper quadrant pain from hepatic capsule distension
Left upper quadrant pain from splenomegaly
Diffuse abdominal pain from abdominal or peritoneal disease with or without obstruction
Pleural infiltration
Gastrointestinal perforation
Biliary obstruction
Ureteric obstruction
Suprapubic pain from bladder infiltration
Perineal pain from infiltration of rectum or perirectal tissue

TABLE 35-17. Pain syndromes related to tumor infiltration of viscera

Mechanism

Visceral pain is defined as pain emanating from organs in the thorax, abdomen, or pelvis. The main factors capable of inducing pain in visceral structures include abnormal distension and contraction of hollow visceral walls, rapid stretching of the capsules of solid visceral organs, ischemia of visceral musculature, formation and accumulation of algogenic substances, direct action of chemical stimuli on compromised mucosa, and traction or compression of ligaments, vessels, or mesentery (151,152 and 153). Mechanical insult to normal mucosa causes no pain, implying that preceding inflammation is necessary.

Localization of visceral pain is difficult. Afferent nerves from viscera to the spinal cord are relatively few in number and account for only 2% to 15% of all afferents to the spinal cord (154,155). These visceral nociceptive afferents can excite many second-order neurons in the spinal cord, which in turn generate extensive divergence within the CNS, sometimes involving supraspinal loops. Such a divergent input activates several systems (sensory, motor, and autonomic) and thus triggers the general reactions that are characteristic of visceral nociception: a diffuse and referred pain and prolonged autonomic and motor activity (151).

The origin of nociceptive impulses determines the site and type of pain. Visceral pain is either true, referred, nonreferred parietal, or referred parietal. True parietal abdominal pain is dull and poorly localized; it occurs in the region of the epigastric, periumbilical, or lower midabdominal region. Patients may describe the pain as gnawing or cramping, and often it is associated with nausea, sweating, pallor, and, occasionally, vomiting. Referred visceral pain is more precisely localized, usually in the dermatomal or myosomal regions of the same segments of the spinal cord involved. Parietal pain may localize directly over the organ without referral.

Patients locate referred parietal pain in a body region distant from the nociceptive site. For example, patients complain of pain in the shoulder area when the cause is inflammation in the middle of the diaphragm.

Tumor invasion of adjacent blood vessels can generate nociception. Mechanisms include perivascular lymphangitis causing vasospasm, occlusion with resultant ischemia, venous engorgement, and edema.

Obstruction of hollow viscera from tumor with resultant distension may cause pain. Distension causes intense contraction of smooth muscle that generates nociception. Patients experience visceral pain that is poorly localized and diffuse but usually localized in the same dermatomal area of the cord segments of the viscera.

Pain from tumor involvement of parenchymal viscera such as liver, spleen, pancreas, and kidney typically results from acute distension of the pain-sensitive fascia. These fascia contain many mechanicoreceptors, and nociception occurs when they are acutely stretched or placed under tension. This type of pain is poorly defined, dull, and generally located in the dermatomal region of the involved organ. The properties of visceral pain are discussed in Chapter 60, Chapter 61, Chapter 62, Chapter 63, Chapter 64, Chapter 65, Chapter 66, Chapter 67, Chapter 68, Chapter 69, Chapter 70, Chapter 71, Chapter 72, Chapter 73 and Chapter 74.

Pain Descriptions by Site

Esophageal cancer usually elicits a history of heartburn, a burning or gnawing substernal discomfort. Patients usually describe the pain as being located in the epigastric or retrosternal areas, which often radiates to the back or interscapular region. The pain occurs often after eating and possibly relates to body position changes such as reclining or bending forward (see Chapter 63).

Gastric pain has a colicky quality associated with delayed emptying and slowed motility and digestive symptoms. The pain also localizes in the epigastrium, is usually sharply focused, and may radiate into the back (see Chapter 66).

Small intestine pain is usually crampy or colicky and localized in the periumbilical area. The cause of pain is usually a lesion causing distension with resultant abnormal mobility. Eating usually precipitates the pain, and defecation or fasting may afford relief. Colon pain tends to occur in the lower abdomen, varying according to which portion of the colon is affected. Change in bowel habits and occult blood in the stool often accompany symptoms of discomfort. Peritoneal carcinomatosis is frequently found with abdominal tumors and advanced ovarian cancer. Pain may result from peritoneal irritation, mesenteric involvement, and abdominal distension with ascites. Bowel obstruction often complicates peritoneal carcinomatosis (see Chapter 69).

Liver parenchyma is insensitive to tumor distension and associated chemical changes. Right upper quadrant pain from liver pathology occurs only when there is acute distension of the liver capsule. It is usually a dull aching sensation in the right upper abdominal quadrant and flank and is often referred to the right scapula and shoulder (see Chapter 67).

Perineal pain, worse when sitting and with an aching and pressurelike quality is the first and, can be for a long time, the only symptom of pelvic tumors (see Chapter 70). The pain may be associated with tenesmus. Fistulas and recurrent infections can aggravate the pain syndrome. Ureteral obstruction is frequent. Direct invasion of the sacrum, sacral roots, plexus, or cauda equina is a frequent complication. Pain from the fundus of the uterus typically occurs in the hypogastrium. Pain originating from the uterine cervix is commonly referred to the low back and sacral area as well as to the hypogastrium. Ovarian pain results from stretching of the surrounding peritoneum to which the ovaries adhere.

NEUROPATHIC PAIN

The following are among the most common cancer pain syndromes that present with a major neuropathic component.

Neuropathic Pain Secondary to Cancer-Related Pathology in Cranial Nerves

Painful cranial neuralgias may occur secondary to base of skull metastases, leptomeningeal metastases, or head and neck cancers (156). Base of skull metastases produce several well-described pain syndromes (157) and are often associated with primary tumors of the breast, lung, and prostate. Constant localized aching pain from bone destruction and neurologic deficits from progressive cranial nerve palsies are cardinal manifestations.

The middle cranial fossa syndrome presents with facial numbness, paresthesias, or dysesthetic neuropathic pain in the distribution of the second or third divisions of the trigeminal nerve. Associated motor deficits include weakness in the masseter or temporalis muscles or abducens palsy.

The jugular foramen syndrome may present as glossopharyngeal neuralgia (158). This pain is distributed over the ear or mastoid region and may radiate to the neck or shoulder. Associated deficits include a Horner's syndrome and paresis of the palate, vocal cords, sternocleidomastoid muscle, or trapezius muscle. Some attribute this syndrome to leptomeningeal metastases (159) and local extension of head and neck malignancies (160). It is sometimes associated with syncope (161).

A syndrome that clinically mimics classical trigeminal neuralgia can occur secondary to tumors in the middle or posterior fossa (161,162,163,164 and 165) or from leptomeningeal metastases (159). This association between trigeminal neuralgia and tumor is uncommon, and cancer patients with a new onset of trigeminal neuralgia should have careful imaging of the base of the skull (163). Trigeminal neuralgia secondary to tumor usually presents as a constant, dull, well-localized pain related to the underlying pathology involving bone and other somatic structures associated with paroxysmal episodes of lancinating or throbbing pain.

Squamous cell carcinomas of the face, which commonly extend by perineural spread, are an important cause of complex trigeminal syndromes (166). Perineural spread, when present, typically involves cranial nerves V and VII because of their extensive subcutaneous distributions (167). Glossopharyngeal neuralgia commonly results from local nerve infiltration in the neck or base of skull. It typically produces throat and neck pain, radiating to the ear and mastoid and is aggravated by swallowing. Occasionally, syncope accompanies severe pain (168,169).

Cervical Plexopathy

Tumor infiltration of the cervical plexus can produce several pain syndromes, depending on the pattern of nerve involvement (170) (see Chapter 55). The upper four cervical ventral rami join to form the cervical plexus. The plexus lies close to the C-1 through C-4 vertebrae. The four cutaneous branches emerge from the posterior border of the sternocleidomastoid muscle into the posterior triangle of the neck. Because sensory afferents from the cervical plexus enter the spinal tract of the trigeminal along with the sensory afferents from cranial nerves V, VII, IX, and X, nociceptive referral patterns from the face and neck overlap. Symptoms usually include local pain with lancinating or dysesthetic components referred to the retroauricular and nuchal areas (lesser and greater auricular nerves), preauricular area (greater auricular nerve), anterior neck and shoulder (transverse cutaneous and supraclavicular nerves), and jaw (156). Associated findings include ipsilateral Horner's syndrome or hemidiaphragmatic paralysis. CT or MRI evaluation may be necessary to rule out associated epidural cord compression. Common clinical settings include local extension of a head and neck tumor or cervical lymph node metastases. In patients with head and neck tumors who have undergone radical neck dissection followed by radiation treatment, new onset or worsening pain includes a differential diagnosis of postradical neck dissection syndrome or tumor recurrence. Infections often complicate and exacerbate pain.

Tumor-Related Mononeuropathy

The most commonly described tumor-related painful mononeuropathy is intercostal nerve injury secondary to rib metastases with local extension. Patients with tumor

invasion of the sciatic notch may present with symptoms resembling sciatica.

Radicular Pain and Radiculopathy

Radiculopathy is a pattern of pain corresponding to the dermatomal territory innervated by the dorsal spinal roots. Patients with cancer-related radiculopathy may present with pain on either or both sides of the midline. The pain tends to be unilateral in the cervical and lumbosacral regions and bilateral in the thorax. In cancer patients, radiculopathy typically results from epidural tumor mass or leptomeningeal metastases. Coughing, sneezing, recumbency, and strain exacerbate the pain, which often has dysesthetic qualities. Radiculopathy may also develop secondary to leptomeningeal metastases. Clinically, leptomeningeal metastases may produce multifocal neurologic signs and symptoms at a variety of levels, including cranial neuralgias. Most commonly, they produce a generalized headache with radicular pain in the low back and buttocks (171).

Leptomeningeal Metastases

Infiltration of tumor into the subarachnoid space produces carcinomatous meningitis. Carcinomatous meningitis is diffuse involvement of the leptomeninges by infiltrating malignant cells. Over the past 15 years, oncologists and neurologists have increasingly reported diffuse leptomeningeal metastases of extracranial malignant tumors (171,172 and 173). This complication occurs most commonly with adenocarcinoma of the lung and breast, lymphomas, and melanomas.

Carcinomatous meningitis may occur in up to 5% of patients with breast cancer (174). Although the incidence of metastatic lesions in the brain is high in patients with small cell carcinoma, clinical problems from metastases to the spinal cord or leptomeninges have been rare (175). Meningeal involvement was once a common complication of acute lymphoblastic leukemia, before the advent of CNS prophylaxis. Now this problem occurs in fewer than 5% of patients. Carcinomatous meningitis develops in 1% to 8% of patients with systemic cancer (176), and has a poor prognosis with a median survival of 3 to 6 months (177). Untreated, the prognosis is dismal, with an average survival of 6 weeks (178).

Tumor cells may reach the leptomeninges by several different routes. This may result from direct extension of a parenchymal brain metastasis. Alternatively, cells may enter the CSF as a direct extension from a paravertebral lymph node metastasis, infiltrating along a spinal nerve root into the spinal canal. The tumor may also seed hematogenously via the capillaries of the arachnoid villi. Leptomeningeal tumors can encase the spinal and cranial nerves or may directly invade them and produce demyelination and axon destruction.

The hallmark of the clinical presentation of carcinomatous meningitis is the simultaneous occurrence of symptoms and signs at more than one area of the neuraxis. The clinical presentation of leptomeningeal metastasis is pleomorphic and commonly affects the cerebral hemispheres, cranial nerves, or spinal cord, and its roots. It is best to describe the symptoms by their location along the neuraxis. Symptoms are usually multifocal and more diffuse than one discrete lesion allows. Symptoms include headache, back and radicular pain, multiple cranial and spinal nerve involvement, and change in mental status. Pain may occur in 30% to 76% of cases (171,179). Table 35-18 lists the frequency of spinal cord symptoms and signs in patients with carcinomatous meningitis.

Symptoms or signs	Percentage
Weakness	33
Paresthesia	31
Back pain	25
Radicular pain	19
Bowel and bladder dysfunction	13
Reflex asymmetry	67
Weakness	4
Cauda equina syndrome	33
Sensory loss	31
Positive straight leg raise sign	13
Decreased tone of anal sphincter	12
Nuchal rigidity	11

From Zachariah B, Zachariah SB, Varghese K, et al. Carcinomatous meningitis: clinical manifestations and management. Int J Clin Pharmacol Ther 1995;33:7-12. with permission.

TABLE 35-18. Frequency of spinal cord symptoms and signs in patients with carcinomatous meningitis

Identification of malignant cells in CSF is diagnostic. In patients with negative CSF cytology results, MRI and contrast- enhanced CT may be both suggestive and diagnostic and are probably most useful in demonstrating bulky disease (180).

Brachial Plexopathy

Brachial plexopathy can present from either compression or tumor infiltration of the brachial plexus from contiguous structures, such as axillary or supraclavicular nodes, or by tumors in the apex of the lung. Neuropathic pain caused by tumor infiltration of the brachial plexus usually stems from lymph node metastases from breast carcinoma or lymphoma, or direct extension from lung carcinoma (i.e., Pancoast's tumor). The designation of Pancoast's tumors relates to the symptom complex or syndrome caused by a tumor arising in the superior sulcus of the lung that involves the sympathetic nerve trunks, including the stellate ganglion. Superior pulmonary sulcus syndrome associated with a Pancoast's tumor is defined as progressively intense pain in the shoulder and ulnar side of the arm, associated with sensory and motor deficits and Horner's syndrome caused by tumor (25).

In neoplastic brachial plexopathy, pain is usually the first symptom in 85% of patients and often precedes neurologic deficits (181,182). The key features of malignant plexopathy are the neuropathic nature of the pain, with numbness, paresthesias, allodynia, and hyperesthesias. Typically, the pain begins in the shoulder girdle where it is often described as pressurelike or aching and may radiate to the elbow, medial forearm, and fourth and fifth fingers. It may also appear to localize at the posterior arm or elbow. The patient may report a burning quality to the pain, with hyperesthesia along the ulnar aspect of the forearm.

Involvement of the lower plexus occurs when tumor arises from the lung apex; associated pain and dysesthesias involve the elbow, medial forearm, and fourth and fifth fingers (C-7, C-8, and T-1). Upper plexus involvement (C-5, C-6), if it occurs alone, usually develops into a panplexopathy. Upper plexus pain typically involves the shoulder girdle, with burning pain in the tips of both the index finger and thumb. Lung tumors can also present with pain involving the axilla and upper chest wall in the distribution of the intercostobrachial nerve (183).

In more than 75% of patients, neurologic signs follow the appearance of dysesthesias. These signs include focal weakness, atrophy, and sensory changes in the distribution of C-7, C-8, and T-1 roots (181). Early loss of the triceps reflex usually occurs. Associated findings can include Horner's syndrome and adjacent vertebral disease. Such patients are at high risk for concurrent epidural extension (179,184). For patients with brachial plexopathy secondary to tumor, we recommend imaging the contiguous epidural space before radiation treatment so that the radiation oncologist can include this area in the treatment field. A Spurling's maneuver * can help to identify the spinal canal as the site of pathology (185). Paraspinal involvement may help to predict epidural extension of tumor.

Neuroradiologic evaluations of choice for brachial plexopathy are CT and MRI. However, Ahmad and colleagues (186) demonstrated that FDG-PET scanning is a useful tool in the evaluation of patients with suspected metastatic plexopathy, particularly if other imaging studies are normal. It may also be useful in distinguishing between radiation-induced and metastatic plexopathy. Electromyography can also help distinguish malignant brachial plexopathy from radiation-induced brachial plexopathy or cervical radiculopathy (Table 35-19). In patients with brachial plexopathy, electromyography usually shows fibrillation potentials and positive waves (evidence of denervation) in affected muscles. Radiation-induced brachial plexopathy is discussed in a following section. Neoplastic brachial plexopathy may differ clinically from radiation-induced plexopathy. Patients with neoplastic plexopathy have a higher frequency of pain as the initial and predominant symptom, a shorter duration of symptoms prior to diagnosis of plexopathy, and a higher incidence of Horner's syndrome (187).

	Tumor infiltration	Radiation fibrosis	Reversible radiation injury
Incidence of pain as initial predominant symptom	80%	10%	40%
Severity of pain	Moderate to severe severe in 22% of patients	All the moderate severe in 15% of patients	Mild
Nature of pain	Dull aching in shoulder. Excruciating pain in elbow and other aspect of hand; occasional dysesthesia, burning, or freezing sensations	Aching shoulder pain; glumes. Paresis in hand and forearm	Aching shoulder pain; paresthesias in hand and forearm
Typical location of pain	Shoulder, upper arm, elbow, radiating to fourth and fifth fingers	Shoulder, wrist, hand	Hand, forearm
Course	Progressive neurologic dysfunction; atrophy and weakness with C-7, T-1 distribution; pain persistent and/or progressive pain; Horner's syndrome	Progressive weakness with C-5, C-6 distribution; variable. Early pain with appearance of weakness	Transient weakness and atrophy affecting C-6, C-7, T-1; complete resolution of motor findings
Computed tomographic scan findings	Circumscribed mass with diffuse infiltration of tissue planes	Diffuse infiltration of tissue planes	Normal
Electromyographic findings	Segmental slowing; low incidence of myokymia	Myokymia present in 67% of patients	Segmental slowing; low incidence of myokymia

Modified from Kori SH: Brachial plexopathy in patients with breast cancer. In Harris JR, Hellman S, Henderson IC, et al, eds. Breast Diseases. Philadelphia: Lippincott, 1987.

TABLE 35-19. Differentiating features of brachial plexopathy induced by tumor infiltration, radiation fibrosis, and reversible radiation injury

Lumbosacral Plexopathy

Direct tumor infiltration from adjacent soft tissues or lymph nodes or by compression from metastases in the adjacent bony pelvis can damage the lumbosacral plexus. Most lumbosacral plexopathy reflects local extension or nodal metastases from colorectal and other pelvic tumors (cervix, uterus, bladder, prostate), sarcomas, and lymphomas, but it may also occur with metastases from breast or lung cancer or melanoma (170). Saphner and colleagues (188) found lumbosacral plexopathy caused by retroperitoneal lymph node metastases the most common neurologic complication in patients with advanced cervical cancer.

The cardinal clinical feature of carcinomatous plexopathy is severe, unrelenting pain (189). The distribution of pain varies and may localize in the pelvis, low back or hip, or refer in a radicular or nonradicular pattern into the leg. The local pain is pressurelike or aching in quality. The referred pain varies with the site of plexus involvement and can be burning, crampy, or lancinating. Weeks to months after pain begins, sensory symptoms of numbness and paresthesias, as well as weakness and leg edema, usually develop. A “hot and dry foot” syndrome may result from lumbosacral plexopathy and may reflect sympathetic fiber dysfunction (190).

Lumbosacral plexopathy may cause different clinical syndromes depending on the level of nerve involvement. Infiltration of the upper plexus occurs in approximately one-third of patients, who present with pain in the back, lower abdomen, flank, iliac crest, or anterolateral thigh. This syndrome has associated L-1 to L-4 distribution neurologic deficits. Involvement of the lower plexus occurs in approximately one-half of patients, and these present with pain in the buttocks and perineum, with referral to the posterolateral leg and thigh. Examination may reveal associated L-4 to S-1 neurologic deficits, leg edema, and bowel or bladder dysfunction. Sacral plexopathy can signal direct bony extension of a bony sacral lesion or a presacral mass. Numbness of the dorsal medial foot and sole with associated weakness of knee flexion, ankle dorsiflexion, and inversion is typical of lumbosacral trunk extension. Involvement of the coccygeal plexus results in sphincter dysfunction and perineal sensory loss. Panplexopathy occurs in one-fifth of patients and pain may refer anywhere in the territory of the plexus. Associated leg edema is relatively common (190).

Jaeckle and colleagues (189) studied 85 cancer patients with lumbosacral plexopathy and documented pelvic tumor by CT or biopsy. They discerned three clinical syndromes: lower (L-4 to S-1), 51%; upper (L-1 to L-4), 31%; and panplexopathy (L-1 to S- 3), 18%. Seventy percent of patients had the insidious onset of pelvic or radicular leg pain, followed weeks to months later by sensory symptoms and weakness. The quintet of leg pain, weakness, edema, rectal mass, and hydronephrosis suggests plexopathy caused by cancer. CT showed pelvic tumor in 96%. On myelography, epidural extension, usually below the conus medullaris, occurs in 45%. With treatment, only 28% of patients had objective responses on CT and 17% on examination.

In previously treated patients, the main differential diagnostic consideration is radiation-induced plexopathy (see following discussion). Taylor et al. (191) found that MRI was more sensitive than CT for diagnosing cancer-induced lumbosacral plexopathy. Thus, MRI is the choice for the diagnostic workup of patients with clinical and electrophysiologic evidence of plexopathy and suspected systemic cancer. Studies should include the L-1 vertebral body through to the true pelvis. Neurologic findings include leg weakness, sensory loss, reflex asymmetry, focal tenderness (in the lumbar region in an upper plexopathy, sciatic notch and sacrum in a lower plexopathy, and lumbosacral region in panplexopathy), rectal mass, decreased sphincter tone, and positive direct and reverse straight- leg-raising signs.

Tumor Infiltration of the Sacrum and Sacral Nerves

Pain in a sacral distribution occurs usually as a result of the spread of bladder, gynecologic, or colon cancer. Dull aching pain occurs in the midline and usually burning or throbbing pain in the soft tissues of the rectal or perineal region. Sitting or lying usually exacerbates the pain. With bilateral involvement, sphincter incontinence and impotence are common. There may be tenderness over the sacrum and in the regions of the sciatic notches. Sometimes limitation of both direct and reverse straight leg raising occurs. Involvement of S-1 and S-2 roots produces weakness of ankle plantar flexion, and the ankle jerks may be absent. Usually, sensory loss occurs in the perianal region and genitalia, and this may be accompanied by hyperpathia.

Spinal and Radicular Pain

Patients perceive radicular pain as arising in a limb or trunk wall. The cause is ectopic activation of nociceptive afferent fibers in a spinal nerve or its roots or other neuropathic mechanisms. The pain is lancinating in quality and travels along a narrow band. It may be episodic, recurrent, or paroxysmal according to the causative lesion or any superimposed aggravating factors. Although patients may experience radicular pain as a deep tissue pain, it also has a cutaneous quality in proportion to the number of cutaneous afferent fibers ectopically activated. Radicular pain differs from nociception in the axons stimulated along their course; their peripheral terminals are not the site of stimulation. Ectopic activation may occur as a result of mechanical deformation of a dorsal root ganglion, mechanical stimulation of previously damaged nerve roots, inflammation of a dorsal root ganglion, and possibly by ischemic damage to the dorsal root ganglia. Acute spine pain may be described as cramping or knifelike, but may also be merely dull or aching. It is worse with movement. Chronic spine pain without a radicular component is generally aching, dull, or burning, or any combination of these three features. It also tends to be made worse with movement.

Central Pain Syndromes Caused by Cancer

Central pain syndromes are relatively infrequent in the cancer population. Although epidural spinal cord compression is almost always painful, central pain is not the predominant symptom; nociceptive input from progressive bony destruction by metastases is the usual cause of pain, with or without concurrent radicular pain from nerve root compression. Radiation myelopathy is a central pain syndrome.

Paraneoplastic Peripheral Neuropathy

Paraneoplastic syndrome refers to a group of disorders (caused by, or associated with, cancers) that are neither direct effects of the primary tumor mass nor metastatic to the involved organs. These disorders can affect virtually any portion of the nervous system. Most paraneoplastic syndromes stem from an autoimmune reaction to an *onconeural* antigen shared by the cancer and the nervous system (192). The immune reaction may retard growth of the cancer, but it also damages the nervous system. Autoantibodies found in individual patients with paraneoplastic syndromes are usually associated with specific tumors. Neurologic disorders, clinically and pathologically identical to paraneoplastic syndromes, may occur in some patients without cancer, but these patients do not have paraneoplastic antibodies. Diagnosis of a paraneoplastic syndrome depends on its increased incidence in patients with cancer, the occasional response of the neurologic syndrome to treatment of the underlying cancer, or the presence of specific autoantibodies.

A subacute sensory neuronopathy or ganglionopathy can cause dysesthesias, paresthesias, and sensory loss in the extremities (193). This represents an inflammatory process involving dorsal root ganglia and may result from antineuronal IgG antibody. The course is usually independent of the primary tumor, which is commonly small cell carcinoma of the lung (194). Sensorimotor peripheral neuropathies presenting with glove and stocking distribution may occur in cancer patients, with production of antibodies against peripheral nerves (195). Paraneoplastic peripheral neuropathies are uncommon (195). They are outnumbered by the more familiar peripheral neuropathies that occur either as a direct result of the cancer (metastases) or its treatment (usually chemotherapy).

Patients with cancer who suffer from a peripheral neuropathy usually do so from causes other than paraneoplastic syndromes. Examples of causes of peripheral

neuropathy in cancer patients are listed in Table 35-20.

Disease	Examples
Neoplastic invasion	Leptomeningeal metastases, neurolymphomatosis
Chemotherapeutic agents	Vinca alkaloids (vincristine), platinum alkaloids (cisplatin), taxoids
Nutritional neuropathies	Cancer cachexia, specific vitamin deficiencies (B_1, B_{12})
Metabolic disorders	Uremia (pelvic tumors), hypothyroidism (postradiation therapy), multiorgan failure (critical illness polyneuropathy)
Unrelated to cancer	Diabetes mellitus

Reprinted from Smith PS, Posner JB. Paraneoplastic peripheral neuropathy. *Baillieres Clin Neurol* 1995;4:443–468, with permission.

TABLE 35-20. Examples of causes of peripheral neuropathy in cancer patients

Nevertheless, paraneoplastic peripheral neuropathies are important because they may be the first sign of an otherwise occult cancer or because they may substantially disable the patient even when the cancer itself is asymptomatic. Paraneoplastic disorders sometimes involve autoantibodies that react with proteins, both in the underlying cancer and in the nervous system. Their detection may lead to an early diagnosis and potential cure of the underlying cancer.

Four types of polyneuropathies constitute most of the cases of paraneoplastic peripheral neuropathy: motor, sensory, sensorimotor, and autonomic. Motor neuropathies may be acute or chronic, progressive or remitting, demyelinating, axonal, or neuronal. Clinically, they are indistinguishable from the more common nonparaneoplastic motor neuropathies, unless they resolve after treatment of the cancer or are associated with a paraneoplastic antibody. These disorders include the Guillain-Barré syndrome, which occurs more frequently in patients with Hodgkin's disease than in the general population; a remitting and relapsing polyneuropathy resembling relapsing chronic inflammatory demyelinating polyneuropathy; and a subacute motor neuronopathy affecting patients with Hodgkin's disease or other lymphomas. The sensory neuropathies include a subacute pansensory neuropathy and a predominantly distal sensory neuropathy. In approximately 20% of all patients with a subacutely developing pure sensory neuropathy, cancer is the underlying cause. Autonomic neuropathy usually develops in association with encephalomyelitis. However, some patients develop an isolated subacute pan-dysautonomia. Intestinal pseudoobstruction of the bowel is the best-characterized isolated autonomic symptom.

Neuropathic Pain Secondary to Therapeutic Interventions

Many pain syndromes occur in the course of or subsequent to treatment of cancer with surgery, chemotherapy, or radiation therapy. In most cases, injury occurs to the peripheral nervous system or spinal cord, with pain as a major and often presenting complaint. In some cases, these syndromes occur long after the therapy is implemented, resulting in a difficult differential diagnosis between recurrent disease and a complication of therapy.

Postsurgical Neuropathic Pain

Postmastectomy. Pain can be a prominent postsurgical finding in breast cancer patients. It tends to appear in the postmastectomy period, a consequence of the disruption of normal neural pathways, or it may follow the development of lymphedema or the presence of metastases. Chronic neuropathic pain after mastectomy occurs primarily in patients whose surgery included axillary dissection (197), although the problem can occur in women who undergo any surgical procedure on the breast from lumpectomy to radical mastectomy (198). Postaxillary dissection pain is probably a more appropriate name than the usual postmastectomy pain for this syndrome (199). The pain pattern typically involves paroxysms of lancinating pain against a background of burning, aching, tight constriction in the axilla, medial upper arm, chest, or all three areas. Hyperesthesia, dysesthesia, hyperalgesia, allodynia, or hypoesthesia in the intercostobrachial nerve distribution may occur. The etiology appears to be surgical damage to the intercostobrachial nerve (199,200). The intercostobrachial nerve is a cutaneous sensory branch of T-1 and T-2. The nerve is highly variable in size and distribution, making it difficult to avoid in these surgical procedures. Usually, the pain develops shortly after surgery, but it can emerge months after surgery. Late onset should prompt a search for other causes, such as recurrent chest wall disease or bone metastases. The postmastectomy pain syndrome differs from metastatic or radiation-induced brachial plexopathy in which there is a different pattern of sensory loss, lymphedema, and usually, more severe pain.

Neck Dissection. Radical neck dissection for head and neck cancers can result in an iatrogenic syndrome characterized by ipsilateral face and neck pain with associated paresthesias. Pain usually emerges weeks to months after surgery, consequent to injury to the cervical plexus or cervical nerves (156). Sensations of tightness with burning dysesthesias in the area of the sensory loss are its characteristic features. Occasionally, patients report acute lancinating pain in the area of sensory loss. Recurrent tumor can also be a cause of pain that occurs or escalates after neck dissection.

Thoracotomy. Shortly after thoracotomy, a neuropathic pain can develop in the distribution of one or several intercostal nerves near the thoracotomy scar. The pain may remain stable after onset and gradually decrease over a period of months or years. Dajczman and colleagues (201) evaluated the prevalence and functional significance of long-term postthoracotomy pain in 56 patients at least 2 months after surgery. Thirty patients (54%) with a median follow-up of 19.5 months had persistent pain; 26 others were pain free at a median of 30.5 months postthoracotomy. Twenty-four of 44 patients (55%) more than 1 year after surgery, 13 of 29 patients (45%) more than 2 years, 6 of 16 (38%) more than 3 years, and 3 of 10 patients (30%) more than 4 years postthoracotomy reported pain. Pain intensity was low, but 13 patients stated that pain slightly or moderately interfered with their lives. Five of 56 patients had sufficiently severe chronic pain to require daily analgesic use, nerve blocks, relaxation therapy, acupuncture, or referral to a pain clinic. Pain that increases with time, or that first appears more than 3 months after surgery, may signal recurrent tumor and should prompt further investigation.

Phantom Pains. Phantom pain disables a significant number of patients undergoing amputation of different body parts for malignancy (202). It can have continuous or paroxysmal qualities and a burning or shooting character, and it frequently invokes dysesthesias. The incidence of phantom limb pain is greater in cases in which pain was present in the body part before amputation (203). Phantom breast pain occurs in 13% of patients up to 1 year after mastectomy (204). Phantom rectal pain occurs in up to 18% of patients after surgery for rectal carcinoma (205). The reappearance or worsening of pain a long while after amputation can indicate tumor recurrence. The clinician must carefully distinguish among phantom pain, nonpainful phantom sensations, neuropathic stump pain, and nonneuropathic stump pain (see Chapter 21).

Radiation Myelopathy, Plexopathy, and Neuropathy

Radiation treatment may cause pain by damage to peripheral nerves or spinal cord by altering the microvascular of connective tissue surrounding peripheral nerve, via fibrosis and chronic inflammation in connective tissues, or bringing about demyelination and focal necrosis of the white and gray matter in the spinal cord. Typically, these changes occur late in the course of a patient's illness. The differential diagnosis should always include recurrent tumor. In all instances, pain is a component of the clinical picture, but it is rarely as severe as that associated with recurrent tumor.

Subacute radiation myelopathy may occur after radiation treatment of extraspinal tumors; it most commonly appears in the cervical cord after treatment for head and neck cancers and after treatment for Hodgkin's disease (206). The syndrome involves shocklike pains in the neck precipitated by neck flexion (Lhermitte's sign), which can radiate down the spine and into the extremities. The syndrome begins one to several months after treatment and resolves after a few months to a year. Dose levels well below those causing chronic radiation myelopathy may produce it (206). Pathogenesis is probably a transient demyelination.

A bimodal distribution of chronic myelopathy, a late complication of spinal irradiation, suggests the existence of different underlying mechanisms (207). The early delayed type occurs 6 to 8 months after treatment and is related to demyelination and necrosis of the white matter. The delayed type typically occurs 1 to 4 years afterward and relates more to vascular damage. Pain typically precedes development of neurologic signs and follows dermatomes at or below the level of damage. Spinal cord signs consistent with a partial transverse myelopathy eventually appear (208). Some patients develop a Brown-Séquard syndrome. Brown-Séquard

syndrome results in ipsilateral pyramidal deficit and posterior column signs and, contralaterally, loss of spinothalamic function.

Neuropathic syndromes associated with chest wall and axillary radiation therapy include brachial plexopathy, malignant peripheral nerve tumors, nerve entrapment in a lymphedematous shoulder, and ischemia. Both early and late onset brachial plexopathy occurs. Clinically, the plexopathy involves mixed sensory and motor deficits, with or without pain.

Although some authors suggest that pain is rarely a prominent symptom in radiation plexopathy (187,209,210), several studies (211,212,213,214 and 215) suggest the opposite. Zeidman and colleagues (212) estimate that up to 20% of such patients may report severe pain. Typically, however, patients with radiation-induced injury of the brachial plexus present with sensory (paresthesias or dysesthesias) or motor (weakness, paresis) dysfunction in the upper extremity.

Olsen and colleagues (216) described the incidence and latency period of radiation-induced brachial plexopathy in 79 patients with breast cancer. Thirty-five percent of patients developed radiation-induced brachial plexopathy. Fifty percent had involvement of the entire plexus, 18% of the upper plexus alone, 4% of the lower plexus alone, and a definite level of involvement could not be determined in 28% of patients. Radiation-induced brachial plexopathy began in most patients either during or immediately after radiation treatment. Radiation-induced brachial plexopathy was more common in patients who received combination treatment with chemotherapy and radiation than with radiation alone. The likelihood of this lesion is less than 1% when 2-Gy fractions have delivered a total dose of 50 Gy; the incidence is approximately 5% after total doses approaching 60 Gy (211). Mondrup and colleagues (215) noted that the most prominent symptoms for radiation-induced brachial plexopathy were numbness or paresthesia (71%) and pain (41%), whereas the most prominent objective signs were decreased or absent muscle stretch reflexes (93%), closely followed by sensory loss (82%) and weakness (71%). The neurologic deficits are relentlessly progressive and ultimately result in a useless limb. In contrast to malignant infiltration, patients with radiation injury to the plexus tend to have abnormal sensory and normal motor nerve conduction studies and characteristically manifest more fasciculations or myokymia on electromyography than patients with neoplastic disease (217). Electrophysiologic studies reveal evidence of chronic partial denervation with increased mean duration of individual motor unit potentials, and decreased amplitude of compound muscle and sensory action potentials (215).

Harper et al. (209) found that myokymic discharges were the only electromyographic result useful in differentiating radiation induced from neoplastic brachial plexopathy. In addition, these authors noted the highest proportion of myokymic discharges in the pronator teres and abductor pollicis brevis muscles and advised a thorough search of these muscles for myokymic discharges during needle examination in patients with suspected radiation-induced plexopathy. However, myokymic discharges in neoplastic plexopathy, although rare, may exist, and there is a need for caution in using this as an absolute criterion for differentiating radiation induced from neoplastic plexopathy.

Radiation fibrosis of the lumbosacral plexus is relatively rare. It may occur more frequently after intracavitary radium implants for carcinoma of the cervix (218). Paresthesias and distal weakness progressing proximally, but rarely pain, occur in the lower extremities 2 to 3 months after irradiation of the sacral plexus (219). The pathogenesis of this is probably reversible demyelination. The symptoms and signs are usually bilateral on presentation. The weakness commences distally in the L-5 to S-1 segments and slowly progresses (220). Painless, indolent leg weakness occurs early in radiation disease, whereas pain with or without unilateral weakness usually characterizes tumor plexopathy. Radiation disease often results in serious neurologic disability.

Peripheral Neuropathy Caused by Chemotherapy

Antineoplastic drugs associated with neurologic deficits include ifosfamide (soft tissue sarcomas, testicular carcinomas, some lymphomas), cisplatin, vincristine, paclitaxel, cytarabine, interferon-a, and methotrexate.

5-Fluorouracil may produce severe stomatitis and palmar-plantar erythrodysesthesia (hand-foot syndrome). Peripheral neuropathy is rare. 5-Fluorouracil is used to treat breast cancer, colorectal carcinoma, gastric carcinoma, pancreatic carcinoma, and carcinomas of the head and neck.

Cisplatin is highly effective against testicular and ovarian cancer and acts against non-Hodgkin's lymphoma, non–small cell lung cancer, SCLC, and squamous cell carcinomas of the head and neck. Myelosuppression is mild except at high doses. The peripheral neuropathy observed with cisplatin is a distal, symmetric, predominantly larger fiber sensory polyneuropathy with paresthesias, vibratory and proprioceptive loss, relative sparing of pin and temperature sensation, and reduced deep tendon reflexes, and is dose related and cumulative (with a total dose usually more than 300 to 600 mg per m^2). Lhermitte's sign, mild weakness, and autonomic neuropathy may occur. Symptoms may begin or progress even after cisplatin termination (221,222 and 223). Concurrent vincristine or etoposide may exacerbate the neuropathy.

Cytarabine is indicated for leukemia and lymphoma, often in combination with other agents, and it rarely causes peripheral neuropathy. A myelopathy with paraplegia or cauda equina syndrome may occur after intrathecal injection.

Methotrexate is used in choriocarcinoma, epidermal carcinomas of the head and neck, lymphoma, lung cancer, maintenance chemotherapy for childhood leukemia, and in high dose with folinic acid rescue for osteogenic sarcoma. It has little or no neurotoxicity when used orally or intravenously in the usual doses. Intrathecal methotrexate may occasionally produce a myelopathy with paraplegia or a cauda equina syndrome. Because of its relative lack of myelosuppression, oncologists combine vincristine with other chemotherapeutic agents for the treatment of many tumors, including leukemia, lymphoma, primary brain tumors, sarcoma, and breast carcinoma. Peripheral neuropathy is almost universal and is the dose-limiting toxicity (224). This typically begins with loss of deep tendon reflex at the ankle and may progress to complete areflexia, distal symmetric sensory loss (pin and temperature more than vibration and proprioception), motor weakness, footdrop, and muscle atrophy. Autonomic neuropathy with constipation may occur in up to 30% of patients. Muscle pain involving the jaw or legs occasionally develops acutely after an injection. The discomfort may last for several hours or days and sometimes requires a dose reduction or discontinuation. Toxicities are dose related with high variability in individual susceptibility. Patients with a preexisting neuropathy may develop severe postchemotherapy neuropathy.

Interferon-a, active against hairy cell leukemia, has been used alone and with other agents against multiple myeloma, lymphoma, melanoma, and colon and renal cell carcinoma. A mild, distal sensorimotor peripheral neuropathy sometimes occurs.

Paclitaxel treats breast, lung, ovarian, and some head and neck cancers. It produces a dose-limiting distal symmetric polyneuropathy similar to that with vincristine (225). Paclitaxel-induced neuropathy tends to be predominantly sensory in character, although minor motor signs may be present. Paclitaxel-induced neuropathy is a dose-dependent phenomenon, occurring with higher cumulative dose and higher dose per cycle. Using 3-weekly 3-hour infusions of paclitaxel, one would expect dose-limiting neurotoxicity in patients treated with 250 mg per m^2 or more each cycle (226).

Hematopoietic Growth Factors. Although these agents do not typically cause neuropathic pain in cancer patients, they are a significant source of pain, and a brief account is included for completeness. Current options for hematopoietic growth factors include erythropoietin, which stimulates red cell production; granulocyte CSF (filgrastim), which stimulates white blood cell production; and granulocyte macrophage–CSF, which has similar effects. Erythropoietin seldom produces systemic side effects, but the granulocyte CSFs cause low-grade fever, myalgias, and a flulike syndrome, which rapidly resolves. Filgrastim is generally well tolerated. The most frequent adverse reaction is mild to moderate medullary bone pain, reported by approximately 20% of patients (227).

BACK PAIN AND METASTATIC EPIDURAL SPINAL CORD COMPRESSION

Metastatic epidural spinal cord compression is compression of the spinal cord or cauda equina nerve roots from a lesion outside the dura mater (Table 35-21). Epidural spinal cord or cauda equina compression is the second most common neurologic complication of cancer, occurring in up to 10% of patients (228,229). The most common tumors causing metastatic epidural compression are breast, lung, prostate, lymphoma, sarcoma, and kidney.

Signs/Site	Spinal cord	Conus medullaris	Cauda equina
Weakness	Symmetric, profound	Symmetric, variable	Decreased
Deep tendon reflexes	Increased or absent	Increased knee, decreased ankle	Decreased
Plantar response	Extensor	Extensor	Plantar
Sensory	Symmetric sensory level	Symmetric saddle	Asymmetric, radicular
Sphincters	Late onset	Early onset	Spared
Progression	Rapid	Variable	Variable

TABLE 35-21. Signs of spinal compression

Mechanism

Metastatic epidural spinal cord compression presumably occurs by hematogenous arterial spread to bone marrow, which leads to vertebral body collapse and formation of an anterior epidural mass. A second mechanism is spread by direct invasion of tumor through the intervertebral foramina from a paravertebral source. This occurs in 75% of patients with epidural spinal cord compression caused by lymphoma, and 15% of patients with metastatic epidural spinal cord compression from other solid tumors (230,231). It is unusual to find epidural spinal cord compression without bony involvement or direct spread through the bony foramina. Constans and colleagues (232) reviewed 600 cases of spinal cord or nerve root compression and found that vertebral metastases had occurred in 563 patients. The vertebral body was involved in 45% of these patients, the posterior arch in 41%, and the entire vertebra in the remaining 14% of patients. Epidural lesions without vertebral involvement occurred in 30 patients and intradural lesions in seven patients.

Multiple levels of vertebral involvement are particularly common in breast and prostatic carcinoma. The primary compression of the spinal cord from metastatic deposits occurs in the thoracic spine of approximately 70% of patients, the lumbosacral spine in 20%, and the cervical spine in 10% of patients (231,233,234). Multiple sites of metastatic epidural spinal cord compression occur in 17% to 30% of all patients (235). This is particularly common in breast cancer and is uncommon in lung cancer (233).

Most epidural spinal cord compression comes from a solid tumor metastasis to the vertebral body, which spreads posteriorly to the epidural space. Other tumors, such as lymphoma, paragangliomas, and neuroblastomas, invade the epidural space through the intervertebral foramina. Pain from vertebral body destruction usually precedes neurologic signs of cord compression for a prolonged period of time. Epidural metastases, entailing invasion of extrathecal and intrathecal nerve roots by neoplasm, dural infiltration, and generation of reactive fibrosis in the subdural space, may increase pain.

Pattern of Pain

The pattern of pain associated with epidural metastasis may be local, radicular, referred, or funicular. The majority of patients have local pain. Local pain over the involved vertebral body, which results from involvement of the vertebral periosteum, is dull and exacerbated by recumbency. The worsening of pain on recumbency is the most distinctive feature of the pain of epidural spinal cord compression. Many patients with cord compression find they must sleep in a sitting position. Even if pain is absent in the lying position, turning over in bed or rising from a lying position may be particularly painful.

Radicular pain from compressed or damaged nerve roots is usually unilateral in the cervical and lumbosacral regions and bilateral in the thorax, where patients often describe it as a tight band across the chest or abdomen. The pain is experienced in the overlying spine, deep in certain muscles supplied by the compressed root, and in the cutaneous distribution of the injured root. The pain is usually least severe when the patient is in a position that minimizes compression of the root and most severe in positions that compress or stretch the root. Pain is also increased by increasing intraspinal pressure (e.g., coughing, sneezing, and straining). Radicular pain is present in 90% of patients with lumbosacral, 79% of cervical, and 55% of patients with thoracic metastatic spinal cord compression (234). It is frequently bilateral in the thoracic area and unilateral or bilateral in the lumbosacral and cervical areas.

Referred pain in the midscapular region or in both shoulders may accompany cervicothoracic epidural disease and bilateral sacroiliac and iliac crest pain occurs with L-1 vertebral compression. The pain has a deep aching quality and is often associated with tenderness of subcutaneous tissues and muscles at the site of referral. Maneuvers that affect local pain usually have the same effect on referred pain. When pain is referred from pathologic processes in the low back, it is usually appreciated in the buttocks and posterior thighs. Pain from the upper lumbar spine is often referred to the flank, groin, and anterior thigh.

Funicular pain may be an early complaint in patients with cord compression and presumably results from compression of the ascending sensory tracts in the spinal cord. It usually occurs some distance below the site of compression and it has hot or cold qualities in a poorly localized nondermatomal distribution. The pain is less sharp than radicular pain but, like root pain, is usually exacerbated by movements that stretch the compressed structure (neck flexion, straight leg raising) or that increase intraspinal pressure (coughing, sneezing, straining).

Presentation and Physical Findings

The clinical picture of metastatic epidural spinal cord compression is uniformly reported as pain, weakness, sensory loss, and autonomic dysfunction (232,236,237). Although severe back pain is the initial symptom in greater than 95% of patients with epidural spinal cord compression, it may be the only neurologic symptom despite a complete or nearly complete block in 10% of patients (157). The intensity of pain and the extent of neurologic deficit depend on the size of the epidural metastasis and, consequently, the degree of epidural block. Patients with small epidural lesions may have no pain and no neurologic deficits (238).

After weeks of progressive pain, the patient may develop weakness, sensory loss, autonomic dysfunction, and reflex abnormalities. Weakness may be segmental owing to nerve root damage, or pyramidal in distribution if the spinal cord is injured. Once weakness is present, progression is often rapid, and urgent investigations and treatment are essential. Sensory abnormalities include ascending paresthesias, a sensory level, or complete loss of all sensory modalities below the dermatomal level in paraplegic patients. The upper level of sensory findings may correspond to the location of the epidural tumor or be below it by many segments. Bladder and bowel dysfunction is rarely a presenting symptom, but may appear after sensory symptoms have developed. The exception to this generalization occurs with compression of the conus medullaris, which presents as acute urinary retention and constipation without preceding motor or sensory symptoms.

Helweg-Larsen and Sorensen (239) described the frequency and the progression of symptoms in 153 patients with metastatic spinal cord compression. At the time of diagnosis, 88% of patients complained of low back pain. Radicular pain was more frequent in tumors localized in the lumbosacral area (91%) than in tumors localized in the thoracic region (69%), whereas the severity of paresis was more pronounced in patients with metastases in the thoracic region.

Certain spinal tracts appear to be more vulnerable to compression than others (240). The corticospinal tracts and posterior columns are particularly vulnerable, and the spinothalamic tracts and descending autonomic fibers less so. As a result, weakness, spasticity, and reflex hyperactivity tend to be the earliest signs of spinal cord compression, with paresthesias and vibratory and position sense loss occurring soon thereafter. Loss of pain and temperature sensation and of bladder and bowel function usually occurs late in the course of spinal cord compression. The spinocerebellar pathways are also sensitive to compression, and at times ataxia may be the only sign of spinal cord compression.

Reflex abnormalities from spinal cord involvement include loss of superficial cutaneous reflexes, increase in deep cutaneous and deep tendon reflexes at or below the level of compression, and extensor plantar responses. Asymmetric flaccid motor weakness and sensory loss, with absent lower limb reflexes, characterize cauda equina compression. Conus medullaris lesions typically cause a rapidly progressive symmetric perineal pain followed by early autonomic dysfunction, saddle sensory loss, and motor weakness. Limited straight leg raising usually points to an epidural or intradural extramedullary lesion causing root compression, whereas segmental pain and sacral sparing suggest intramedullary disease.

Approximately 1% of patients with epidural compression present initially with ataxia without pain. In patients with back pain and a normal neurologic examination, the

presence of greater than 50% collapse of the vertebral body on plain radiography is associated with an 86% chance of epidural spinal cord compression (238). Back pain in patients with normal radiographic results requires further workup, including bone scan and CT scan.

The diagnosis of epidural spinal cord compression is often delayed 1 week or more (241), even after the onset of other neurologic symptoms. Ventafridda and colleagues (242) reported an association between Lhermitte's sign and epidural spinal cord compression. In their series, the sign appeared at an early stage of compression, particularly with thoracic lesions. Lhermitte's sign, however, lacks specificity and also occurs in patients with radiation myelopathy (206), after cisplatin chemotherapy (243), and in noncancer-related problems such as multiple sclerosis (244) and subacute combined degeneration of the cord (245).

Differential diagnosis for the individual patient with back pain includes intramedullary metastases, herniated disks, epidural hematoma or abscess, transverse myelopathy, and subluxation of the spine from pathologic fractures.

Investigations

Plain radiography is an essential, highly predictive, inexpensive, quick investigation that should be obtained if myelography or MRI scanning is pending. Between 85% and 94% of patients with metastatic epidural spinal cord compression have an abnormal plain film at the time of diagnosis (233). Spinal radiography has a sensitivity of 91% for predicting epidural disease and a specificity of 86% (238). Bone scanning has a similar sensitivity but a specificity of only 53%. Particularly useful radiologic predictors for epidural disease are greater than 50% vertebral collapse and pedicular erosion. CT is valuable in investigating cancer patients with local back pain who have a normal examination and spinal radiography results. Two-thirds of these patients have spinal metastases on CT, but only 17% have metastatic epidural spinal cord compression, and in these cases none has greater than 50% block (246).

When definitive imaging of the epidural space is required, the best approach is MRI. MRI is noninvasive, effectively demonstrates metastatic epidural spinal cord compression, and gives a positive image of the spinal cord to better diagnose intramedullary disease. CT myelography and standard myelography are alternative procedures of choice. Myelography is as sensitive as MRI at identifying extradural or intradural extramedullary lesions and has the added advantage of yielding CSF, which may help exclude or confirm alternative diagnoses. Bone scan and plain radiography provide useful screening tests but are nonspecific and less sensitive than MRI or CT. Electrical studies can also be useful in assessing the level of cord compression (see Chapter 13).

Prognosis

Metastatic spinal cord compression is a disabling complication of malignant disease (247). Effective therapy is necessary to maintain functional integrity for the remainder of life (see Chapter 36). The mean survival time from the diagnosis of epidural compression is 14 months in breast cancer (range, 0.6 to 49.0 months), 12 months in prostate cancer (range, 0.2 to 61.0 months), 6 months (range, 3 weeks to 7 months) in malignant melanoma, and 3 months (range, 0 to 18 months) in lung cancer (248,249). Overall median survival time in patients with epidural compression is 7 months, with a 36% probability of 1-year survival.

The extent of disease and neurologic injury, rather than the primary pathology, determine the outcome of spinal cord compression. The clinical course of spinal cord compression resulting from malignant melanoma is similar to that resulting from breast or prostate cancer. The time from the original diagnosis of melanoma to the development of metastatic spinal disease averages 32 months (range, 0 to 114 months), and the average time from diagnosis of skeletal metastases to spinal cord compression is 27 months (range, 0 to 113 months).

The severity of weakness at presentation is the most significant prognostic variable for recovery of function. Eighty percent of patients who were ambulatory at presentation remain so after treatment (234).

STEPWISE APPROACH TO PAIN ASSESSMENT

Assessing cancer pain is more than quantifying pain with a tool and recording it. A stepwise approach to cancer pain assessment begins with data collection and ends with a clinically relevant diagnosis. It involves determining the etiology of the pain and forecasting its future trajectory. It also involves determining the number of sites from which pain originates and the probable mechanisms involved. Assessment must include evaluation of the effect of pain on sleep, functional capability, activity level, and psychological well-being. In addition, the clinician must determine the nature, course, and effect of the cancer on the patient. A thorough evaluation allows the clinician to obtain a basis for evaluating therapeutic intervention and determining the long-term goals of the patient and the patient's family.

The goals of the pain-related history are listed in Table 35-22. Optimal assessment includes a detailed description of these goals and classification by both pain syndrome and likely underlying mechanisms (see following discussion).

Define the features of the pain.
Outline the anatomic extent of the disease.
Determine responses to previous disease-modifying and analgesic therapies.
Clarify the effect of the pain on activities of daily living, psychological state, and familial and professional function.
Determine the presence of associated symptoms that may modify the perception of pain.

TABLE 35-22. Goals of the pain-related history

Features of Pain History

Table 35-23 lists the key components to assessing the characteristics of the pain complaint.

Location
Intensity
Quality
Timing
Exacerbating/relieving factors
Response to previous analgesic and disease-modifying therapies
Effect of pain
Effect of pain on activities of daily living
Psychological state
Familial and professional function

TABLE 35-23. Key components of pain characteristics

Location

Many patients with advanced disease have multiple pains at different sites. Multiple pain complaints are more common in patients with breast, lung, and prostate cancer compared with gastrointestinal cancers (43). Pain of tumor origin may be characterized by its location. For example, somatic pain resulting from bone metastases tends to be well localized, whereas visceral pain tends to be diffuse and is often referred. Neuropathic pain may be radicular in location (Fig. 35-6).

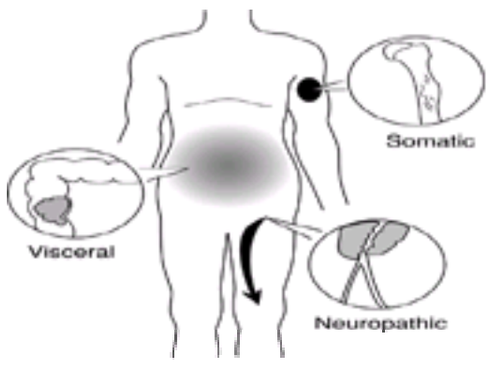

Figure 35-6. Schematic location of nociceptive (somatic, visceral) and neuropathic pain. Pain complaints resulting from somatic sources of pain (e.g., from bone metastasis) tend to be well localized; visceral sources (e.g., tumor infiltration of bowel) more diffuse; and neuropathic sources (e.g., tumor-associated lymphadenopathy infiltrating the femoral neck) radicular in distribution.

Intensity

Guidelines from the Agency for Health Care Policy and Research (250), the American Pain Society (251), and the American Society of Anesthesiologists (252) recommend the regular use of pain rating scales to assess pain severity and relief in all patients who commence or change treatments. These recommendations urge that clinicians teach patients and families to use assessment tools in the home to promote continuity of pain management in all settings. Assessment tools for determining the intensity of pain are discussed previously.

Quality

Tumor-associated pain can be nociceptive (somatic or visceral structures) or neuropathic in origin. Each source of pain has distinguishing qualities. For example, patients tend to describe pain that is neuropathic in origin as burning, shocklike, or shooting in quality, whereas they often describe pain originating from somatic structures as aching, nagging, throbbing, or sharp.

Timing

Cancer patients may have constant or intermittent pain. Constant pain is present continuously and usually fluctuates in intensity. Intermittent pain implies that pain is present for definite periods of time and that the patient is relatively pain free between episodes of pain. Patients and their caregivers need to understand the concept of breakthrough pain, as should health care providers. Breakthrough pain is discussed previously (see Patterns of Cancer Pain).

Exacerbating and Relieving Factors

Cancer patients with pain may experience a worsening of their pain over a wide range of activities. Commonly, patients with metastatic disease to weight-bearing bones experience an increase of their pain on standing or sitting. Patients with breast cancer metastatic to the axillary nodes may have severe pain on abduction of their upper extremity on positioning for external beam radiation therapy. Knowledge of these factors helps clinicians to design an appropriate pain treatment plan.

Responses to Previous Analgesic and Disease-Modifying Therapies

It is important to determine previous opioid use and benefits or side effects encountered during use. Previous unacceptable side effects to a particular opioid may limit successful future titration with the same opioid. Successful tumor shrinkage by chemotherapy or radiation therapy may indicate the need for further evaluation on tumor recurrence.

Effect of Pain

The initial pain assessment should elicit information about changes in activities of daily living, such as work and recreational activities, sleep patterns, mobility, appetite, sexual functioning, and mood. Numerous instruments, including symptom checklists and quality of life measures, may prove useful in this evaluation and are detailed in Chapter 12.

The Memorial Pain Assessment Card is a brief, validated measure that uses Visual Analog Scale scores to characterize pain intensity, pain relief, and mood, and an eight-point verbal rating scale to further characterize pain intensity. The mood scale, which is correlated with measures of global psychological distress, depression, and anxiety, is considered to be a brief measure of global symptom distress. Although this instrument does not provide detailed descriptors of pain, its brevity and simplicity may facilitate the collection of useful information while minimizing patient burden and encouraging compliance.

The Brief Pain Inventory measures both the intensity of pain (sensory dimension) and interference of pain in the patient's life (reactive dimension). It also queries the patient about pain relief, pain quality, and patient perception of the cause of pain. Numeric scales indicate the intensity of pain in general, at its worst, at its least, and right now. An average scale quantifies relief from current therapies. The patient marks a figure representing the body by shading the area corresponding to his or her pain. Seven items determine the degree to which pain interferes with function, mood, and enjoyment of life. Advantages of this questionnaire include that it is self-administered, easy to understand, and available in many languages.

Effects of the Pain on Activities of Daily Living

Many patients function quite effectively with a background level of mild pain that does not seriously impair or distract them (31). As pain severity increases, the pain passes a threshold beyond which it is hard to ignore. At this point, it becomes disruptive to many aspects of the patient's life. Constant daily pain can significantly affect a patient's daily activities. Williamson and Schulz (253) showed that as pain increased over time, restriction in activity occurred, which in turn predicted increases in depressed affect. General measures of functioning should include indicators of physical, psychological, and social functional status. Some factors may include interference on general activity, mood, walking, ability to work, relations with others, and sleep.

Maltoni and colleagues (254) confirmed the importance of certain clinical parameters as prognostic indicators for patients with terminal cancer (clinical experience, physical activity level, and clinical symptoms related to and unrelated to nutritional state). Performance status tables can help the physician assess physical activity levels (Table 35-24). However, the palliative treatment of advanced cancer and the terminally ill requires a broad concept of well-being that goes beyond one based only on physical functioning (255).

Grade	Performance level
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

TABLE 35-24. Eastern Cooperative Oncology Group performance status

Psychological State

Psychological assessment of the cancer patient with pain is imperative and should reflect an understanding of the many factors that modulate distress, such as personality, coping, and both past and present psychiatric disorders. Knowing that the patient has received outpatient or inpatient psychiatric care helps to clarify the psychological risk. Information on how the patient handled previous painful events may provide insight into whether the patient has demonstrated chronic illness behavior.

Familial and Professional Function

The clinician must learn about the patient's familial and social resources, financial situation, and the physical environment in which he or she lives. Knowledge of the patient's and family's previous experience with cancer, or other progressive medical disease, may provide useful insights into the response to physical illness or the genesis of psychological symptoms. Although the influence of social factors on treatment preferences and desire for aggressive cancer therapy is still poorly defined, Yellen and Cella (256) demonstrated that positive social well-being, as well as having children living at home, predicted patient willingness to accept aggressive treatment.

General Assessment

The initial step in the general assessment of the symptomatic cancer patient is a complete medical history that reviews the cancer diagnosis, chronology of significant cancer-related events, previous therapies, and all relevant medical, surgical, and psychiatric problems (Table 35-25). A detailed history of drug therapy should include current and prior use of prescription and nonprescription drugs, drug allergies, and previous adverse drug reactions including side effects. The patient should provide information about prior treatment modalities for each symptom. In the course of this assessment, the interviewer should document the patient's understanding of his or her current disease status. Discussion with other providers involved with the patient's care also helps determine disease status. Table 35-26 lists the different possible categories for a patient's clinical status.

Cancer history	Current medications and past medical history	Psychosocial issues
Diagnosis	Previous medical and surgical illness	Family history
Chronology	Concurrent medical condition	Social resources
Therapeutic interventions including operations and treatments	Drug reactions	Effects of disease and response on patient and family
Patient's knowledge of extent of disease		Patient's and family's goals of care
Current clinical status		

TABLE 35-25. Components of medical history: cancer history, medications, past medical history, and psychosocial factors

Category	Status
I	Active disease; care, palliative and supportive only
II	Active disease; treatment (e.g., chemotherapy, radiation therapy) in progress
III	Active disease; no current treatment, surveillance of tumor status
IV	No active disease; treatment of tumor in progress
V	No active disease; no current treatment, surveillance of tumor status
VI	No active disease; no current treatment, specialized care (e.g., medical oncology) not required

TABLE 35-26. Clinical status of patients defined by disease state and treatment strategy

A careful review of previous laboratory and imaging studies can provide information about the cause of pain and the extent of the underlying disease. Evaluation of concurrent concerns includes other symptoms and related psychosocial problems. Additional investigations are often needed to clarify uncertainties in the provisional assessment. The extent of these investigations must be appropriate to the patient's general status and the overall goals of care (Table 35-27).

Physical examination		
Review of available laboratory and imaging data		
Further diagnostic investigations and specific assessments	Diagnostic investigations, symptom-specific, extent of disease	Other assessments, psychosocial, functional

TABLE 35-27. Components of medical history: physical examination, investigations, and further evaluation

Associated Symptoms

Symptoms interact, and therefore it is important to clarify the degree to which each symptom induces or exacerbates other physical or psychological symptoms. The evaluation should determine whether symptoms are concurrent but unrelated in etiology, concurrent and related to the same pathologic process, concurrent with the one symptom directly or indirectly a consequence of a pathologic process initiated by another symptom, or concurrent with one symptom a consequence or side effect of therapy directed against the other. Fatigue may be the most prevalent symptom reported by cancer patients (257). Disease progression increases the number of factors diminishing quality of life as well as the prevalence and severity of physical and psychological symptoms. In addition to pain, patients with advanced cancer have fatigue, generalized weakness, dyspnea, delirium, nausea, and vomiting. These symptoms may have a major effect on both pain reporting and quality of life.

The Memorial Symptom Assessment Scale is a patient-rated instrument that was developed to provide multidimensional information about a diverse group of common symptoms. The Memorial Symptom Assessment Scale is a reliable and valid instrument for the assessment of symptom prevalence, characteristics, and distress. This approach to comprehensive symptom assessment is helpful for clinical trials that incorporate quality of life measures or studies of symptom epidemiology (258). Portenoy and colleagues (259) evaluated patients with prostate, colon, breast, or ovarian cancer using the Memorial Symptom Assessment Scale and other measures of psychological condition, performance status, symptom distress, and overall quality of life. The Karnofsky Performance Status score was less than or equal to 80 in 49.8%. Across tumor types, 40% to 80% experienced lack of energy, pain, feeling drowsy, dry mouth, insomnia, or symptoms indicative of psychological distress. Although symptom characteristics were variable, the proportion of patients who described a symptom as relatively intense or frequent always exceeded the proportion who reported it as highly distressing. The mean (plus or minus standard deviation range) number of symptoms per patient was 11.5 ± 6.0 (0 to 25).

Laboratory and Imaging Data

Careful review of previous laboratory and imaging studies can provide important additional information. Specific radiologic or laboratory tests may help the clinician understand the pathophysiology of symptoms and their relationships to the disease. This information provides the basis for a provisional pain diagnosis that clarifies both the status of the disease and the nature of other concurrent concerns that may require therapeutic focus.

Some patients require multiple studies to evaluate the pain problem, clarify extent of disease, or assess other symptoms. Assistance from physicians in other disciplines, nurses, social workers, psychologists, or others may prove necessary to evaluate related physical or psychosocial problems identified during the initial assessment. It is appropriate and useful to review the findings of this evaluation with the patient, family, and other appropriate persons, so that they can prioritize problems according to their importance for the patient. It is also useful to identify potential outcomes that would benefit from contingency planning, including the need for advanced medical directives, the evaluation of home care resources, and prebereavement interventions with the family.

Physical Examination

A physical examination, including a neurologic and musculoskeletal examination, is a necessary part of the initial pain assessment. The need for a thorough neurologic assessment is justified by the high prevalence of painful neurologic conditions in the cancer population (260). The physical examination should clarify the underlying causes of the pain problem, detail the extent of the underlying disease, and discern the relation of the pain complaint to the disease.

Diagnosis

The provisional pain diagnosis includes inferences about the pathophysiology of the pain and an assessment of the pain syndrome. Evaluation of concurrent concerns includes other symptoms and related psychosocial problems. Additional investigations can often clarify uncertainties in the provisional assessment.

STAGING SYSTEMS FOR CANCER PAIN

A clinical staging system allows for precise definition of patient characteristics in clinical research trials, resulting in accurate interpretation of data, successful application of therapies, and subsequent formulation of more advanced clinical research studies. The development of clinical staging systems for different tumors marks a major advance in clinical research and treatment. Although pain is a subjective state and therefore more difficult to assess than a tumor, a number of definable features are well known to influence its response to treatment. Several authors have described neuropathic pain, incidental pain, total suffering, and addictive personality as the most intractable pain syndromes (261,262).

Bruera and colleagues (263) developed a clinical staging system (Edmonton staging system) for cancer pain. This system evaluates seven features in a patient's pain: mechanism (visceral, bone and soft tissue, neuropathic, mixed, and unknown), character (nonincidental, incidental), previous exposure to opioids, cognitive function (normal, impaired), psychological distress (without major psychological distress, with major psychological distress), tolerance, and addictive history (alcoholism or drug dependence).

In a prospective study of 56 patients, Bruera and colleagues (263) assessed the effectiveness of a staging system in predicting the outcome of patients with cancer pain. The purpose of the study was not to assess the effectiveness of different treatments but to try to identify prospectively a population with poor prognosis to the best known treatment combination. The authors demonstrated that sensitivity, specificity, and negative predictive value of the system were 0.75, 0.86, and 0.80, respectively. Adequate characteristics of patients allow a better assessment of the effects of different opioids, anesthetic, and neurosurgical procedures in cancer pain. It also allows a better assessment of antineoplastic treatments, such as radiotherapy, chemotherapy, or hormones on cancer pain. In a follow-up prospective multicenter study of 227 patients, Bruera and colleagues (264) proposed a simpler staging system consisting of five categories (mechanism, characteristic, previous opioid dose, tolerance, and addiction) and two stages (good and poor prognosis). The authors conclude that the staging system was highly accurate in predicting patients with good prognosis, but patients with poor prognosis can still achieve good pain control in more than 50% of cases.

SUMMARY

Cancer is one of the medical conditions patients fear most. In addition to anxiety about cancer as a potentially lethal disease, patient and family expectancies that pain is an inevitable and untreatable consequence are major sources of distress. Controlling pain associated with cancer is a major health care problem. Lack of expertise by clinicians in assessing pain is an important cause of poor pain control. A stepwise approach to cancer pain assessment begins with a systemic clinical interview and ends with a clinically relevant diagnosis that outlines the mechanisms and contributing factors to the pain complaint. It involves determining the etiology of the pain and forecasting its future trajectory. It also involves determining the number of sites from which pain originates and the probable mechanisms involved. Assessment must include evaluation of the effect of pain on sleep, functional capability, activity level, and psychological well-being. In addition, the clinician must determine the nature, course, and effect of the cancer on the patient. A thorough evaluation allows the clinician to obtain a basis for evaluating therapeutic intervention and determining the long-term goals of the patient or the patient's family.

Many health care professionals may become involved with the cancer pain patient at any one time. Successful pain management requires that the person or persons responsible for pain management adopt, or at least become familiar with, an interdisciplinary approach to care.

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*This estimate includes bladder carcinoma in situ only; it excludes skin basal and squamous cell cancer.
*Spurling's maneuver requires the examiner to produce oblique extension of the neck on the affected side with axial compression to the head. By narrowing the affected foramen, pain may be produced in the upper extremity.

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CHAPTER 36

Cancer Pain: Management

Dermot R. Fitzgibbon

The number of cancer patients in the world is increasing. Of the estimated 9 million new cancer cases every year, more than one-half occur in developing countries. The majority of the world's cancer patients present with advanced disease, and for such patients, the only realistic treatment options are pain management and palliative care. Some cancer patients need pain relief at all stages of their disease; pain occurs in approximately one-third of patients receiving anticancer treatment. For these, pain relief efforts and anticancer treatment should go hand in hand. Thirty-three percent of patients receiving active treatment for metastatic disease have significant cancer-related pain, and this percentage increases to 60% to 90% in those with advanced disease (1,2 and 3), with the management of pain ultimately becoming the main focus of treatment. Unfortunately, approximately 25% of cancer patients die without adequate pain relief in spite of appropriate tools for adequate pain control being available (4,5).

Undertreatment of chronic cancer pain persists despite decades of efforts to provide clinicians with information about analgesics and pain-relieving techniques. Although the reasons for inadequate treatment of cancer pain are complex, certain barriers to adequate pain relief can be identified. These issues are discussed in Chapter 84 and include factors such as deficiencies in physicians' and nurses' undergraduate and graduate education about pain treatment options (6,7,8,9,10 and 11), concerns of clinicians and patients about the risk of addiction to opioids (12,13), state and federal regulation of the prescribing of opioid analgesics (14), and reimbursement policies for pain-relieving treatments (15).

Several studies demonstrate that many physicians continue to manage cancer pain inadequately (16,17 and 18). Van Roenn and colleagues (9) conducted a survey on cancer pain management within the Eastern Cooperative Oncology Group. The Eastern Cooperative Oncology Group consists of medical oncologists, hematologists, surgeons, and radiation oncologists. Respondents answered questions about the magnitude of their patients' pain, their perceptions of the adequacy of pain management, and whether or not their settings had implemented a management plan for cancer pain. Eighty-six percent of respondents said that pain in their practices was undermedicated. Thirty-one percent said that they would not maximize analgesia unless a patient's life span was less than 6 months. The majority reported not using adjunctive forms of analgesics or having a prophylactic side effect management plan in place.

The Eastern Cooperative Oncology Group survey further identified certain barriers to adequate pain management. The most prevalent single factor (76%) among the respondents was a perceived inability to assess pain appropriately. Sixty-two percent attributed inadequate patient reporting of pain as a significant barrier, and 62% attributed the patients' reluctance to take analgesics as an additional barrier. Sixty-one percent said that the physicians' reluctance to prescribe adequate quantities or doses of opioid analgesics was also a barrier to adequate pain control. In a 1994 follow-up report on the adequacy of outpatient metastatic cancer pain management, Cleeland and colleagues (16) reported that 67% of patients had pain associated with their cancer, of whom 36% had impaired function of activities of daily living associated with their pain. Forty-two percent of these patients said that their pain was inadequately controlled.

Failure to provide adequate cancer pain relief is not unique to the United States. Reports from other modern, industrialized countries reveal varying degrees of success and inadequacy in managing cancer pain (19,20,21,22,23,24,25,26,27,28,29,30 and 31). In 1995, Larue and colleagues (17) reported on cancer pain management in France. Fifty-seven percent of their patients (of a total of 605 patients) had pain associated with cancer, of whom 69% had impairment of function. Thirty percent of the patients consulted had no form of pain medication, and 51% of patients said that despite pain medications, their pain was inadequately relieved. These findings suggest a persistent international pattern of undermedication and suboptimal pain control.

Internationally, many reasons exist why patients receive inadequate cancer pain control (32). Table 36-1 lists some of these reasons. To respond to these issues, the World Health Organization (WHO) advocates a strategy that includes the development of national or state policies that support cancer pain relief through government

endorsement of education and drug availability; educational programs for the public, health care personnel, regulators, and so forth; and modification of laws and regulations to improve the availability of drugs, especially opioid analgesics.

Absence of national policies on cancer pain relief and palliative care
Lack of awareness on the part of health care workers, policy makers, administrators, and the public that most cancer pain can be relieved
Shortage of financial resources and limitations of health care delivery systems and personnel
Concern that medical use of opioids will produce psychological dependence and drug abuse
Legal restrictions on the use and availability of opioid analgesics

From World Health Organization. *Cancer pain relief and palliative care.* Technical report series 804, Geneva, Switzerland, 1990, with permission.

TABLE 36-1. International reasons for inadequate cancer pain control

In the United States, the undertreatment of cancer pain has attracted substantial attention (16,33,34,35,36,37 and 38). The factors contributing to undertreatment of cancer pain appear in Table 36-2.

Factor	Reason
Patient related	Pain underreporting: • Fear of disease progression • Perceived lack of time or inadequate amount of time spent in physician's office discussing pain problems
	Poor compliance with prescribed medications
Physician related	Legal issues regarding overprescription or perceived overprescription of opioids; physician reluctance to prescribe opioid analgesics has multiple causes (49)
	Difficulty assessing pain complaints
	Lack of information or lack of expertise on contemporary strategies for cancer pain management
	Desire to provide the patient with the latest and greatest pain management strategies may pose difficulties with untried or unproven techniques or methods

TABLE 36-2. Factors contributing to undertreatment of cancer pain in the United States

The problem of undertreatment is both complex and multifactorial, and solutions for this problem are not clear-cut. Potential solutions include the following suggestions:

- *Education of patients and health care providers*: Many cancer patients worry that their pain will not be controlled during the course of their disease. Moreover, they report fears of drug addiction, side effects, and tolerance. Educating patients about common barriers to cancer pain treatment can be an effective pain management strategy (39). In addition, each patient should receive a *bill of rights* indicating that the provider is committed to achieving optimal pain control. Health care providers should learn pain assessment techniques and routinely question all patients with cancer for pain prevalence and severity.
- *Establishment of pain management practice plan*: Several guidelines cover cancer pain management from the WHO (40), the American Pain Society (33), the Agency for Health Care Policy and Research (35), and the American Society of Anesthesiologists (38). In addition, each institution should establish and follow a pain management practice plan to anticipate and deal with pain in the cancer patient. Physicians caring for cancer patients should maintain a list of advanced pain management referral sources and protocols, and seek expert consultation when routine management strategies fail.
- *State cancer pain initiatives*: These initiatives are grass roots, multidisciplinary organizations in the United States committed to making optimal cancer pain control a reality. The first initiative began in Wisconsin (41), and they now exist in all states in the United States. A Role Model Education Program has evolved from the Wisconsin Cancer Pain Initiative (34). The key concept in the initiative movement is the provider triad: physician, nurse, and pharmacist. In most states, this program involves attendance of the triad at a day-long course covering all aspects of cancer pain management. In many respects, this program resembles programs currently in practice for Advanced Cardiac Life Support and Advanced Trauma Life Support.

A clinician may achieve pain relief in the cancer patient by several means (Table 36-3). Success requires tailoring treatment to the individual patient: matching drug treatment, anesthetic, neurosurgical, psychological, and behavioral approaches to the patient's needs. Successful management requires that the person or persons responsible for pain management be familiar with all these aspects of care.

Psychological approaches (Chapters 88–94)	Understanding Companionship Cognitive behavioral therapies
Modification of pathologic process (Chapters 36–38)	Radiation therapy Hormone therapy Chemotherapy Surgery
Drugs (Chapters 83–87)	Analgesics Antidepressants Anxiolytics Neuroleptics
Interruption of pain pathways (Chapters 102–106)	Local anesthetics Neurolytics Neurosurgery
Modification of daily activities	
Immobilization (Chapter 95)	Rest Cervical collar or corset Plastic splints or slings Orthopedic surgery

Adapted from World Health Organization. Cancer pain relief and palliative care. Technical report series 804, Geneva, Switzerland, 1990, with permission.

TABLE 36-3. Approaches to pain management in cancer patients

Many pain clinician-educators now believe that traditional medical educational approaches require complementary interventions in health care systems that directly influence the routine behaviors of clinicians and patients (34,42,43,44,45 and 46). This perspective echoes that advocated by the quality improvement movement (47,48). The quality improvement approach to pain treatment is based on the assumption that, although clinicians are concerned with patient comfort, their habits and procedures of practice do not support the achievement of effective pain relief. Although pain has received the most study, some experts believe that many symptoms of medical illness are neglected because patterns of medical practice and accountability have evolved out of a focus on structural disease rather than on patient complaints (49,50). Quality improvement programs designed to enhance treatment of cancer pain should include the following key elements:

- Ensure that a report of unrelieved pain raises a *red flag* that attracts clinicians' attention
- Make information about analgesics available in settings in which physicians write orders
- Promise patients responsive analgesic care and urge them to communicate their pain
- Implement policies and safeguards for the use of modern analgesic technologies
- Coordinate and assess implementation of these measures

The American Pain Society Quality of Care Committee issued guidelines for the treatment of acute pain and cancer pain (33). These guidelines attempted to embody key elements for favorably influencing behaviors of both patients and clinicians. The guidelines addressed settings that used conventional pain relief methods (e.g., intermittent parenteral or oral analgesics) exclusively and those using current technology for pain management. Although the guidelines focused on the assessment of pain and its treatment with analgesic drugs, they also identified that nonpharmacologic measures were an effective therapy.

Bookbinder and colleagues (46) studied the effect of implementing American Pain Society guidelines in a focused program at an academic cancer hospital. The program included routine monitoring of pain, staff education, and focus groups to identify organizational obstacles to effective pain management. During the first year of the program, patient satisfaction increased significantly, but the “worst pain levels over the past 24 hours” remained unchanged. Results from the second and third years suggested further reduction of pain intensity on targeted hospital units. Major change did not occur until pain assessment became routine and the resulting data had convinced physicians to participate in the programs.

Pain Education Programs at a community level have shown mixed results. Elliott and colleagues (51) failed to show a significant reduction in pain prevalence, pain management index, pain intensity scores, patient and family attitude scores, and physicians' and nurses' knowledge and attitude scores. In contrast, de Wit and colleagues (52) reported that patients significantly increased their knowledge of pain and its mechanisms, with a decrease in pain intensity of approximately 20% to 30%.

MANAGEMENT OF THE CANCER PATIENT WITH PAIN

Successful management of the cancer patient with pain depends on the ability of the clinician to assess initial problems, identify and evaluate pain syndromes, and formulate a plan for continuing care that is responsible to the evolving goals and needs of the patient and the patient's family (see Chapter 35). The formulation of an effective therapeutic strategy for the management of cancer pain requires a comprehensive assessment of the patient and the pain complaint. The goals of patient care are often complex, but they broadly comprise prolonged survival and optimizing comfort and function. Adoption of these goals logically leads to a multimodality treatment approach targeted to specific problems (Fig. 36-1).

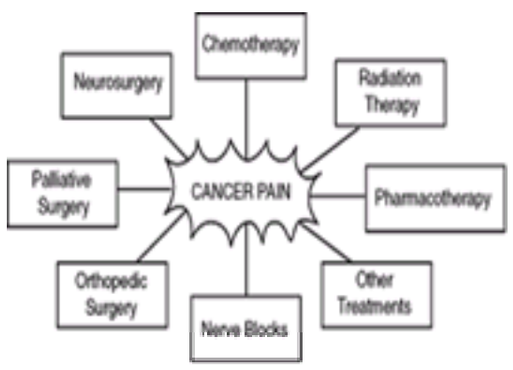

Figure 36-1. Multimodality therapeutic management of cancer pain. Other treatments include psychosocial interventions, nursing care, alternative pain management strategies, and end-of-life issues.

Comprehensive cancer care encompasses a continuum that progresses from disease-oriented, curative, life-prolonging treatment through symptom-oriented, supportive, and palliative care extending to terminal hospice care. Pain management is, and should be, an integral component of comprehensive cancer care (53). Designing an effective pain control strategy for the individual patient requires knowledge of the ways in which a patient's cancer, cancer therapy, and pain therapy can interact. Collaboration with different health care providers (e.g., medical oncologists and radiation oncologists) is essential to successful pain management.

Two important aspects of cancer affect management: (a) the oncologist's ability to treat the cancer and (b) components of the tumor pathophysiology that of themselves do not cause pain (the cancer's *nonpain* pathophysiology) (54). The ability to treat cancer modifies the need for pain management (successful treatment reduces the likelihood of pain) and the appropriateness of invasive pain procedures. Cancer nonpain pathophysiology can interfere with the oral administration of medications, narrow the patient's therapeutic window for analgesic drugs, limit the effectiveness of psychological pain therapies, and complicate or preclude invasive pain-reducing procedures. In addition, cancer therapy can interfere with or enhance pain therapy and vice versa. Antineoplastic treatment can interfere with pain therapy by causing pain or by producing other adverse effects. Cancer treatment can enhance pain therapy by reducing the extent of cancer, acting as an adjuvant analgesic, and providing intravenous access for parenteral drug administration to patients who require it. Pain therapy can sometimes interfere with cancer therapy by increasing or complicating the adverse effects of cancer therapy. It can enhance cancer therapy by improving patient function or sense of well-being, and certain palliative surgical procedures may have the ancillary effect of improving organ function.

The basic principles of tumor-directed pain control include (a) modifying the source of pain by treating the cancer and the inflammatory response of cancer; (b) altering the central perception of pain (e.g., by the use of analgesics, antidepressants, anxiolytics, and psychotherapy); and (c) interfering with nociceptive transmission within the central nervous system (CNS), for example, with anesthetic techniques (e.g., neuraxial analgesia and spinal neurolysis) or neurosurgery procedures (e.g., cordotomy and myelotomy).

The pain experienced by most cancer patients responds to direct and indirect modification of the source of the pain combined with pharmacologic and nonpharmacologic alteration of the central perception of pain (5,55,56).

The guiding principle in developing pain management goals is to individualize the approach to the patient's needs. Part of the process of developing treatment goals is to take into consideration the risks and benefits of different treatment options and the *price* that the patient and family is willing to pay for pain relief. Clinicians may find that patient treatment goals differ from their own, either because patients feel that pain is inevitable, or because patients expect pain to be relieved with minimal effort on their part. Issues that physicians should discuss with patients include expected lifestyle, cost and reimbursement issues, and concerns about opioid tolerance, addiction, and side effects. Discussing these issues in advance may uncover and address potential barriers to treatment. Moreover, treatment goals may change during the course of the patient's illness, and all health care providers interacting with the patient during the course of the illness need to keep abreast of such changes.

Patient life expectancy should influence treatment decisions. For example, if life expectancy exceeds several weeks, then treatment may focus on how to enable the patient to function at the highest possible level. One goal should be to relieve pain and prevent therapy from interfering with normal activities. On the other hand, those likely to die within a few days or weeks require less emphasis on maintaining an active lifestyle and more on tolerance of the side effects associated with pain therapies. The emphasis for these patients should be on treatments that provide immediate relief, rather than those that require a long period of time to become effective. Because maintenance of mental clarity and alertness is always valued, even in the last days or hours of life, patients may be willing to undergo more interventional methods of pain management to achieve better pain control.

Primary Anticancer Treatment

Pain produced by tumor infiltration may respond to antineoplastic treatment with surgery, radiation treatment, or chemotherapy, and pain caused by infections may diminish with antibiotic therapy or drainage procedures (see Chapter 37). Specific analgesic treatments are appropriate adjuncts to the primary therapy. The three major types of antineoplastic treatments are surgery, radiation therapy, and systemic therapy (chemotherapy, hormone therapy, and biotherapy). Surgery and radiation treatment generally attempt to cure localized malignancies, whereas chemotherapy treats disseminated neoplasm. The advantages of combined therapy have become evident, and an increasing number of patients receive combinations of these three therapeutic approaches. The rationale for such combination therapy comes from observations that surgery is most likely to fail locally at the edges of tumor resection (positive surgical margins), radiation therapy is most likely to fail in the center of tumors, and chemotherapy is most likely to fail in the presence of bulk disease.

Radiation Therapy

Radiation therapy is one of the most widely used treatments for cancer (57) (see Chapter 37). Research suggests that DNA is the target of the cytotoxic effects of radiation (58). Radiation therapy has a pivotal role in the treatment of cancer pain caused by bone metastases (see Chapter 37), epidural neoplasm, and cerebral metastases. Especially when combined with cytotoxic chemotherapy, limited surgical excision, or both, radiation can control disease at the primary site and regional nodes without the need for surgical extirpation as was frequently used in past years. New developments in three-dimensional treatment planning and the precise delivery of high-dose radiation promise to increase the benefit of radiation treatment. Table 36-4 lists diseases commonly treated by radiation.

Hodgkin's disease
Non-Hodgkin's lymphoma
Cervical carcinoma
Prostate carcinoma
Head and neck cancers
Seminoma
Tumors of the central nervous system
Retinoblastoma
Choroidal melanoma
Unresectable lung carcinoma
Unresectable pancreatic carcinoma
Unresectable sarcoma

TABLE 36-4. Diseases commonly treated by definitive radiation

Approximately 40% of patients referred for radiation treatment have advanced cancer that does not respond to curative treatment and is accompanied by pain (59). Rutten and colleagues (60) evaluated the pain characteristics that help to predict the pain-relieving efficacy of radiation therapy for cancer pain. In a study of 51 patients, they found a significant relationship between pain characteristics (the presence of radiating pain and a low pain score, i.e., pain scores less than 35, before radiation) and a complete response to palliative radiation treatment. Complete responses to treatment occurred within 21 days of the start of radiation.

Chemotherapy and Biotherapy

Pain relief often occurs after chemotherapy for responsive tumors such as lymphoma, small cell lung cancer, germ cell tumors, and possibly breast cancer. Combination chemotherapy regimens with agents having different modes of action and exhibiting different forms of toxicity are more likely to cure than single-agent therapy, because the chance of double resistance to two drugs is much less than the risk of single-drug resistance. Maximally tolerated drug doses are indicated because the fraction of cells killed is proportional to the dose employed. Single drugs, low doses, and long intervals between chemotherapy cycles encourage the development of resistant tumor cell clones. High-dose chemotherapy with autologous hematopoietic stem cell transplants is currently indicated for the treatment of high-grade non-Hodgkin's lymphoma (relapsed) and acute myelocytic leukemia when an allogeneic donor is not available. Some use this approach for stage IV breast cancer in remission and to complete the adjunctive therapy of high-risk primary breast cancer. Trials are under way in myeloma, ovarian, and testicular cancer, and certain other solid tumors.

Biological response modifiers now play an established role in the treatment of certain cancers (e.g., interleukin-2 in renal carcinoma, interferon as adjunctive therapy in melanoma, bacille Calmette-Guérin as local therapy for bladder tumors). Other modifiers include granulocyte colony-stimulating factor (filgrastim) and granulocyte-macrophage colony-stimulating factor (sargramostim), which stimulate the production of white blood cells. These hematopoietic growth factors facilitate host recovery from severe chemotherapy-induced myelosuppression and permit an increase in the dose intensity of standard chemotherapeutic agents.

Surgery

The surgeon treating a patient with newly diagnosed cancer must meet several responsibilities: biopsy for tissue diagnosis, adequate staging, consultation with medical and radiation oncologists for adjuvant therapy, and surgical resection. Surgery may also play a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bone structures, and compression of neural tissues. A variety of surgical disciplines (e.g., general, orthopedic, gynecologic, neurosurgical, plastic, and reconstructive) may participate in the care of the cancer patient. Beginning in the 1960s and 1970s, surgery for certain tumors such as breast, colon, and lung cancer became more conservative. Because surgeons now know that regional lymph node spread often occurs independently from systemic metastasis, many surgeons take a more conservative approach when resecting the primary tumor.

Although the development of metastatic cancer usually indicates incurable disease, curative surgical resection is possible in rare instances. These instances must meet several criteria before the surgeon can operate: The primary lesion must be controlled; there must be the potential for complete resection of the metastases; there must be no other equally effective or better antitumor therapy available; metastases should involve only one organ; one should anticipate reasonable postoperative function; expected survival should be better than if left untreated; and the patient must be able to tolerate the surgical procedure. Sometimes excision of the primary tumor is indicated in the presence of unresectable metastatic disease. Locally advanced tumor can be painful and unsightly, can interfere with vital functions such as breathing and swallowing, and produce complications such as bleeding and local infection.

Stenting, Drainage Procedures, and Antibiotics

Common complications of advanced cancer include gastrointestinal, hepatobiliary, and ureteric obstructions. Stents and laser treatment have a place in both upper gastrointestinal and rectal obstruction caused by advanced malignancy (61,62 and 63). Endoscopic retrograde placement of ureteric stents under cystoscopic control is the most common urologic approach for the management of malignant ureteric obstruction. Difficult clinical situations may require alternative procedures such as palliative cutaneous ureterostomy, percutaneous anterograde ureteric stent placement, and a combined anterograde and retrograde technique. The insertion of internal biliary stents by endoscopic or percutaneous methods is common practice for the palliative management of obstructive jaundice caused by malignancy, and most surgeons prefer this to the use of external biliary drains (64).

The goals of antibiotic use in terminally ill patients are sometimes to prolong life, and always to relieve symptoms. Treatment for cystitis does not usually prolong life, but may relieve the patient from painful dysuria and troublesome polyuria. Antibiotics may also have pain-relieving effects when the source of pain involves infection, as illustrated by the treatment of pyonephrosis and osteitis pubis.

Symptomatic Cancer Pain Management

The management of the cancer patient with pain is complex and requires interdisciplinary collaboration. Successful management strategies usually require a team approach that focuses not only on the nociceptive processes but also on other factors that influence the final perception of pain. Figure 36-2 outlines tumor pain management strategies directed at the treatment of nociceptive and neuropathic pain at our institution.

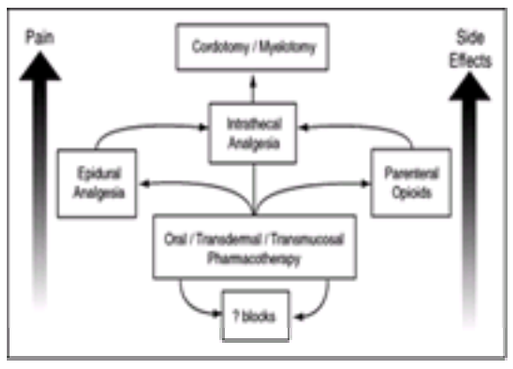

Figure 36-2. Tumor pain management algorithm.

Increasingly severe pain and increasing and intractable side effects determine the appropriate treatment strategy. Most patients respond satisfactorily to relatively simple oral pharmacotherapeutic strategies. When the patient requires drug treatment, therapy should comply with two basic principles: Use oral analgesics and other noninvasive routes of administration (e.g., transdermal and transmucosal) whenever possible, and administer them in accordance with the principles in the WHO analgesic ladder (see World Health Organization Analgesic Ladder). Titrate these analgesics to maximally effective doses or to the appearance of dose-limiting side effects before considering more specialized (and usually) invasive approaches. As an adjunct to medication management, many patients benefit from the use of additional, relatively simple, single-injection anesthetic blocks such as celiac and superior hypogastric plexus blocks, neurolytic subarachnoid and intercostal blocks, and selected peripheral nerve blocks. The intent of these procedures is not to replace medication management, but rather to supplement it.

Severe, uncontrolled pain or intractable side effects require interventional pain management to achieve rapid pain control. Such interventions may include epidural analgesia, parenteral opioid therapy, or both (usually intravenous or subcutaneous administration). As many of these patients have large systemic opioid requirements, it is not unusual to combine epidural and parenteral therapies. A small percentage of patients may fail on these therapies and should then be treated with intrathecal drugs, cordotomy, or myelotomy (see Interventional Pain Management, below).

Occasionally, patients have pain refractory to all interventional measures outlined. For these patients adequate relief may only come at the cost of profound sedation. One can accomplish sedation through the use of benzodiazepines (65), neuroleptics, barbiturates, and (for hospitalized patients) propofol (66). The ethical acceptability of sedation at the end of life depends on informed consent and an acknowledgment of the *principle of double effect*, which distinguishes between the compelling primary therapeutic intent (to relieve suffering) and unavoidable, untoward consequences.

WORLD HEALTH ORGANIZATION ANALGESIC LADDER

In 1986, WHO proposed a method for relief of cancer pain, based on a small number of relatively inexpensive drugs, including morphine (67). This guideline has been translated into 22 languages, and a total of more than 500,000 copies have been sold. A second edition (40) takes into account many of the advances in understanding and practice that have occurred since the mid-1980s. The groundwork for this revision was started in 1989, in the context of the meeting of a WHO Expert Committee on Cancer Pain Relief and Active Supportive Care (32).

The WHO analgesic ladder is a simple and effective method for controlling cancer pain, and the proportion of cancer patients who should receive effective pain relief varies from 75% to 90% (35,68). According to Zech and colleagues (5), 88% of patients with cancer pain should receive good pain control via the guidelines. Similarly, Schug and colleagues (69) estimated that only 11% of cancer pain patients managed with WHO guidelines required alternate methods of pain management. Grond and colleagues (70) found that 75% of terminally ill cancer patients received effective management with these guidelines. Although the effectiveness of the ladder appears to have received widespread approval, some authors have expressed concern on the validity and scientific effectiveness of published data. Jadad and Browman (71) conducted a systematic review of studies (Medline from 1982 to 1995, a hand search of textbooks and meeting proceedings, reference lists, and direct contact with authors) evaluating the effectiveness of the WHO ladder as an intervention for cancer pain management. Although the studies available provide valuable information on the course of cancer pain and its treatment, they fail to estimate confidently the effectiveness of the WHO analgesic ladder. Until results from carefully designed controlled trials become available, it is inappropriate to judge the performance of clinicians, programs, and institutions or to design policies based on such evidence.

Treatment for cancer pain should begin with a straightforward explanation to the patient of the causes of the pain or pains. Many pains respond best to a combination of drug and nondrug measures. Nevertheless, analgesics and a limited number of other drugs are the mainstay of cancer pain management (Table 36-5). Concurrent anticancer treatment and analgesic drug therapy for cancer pain poses no problem. Some pains respond well to a combination of a nonopioid and an opioid drug. Others require combining a corticosteroid and an opioid. Neuropathic pains often respond poorly to nonopioids and opioid analgesics, but tricyclic antidepressants and anticonvulsants may prove effective. Pharmacologic strategies for the control of tumor pain appear in Table 36-6. Table 36-7 lists the principles of pharmacotherapy endorsed by WHO.

Category	Basic drugs	Alternatives
Nonopioids	Acetylsalicylic acid	Choline magnesium trisalicylate
	Acetaminophen	Diflunisal
	Ibuprofen	Naproxen
	Indomethacin	Diclofenac
Opioids for mild to moderate pain	Codeine	Dihydrocodeine
		Dextropropoxyphene
		Standardized opium
		Tramadol
Opioids for moderate to severe pain	Morphine	Methadone
		Hydromorphone
		Oxycodone
		Levorphanol
		Meperidine
		Buprenorphine
Opioid antagonist	Naloxone	—
Antidepressants	Amitriptyline	Imipramine
Anticonvulsants	Carbamazepine	Valproic acid
Corticosteroids	Prednisolone	Prednisone
	Dexamethasone	Betamethasone

From World Health Organization. Cancer pain relief with a guide to opioid availability. Geneva: World Health Organization, 1996, with permission.

TABLE 36-5. A basic drug list for cancer pain relief

Select the appropriate analgesic drug.
Prescribe the appropriate dose of that drug.
Administer the drug by the appropriate route.
Schedule the appropriate dosing interval.
Prevent persistent pain and treat breakthrough pain.
Titrate the dose of drug aggressively.
Prevent, anticipate, and manage drug side effects.

TABLE 36-6. Pharmacologic strategies for the control of tumor pain

By the mouth
By the clock
By the ladder
For the individual
With attention to detail

From World Health Organization. *Cancer pain relief with a guide to opioid availability*. Geneva: World Health Organization, 1996, with permission.

TABLE 36-7. Principles of drug therapy for cancer pain

These principles of pharmacotherapy are as follows:

By Mouth

When possible, patients should take analgesic medications by mouth. However, alternative routes such as rectal, transdermal, sublingual, and parenteral (subcutaneous and intravenous) administration may better serve patients with dysphagia, uncontrolled vomiting, or gastrointestinal obstruction.

By the Clock

Patients with continuous pain should take analgesic medications at fixed intervals of time. Titrate the dose of analgesic drug against the patient's pain (i.e., gradually increasing dose until the patient is comfortable). The patient must take the next dose before the effect of the previous dose has fully worn off. Some patients may need to take rescue doses for incident and breakthrough pain, in addition to the regular schedule.

By the Ladder

The WHO analgesic ladder (1996) is based on the premise that most patients throughout the world gain adequate pain relief if health care professionals learn how to use a few effective and relatively inexpensive drugs well (Fig. 36-3). Step 1 of the ladder involves the use of nonopioids. If this step does not relieve pain, add an opioid for mild to moderate pain (step 2). When the opioid for mild to moderate pain in combination with a nonopioid fails to relieve the pain, substitute an opioid for moderate to severe pain (step 3). Use only one drug from each of the groups at the same time. Give adjuvant drugs for specific indications (see Adjuvant Drugs, below).

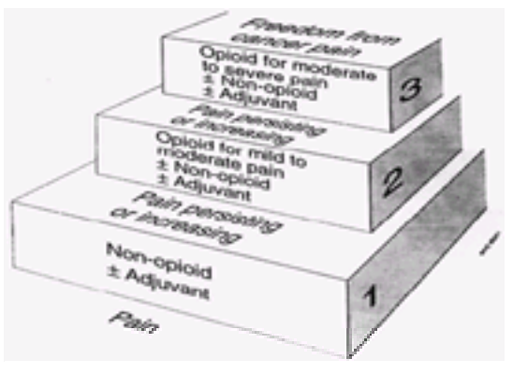

Figure 36-3. World Health Organization analgesic ladder. (From World Health Organization. *Cancer pain relief with a guide to opioid availability*. Geneva, Switzerland: World Heath Organization, 1996.)

For the Individual

No standard doses for opioids exist. The *right* dose is the dose that relieves the patient's pain with the minimum of side effects. Drugs used for mild to moderate pain have a dose limit in practice because of formulation (e.g., combined with acid or acetaminophen, which are toxic at high doses) or because of a disproportionate increase in adverse effects at higher doses (e.g., codeine). Do not use the same opioid if patients had previous unsatisfactory experiences with that drug.

With Attention to Detail

Carefully outline and monitor the patient's analgesic regimen. Follow up regularly with the patient by monitoring compliance, drug efficacy, and side effects. Anticipate adverse effects and, in some situations, treat them prophylactically.

The WHO ladder advocates the use of three classes of analgesics: nonopioid, adjuvant, and opioid. Each of these classes is considered separately.

NONOPIOID ANALGESICS

Because nonopioid analgesic agents and antipyretics are basic drugs for the management of acute and chronic pain, including rheumatic conditions, clinicians should become familiar with the use, efficacy, and adverse effects of these agents. Nonopioid analgesics are important to the successful use of oral pharmacotherapy in the cancer patient with pain. These drugs may function to control pain independently (e.g., in the management of bone pain) or may help reduce the dose of opioid required for pain control (opioid-sparing effect). However, a wide range of drugs with varying effects and side effects are available.

Three groups of nonopioid analgesics exist: acetylsalicyclic acid, acetaminophen, and nonsteroidal antiinflammatory drugs (NSAIDs) (see Chapter 83). Although acetylsalicyclic acid may be considered an NSAID, it merits separate discussion because it is effective, cheap, and widely available.

Aspirin

Aspirin is a salicylate ester of acetic acid. Aspirin irreversibly acetylates and inactivates cyclooxygenase. The antipyretic activity of aspirin probably results from the secondary inhibition of pyrogen-induced release of prostaglandins in the CNS and possibly to centrally mediated peripheral vasodilation. Aspirin acetylates platelet cyclooxygenase and prevents the synthesis of thromboxane A_2, a potent vasoconstrictor and inducer of platelet aggregation.

After oral administration, aspirin has an onset of action in 5 to 30 minutes, peaking after 0.5 to 2.0 hours, and lasting approximately 3 to 7 hours. The standard dose is 500 to 600 mg every 4 to 6 hours. The administration of more than 4 g per day is likely to lead to toxic effects. A review of aspirin's effect on the renal function of experimental animals after acute and chronic administration (72) revealed that although the findings are inconsistent, chronic administration can cause analgesic-associated nephropathy.

Nonacetylated salicylates, such as choline magnesium trisalicylate (CMT) and salsalate, have less ulcer-producing potential than aspirin, and at usual clinical doses do not impair platelet aggregation (73). Kilander and Dotevall (74) compared the effect of aspirin and CMT on gastric and duodenal mucosa by gastroduodenoscopy after 5-day periods of administration in 10 healthy volunteers. Serum salicylate levels were similar in the two groups. All subjects given aspirin developed multiple mucosal lesions, but in only four subjects given CMT were slight mucosal changes noted, suggesting that the risk of developing mucosal lesions is much less during treatment with CMT than with aspirin. Danesh and colleagues (75) measured parameters of platelet thromboxane biosynthesis 24 hours after ingestion of equivalent salicylate doses (500 mg) of aspirin and CMT. In random order, 10 healthy volunteers received these drugs on 2 separate days, 2 weeks apart. Although aspirin significantly prolonged bleeding time, and decreased plasma thromboxane generation and serum thromboxane B_2 levels, CMT failed to produce such effects. CMT has no inhibitory effect on platelet thromboxane biosynthesis, and may therefore be considered safer than aspirin for therapeutic use, when inhibition of platelet function can be hazardous.

Acetaminophen

Acetaminophen, indicated for noninflammatory pain and for fever control, is available in a variety of oral preparations and as a suppository. It has no antiinflammatory action and no antiplatelet activity. I commonly use 650 mg every 6 hours and occasionally prescribe 1,000 mg every 6 hours (particularly if encountering opioid-related side effects). The maximum dose for long-term use is 4 to 6 g per day. This dose may produce adverse effects so if higher doses (more than 4 g per day) are used, it is important to monitor carefully for the occurrence of toxicity. No evidence exists for the development of chronic analgesic nephropathy with acetaminophen alone (76). Epidemiologic studies in healthy individuals have failed to demonstrate a significant correlation between acetaminophen use and chronic renal disease and classic analgesic nephropathy (77). The only reports on this subject suggest that combination therapy with aspirin (78) or ingestion of toxic doses of acetaminophen (79) may induce nephrotoxicity. Hepatotoxicity is predominantly associated with the use of acetaminophen and occurs after single, acute, or short-term exposure to larger (more than 10 g) doses or long-term exposure with lower (less than 4 g) doses, especially in alcoholics (80,81). The majority of acetaminophen- induced fatalities occurs in younger patients after intentional overdose, usually after an acute ingestion of greater than 10 to 15 g of acetaminophen. However, certain subgroups of patients tend to develop acute hepatotoxicity after chronic ingestion of less than 10 g per 24 hours (81,82,83 and 84). These include patients who are fasting or malnourished, and those who have a chronic intake of alcohol or anticonvulsants.

Nonsteroidal Antiinflammatory Drugs

In deciding what is the optimal nonopioid analgesic for a given patient, one must consider the underlying cause of pain, its chronicity and acuity, the patient's concurrent disease states, if any, and the potential for drug interactions with the patient's concomitant medications. It seems prudent to use acetaminophen as the first-line agent for those patients who cannot tolerate aspirin or other NSAIDs. If the relative efficacy of acetaminophen and NSAIDs was similar for a particular patient, then the risk to benefit ratio and economic consequences would favor the use of acetaminophen.

NSAID pain relief is typically characterized both by a ceiling dose, beyond which additional increments fail to yield further pain relief or more severe side effects but no further pain relief, and by a lack of demonstrable physical dependence or tolerance. One cannot predict the minimal effective analgesic dose, the ceiling dose, or the toxic dose in advance for the individual patient with cancer pain, and this dose may be higher or lower than the usual dose range recommended for the drug involved. Standard recommended doses for nonopioid drugs derive from studies performed in populations (generally healthy patients with inflammatory diseases) that may have little in common with cancer patients, the latter often have numerous medical problems and use several other drugs).

The successful use of NSAIDs in the cancer patient necessitates a strategy that involves both low initial doses and dose titration. With gradual dose escalation, one can usually identify the ceiling dose and reduce the risk of significant toxicity. Weekly intervals are usually adequate to evaluate the efficacy of a dose. The potential for dose-dependent toxicity requires the use of an empirical upper limit for dose titration, which is usually in the range of 1.5 to 2.0 times the standard dose of the drug in question. Because failure with one NSAID does not predict a similar outcome with another, the physician may need sequential trials of several NSAIDs to identify a drug with a favorable balance between pain relief and side effects.

In general, the following guidelines for nonopioid dosing may be used:

- An increase in dose generally results in increased side effects.
- There is a questionable ceiling effect in cancer pain; to correctly titrate nonsteroidals or nonopioids in cancer pain patients, limit dosing to 1.5 to 2.0 times the standard recommended dose.
- At this higher dosage, check patients' stools for occult blood, monitor urine for protein, and check plasma creatinine levels bimonthly.
- Titrate doses at weekly intervals and, if there is no response at the higher levels, then decrease the dosage.

Use of Nonsteroidal Antiinflammatory Drugs in Cancer Pain

Studies of cancer pain have involved several NSAIDs. Single- and multiple-dose trials have shown benefit from ibuprofen (85), naproxen (86), ketoprofen (87), and ketorolac (88). Prolonged subcutaneous infusions of naproxen (89), diclofenac (90), and ketorolac (91) have also been reported. NSAIDs are widely believed to be especially helpful for the management of malignant bone pain (92,93). However, specific clinical data about pain-reducing responses to NSAIDs in cancer patients are sparse; many of the assumptions that guide oncologic pain management are based on either clinical impressions or trials in nonmalignant pain. Several authors have questioned the efficacy of NSAIDs for cancer pain (94,95).

Eisenberg and colleagues (94) examined the scientific evidence on efficacy and safety of NSAIDs in the treatment of cancer- related pain. They conducted a metaanalysis of data from 25 randomized controlled trials. The studies provided data on 1,545 cancer patients. Although all 25 trials reported analgesic efficacy, only the single-dose studies were comparable for analgesic efficacy analysis. Single doses of placebo produced a 15% to 36% rate of analgesia, whereas NSAIDs produced roughly twice as much analgesia (31% versus 60%). These results support the WHO position that although placebo produces some pain relief in cancer patients, true nonopioid analgesics have a significantly higher analgesic efficacy in patients with cancer pain (32). The comparative efficacy of one NSAID versus another is somewhat limited. Four studies compared the single-dose efficacy of aspirin with three other NSAIDs (indoprofen, ketoprofen, and naproxen). The results suggested slightly superior pain relief from NSAIDs compared with aspirin, but without statistical significance.

The dose-response analgesic efficacy of NSAIDs in cancer pain is not yet determined and the results of the metaanalysis are still only suggestive. The dose-response relationship was evaluated by comparing the analgesic efficacy of 600 versus 1,000 mg of oral aspirin, 100 versus 200 mg of oral indoprofen, and 10 versus 20 mg of intramuscular ketorolac. The two scores used for analgesic efficacy (peak pain intensity difference and summed pain intensity difference) were approximately 1.3 greater in the high- dose patients than in the low-dose patients, but these differences did not reach statistical significance.

The ceiling analgesic effect was tested by comparing pain scores for recommended and supramaximal single doses of three NSAIDs: ketoprofen, 100 versus 300 mg and 75 versus 225 mg orally; zomepirac, 100 versus 200 orally; and ketorolac, 10 and 30 mg versus 90 mg intramuscularly. The recommended and supramaximal doses showed similar efficacy according to all four scores used (peak pain intensity difference, summed pain intensity difference, peak pain relief, and total pain relief), which indicates a ceiling effect. The authors concluded that the metaanalysis precluded testing the hypothesis that NSAIDs are particularly effective for malignant bone pain because of a lack of comparable studies (95). Well-designed analgesic trials in which bone pain or pain caused by other specific cancer-related syndromes is assessed separately from nonbone pain are required.

Adverse Effects

The ingestion of NSAIDs can produce multiple adverse effects on the kidney (96) and other organ systems (97) (see Chapter 83). Common side effects of NSAIDs include upper gastrointestinal upset, dizziness, and drowsiness. Multiple doses generally produced more side effects than single doses.

NSAIDs may cause bleeding, altered platelet function, or gastric irritation. Gastric mucosal integrity is maintained by the interplay of three protective networks: prostaglandin synthesis, nitric oxide synthesis, and the activity of the enteric nervous system. Patients taking any NSAID require monitoring for gastropathy, renal failure, hepatic dysfunction, and bleeding (94,98,99). Gastric distress should be ameliorated by the use of a histamine H_2 antagonist or sucralfate (100). Misoprostol is a synthetic analog of prostaglandin E_1. It inhibits gastric acid production and has cytoprotective effects on the gastroduodenal mucosa. Misoprostol, in a dose of 200 µg taken orally four times a day, is more effective than 150 mg of ranitidine taken orally twice daily in preventing asymptomatic, NSAID-induced gastric ulceration (101). Side effects include sedation, tremor, abdominal pain, and diarrhea. Mild diarrhea and gastointestinal intolerance may occur in 20% to 40% of patients and may

limit tolerance to the drug (102,103).

All NSAIDs should be used cautiously in patients with renal insufficiency. Although sulindac may have relatively less effect on the kidney (104) and might seem a safer choice when potent antiinflammatory effects are desirable in the cancer patient with renal insufficiency, the clinical relevance for this renal-sparing effect is controversial. Nabumetone may require dose adjustment in the elderly, other patients with active rheumatic disease, and those with hepatic impairment, but not in patients with mild to moderate renal insufficiency (105). The development of cyclooxygenase-2 inhibitors (e.g., celecoxib) as potentially gastro-safe NSAIDs is based on the notion that COX-1 predominates in the stomach, yielding protective prostaglandins, whereas COX-2 is induced in inflammation giving rise to pain, swelling, and stiffness (106). However, the long-term safety and efficacy of selective COX-2 inhibitors have not been studied in the cancer pain population and therefore are not currently recommended over the more commonly available NSAIDs.

ADJUVANT DRUGS

Adjuvant drugs may become necessary in the care of the cancer patient for one of three reasons: (a) to treat the adverse effects of analgesic medications (e.g., antiemetics and laxatives); (b) to enhance pain relief; and (c) to treat concomitant psychological disturbances such as insomnia, anxiety, depression, and psychosis.

Antiemetics

The most widely used of the antiemetic drugs are those that block dopamine receptors, such as metoclopramide, the phenothiazines (prochlorperazine, promethazine), and the butyrophenones (haloperidol, droperidol). Metoclopramide acts both centrally and on gastric motility. Doses greater than 1 to 3 mg per kg act as an antiemetic by antagonizing 5-HT_3 receptors in the gastrointestinal tract and perhaps also in the CNS (107). However, because of its dopamine-receptor antagonism, extrapyramidal side effects appear, limiting usefulness at this dose level. The butyrophenones act by blocking dopamine receptors in the chemoreceptor trigger zone. Similar extrapyramidal side effects may also appear with higher doses. The development of the 5-HT_3 receptor antagonists, such as granisetron, ondansetron, and tropisetron, is an important advance in the treatment of nausea and vomiting. Rung and colleagues (108) demonstrated that intravenous ondansetron is effective for postsurgical opioid-induced nausea and vomiting and has a low incidence of side effects.

If the patient has nausea when beginning an opioid, prescribe a neuroleptic antiemetic concurrently (e.g., haloperidol, 1 to 2 mg once a day, increasing to a maximum of 5 mg). Prochlorperazine is a useful alternative, 5 mg every 8 hours, increasing to a maximum of 10 mg every 4 hours. Some patients receiving morphine develop nausea and vomiting that does not respond to neuroleptics, probably because of drug-induced delayed gastric emptying. In such cases, substitute metoclopramide (10 mg every 8 hours, increasing to a maximum of 20 mg every 4 hours) for the neuroleptic. If vomiting persists, consider changing to a continuous subcutaneous infusion of morphine with metoclopramide, 60 mg per day, for several days. If a patient vomits several times a day, it becomes necessary to give the antiemetic by injection, initially for 2 days. For patients with inoperable bowel obstruction, use an antihistaminic antiemetic, such as cyclizine. To reduce gastrointestinal secretions, an atropinelike drug, such as hyoscine butylbromide, may be necessary (109). Octreotide has proved an effective agent for the palliation of refractory malignant intestinal obstruction. It presumably exerts a proabsorptive effect on the small bowel mucosa, an effect on improving gastrointestinal motility, by a reduction in gastrointestinal hormone levels and by a direct antineoplastic effect on the obstructing tumor (110). Administer octreotide at doses starting with 0.3 up to 0.6 mg (mean, 0.44 mg) a day by subcutaneous continuous infusion (111).

Laxatives

Laxatives should be prescribed whenever starting an opioid drug. The appropriate dose of laxative varies considerably from patient to patient. For most patients, the regular use of a stool softener, such as docusate sodium, and a peristaltic stimulant, such as senna, counteracts opioid-induced constipation. Prescribe stool softeners every 12 hours. Titrate the dose of the stimulant for each patient until a satisfactory result is achieved. One tablet of standardized senna at nighttime is a typical starting dose, increasing to two tablets every 4 hours if necessary. If the patient is already severely constipated when an opioid is first prescribed, consider lactulose, 15 to 30 mL.

Adjuvant Analgesics

An adjuvant analgesic is a medication with primary indication other than pain relief, but it may provide or enhance analgesia in certain circumstances. In the area of cancer pain, the common adjunctive analgesics are corticosteroids, anticonvulsants, and antidepressants. These drugs play an important role for some patients who cannot otherwise attain an acceptable balance between relief and opioid side effects. Adjuvant analgesics divide broadly into general purpose analgesics and those with specific use for neuropathic, bone, or visceral pain.

General Purpose Adjuvants

Corticosteroids are the most widely used general purpose adjuvant analgesics and are available in a wide variety of formats (112). The painful conditions that commonly respond to corticosteroids include increased intracranial pressure, acute spinal cord compression, superior vena cava syndrome, metastatic bone pain, neuropathic pain caused by infiltration or compression, symptomatic lymphedema, and hepatic capsular distension. Patients with advanced cancer who experience pain and other symptoms that may respond to corticosteroids usually receive relatively small doses (e.g., dexamethasone, 1 to 2 mg twice a day). Using a short course of relatively high doses (e.g., dexamethasone, 100 mg intravenously followed initially by 96 mg per day in divided doses) can help manage an acute episode of severe pain related to a neuropathic lesion (e.g., plexopathy or epidural spinal cord compression) or bony metastasis that does not respond to opioids. In all cases, gradually lower the dose after pain reduction to the minimum needed to sustain relief.

Corticosteroids are sometimes indicated for symptoms such as mood elevation, for their antiinflammatory effect, as antiemetics, and as appetite stimulants. For such purposes, one should follow the low-dose regimen outlined previously. However, side effects such as myopathy, hyperglycemia, or psychosis may prove problematic.

Topical local anesthetics, such as EMLA cream (eutectic mixture of lidocaine and prilocaine), have a role in the management of painful cutaneous and mucosal lesions. Apply EMLA cream thickly and cover with an occlusive dressing. Lidocaine viscous can control pain associated with oropharyngeal ulceration.

Neuropathic Pain Adjuvants

The use of adjuvants can contribute substantially to the successful management of neuropathic pain. The drugs used empirically for this indication include selected antidepressants (113), orally administered local anesthetics, anticonvulsants, and others. For the purpose of drug selection, it is useful to distinguish between continuous, lancinating, and sympathetically maintained pain. Given the great interpatient and intrapatient variability in the response to adjuvants in this setting (including those within the same class), many patients require sequential trials (see Chapter 85 and Chapter 86).

The common anticonvulsants are carbamazepine and valproic acid. Carbamazepine causes enzyme induction, thereby enhancing its own metabolism. Consequently, adverse effects (e.g., drowsiness, ataxia) improve with time. Carbamazepine may exacerbate preexisting chemotherapy-induced suppression of bone marrow. Valproic acid has a long plasma half-life and is sedative. Because the drug accumulates in the body, it may be necessary to reduce high doses.

Gabapentin (Neurontin) has been used for the treatment of neuropathic pain. Gabapentin, a cyclohexane amino acid, is related structurally to GABA, yet has neither properties of GABAnergic nor GABA prodrug. It may facilitate GABA release and may act at the *N*- methyl-d-aspartate (NMDA) receptor site. Although developed as an anticonvulsant drug, gabapentin's serendipitous actions in pain relief soon emerged (just as carbamazepine relieves some cases of neuropathic pain). However, no prospective, randomized, double-blind clinical trials are yet available to evaluate the role of gabapentin for malignant neuropathic pain.

Gabapentin appears to have fewer side effects than the other anticonvulsant agents used for the treatment of neuropathic pain, thus facilitating more aggressive dose titration. The initial dose is usually 300 mg twice a day. Increase this dose in frequency to four times a day as tolerated. If symptoms persist, increase the dose strength to an average daily dose of 2,400 mg. The most common side effect encountered is dizziness, then somnolence, ataxia, and nystagmus. These effects usually wane with continued use.

Tricyclic antidepressants can help control pain of a burning nature, depression, and sleep disorders (see Chapter 85). Max and colleagues reported that the character of the pain complaint did not predict response to antidepressants (114). Amitriptyline and imipramine are both widely available. Alternative drugs, available in most

countries, may be more suitable for some patients. Nortriptyline has less sedating properties than amitriptyline; desipramine is relatively nonsedative and has minimal anticholinergic effects. Starting doses depend on the patient's age, weight, previous use of such drugs, and concurrent medications. A dose as low as 10 mg may be appropriate for some patients, but most can take 25 to 50 mg. Increase the dose to 30 to 50 mg as rapidly as tolerated (usually in terms of sedation, postural hypotension, and dry mouth). After that, increase the dose weekly until the pain is relieved or adverse effects preclude further escalation. Pain reduction, independent of changes in mood (115), occurs in many patients after a few days on doses of 50 to 100 mg (116,117).

Bone Pain Adjuvants

The clinical development of bone-seeking radiopharmaceuticals is based on the rationale that medium- to high-energy beta particle radiation, targeted and delivered to skeletal sites involved with tumor, can potentially result in more effective antitumor activity while sparing normal tissues the damaging effects of radiation. Metastatic lesions that produce a significant osteoblastic response in bone will concentrate bone precursors, such as the radiopharmaceuticals.

The most commonly used radiopharmaceutical for the treatment of bone pain caused by metastatic disease is strontium 89. Strontium chloride (^{89}Sr) is a beta particle–emitting calcium analog selectively taken up by osteoblasts. Physiologically, the drug acts as calcium and achieves preferential binding in the inorganic matrix of bone. It is absorbed into areas of high bone turnover and can reduce pain, generally without causing significant bone marrow depression. Because treatment with this agent can compromise marrow reserve and irreversibly lower platelet count, it is contraindicated if significant thrombocytopenia is present.

Robinson and colleagues (118) reviewed findings through December 1994 to evaluate ^{89}Sr therapy for the palliation of pain due to osseous metastases from breast and prostate cancer. Doses of ^{89}Sr ranged from 0.6 MBq per kg (16 µCi per kg) to 400 MBq (10.8 mCi) per patient. Baseline pain assessment and periodic pain estimates as measured by the Karnofsky index, medication diaries, changes in mobility, sleep patterns, and ability to work provided the basis for assessment of response. As many as 80% of selected patients with painful osteoblastic bony metastases from prostate or breast cancer may experience some pain relief after ^{89}Sr administration. In addition, as many as 10% or more may become pain free. Duration of clinical response may average 3 to 6 months in some cases. Hemotoxicity is mild. The nadir of platelet and white blood cell counts appears at approximately 4 to 8 weeks after injection, with a partial return to baseline by 12 weeks. Some patients have received up to 10 injections spaced 3 months apart with repeated palliative effect and without serious hemotoxicity.

Several other radiopharmaceuticals are available for clinical use. These include rhenium 186, phosphorus 32, samarium 153, and gallium nitrate. Prospective clinical studies are needed to evaluate the role of these agents in the cancer patient with painful bone metastases.

Bisphosphonates inhibit bone turnover by decreasing the resorption of bone. They do this both directly, by inhibiting the recruitment and function of osteoclasts, and indirectly, by stimulating osteoblasts. Bisphosphonates may also shorten the life span of osteoclasts. A variety of bisphosphonate compounds are available and include pamidronate, clodronate, etidronate, tiludronate, alendronate, and ibandronate. Although these compounds differ markedly in potency, they share common properties: They are poorly absorbed from the gut and are concentrated in bone, where they remain until the bone is resorbed.

Clinically, bisphosphonates can be strikingly effective in clinical disorders associated with increased bone resorption such as Paget's disease, hypercalcemia of malignancy, myeloma, bone metastases, and osteoporosis. They are now the standard therapy for hypercalcemia after rehydration (119). In malignancy, the clinical effects of bisphosphonates are greatest and most clearly defined in breast cancer and multiple myeloma, but they promise clinical benefit across the entire spectrum of metastatic bone disease (120,121). The efficacy of clodronate is nearly complete in patients with myelomatosis, less complete in solid tumors with hypercalcemia but without skeletal metastases, and intermediate in patients with solid tumors in the presence of skeletal metastases (122).

The choice of therapeutic regimen for bisphosphonates poses interesting questions (e.g., the effect of intermittent dosing versus continuous, intravenous versus oral therapy, the optimal duration of therapy, and the role of individual variability in response). The acute pain-relieving effect, which occurs within days or a week, probably derives from the reduction of various pain-producing substances. Patients with bone metastases and bone pain may obtain benefit from a trial of clodronate, 600 to 1,500 mg intravenously in 500 mL of normal saline over 3 hours given every 1 to 2 weeks, in association with other modalities such as radiotherapy and analgesic medications (119). Oral clodronate or intravenous pamidronate should be given as a preventive measure in patients with established bone metastases from breast cancer (123) and myeloma (124). Although bisphosphonates may delay the emergence of bone metastases in patients with no evidence of bone metastases (125,126), at present this remains under clinical investigation.

The physiologic role of calcitonin is the preservation of osseal integrity through reduced osteoclast activity. As such, the role of calcitonin in the management of tumor pain relates to bone metastases. Repeated doses of calcitonin reduced bone pain in one trial (127), but not in another (128). One can give the drug, salmon calcitonin, 100 IU twice daily subcutaneously or by nasal spray for several weeks. This entails close monitoring, including repeated assessments of calcium and phosphorus. Reports indicate that neuraxial (epidural and intrathecal) administration can reduce metastatic cancer pain (129), but this mode of administration requires further evaluation in controlled randomized clinical trials. Overall, the use of calcitonin for the long-term suppression of osteolysis has proven disappointing, and I do not recommend it as a means of controlling metastatic bone pain.

Bone metastases arise, in general, from blood-borne spread of a primary tumor site. Consequently, even patients with localized bone pain usually have occult sites of metastasis, and many patients develop new pain at new sites. Hemibody irradiation has attracted some interest in this setting. A large randomized trial using hemibody irradiation demonstrated reduced requirements for further bone radiation therapy when patients receive the treatment at the time of presentation of local bone pain (130). However, the role of such prophylactic therapy in clinical practice remains uncertain at this time. Scarantino and colleagues (131) evaluated the effect of fractionated hemibody irradiation in the treatment of osseous metastases. The maximum tolerated dose of fractionated (2.50 Gy) hemibody irradiation was 17.5 Gy, and the major dose limiting toxicity was hematologic (thromboleukopenia).

Visceral Pain Adjuvants

The literature offers little support for the potential efficacy of adjuvant agents for the management of bladder spasm, tenesmoid pain, and colicky intestinal pain. A trial of NSAIDs may help patients with painful bladder spasms (132). Although no well-established pharmacotherapy exists for painful rectal spasms, diltiazem can help in the management of proctalgia fugax (133). The treatment of pain caused by inoperable bowel obstruction has been described previously.

Psychotropic Drugs

Many cancer patients require a psychotropic drug. Some need it for pain relief (e.g., tricyclic antidepressants for nerve injury pain), whereas others need an antiemetic (e.g., haloperidol for opioid-induced nausea). Still others require an anxiolytic, such as clonazepam or alprazolam. Some require a night sedative and others an antidepressant for identifiable depression. The concurrent use of two centrally acting drugs (e.g., opioid with psychotropic drug or two psychotropic drugs together) is more likely to produce sedation in ill and malnourished cancer patients than in others.

OPIOID ANALGESICS

All opioids act by the same mechanisms; therefore, it is seldom advantageous to combine them in significant numbers to treat pain. Such polypharmacy is all too common, probably because of a reluctance to increase the dose of a single opioid to an effective one, which may exceed the usual or recommended dose. In addition, too rapid titration with a single agent causes unacceptable side effects and commonly leads to multiple trials of different agents. When a single drug is used in an adequate dose at an appropriate titration rate, it is less confusing to the patient and may produce more satisfactory pain control.

The use of opioids over time may cause the development of physical dependence and tolerance. In practice, physical dependence and tolerance do not prevent the effective use of these drugs. Patients with stable disease often remain on a stable dose for weeks or months (134). Collin and colleagues (135) demonstrated a relationship between tumor progression and escalation of opioid doses over time such that the development of opioid tolerance as a result of chronic opioid use was unlikely in cancer patients with pain. Furthermore, wide clinical experience has shown that addiction does not occur in cancer patients as a result of receiving opioids for relief of pain (4,136,137).

Several factors must be considered if opioids are to be used effectively. These include (a) previous opioid exposure and preference; (b) severity and nature of disease; (c) age of patient; (d) extent of cancer, particularly hepatic and renal involvement altering normal opioid pharmacokinetics (Table 36-8); and (e) concurrent

disease.

Opioid	Effect
Dihydrocodeine	Decreased clearance
Dextropropoxyphene	Increased norpropoxyphene (toxic metabolite)
Morphine	Increased morphine-6-glucuronide (active metabolite)
Meperidine	Increased normeperidine (toxic metabolite)

TABLE 36-8. Effects of renal failure on opioid pharmacokinetics

The degree of pain relief that a given opioid provides varies both intraindividually and interindividually, and depends on the type and time aspects of the pain experienced, the drug and drug characteristics, and the route of administration. Neuropathic pain and incident pain are among the poor prognostic factors for opioid treatment outcome. The treatment of incident pain is difficult, because the doses of analgesics needed to control the incident pain are often so high that toxicity occurs when the incident pain is absent.

Mixed agonist-antagonists and partial agonist drugs have predominantly agonist actions, but many also have a potentially significant antagonist action. Never change patients currently treated with pure agonists to either mixed agonist-antagonists or partial agonists because this may precipitate a withdrawal reaction. However, it is safe to change patients treated with mixed agonist-antagonists or partial agonists to pure agonists.

It is helpful to consider opioid analgesics as those used for mild to moderate pain and those used for moderate to severe pain. This distinction is arbitrary; it is based on a ceiling effect and on the manner in which these drugs are usually prescribed. Of interest, WHO considers codeine as the basic opioid for mild to moderate pain with dihydrocodeine, dextropropoxyphene, standardized opium, and tramadol as possible alternatives (40). Low-dose (0.2 mg every 8 hours) buprenorphine, a partial agonist, is also considered an alternative drug. For moderate to severe pain, morphine is considered the basic opioid, with methadone, hydromorphone, oxycodone, levorphanol, meperidine, and buprenorphine (high dose up to 1 mg every 8 hours) as possible alternatives (see Table 36-5).

Morphine

Although many compounds produce morphine-like pain relief and other effects, morphine is the standard opioid against which all new analgesics are measured, and it still remains the opioid of choice for the control of moderate to severe cancer pain.

Controlled-release opioid medication facilitates pain relief on a regular around-the-clock rather than on an as-needed basis. A fixed dose schedule has many advantages over as-needed dosing for patients with chronic pain. In particular, scheduled time-release medication allows for a more stable plasma level of drug with fewer *overshoots* (and consequently more adverse effects) and *undershoots* (with inadequate pain control) than short-acting opioids. Additional advantages include less frequent dosing, improved medication compliance, and the ability to relieve pain through the night as the patient sleeps.

The correct dose is that which controls pain but does not cause unacceptable side effects. Titrate the dose against side effects for each patient, and determine the starting dose from previous analgesic treatment. No upper limit exists to morphine dosing. Long-term treatment with 10- to 20-fold increase of oral doses over a period of 6 to 8 months does not seem to change the kinetics of oral morphine (138). Dose requirements may vary 1,000-fold, but relatively few patients need daily doses above 200 to 300 mg (137). Peak plasma concentrations usually occur within the first hour after oral administration of morphine in solution (138) and slightly later with immediate release tablets (139). Both short-acting formulations have a rapid effect, and analgesia lasts for approximately 4 hours. In contrast, controlled-release morphine tablets produce delayed peak plasma concentrations after 2 to 4 hours (140,141), the peak is attenuated, and analgesia usually lasts for 12 hours (142). This means that, with controlled-release morphine, it is more difficult to assess the adequacy of analgesia and to adjust the dose during the dose-finding period and to make rapid changes in dose. Ideally, one should maintain dosing at 12-hourly intervals.

Controlled-release morphine is considered the gold standard for long-acting opioids. In the United States, three preparations of controlled- or sustained-release morphine are available (Table 36-9). Both MS Contin and Oramorph SR are manufactured in a resin matrix that slowly dissolves in the gastrointestinal tract, releasing morphine over approximately a 12-hour period. The controlled- release form of morphine includes macromolecules from two different classes. The proportion of these macromolecules provides gradual, measured release of morphine by dissolution and diffusion. The first type of macromolecule, a polymer, is a highly polar cellulose of variable branching and molecular weight distribution. It passes through the gastrointestinal tract unchanged, except for binding water to allow slow release of the active drug. The second class of macromolecules consists of long-chain aliphatic alcohols. Inclusion of both types is designed to result in both a hydrophilic and a hydrophobic molecular phase during preparation of the granules used to compress the tablets.

Duration of action	Preparation	Dosage formats
Immediate release	Tablet/capsule	15 mg, 30 mg
	Soluble/ sublingual	10 mg
	Solution	Variety, commonly 20 mg/5 mL
	Suppository	5 mg, 10 mg, 20 mg
Controlled/sustained release	MS Contin	15 mg, 30 mg, 60 mg, 100 mg, 200 mg
	Oramorph SR	15 mg, 30 mg, 60 mg, 100 mg
	Kadian	20 mg, 50 mg, 100 mg

TABLE 36-9. Available oral/rectal preparations of morphine in the United States

One advantage of this delivery system is that it permits regulation of a drug's release rate through variation in the proportion of hydrophilic and hydrophobic components. When a tablet reaches an aqueous environment, the drug-containing cellulose matrix is hydrated and swells, reaching a predetermined degree of porosity, but otherwise remaining intact. The absorption of water by the polymer within the tablet matrix, in addition to causing swelling and dissolution, allows the drug to diffuse smoothly and evenly from the surface and from more interior portions of the tablet. The drug release rate is determined by the size of the pores and by the aliphatic alcohol acting as a barrier. The rate of release is primarily determined by the system itself, rather than by pH.

Numerous studies demonstrate the efficacy and safety of MS Contin and Oramorph SR for patients with cancer pain (143,144,145 and 146). However, MS Contin and Oramorph SR tablets have different physical, pharmacokinetic, and clinical characteristics. Results of biopharmaceutical studies indicate that these two products are not bioequivalent. Hunt and Kaiko (147) compared the pharmacokinetic profiles of MS Contin and Oramorph SR by administering a single 60-mg dose to 18 healthy volunteers. Analysis of variance revealed significant differences between the treatments for maximum plasma concentration (p <.001), area under the plasma concentration curve from 0 to 12 hours (p <.01), and apparent elimination half-life (p <.001), indicating that the two morphine preparations were not bioequivalent. Food does not affect the oral bioavailability of MS Contin or Oramorph SR (148,149).

It is particularly important to instruct patients not to chew on or crush these preparations, because this would alter the controlled-release mechanism and cause a potentially toxic dose of medication. Although it is standard practice to prescribe MS Contin and Oramorph SR every 12 hours, it is sometimes necessary to prescribe these medications every 8 hours, particularly when higher doses are required.

Kadian, controlled-release morphine, is available in clear capsules containing small polymer-coated pellets of drug and is currently undergoing clinical trials in the United States. It is intended for 24-hour administration. Each capsule contains multiple pellets (e.g., a 100-mg capsule contains on average 300 pellets), and this has the effect of providing more controlled and uniform release characteristics. Each pellet consists of a morphine sulfate–containing core that acts as a drug reservoir. Three factors, namely, the nature of the core, the nature of the polymer coat, and the thickness of the coat, collectively control the release of morphine from each pellet. A dissolution-containing polymer membrane surrounds the core of each pellet. After ingestion, the outer gelatin capsule dissolves rapidly into the stomach. The polymer coating controls the rate of release of morphine. The coating has three components: an insoluble polymer layer consisting of ethylcellulose, which has an enteric polymer component (methacrylic acid copolymer, which is insoluble and relatively hydrophobic at pH 1.2); a water-soluble component (polyethylene glycol that is soluble and hydrophilic at pH 1.2); and a plasticizer (diethyl phthalate). The core coating is partially soluble at an acidic pH (as in the stomach), and some slow release of morphine occurs in the stomach. At higher pHs, approximating those in the human intestine, the remaining hydrophilic and enteric components of the coating dissolve and absorption occurs in the small and large intestines.

Kadian's pharmacokinetic profile may offer some advantages over the other available controlled-release morphine preparations (150). The pharmacokinetic profile of MS Contin shows a short time to peak plasma concentration and relatively large fluctuations in plasma concentrations at steady state (151). Administration of Kadian every 12 hours is equivalent to the administration of MS Contin every 12 hours with respect to the measured area under the curve. However, the pharmacokinetic profile of Kadian exhibited a significantly higher minimum plasma morphine concentration, less fluctuation in plasma morphine concentration throughout the dosing interval, a longer time associated with the maximum morphine concentration, and a greater time that the plasma morphine concentration was greater than or equal to 75% of an index of the control the formulation exerts over the morphine release rate, compared with that of MS Contin (151).

Broomhead and colleagues (150) compared the efficacy and safety of Kadian administered either 24-hourly or 12-hourly to MS Contin administered 12-hourly. There were no statistically significant differences among the treatments for any morphine-related side effects when adjusted for baseline. Kadian administered 12-hourly had efficacy and safety profiles similar to MS Contin, but had the advantage of 12- or 24-hourly administration. However, patients favored the convenience of 24-hour administration of Kadian (p = .018). Further trials are required to evaluate the 24-hour use of Kadian. Additional potential advantages of Kadian include its use by sprinkling (i.e., breaking the capsule and sprinkling the pellets onto juice or yogurt) because this does not affect the time-release mechanism. This offers a particular advantage for patients with swallowing difficulties.

Hydrocodone

Hydrocodone is the hydrogenated ketone derivative of codeine. The usefulness of hydrocodone has been limited by its preparation in fixed combination with nonopioid analgesics (aspirin, acetaminophen, and ibuprofen). Combination hydrocodone is available in a variety of strengths (2.5, 5.0, 7.5, and 10.0 mg). The strength of the nonopioid component varies in these preparations, and it is important not to exceed toxic doses when prescribing these medications for breakthrough pain, particularly when using acetaminophen combinations. Vicoprofen, consisting of hydrocodone bitartrate, 7.5 mg, and ibuprofen, 200 mg, may be useful as a short-acting opioid in limited doses for patients with preexisting liver disease.

Oxycodone

Oxycodone is a semisynthetic mu-agonist with a pharmacokinetic profile resembling that of morphine (152). Ross and Smith (153) suggest that the intrinsic antinociceptive effects of oxycodone derive from its actions at kappa-opioid receptors, in contrast to morphine, which interacts primarily with mu-opioid receptors.

Pharmacokinetic studies have revealed that after oral administration, oxycodone is rapidly absorbed to produce an initial peak plasma oxycodone in approximately 2 hours (154,155). Once peak plasma concentrations are reached, oxycodone concentrations rapidly decline, with an apparent terminal half-life ranging from 3.0 to 5.7 hours (154,156). Because oxycodone is rapidly absorbed and quickly eliminated after oral administration, frequent dosing is required to maintain plasma concentrations within the therapeutic analgesic range.

Oxycodone is formulated with hydrochloride or pectinate. As the pectinate, oxycodone can be administered rectally, giving a slightly longer duration of action (157). The parenteral (not available in the United States) potency of oxycodone is approximately 0.75 that of parenteral morphine (158). Like morphine, oxycodone has a short elimination half-life (152). Oxycodone, however, has a higher oral bioavailability (60% to 87%) (156,159,160) than morphine (20% to 25%) (161,162), probably because of the methoxy group at carbon 3 (not present in morphine), which protects it from extensive first-pass glucuronidation (158). These bioavailability values for oxycodone are in accord with the higher oral to parenteral efficacy ratio (0.5 to 0.75) (158) for oxycodone compared with that of morphine (0.17). Oxycodone is extensively metabolized to noroxycodone, oxymorphone, and their metabolites. Noroxycodone is a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations.

To alleviate cancer-related pain, less oxycodone than morphine is required orally, but more oxycodone is needed intravenously (155,163). According to Beaver and colleagues (158,164), twice the amount of oxycodone in milligrams is required orally than intramuscularly for equianalgesia; intramuscular oxycodone is two-thirds as potent as intramuscular morphine.

Steady-state pharmacodynamic studies with immediate-release oxycodone have shown it to be well tolerated (156,163,165). The side effects of oxycodone are common to all opioids, with sedation and constipation being most frequent (165). Kalso and Vainio (163) administered morphine and oxycodone hydrochloride in a double-blind crossover study to 20 patients who were experiencing severe cancer pain. Morphine caused more nausea than oxycodone, and hallucinations occurred only during morphine treatment. Otherwise, no major differences in the side effects between the two opioids were observed. Maddocks and colleagues (166) reported an attenuation of morphine-induced delirium in cancer patients when changed to oxycodone.

A controlled-release formulation of oxycodone (Oxycontin) is available in strengths of 10, 20, 40, and 80 mg. A significant advantage of this formulation compared with the immediate-release preparation is the relatively long duration of action of approximately 12 hours.

Mandema and colleagues (167) showed that the controlled-release dosage form has pharmacokinetic characteristics that permit 12- hourly dosing. The absorption profile of Oxycontin is characterized by a rapid absorption component (half-life absorption = 37 minutes) accounting for 38% of the available dose and a slow absorption component (half-life absorption = 6.2 hours) accounting for 62% of the available dose.

Controlled-release oxycodone is a useful alternative to controlled-release morphine (168,169) and to immediate-release oxycodone (170). Reder and colleagues (170) noted that immediate-release oxycodone caused approximately twice as many adverse experiences, several of longer duration, than controlled-release oxycodone. Heiskanen and Kalso (159) compared the steady-state pharmacodynamic profiles of Oxycontin and MS Contin in 27 patients with chronic cancer pain in a double-blind, randomized, crossover design. The total opioid consumption ratio of oxycodone to morphine was 2:3 when oxycodone was administered first, and 3:4 when oxycodone was administered after morphine. The total incidence of adverse experiences reported by patients was similar, but significantly more vomiting occurred with morphine, whereas constipation was more common with oxycodone. The mean daily dose of oxycodone at the end of titration was 123 mg and that of morphine, 180 mg. In this study, the two opioids provided comparable pain relief.

Codeine and Dihydrocodeine

Codeine is commonly prescribed for the management of mild to moderate pain. It is most commonly used in combination with aspirin or acetaminophen. Although some variability exists, its plasma half-life and duration of action are usually in the range of 2 to 4 hours. The value of codeine is limited by the increasing incidence of side effects at doses above 1.5 mg per kg of body weight (55,171). Patients with a deficiency of CYP2D6 enzymes or those taking inhibitors of CYP2D6, such as quinidine, cimetidine, or fluoxetine, may not be able to convert codeine into morphine and therefore may get little or no analgesic effect from codeine (172,173 and 174).

Dihydrocodeine is an equianalgesic codeine analog. In the United States, it is available only in combination with acetaminophen or aspirin.

Hydromorphone

Hydromorphone is a versatile, short-half-life opioid available for administration via several routes. It is a semisynthetic congener of morphine, first synthesized in 1921. Despite its introduction into clinical medicine in 1926, data on the clinical efficacy and safety of hydromorphone are sparse, in part because of the widespread use of morphine in the management of moderate to severe pain. The short elimination half-life of hydromorphone necessitates at least 4-hourly administration of the drug to maintain adequate plasma levels for patients with chronic cancer pain. Hydromorphone is approximately five times as potent as morphine on a milligram per milligram basis. A controlled-release preparation of hydromorphone (Hydromorph Contin) (not currently available in the United States) exists. The primary benefit from this preparation lies in the convenience of the capsule formulation, which allows the patient to sprinkle it onto liquids or food. Preliminary data indicate some benefits and efficacy for cancer pain management (175). Hydromorph Contin is available in strengths of 3, 12, and 24 mg.

Methadone

Methadone is available as methadone hydrochloride powder that can be used for the preparation of oral, rectal, and parenteral solutions and is available commercially in a variety of preparations. Methadone has several advantageous characteristics including excellent oral and rectal absorption (oral bioavailability varies from 41% to 99%), no known active metabolites, high potency, high lipid solubility, low cost, and longer administration intervals. Other advantages include possibly enhanced analgesia from incomplete cross-tolerance with the potential to control pain no longer responsive to other mu-opioid receptor agonist drugs (176,177,178 and 179).

Like morphine, methadone binds preferentially to the mu-type opioid receptor, but differs by non-competitive antagonist activity at the NMDA receptor (180). Activation of NMDA receptors within the spinal cord has been shown to play a crucial role in the development of tolerance to the analgesic effects of morphine (181). Clinically, NMDA appears to be involved in inflammatory pain, neuropathic pain, allodynia, ischemic pain, and other prolonged pain states (182), and the NMDA receptor is involved in the generation and maintenance of spinal states of hypersensitivity. The use of opioids (e.g., methadone) possessing properties of NMDA receptor antagonism may improve pain control by attenuating the development of tolerance to morphine.

A successful conversion from one opioid to another requires an understanding of opioid pharmacokinetics and relative analgesic potency. The latter can be defined as the ratio of the doses of two opioids required to produce the same degree of pain relief. Equianalgesic tables propose a morphine-methadone ratio varying between 4:1 and 1:1 for the oral route and between 1:1 and 2.7:1 for the parenteral route (33,35,36,40). Although one can administer morphine and methadone in a 1:1 ratio for short-term use (183,184), these results do not apply to the management of patients with multiple repeated doses. Major differences exist between the dose of methadone required to control pain in cancer patients and other opioid agonists including morphine and hydromorphone.

Methadone is much more potent than previously recognized, particularly with repeated dose administration (178,179,185,186). The dose ratio between hydromorphone and methadone is also higher than suggested by standard equianalgesic tables (187). Lawlor and colleagues (186) evaluated consecutive rotations involving morphine and methadone using standard selection criteria and identified a total of 20 rotations (14 from morphine to methadone and 6 from methadone to morphine). Median dose ratios (lower upper quartiles) for morphine to methadone and methadone to morphine rotations were 11.36 (range, 5.98 to 16.27) and 8.25 (range, 4.37 to 11.3), respectively (p = .23). Combining all 20 rotations, a unified median dose ratio of 11.2 (range, 5.06 to 13.24) was calculated. Significant differences in pain intensity levels as recorded on a visual analog scale were not observed prerotation and postrotation. Patients receiving more than 1,165 mg per day before methadone rotation demonstrated a median dose ratio of 16.81 (range, 12.25 to 87.95), which was approximately three times higher compared with a median dose ratio of 5.42 (range, 2.95 to 9.09; p = .007) for the 50% of patients receiving lower morphine doses. Ripamonti and colleagues (188) defined the dose ratio between morphine and methadone relative to the previous morphine dose and the number of days needed to achieve equivalent pain relief in 38 patients with advanced cancer. Before the switch, the median oral equivalent daily dose of morphine was 145 mg per day; after the switch, the median equivalent oral dose of methadone was 21 mg per day. A median time of 3 days (range, 1 to 7 days) was necessary to achieve equivalent pain relief with methadone. Dose ratios ranged from 2.5:1 to 14.3:1 (median, 7.75:1), indicating that the dose ratio was much higher than that suggested by published equianalgesic tables. These analyses suggest the need for a highly individualized and cautious approach when rotating from morphine to methadone in patients with cancer pain.

Methadone is characterized by a large interindividual variation in pharmacokinetics and by rapid and extensive distribution phases (half-life alpha = 2 to 3 hours; half-life beta = 15 to 60 hours). Some outpatients have considerably longer elimination half-lives, even extending to 120 hours (189). Repeated doses of methadone at fixed intervals may lead to its accumulation and potential toxic effects. This raises concerns about its use in cancer pain, particularly in situations that require rapid dose escalation (190). Urinary elimination is a minor pathway; fecal excretion accounts for the greater part of the dose elimination. Relatively high daily doses of methadone (40 to 50 mg per day) have been used successively in patients with chronic renal disease (191).

As with other potent opioids, caution must be exercised in elderly patients, in patients with encephalopathy or a major organ failure, in those who are difficult to monitor, and in patients who are noncompliant with treatment regimens. Substantial interindividual variation in the relationship between changes in plasma concentration and pain relief can occur in patients with chronic pain receiving methadone (192). Information about interpatient variation in pain perception has led to the concept of individualization of methadone dosing in the management of cancer pain. Therefore, high individual variation in bioavailability and the long duration of its activity require personalized treatments.

A high individual variation in terminal elimination half-life can result in different rates and extents of drug accumulation, particularly with steady-state levels. To overcome these disadvantages, I suggest an oral dosing titration schedule by patient-administered analgesia (193,194). Patient-administered analgesia with oral methadone appears to be a simple, cheap, and relatively safe technique for controlling cancer pain, permitting self-individualization and potentially avoiding the risk of accumulation. However, during the titration phase, continuous assessment is necessary. The regimen involves self-administered oral methadone at fixed doses and flexible patient-controlled dosage intervals. The original study involved 14 cancer patients (194). Patients hospitalized between days 1 and 6 received a fixed dose of methadone, 10 mg as necessary, at intervals not more than every 4 hours. On the seventh day, patients received a fixed dose at 8 to 12 hourly intervals based on the sixth day average requirements. Generally, on day 1, patients used between 30 and 100 mg of methadone approximately every 3 to 7 hours. On day 7, the average use was 21.5 mg, which then was administered every 8 to 12 hours. Eleven to 14 patients had complete analgesia, and there was only mild sedation in 3 of the 14 patients.

Mercadante and colleagues (193) reported the successful use of this technique in 24 outpatients with advanced disease. During a priming period of 3 days, opioid-naive patients took fixed doses of 3 to 5 mg of methadone three times a day, and those switched from morphine received 50% of the morphine equivalent of methadone. Providers adjusted doses by frequent telephone contact or home visit. After achieving a dose of methadone capable of maintaining acceptable pain relief for more than 6 to 8 hours, patients and relatives learned how to manage pain with rescue doses taken as needed plus a fixed dose at bedtime. During the course of treatment, when patients self-administered methadone more than four times per day, including the nighttime dose, the dose increased. Pain control was deemed satisfactory in the majority of patients. The mean dose number per day was 2.4, including the fixed nighttime dose. Average daily starting dose of methadone per day was 16.5 mg, with an average maximum dose of 30.2 mg. Only one patient on a relatively high dose of methadone presented frequent episodes of confusion. Approximately 20% of patients reported some drowsiness, sweating, and nausea and vomiting.

Morley and colleagues (195) recommend the switch to methadone in all situations in which morphine has ceased to be effective for the control of cancer pain except when the dominant mechanism of pain is neuropathic in origin. The authors recommended using an initial dose of methadone that is one-tenth of the total daily morphine dose, but not greater than 100 mg. Give this dose at intervals determined by the patient as recommended by Sawe and colleagues (194), but not more frequently than 3 hourly. In typical situations, patients may require three to eight doses per day for the first few days, then settle on a lower fixed intake (one to four doses per day) after the first week.

In general, one should reserve methadone as a second-line drug in the treatment of moderate to severe cancer pain. Use methadone if morphine causes intolerable side effects and the patient wishes to continue with noninterventional approaches or if a change in opioid may enhance analgesia because of incomplete cross-tolerance.

Levorphanol

Levorphanol, a morphine congener with a long half-life (12 to 16 hours), is available in both oral and parenteral formulations. It is approximately five times more potent than morphine. The normal starting dose is 2 mg every 6 hours. If given by injection, use half this dose. Like methadone, drug accumulation may follow initiation of

therapy or dose escalation. Guidelines similar to those suggested for methadone may prove helpful for managing the patient requiring high doses of levorphanol.

Fentanyl

Fentanyl is a synthetic phenylpiperidine derivative and a chemical congener of the reversed ester of meperidine. It is an opioid characterized by high potency and lipophilicity. The drug is 75 to 100 times more potent than morphine on a molar basis. It has a short duration of action, 30 to 60 minutes after a single intravenous bolus of 100 µg, mainly because of its large volume of distribution and redistribution and uptake into fatty tissues. It is available in several preparations including transdermal, transmucosal, and parenteral. Parenteral fentanyl is a short-acting analgesic at steady-state conditions, when half-life is primarily determined by redistribution. Because of its low molecular weight and high lipid solubility, fentanyl can be administered transdermally (196).

Transdermal Fentanyl

Transdermal therapeutic system fentanyl (TTS-fentanyl) patches are rectangular transparent units, each comprising a protective liner and four functional layers. These layers consist of a backing layer of polyester film, a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose, an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface, and a fentanyl-containing silicone adhesive. The amount of fentanyl released from each system per hour is proportional to the surface area (25 µg per hour per 10 cm^2).

The transdermal system releases fentanyl from the reservoir at a nearly constant amount per unit of time. The concentration gradient existing between the saturated solution of drug in the reservoir and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the copolymer release membrane and the diffusion of fentanyl through the skin layers. Although the actual rate of fentanyl delivery to the skin varies over the application period, each system is labeled with a nominal flux, which represents the average amount of drug delivered to the systemic circulation per hour across average skin. Although variation occurs in the dose delivered among patients, the nominal flux of the systems is sufficiently accurate to allow individual titration of dosage for a given patient.

After patch application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. A lag time of approximately 2 hours occurs before clinically useful systemic levels of drug are achieved after applying the patch (197). Serum fentanyl concentrations increase gradually after application, generally leveling off between 12 and 24 hours. The system delivers fentanyl continuously for up to 72 hours. After sequential 48- or 72-hour applications, patients reach and maintain steady-state serum concentrations that are determined by individual variation in skin permeability and body clearance of fentanyl. A number of studies demonstrate that constant serum levels are maintained with the second transdermal system and that fluctuations of serum levels are small after the first 72 hours (198,199).

After system removal, serum fentanyl concentrations decline gradually, falling approximately 50% in approximately 17 hours (range, 13 to 22). Because of the possibility of temperature-dependent increases in fentanyl release from the system, it is important to advise patients to avoid exposing the application site to direct external heat sources, such as heating pads, heat lamps, and heated waterbeds. Prolonged exposure to heat can cause a toxic overdose.

TTS-fentanyl offers the advantage of providing continuous administration of a potent opioid in the absence of needles and expensive drug-infusion pumps for the treatment of cancer pain. Several studies have investigated the management of cancer pain with TTS-fentanyl (200,201,202,203,204,205,206,207 and 208). Some authors have expressed concerns about using the manufacturer's dose conversions and dosing intervals, believing that these recommendations are too conservative (203,204,209). The manufacturer's recommended doses for opioid-tolerant patients derive from the incorrect oral to parenteral morphine dose ratio of 6:1 (or a ratio of oral morphine to TTS- fentanyl of 150:1).

Patients receiving doses of TTS-fentanyl believed to be equianalgesic to the patients' previous opioids based on the package labeling conversions may experience markedly increased pain because of the fentanyl equivalent dose being as little as one-half that required for equianalgesia. Grond and colleagues (202) (Table 36-10) have indicated from intravenous fentanyl patient-controlled analgesia (PCA) studies that higher initial doses of TTS-fentanyl may be required. Transdermal administration of opioids provides a simple and noninvasive alternative producing stable blood concentrations comparable with continuous intravenous infusion.

Patient-controlled analgesia fentanyl (intravenous) dose (mg/day)	Transdermal therapeutic system fentanyl delivery rate (mg/day)	Size (cm^2)
0.2–0.6	0.6[a]	10
0.6–1.0	1.2	20
1.0–1.4	1.8	30
1.4–1.8	2.4	40
Every additional 0.4	Additional 0.6	Additional 10

[a]Fentanyl delivery rate of 0.6 mg/day corresponds to a rate of 25 µg per hour.
From Grond S, Zech D, Lehmann KA, et al. Transdermal fentanyl in the long-term treatment of cancer pain: a prospective study of 50 patients with advanced cancer of the gastrointestinal tract or the head and neck region. Pain 1997;69: 191–196, with permission.

TABLE 36-10. Conversion table for parenteral fentanyl dose to initial transdermal therapeutic system fentanyl

In a pilot study of 20 cancer patients, Zech and colleagues (207) demonstrated that intravenous PCA with fentanyl allowed effective, safe, and rapid dose finding for transdermal treatment. However, the conversion ratio used of 1:1 from intravenous to transdermal was considered too low. In a follow-up study (202) of 50 patients, the conversion ratio was increased by 50% to a ratio of 1.0:1.5. In spite of these increases, the authors considered the conversion ratio still too low in the majority of patients as the delivery rate of the second patch needed to be increased markedly, on average increasing by 100% at the end of the first week. Despite this, the authors noted that three patients had a low respiratory rate during the titration period and recommended a conversion ratio of 1:1.

Donner and colleagues (200) studied the direct conversion from long-acting oral morphine to TTS-fentanyl with a ratio of 100:1 in 98 cancer patients with constant pain relief under oral opioids. During the prestudy phase of 6 days, they stabilized patients on long- acting morphine. After this phase, patients shifted to TTS-fentanyl using a conversion ratio of 100:1, changing the fentanyl patches every 3 days. The initial fentanyl dose proved satisfactory in 42% of patients, but a significant percentage of patients (58%) required a further dose escalation of at least 100%. On completion of the study after 15 days, Donner and colleagues estimated the conversion ratio for oral morphine to TTS-fentanyl at 70:1. Of interest, none of the patients required a dose reduction during the fentanyl phase of the study.

Pharmacokinetic studies indicate a relative steady state (pseudo-steady state) 15 hours (210) and 16 to 20 hours after application of the patch (211), suggesting the possibility of early titration with TTS-fentanyl at 24-hour intervals. Korte and colleagues (203) investigated the conversion doses of oral morphine to TTS-fentanyl according to the clinical experiences of Zech and colleagues (212) and dose finding requirements by day-to-day titration with TTS-fentanyl in 39 cancer patients. The investigators assumed satisfactory pain relief when the mean daily visual analog score (VAS) value was less than 35 mm as previously defined by Miser and colleagues (213). If pain relief was inadequate after 24 hours, they added further TTS-fentanyl if no toxicity or intolerable side effects were present. Patients repeated titration every day with an additional 25 µg per hour until they achieved adequate pain control. Patients changed patches every 3 days unless pain profiles suggested changes at 2-day intervals. Mean VAS scores improved significantly from day to day during week 1. Both dose increases of TTS-fentanyl and the use of rescue medication were necessary to maintain pain control. Forty-nine percent of patients needed one or more dose increases during days 1 to 3; 38% needed two or more increases during days 1 to 6; and 26% needed three or more dose increases during days 1 to 9 of treatment. The goals of pain control with day-to-day titration were almost reached by day 2 and were completed by day 5. No compliant outpatient experienced severe side effects. The authors demonstrated a way to titrate TTS-fentanyl effectively and safely on a day-to-day basis with an increased initial dose and adequate patient monitoring. Note, however, that it took a relatively long time to optimize pain control.

In another study, the long-term efficacy of TTS-fentanyl was evaluated in 51 cancer patients by Donner and colleagues (201). Seventy-five percent of patients had metastases. Patients used TTS-fentanyl for an average of 158 days (range, 15 to 855 days). Seventy-three percent of patients received treatment for a period of 3 to 12 months. The investigators discontinued TTS-fentanyl in 16% of patients because of insufficient pain relief. In these patients, the last TTS-fentanyl dosage was a

mean of 233.3 µg per hour (range, 25 to 700 µg per hour). In addition, four patients returned to oral morphine therapy. At the start of therapy, patients needed 69.5 µg per hour of TTS-fentanyl (25 to 250 µg per hour). At the end of therapy, the dosage was 167.7 µg per hour (25 to 1,000 µg per hour). Most patients changed patches every 3 days, but 24% of patients required more frequent changing (varying from 48 to 60 hours). Pain relief was good throughout the study. The seventy-fifth percentile of the VAS scores ranged between 2.5 and 3.4. Only 15% of patients did not require additional oral opioid (liquid morphine). Constipation decreased during the transdermal therapy. At the end of the study, 70% of therapy days were free of constipation. In addition, the need for laxatives decreased during therapy.

Payne and colleagues (206) compared pain-related treatment satisfaction, patient-perceived side effects, functioning, and well- being in 504 patients with advanced cancer who received either TTS-fentanyl or sustained-release oral forms of morphine. The mean dose of fentanyl was 84.4 µg per hour (range, 25 to 400 µg per hour). For those who received morphine, the mean 24-hour dose was 195 mg (range, 15 to 3,000 mg). There were no significant differences between measures of pain intensity and sleep adequacy. However, patients who received TTS-fentanyl were more satisfied with their pain medication than those who received oral morphine. Patients receiving fentanyl also experienced a significantly lower frequency and effect of pain medication side effects. However, because assessment of side effects was global in nature, the investigators could not distinguish between the frequency, effect, or both of individual, particular side effects.

As a rough guide for conversion, consider the 8-hourly dose of MS Contin equal to the µg per hour dose of TTS-fentanyl. For example, if a patient is receiving MS Contin, 75 mg three times a day, then the TTS-fentanyl conversion dose is 75 µg.

The TTS-fentanyl system may be considered a first-line treatment modality for moderate to severe cancer pain. Appropriately used and titrated, pain control appears satisfactory with apparent high levels of patient satisfaction. In situations in which compliance may be a problem, the system may have particular advantages. In addition, the system may be used for patients who are unable to take medications by mouth.

Oral Transmucosal Fentanyl

Oral transmucosal fentanyl citrate (OTFC) units consist of a lozenge with a handle and are of uniform size and shape. Product manufacture involves dissolving fentanyl in a sucrose solution, pouring it into a mold, and allowing it to harden on a handle. Fentanyl is compounded in a hardened matrix form on a stick. The lozenge is available in a variety of strengths, from 200 to 1,600 µg. In the mouth, the unit dissolves in saliva: A portion of the fentanyl diffuses across the oral mucosa, and the patient swallows the rest, which is partially absorbed in the stomach and intestine. Patients must smear the lozenge on either the buccal mucosa or under the tongue and not swallow. Smearing avoids first-pass metabolism in the liver, whereas swallowing does not. Ideally, the lozenge should be consumed within a 15-minute period. Onset of action is rapid (5 to 15 minutes). Peak analgesic effect is 20 to 30 minutes, and duration is approximately 2 hours. Of the total available dose, 25% is absorbed transmucosally over a 15-minute period, and an additional 25% is absorbed through the gastric mucosa during the next 90 minutes (214). Potential advantages of this drug delivery system include rapid-onset analgesia, transmucosal absorption (i.e., no need to swallow), ease of titration, and ease of use.

Farrar and colleagues (215) evaluated the effect of OTFC for breakthrough pain in a double-blind, randomized trial of 130 patients. All subjects were started on the lowest dose of OTFC (200 µg) and then titrated to an effective dose for breakthrough pain up to the maximum available dose (1,600 µg) over a 2-week period. All subjects who were able to achieve adequate relief with OTFC advanced to the double-blind phase, which was designed as a 10-period crossover. In this phase, each subject received a box of 10 sequentially numbered units. Of the 10 units, seven contained fentanyl at the same dose found effective for that patient during the titration phase, and three were placebo units. Instructions told patients to consume the total dose in 15 minutes and to take rescue medication after 30 minutes for inadequate pain relief. The pain types treated in the study included somatic (53%), visceral (31%), neuropathic (15%), and unknown (1%). Of the original 130 patients, 93 completed the open-label titration phase and 37 did not. Twenty patients did not complete the full 10 doses of the double-blind phase. Eighty-six patients were included for efficacy comparisons, and six were not because of protocol violations. In these patients, patients receiving placebo required significantly more additional rescue medication than those treated with active drug (34% versus 15%). OTFC produced significantly larger changes in pain intensity and better pain relief than placebo at all time points (two-sided $p < .0001$). The most frequent opioid-related adverse events reported as possibly related to OTFC were dizziness (17%), nausea (14%), somnolence (8%), constipation (5%), asthenia (5%), confusion (4%), vomiting (3%), and pruritus (3%). The authors concluded that the OTFC drug-delivery system is highly efficacious for the treatment of cancer-related breakthrough pain with a large margin of safety in patients on chronic opioid therapy. Of interest, the dose of OTFC required to control breakthrough pain is not predicted by the around-the-clock opioid dose (216). Each patient should be titrated to a dose that is effective for control of breakthrough pain.

The Food and Drug Administration has approved the use of transmucosal fentanyl for the management of procedure-associated pain and for the management of breakthrough pain in cancer patients. The main clinical application for this preparation may be for breakthrough and incident pain in the cancer patient (217), but further clinical evaluation is under way. The concurrent use of TTS- fentanyl patches with OTFC units appears attractive and merits future study.

Tramadol

Tramadol is a synthetic 4-phenyl-piperidine analog of codeine. It is a central analgesic with a low affinity for opioid receptors (218,219,220 and 221). There are few reports of the use of tramadol in cancer pain. Wilder-Smith and colleagues (222) compared the analgesic efficacy of tramadol and morphine in 20 cancer patients. After 4 days, the mean daily doses were 101 ± 58 mg of morphine and 375 ± 135 mg of tramadol, indicating a relative potency of 4:1 with oral dosing. Side effects such as nausea and constipation were fewer with tramadol, but pain control was less satisfactory. Patients with cancer who are most likely to benefit from tramadol are those with mild to moderate pain not relieved by acetaminophen who cannot tolerate NSAIDs and wish to avoid taking opioids.

Opioids Not Recommended for Routine Use in Cancer Pain Control

I recommend avoiding several opioids for the control of moderate to severe cancer pain. These are meperidine, buprenorphine, pentazocine, butorphanol, dezocine, and nalbuphine. Meperidine has a short half-life, and its metabolite, normeperidine, is toxic (223). Partial agonists such as buprenorphine are of limited benefit because of their low maximal efficacy. Above a certain dose, toxicity without additional analgesia is observed. Mixed agonist-antagonists such as pentazocine, butorphanol, dezocine, and nalbuphine present other problems. Although these agonist-antagonists are often classified as a kappa-receptor agonist and a mu-receptor antagonist, they are more accurately described as a partial agonist at both kappa and mu receptors. These agents have a low maximal efficacy and have the potential to reverse mu-receptor analgesia, and even precipitate a physical withdrawal syndrome when taken by patients already receiving full agonists such as morphine (224). In addition, agonist-antagonist opioids have a ceiling effect (218,224). Propoxyphene is a poor choice for routine use because of its long half-life and the risk of accumulation of norpropoxyphene, a toxic metabolite (219).

Selection and Dosing of Oral Opioids

It has become common practice in the United States to initiate opioid therapy with a commercial product that contains an opioid combined with aspirin or acetaminophen. If pain worsens, the dose of these products can be increased only until the safe maximum level of the nonopioid component is reached. The value of codeine is limited by the increasing incidence of side effects at doses above 1.5 mg per kg. Patients who fail to obtain adequate analgesia at the maximum doses of a combination product typically change to opioids commonly used for the management of moderate to severe pain (see Table 36-5).

For moderate to severe pain, morphine is the opioid of first choice. Because great intraindividual variability exists in the patient response to the different opioids, any of the other opioids may yield a more favorable balance between pain relief and side effects. Sometimes sequential trials are necessary to identify the optimal drug. One can calculate equivalent doses of other opioids from the relative potencies listed in Table 36-11. When using morphine, employ an oral-to-parenteral relative potency ratio of 3:1 for these calculations. Patients already receiving regular opioid doses and switching to another opioid should receive 50% to 75% of the equianalgesic dose initially because cross-tolerance is incomplete. It is wise to plan a dose reduction of approximately 25% for the elderly or medically frail patient. When switching to methadone particularly, when the patient is requiring high doses of opioids, exercise extreme care. Titration of the opioid dose usually is necessary at the start of therapy and repeatedly during the patient's course. At all times, address inadequate pain relief through gradual escalation of the dose until adequate pain relief is reported or intolerable and unmanageable side effects limit further dose escalation. Titration in this fashion requires repeated assessment and the ongoing management of side effects.

Drug	Equianalgesic dose (mg)[a]	
	Oral	Parenteral
Morphine	30	10
Hydromorphone	6	2
Oxycodone	20–30	NA
Methadone	10[b]	10[b]
Levorphanol	2–3[b]	2[b]
Codeine	130[c]	75

NA, not available in the United States
[a]Suggested doses are guidelines only. Doses are based on chronic opioid use.
[b]Particular care with titration is recommended as doses may need to be reduced significantly when steady-state levels are reached after 2 to 3 days.
[c]Codeine doses greater than 65 mg may be associated with significant constipation.

TABLE 36-11. Opioids used orally or parenterally to treat cancer pain

Doses can become extremely large during titration for cancer pain relief. The absolute dose is not important as long as therapy is not compromised by dose-limiting toxicity, cost, or excessive inconvenience produced by the number of pills. The rate of titration depends on the severity of pain, appearance of side effects, or both. Patients who present with severe pain may be best managed initially by repeated intravenous boluses of opioid until pain is partially relieved. In contrast, patients with relatively moderate pain can undergo dose increments of 30% at intervals greater than those required to approach steady state after each change—for example, every 24 to 48 hours for morphine, every 72 hours for methadone, and every 48 hours for TTS-fentanyl.

Most patients have constant or frequently recurring pain and respond best to a fixed dosing schedule (around-the-clock dosing). As- needed dosing alone may prove helpful, however, in selected circumstances, such as the start of opioid therapy in the opioid-naive patient (see Methadone, previously in this chapter), during periods of rapidly declining pain (such as may follow radiation treatment), and in the treatment of patients with intermittent pain.

The following rules provide a guide to dose titration with controlled-release morphine:

- If the every-12-hour interval dose is less than 60 mg, then titrate upward by 15 mg.
- If the every-12-hour interval dose is between 60 and 120 mg, titrate up by 30 mg.
- If the every-12-hour interval dose is between 120 and 300 mg, titrate up by 60 mg.
- If the every-12-hour interval dose is more than 300 mg, titrate up by 100 mg.

Another useful approach to dose titration involves the concurrent use of a regularly scheduled dose and a rescue dose. The rescue dose is a supplemental dose provided as needed to treat breakthrough pain. The ideal drug for breakthrough pain should be short-acting, identical to the regularly scheduled drug, and the dose may be equivalent to approximately 10% to 20% of the total daily dose, offered every 2 hours as needed. The number of rescue doses required daily could then guide the size of the increment in the regularly scheduled dose as it is titrated upward.

Patients should be advised to follow a 1:2:3 regimen (i.e., take one tablet initially, and if ineffective in 2 hours, take two tablets, and if ineffective in 2 hours, then take three tablets). Repeat this dose every 2 hours until either the pain is controlled or side effects are encountered. Alternatively, if three tablets every 2 hours control pain but cause side effects, the patient may reduce the number of tablets by one tablet every 2 hours until the side effects become tolerable. Once pain is controlled on the short-acting medication, increase the dose of the controlled-release preparation appropriately. This regimen has been effective for the majority of situations in which rescue medication is required. It is easy for both patients and family members to remember.

Opioid-Related Side Effects

The side effects or toxicities associated with opioids can significantly distress the patient and impair normal functioning. Effective opioid intervention requires careful dose titration targeted at an optimal pain relief to side effect ratio. Table 36-12 lists the major side effects and indicates the frequency with which they occur. Most patients report more than one side effect, although a few report only constipation.

Side effect	Frequency with oral long-acting opioids	Does toxicity diminish with tolerance?
Constipation	Very common	No
Sedation	Common	Yes
Nausea	Common	Yes
Cognitive impairment	Occasional	Yes
Pruritus	Occasional	Yes
Dysphoria	Occasional	Yes
Hypnogogic imagery	Rare	Yes
Myoclonus	Rare with oral route	No
Respiratory depression	Very rare	Yes

TABLE 36-12. Opioid-related side effects

The distress imposed by one or more side effects typically determines the upper limit or the rate of dose titration. Patients with similar pain problems differ markedly in side-effect burden even when they receive similar dosages of a single opioid drug. For a given patient, a specific drug may cause a heavy side-effect burden, whereas an alternative drug delivered at equianalgesic concentrations may produce a mild side-effect burden. For this reason, adept prescribers often ask about patients' previous experiences with opioid drugs in an attempt to avoid trial-and-error drug selection.

Because marked interindividual differences exist among patients, the best predictor of patient response to an opioid is the patient's past experience with that drug. Although the side-effect burden depends in part on the idiosyncratic fit between the patient and the drug administered, it depends primarily on dose magnitude and the rate of dose increase. With increments in drug dosage or rapid rates of titration, the probability of a particular side effect occurring typically increases and the severity of any existing side effect increases as well.

The severity of the side-effect burden also depends on the duration of drug use. Fortunately, patients develop tolerance to most side effects more rapidly than to pain relief (220). Consequently, the longer a patient uses an opioid, the fewer the side effects and the less severe persisting side effects become.

Assessment and treatment of side effects are basic aspects of opioid therapy. When side effects are strong and poorly controlled, patients are likely to report poor pain relief as well. Patients tend to take opioids on an as-needed rather than an around-the- clock basis. Often, they use drugs only when the pain becomes unbearable. Moreover, intermittent drug use prevents patients from developing tolerance to side effects, so bothersome side effects never abate. Side effects are also a significant source of discomfort and suffering in their own right. The extremely nauseated patient feels miserable, tends to avoid comforting social interactions, and cannot engage in productive activity. The cognitively impaired patient cannot cope effectively with the simple mental demands of everyday life and becomes increasingly dependent on others. In these and other ways, untreated side effects compromise the quality of life in patients using opioids for pain relief.

Opioid-related side effects occur because of opioid receptor pharmacodynamics, the production of toxic metabolites, or both. Activation of mu $_2$-receptors appear to cause certain side effects, such as sedation and respiratory depression, but other side effects are linked to other receptor types or subtypes (221). Evidence suggests that kappa-receptor agonism contributes to dysphoria as well as to pain relief (218). Sigma-receptor agonism produces purely negative effects: dysphoria, depersonalization, and psychotomimetic experiences such as hypnogogic imagery (225). The sigma receptor is a naloxone-inaccessible opioid receptor, so standard

opioid receptor antagonism does not relieve these side effects. However, this receptor has a high affinity for haloperidol, and this may antagonize negative side effects (226).

Some side effects result from the toxic metabolites associated with a particular drug. The side effects associated with the accumulation of normeperidine and norpropoxyphene are well recognized (219,223). The role of M3G, a metabolite of morphine, is less clear because it does not bind to opioid receptors and yet it seems to exert antagonist effects (227,228). Some authors speculate that the antagonist effects of M3G are responsible for some of morphine's side effects, including myoclonus (227).

Preventing or Minimizing Opioid-Related Side Effects

Appropriate dosing of opioids requires minimizing or preventing opioid-related side effects (see Dosing of Oral Opioids, earlier in this chapter). For patients with constant pain, the early use of a long-acting in preference to short-acting opioids as soon as dose titration permits may help to attenuate side effects. If side effects are significant, the clinician should allow time for tolerance to develop. This may require a period of 3 to 7 days. Protecting the patient from severe side effects during this period is appropriate and does not prevent tolerance development. For example, a patient with nausea could benefit from a 1-week course of antiemetic medication at the outset of opioid therapy.

If side effects do not diminish satisfactorily over time, there are two alternatives: changing drugs and introducing supplementary medications that control the side effects. Changing from one opioid to another may enhance pain relief and reduce opioid-related side effects, particularly if incomplete cross-tolerance to opioid effect is experienced (185,229,230,231 and 232). In some cases, changing the route of administration for a particular drug, such as morphine, may eliminate certain difficult side effects (233). It is possible to alleviate many of the most difficult side effects pharmacologically when necessary. For example, administering methylphenidate can help protect the cognitive functioning of patients using high doses of opioids (234,235). Table 36-13 lists side effects and their treatments.

Side effect	Treatment
Constipation	Stool softener, laxative
Sedation	Methylphenidate
Pruritus	Diphenhydramine, hydroxyzine
Nausea	Prochlorperazine, haloperidol, metoclopramide, ondansetron, antihistamine
Dysphoria	Haloperidol
Hypnogogic imagery	Haloperidol
Cognitive impairment	Methylphenidate
Respiratory depression	Naloxone
Myoclonus	Clonazepam, dose reduction, opioid rotation

TABLE 36-13. Pharmacologic treatments for opioid-related side effects

In cancer patients, certain pathophysiologic conditions commonly contribute to side-effect problems or masquerade as side-effect problems. For example, renal insufficiency in patients using morphine can lead to accumulation of M6G, which in turn can exacerbate side effects. Nausea is a frequent opioid toxicity, but it has other potential causes: gastric irritation, constipation, or other changes in gut motility, chemotherapy, or hypercalcemia induced by bone metastases. Similarly, sedation and confusion may accompany opioid use, but other potential causes in the cancer patient such as raised intracranial pressure, metabolic disturbances (e.g., hypercalcemia), sepsis, or concomitant drug use merit consideration. Opioid-induced changes in mental status become less probable when the patient has been on a stable dose without recent significant dose escalation.

Opioid-induced gastrointestinal problems may manifest as nausea and vomiting, mild abdominal discomfort, constipation, gaseous abdominal distension, and functional colonic obstruction. Kaufman and colleagues (236) suggest that opioids may cause constipation in part by slowing colonic transit in the proximal colon and by inhibiting defecation. Opioids also affect the gut by increasing electrolyte and water absorption in the small intestine and colon and by increasing tone in the ileocecal and anal sphincters. This results in delayed passage of increasingly viscous stool.

Opioid receptors exist on gut smooth muscle and at all levels of nervous input to the intestine; mu- and delta-receptors appear to be the most important in gut motility. In animals, opioid effects on the gut involve central and peripheral receptors (237,238). Oral and parenterally administered opioids produce constipation; subcutaneous morphine reduces stool frequency and slows transit (236). Undoubtedly, opioid receptors in the gut wall are accessible not only to opioids in the lumen but also to those in the circulation.

The constipating effects of morphine probably result mainly from its action on colonic motility. Morphine stimulates colonic motility in humans by action on both central and peripheral sites (239). This increase in colonic motility and the delay in colonic transit are associated with a reinforcement of tonic contractions and reduced propulsive waves. Opioid peptides participate in the colonic motor response to eating in humans and animals (239).

When healthy volunteers take opioids in single doses, opioid analgesics impair reaction time, muscle coordination, attention, and short-term memory sufficiently to affect driving and other skilled activities. However, such studies do not correspond to the situation of cancer patients who develop tolerance to side effects. Psychomotor and cognitive dysfunction in cancer patients falls into two main categories according to etiology: disease-induced factors (metabolic disturbances, brain metastasis, pain, and so forth) and treatment-related factors (drugs, antineoplastic therapy, and so forth) (240). Bruera and colleagues found that cancer patients receiving chronic oral opioid therapy had prolonged continuous reaction times, and opioids seemed to be mainly responsible for the prolongation (223). Significant dose escalations of short-acting opioids (more than 30%) over a short period of time (3 days) transiently impaired psychomotor and cognitive functions in cancer patients. The impairment disappeared 1 week after the increase.

Clemons and colleagues (241) studied the effects of morphine on alertness and cognition in patients with advanced cancer. Twenty-nine subjects were recruited into three groups: healthy volunteers (16 subjects without cancer and not on opioids), inpatients and outpatients with advanced cancer not taking any opioids (six subjects), and inpatients and outpatients with advanced cancer on a stable and regular dose of oral morphine (seven subjects). Subjects were tested with a battery of tests designed to test the global effects of alertness on cognitive function on either five or six occasions. The New Adult Reading Test, Reaction Time, and Stroop Colour-Word tests failed to show any difference between the two cancer groups, whereas they did show a difference between the healthy control subjects and the cancer patients, suggesting that the tests were sensitive to the effects of cancer but not to the effects of morphine. The Stroop Colour-Word test is a complex measure of cognitive function, and the difference between healthy volunteers and cancer patients receiving no morphine suggests that advanced cancer itself may be impairing performance. The authors noted that the cancer with morphine patients subjectively felt less generally well, less alert, less active, more depressed, had poorer concentration, and were more anxious than either of the other groups.

Vainio and colleagues (242) examined the effects of continuous morphine medication on the driving ability of cancer patients. They conducted psychological and neurologic tests, originally designed for professional motor vehicle drivers, in two groups of cancer patients who were similar apart from their experience of pain. Twenty-four patients received continuous morphine (mean, 209 mg of oral morphine daily) for cancer pain, and 25 were pain free without regular analgesics. Although the results were a little worse in the patients taking morphine, there were no significant differences between the groups in intelligence, vigilance, concentration, fluency of motor reactions, or division of attention. Of the neural function tests, reaction times (auditory, visual, associative), thermal discrimination, and body sway with eyes open were similar in the two groups; only balancing ability with closed eyes was worse in the morphine group. These results indicate that in cancer patients receiving long-term morphine treatment with stable doses, morphine has only a slight and selective effect on functions related to driving.

Opioids can cause or exacerbate confusion, and these effects may range from mild impairment in concentration to frank delirium with disorientation, disorganized thinking, perceptual distortions, and hallucinations. Hallucinations are the product of sigma receptor activation, and they can occur in the context of intact cognitive function (243). Obviously, when this problem occurs it is important to consider other causes of altered mental status. When a confusional state is caused by opioids, it generally follows a recent increase in dose and usually resolves with tolerance or as the dose is reduced. Rapid discontinuation of the opioid results in severe pain, withdrawal symptoms, and possible exacerbation of confusion; it should be avoided. Dysphoria is probably more common than euphoria after opioid administration in

patients with cancer.

Opioid Tolerance in Cancer Pain

The development of tolerance to opioids and its effect on analgesia is a controversial area in cancer pain management (134). Tolerance is a complex pharmacologic phenomenon characterized by the need for higher opioid doses to maintain constant effects. It represents the accommodation of the CNS to the presence of drugs that look like the brain's own endogenous ligands. The interaction of opioid systems with many neurotransmitters [serotonin, dopamine, noradrenaline, glutamate, gamma-aminobutyric acid (GABA), and so forth] or neuromodulators (cholecystokinin, neuropeptide FF, and so forth) may change during the development of morphine tolerance, dependence, or both. The central activation of NMDA receptors is involved in the development of morphine tolerance (180). Noncompetitive NMDA receptor antagonists can attenuate the development of tolerance to the analgesic effect of morphine without affecting acute morphine analgesia (244). Intracellular events (increase in Ca^{++} concentration, production of nitric oxide, and possibly regulation of gene expression) initiated by NMDA receptor activation may initiate neuronal plastic changes in the CNS and thus mediate morphine tolerance (181). With chronic morphine use, a functional uncoupling of opioid receptors from guanosine triphosphate–binding proteins (G proteins) occurs and the acute effects of the drug decrease. As a result, triggering the second messenger response requires higher doses of opioid (245).

Any patient who requires dose escalation for pain relief, or who has experienced an opioid side effect (e.g., sedation) that has disappeared with repetitive dosing, is showing tolerance. Progression of malignancy with increased nociception, a modification in pain mechanisms not well controlled by opioids (e.g., neuropathic pain resulting from tumor invasion of nerve plexuses), or both may lead to opioid dose escalation and thus complicate identification of true opioid tolerance. Several authors believe that escalation of doses in cancer patients results from disease progression rather than from development of tolerance (246,247). Although tolerance to the different opioid effects develops at different rates, it is usually possible to titrate the opioid dose to the amount that works for the individual patient without encountering any dose-limiting side effects. Tolerance to respiratory depression develops rapidly. Tolerance to the constipating effects of opioids, a largely peripheral effect, does not usually develop. Tolerance to nausea, vomiting, or both typically appears within 2 to 3 days. Opioid-induced sedation is usually transient (223). Dysphoria, confusion, and hallucinations generally occur with rapid opioid dose escalation and resolve with either dose stabilization or reduction.

Intrathecal Morphine and Tolerance

Repeated intrathecal or epidural morphine administration has produced conflicting results. Ventafridda and colleagues (248) observed a rapid loss of effectiveness of 1 mg of morphine during a 3- to 5-day sequence of once-daily intrathecal injections in cancer patients. Greenberg and colleagues (249) reported one case of tolerance to continuous intrathecal infusion of morphine via an Infusaid pump for a patient with painful metastatic lumbosacral plexopathy. The effective dose increased from 1 mg during the trial period to 10 mg per day 1 week later and 150 mg per day 3 months later. In a retrospective study of the doses of morphine administered intrathecally by chronic infusion in a population of 163 patients treated by 19 physicians, Yaksh and Onofrio (246) reported a marked time- dependent increase from 4.8 ± 0.4 mg per day at week 1 (n = 130), to 16 ± 4 mg at 24 weeks (n = 33), and to 21 ± 9 mg at 52 weeks (n = 10). In a series of 35 patients treated with continuous intrathecal morphine (mean, 5.4 months) for intractable cancer pain, Penn and Paice (250) reported that the occurrences of tolerance can be managed effectively. Sallerin-Caute and colleagues (251) retrospectively examined the records of 159 patients with refractory cancer pain treated with intrathecal morphine for the development of opioid tolerance. The mean follow-up period was 95 days (range, 5 to 909 days), the mean starting dose of intrathecal morphine was 2.69 mg (range, 1.0 to 7.5 mg), and the mean terminal dose was 7.82 mg (range, 1 to 80 mg). Only a moderate increase in daily dose of intrathecal morphine was required during the course of treatment (a two- to threefold increase for a 3-month period). The dose increment was similar for patients followed up for more or less than 60 days. These studies suggest that, although tolerance to the effect of spinal morphine may develop in the cancer patient, tumor progression is much more likely to increase opioid requirements.

Opioid Rotation in Cancer Pain

A change in drug, which is known as *opioid rotation* or *sequential opioid trials*, has become an accepted strategy to address an initially poor response to a specific opioid. The approach derives from the observation that there is large interindividual variation in the pattern of adverse effects produced by different opioids, and that the balance between analgesia and adverse effects improves after a switch to an alternative drug. The equianalgesic dose ratios largely represent average data from controlled single-dose studies in selected populations. These values are approximations in the setting of long-term administration of the drugs to medically ill patients. The ratios also fail to account for the possibility of incomplete cross-tolerance, which would render the new drug more potent than anticipated and the effect on administration of either unrelieved pain or a predisposition to opioid toxicity. Guidelines for the use of the equianalgesic dose table include a standard reduction in the calculated equianalgesic dose, which requires further adjustment based on the clinical characteristics of the patient. The new dose becomes the starting point for the process of dose titration.

These guidelines require further adaptation for two special cases: a switch to methadone (which yields a potency much greater than expected) and conversions that involve the TTS-fentanyl system. Morphine's side effects, particularly sedation, cognitive impairment, and myoclonus at high doses, have provoked the use of opioid rotation to alternatives such as methadone and hydromorphone. This involves equianalgesic dose tables. These tables generally propose a dose ratio of 5:1 between morphine and hydromorphone. In the case of a change from subcutaneous hydromorphone to methadone, the tables indicate dose ratios ranging from 1:6 to 1:10. Morphine and hydromorphone are commonly used opioid analgesics for cancer pain. Lawlor and colleagues (252) suggest that hydromorphone is five times more potent than morphine when given second, but is only 3.7 times more potent when given first. Bruera and colleagues (185) showed that the hydromorphone to methadone ratio correlated with total opioid dose (correlation coefficient = 0.41, $p < .001$) and was 1.6 (range, 0.3 to 14.4) in patients receiving more than 330 mg of hydromorphone per day before the change, versus 0.95 (range, 0.2 to 12.3) in patients receiving an average of 330 mg of hydromorphone per day ($p = .023$).

The process of switching from a high-dose opioid agonist to methadone is complex and should only be attempted by physicians with experience in cancer pain management. Even among experienced physicians, occasional serious toxicity can occur during the administration of methadone (253). Contrary to expectations, toxicity occurs more frequently in patients previously exposed to high doses of opioids than in patients receiving low doses. Manfredi and colleagues (178) described the conversion of four patients receiving high continuous infusions of either morphine or hydromorphone to methadone. All four patients had excellent pain relief without significant side effects at a dose that, according to the conversion charts, was approximately 3% of the calculated equianalgesic dose of hydromorphone. When converting from continuous intravenous hydromorphone to continuous intravenous methadone, use much lower doses than those suggested by the opioid conversion charts as starting doses. This author reported on the conversion of a patient receiving approximately 2,000 mg per day of morphine intravenously by PCA and continuous infusion to methadone by the same treatment modalities (179). Although the patient required 1,800 mg of methadone on the first day of conversion, the total daily dose decreased by one-tenth the initial dose on day 3 once the patient reached steady-state plasma levels.

Bruera and colleagues (185) provide some guidelines for the conversion of patients from high-dose oral opioids to oral methadone. They recommend decreasing the previous opioid dose by one-third over the first 24 hours and replacing it with methadone using an equianalgesic dose ratio. One milligram of oral methadone is equal to 10 mg of oral morphine (i.e., a patient receiving 1,000 mg of oral morphine per day will switch to 660 mg of oral morphine per day plus 33 mg of oral methadone during the first day). Administer methadone every 8 hours by the oral route. During the second day, if pain control is adequate, the patient requires a further one-third decrease in the dose of the previous opioid. The dose of the methadone should only increase if the patient experiences moderate to severe pain. Manage transient episodes of pain with intermittent rescue doses of short-acting opioids. During day 3, discontinue the final one-third of the previous opioid and maintain the patient on regular methadone every 8 hours, plus approximately 10% of the daily methadone dose as an extra dose orally for breakthrough pain. Assess pain and methadone requirements frequently until a stable methadone dose is reached. Until the equianalgesic dose ratio of parenteral and oral opioids to methadone is clearly established, patients receiving high doses of oral or parenteral opioids who require conversion to methadone should undergo this conversion only under close supervision and preferably in an inpatient environment. In general, the safe use of methadone to control cancer pain requires meticulous follow-up care and anticipatory downward dose titration.

INTERVENTIONAL PAIN MANAGEMENT

Physicians managing terminally ill cancer patients with pain generally turn to interventional pain management only after medication management has failed. Failure of therapy exists when the patient considers the pain relief inadequate and cannot obtain further relief without unacceptable side effects. In some situations, the use of interventional modality can be less invasive and troublesome to the patient than continued aggressive medication management. Interventional strategies comprise two categories: ablative and augmentative modalities.

Ablative Modalities

These modalities involve blocking nociceptive transmission by neurolytic injections or surgical lesions. The goal is to use chemicals (e.g., phenol, alcohol), heat, cold, or a scalpel to destroy nociceptive pathways and thereby achieve pain relief. Surgical sectioning of nervous tissue and radiofrequency denervation may provide more complete or longer lasting pain relief than chemicals.

Neurosurgical Procedures

The common ablative neurosurgical procedures available for the management of cancer pain are discussed in detail in Chapter 105, Chapter 106, Chapter 107 and Chapter 108. The aggressive use of opoids has dramatically reduced the role of ablative procedures since 1980.

pinal Neurolysis

Both intradural (especially in the cauda equina) or extradural (at the spinal foramina) blocks or denervations introduce lesions at the nerve root level (see Chapter 104). Techniques used include injections of phenol or alcohol, electrodes for radiofrequency or cryoablation destruction, or open surgical section of nerves.

Spinal neurolysis may be an effective method for pain control in cancer patients with limited life expectancy, who have nociceptive pain covering two or three dermatomes (especially in sacral, perineal, and thoracic areas), and in patients who are severely compromised or who have absent bladder, bowel, or bladder and bowel function. Intrathecal neurolysis with small volumes of alcohol or phenol requires careful positioning to place the affected sensory nerve root uppermost (for alcohol) or in the most dependent position (for phenol). Patient movement during or shortly after injection can spread the drug to other dermatomes or to motor roots. The popularity of spinal neurolysis has waned with the increasing use of neuraxial infusional therapy. Randomized, prospective studies on the effects of spinal neurolysis on pain relief are lacking. Indeed, much of the published data in this area lack uniform patient selection, inadequately report preblock analgesic therapy, or inconsistently evaluate outcome and inadequately follow up with patients in the long term. Based on the studies available, good pain relief may be anticipated in approximately 51% of appropriately selected patients, moderate pain relief in 23%, and poor relief in 26% (254,255). Gerbershagen (256) showed that the success rate of intrathecal alcohol neurolysis declined with repeated injections, with approximately 60% of patients obtaining some relief with the first block, 30% with a second block, 8% with a third block, and 3% with more than three blocks. Papo and Visca (254) reported on the use of phenol for subarachnoid rhizotomy in 290 cancer patients. They reported good results (pain free until death) in 40%, and fair results (reduced analgesic requirements or temporary complete relief) in 35%. Patients with pain localized to sacral dermatomes had the best results. Swerdlow (255) reviewed 13 reports of the results of phenol and alcohol rhizotomies and found good relief of pain in approximately 60% of patients. In reviewing results of his own patients, he found that pain relief lasted less than 2 months in one-half the patients and less than 1 month in 25%. Complications lasting longer than 1 week occurred in 15%.

Other Procedures

Autonomic nervous system blocks for visceral pain, although often overlooked, can prove quite effective. In general, these blocks should be considered as analgesic adjuvants and not definitive pain relief treatment. These procedures should allow patients to lower drug dosages and thereby reduce side effects, or to experience better pain relief from current dosages to improve their quality of life. It is inappropriate to promise patients permanent relief, because their disease may progress and spread.

Celiac Plexus Block

The celiac plexus, originating from the sympathetic fibers of the thoracic splanchnic nerves, contains preganglionic splanchnic afferent fibers, parasympathetic preganglionic fibers from the phrenic and vagus nerves, and postganglionic sympathetic fibers, both efferent and afferent (see Chapter 104). It is the main target in abdominal visceral nociceptive innervation. Nociceptive impulses originating from all the abdominal viscera (pancreas, liver, stomach, intestine proximal to transverse colon, renal pelvis, proximal ureter, and gallbladder) are carried by visceral nerve fibers that pass through the celiac plexus and thoracic splanchnic nerves. The celiac plexus surrounds the axis of the celiac artery and overlaps the aorta at this level. The plexus varies anatomically in relation to the vertebral column from the bottom of T-12 to the middle of L-2 (257). The plexus is not a separate and distinct structure, but rather a dense network of ganglia around the aorta between the celiac and superior mesenteric arteries. It has a more consistent anatomic relationship with the celiac artery. It lies in areolar tissue behind the stomach, pancreas, and omental bursa; retroperitoneal in front of the aorta and crura of the diaphragm, and between the adrenal glands.

Interruption of nociceptive input at the level of either the celiac plexus or the thoracic splanchnic nerves is a potentially effective means of visceral pain control. Preblock computed tomographic (CT) scanning is useful to define the retroperitoneal anatomy and the vertebral relationship for the origin of the celiac artery.

De Cicco and colleagues (258) suggest that, when the celiac area is free from anatomic distortions, and the single-needle neurolytic celiac plexus block (NCPB) technique is used, the needle tip should be positioned cephalad to the celiac artery to achieve a wider neurolytic spread. It appears that only a complete (four-quadrant) neurolytic spread in the celiac area can guarantee long-lasting analgesia. When the celiac area is free from anatomic alterations and a single-needle precrural approach is chosen, the needle tip position in relation to the celiac artery may be critical.

Eisenberg and colleagues (259) performed a metaanalysis of the efficacy and safety of NCPB for cancer pain. Twenty-one studies were retrospective, one was prospective, and two were randomized and controlled. Sixty-three percent of cancer types were pancreatic in origin, and 37% were nonpancreatic. A bilateral posterior approach with volumes varying from 15 to 50 mL of 50% to 100% alcohol was the most common technique. Nonradiologically guided NCPB was performed in 32%; guidance was by CT in 28%, radiography in 34%, fluoroscopy in 5%, or ultrasound in less than 1%. Good to excellent pain relief resulted in 89% during the first 2 weeks after NCPB. Long-term follow-up beyond 3 months revealed persistent benefit. Partial to complete pain relief continued in approximately 90% of patients alive at 3 months post-NCPB and in 70% to 90% until death even if beyond 3 months post-NCPB. Patients with pancreatic cancer responded similarly to those with other intraabdominal malignancies. Common adverse effects were transient, including local pain (96%), diarrhea (44%), and hypotension (38%); complications occurred in 2%. This analysis suggests that NCPB has long-lasting benefit for 70% to 90% of patients with pancreatic and other intraabdominal cancers, regardless of the technique used, that adverse effects are common but transient and mild, and that severe adverse effects are uncommon.

Polati and colleagues (260) compared the efficacy of NCPB with pharmacologic management in a randomized, prospective, double-blind trial of 24 patients with pancreatic cancer. Immediately after the block, patients reported significant pain relief compared with those who received only pharmacologic management ($p < .05$), but long-term results did not differ between the two groups. NCPB was associated with a reduction in analgesic drug administration and drug-related adverse effects and was considered an effective tool in the treatment of pancreatic cancer pain.

Unfortunately, NCPB is associated with both minor and major complications. Documented side effects and complications from celiac plexus block include myofascial back pain (259), hypotension (259,260), intravascular injection (261), damage to the artery of Adamkiewicz (262,263) with a subsequent anterior spinal artery syndrome (264), paraplegia (265,266) secondary to either a spinal with a neurolytic solution or the spinal artery syndrome (267), retroperitoneal pain (268), reversible paraplegia (269), infection (270), loss of anal and bladder sphincter function (266), mild or persistent diarrhea (259,271), retroperitoneal fibrosis (272), pleural effusion (273), chylothorax (274), neurologic injury (footdrop) (275), intradiskal injection (276), and aortic pseudoaneurysm (270). Other possible problems include diskogenic backache, spinal or epidural spread of injected solution, postdural puncture headache, piercing of renal parenchymal tissue, pneumothorax, L-1 and L-2 neuralgia, lumbar plexus block, psoas muscle injection, spasm or damage to the celiac artery, intrabowel injection, bleeding into the peritoneal cavity or retroperitoneum, and thrombosis of any pierced vessels.

Davies (266) determined the incidence of major complications after NCPB. In 2,730 neurolytic blocks performed from 1986 to 1990, the overall incidence of major complications (paraplegia, bladder and bowel dysfunction) was 1 per 683 procedures. A number of other authors suggest that the incidence of a catastrophic sequela after NCPB to be in the region of 1 to 2% (259,277,278). Eisenberg and colleagues (259) quote a 1% incidence of neurologic complications, defined as lower extremity weakness, paresthesia, epidural anesthesia, and lumbar puncture, although it is difficult to determine the incidence for any particular complication. Unilateral paralysis caused by spread of neurolytic solution to the lumbar plexus (279) and bilateral paresis caused by subarachnoid injection have been reported (280). Galizia and Lahiri (281) presented a case of total bilateral sensory and motor loss in an L-1 to L-5 distribution immediately after celiac plexus block. Cherry and Lamberty (265) also reported paraplegia 2 hours after an alcohol injection. They speculated that the cause of the paraplegia was an anterior spinal artery syndrome caused by lumbar artery ischemia caused by spasm. Anterior spinal artery syndrome caused by anterior spinal artery ischemia results in a predominantly motor lesion, because the anterior two-thirds of the spinal cord, including the anterior horn cells, is supplied almost exclusively by the anterior spinal artery. Loss of pain and temperature sense, intact fine touch and position sense, and lower extremity paralysis are characteristic.

Transcrural and transaortic techniques attempt to minimize the neurologic complications occasionally reported with the retrocrural approach. Singler (282) and Hilgier and Rykowski (283) reported using the transcrural approach in 41 patients, with transient diarrhea as a side effect in some patients. In 148 patients who received the transaortic approach (284,285 and 286), transient orthostatic hypotension and diarrhea occurred as the main side effects in some. However, Kaplan and colleagues (287) reported on a case of aortic dissection as a complication of transaortic celiac plexus block. Sett and Taylor (270) reported the development of a traumatic pseudoaneurysm after the procedure. Naveira and colleagues (288) described the presence of an atheromatous plaque as a cause of resistance to needle passage during a transaortic celiac plexus block under CT guidance. Although the incidence of major vascular complications following this approach is largely undetermined, note that translumbar aortography, which punctures the lumbar aorta, has a mortality of 0.05%, with 27% of fatalities resulting from aortic dissection and aneurysm rupture (289), yielding an incidence of 1.35 per 10,000 procedures.

Some authors have recommended the use of CT scanning, guided by a radiologist, as a method of reducing or eliminating the morbidity associated with celiac neurolysis (290). However, one can surmise that not all adverse events from celiac plexus blocks were reported, regardless of the approach used. The only truly accurate determination of complication rates associated with celiac plexus blocks will be through a mandatory central registry of all procedures.

Superior Hypogastric Plexus Block

Pelvic pain associated with cancer arises from visceral involvement, from tumor extension to the muscles and bones of the pelvic wall, and from nerve involvement. Visceral pain may be a significant feature of advanced stage cancers of the pelvis such as cervical, bladder, prostate, and rectum. Relief of pain from pelvic organ nociception is possible because afferent fibers innervating these structures travel in the sympathetic nerves, trunks, ganglia, and rami. The superior hypogastric plexus is situated in the retroperitoneum, bilaterally extending from the lower third of the fifth lumbar vertebral body to the upper third of the first sacral vertebral body. The plexus innervates the pelvic viscera via the hypogastric nerves and inferior hypogastric plexuses.

The surgeon can divide the superior hypogastric plexus (presacral neurectomy) either at laparotomy (291) or at laparoscopy (292). Various nonsurgical approaches to the plexus are also possible. Plancarte and colleagues (293) used a bilateral percutaneous phenol nerve block approach for the management of intractable pelvic visceral pain. The block offers a practical, minimally invasive alternative for controlling cancer pain associated with tumor extension into the pelvic viscera. An incomplete block may occur in patients with retroperitoneal disease caused by limited spread of phenol (294). Despite the use of a unilateral needle insertion under CT guidance (295), the results are sometimes less favorable than those obtained with bilateral needle placement because of the bilateral distribution of pelvic pain (296). Ina and colleagues (297) advocated the deliberate passage of needles through the L-5 to S-1 disk (transdiskal approach) for patients with difficult anatomy and reported on the safe and successful use of this technique in eight patients. I have used this approach successfully on a patient with intractable pelvic visceral pain where a decubitus ulcer overlying the right posterior iliac crest prevented a bilateral percutaneous needle approach.

A study by de Leon-Casasola and colleagues (294) evaluated the efficacy and safety of the block in 26 patients with extensive gynecologic, colorectal, or genitourinary cancer who suffered uncontrolled, incapacitating pelvic pain. Neurolysis was carried out under fluoroscopy with bilateral needle placement and injection of 8 mL of 10% phenol on each side. Criteria for success of the block were (a) a decrease in VAS of at least 70%, or (b) pain intensity of less than $^{3}/_{10}$ during the first 2 weeks after the block, and (c) a decrease in oral opioid requirements of at least 30% with disappearance of bothersome side effects 2 weeks after the block. All patients reported a VAS of $^{10}/_{10}$ before the block, despite oral opioid therapy. Mean use of morphine before the first neurolytic block in all patients was 953 ± 722 mg per day with a median of 780 mg per day (range, 80 to 2,780 mg per day). Postprocedure patients in the success group demonstrated significantly less daily oral intake of morphine than patients in the failure group (736 ± 633 versus 1,443 ± 703 mg per day, $p = .02$; Table 36-14) Sixty-nine percent of patients had satisfactory pain relief (VAS less than $^{4}/_{10}$). Fifty-seven percent of these patients had satisfactory relief after one block, the remaining 12% after a second block. Thirty- one percent had moderate pain control (VAS $^{4}/_{10}$ to $^{7}/_{10}$) after two blocks and received supplementary neuraxial analgesia therapy. Both groups of patients experienced significant reductions in oral opioid therapy after the neurolytic blocks. Patients who had a good response during a 6-month follow-up period required no additional blocks. No intraoperative complications such as bladder puncture or retroperitoneal hematomas occurred. Two patients had transvascular neurolytic blocks without problems. There were no long-term complications such as urinary or fecal incontinence.

	Success	Failure	p Value
Preblock	736 ± 633	1,443 ± 703	.02
Postblock	251 ± 191	800 ± 345	.001
% Reduction in use	67	45	–
p Value	.001	.01	–

Values expressed as mean ± standard deviation.
From de Leon-Casasola OA, Kent E, Lema MJ. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Pain 1993;54:145–151, with permission.

TABLE 36-14. Comparison of oral doses of morphine before and after neurolytic blocks between the success and failure groups (mg/ day)

Neurolytic superior hypogastric plexus blocks are useful for patients with intractable visceral pelvic pain and have a low incidence of side effects or complications.

Augmentative Modalities

Augmentative modalities comprise infusional and electrical stimulation techniques (see Chapter 99, Chapter 100, Chapter 101, Chapter 102 and Chapter 103). Medication infusion has emerged as a major resource in cancer pain management, whereas electrical stimulation plays a relatively minor role. Much of the growing interest in infusion therapy results from improved technology for continuous infusion, using epidural, intrathecal, or intracerebroventricular (ICV) catheters connected to external infusion pumps, subcutaneous injection reservoirs, or implanted programmable infusion pumps. The use of infusion techniques can be cumbersome, labor intensive, and technically demanding. Most modalities require initial inpatient care and screening with a temporary device. After successful implantation and adequate pain control, domiciliary care requires the aid of a home infusion service with regular monitoring and adjustments by the managing physician.

Intravenous Opioid Therapy

Parenteral routes should be considered for patients who require rapid onset of analgesia, and for highly tolerant patients who require doses that cannot otherwise be conveniently administered (298). Intravenous opioids allow for rapid control of pain. Ideally, patients with severe, uncontrolled pain who require intravenous therapy should start treatment in a monitored inpatient setting. High doses of intravenous opioids via PCA or continuous infusion offer a means of rapidly controlling increasing severe pain. Because of high interindividual variation in opioid requirements, ascertain previous opioid exposure and consider the patient's tolerance. Flexibility for individual titration and the PCA modality are important considerations for patients requiring intravenous opioid therapy. Once patients begin opioid therapy for tumor pain control, titrate doses according to patient comfort or the appearance of intolerable side effects. For severe pain, employ a minimum lockout interval of 6 minutes. However, for patients with inadequate pain control and minimal opioid-related side effects, increase incremental doses by 50% every 4 hours. Order additional nurse-administered loading doses to achieve pain control. Once pain is under control, it is possible to continue therapy safely at home with the aid of a home infusion service (299,300and301).

Intravenous therapy can use any of several opioids: morphine, hydromorphone, fentanyl, sufentanil, and methadone. The use of opioids (e.g., methadone) with properties of NMDA receptor antagonism may improve pain control by attenuating the development of tolerance to morphine (181). This degree of incomplete cross-tolerance is probably unique to methadone (185) and may stem from isomers of methadone interacting with the NMDA receptor to reverse tolerance, and thereby reduce dose requirements (180).

Postoperative pain studies comparing opioid-related side effects failed to show a difference between morphine and hydromorphone (302) and morphine, meperidine,

and fentanyl (303). Coda and colleagues (304) found differences in efficacy and side effects for morphine, hydromorphone, and sufentanil in bone marrow transplantation patients with severe oral mucositis pain. The pain relief achieved in all three opioid groups was nearly equivalent, whereas measures of side effects, especially for the combination of sedation, sleep, and mood disturbances, were statistically lower in the morphine group than in the hydromorphone or sufentanil groups. Daily opioid consumption patterns showed continual dose escalation during the first week of therapy for all three opioids, coincident with worsening mucositis. Morphine consumption reached a plateau by day 5, whereas hydromorphone and sufentanil consumption continued to increase until days 7 and 9, respectively. Sufentanil dose requirement increased by approximately tenfold compared with morphine and hydromorphone, whose requirements increased only fivefold, suggesting the possibility of development of acute pharmacologic tolerance in some patients with this phenylpiperidine opioid.

Knowledge of intravenous opioid pharmacokinetics and pharmacodynamics helps guide opioid selection for the management of severe cancer pain. Coda and colleagues (305) defined the intravenous dose-effect characteristics of hydromorphone. Bolus doses of 10, 20, and 40 µg per kg of hydromorphone in human subject volunteers produced log linear dose-dependent analgesia. Onset of analgesia after an intravenous bolus was rapid, within 5 minutes, and the maximum analgesic effect was seen between 10 and 20 minutes after maximum plasma concentrations with analgesia lasting approximately 2 hours after a bolus injection. Hydromorphone is approximately three to five times as potent as morphine on a milligram basis (305,306). Peak CNS effects of methadone coincide with peak plasma concentrations, thus corresponding well to the observed early onset of action of 3 to 5 minutes after intravenous administration (192).

Morphine, on the other hand, has a slower onset of action, probably related to its relatively poorer lipid solubility. Hug and colleagues (307) administered an intravenous bolus of morphine to dogs and showed that the peak concentration in CSF did not occur for approximately 15 to 30 minutes. Fentanyl, a highly lipophilic opioid, has a rapid analgesic onset and time to peak effect (less than 6 minutes) (308). Intermittent boluses of opioids (such as fentanyl) with rapid onset and early peak effect offer advantages for patients whose predominant pain stems from activity or weight-bearing and occurs intermittently. Patients with constant, severe, intractable cancer pain and large opioid requirements may benefit from the use of intravenous methadone by PCA and continuous infusion. This approach offers some advantages over the more hydrophobic drugs such morphine and hydromorphone. The more rapid peak analgesic effect and longer elimination half-life of methadone foster earlier intense analgesia with prolonged analgesic effect, particularly after patients reach steady-state plasma levels with repeat administration.

Systemic opioid therapy has limitations: Most commonly, drowsiness and sedation are dose limiting; in such situations consider alternate therapies (e.g., neuraxial analgesia). Less frequently, CNS side effects of high-dose opioids occur. These effects include hyperexcitability, myoclonus, confusion, and hyperalgesia (309). Myoclonus, the most common problem for patients receiving high-dose opioid infusion therapy, appears localized, but it can spread and eventually progress to grand mal seizures. These effects can occur with opioids administered via different routes (oral, parenteral, and neuraxial). The cause of opioid- induced myoclonus is still unknown. Some speculate that the active metabolite of morphine, M3G, may be responsible for the hyperalgesia and myoclonus seen with high-dose morphine therapy (227). Intravenous hydromorphone in doses of more than 60 mg per day has resulted in hyperalgesia and myoclonus. Doses of intravenous morphine greater than 60 mg per hour have resulted in similar problems. Although treatments including phenobarbital loading and clonazepam have occasionally proved helpful (310), definitive treatment for myoclonus usually involves either dose reduction, a change in opioid, or both (231). Switching to intravenous methadone therapy may also prove helpful. If these strategies fail, consider alternative pain management techniques (311).

Subcutaneous Opioid Therapy

Continuous subcutaneous infusion of opioids is both an efficacious and safe method to control the chronic pain of the home-bound and hospitalized patient (301,312,313 and 314). Hypothetically, absorption of opioid from the subcutaneous compartment into the systemic circulation should be slow, but it is not, even for morphine (315). Moulin and colleagues (316) reported equianalgesic responses in a comparison of intravenous versus subcutaneous infusions of hydromorphone. Breakthrough pain control was equal in both groups and only occasionally did patients experience undue dermal irritation or recurrent infection. A wide variety of opioids are suitable for subcutaneous infusion: morphine, hydromorphone, methadone, fentanyl, and sufentanil.

Hydromorphone's solubility, its high bioavailability by continuous subcutaneous infusion (78%) (316), and the availability of a high-concentration preparation (10 mg per mL) make it a good choice for subcutaneous infusion. Parenteral hydromorphone is six times as soluble in aqueous solutions as morphine and five times as potent, allowing for smaller injection or infusion volumes in patients who require parenteral opioids (168).

Continuous subcutaneous infusions offer a safe, simple, effective alternative to intravenous infusion when patients cannot take medications orally. Moulin and colleagues (316) compared the safety and efficacy of subcutaneous versus intravenous infusion of hydromorphone in cancer patients. Pain intensity, pain relief, mood, and sedation did not differ between the two techniques. The mean bioavailability of hydromorphone from subcutaneous infusion was 78% of that with intravenous infusion. Simplicity, technical advantages, and cost-effectiveness are clear advantages of continuous subcutaneous opioid infusion into the chest wall or trunk. Paix and colleagues (317) described the successful use of subcutaneous fentanyl and sufentanil for morphine, noting the effective substitution of sufentanil for fentanyl when the patient needs higher doses of a lipophilic opioid.

Most patients require a weekly change of the site of subcutaneous infusion (313). The usual initial concentrations of morphine and hydromorphone are 5 mg per mL and 1 mg per mL, respectively, calculated according to the hourly infusion rate. Ideally, the subcutaneous rate should not exceed 2 mL per hour although some have established considerably higher rates (rates of 20 to 80 mL per hour by adding hyaluronidase to the infusion to promote hypodermoclysis) (318). One might expect a longer time to peak plasma levels after bolus injection with subcutaneous use than with intravenous use and consequently the subcutaneous route requires a longer lockout interval (10 to 15 minutes compared with 6 to 8 minutes for the intravenous). PCA doses may equal 25% to 50% of the hourly infusion rate every 10 to 15 minutes as needed. Subcutaneous administration of opioids may prove impractical in patients with generalized edema, who develop erythema, soreness, or sterile abscesses with subcutaneous administration, in patients with coagulation disorders, and in patients with poor peripheral circulation.

Intracerebroventricular Opioids

After neurosurgical consultation, it becomes possible to deliver opioids directly into cerebral ventricles through ICV catheters from subcutaneous reservoirs. Morphine sulfate, the usual agent, gains a marked increase in potency when delivered ICV as compared with intrathecal or epidural infusion routes, and the ICV route appears to affect supraspinal pathways for analgesia (319). Daily morphine doses for ICV delivery range from 50 to 700 µg per day (320,321). Generally, an implanted infusion pump, placed subcutaneously in the anterior abdominal wall and connected by subcutaneous tubing to an implanted ventricular catheter, delivers the drug. The duration of pain relief after ICV injections appears to be significantly longer than with intraspinal, and some patients gain adequate relief via an implanted ventricular catheter connected to a subcutaneous Ommaya reservoir-type device with one to two injections per day (322). This form of drug delivery is indicated for head and neck cancer pain, or, rarely, for patients with a good initial response to intraspinal infusions of opioids and subsequent development of apparent tolerance, but with limited (1 to 3 months) remaining survival time. The safety and side effects of ICV injections or infusions resemble those for intraspinal infusions, except that an increased risk of respiratory depression exists the first 3 days of therapy (322).

Some refractory head and neck pain responds only to ICV opioids, but pain below the waist may be most amenable to spinal treatment. In a metaanalysis of 1,587 cancer patients, Ballantyne and colleagues (323) compared ICV with the more common epidural and intrathecal opioid treatments in an attempt to establish the utility and safety of ICV therapy. All patients considered had intractable cancer pain that proved resistant to systemic treatment. Sedation and confusion occurred in 4% to 5% of patients receiving ICV therapy. Persistent nausea, urinary retention, and pruritus occurred more frequently with the two spinal treatments than with ICV therapy. Initial doses for ICV trial patients were in the range of 0.25 to 2.0 mg. Onset of effect was 2 to 30 minutes, and average duration of pain relief after a single dose was 12 to 48 hours. Tolerance proved less of a problem than with epidural or intrathecal therapy because the dose escalation was gradual (the average increase in daily dosage was 0.375 mg per month). However, because most of the studies that Ballantyne and colleagues reviewed were uncontrolled trials, she and her colleagues could not reach definitive conclusions on the comparative analgesic efficacy, side effects, and complication rate of the different treatments. No studies to date directly compare ICV therapy with epidural or intrathecal opioids. None of the trials that Ballantyne and colleagues reviewed quantified pain relief with a formal measure of pain, such as a pain scale.

Intraspinal Opioids

The intraspinal (epidural or intrathecal) infusion of opioids has been well established for the treatment of cancer pain for more than two decades (see Chapter 103). Initial reports of the efficacy and lack of complications associated with intrathecal and epidural morphine for cancer pain relief led many to believe that the solution to intractable pain awaited the development of satisfactory long-term neuraxial delivery systems (324). Epidural or intrathecal infusions can involve externalized spinal catheters, subcutaneous reservoirs for intermittent injection, or implanted infusion pumps, with either a constant rate or a programmable rate (325). Although such delivery systems have come into widespread use, particularly for the management of chronic nonmalignant pain, the overall success of long-term intrathecal and

epidural opioid administration is somewhat lower than initially anticipated for cancer pain.

Choice of Spinal Delivery System. Table 36-15 lists the spinal opioid delivery systems available (325). Ever since Behar and colleagues (326) first reported the use of epidural morphine for the treatment of cancer pain, anesthesiologists have been looking for a means to overcome the technical problems that can arise during chronic treatment with epidural opioids. These complications include catheter dislodgment, infection, pain on injection, leakage, and occlusion. Options to reduce these problems included tunneling the catheter to the flank or the anterior abdominal wall or implantation of a subcutaneous injection port located on the patient's anterior chest wall.

Type	System
I	Percutaneous epidural or intrathecal catheter
II	Percutaneous epidural or intrathecal catheter with subcutaneous tunneling
III	Totally implanted epidural or intrathecal catheter with subcutaneous injection port
IV	Totally implanted epidural or intrathecal catheter with implanted reservoir and manually activated pump
V	Totally implanted epidural or intrathecal catheter with implanted externally programmable infusion system

Adapted from Waldman SD, Feldstein CS, Allen ML, et al. Selection of patients for implantable intraspinal narcotic delivery systems. *Anesth Analg* [illegible], with permission.

TABLE 36-15. Spinal delivery systems

Many reviews of epidural treatment of cancer pain have reported technical complications (Table 36-16). The use of percutaneous catheters (not tunneled or tunneled) is somewhat limited. Advantages include ease of placement and ability to attach to an external pump. Disadvantages include the risk of infection with long-term use, a high incidence of displacement of the catheter, and fibrosis around the catheter tip resulting in pain on injection. A three-piece silicone-rubber exteriorized epidural catheter system described by DuPen and colleagues (327) allows for specific spinal level location of the catheter tip from a lumbar entry site and may help reduce the incidence of displacement and pain on injection. Disadvantages include a relatively high incidence of infection (both subcutaneous and epidural space) associated with long-term use. The rate of epidural and deep track catheter-related infections was 1 in every 1,702 days of Silastic catheter use (328). Tunneled epidural catheters with subcutaneous injection ports reduce the complication rate of simple percutaneous and tunneled epidural catheters, particularly for catheter dislodgment and early infections (329). Plummer and colleagues (330) noted in a series of 313 patients that the most frequent complications of subcutaneous injection ports were pain on injection (12.0% incidence), occlusion of the portal system (10.9%), infection (8.1%), and leakage of administered morphine such that it did not all reach the epidural space (2.1%). Possible disadvantages of these systems include the need for skin puncture with each delivery system use and the increased cost of the system. No direct comparison studies of Silastic tunneled exteriorized epidural catheters and subcutaneous ports are available.

Author	Type of catheter (no. of catheters)	Occlusion	Infection of subcutis	Major infection	Pain on injection	Dislodgment	Leakage
Wadler et al. (47)	Port (6)	0	0	0	0	0	2
Malone et al. (478)	Tunneled (1)	0	0	0	1	0	0
Zenz et al. (479)	Percutaneous (139)	10	10	2	0	28	0
DuPen et al. (327,328)	Tunneled (108)	0	28	15	2	0	0
Downing et al. (480)	Percutaneous (2)	0	1	0	0	0	0
Hamamoto et al. (481)	Port (15)	1	0	0	0	0	1
Plummer et al. (330)	Port (313)	31	22	1	34	0	6
Erdine and Ozdemir (482)	Mixed (225)	8	9	0	0	14	5
Oral and Ozcelikay (335)	Percutaneous (90)	10	4	0	34	23	17
Hogan et al. (341)	Mixed (26)	0	3	0	4	19	1

From de Jong TC, Kanters PL. A comparison of epidural catheters with or without subcutaneous injection ports for treatment of cancer pain: [illegible], with permission.

TABLE 36-16. Technical complications of epidural catheters: review of the literature

The intrathecal route is sometimes more efficient and less expensive than epidural delivery for the treatment of refractory cancer pain (331). Potential advantages of intrathecal administration include better distribution of medication to the target site and enhanced pain relief (332). However, the intrathecal route is less frequently used than the epidural route (333). Concerns about externalized intrathecal catheters focus around potentially higher risks of complications (particularly meningitis, CSF fistula, and CSF hygroma) than an epidural catheter. Therefore, physicians who use the intrathecal route tend to avoid percutaneously inserted, subcutaneously tunneled, *open* or externalized catheters, preferring a totally implanted system that, it is hoped, will reduce or abolish these complications. However, such concerns appear to be largely unfounded (334). Implanted systems, especially if programmable, are the most convenient for long-term treatment with intrathecal opioids. Use of infusion technology is not without problems, and complication rates varying from 5% to 15% appear in the literature (248,322,330,335,336). They appear to offer a lower risk of certain complications (infection, displacement, and pain on injection) than other systems, but may also introduce specific delivery system problems (battery failure, pump torsion, overfilling of reservoir, programming errors, and so forth) (337). In addition, the high cost of the devices, which can be used in only one patient, and the relatively low capacity of the implanted infusion reservoir limit both the choice of drugs or further treatment options and necessitate restriction of use of these devices in cancer patients with pain.

According to cost-benefit analysis, an implanted infusion pump is more favorable when survival times exceed 3 months (338). With a median follow-up of 7.1 months, long-term epidural infusions of morphine sulfate have produced satisfactory pain relief in over 80% of patients. Mean pain ratings decreased from 8.6 before pump placement to 3.8 at 1 month after pump placement and remained relatively stable thereafter. Mean systemic morphine equivalents likewise decreased from 77.7 mg per day preimplantation to 27.9 mg per day at 1 month postimplantation with stable doses thereafter, but with increasing mean spinal infusion rates from 20.7 mg per day at 1 month after pump placement to 49.3 mg per day at 9 months (339). The experience with long-term intrathecal infusions reveals still greater efficacy with intrathecal infusion rates increasing from 3.8 mg per day (1 month postimplantation) to 9.5 mg per day (4 months postimplantation) and daily systemic analgesic doses decreasing significantly to 1 month postimplantation and remaining relatively stable thereafter (340).

The best application for this technique appears to be for patients with nociceptive or visceral pain localized in the lower body who have experienced some pain relief with systemic opioids. The intraspinal infusions usually are used in patients who either cannot tolerate systemic opioids because of intolerable side effects, such as nausea, vomiting, or sedation, or in patients who require large systemic opioid doses (e.g., greater than 20 mg per hour morphine systemic equivalents).

Issues relating to the use of such delivery systems include determining when in the course of treatment to initiate spinal opioids, which patients are suitable candidates, and what types of pain respond reliably and well to this method. Although no one would recommend indiscriminate or widespread use of spinal opioids, many clinicians experienced in cancer pain management remain convinced of the efficacy and safety of spinal opioids. Potential indications for use may include patients treated by systemic opioids with effective pain relief but unacceptable and refractory opioid-related side effects or patients unsuccessfully treated with opioid rotation. However, we must recognize the limitations of the technique (in terms of efficacy and potential side effects or complications).

It is difficult to determine the long-term benefits of epidural and intrathecal opioid therapy for cancer pain for the following reasons: (a) The criteria for treatment success are usually vague and vary between reports, and (b) the selection criteria for initiation of neuraxial opioid administration vary tremendously. In some centers, neurologists or oncologists manage pain, and they may be more aggressive with systemic analgesics and more conservative with invasive measures than anesthesiologists. They tend to refer patients for neuraxial therapy late in the course of the illness, when metastases are widespread, nociceptive inputs are high, and tolerance is a substantial problem. Frequently, such patients require supplementary local anesthetics for pain control. Alternatively, other centers may initiate spinal therapy at an early stage, possibly when systemic therapy may be equally if not more effective.

Hogan and colleagues (341) determined that in a population of 1,205 cancer patients, the aggressive use of systemic opioids limited the trial of epidural analgesia to only 16 cases. Successful analgesia was obtained with epidural morphine alone in 6 of these 16 cases after systemic opioid failure. Complications occurred in 11 of the 16 cases of epidural analgesia and included dislodged or broken catheters, pain on injection, hyperesthesia from epidural morphine, and bleeding or infection related to the epidural catheter.

Hassenbusch and colleagues (339) evaluated the efficacy and safety of continuous epidural morphine infusions in 69 patients with refractory midline, bilateral, or both kinds of lower body cancer pain unresponsive to systemic opioid therapy. Sixty percent of these patients gained adequate pain relief during a pretrial assessment and underwent subsequent implantation with an epidural Infusaid infusion pump. Preinfusion VAS scores were 8.6 ± 0.3, and postimplantation values at 1 month were 3.8 ± 0.4 (p <.001). Eighty percent of these patients continued to experience satisfactory pain relief (based on a minimum of 30% decrease in VAS compared with preinfusion values) at 3- and 6-month follow-up. Over the first month, requirements of systemic morphine equivalents decreased by 79% compared with preinfusion requirements. At 9 months, systemic opioid requirements remained 64% lower than preinfusion requirements. The mean epidural dose after 1 month of infusion was 20.7 ± 2.6 mg per day, increasing to 49.3 ± 9.9 mg per day after 9 months of infusion. There were no instances of epidural scarring, respiratory depression, epidural infections, meningitis, or catheter blockage. The study suggests that chronic epidural morphine infusion can yield significant reductions in cancer pain with few complications and a low morphine tolerance rate, although this report omitted specifics relating to the pain characteristics.

Clearly, certain patients who experience inadequate analgesia, intolerable side effects from systemic opioids, or both may have an excellent response to spinal or epidural administration of the same drugs. However, some patients never experience adequate analgesia from neuraxial opioids (so-called treatment failures; see Intrathecal Administration, later in this chapter). Pain characterization is important in providing optimal spinal opioid analgesia for cancer pain (342). Arner and Arner (343) examined the differential effects of epidural morphine on cancer pain. They provided intermittent bolus doses of morphine to 55 patients with different types of cancer pain (daily dose range, 4 to 480 mg; dose interval range, 3 to 12 hours). Twenty-eight of the 55 patients became pain free. Twenty-one of the remaining patients were completely relieved from one or two pain types, whereas other coexisting pain types were either unaffected or partially relieved. In six cases the treatment proved ineffective. The best response to epidural morphine occurred when pain was continuous and originated from deep somatic structures. In coexisting continuous visceral pain or intermittent somatic pain originating from a pathologic fracture, for example, the outcome of treatment was variable. Cutaneous pain, neuropathic pain, and intermittent pain caused by intestinal obstruction responded only occasionally. Ten of the patients had coexisting pain that was nonmalignant in origin, and none gained relief. This study and others (344) suggest that one can, to some extent, predict outcome of treatment with epidural morphine from the character of the pain requiring relief.

Development of tolerance and opioid resistance to some types of pain may limit the effectiveness of spinal opioids for intractable cancer pain. Gourlay and colleagues (345) found a significantly greater degree of dose escalation in patients receiving a continuous infusion of morphine compared with patients receiving repeated bolus doses, whereas Hassenbusch and colleagues (339) reported a low morphine tolerance rate using chronic epidural morphine infusions.

Selection of Opioid for Neuraxial Administration

Epidural Administration. The objective of epidural administration is to restrict the drug to analgesic sites in the spinal cord. Nonetheless, all epidurally administered drugs reach the systemic circulation to some extent. Thus, to determine whether epidural administration of a drug is appropriate, we need to know for each drug whether the observed analgesia is the result of a selective spinal action, the result of systemic uptake and redistribution to extraspinal sites, or some combination of these actions. Morphine was the first spinally active analgesic administered into the epidural space. It clearly produces analgesia by actions in the spinal cord (346) and it is the standard of comparison for all other epidural opioids. Several clinical studies of postoperative patients have clearly shown that the dose of fentanyl consumed, the plasma concentration at equivalent analgesia, or both are no different when the drug is given epidurally or intravenously (347,348 and 349). Miguel and colleagues (350) used a randomized double-blind study design to compare epidural versus intravenous sufentanil for analgesia after abdominal surgery. They found no difference in sufentanil dose, plasma concentration, pain score, or sedation between the two routes of administration. Coda and colleagues (351) demonstrated that at clinically equivalent degrees of analgesia the plasma concentration of alfentanil was the same whether the subjects received alfentanil intravenously or in the lumbar epidural space. These studies suggest that little or no value exists in administering highly lipophilic drugs such as fentanyl, sufentanil, or alfentanil into the lumbar epidural space. Meperidine may yield greater efficacy with epidural versus intravenous administration. Paech and colleagues (352) demonstrated that patients using lumbar epidural meperidine PCA required less drug and generated lower plasma meperidine concentrations while reporting better pain relief, less sedation, and better satisfaction than others using intravenous PCA meperidine. Presumably, this reflects a spinal mu-receptor site of action for meperidine. However, the drug's well-known local anesthetic effects could also explain the greater efficacy of epidural meperidine. Approximately 30 times more meperidine than morphine is required for epidural analgesia (353). Epidural methadone is only one-half as potent as epidural morphine (353). In summary, although a variety of opioids are administered epidurally, morphine appears to be the drug of choice for epidural administration.

Intrathecal Administration. Implanted drug administration devices can deliver any of several opioids for the management of chronic noncancer and cancer-related pain. These opioids include morphine, hydromorphone, sufentanil, fentanyl, meperidine, and methadone. The intrathecal use of opioids for cancer pain has been studied in numerous reports (246,248,249 and 250,322,339,340,354,355,356,357,358,359 and 360). Although many of these reports imply significant benefit from the use of intrathecal opioid therapy, few have accurately quantitated pain relief. An additional problem noted in many series is treatment failure; these were patients who received intrathecal catheter implants but reported no significant pain relief, despite escalation of opioid doses to sometimes enormous proportions (356,360,361 and 362). The true incidence of treatment failure with implantable intrathecal infusion systems is unknown. Paice and colleagues (358) evaluated the efficacy of intraspinal opioid therapy for cancer and noncancer pain. Patients with cancer pain of somatic origin had greater relief with intrathecal opioid infusions than patients with other types of pain. Compared with those with noncancer pain, cancer pain patients had a higher average initial dose of opioid. The average dose used by cancer patients escalated quickly and then stabilized, whereas the average doses used by noncancer pain patients exhibited a more gradual, linear increase in dose. Yaksh and Onofrio (246) analyzed changes in continuous infusion doses of morphine over time in 130 cancer pain patients and found a prominent time-dependent increase from 4.8 ± 0.4 mg per day to 21 ± 9 mg per day at 52 weeks. Plummer and colleagues (330) reported that patients with implantable subcutaneous intrathecal catheters receiving continuous infusions of morphine exhibited wide variations in dose requirements to control cancer pain. This suggests that the response to intrathecal opioid therapy may depend more on pain characteristics (similar to those defined for epidural opioid therapy outlined previously) than on the specific opioid used. Curiously, intrathecal methadone produces analgesia of inferior quality even in dosages 10 times higher than morphine (363).

Side Effects of Neuraxial Opioid Therapy. The side effects of systemic morphine are well described in the medical literature. The spinal administration of this drug results in a similar range of side effects, despite the more limited distribution of the drug in the body. Some of these side effects are temporary, normally lasting for the first several days after initiation of therapy and then resolving; others are more enduring (364). In a retrospective study of 82 patients receiving long-term opioid therapy for noncancer pain, Winkelmuller and Winkelmuller (365) reported the most frequent side effects were constipation (50%), disturbance of micturition (42.7%), and nausea (36.6%). These occurred early in the course of therapy and responded to appropriate medication. Some patients experienced a loss of libido or amenorrhea for the first 6 to 8 months of therapy, but these side effects proved self-limiting to most patients and disappeared after 12 to 14 months of therapy. Escalating doses of intrathecal morphine may prove problematic because of increased risk for hyperalgesia and myoclonus (356). To avoid this problem, intrathecal doses of morphine should not exceed 15 mg per day.

Current knowledge on spinal opioids in tumor pain permits the following generalizations:

- A slow increase occurs in mean daily opioid dose requirements in many series, generally at a rate that doubles every few months. Some individuals escalate their dose requirements more rapidly, particularly in the terminal phase of their disease.
- Dose escalation tends to be slower with intrathecal administration systems. This may relate to the tendency for fibrosis to occur around epidural catheters (335).
- The escalation of dose over time tends to be slower in patients receiving continuous infusions as opposed to intermittent bolus injections (366). This may be related to the more rapid development of tolerance when spinal opioid receptors are exposed intermittently to high opioid doses.
- Higher spinal opioid doses are required for pain that is neuropathic in origin than for somatogenic pain (343). Opioid requirements for visceral pain are intermediate between neuropathic and somatic.
- Incident pain (occurring with activity) is difficult to control with either neuraxial or systemic opioids.
- Higher systemic opioid requirements predict higher neuraxial requirements.

Many patients who do not obtain pain relief with systemic opioids eventually demonstrate no benefit from epidural or intrathecal opioids. Although pain relief is excellent in 45% to 90% of patients with initiation of intraspinal opioid therapy, dose escalation and increased need for supplemental oral opioid therapy occur commonly over 2 to 4 months of therapy (246,248,340,343,366). Van Dongen and colleagues (367) noted that 33% of patients failed intrathecal morphine therapy (after intrathecal therapy started because of failure of epidural therapy) and required the addition of bupivacaine for pain control.

OTHER CONSIDERATIONS FOR INTRASPINAL ANALGESIA

Intraspinal opioid analgesia combined with local anesthetic agents is a well-established method of pain relief for postoperative pain control (368,369,370,371 and 372). Ambulatory epidural analgesia is now relatively commonplace for the control of labor pain (373). Concern over toxicity and adaptation to sympathetic block associated with the chronic use of spinal local anesthetics has limited the consideration of this technique for home care of cancer patients with intractable pain or opioid-related side effects. DuPen and colleagues (374) demonstrated the safety and efficacy of long-term epidural bupivacaine-opioid infusion in 68 patients with cancer pain refractory to epidural opioids alone. The majority of patients experienced pain relief with little or no sympathetic or sensorimotor impairment after the first 24 hours at bupivacaine concentrations of 0.125% to 0.25% and could receive management at home or in chronic care settings without the need for rehospitalization. Transient postural hypotension during the first 24 hours occurred in only 9% of patients, and this supports the requirement for close monitoring and fluid therapy during initiation of therapy.

Segmental limitations of epidural analgesia with local anesthetic agents mandate placement of the tip of the catheter at a site adjacent to the dermatome covering the field of pain. Failure to do so limits the effectiveness of the technique. In general, if a pain complaint merits an epidural trial, first place a site-specific, percutaneous epidural catheter. Titrate epidural bupivacaine-opioid combinations according to the guidelines listed in Table 36-17.

Patient rating of pain management	Response[a]
Unsatisfied	Increase opioid by 50%
	Increase bupivacaine by a concentration factor of 0.03% (e.g., 0.12% to 0.15%)
Uncomfortable/ functional	Increase opioid by 25%
	Increase bupivacaine by a concentration factor of 0.02% (e.g., 0.12% to 0.14%)
Uncomfortable/ function impaired	Increase opioid by 25%
	Decrease bupivacaine by a concentration factor of 0.1%
Uncomfortable/ nausea + sedated	Increase bupivacaine by a concentration factor of 0.02%
	Decrease opioid by 10%
Comfortable	No change

[a]Range of bupivacaine changes, 0.01% to 0.03%. Range of opioid changes, 10% to 50%.

TABLE 36-17. Guidelines for titration of epidural bupivacaine- opioid combinations

The space-occupying role of epidural metastases may reduce the efficacy of epidural pain management (375) (see Implications of Epidural Metastasis and Spinal Canal Occlusion for Intraspinal Drug Treatment , later in this chapter). Advancement or progression of disease may result in multiple sites of pain complaint, some of which may resist epidural therapy. In such situations consider alternative routes, drugs, or strategies.

DuPen and colleagues (328) have issued guidelines for the management of epidural catheter–related infections. Infection of epidural catheter systems usually begins at the exit site. The bacteria cultured from the space are most frequently from skin flora contamination (*Staphylococcus aureus*, *Staphylococcus epidermidis*), but occasionally include *Escherichia coli*. Patients who are immunosuppressed may yield a wider variety of organisms. Catheter infections involve *S. aureus* more than 90% of the time. If organisms such as *Campylobacter* appear, suspect a contaminated infusion solution. Track infections may also occur. Suspect a deep catheter or epidural infection on clinical grounds (pain during epidural injection, soft fluctuant mass under incision, decreasing epidural analgesia even with increasing dose, constant and nonspecific back pain). Thorough daily cleaning with povidone-iodine treats superficial track and exit site infections. Use topical, oral, or both kinds of antibiotics depending on the extent of involvement and the response to treatment. All deep catheter track and epidural infections require catheter removal and treatment with parenteral antibiotic therapy. The duration of treatment depends on the organism cultured. Replace catheters after completion of antibiotics and a magnetic resonance imaging scan indicates no further epidural involvement or inflammation. Deep catheter infections require inpatient management. Flush the catheter with 1 mL of saline. Aspirate and, if positive, send for culture. Continue aspirating until clear. Wait for the culture results and treat systemically. Leave the catheter until no further aspirate is visible (acts to decompress) and then remove the catheter. Treat with antibiotics (usually vancomycin) for 10 days, then replace the catheter if indicated.

Clonidine

Several reasons exist to consider spinal clonidine for intractable cancer pain. Clonidine is a centrally acting a_2-adrenergic agonist with established analgesic effects (376,377) and has synergistic effects with both spinal opioids (378,379) and spinal local anesthetics (380,381). Like opioid receptors, a high density of a_2-adrenoreceptors occurs in the superficial dorsal horn of the spinal cord (382). a_2-Adrenoreceptor activation blocks transmission of noxious sensory information at the level of the spinal cord by both presynaptic and postsynaptic mechanisms (383,384,385). Epidural clonidine produces analgesia by a spinal mechanism in patients after surgery and in those with cancer pain (386), and it appears to be an effective treatment for severe cancer pain in patients in whom other treatments fail (387). For this reason, clonidine is an effective analgesic when administered intraspinally but a poor analgesic when administered systemically (388). Also, because clonidine does not interact with opioid receptors, it fails to cause treatment-limiting side effects common to opioids.

Clinical experience with spinal clonidine largely consists of postoperative analgesia studies, although Eisenach (387) has reported on its long-term use in cancer pain. This and other clinical studies (389,390 and 391) suggest that intrathecal and epidural clonidine in combination with other agents such as opioids or local anesthetics is a suitable treatment for intractable cancer pain. Eisenach and colleagues (387) investigated the efficacy of epidural clonidine in 85 patients with cancer who continued to have either severe pain despite large systemic or epidural doses of opioids or who were experiencing therapy-limiting side effects from opioids. Patients were randomized to receive either epidural clonidine, 30 µg per hour, or a placebo in a double-blind, multicenter study. All patients received rescue medication (epidural morphine) by PCA. patients' primary pain was considered neuropathic in nature in 42% and nonneuropathic in 58%. Successful analgesia (defined as a decrease in either morphine use or VAS scores) was more common with epidural clonidine (45%) than with placebo (21%) and was particularly prominent in those patients with neuropathic pain (56% versus 5%). The onset of side effects from epidural clonidine occurred early in treatment, without any delayed- onset effects. Clonidine decreases blood pressure after epidural administration by actions in the spinal cord (392,393), brainstem (394), and periphery (395). Blood pressures remained approximately the same level as baseline in the placebo group but decreased by approximately 10 mm Hg in the clonidine group. This was a serious complication in two patients. Of interest, the hypotensive action of clonidine is counteracted at larger doses by a peripheral vasoconstrictive action. For patients in the nonneuropathic pain groups, the likelihood of success was similar for each treatment group regardless of whether the pain was characterized as visceral or somatic, which suggests that the addition of clonidine in the treatment of such conditions does not confer additional benefit over epidural opioids.

Good reason exists to believe from laboratory and clinical experience that intrathecal clonidine may also be effective in the treatment of neuropathic pain. Intrathecal injection of clonidine reduces autotomy behavior in an animal model of neuropathic pain (396). A number of clinical reports document the efficacy of intrathecal clonidine for intractable cancer pain (390,391,397). Clinical investigators have administered intrathecal clonidine in bolus doses of 30 to 150 µg and in continuous infusions of 8 to 400 µg per day, usually in combination with morphine. The analgesia dose requirements for drugs with moderate to high lipophilicity, such as fentanyl or sufentanil, may diminish with epidural versus systemic administration (348,350) because of rapid systemic absorption after epidural injection and nonspecific binding to epidural fat. In contrast, significant dose sparing compared with systemic administration occurs with intrathecal fentanyl or sufentanil (398,399). Given clonidine's lipophilicity (similar to fentanyl), one would expect its spinal effects to be more pronounced and selective after intrathecal rather than epidural administration.

Neostigmine

Cholinergic mechanisms are involved in the control of nociceptive input in the CNS. Human studies have confirmed the analgesic action of the anticholinesterase physostigmine given intravenously (400,401), but the duration of analgesic action is short. In contrast, the longer-acting anticholinesterase neostigmine lacks antinociceptive properties after systemic administration in laboratory animals, probably because of its inability to cross blood–brain barriers. Because neostigmine is water soluble, chemically stable, and commercially prepared without preservative, it is possible to give it by the subarachnoid route. Unfortunately, the sole manufacturer of the preservative-free neostigmine solution used in the initial clinical studies no longer markets this preparation. Although solutions containing preservatives are generally avoided for intrathecal injection, methyl- and propylparabens have not proven toxic. Eisenach and colleagues (402) performed a phase I

tolerability and safety study of the commercially available neostigmine formulation in human volunteers and found no evidence of toxicity. Studies in human volunteers have shown that intrathecal neostigmine lacks neurotoxicity and produces low plasma concentrations (403), in contrast to a long-lasting, measurable CSF concentration. Klamt and colleagues (404) reported on the successful use of bolus injection of neostigmine in two patients with cancer pain. The pain-relieving effect of neostigmine was of slow onset and long duration in both patients. Gastrointestinal discomfort occurred in both cases, even with dose reduction.

Intrathecal Therapy with Bupivacaine and Morphine

Some types of tumor-associated pain are less likely to respond to epidural analgesia. These include mucocutaneous ulcers, pain caused by body movements as a result of fracture, edematous swelling or ischemia of an extremity, and neuropathic pain from plexus infiltration (332). The administration of intrathecal morphine does not appear to offer any significant advantages (see previous discussion). However, the combination of intrathecal bupivacaine with morphine may be more efficacious than epidural administration when given for cancer pain relief. These two agents may act synergistically through different mechanisms at the spinal cord level. Local anesthetics given intrathecally even at subanesthetic concentrations can reduce the maximum firing rates of nociceptive fibers with opioids that reduce the sensitivity of wide dynamic range neurons. The mechanism may involve specific neurons in the dorsal horn that process high threshold nociceptive input (405). Intrathecal bupivacaine with its predilection for unmyelinated axons could contribute to the clinical efficacy by blocking slow, burning pains (406), which may not respond to bupivacaine alone. In addition, this approach probably delays the occurrence of tolerance to intrathecal morphine because of the smaller doses and the added analgesic effects of bupivacaine.

Nitescu and colleagues (331) compared the efficacy of epidural and intrathecal pain treatment with morphine and bupivacaine in 25 patients with severe, multifocal cancer pain, in whom epidural administration of morphine and bupivacaine failed to provide acceptable pain relief. Both epidural and intrathecal catheter systems consisted of open, subcutaneously tunneled catheters. Fifteen patients had infradiaphragmatic pain, and 10 had both infradiaphragmatic and supradiaphragmatic pain. The investigators assessed consecutive epidural and intrathecal periods (2 to 174 days, median, 50 days; and 1 to 305 days, median, 37 days, respectively) in terms of daily analgesic dosages giving acceptable pain relief and quality of life expressed as sleeping hours and walking and daily activities. They placed both epidural and intrathecal catheters using a midline approach from T-11 to T-12 or between T-12 and L-5. Eleven patients received preservative-free morphine solutions 0.2 to 2.0 mg per mL, and the other 14 received morphine with preservatives in solutions of 10 mg per mL. Bupivacaine 2.5 to 5.0 mg per mL, diluted or not with isotonic saline, was added to morphine until concentrations judged to be suitable with respect to the daily dosages and volumes were obtained. Epidural solutions were administered as intermittent injections two to six times per day, for a total of 1,242 treatment days (range per patient, 2 to 174 days; median, 50 days). All patients receiving intrathecal treatment began with intermittent injections given 1 to 15 times per day (mean, 3; median, 2) and continued in 18 patients. In seven patients, the initial, intermittent administration continued until termination of treatment by continuous infusion of morphine, with or without bupivacaine. The combined, intermittent and continuous treatment ranged from 1 to 305 days (median, 37 days). Eleven patients received treatment at home for 7 to 125 days (median, 46 days). With intrathecal treatment, the total opioid consumption and the daily doses of spinal morphine and bupivacaine decreased significantly both at the start of treatment and for the 6-month follow-up period. Intrathecal treatment provided more satisfactory pain relief, and because of lower daily doses and volume, proved to be more suitable for treatment at home than epidural treatment.

Since this report was published a number of different studies have confirmed the efficacy of intrathecal morphine and bupivacaine combinations for the treatment of severe, refractory cancer pain (332,367,407,408,409,410 and 411). Sjoberg and colleagues (332) reported on the applicability of long-term (1 to 305 days; median, 23 days) intrathecal bupivacaine and morphine in 52 patients with complex *refractory* cancer pain. Particular consideration was given to the dosages, concentrations, volumes and proportions of the drugs, and side effects and complications that they could attribute to the long-term administration of bupivacaine. The investigators estimated efficacy from the daily dosage (intraspinal and total opioids, and intraspinal bupivacaine), scores of nonopioid analgesic and sedative consumption, gait and daily activities, and amount and pattern of sleep. Intrathecal treatment began with a test dose of 1 to 6 mg of morphine (median, 2) and 1.0 to 12.5 mg of bupivacaine (median, 4.5), given in a volume of 1.0 to 8.0 mL (median, 4). Intrathecal daily volumes ranged from 1 to 114 mL and increased with the duration of the intrathecal treatment, the median values being approximately three times higher at 6 months (30 mL) than at 2 days after the start (9 mL).

Eighty-five percent of patients obtained continuous and acceptable pain relief (VAS 0 to 2 versus pretrial values of 7 to 10 out of 10), 60% of them with daily doses of intrathecal bupivacaine of 30 mg per day (1.5 mg per hour). Temporary, moderate, or severe breakthrough pain (VAS of 3 to 8), not always relieved by escalating intrathecal treatment, was experienced in eight patients (15%). Higher intrathecal bupivacaine doses (more than 60 to 305 mg per day), not always giving acceptable pain relief, were necessary in 13 patients (25%) with deafferentation pain spinal cord, plexus (brachial, lumbosacral), or celiac plexus, or from large, ulcerated mucocutaneous tumors. By combining intrathecal bupivacaine with intrathecal morphine, it was possible to use relatively low intrathecal morphine doses (10 to 25 mg per day during the first 2 months of treatment) in more than one-half of the patients. The intrathecal treatment significantly decreased the total (all routes) opioid consumption and significantly improved sleep, gait, and daily activities. For the whole period of observation (6 months), the intrathecal treatment was assessed as adequate in 3.8%, good in 23.1%, very good in 59.6%, and excellent in 13.5% of the cases. Adverse effects of the intrathecal bupivacaine (paresthesia, paresis, gait impairment, urinary retention, anal sphincter disturbances, and orthostatic hypotension) did not occur with doses of 2.5 to 3.0 mg per hour (approximately 60 to 70 mg per day). Paresthesia in patients at bolus doses exceeding 1.25 mg was sometimes experienced as very unpleasant. Two patients who experienced paresthesia refused to continue intrathecal bupivacaine therapy for fear of becoming paralyzed. Because of this, the authors suggested an upper limit of the incremental dose of intrathecal bupivacaine per demand of 1.25 mg. With intrathecal bupivacaine infusion, most of the patients did not complain of unpleasant paresthesias at doses up to 3 mg per hour. Paresis and gait impairment usually did not occur with infusion doses (3 mg per hour). This was particularly true for patients whose skeleton, muscles, and nervous system were not impaired by the basic disease, radiation therapies, or both. The incidence of early urinary retention was 27%. Late urinary retention appeared consistently at daily dose of bupivacaine equal to or greater than 60 mg per day.

In a follow-up study, Sjoberg and colleagues (411) tested the clinical efficacy of a constant infusion of 0.5 mg per mL of morphine plus 4.75 mg per mL of bupivacaine (morphine to bupivacaine ratio approximately 1:10), given through open intrathecal catheters to 53 patients. They obtained satisfactory pain relief, defined as VAS scores of 0 to 2 versus 6 to 10 in the preintrathecal stage, with relatively low daily doses of intrathecal morphine (median, 6 mg). Daily intrathecal volumes (median, 10 mL) were low, whereas the daily dose of intrathecal bupivacaine was relatively high (median, 50 mg). Side effects attributable to intrathecal bupivacaine occurred in the forms of late urinary retention (33%), paresthesias (41%), paresis and gait impairment (33%), and occasional episodes of orthostatic arterial hypotension (1.8%).

The importance of intrathecal volumes, versus that of the concentrations and doses, for the intensity and spread of spinal analgesia during chronic infusions of intrathecal morphine and bupivacaine is still unclear. Kroin and colleagues (412) could not demonstrate any advantage in placing the catheter tip at more rostral locations, such as at the midthoracic or cervical cord when using hydrophilic drugs for pain relief. Van Zundert and colleagues (413) demonstrated that a constant 70-mg dose of subarachnoid lidocaine produced the same pinprick level of analgesia, degree of motor block, and duration of spinal anesthesia. Wagemans and colleagues (360) measured the pH of CSF in a patient receiving high doses of intrathecal morphine who failed to demonstrate either motor or sensory block after injection of 75 mg of lidocaine, 5%. This patient's CSF pH fell outside the physiologic range at 7.19 (normal range, 7.27 to 7.37), suggesting a possible explanation for the decreased activity of the local anesthetic. Kroin and colleagues (414) noted an absence of ataxia at intrathecal bupivacaine doses of 0.4 to 0.5 mg per hour in dogs. The human CSF volume is approximately 10 times that of a dog. Therefore, one might reasonably assume that doses up to 3 mg per hour are safe in patients without evidence of neurologic deficit. When patients have neurologic deficits caused by nerve damage or polyneuropathies, it is appropriate to reduce doses substantially (0.5 to 1.0 mg per hour) to avoid causing motor disturbances.

The intrathecal route offers distinct pain relief advantages for cancer pain compared with the epidural route: enhanced pain relief efficacy; ease of insertion; aspiration of CSF provides a definite end-point for placement; after placement, correct placement may easily be confirmed by CSF aspiration; absence of systemic effects of drugs; uniform drug distribution to the target area within CSF; and low reported incidence of complications.

Sjoberg and colleagues (332) offered guidelines for starting intrathecal therapy for morphine and bupivacaine in patients with refractory cancer pain.

1. Place intrathecal catheter tips in the center of segments of maximum pain (particularly with thoracic and cervical pain).
2. Titrate intrathecal dosage individually:
   a. Start with low morphine (0.5 to 1.0 mg per mL) and relatively high bupivacaine (4.75 to 4.5 mg per mL) concentrations and low volumes (3 to 4 mL per day).
   b. Gradually increase the volumes until the patient reports adequate pain relief (VAS of 0 to 2 of 10).
   c. Set the incremental dose per demand below 1.25 mg of intrathecal bupivacaine.
3. Be prepared to use higher intrathecal bupivacaine doses (per hour, and on demand) in patients with deafferentation pain from the spinal cord, brachial or lumbosacral plexus, pain from celiac plexus, ischemic and colicky pain, and smarting pain from large, ulcerated mucocutaneous tumors.
4. Limit the daily dose of intrathecal morphine to less than 15 mg to avoid the possibility of opioid-induced myoclonus and hyperalgesia.
5. Most patients do not experience side effects from intrathecal bupivacaine if the daily dose is less than 60 mg. Patients may start at doses of 30 mg per day. Some patients may require doses as high as 300 mg per day.

6. Treat opioid withdrawal independently of intrathecal morphine doses.
7. Decrease, but do not interrupt, administration of sedatives.
8. Contact the patient every day and adjust the dosages as necessary.

The safety of externalized tunneled intrathecal catheters, particularly in relation to the development of meningitis and epidural abscess, has come under question (330,333,336,338). Crul and Delhaas (335) reported on the type and incidence of technical complications (e.g., obstruction and dislocation of the catheter and infection) in long-term (10 to 366 days) spinal morphine administration in terminally ill cancer patients by means of an epidural or intrathecal catheter. During the first 20 days of treatment, a significant difference ($p = .02$) in the incidence of complications differentiated the epidural group (8%) from the subarachnoid group (25%). During the remainder of the treatment period, the complication rate rose to 55% in patients receiving epidural morphine and declined to 5% in the subarachnoid group, a significant difference ($p = .001$). The most frequent complication in the epidural group was obstruction and dislocation of the catheter, probably because of the development of epidural fibrosis. This problem became apparent in 50% of patients during the treatment period from day 20 to 366. In patients receiving intrathecal morphine, the prevalent complication was CSF leakage, which was observed only during the first 2 weeks of treatment. Crul and Delhaas concluded that the intrathecal route is the route of choice for patients expected to live longer than 1 month, and for patients with a shorter life expectancy, epidural administration can yield acceptable results. In contrast, Bedder and colleagues (338) recommended against using intrathecal catheters for long- term pain control because of the potential risks of meningitis and spinal headache.

To correctly define the role of externalized intrathecal catheters in the treatment of intractable cancer pain, Nitescu and colleagues (334) compared the rates of postinsertion complications of externalized intrathecal catheters with the rates reported in the literature for externalized epidural and intrathecal catheters, as well as implanted epidural and intrathecal catheters connected to subcutaneously implanted ports, reservoirs, or pumps. The authors studied 200 patients with refractory cancer pain treated for 1 to 575 days (median, 33; total, 14,485). Seventy-nine patients received treatment at home for 2 to 226 days (median, 36; total, 4,711). Standardized care after insertion included daily telephone contact with the patients, their families, or the nurse in charge; weekly dressing changes at the tunnel outlet by the nurses; refilling of the infusion containers by the nurses; and exchange of the infusion systems when empty (within 1 month) and of the antibacterial filter once a month by nurses. Providers carefully avoided all contact between the connections of the syringes, cassettes, and needles with the operator's hands during filling and refilling of the infusion containers and exchange of the antibacterial filters. However, they took no further aseptic precautions. Table 36-18 lists the rates (as a percentage of the number of patients) of perfect function and complications of the systems in Nitescu and colleagues' series versus the range of rates reported in the literature (334).

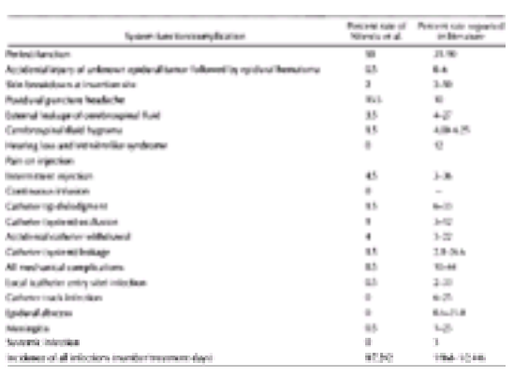

TABLE 36-18. Rates (as a percentage of the number of patients) of perfect function and complications of the systems in the series by Nitescu et al. versus the range of rates reported in the literature (334)

Of interest, infectious complications such as tunnel exit and deep catheter track infections did not occur in this study. No epidural abscess was recorded, and meningitis occurred in only one patient. The authors speculated that the most important factor in preventing local infection was the secure fixation of the catheter with the externalized systems to prevent to-and-fro movements of the catheter and the transport of skin bacteria into the subcutaneous reactive passage formed around the catheter. The fear of meningitis has presented a major obstacle to the use of intrathecal pain treatment. However, the few reports presented do not support such fears (415). Nitescu and colleagues attributed the low rate of meningitis in their study to the technique of insertion and care of the intrathecal catheters, as well as to the use of mixtures of morphine with preservatives and bupivacaine as analgesic solutions. Both preservatives (sodium pyrosulfite and sodium edetate) from morphine solution and bupivacaine have bacteriostatic effects (416,417).

Novel Techniques with Intrathecal Therapy

Continuous Intracisternal and High Cervical Intrathecal Bupivacaine

Progressive tumor growth in the head and neck often leads to various types of pain localized to the distribution of both the cervical nerve roots and cranial nerves. The upper cervical components of the spinomesencephalic tract cells and cranial nerves V, VII, IX, and X are involved in mechanisms of pain from head, face, and neck structures. The pain is seldom limited to one side or confined to the distribution of one nerve. In patients with diffuse upper neck and head pain, the source of pain often involves multiple nerves. Cranial nerves and peripheral somatic nerves often provide nociceptive afferent input. In addition to somatic pain, burning discomfort may result from nociceptive pathways within the sympathetic chain. These circumstances restrict the usefulness of nerve blocks and neuroablative procedures.

Appelgren and colleagues (407) reported on 13 patients with complex, refractory pain who received continuous intracisternal or high cervical subarachnoid infusions of bupivacaine as a method to control pain in the head, face, mouth, neck, and upper extremities. Patients received bupivacaine continuously at rates of 1 to 7 (median, 1.5) mg per hour, with optional bolus doses of 0.5 to 2.0 mg two to four times per hour. They assessed efficacy from VAS scores, daily dose of intracisternal bupivacaine and total opioid, amount of nocturnal sleep, and rates of adverse effects. Patients were treated from 3 to 182 days (median, 37; total, 712 days).

The investigators could not evaluate one patient because of the patient's advanced senility. For most patients (11 of the remaining 12), infusions of bupivacaine provided satisfactory pain relief, decreased systemic opioid consumption, improved nocturnal sleep patterns, and improved overall function. Daily doses of intracisternal bupivacaine ranged from 20 to 118 mg (median, 37 mg). Average VAS scores decreased from 7 to 2. Total daily opioid dose decreased from median values of 53 to 36 mg of parenteral morphine equivalents. Nocturnal sleep increased from median values of 2 to more than 6 hours. In patients with refractory pain from the shoulders and upper extremities, the intracisternal administration of bupivacaine gave less pain relief than intrathecal administration of the same bupivacaine doses at the midcervical (C-4–C-5) levels.

Associated side effects generally were dose related and similar to those described with lower sites of infusion. Signs of motor impairment of the cranial nerves occurred for the somatic fibers of the vagal nerve, expressed as hoarseness after intrathecal injection of 5.0 mg of bupivacaine, in all intracisternal tests, and of the glossopharyngeal nerve (dysphagia) after a bolus dose of 7.5 mg of bupivacaine. No signs of motor impairment from the other cranial nerves appeared at therapeutic doses. Paresis of the upper extremities occurred in two patients at intracisternal doses of bupivacaine of 1.5 and 5.0 mg per hour, respectively. No patient experienced gross impairment of phrenic nerve activity. The absence of obvious phrenic nerve paralysis is notable, and it probably reflects the greater resistance of the large motor fibers of the phrenic to the effects of local anesthetic agents (418).

Novel side effects included one patient experiencing severe tiredness, faintness, and malaise and one experiencing somnolence and sleep. These side effects emerged transiently with relatively high infusion rates or large bolus doses and resolved after decreasing the infusion rate or withholding the bolus dose. These symptoms occurred at doses equal to or greater than 3 mg per hour. They may derive from a decrease of skeletal muscle tone, inhibition of the tonic activity of the reticular substance by reduction of signals from the peripheral receptors, and loss of control of fairly specific motor tasks, such as rhythmic locomotor movements and of eye, head, and body movements in response to optic and vestibular stimuli. No persistent neurologic deficit or death could be attributed to the intracisternal pain treatment.

Appelgren and colleagues concluded that long-term intracisternal administration of bupivacaine might help the rare, well- selected patient with refractory pain from the

head, face, and neck structures to obtain adequate pain relief when alternate methods have failed. Although the actual mechanism of pain relief is unknown, Carpenter and Rauck (419) contend that the low doses of bupivacaine used in the study suggest the possibility of a central neuronal analgesic effect, and they advocated further research to explore this possibility.

Intrathecal Adrenal Medullary Transplants

Adrenal medullary chromaffin cells secrete both catecholamines and opioid peptides, endogenous substances that independently and possibly synergistically reduce pain when injected locally into the spinal subarachnoid space (420,421 and 422). An advantage of this transplant approach for the alleviation of pain is that it acts as a living biological pump that can serve as a local endogenous source of pain-reducing, neuroactive substances on a long-term basis, reducing or even eliminating the need for repetitive exogenous opioid administration. Inserting a source for substances that act via conventional spinal receptors to alter nociceptive transmission is attractive.

The technique is relatively straightforward and involves a simple approach. Winnie and colleagues (423) introduced 2 mL of human adrenal medullary tissue via lumbar puncture into the subarachnoid space in five patients with cancer pain. They assessed VAS scores, functional activity, and opioid intake before and after the transplantation procedure. Four of the five patients demonstrated progressive decreases in pain scores after the procedure, with concomitant reductions in opioid intake. Three of these four patients remained pain free, two for over 10 months. Although the results of this study are encouraging, they merit caution in interpretation because the study lacked a parallel control group of patients.

Foley and Yaksh (424) contend that evolution of transplant therapy requires the same systematic characterization as any novel therapy. In particular, the functional and biochemical characteristics of each implant (i.e., cell type, content, and viability at the time of delivery) require accurate definition. Until this appears in the literature, these authors called for a moratorium on further transplant injections.

Patient-Controlled Intrathecal Analgesia

A variety of medications, including morphine, bupivacaine, and clonidine, may be used both intrathecally and by PCA for the control of cancer pain. One aspect of the efficacy and high acceptance of PCA is the higher degree of satisfaction of patients who are involved in self-administration of drugs and self-monitoring of pain and side effects (425,426). Ferrante and colleagues (427) demonstrated a significant reduction of the total bupivacaine requirement without any change in pain relief when comparing epidural PCA and continuous epidural infusion. Rundshagen and colleagues (428) described intrathecal PCA using bupivacaine for the control of postoperative pain, and Hardy and Wells (429) described using intrathecal PCA morphine for cancer pain. Further reports are needed with a variety of different agents including morphine, bupivacaine, and clonidine by intrathecal PCA.

IMPLICATIONS OF EPIDURAL METASTASIS AND SPINAL CANAL OCCLUSION FOR INTRASPINAL DRUG TREATMENT

The onset of back pain accompanies epidural metastasis in more than 60% of cancer patients and 80% to 95% of patients with confirmed epidural metastasis experience pain at some time during the course of the disease (430,431). The intensity of pain and the associated neurologic deficit depends on the size of the epidural metastasis and consequently determine the degree of epidural block. Patients with small epidural lesions may have no pain and no neurologic deficit (432). The occurrence and severity of complications during insertion of epidural and intrathecal catheters may depend on the location of the epidural tumor in relation to the puncture site, to the inserted catheter length in relation to the location of the epidural tumor, and to the degree (total or partial) of spinal canal stenosis.

Epidural metastasis with invasion of extrathecal and intrathecal nerve roots by neoplasm, dural infiltration, and generation of reactive fibrosis in the subdural space may increase the intensity of nociceptive stimulation and hinder diffusion of drugs to the nerve roots and spinal cord, thereby reducing the effectiveness of intraspinal pain treatment. Significant interpatient variation in daily doses of analgesics may occur for both epidural and intrathecal pain treatments. Epidural morphine doses varying from 6 to 120 mg per day at the start of treatment (331), 16 to 600 mg per day at steady state, and 28 to 600 mg per day at the final stage of treatment have been reported (334). Similar wide variations in epidural bupivacaine doses of 96 to 2,100 mg per day also occur (374). For intrathecal treatment, morphine doses have varied from 0.8 to 200 mg per day and bupivacaine doses from 15 to 305 mg per day (332).

Appelgren and colleagues (375) retrospectively reviewed 201 consecutive patients with cancer pain who received intrathecal pain treatment between 1985 and 1993. These patients participated in a study undertaken to test the hypothesis that epidural metastasis is a common cause of *refractory* cancer pain and that its presence may affect the efficacy and the complication rates of intraspinal pain treatment. Epidural metastases occurred in 40 (70%) and spinal stenosis in 33 (58%); 7 patients had total and 26 partial occlusion of the spinal canal. The presence of epidural metastasis affected catheter insertion complications, daily dosages, and complications of the intrathecal pain treatment only when it was associated with spinal canal stenosis (partial or total). During the period of intrathecal treatment, patients with confirmed epidural metastasis and total spinal canal stenosis needed significantly ($p < .05$) higher daily doses of morphine (means, 77 ± 103 versus 22 ± 29 mg) and intrathecal bupivacaine (means, 65 ± 44 versus 33 ± 20 mg) and had significantly ($p < .05$) higher rates (14% versus 0%) of radicular pain at injection and poorer distribution of analgesia than those without epidural metastasis and spinal canal stenosis. Unexpected paraplegia occurred in four patients caused by accidental injury during attempted dural puncture (n = 1) and collapse [caused by CSF leakage leading to *medullary coning* of an unknown epidural metastasis (n = 3)].

Because most pathologic changes are limited to the epidural space, and the prevalence of intrathecal metastasis is 1% to 4% (433) compared with approximately 70% for epidural metastasis, epidural pain treatment is more often affected than intrathecal therapy by the presence of spinal metastasis. The presence of epidural metastasis with invasion of the extrathecal and intrathecal nerve roots, infiltration of the dura, and generation of reactive fibrosis in the subdural space may increase the intensity of nociceptive stimulation and hinder diffusion of drugs to nerve roots and the dorsal horn of the spinal cord, thereby reducing the efficacy of intraspinal treatment. The risk of rapid neurologic deterioration after lumbar puncture removal of CSF below the level of a subarachnoid block has been known since 1940 (434). In such situations, it is possible that lumbar puncture may remove CSF that has acted as a critical buffer between the spinal cord and the extramedullary tumor. Hollis and colleagues (435) recommend avoiding lumbar puncture and intrathecal catheterization below the level of a suspected mass causing complete block, estimating the risk of neurologic deterioration at approximately 14% after lumbar puncture in patients with complete spinal block.

MANAGEMENT OF SPINAL CORD AND CAUDA EQUINA COMPRESSION

The management of spinal cord or cauda equina compression must delicately balance the need to deliver a sufficient dose of radiation to kill the tumor and the need to avoid further injuring the spinal cord. The restrictions imposed by the radiation tolerance of the cord can limit the success of therapy. The ceiling of response, defined as maintaining pretherapeutic levels of ambulation and motor function, is 80% with radiation therapy alone (436). This is particularly true in extensive tumor burdens, such as spinal cord compression associated with a paravertebral mass, which require high doses of radiation to achieve local control. Lung cancers, specifically apical tumors, account for 60% of the presentations of epidural spinal cord compression associated with a paravertebral mass. Combining surgery with radiation treatment may help improve therapeutic outcome. In some cases, surgical decompression by vertebrectomy or laminectomy can promptly reduce pain and improve neurologic status. These clinical improvements follow promptly on relieving the mechanical compression produced by collapse of a vertebral body and improving spinal stability. A statistically significant increase in functional outcome occurred with laminectomy and radiation treatment of epidural spinal cord compression versus either modality alone (437,438).

Surgical intervention is an alternative for patients presenting with a high-grade epidural lesion, particularly a lesion caused by a radiation-insensitive tumor. Surgery often is the only available option for therapy because previously administered radiation may preclude further radiation in the area of compression. This is often the case in lung cancer, because over 70% of spinal cord involvement in lung cancer is located in the thoracic spine, and many of these patients have received mediastinal radiation. Surgical intervention may provide significant benefit in specific groups with spinal cord or cauda equina compression. Patient selection should depend on prognostic factors, so far as possible. For example, median survival in breast cancer patients with epidural metastases is significantly less if visceral metastases are evident (439). Even patients with advanced malignancies may benefit from surgical intervention if it is possible to maintain neurologic integrity (440).

Complete response to radiation treatment is achieved in 30% of all tumor types, including breast cancer and malignant melanoma (436). Radiosensitive tumors, such as lymphoproliferative malignancies, multiple myeloma, and germ cell tumors, have a better outcome, with 77% of these tumors achieving a complete response to radiation alone.

Measures of response involve pain and functional status. With radiation treatment alone, back pain resolves in 60% to 80% of patients (441,442,443 and 444). Improvement in motor and autonomic dysfunction occurs in 40% to 60% of cases (441,442). Pretreatment functional status is maintained at 3 years in follow-up after

radiation treatment in more than 90% of surviving patients.

HOME INFUSION THERAPY

Home care is a dynamic component of the health care system. In the United States, several factors have contributed toward change as well as growth in the home care industry. Since the 1990s, the use of home care and home infusion therapy continues to expand and grow. Several areas may account for this growth. Prospective payment for hospital services and diagnosis-related groups for Medicare patients, implemented in the mid-1980s, resulted in earlier discharge from hospital. An aging population and improved survival rates for chronic illnesses, including cancer, have led to an increased use of home care. In addition, marketplace regulation has forced the delivery of health care from its traditionally hospital-based center of services into alternative settings. Advances in pain management technology, such as ambulatory PCAs and the use of silicone subcutaneously tunneled neuraxial catheters, have expanded the scope and success of interventional pain management beyond the hospital to the home.

Ambulatory infusion pumps are either designed to be therapy specific or are multipurpose, enabling treatments such as chemotherapy, systemic antibiotics, total parenteral nutrition, hydration therapy, and opioid pain control. Developments in pump design include remote access capability by modem with the ability to change pump settings and download data.

Home-based PCA therapy provides select patients with the ability to deliver analgesia based on their own perception of need. PCA therapy may be superior to oral analgesia, especially in the treatment of severe oscillating pain. Patient selection criteria include intact cognition and proper supervision from a family member or health professional. A collaborative interdisciplinary approach is necessary for effective pain control for the cancer patient receiving interventional pain management at home. Collaboration between the patient, the patient's family, the home care nurse and home care agency, and the patient's physician is necessary. The physician remains responsible for determining the appropriate drug, bolus dose, background infusion rate, and lockout interval.

Potential benefits of home infusion therapy include decreased health care costs, patient and caregiver convenience, and less time spent in hospital, with the ability to extend interventional pain management strategies into the patient's home. A possible disadvantage to home infusion therapy may include the additional burden placed on the patient or caregiver in terms of role responsibilities and schedules. Home care agencies must have explicitly defined policies and procedures consistent with regulatory bodies and national and regional standards of practice.

PCA is increasingly more commonly used in the home setting as an effective option in pain management. As discussed previously, the subcutaneous and intravenous routes are the primary methods of administration. The availability of a central vascular access device such as a tunneled or peripherally inserted central catheter offers advantages over peripheral access to ensure safe and consistent administration of intravenous analgesia.

The safety and efficacy of home-based PCA opioid therapy has not been extensively reported as in-hospital use. One study (299), however, reported on the use of morphine PCA in the home environment of 143 preterminally and terminally ill tumor patients suffering either from excruciating chronic pain or severe chronic or acute complex pain that could not be relieved adequately by oral analgesia. After initial dose adjustment, which lasted 2 to 3 days, the median morphine dosage was 93 mg per day (range, 12 to 464 mg per day). This median was 28% lower than the median dose administered orally before PCA therapy. During the course of treatment, morphine requirements increased by a median of 2.3 mg per day (range, –29 to 52 mg per day). Most patients were treated continuously in the home care setting until death, the median duration of treatment was 27 days (range, 1 to 437 days). Terminal morphine demands reached a median of 188 mg per day (range, 15 to 1,008 mg per day). The authors concluded that PCA was both safe and effective in the home environment, attaining excellent results in 95 (66%) patients and satisfactory pain relief in 43 (30%). PCA was considered insufficient in five (4%) cases. Side effects, in general, were considered mild: the most common being constipation, fatigue, and nausea.

Although further study is warranted, safe provision of domiciliary interventional pain management probably requires selection of appropriate patients, effective patient and caregiver education, well-defined policies, and use of experienced and knowledgeable home care agencies.

MANAGEMENT OF PAINFUL BONE METASTASES

Metastasis to bone is a significant problem for a large number of cancer patients; up to 85% of patients dying breast, prostate, or lung cancer primary tumors demonstrate bone involvement at autopsy (445). The morbidity of bone metastases can become significant because of pain and pathologic fracture. Radiation therapy for bone metastases is discussed in detail in Chapter 37.

Bone metastasis represents systemic spread of disease, and oncologists often treat bone metastases with systemic therapies, such as chemotherapy and hormonal therapy (446,447). Chemotherapeutic options can provide excellent pain relief, especially in breast or prostate cancer patients. Physiologic bone turnover maintains normal skeletal integrity through a coupled process of bone resorption, mediated by osteoclasts, followed by new bone formation. Major features of the pathogenesis of tumor-associated skeletal destruction are enhanced osteoclast-mediated bone resorption and disruption of normal bone formation. Bisphosphonates, by inhibiting bone turnover and decreasing the resorption of bone, benefit the management of bone metastases. Their role is most clearly defined in breast cancer and multiple myeloma, but clinical benefit may extend to the entire spectrum of metastatic bone disease (120,121).

Surgery

Structural weakness secondary to extensive bone loss is not acutely reversed with medical or radiation treatment. The local effects of chemotherapy and radiation depress the rate of bone regeneration in compromised areas. In such cases, an approach that supports the bone during recovery is often necessary. Long bone fractures most commonly occur in the femur and humerus and are typically internally fixed by intramedullary devices that control impaction, distraction, and torque stresses by the use of proximal and distal interlocking fixation. Orthotic devices can often protect upper extremity lesions. The lower extremity is less tolerant, largely because of the high stress experienced during ambulation. Impending fractures of the lower extremity generally require surgical stabilization with fracture fixation devices or prosthetic reconstruction. The indications for prophylactic fixation of impending fractures remain poorly defined. Table 36-19 lists guidelines for indications for prophylactic fixation of impending long bone fractures.

Cortical bone destruction of more than 50%

Lesion of more than 2.5 cm in the proximal femur

Pathologic avulsion fracture of the lesser trochanter

Persisting stress pain despite irradiation

From Harrington KD. Orthopaedic management of metastatic bone disease. St. Louis: Mosby, 1988, with permission.

TABLE 36-19. Indications for prophylactic fixation of impending long bone fractures

One of the problems with plain roentgenography is that bone loss must approach 30% to 50% before it becomes apparent. In addition, in metastatic lesions characterized by bone production (e.g., prostate), clear evidence of bone destruction can be difficult to assess roentgenographically. Once a pathologic fracture has occurred, aggressive surgical treatment is normally in order. Patients who are unstable medically or who have a life expectancy of less than 4 weeks are not surgical candidates. Habermann and colleagues (448) found that 97% of patients had good to excellent pain relief after internal fixation or prosthetic replacement. Harrington (449) reported a success rate of 95% in returning patients to prefracture ambulatory status with surgical intervention. Current fracture fixation methods have led to improved patient survival (24.6 months versus 11.6 months) after pathologic fracture (449).

The spine is the most common site for skeletal metastasis. Oncologists can manage most spinal metastases conservatively. CT and magnetic resonance imaging of the spine are reserved for patients who present with vertebral body compression of more than 50% or who present with neurologic involvement. Once the workup is complete, patients fall into five categories, depending on the extent of neurologic involvement or bone destruction (Table 36-20).

Class	Degree of involvement
I	No major neurologic involvement
II	Involvement of bone without collapse and instability
III	Major neurologic involvement (sensory or motor) without significant bone involvement
IV	Vertebral collapse with pain caused by mechanical causes or instability but without significant neurologic impairment
V	Vertebral collapse or instability combined with major neurologic impairment

Data from Harrington KD. Metastatic disease of the spine. *J Bone Joint Surg Am* 1986;68:1110–1115.

TABLE 36-20. Categories of skeletal spinal metastasis

The majority of patients fall into categories I, II, or III, and if they are candidates for nonoperative treatment with either chemotherapy, hormonal manipulation, or radiation therapy. Operative intervention is reserved for patients in categories IV or V. The treatment of choice is anterior resection of the diseased vertebral body and reconstruction with bone graft or methylmethacrylate and spinal instrumentation as needed. Advances in spinal instrumentation have resulted in better methods for the stabilization of vertebral body collapse secondary to metastatic disease.

MANAGEMENT OF DEPRESSION IN CANCER PATIENTS WITH PAIN

Treatment decisions for depression in the cancer patient presume that a thorough medical and psychiatric assessment has led to an accurate diagnosis that will allow specific and effective intervention. Patients with severe depression, suicidal ideation or intent, or both require psychiatric consultation. Before planning an intervention, the physician should consider a history of previous depressive episodes and substance (including alcohol) abuse, family history of depression and suicide, concurrent life stresses, losses secondary to cancer (e.g., financial, social, and occupational) in addition to loss of good health, and the availability of social support. Once it becomes clear that the patient is depressed, one must consider coexisting organic factors before starting treatment.

Standard therapeutic approaches, such as the use of corticosteroids (450), chemotherapeutic agents [tamoxifen (451), asparaginase (452), interferon (453), and interleukin (454)], whole brain radiation (455), and amphotericin (456) can cause or exacerbate depressive symptoms in cancer patients. Likewise, the presence of brain metastases or tumors (457), metabolic and endocrine complications (458), and paraneoplastic syndromes (459) often contribute to the presence of depressive symptoms.

Depressed patients with cancer should be treated with a combination of psychological treatments (cognitive behavioral and supportive psychotherapy) and psychopharmacologic interventions (antidepressants and psychostimulants). For patients with cancer pain, interventions that help diminish mood disturbance also help reduce pain (460). Reducing severe pain often relieves depression.

Psychotherapy

The goals of psychotherapy are to reduce emotional distress and to improve morale, coping ability, self-esteem, sense of control, and resolution of problems. It consists of four basic components: social support, emotional expression, cognitive restructuring, and coping skills training. These are discussed in Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92 and Chapter 93.

Antidepressant Medications

The antidepressant agents appropriate for use in the cancer patient include the tricyclic antidepressants, atypical antidepressants, selective serotonin reuptake inhibitors, psychostimulants, and the anxiolytics (see Chapter 85). Although a number of studies report on the efficacy of antidepressants in depressed patients with cancer, there are only two double-blind, placebo-controlled studies demonstrating efficacy (461,462).

Tricyclic Antidepressants

These agents are particularly helpful for cancer patients with insomnia, pain, and depression and can be effective in relatively low doses (see Chapter 26 and Chapter 85). The literature supports the use of tricyclic antidepressants in the treatment of a wide variety of chronic pain syndromes (115). Studies show potent direct analgesic effects of tricyclic antidepressants, as well as enhancement of morphine analgesia (463). Dosing may be initiated at 10 to 25 mg at bedtime and the dose increased every 2 to 3 days until benefit is achieved. The effects on appetite and sleep are frequently rapid; the effects on mood may be delayed or not clinically apparent. The choice of tricyclic antidepressant depends on the nature of the depressive symptoms, medical problems present, and side effects of the particular drug. The depressed patient who has insomnia may benefit from the use of a tricyclic antidepressant that has sedating properties, such as amitriptyline or doxepin. Patients with psychomotor slowing benefit from agents with the least sedating properties, such as desipramine. Patients with stomatitis secondary to chemotherapy or radiation therapy, or who have slow intestinal motility should receive agents with the least anticholinergic effects, such as desipramine or nortriptyline.

Patients who cannot swallow pills may be able to take an antidepressant in a liquid suspension (amitriptyline, nortriptyline, or doxepin) or in intramuscular form (amitriptyline or imipramine). Consider parenteral administration of tricyclic antidepressants for the cancer patient unable to tolerate oral administration (absence of swallowing reflex, presence of intestinal drainage tubes, or intestinal obstruction). Three tricyclic antidepressants are available in injectable form: amitriptyline, imipramine, and clomipramine. All three have been given intravenously; however, only imipramine and amitriptyline are available for intramuscular injection.

Imipramine, doxepin, amitriptyline, desipramine, and nortriptyline are commonly used in the management of neuropathic pain in cancer patients. Dosing is similar to the treatment of depression, and analgesic efficacy, if it occurs, is usually observed at a dose of 50 to 150 mg daily; higher doses are sometimes necessary.

Atypical Antidepressants

The atypical antidepressants are generally considered to be less cardiotoxic than the tricyclic antidepressants (464). Consider bupropion if patients have a poor response to a reasonable trial of other antidepressants. It may be somewhat activating in medically ill patients and is contraindicated for patients with seizure disorders and brain tumors and in those who are malnourished. Trazodone is strongly sedating and in low doses (100 mg at bedtime) is helpful in the treatment of the depressed cancer patient with insomnia. Effective antidepressant doses are often greater than 300 mg per day. Trazodone may produce priapism.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors and new agents help depressed patients with medical illnesses because the drugs lack the significant adverse anticholinergic and cardiovascular effects of tricyclic antidepressants and other classes of antidepressants. Commonly selected agents in this category include fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil). These drugs have fewer sedative and autonomic effects than tricyclic antidepressants. The more common side effects are mild nausea, insomnia, headache, somnolence, and a brief period of increased anxiety. These drugs can cause appetite suppression that usually lasts for a period of several weeks. Typical onset of action occurs within 2 to 6 weeks after initiation of antidepressant therapy. Thus, 6 weeks of treatment at therapeutic doses

constitutes an adequate antidepressant trial.

The energizing properties of fluoxetine help in cancer patients who are persistently fatigued. Nausea, a common side effect with fluoxetine, usually diminishes after several weeks of treatment (465). Its relatively long half-life and its active metabolite nofluoxetine can be problematic in the medically ill patient in whom the ability to clear the drug is impaired. Razavi and colleagues (466) failed to demonstrate any benefit with fluoxetine for cancer patients with symptoms of anxiety and depression.

Paroxetine and sertraline have shorter half-lives and inactive metabolites and may be more useful in a medically ill population. Therapeutic daily dosage for paroxetine is 10 to 50 mg and for sertraline is 25 to 200 mg daily. The starting dose of sertraline, 50 mg per day, is the usually effective therapeutic dose, and the optimal dose when considering both efficacy and tolerability for most patients. For patients who do not show an adequate therapeutic response, the dose of sertraline can be increased in 50-mg-per-day increments at no less than weekly intervals to a maximum of 200 mg per day (467).

The development of newer antidepressants has focused on those that have low affinities for muscarinic cholinergic, histaminergic, and a_1-adrenergic receptors. Drugs that have low affinities for muscarinic receptors are associated with decreased likelihood of anticholinergic effects (dry mouth, constipation). Those possessing low affinities for histaminergic receptors would be expected to produce less sedation and weight gain, and those that have less affinity for a_1-adrenergic receptors would produce fewer cardiac effects (e.g., orthostatic hypotension).

Psychostimulants

Psychostimulants such as dextroamphetamine, methylphenidate, and pemoline help diminish sedation secondary to opioid analgesics and are useful antidepressants in the medically ill. Dextroamphetamine has been reported to have additive analgesic effects when used with opioids (235). Treatment with dextroamphetamine or methylphenidate usually begins with a dose of 2.5 mg on awakening and at noon. The dosage is slowly increased over several days until a desired effect is achieved or side effects (overstimulation, anxiety, insomnia, paranoia, and confusion) become apparent. Occasional doses of 60 mg per day are required, but doses of not more than 30 mg per day are more typical.

A strategy for treating depression associated with cancer pain is to start the patient on a stimulant and then add a tricyclic antidepressant after several days to help prolong and potentiate the effects of the stimulant (468). Psychostimulants used for the treatment of depression may result in a rapid response, usually within the first 2 days of treatment (469). Pemoline may be useful as both an antidepressant and adjuvant analgesic in cancer patients (470). Pemoline can be started at a dose of 18.75 mg in the morning and at noon, which is gradually increased over several days. Typically patients require 75 mg per day or less. Liver function tests should be monitored periodically with long-term treatment (471).

Anxiolytics

Several types of anxiety syndromes can appear in cancer patients with and without pain. These include reactive anxiety related to the stress of cancer and its treatment, anxiety that is a manifestation of a medical or physiologic problem related to cancer such as uncontrolled pain, and chronic anxiety disorders that predate the cancer diagnosis but are exacerbated during illness. The pharmacotherapy of anxiety in cancer patients involves the judicious use of a variety of agents, including the benzodiazepines, antihistamines, and antidepressants.

Hydroxyzine, an antihistamine, is a mild anxiolytic with sedative and analgesic properties that are useful in the mildly anxious cancer patient with pain. The addition of 25 to 50 mg of hydroxyzine every 6 hours to a regimen of opioids often helps relieve anxiety as well as provides adjuvant analgesia.

The main actions of benzodiazepines (hypnotic, anxiolytic, anticonvulsant, myorelaxant, and amnesic) confer a therapeutic value in a wide range of conditions. In general, use benzodiazepines in conjunction with other interventions (psychological treatments, antidepressants, other drugs), although such interventions have a slower onset of action. Indications for benzodiazepines include acute stress reactions, episodic anxiety, and fluctuations in generalized anxiety, and and as initial treatment for severe panic and agoraphobia.

The major clinical advantages of benzodiazepines are high efficacy and rapid onset of action. Adverse effects include psychomotor impairment, especially in the elderly, and occasionally paradoxical excitement. The high-potency benzodiazepines (e.g., clonazepam, alprazolam, lorazepam) are indicated for the treatment of panic disorder and mania. Benzodiazepines have so many uses in cancer patients that the physician may target more than one advantage as he or she considers choice of drug and dose. It is possible to treat nausea, pain, and anxiety simultaneously. These drugs treat reactive anxiety, insomnia, claustrophobia, and panic disorder. As they ameliorate anticipatory anxiety and phobia, they mitigate anticipatory nausea and a component of posttreatment nausea. With chemotherapy itself, they cause sedation, suppress recall of treatment, and limit vomiting, and most patients find them desirable. They suppress the restlessness associated with metoclopramide and other dopamine-antagonist antiemetics.

Although benzodiazepines relieve acute anxiety, they are relatively ineffective for chronic anxiety (472). Drugs such as antidepressants and anxiolytics such as buspirone, which combine anxiolytic and antidepressant actions, are more effective for the management of chronic anxiety. The starting dose of buspirone is 5 mg three times a day. Dosage may be increased by 5 mg per day until the desired effect is achieved. The usual daily maximum dose is 60 mg. Onset of anxiolysis is delayed relative to benzodiazepine and it is not uncommon for onset of effect to occur after 5 to 10 days.

The apparent efficacy of benzodiazepines in patients with major depressive disorder may depend on the patient's level of anxiety. In patients with chronic anxiety who are either unresponsive to or unable to tolerate antidepressants, triazolo-benzodiazepines or nonbenzodiazepine anxiolytics such as buspirone are preferable to other benzodiazepines as first-line drugs.

Because drug interactions and decreased clearance are often factors in treating cancer pain patients, benzodiazepines with shorter half-lives are desirable. Alprazolam is a benzodiazepine that produces dose-related sedation and relief of anxiety. Compared with other benzodiazepines, alprazolam has particular efficacy in the treatment of panic disorders and may have antidepressant effects. It may help cancer patients who have mixed symptoms of anxiety and depression, or serve as an adjuvant analgesic for certain types of neuropathic pain secondary to tumor growth (473). A typical starting dose is 0.25 mg three times a day. Therapeutic effects may require 4 to 6 mg daily (474).

Clonazepam also produces dose-related sedation and relief of anxiety. Its relatively long duration of action of 6 to 10 hours is attractive, particularly for long-term use. The usual dose range is 0.5 to 4.0 mg three times a day. Clonazepam, more than any other benzodiazepine, is used alone or with other drugs as an anticonvulsant. It may also be useful in the management of lancinating pains in the cancer setting and may possibly be an effective analgesic for patients with trigeminal neuralgia and postherpetic neuralgia (475,476).

SUMMARY

The goals of cancer therapy include cure, symptom palliation, psychological support, and research. Comprehensive cancer care encompasses a continuum that progresses from disease-oriented, curative, life-prolonging treatment through symptom-oriented, supportive, and palliative care extending, for some patients, to terminal hospice care. Pain relief must be a priority in cancer patients. Pain is the most common symptom experienced by cancer patients, and it requires aggressive treatment to maximize both quality and quantity of the patient's life.

Interdisciplinary collaboration is essential for comprehensive care of the cancer patient. Disciplines and specialties involved in care commonly include anesthesiologists, oncologists, surgeons, psychiatrists, psychologists, physical therapists, pharmacists, nurses, and social workers.

Detailed assessment of pain and other quality-of-life concerns is the foundation for successful pain management in the cancer patient. Typically, the pain experience is multidimensional, and treatment must address both the physical and emotional components. Aggressive therapy of both cancer and pain are mutually beneficial and are best done by skilled, interdisciplinary teams.

Most patients can attain adequate symptomatic relief of cancer pain using appropriate oral pharmacotherapy. The concurrent use of adjunctive or specialized therapies is sometimes necessary, however, and referral for specialized surgical, anesthetic, or psychological intervention benefits a significant number of patients. In

addition, the growth of the home care industry has broadened the possibilities of extending interventional pain management strategies into the home.

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CHAPTER 37

Part A: Radiotherapeutic Management of Symptomatic Disease

Nora A. Janjan

BASIC CONSIDERATIONS

In the 1990s 11 million cases of cancer were diagnosed, and 5 million people died from cancer. Approximately one-half of patients diagnosed with cancer develop metastatic disease. More than 70% of all cancer patients develop symptoms from either their primary or metastatic disease (1,2,3 and 4). Although any site can be involved, 64% of the palliative therapy administered in the United States is prescribed to relieve symptoms from bone metastases. Reflecting the systemic spread of disease, metastatic involvement of a solitary bony site or of only the bones is rare and occurs in fewer than 10% of patients. Prognosis is influenced by the overall metastatic burden and the number and location of the sites involved by disease. When metastases are found also in the lung, liver, or central nervous system, the prognosis is especially poor.

Palliation represents a large component of cancer treatment and includes the use of therapeutic and supportive care measures. Unlike other aspects of cancer therapy, tumor control and survival are not the end points of therapeutic success in palliative care. The goal of palliative care is to effectively and efficiently relieve symptoms and maintain the maximum quality of life for the duration of the patient's life (2,3,4,5,6,7,8 and 9). Effective palliation of cancer-related pain can enhance quality of life by improving functional and emotional well-being. The factors that determine the effectiveness of palliative radiation include the percentage of patients who experience persistent and recurrent symptoms in the radiated area, whether reirradiation is possible, and if persistent and recurrent symptoms can be relieved with reirradiation or other therapeutic modalities (9,10 and 11).

Bone metastases are the most common cause of cancer-related pain, and more than 70% of patients with bone metastases are symptomatic. Among hospitalized patients, severe pain was experienced by more than 50% of patients with bone metastases (4). One of the most important goals in the treatment of bone metastases is to relieve suffering and return the patient to independent function (12,13). The location of the metastasis, however, can influence the degree of pain relief achieved with palliative interventions. Metastatic involvement of weight-bearing bones, and bones responsible for ambulation and activities of daily living are often less likely to respond completely to palliative interventions. Pain relief is achieved in 73% of spine metastases, 88% of limb lesions, 67% of pelvic metastases, and 75% of metastases to other parts of the skeleton (10).

The debility that results from cancer and its treatment is a significant issue on a socioeconomic level. Cancer was diagnosed in sites other than the skin in 1,647 of 9,745 (17%) elderly community-based Medicare beneficiaries. Cancer patients had poorer health, more limitations of the activities of daily living, and greater levels of health care use (14). Limitations in activities included difficulty walking (38%), getting out of a chair (21%), completing heavy housework (34%), and shopping (17%). Poorer health was observed more frequently in lung, breast, prostate, and colon cancer patients. Lung cancer most frequently limited the activities of daily living. Lung, bladder, and prostate cancers predicted for increased health care use, and the mean annual Medicare reimbursement for lung cancer was more than twice that for colon, breast, and prostate cancers. Even though the decrease in functional capacity for cancer patients was not as great as with other chronic diseases, such as arthritis, stroke, and emphysema, the health care costs for cancer patients were greater than those for other chronic diseases (15). This most likely results from the inability to determine how many of the cancer patients evaluated had active disease at the time of the evaluation. If this assumption is true, then an even greater percentage of cancer patients with active disease are functionally impaired and use more health care resources. Quality of life measurements have been shown to predict for survival and add to the prognostic information derived from the Karnofsky Performance Status (KPS) and extent of disease. Physical symptoms that include pain, dry mouth, constipation, change in taste, lack of appetite and energy, feeling bloated, nausea, vomiting, weight loss, and feeling drowsy or dizzy portend a poorer prognosis (16).

DEMOGRAPHICS

The three most common cancers, lung, breast, and prostate cancers, have high rates of metastatic spread to bone and visceral structures (17,18 and 19). Occasionally, musculoskeletal pain is an indicator of an undiagnosed malignancy. Among 491 patients with new or recurrent complaints of bone pain and no known underlying malignancy, 4% of the entire group and 9% of patients 50 years of age or older had definite evidence of metastases (20). Of the group that had any abnormality noted on bone scan, 20% had evidence of metastatic disease, and all of these occurred among patients 50 years of age or older. For all patients, 52% of pain localized in the back, 16% in the hips or pelvis, and 15% in the extremities. Among cancer patients, diffuse pain was identified in 57%, 18% had neck or upper T-spine pain, and 18% had pain in the hips, pelvis, or the extremities. Malignancies were subsequently diagnosed in the lung (32%) and prostate (16%).

Because of an aging population, the incidence of prostate cancer is increasing significantly. Prostate cancer represents the second leading cause of death from cancer among men (21). Each year between 1995 and 1999, more than 1 million men older than age 50 in the United States died of prostate cancer (22). The clinical presentation of prostate cancer has changed with routine use of digital rectal examination and prostate-specific antigen (PSA) screening. In the 1970s, only 50% of cancers were confined to the prostate gland, and metastases were present in 30% of cases at diagnosis. When patients were referred to a urologist for symptoms, 70% of cases had disease confined to the prostate gland; but pathologic confirmation of disease confined to the prostate gland occured in only 50% of patients undergoing prostatectomy. However, with routine screening using digital rectal examination and PSA more than 90% of cases have disease confined to the gland, and 70% of these are pathologically confirmed.

The natural history of prostate cancer based on a therapeutic approach that does not include routine screening and is limited to palliative intervention showed a statistically significant relationship between disease-specific death, stage of disease, and tumor differentiation. Of 719 new cases, 45% were diagnosed incidentally and 31% had organ-confined disease (23). Symptoms at diagnosis included prostatism (42%), bone pain (12%), and fatigue (9%). The median age of diagnosis was 75 years. Age at diagnosis, however, did not influence disease-specific survival rates. Prostate cancer was the cause of death in 62% of patients and the disease-specific survival rates at 1, 5, and 10 years were 80%, 38%, and 17%, respectively (Table 37A-1).

	5 Yr (%)	10 Yr (%)
Stage of disease[a]		
T^a	84	74
T^b	60	29
T^1	47	12
$T_{1,2}$	20	4
$T_{1,2}$, N_x, M_b	71	42
$T_{1,2}$, N_x, M_x, or all three	20	4
Tumor grade[a]		
G1	65	42
G2	42	12
G3	21	8

[a]$p < .0001$.

From Bonne M, Nerstrom B, Overgaard J. The natural history of prostate carcinoma based on a Danish population treated with deferment policy. Cancer 1987;59:917–926.

TABLE 37A-1. Disease-specific survival rates at 5 and 10 years based on stage of disease and tumor differentiation among 623 prostate cancer patients treated only with palliative intent

The risk for the subsequent development of distant metastases is significantly lower when the primary tumor is controlled. Survival rates after an isolated recurrence of disease in prostate cancer are influenced by the initial stage of the disease and the disease-free interval from initial treatment (24,25). In over 70% of cases of locally recurrent prostate cancer, radiation can control symptoms that include hematuria, urinary outflow obstruction, ureteral obstruction, and lower extremity edema (24). With or without local recurrence, the survival rate is most compromised by the presence of distant metastases. The survival rates at 5 and 10 years after pelvic recurrence alone equal 50% and 22%, respectively. With distant metastases, the survival rate at 5 years is 20% and less than 5% at 10 years (25).

Bone metastases are evident in 30% to 40% of prostate cancer patients at diagnosis, but pain is the presenting symptom in only 11% of these newly diagnosed patients (23,26). However, pain develops in 75% of prostate cancer patients during the course of their disease (27). Radiographically detectable bone metastases develop in 20% of patients with stage A_2 (T_{Ib}) and B (T_2) disease, 40% of patients with stage C (T_3), and 62% of patients with stage D1 (T_4) disease presentations (23,25,28).

Bone scans are the most sensitive and specific method of detecting bone metastases, but magnetic resonance imaging (MRI) is the best available technique for evaluating the bone marrow, neoplastic invasion of the vertebrae, central nervous system, and peripheral nerves (29,30,31 and 32). Bone or other metastases rarely fail to be detected when radiographic diagnosis is pursued. When radiographic confirmation of malignancy is equivocal, bone biopsy should be considered (33,34 and 35).

After bone metastases are diagnosed, the median survivals are 12 months for breast cancer, 6 months for prostate cancer, and 3 months for lung cancer. In breast cancer, the median survival rate is 48 months when metastases are confined to the skeletal system, but it decreases to only 9 months if visceral metastases are also present (18,19). In prostate cancer, the distribution of bone metastases on scintigraphy also has prognostic significance. The rate of survival is significantly longer when the metastases are restricted to the pelvis and lumbar spine, and among patients who respond to salvage hormone therapy (25,28,29). Any metastatic involvement outside the pelvis and lumbar spine results in lower rates of survival irrespective of response to salvage hormone therapy. The median length of survival is critical to evaluating response to and determining the appropriate recommendations for palliative therapy.

Although the length of survival can vary significantly after the development of bone metastases, two factors are constant. First, the presence of bone metastases predicts for progression of disease to other sites, and second, bone metastases are the most common cause of cancer-related pain (1,7,8,9,10,11,12,13,14,15,16,17,18 and 19,23,24 and 25,28,29). Factors that influence prognosis among patients with metastatic disease include the site of the primary disease, metastatic burden, interval between primary diagnosis, symptoms of disease, and KPS. The KPS has been shown to consistently predict survival after palliative irradiation. The site of the primary disease and the presence of a solitary metastatic site are predictive of a more prolonged survival (16,36,37,38 and 39).

Bone metastases in prostate and breast cancers involve the axial skeleton more than 80% of the time because of the predilection of these tumors to involve the red marrow. Metastatic invasion of the bone cortex rarely happens without red marrow involvement (30,31,32,33,34 and 35,40,41,42,43,44,45 and 46). For this reason, the spine, pelvis, and ribs are generally involved before metastases become evident in the skull, femora, humeri, scapula, and sternum. The mechanisms involved in the metastatic spread of cancer to the bone are complex. The predilection of specific types of tumors, such as prostate cancer, that metastasize to bone is not well understood.

Bone is unique because it is continuously remodeled by local and systemic growth factors. The process involved in bone remodeling includes an increase in osteoclast activity followed by an increased attraction and proliferation of osteoblast precursors, which mature and lay down new bone (34,35,40,41,42 and 43,45,46). Tumors can release osteoclastic stimulatory factors either locally or systematically including parathyroid hormone-related protein, transforming growth factor-a, transforming growth factor-b, prostaglandins, and cytokines. Tumors can also indirectly stimulate bone loss through the activation of immune mechanisms that release cytokines including tumor necrosis factor and interleukin-1. Metastases to bone result from a synergistic relationship between the cancer cell and the bone that results in increased bone resorption because of release of mediators from the cancer cells or leukocytes. Factors released during bone resorption promote growth of the cancer through activation of proliferation-associated oncogenes. The relationship between bone invasion and bone pain is unknown. Pain may result from the stimulation of nerve endings from the release of factors such as prostaglandins, bradykinin, histamine, or substance P in areas of bone involvement (43). Mass effect from stretching of the periosteum, pathologic fracture, or direct tumor growth into adjacent nerves and tissues may be the mechanisms for pain in larger metastatic deposits.

ROLE OF RADIOTHERAPY

Although palliation constitutes a large part of radiotherapeutic practice, radiation is underused in palliative care. At the M. D. Anderson Cancer Center in Houston, approximately 25% of all radiation treatments were administered with palliative intent. This pattern of practice has been consistent for over 35 years, and it has specifically been the same through the 1990s. When compared with a course of curative radiation, 30% fewer radiation treatments are given during a course of palliative radiation. Because of this, over 40% of the total number of patients who had radiation at the M. D. Anderson Cancer Center were treated with palliative intent (13).

Consistent with radiotherapeutic practice in the United States, palliative radiotherapy for bone metastases was administered to approximately 25% of all radiotherapy patients in Sweden. However, this corresponded to only 10% of all Swedish cancer patients (47). It is considered that palliative radiotherapy for bone metastases is underused in Sweden because metastatic disease occurs in more than 10% of cancer patients. It is also unclear if the other therapeutic options used to treat bone metastases are providing pain relief that is comparable with radiation. In 1993, approximately 800,000 patients were estimated to have metastatic disease, and bone metastases were the most frequent symptomatic site (48). Approximately 300,000 patients nationwide receive palliative radiation costing $900 million per year. Approximately 100,000 patients receive curative radiation therapy costing a total of $1.1 billion per year (49). Although more abbreviated radiation courses may result in cost savings, the response to therapy must be critically analyzed to ensure that treatment efficacy is not compromised. Ineffective therapy may prove more costly than a more prolonged and effective radiation schedule because of the continued need for analgesics and the functional limitations caused by unrelieved pain and disability (50,51).

Multidisciplinary evaluation of patients with metastatic disease to the bone allows comprehensive management of the associated symptoms, determines the risk for pathologic fracture, and helps coordinate administration of a wide range of available antineoplastic therapies (9). Bone metastases can be treated with localized, systemic, or both kinds of therapies (12,34,43,44,45,46,47,48,49,50,51,52,53,54,55 and 56). Because radiation provides treatment only to a localized symptomatic site of disease, it is frequently used in coordination with systemic therapies such as chemotherapy, hormonal therapy, and bisphosphonates. Radiopharmaceuticals are another systemic option that treats diffuse symptomatic bone metastases. Because the radiation is deposited directly at the involved area in the bone, radiopharmaceuticals, such as strontium 89, can also be used to treat bone metastases when symptoms recur in a previously irradiated site (57,58,59,60,61,62,63,64,65,66,67,68,69,70,71 and 72). Radiopharmaceuticals can also act as an adjuvant to localized external beam irradiation and reduce the development of other symptomatic sites of disease.

Control of cancer-related pain with the use of analgesics is imperative to allow comfort during and while awaiting response to therapeutic interventions. Pain

represents a sensitive measure of disease activity. Close follow-up should be performed to ensure control of cancer and treatment-related pain, and to initiate diagnostic studies to identify progressive or recurrent disease. Pain, risk for pathologic fracture, and spinal cord compression are the most common indications to treat bone metastases with localized therapy including radiation and surgery.

CLINICAL CONSIDERATIONS

A number of clinical, prognostic, and therapeutic factors must be considered to determine the most optimal treatment regimen for a course of palliative radiotherapy. The clinical status is accounted for in the treatment setup and in the number of treatments prescribed. Palliative radiation should effectively and efficiently relieve pain and suffering and minimize treatment-related morbidity. The radiation dose and fractionation schedule also should consider the integration of other therapies. Many options exist in the radiotherapeutic management of tumors that cause localized symptoms. Although any site of disease can be effectively palliated, treatment of bone metastases is one of the most common indications for palliative irradiation with external beam therapy (12,44,47,51).

The limited radiation tolerance of the normal tissues, such as the spinal cord, that are adjacent to a bone metastasis make it impossible to administer a large enough dose of radiation to eradicate a measurable volume of tumor. Palliative radiation should result in sufficient tumor regression of critical structures to relieve symptoms for the duration of the patient's life. Symptoms that recur after palliative radiation most commonly result from localized regrowth of tumor in the radiation field.

Because patients with metastatic disease have a limited life expectancy, palliative radiation is generally given over a shorter period of time. Unlike curative therapy, in which a high total dose of radiation is administered over 5 to 7 weeks to eradicate tumor (conventional radiation schedule), a low total dose is given with palliative radiation over 1 to 2 weeks (hypofractionated radiation schedule). Based on the radiation tolerance of normal tissues, a low daily radiation dose (1.8 to 2.0 Gy) is given with conventional radiation; in contrast, large daily radiation fractions are given with hypofractionated radiation schedules. Hypofractionated radiation schedules for palliative therapy can range from 2.5 Gy per fraction administered over 3 weeks for a total dose of 35 Gy to a single 8-Gy dose of radiation. Most frequently, 30 Gy is administered in 10 fractions over 2 weeks (9,12,43,44,47,48,73,74,75,76,77 and 78). Especially among patients with short life expectancies, many centers administer 20 Gy in 1 week because the rates of pain relief, mobility, and frequency of pathologic fractures are similar to more protracted radiation schedules.

Symptom Relief of Locally Advanced or Metastatic Disease

Most cancer patients present with symptoms. Symptoms must be controlled whether treatment is administered with curative or palliative intent. Curative treatment attempts to render the patient disease free. Curative therapy can be applied to either primary or metastatic disease. The prognosis of a patient who is rendered disease free after resection of a single liver metastasis from rectal cancer is better than the case of a patient who has an inoperable lung cancer who does not have metastatic disease.

Treatment with palliative intent is intended to control the symptoms of disease when the disease cannot be eradicated. Effective antineoplastic therapy provides the most palliative benefit for locally advanced or metastatic cancer in any organ. Radiation can be used alone, or in combination with other antineoplastic therapies such as chemotherapy and surgery. The symptoms most commonly relieved by radiation are pain, bleeding, and obstruction. The palliative interventions recommended depend on the patient's clinical status, burden of disease, and location of the symptomatic site. For either locally advanced or metastatic disease, these factors are indexed to the relative effectiveness, durability, and morbidity of each palliative intervention. The prognosis represents the single most important factor in deciding palliative therapy.

The symptomatic site becomes more important to the palliative approach than whether it results from locally advanced or metastatic tumor. Similar radiation portals are used to palliate bronchial obstruction caused by a primary lung cancer, recurrent breast cancer, or metastatic melanoma. The number of radiation fractions prescribed for treatment with palliative intent depends on prognosis and not primary histology. Common sites palliated by radiation, either alone or in combination with other treatments, include tumor involvement of the lung, pelvis, skin and subcutaneous tissues, brain, and bone. Symptoms resulting from cancer in these sites include pain, bleeding, visceral obstruction, and lymph-vascular obstruction.

Lung

Locally advanced primary or metastatic involvement of the lung often requires palliative intervention because cure is possible in only a few of these cases. A variety of symptoms, some of them emergent, can manifest because of tumor involvement of the lung (79). Pain can result from tumor invasion of the ribs and nerve roots of the chest wall. Vertebral involvement can be associated with spinal cord compression. Obstructive pneumonitis and hemoptysis can result from bronchial obstruction. Mediastinal infiltration can cause superior vena cava syndrome. All of these clinical presentations can be palliated with external beam radiation that encompasses the disease that is evident on diagnostic images and that treats pain referred along involved nerve roots. Radiation schedules that administer 30 Gy in 10 fractions over 2 weeks are typically prescribed to previously unirradiated sites. If the area has been previously irradiated, techniques that exclude critical anatomic structures, such as the spinal cord, are applied. Other approaches can be used when the symptomatic site is well localized and accessible. Brachytherapy, which applies radioactive sources next to tumors, can be used to treat bronchial obstruction and bleeding by placing a radioactive source directly against the tumor under bronchoscopic guidance. In these cases, large doses of radiation can be delivered over a few minutes by a high-dose-rate brachytherapy unit.

Pelvis

Hemorrhage and visceral, lymph-vascular, and nerve root obstruction present most commonly with locally advanced or metastatic disease in the pelvis. Treatment may require emergent radiotherapeutic, surgical interventions, or both. Hemorrhage is commonly associated with tumors involving the rectum and genitourinary tracts. As with tumors in the lung, radiation is an effective means of stopping active bleeding. Colorectal cancers are often diagnosed among patients with unexplained bleeding. Because these tumors are generally locally advanced, preoperative radiation is given in 25 treatments over 5 to 6 weeks if no or limited metastatic disease is evident; this is intended to stop bleeding, render the patient operable, and provide a chance for cure. With extensive metastatic disease, 30 Gy can be given over 2 to 3 weeks to palliate symptoms of bleeding and obstruction. Colorectal tumor involvement may also result in obstruction requiring stent placement to maintain the integrity of the visceral lumen while administering radiation (79). Occasionally, a diverting colostomy is required to bypass intestinal obstruction or fistula formation.

Tumors involving the cervix can hemorrhage and require emergent radiotherapeutic intervention. Superficial x-rays are applied directly to the bleeding cervix through a cone and treat the bleeding site and do not compromise later radiation of other pelvic structures. Usually, radiation doses between 5 and 10 Gy are administered in one to three applications of cone therapy. Brachytherapy also can be used to treat gynecologic tumors, especially in the vagina, cervix, and endometrium.

Bladder cancers or tumors that secondarily invade the bladder can also result in significant bleeding that can be palliated by external beam radiation. Urinary obstruction commonly occurs with locally advanced pelvic cancers, especially with prostate and cervical cancers. Occasionally, placement of a urinary stent or urostomy or nephrostomy is required until sufficient tumor regression can be accomplished by radiation to reestablish integrity of the urinary tract (79). As with the bowel and gynecologic tracts, a vesical fistula, resulting from either the tumor itself or from tumor regression, remains a concern.

The pelvic lymph nodes and major blood vessels may become obstructed by tumor. This most frequently is seen when tumors arise in pelvic structures, but can also occur with pelvic metastases from breast and other cancers. Lymph-vascular obstruction results in painful edema that is refractory to diuretic and other therapies. When severe, fluid and electrolyte imbalances can occur. Pelvic radiation can relieve lymph-vascular obstruction through tumor regression.

Pelvic tumors can also invade the sacral plexus and result in intractable pain. Tumor can track along nerve roots and can be associated with bony invasion of the sacrum. Pain caused by visceral, lymph-vascular, or both kinds of obstructions often responds more rapidly to palliative radiation than the neuropathic pain seen with sacral plexus involvement. Other radiotherapeutic approaches, such as brachytherapy, are extremely limited when the cancer persists or recurs after external beam radiation. Interventional pain management techniques are frequently required to control pain associated with sacral plexus involvement.

Skin and Subcutaneous Tissues

Tumors can cause ulceration of the skin and subcutaneous tissues that are often painful and distressing because of constant drainage. Representing a source for the development of sepsis in immunocompromised patients, localized radiation can be applied to destroy tumor and allow reepithelialization of the skin. Radiation that treats only the skin and subcutaneous tissues (electron beam therapy) is generally used to avoid radiation side effects to underlying uninvolved normal structures. Although usually 10 radiation treatments are given, the course of radiation can be abbreviated further, ranging from 1 to 5 days. Occasionally, these lesions are treated with brachytherapy. The radioactive sources can be placed in a mold that sits on top of the tumor and delivers treatment over a few minutes (high-dose rate)

or a few days (low-dose rate).

Brain Metastases

Radiation is used to relieve the symptoms of headache, seizure, nausea and vomiting, and neurologic dysfunction associated with brain metastases. Surgery, either alone or in combination with radiation, is often performed when a solitary brain metastasis is present, if the performance status is good and if the cancer burden is otherwise limited. Radiation is generally given over 2 to 3 weeks with daily fractions of 2.5 to 3.0 Gy per day; total radiation doses range from 25 Gy after resection to 30 Gy with unresectable disease and a poor prognosis (80).

Bone Metastases

There are two major sets of experience with palliative radiation for bone metastases. The Radiation Therapy Oncology Group (RTOG) conducted a prospective trial that included a variety of treatment schedules. To account for prognosis, patients were stratified on the basis of whether they had a solitary or multiple sites of bony metastases. The initial analysis of the study concluded that low-dose, short-course treatment schedules were as effective as high-dose protracted treatment programs (81). For solitary bone metastases, no difference existed in the relief of pain when 20 Gy using 4-Gy fractions was compared with 40.5 Gy delivered as 2.7 Gy per fraction. Relapse of pain occurred in 57% of patients at a median of 15 weeks after completion of therapy for each dose level. In patients with multiple bone metastases, the following dose schedules were compared: 30 Gy at 3 Gy per fraction, 15 Gy given as 3 Gy per fraction, 20 Gy using 4 Gy per fraction, and 25 Gy using 5 Gy per fraction. No difference was identified in the rates of pain relief between these treatment schedules. Partial relief of pain was achieved in 83% and complete relief occurred in 53% of the patients studied. More than 50% of these patients developed recurrent pain, the fracture rate equaled 8%, and the median duration of pain control was 12 weeks for all the radiation schedules used for multiple bony metastases. Prognostic factors for response included the initial pain score and site of the primary cancer.

In a reanalysis of the data, a different definition for complete pain relief was used and excluded the continued administration of analgesics. Using this definition, the relief of pain was significantly related to the number of fractions and the total dose of radiation that was administered (82). Complete relief of pain was achieved in 55% of patients with solitary bone metastases who received 40.5 Gy at 2.7 Gy per fraction as compared with 37% of patients who received a total dose of 20 Gy given as 4 Gy per fraction. A similar relationship was observed in the reanalysis of patients who had multiple bone metastases. Complete relief of pain was achieved in 46% of patients who received 30 Gy at 3 Gy per fraction versus 28% of patients treated to 25 Gy using 5-Gy fractions. In most cases, the interval to response was 4 weeks for both complete and minimal relief of symptoms.

Three important issues are identified from the RTOG experience. First, the results of the reanalysis demonstrate the importance of defining what represents a response to therapy. Second, this revised definition of response showed that the total radiation dose did influence the degree that pain was relieved (81,82). The response rates and the radiobiologically equivalent doses are listed from the reanalysis in Table 37A-2 for each of the treatment schedules used. Showing that higher radiation doses result in higher rates of pain relief, these results also correspond well to the results in another study with breast, prostate, and lung cancer patients (Table 37A-3). Patients treated with total doses of 40 Gy or more had a 75% rate of complete pain relief versus a 62% rate of complete pain relief for patients treated with total doses of less than 40 Gy (10). Third, the RTOG experience identified the amount of time that was needed to experience relief of pain after radiation for bone metastases (Table 37A-4). It is important to note that only one- half of the patients who were going to respond had relief of symptoms at 2 to 4 weeks after radiation (81,82). This underscores the need for continued analgesic support after completing radiation. Consistently, it took 12 to 20 weeks after radiation to accomplish the maximal level of relief. That period of time may reflect the time needed for reossification. Radiographic evidence of recalcification is observed in approximately one-fourth of cases, and in 70% of the time recalcification is seen within 6 months of completing radiation and other palliative therapies (42,43,45,46). Therefore, determining the time to response as well as defining the parameters of response are critical to an evaluation of outcome. The total dose of radiation may also be a significant factor for complete pain relief.

	Dose per fraction (Gy)	Total dose (Gy)	Tumor dose at 2 Gy per fraction[a]	Complete response rate (%)[b]	p Value
Solitary bone metastases					p < .0005
	2.7	40.5	42.9	55	
	4.0	20.0	23.3	37	
Multiple bone metastases					p < .0005
	3.0	30.0	32.5	46	
	3.0	15.0	16.2	36	
	4.0	20.0	23.3	49	
	5.0	25.0	31.25	38	

[a]The radiobiological equivalent dose if administered at 2 Gy per fraction.
[b]The complete response rate using the definition that excludes the use of analgesics and thus accounts for re-treatment.

TABLE 37A-2. Dose response evaluation from the reanalysis of the radiation therapy oncology group bone metastases protocol

	Complete response (%)	Less than 40 Gy (%)	Equal to or greater than 40 Gy (%)
Breast	66	41	71
Prostate	73	62	75
Lung	57	44	63

[a] The overall complete response rate and complete response rate stratified to total radiation dose administered are presented (10).

TABLE 37A-3. Rate of complete response after treatment of bone metastases with conventional fractionation (2 Gy per fraction) [a]

Total dose (Gy)	Dose per fraction (Gy)	Tumor dose at 2 Gy per fraction	Weeks after radiation			
			<2 (%)	3-4 (%)	4-12 (%)	12-20 (%)
Solitary metastases						
40.5	2.7	42.9	7	29	53	71
20	4	23.3	16	30	46	62
Multiple metastases						
30	3	32.5	19	41	73	84
15	3	16.2	24	70	84	95
20	4	23.3	28	53	75	82
25	5	31.25	22	41	72	82

[a]This prospective trial, conducted by the Radiation Therapy Oncology Group, randomized radiation dose and number of fractions and treated the randomization on the basis of solitary or multiple bone metastases (RTOG). Also listed is the radiobiological equivalent dose if administered at 2 Gy per fraction.

TABLE 37A-4. Percentage of patients who responded to radiation relative to time, designated in weeks after completion of radiation therapy [a]

Similar issues were observed when pretreatment pain characteristics were used to determine the efficacy of palliative radiation. Among patients who had a life expectancy of only a few months, fewer than 25% of patients had a complete response to palliative radiation. In this case, a complete response was defined as becoming pain free within 28 days after the start of treatment with stable analgesic consumption. A partial response was achieved in 35% of patients, and 42% had no response to palliative radiation. Pretreatment evidence of neuropathic pain was the only significant prognostic or clinical variable that predicted for failure to respond to palliative radiation and severe neurogenic symptoms were present in 33% of patients treated (36,(83,84 and 85).

SINGLE FRACTION RADIATION

A single large radiation fraction is reportedly as effective in relieving pain as other radiation schedules that have more treatments. Radiobiologically, a single 8-Gy fraction would give the same side effects to late reacting tissues (tissues that do not regenerate like the spinal cord) as if 18 Gy were given over nine treatments at 2 Gy per fraction (86). Because the tumor and acute reacting tissues, such as the esophagus and other mucosal structures, respond differently than the late reacting tissues, the radiobiologically equivalent dose to the tumor for a single 8-Gy fraction would be 12 Gy if 2 Gy fractions were used. The most common dose fractionation schedule used for palliative radiation in the United States is 30 Gy over 10 fractions. Radiobiologically, this is equivalent to 36 Gy at 2 Gy per fraction for late reacting tissues and 32.5 Gy to the tumor. When a single dose of radiation was compared with a radiation schedule with multiple radiation fractions, no difference was reported in either how quickly symptoms resolved or the duration of pain relief (9,47,48,73,76,78,87,88,89 and 90). In each case, symptom relief lasted 3 months in 70% of patients, 6 months in 37%, and 12 months in 20% of cases. Like the RTOG study, approximately 69% respond at 4 weeks, and response rates plateau, totaling 80%, at 8 weeks (81,82,87,88,89 and 90). Complete response rates after a single 8-Gy fraction total 15% at 2 weeks, 23% at 4 weeks, 28% at 8 weeks, and 39% at 12 weeks postradiation.

Despite the radiobiological differences in the dose administered, the similarities in response may be caused by tumor regression and reossification that occurs at 3 months. The RTOG experience showed that the maximum response to therapy was seen consistently at 3 months and was independent of dose administered (81,82). The disparity in the relationship between radiation dose and clinical response may also be attributed to limited follow-up in the single fraction study because a significant proportion of patients in the study were lost to follow-up after 3 months (87,88,89 and 90). With longer follow-up, the response to a single radiation fraction may not prove to be as durable as multiple fractions that give high total radiation doses. These data demonstrate that prognosis needs to be linked to issues such as site irradiated, total radiation dose, and reirradiation (11).

A shorter radiation schedule, such as a single fraction, is advantageous for patients with poor prognostic factors. First, it is easier for patients with a poor KPS to complete therapy. Second, response rates are equal for single and multifraction therapy at 3 months because median survival is less than 6 months among patients with poor prognostic factors (9,48,73,75,87,88,89 and 90). The option of re-treatment after a single fraction of radiation may also provide an advantage among patients with good prognostic factors as a means to periodically reduce tumor burden and control symptoms in noncritical anatomic sites. Higher radiation doses that provide more durable pain relief are considered warranted for patients with good prognostic factors who require treatment over the spine and other critical sites (9,10,12,44,48,73,74,78,91,92,93,94,95,96 and 97).

The projected length of survival is the critical issue to determine the optimal radiation dose and schedule for palliative radiation. In one study, only 12 of 245 patients were alive at the time of analysis, with approximately 50% alive at 6 months, 25% at 1 year, 8% at 2 years, and 3% at 3 years after palliative radiation. For breast cancer patients the survival rates at these time points after palliative radiation were 60%, 44%, 20%, and 7%, respectively. For prostate cancer, the survival rates were 60% at 6 months, 24% at 1 year, and there were no patients who survived 2 years (77). In the RTOG trial the median survival for solitary bone metastases was 36 weeks and was 24 weeks for multiple bone metastases (81,82). The RTOG study also demonstrated that the level of pain correlated with prognosis among patients with multiple bone metastases. This survival difference may be an important observation because unrelieved pain and the resultant sequelae of immobility may contribute to mortality as well as morbidity (14,15 and 16,25,28,37,83). Larger data sets that include prognostic factors in multivariate analysis are required to determine the effect of pain and response to therapy on quality of life and survival outcomes. Although equal rates of response are observed between a single and multiple fractions of radiation, future analyses should evaluate survival and durability of response. Most important, these analyses should assess the efficacy and costs of treating symptoms that recur in an irradiated field.

Reirradiation for persistent or recurrent pain is often precluded when higher radiation doses are administered. Because the radiobiological dose is relatively low when a single fraction of radiation is administered, reirradiation is generally possible (11,86,87,88,89 and 90). Reirradiation was necessary in 25% of patients who received a single 8-Gy radiation fraction, but all of these patients were reported to respond to the second dose of radiation (87,88,89 and 90). When a single fraction of 4 Gy was compared with a single 8-Gy fraction, the rate of response was slightly lower and fewer acute radiation reactions were noted, but a greater proportion of patients required reirradiation (89). With reirradiation, the overall rate of response was equivalent for 8- and 4-Gy fractions. Acute radiation toxicities are a function of the dose per fraction, total dose, and the area and volume of tissue irradiated. If mucosal surfaces such as the upper aerodigestive tract, bowel, and bladder can be excluded from the radiation portals, acute radiation side effects can be significantly reduced. The radiation schedule used for palliative radiation is therefore influenced by the radiation tolerance of adjacent normal tissues as well as prognosis.

PATHOLOGIC FRACTURE

The most significant morbidity of bone metastases relates to pathologic fracture and spinal cord compression. Pain that persists or that recurs after palliative radiation should be evaluated to exclude progression of disease, possible extension of disease outside the radiation portal that results in referred pain, and bone fracture. Reduced cortical strength can result in compression, stress, or microfractures associated with reduced cortical strength. Plain radiography has a 91% concordance rate in detecting posttreatment disease progression and fractures in comparison with the 57% specificity rate of bone scans performed after radiotherapy (45). Pathologic fractures occur in 8% to 30% of patients with bone metastases (98,99,100,101,102 and 103). Proximal long bones are more commonly involved than distal bones. Consequently, pathologic fractures occur 50% of the time in the femur and 15% in the humerus (Fig. 37A-1). The femoral neck and head are the most frequent locations for pathologic fracture because of the propensity for metastases to involve proximal bones and the stress of weight placed on this part of the femur. More than 80% of pathologic fractures occur in breast (50%), kidney, lung, and thyroid cancers.

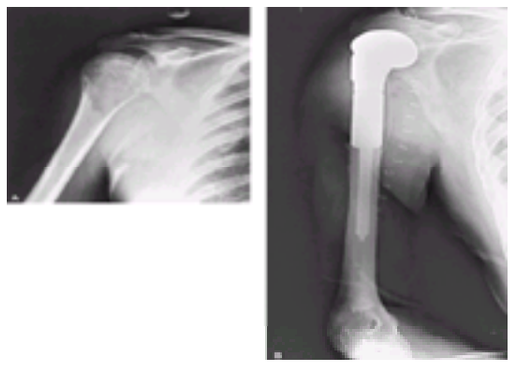

Figure 37A-1. **A:** An extensive lytic lesion in the proximal humerus. **B:** Prophylactic internal fixation performed to prevent pathologic fracture. This patient, who complained primarily of pain in the hip, would have been placed on crutches to reduce stress on the involved femur. A bone scan and radiography, obtained to exclude other sites of metastatic involvement, identified this lesion in the humerus. The humerus would have certainly fractured if all the patient's weight had been displaced to the upper extremities with crutches.

Approximately 10% to 30% of metastatic lesions in long bones develop a pathologic fracture that requires surgical intervention. Patients with pathologic fracture caused by bone metastases have clinical outcomes after surgical repair that are comparable with patients sustaining a traumatic fracture (99,100 and 101). Prognosis is generally poor if hypercalcemia is present and if parenteral opioids are required to control pain from other sites of bone metastases; in these cases, the decision for surgical intervention should be based on the severity of and the symptoms associated with the fracture (99). As shown in Figure 37A-2, postoperative radiation is often given after surgical fixation of a pathologic fracture to reduce risk of progressive disease in the bone that could result in instability of the internal fixation (100).

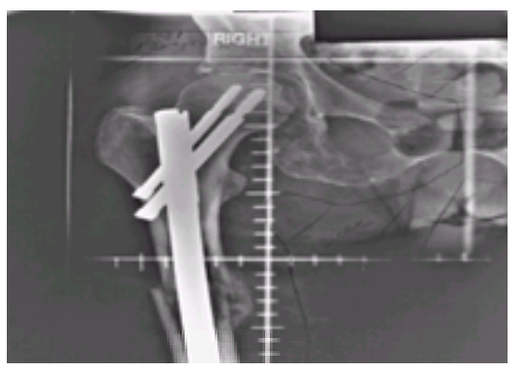

Figure 37A-2. ****missing****

Treatment of pathologic fracture or impending fracture depends on the bone involved and the clinical status of the patient. Indications for surgical intervention of pathologic fracture or impending fracture include these factors: (a) an expected survival of more than 6 weeks; (b) an ability to accomplish internal stability of the fracture site; (c) no coexistent medical conditions that preclude early mobilization; (d) metastases involving weight-bearing bones; (e) and lytic lesions more than 2 to 3 cm in size or metastases that destroy more than 50% of the cortex (99,100,101,102 and 103). It is unclear whether osteolytic metastases are more likely to fracture than osteoblastic lesions, because osteoblastic lesions, by definition, have an osteolytic component so that new bone can be formed.

SPINAL CORD COMPRESSION

Pain is the initial symptom in approximately 90% of patients with spinal cord compression, and the development of spinal cord compression is associated with a poor overall prognosis. Paraparesis or paraplegia occurs in more than 60%, sensory loss is noted in 70% to 80%, and 14% to 77% have bladder, bowel, or both kinds of disturbances (74,91,92,93,94,95,96 and 97). The extent of the epidural mass influences prognosis, because a complete spinal block results in greater residual neurologic impairment than a partial block. The clinical course of spinal cord compression resulting from malignant melanoma is similar to that resulting from breast or prostate cancer. The time from the original diagnosis of melanoma to the development of metastatic spinal disease averages 32 months, and the average time is reported to be 27 months from diagnosis of skeletal metastases to spinal cord compression. Median survival among patients with spinal cord compression is 7 months, with a 36% probability for a 1-year survival. For specific types of cancers, the mean survival time is 14 months for breast cancer, 12 months in prostate cancer, 6 months in malignant melanoma, and 3 months in lung cancer once epidural spinal cord compression is diagnosed (17,91,98). After the diagnosis of epidural spinal cord compression, the overall survival time averages 12 months, with a median survival time of 5 months. The vertebral column is involved by metastatic tumor in 40% of patients who die of cancer. Approximately 70% of vertebral metastases involve the thoracic spine, 20% the lumbosacral region, and 10% the cervical spine.

Weakness can signal the rapid progression of symptoms, and 30% of patients with weakness become paraplegic within 1 week. Rapid development of weakness, defined as occurring in less than 2 months, most commonly occurs in lung cancer, whereas breast and prostate cancers can progress more slowly. Neurologic deficits can develop within a few hours in up to 20% of patients with spinal cord compression (91,92,93,94,95,96 and 97,104). The severity of weakness at presentation is the most significant factor for recovery of function. Ninety percent of patients who are ambulatory at presentation are ambulatory after treatment. Only 13% of paraplegic patients regain function, particularly if paraplegia is present for more than 24 hours before the initiation of therapy. More than 30% of patients who develop spinal cord compression are alive 1 year later, and 50% of these patients remain ambulatory with appropriate therapy.

Pain can be present for months to days before neurologic dysfunction evolves. Unlike degenerative joint disease, which primarily occurs in the low cervical and low lumbar regions, pain caused by epidural spinal cord compression can occur anywhere in the spinal axis and is aggravated by recumbency. Any cancer patient with back pain, especially with known metastatic involvement of the vertebral bodies, should be suspected as having spinal cord compression. The risk of spinal cord compression exceeds 60% among patients with back pain and plain film evidence of vertebral collapse caused by metastatic cancer (74,91,92,93,94,95,96 and 97,105,106,107,108 and 109). Epidural spinal cord disease is documented in 17% of asymptomatic patients who have an abnormal bone scan but normal plain film results; 47% of asymptomatic patients with vertebral metastases noted both on bone scan and plain film also have associated epidural disease (104). Symptomatic patients with a normal vertebral contour and osteoblastic changes on plain film and bone scan should also be evaluated for spinal cord compression (Fig. 37A-3).

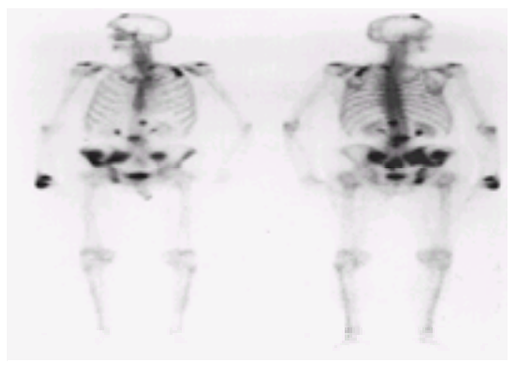

Figure 37A-3. Bone scan that demonstrates multifocal disease involvement. Metastatic involvement in weight-bearing areas such as the pelvis and lower lumbar area significantly affects mobility.

Radiographic determination of the involved spinal levels is critical to radiation treatment planning. Clinical determination of the location of epidural spinal cord compression in 33% of cases is incorrect (91,92 and 93). Plain film radiography shows involvement of more than one spinal level in approximately one-third of patients. If the results of MRI, tomographic studies, and surgical findings are included, more than 85% of patients have multiple sites of vertebral involvement (91,92,93,94,95,96 and 97,104,105,108). With plain radiography, the destruction of the pedicles is the most common finding that identifies spine metastases. In contrast, computed tomography shows that the initial anatomic location of metastases is in the posterior portion of the vertebral body and that destruction of the pedicles occurs only in combination with involvement of the vertebral body (Fig. 37A-4) (108). Osteoblastic bony expansion, commonly seen in both prostate and breast cancers, can result in spinal cord compromise as well as osteolytic vertebral compression fractures (107).

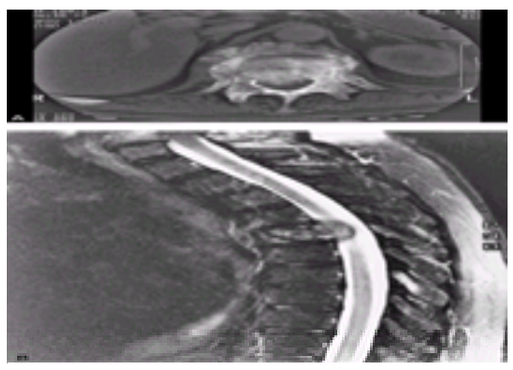

Figure 37A-4. **A:** Computed tomographic scan showing involvement of the posterior aspect of the vertebral body resulting in partial spinal cord compression. **B:**

Magnetic resonance imaging showing involvement of the posterior aspect of the vertebral body resulting in partial spinal cord compression.

Treatment of spinal cord compression includes emergent corticosteroids, radiotherapy, neurosurgical intervention, or all three therapies. Radiotherapy is the treatment of choice for most cases of spinal cord compression and is a radiotherapeutic emergency (Fig. 37A-5). Functional outcome is dependent on the level of symptoms at the time radiation is administered. Spinal cord compression resulting from metastatic tumor can be prevented or effectively treated when diagnosed early (91,92,93,94,95,96 and 97, 104,105). Most commonly, 30 Gy in 10 fractions is administered in the treatment of spinal cord compression and carcinomatous plexopathy. Pain relief can be accomplished in 73% of patients after treatment (104,105). A statistically significant improvement in functional outcome has been reported with laminectomy and radiotherapy in treatment of epidural spinal cord compression over either modality alone for selected clinical presentations. Laminectomy has been recommended to promptly reduce tumor volume in an attempt to relieve compression and injury of the spinal cord and provide stabilization to the spinal axis. The rate of tumor regression after radiotherapy is too slow in these cases to effect recovery of lost neurologic function. Surgical intervention should be considered among patients presenting with a complete spinal cord block because the results are significantly worse than those achieved with radiotherapy alone for partial compression of the spinal cord. After radiation alone to treat a partial spinal cord block, 64% of patients regain ambulation, 33% have normalization of sphincter tone, 72% are pain free, and median survival is 9 months (94,96,97,104,105). With a complete spinal cord block, only 27% have improvement in motor function, and 42% continue to have pain after radiation alone. In paraparetic patients who undergo laminectomy and radiation, 82% regain the ability to walk, 68% have improved sphincter function, and 88% have relief of pain.

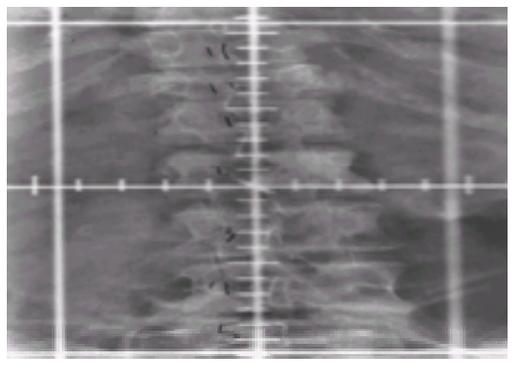

Figure 37A-5. Typical radiation portal to treat multifocal areas of disease involvement in the vertebral bodies and epidural region.

Neurosurgical intervention for vertebral and epidural metastases involves spinal cord decompression accomplished by a laminectomy. Laminectomy is indicated in a variety of clinical presentations (91,92 and 93,95,96 and 97,109). These include rapid neurologic deterioration, tumor progression in a previously irradiated area, and stabilization of the spine; in paraplegic patients with limited disease and good probability of survival; and to establish a diagnosis. Adjuvant radiotherapy is often given to treat microscopic residual disease after neurosurgical intervention (91,92,95,104). Laminectomy, however, carries risks associated with surgery and anesthesia. Pain may worsen after laminectomy if operative procedures fail to stabilize the spine. Surgical restoration of the vertebral alignment may be required because of neurologic compromise and pain caused by progressive vertebral collapse. Vertebral collapse may occur because of cancer or vertebral instability after cancer therapy (Fig. 37A-6). Appropriate diagnostic studies and intervention should be pursued because the neurologic compromise and pain from vertebral instability can be as devastating as that with epidural spinal cord metastases (96,109).

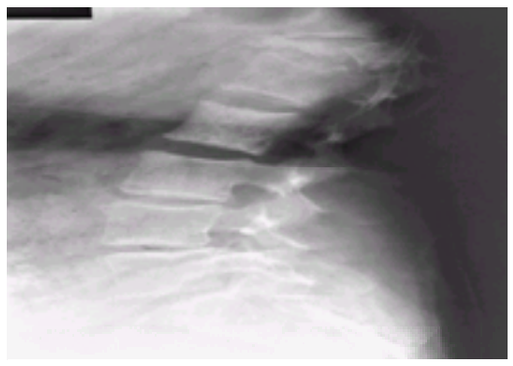

Figure 37A-6. Compression fracture of the twelfth thoracic vertebral body following an initial pain-free interval after palliative radiation. Vertebral weakness with rapid tumor regression resulted in a compression fracture that caused recurrent back pain because of spinal instability.

Paravertebral masses are most commonly associated with lung cancer and are rare in prostate cancer despite studies reporting that prostate cancer is the second most common primary tumor associated with and accounting for 22% of the incidence of spinal cord compression (98,110,111). Overall, approximately 20% of patients with epidural cord compression have an associated paravertebral mass. Surgical resection combined with radiation therapy has been suggested to improve functional outcome when a paravertebral mass is associated with spinal cord compression because radiation alone is less effective with larger tumor burdens.

Radiation Tolerance of the Spinal Cord

The potential for the development of radiation myelitis with total radiation doses that exceed 40 Gy at 2 Gy per fraction represents the limiting factor in the treatment of large tumor burdens near or involving the spinal canal. Furthermore, the length of spinal cord that needs to be irradiated significantly affects the radiation tolerance of the spinal cord (112,113 and 114). Histopathologic changes experimentally observed after fractionated irradiation of the spinal cord include white matter necrosis, massive hemorrhage, and segmental parenchymal atrophy that are consistently associated with abnormal neurologic signs (114). Other pathologic responses involve focal fiber loss and white matter vacuolation. Experimental data also have shown that the time course and the extent of long-term recovery from radiation are dependent on the specific type and age of tissue (112,114).

Radiation tolerance is based on the dose per fraction, total dose, and the volume of tissue treated. The dose per fraction is the most important factor in the tolerance of tissues to radiation. Clinical and experimental experience has failed to demonstrate any difference in radiosensitivity in different segments of the spinal cord (112). The risk of radiation myelitis in the cervicothoracic spine is less than 5% when 6,000 cGy is administered at 172 cGy per fraction, or 5,000 cGy is given with daily fractions of 200 cGy per fraction. Especially among patients who have received chemotherapy, the total dose to the spinal cord is generally limited to 4,000 cGy administered at 200 cGy per fraction to minimize any risk of irreversible radiation injury to the spinal cord. The total dose is also an extremely important factor defining the radiation tolerance of the spinal cord. A steep curve based on total radiation dose predicts the risk of developing radiation myelopathy; a small increase in total radiation dose can result in a large increased risk for radiation myelopathy (112,114). Re-treatment of a previously irradiated segment of spinal cord results in high risk for radiation-induced myelopathy because other neurologic pathways cannot compensate for an injury to a specific level of the spinal cord.

The radiation tolerance of the spinal cord can be compromised by prior injury. Difficulty arises in separating the pathologic and radiotherapeutic injury to spinal cord compression. Vasogenic edema of the spinal cord and nerve roots can be caused by compression injury. Metastatic epidural compression results in vasogenic spinal cord edema, venous hemorrhage, loss of myelin, and ischemia. Vasogenic edema results in an increased synthesis of prostaglandin E_2 that can be inhibited by corticosteroids or nonsteroidal antiinflammatory agents. Other consequences of pathologic compression include hemorrhage, loss of myelin, and ischemia (112,113

and 114).

Two separate mechanisms of radiation injury can occur and result from white matter damage and vasculopathies. White matter damage is associated with diffuse demyelination and swollen axons that can be focally necrotic and have associated glial reaction. Vascular damage has been shown experimentally to be age dependent and can result in hemorrhage, telangiectasia, and vascular necrosis (112,113 and 114). Six major types of injuries have been shown experimentally to result from radiation to the spinal column. Five of these occur in the spinal cord and one in the dorsal root ganglia. The most severe spinal lesions, all of which are caused by vascular damage and result in neurologic dysfunction, include white matter necrosis, hemorrhage, and segmental parenchymal atrophy. The two less severe spinal lesions included focal fiber loss and scattered white matter vacuolation caused by damage to glial cells, axons, the vasculature, or all three; these less severe sequelae are seen with lower total doses of radiation and are less likely to result in neurologic dysfunction. In dorsal root ganglia, radiation damage included intracytoplasmic vacuoles and loss of neurons and satellite cells that could affect sensory function. These findings are distinct from the demyelination of the posterior columns associated with the self-limiting Lhermitte's syndrome (113). Meningeal thickening and fibrosis can also be observed after radiation, but the clinical significance of this is unknown. Ependymal and nerve root damage from radiation is rare.

Clinical Management

Persistent pain after radiotherapy for vertebral metastases should be investigated to exclude the possibility of progressive disease in or outside the radiation portal, or mechanical spinal instability because of a vertebral compression fracture. Changes seen in the bone marrow on MRI after palliative radiotherapy initially include decreased cellularity, edema, and hemorrhage, followed by fatty replacement and fibrosis. These well-defined changes on MRI after radiotherapy can be distinguished from those seen with progressive disease (30,31 and 32,108,115,116).

Prior radiation portals may affect the ability to radiate spine metastases, especially in breast and lung cancer patients. Standard radiation portals currently used for breast cancer therapy infrequently treat the spinal axis. The upper thoracic and lower cervical region, however, may be irradiated in a field encompassing the supraclavicular nodes and axillary apex if significant axillary node involvement is documented. With techniques used in the past for breast cancer, the thoracic spine would receive a significant dose of radiation from a field that treated the internal mammary lymph nodes (105). Treatment of the mediastinum in lung cancer generally includes the majority of the thoracic spine treated to the maximum dose tolerated by the spinal cord (111). Previous radiation of the spine as part of definitive therapy does not reduce the risk for subsequent spinal cord compression as part of persistent or recurrent disease.

Surgery often is the only available option for therapy because previously administered radiation may preclude further radiotherapy in the region of the malignant spinal cord compression. This is often the case in lung cancer because metastases are located in the thoracic spine in over 70% of cases, and many of these patients have received mediastinal irradiation (111). Early involvement by the radiotherapist in the management of the patients with suspected spinal cord involvement is important to allow time to obtain prior radiotherapy records and determine if further radiation is possible and expedite the clinical decision-making process.

Based on clinical and radiographic grounds, leptomeningeal carcinomatosis must also be considered in the diagnostic evaluation. Leptomeningeal carcinomatosis occurs more commonly than expected. For example, only one-half of breast cancer patients with leptomeningeal carcinomatosis are diagnosed before death (91,97,105,117,118). Performing a lumbar puncture is a relative barrier to the diagnosis; at least three cerebrospinal fluid samples are necessary to cytologically exclude the diagnosis of leptomeningeal disease because in 10% to 40% of patients the initial cerebrospinal fluid sample fails to document tumor cells (117). MRI can identify leptomeningeal disease among patients with normal cerebrospinal fluid cytology and is sensitive and specific in locating regions of nodular leptomeningeal involvement. Except in the case of nodular leptomeningeal involvement, in which localized radiotherapy may be of benefit as an adjuvant, intrathecal chemotherapy is generally the treatment of choice (118).

TREATMENT OF DIFFUSE BONE METASTASES

Other therapeutic approaches, including wide field radiotherapy, systemic radionuclides, and bisphosphonates, have been used among patients with disseminated bone metastases. Both approaches are useful in augmenting the therapeutic effect of localized radiation and in preventing asymptomatic bony lesions from progressing. Although usually not a significant consideration in localized irradiation, adequate bone marrow reserve is required for wide field radiotherapy and systemic radionuclides. Bone marrow scans can be performed to determine the volume of functioning marrow and assess the feasibility of delivering wide field radiotherapy or radionuclides (9,30,34,61,62,65).

Wide Field Radiotherapy

Hemibody irradiation has been used to treat diffuse bone metastases by administering 6 to 10 Gy in one fraction to the upper, mid, or lower body. Response rates are consistently reported to be greater than 70%, and more than 20% of patients have complete relief of pain. In prostate cancer patients, the overall response rate is 80%, and complete relief of pain is 30%, respectively (119,120). Approximately one-half of patients experience relief of pain within 48 hours of treatment, and the overall response rates equal 80% for all types of primary tumors. More than one-half of the patients treated did not require further palliative irradiation for recurrent bone pain over the duration of their lives. For prostate cancer patients, the mean duration of pain relief is 15 weeks and mean survival time is 25 weeks.

An RTOG study demonstrated that hemibody radiation reduced the time to disease progression and decreased the need for subsequent palliative radiation of bone metastases at 1 year of follow-up when compared with local field irradiation alone. These results from the RTOG study are consistent with other reported experience using hemibody irradiation (119,120). Median survival after hemibody irradiation is significantly better among patients who present with a good performance status. Approximately 90% of patients with a complete response and 70% of patients with a partial response had a good to excellent performance status before radiotherapy. Prior systemic therapy does not influence response to wide field radiotherapy. Symptomatic bone metastases, which are also refractory to chemotherapy or hormonal therapy, have complete response rates of 70% and partial response rates of 24% with hemibody radiation. Symptoms are palliated in 88% of cases when a previously treated area is reirradiated. Premedication prevents nausea, and partial shielding minimizes lung dose and the risk for radiation pneumonitis. Hematologic depression is limited. Toxicity is observed in less than 10% of patients, whereas 50% experience stabilization of disease at 1 year.

Because of the potential toxicities to visceral structures and the difficulties in treatment setup, hemibody radiation is not routinely used to palliate multifocal bone metastases. Concerns regarding the permanent effects on bone marrow reserve also exist relative to the subsequent need for chemotherapy. For these reasons, radiopharmaceuticals, which have no systemic toxicities other than the effect on blood counts, have gained popularity over hemibody radiation in the treatment of multifocal bone metastases. However, radiopharmaceuticals are most useful in blastic bony lesions and hemibody radiation may be an important palliative option among patients with diffuse lytic bone metastases that are refractory to other therapies.

Radiopharmaceuticals

An alternative to hemibody irradiation for the treatment of widely disseminated bone metastases is the use of systemic radioisotopes. The most commonly used radiopharmaceutical in the treatment of bone metastases is strontium 89. Strontium 89 combines with the calcium component of hydroxyapatite in osteoblastic lesions. Many reports indicate effective palliation of pain lasting more than 6 months in 60% to 80% of patients with breast and prostate cancers (57,58,59,60,61 and 62,65,67,68,71). Improvements in functional status and quality of life have been observed, and approximately 20% of patients have complete resolution of pain. Pain control has been reported to be superior among patients with disseminated prostate cancer treated both with strontium 89 and local radiotherapy as compared with localized irradiation alone. Because the activity of strontium 89 is limited to bone, use of radiopharmaceuticals is contraindicated when epidural disease is associated with vertebral metastases. Myelotoxicity, resulting in a 25% decline of initial platelet and white blood cell counts, is usually transient and represents the only significant toxicity associated with strontium 89 (58,62,65). Experience from a number of clinical trials has demonstrated strontium 89 to be an effective therapy that is easily administered in an outpatient setting. The radiation dose absorbed by the bone marrow is 2 to 50 times less than the dose administered by strontium 89 to the osteoblastic lesion. Radiation doses to metastatic bony lesions with strontium 89 can range from 3 to more than 300 Gy.

Marrow suppression caused by radioisotopes is either caused by penetrating gamma radiation or by a radioisotope with a long half-life. For example, transient cytopenia is observed with strontium 89 because it has a fairly long half-life of 51 days, even thought it emits a beta particle of low penetrance and low energy (1.46 MeV) (Table 37A-5). Hematotoxicity is more pronounced in patients with pretreatment platelet counts of less than or equal to 60×10^3, white blood cell counts of less than or equal to 2.5×10^3, or greater than or equal to 30% involvement of the red marrow–bearing bone (62,65). Compromise of the red marrow–bearing bone can be a consequence of tumor or prior radiation and chemotherapy.

Radionuclide	Half-life (days)	Beta energy (MeV)	Gamma energy (keV)	Response rate (%)	Duration of response (mo)	Toxicity
^{32}P	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Moderate
^{89}Sr	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Low
^{117m}Sn	[illegible]	[illegible]	[illegible]	NR	NR	NR
		[illegible]			[illegible]	
^{186}Re	[illegible]	[illegible]	[illegible]	[illegible]	–	Low
		[illegible]				
^{153}Sm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Low
		[illegible]				

NR, no response.

[illegible]

TABLE 37A-5. Physical characteristics and clinical data for radionuclides

Clinical response to strontium 89 is comparable with wide field radiotherapy. Response to strontium 89 therapy has been documented both subjectively and objectively. Subjective response, manifested as symptomatic improvement, was reported by more than 80% of prostate cancer patients using a validated survey. Objective evidence of response was documented by reductions in alkaline and acid phosphatase levels that were also associated with a decrease in the uptake in metastatic lesions on sequential bone scans (58,59,60,61 and 62, 65,68). Prior therapies for prostate cancer, including local radiation therapy and systemic chemotherapy or hormone therapy, do not influence toxicity or affect clinical response to strontium 89. Administered as an adjuvant to localized external beam radiotherapy in metastatic prostate cancer, strontium 89 has been shown to improve pain relief and delay progression of disease in prospective randomized clinical trials. Almost twice as many patients treated with strontium 89 were reported to be pain free at 3 months in follow-up when compared with patients treated with localized external beam radiation. Analgesics were no longer required by 17% of patients treated with strontium 89, whereas only 2% of the patients treated with localized radiotherapy alone were able to discontinue analgesic use. Quality-of-life assessments demonstrated increased physical activity along with improved pain relief after strontium 89 was administered in conjunction with localized external beam radiation therapy. Cost-benefit analysis has also suggested an advantage to the administration of strontium 89 with reductions in costs of hospitalization for tertiary care (59,60,71).

Several other radiopharmaceuticals are available for clinical application including samarium 153, gallium nitrate, phosphorus 32, and rhenium 186 (57,63,64,66,69,70,72). The therapeutic mechanism of action relates to the physical and biological half-life in the bony lesion, the mean energy, and the delivered dose of the radiopharmaceutical. Table 37A-5 summarizes some of the physical characteristics and clinical data for various radionuclides. Phosphorus 32 and strontium 89 emit pure beta rays (little penetration in tissue), whereas rhenium 186 and samarium 153 emit both beta rays and relatively high energy gamma-ray photons that penetrate tissue for some distance (103 to 159 keV).

Because samarium 153 has a gamma-ray component, it is possible to directly image the distribution of the radiation dose. The scans after injection of samarium 153 are comparable to diagnostic scans obtained with technetium 99m. The mean skeletal uptake is over 50% of the dose (70). Nonskeletal sites receive negligible radiation doses, and complete clearance of radiation not absorbed by the radiation occurs within 6 to 8 hours of administration (69). In a double-blind placebo-controlled clinical trial, samarium 153 has been shown to be an effective agent in palliating painful bone metastases in breast cancer patients. Pain relief occurred within 1 week and lasted at least 16 weeks after administration (64). Approximately 65% of patients responded within the first 4 weeks and 43% had relief of pain of at least 16 weeks' duration. No significant bone marrow toxicities have been observed. Recommended doses range between 1.0 and 1.5 mCi per kg. In more than one-third of patients, multiple administrations are possible (72).

Selectively concentrating in bone, the mechanism of action of rhenium 186 is similar to that of technetium diphosphonate 99m, which is used in diagnostic bone scans. This characteristic allows direct imaging of the deposition of rhenium 186 in bony metastases. The metastatic lesion receives tens of grays in dose after the administration of rhenium 186, whereas the radiation dose to the marrow is limited to 0.75 Gy (57,66). Thrombocytopenia appears to be the dose-limiting toxicity. Similar to the reports that use strontium 89 among prostate cancer patients, decreases in PSA have been also observed after the administration of rhenium 186 (66).

Phosphorus 32 has been used to treat bone metastases in prostate cancer patients for over 30 years, with 77% of patients experiencing significant relief of pain (57). The response rates and duration of response with phosphorus 32 are similar to wide field radiation and strontium 89. However, the main disadvantage of phosphorus 32 is that more than 30% of patients develop severe hematologic toxicity.

Comparative clinical trials are necessary to determine whether any difference exists in the onset and pattern of response between samarium 153, strontium 89, and other radiopharmaceuticals. Clinical data for rhenium 186 and other radiopharmaceuticals is still limited and these agents are in various stages of clinical investigation (57,62,63,64,65 and 66). Several strategies have been proposed to further enhance the therapeutic response of radiopharmaceutical agents. These options include further dose intensity studies, adjunctive administration of bisphosphonates, and concurrent administration with chemotherapy (67). Although bone marrow toxicity is relatively limited in the doses of radiopharmaceuticals currently administered either alone or in combination with other agents, future dose intensity studies may require hematologic support with colony-stimulating factors.

Sequential radiography and bone scans after hormonal and radiopharmaceutical therapy for breast and prostate cancers demonstrate an osteoblastic response that reflects remodeling of the bone in osteolytic osseous metastases (45,46). Approximately one- third of patients have evidence of increased tracer uptake on bone scans (flare) obtained 8 to 16 weeks after treatment. Of these patients with a flare response on bone scan, 72% experience a response to the treatment. By comparison, only 36% have a response to treatment when a limited response or no flare response is observed.

Relapse of disease has been associated with an increase in the osteolytic component. Osteoclast resorption in bone metastases is associated with the release of acid and acid-dependent proteases that dissolve the organic matrix of the bone. Gallium nitrate has been shown to inhibit accelerated bone turnover among patients with widespread bone metastases and has been clinically applied in the treatment of hypercalcemia. Preferentially accumulating in the cortical surface, the most metabolically active region of the bone, gallium nitrate acts to inhibit osteoclast resorption. Additionally, gallium nitrate increases the absorption of calcium and phosphorus and the incorporation of collagen into the bone.

BISPHOSPHONATES

Bisphosphonates are a group of substances that have a high affinity for bone, a long half-life in the skeleton, and inhibit osteoclast activity. Acting as a metabolic toxin, biphosphonates block osteoclasts from generating acid. The efficacy of pain relief may be improved with the adjuvant administration of biphosphonates through these direct mechanisms of action or possibly by also increasing retention of the radiopharmaceutical in involved bone. Bisphosphonates have been shown to be effective in multiple myeloma and bone metastases from other cancers (52,53,54,55 and 56).

Considerable experience exists with the administration of bisphosphonates in breast cancer. Significantly fewer skeletal complications have been reported when bisphosphonates are administered to breast cancer patients with documented bony metastases (53,54,55 and 56). Sequential bone scans showed that the median time to disease progression was increased by 48% among patients who received pamidronate (56). Symptomatic improvement has been observed at 15, 18, 21, and 24 months in association with monthly infusions of pamidronate to a cohort of 382 women with metastatic breast cancer for over 2 years. The median time to progressive symptoms needing radiation or surgical intervention was 14 months in the pamidronate-treated group and 7 months in the placebo group. Palliative radiation was administered to 28% of the pamidronate group as compared with 45% of the placebo group. No difference was seen, however, in the rate of vertebral pathologic fracture between pamidronate and placebo groups. Prolonged administration was not associated with reduced tolerance to therapy (55). The costs of administration of pamidronate, especially over a prolonged period of time, may be offset by reducing the need for radiation and surgical interventions and by avoiding the functional impairment associated with progressive disease.

CONCLUSIONS

Diagnostic Recommendations

Pain that persists after palliative radiation should be evaluated to exclude progression of disease in the treated area, possible extension of disease outside the

radiation portal that causes referred pain, and bone fracture. Reduced cortical strength can result in compression, stress, or microfractures. Plain radiography often clearly delineates lytic changes and fractures after radiotherapy.

Therapeutic Recommendations

Radiation remains an important modality in palliative care. A number of clinical, prognostic, and therapeutic factors must be considered to determine the optimal treatment regimen in palliative radiotherapy. Adequate management of cancer-related pain is important both during and after completing palliative irradiation. Efficient and effective palliative treatment is imperative for locally advanced and metastatic cancer to relieve symptoms, improve function, and minimize disease-related morbidity.

Radiopharmaceuticals, such as strontium 89, are being used with greater frequency to treat bone metastases both as a primary modality for patients whose symptoms recur in a previously irradiated site, and as an adjuvant to external beam irradiation.

More specific criteria need to be delineated for prognosis to determine the appropriate treatment regimen for bone metastases. A staging system within the category of metastatic disease should incorporate the performance status, type and extent of bone and visceral involvement, time to disease progression, and primary tumor site and account for prior failed therapies. Because only the bone is treated, external beam radiation or radiopharmaceuticals continue to be considered localized therapies for systemic disease. Therefore, the response to and outcomes after radiation therapy must be specifically defined relative to the radiated and unirradiated sites of disease, and the other antineoplastic and supportive care therapies administered.

Radiation therapy is an important means of treating localized symptoms related to tumor involvement by providing a wide range of therapeutic options. Radiobiological principles, the radiation tolerance of adjacent normal tissues and the clinical condition influence the selection of radiation technique, dose, and fraction size. The optimal dose and treatment schedule, however, are not fully defined for palliative radiation of bone metastases. Further study is necessary to integrate validated pain scores, analgesic use, prognostic factors, and radiobiological principles to better define the most efficient and efficacious treatment schedule according to the clinical presentation.

Palliative irradiation should be integrated in a multidisciplinary therapeutic approach because of the need to treat associated symptoms and other underlying medical problems. Antineoplastic therapy can provide tumor regression, relief of cancer-related symptoms, and maintain functional integrity. Control of cancer-related pain with the use of analgesics is imperative to allow comfort during and while awaiting response to radiotherapy. Pain represents a sensitive measure of disease activity. Close follow-up should be performed to ensure control of cancer and treatment-related pain and assess for progressive disease or recurrent disease.

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CHAPTER 37

Part B: Chemotherapeutic Management of Symptomatic Disease

J. Cameron Muir

“Cancer pain is best controlled by removing the cancer or causing it to regress” (1). These words of the renowned oncologist and palliative medicine specialist Dr. Neil MacDonald are a useful framework from which to consider the role of chemotherapy in the management of symptomatic disease. Half of all cancers are, in fact, cured surgically. Yet, when a tumor is deemed surgically unremovable (inoperable), the likelihood of long-term survival is remote: Of the remaining 50% of tumors that are not surgically curable, only 10% are cured by other modalities, namely radiotherapy or chemotherapy. Thus, “for the majority of patients . . . attempts to cure or bring about long term disease regression ultimately fail, and the patient, after an often prolonged period of pain and suffering, will die. Although improved understanding of the molecular biology of cancer may lead to fundamentally new techniques for its prevention, diagnosis, and treatment, this promise, for the moment, remains in the laboratories, and major changes in the curability of human malignancy are unlikely to occur during the next 5 years” (1). In fact, in 1998 in the United States, when 1.2 million cancers were diagnosed, the number of cancer deaths was 564,000 (2).

The emergence of the field of palliative medicine has placed increased emphasis on the assessment of subjective symptoms of life-threatening diseases such as cancer. Thus, there is reason to hope that, although the research toward the “magic bullet” to cure cancer marches on, increased attention will be paid to the management of patients' symptoms. Although a number of new chemotherapeutic agents have received Food and Drug Administration approval in the 1990s their impact on long-term survival remains to be fully appreciated. In fact, the death rates from the major solid tumor malignancies have not changed in over three decades— the time to treatment failure or disease progression, however, has increased (2).

The primary outcomes of oncologic therapy traditionally have been overall survival and radiographic response of the tumor to cytotoxic therapy (3,4 and 5). Only very recently has emphasis been placed on palliative outcomes of chemotherapy. Interestingly, due to the careful monitoring of acute and long-term drug toxicities in the field of oncology, there are far more data regarding the pain induced by chemotherapy (usually in the form of neurotoxicity) than there are for relief.

An important issue of ambiguity and confusion is the use of the term *palliative chemotherapy*: Technically speaking, there is very little evidence to support the existence of palliative chemotherapy. For something to be truly palliative it has to have a subjective benefit for the patient—relief of symptoms, improvement in quality of life, or both. Until very recently, these palliative end points have not been a component of clinical trials in oncology. In fact, it has only been recently that quality-of-life assessments have been included in active chemotherapy protocols; pain assessment remains an infrequent end point. Instead, the administration of chemotherapy to patients who are not going to be cured from their cancer has been called *palliative chemotherapy*. One could argue that, in the absence of true palliative data end points, it is impossible to distinguish chemotherapy that provides a subjective benefit to the patient—thus achieving a palliative end point—from that which is purely futile (no objective or subjective benefit).

It seems intuitive that any treatment that decreases the size of a tumor should lead to relief of cancer pain. However, many chemotherapeutic agents provide only relatively small objective response rates in the majority of common adult solid tumors. These antimitotic drugs are often highly toxic, particularly in patients with low performance status as a result of either disease or previous treatments. Consequently, one of the critical assessment and decision-making skills of the medical oncologist is to balance the expected benefits of chemotherapy against the risk of significant toxicities (3). Chapter 35 and Chapter 36 present general information about the diagnosis and treatment of cancer pain.

CHEMOTHERAPEUTIC AGENTS

Many different types of anticancer drugs are available (3,4,5,6,7 and 8), and they fall into six major classes based on their mechanisms of action: (a) alkylating agents, (b) antimetabolites, (c) plant alkaloids, (d) antitumor antibiotics, (e) endocrine agents, and (f) a miscellaneous group. The most important chemotherapeutic agents, their side effects, and indications are listed in Table 37B-1. All of these cytotoxic drugs interfere with cell division through a variety of mechanisms (interference with mitotic spindle formation, specific enzyme inhibition, cross-linkage of DNA or RNA), and some exert several actions simultaneously at different sites of the cell. The exact mechanism of action for each drug differs slightly, and this accounts for the variation in the pattern of normal tissue toxicity.

TABLE 37B-1. Commonly used cytotoxic anticancer agents

USES OF CHEMOTHERAPY

Chemotherapy is used for some patients after radiation therapy or surgery (as an adjuvant to these therapies). For others, a combination of these therapies is considered the primary treatment (combined-modality therapy). In still other patients, chemotherapy is used alone as the primary therapy (6,7). The administration of systemic chemotherapy has the distinct antitumor advantage, when compared with the local therapies of surgery or radiotherapy, of traveling throughout the body—wherever the bloodstream might take a cancer cell (this also accounts for the increased systemic toxicity of chemotherapy). Thus, adjuvant chemotherapy is used in patients who appear cured after surgery but are suspected of having residual disease or micrometastasis. Adjuvant chemotherapy has proven effective in node-positive breast cancer, Duke's B2 and C colorectal carcinoma, stage III ovarian carcinoma, and testicular carcinoma (7). Clinical trials are now under way to determine whether chemotherapy administered before surgery or radiation therapy (so-called neoadjuvant chemotherapy) can (a) decrease the size of the tumor to be removed or radiated; (b) increase the likelihood that the tumor will be surgically extirpable; and (c) decrease the likelihood of micrometastatic spread/seeding at the

time of surgery. Systemic chemotherapy is the primary treatment for disseminated/metastatic malignant disease.

Based on the mechanisms mentioned above, the goal of systemic chemotherapy is to interrupt the division of rapidly dividing cancer cells. It is usually administered in multiple (usually 4 to 6) cycles every 3 to 4 weeks. The timing and dosing of chemotherapy are established to maximize malignant cell kill, while at the same time not exceeding the body's ability to regenerate the normally rapidly dividing cells that are “innocent bystanders” of the cytotoxic effects of chemotherapy, namely the bone marrow progenitors, gastrointestinal epithelial cells, and hair follicles. The predominant effect of chemotherapy on the intestinal tract occurs in the first few days to a week after administration, whereas the peak effect on the blood progenitor cells occurs 10 to 14 days posttherapy. Thus, patients often receive prophylactic antiemetics for the days around therapy (of which the newer agents are usually quite effective) and “nadir” their blood counts, with variable risks of infection and bleeding, approximately 2 weeks after receiving treatment, respectively.

Regardless of the setting of administration (primary, adjuvant, neoadjuvant, or combined modality), substantial evidence suggests that combination chemotherapy with agents that have different mechanisms of action as well as different (noncumulative) toxicities yields significantly higher efficacy than single-agent chemotherapy. On the basis of an extensive review of *in vivo* and *in vitro* laboratory research and clinical experiences acquired during the 1950s and 1960s, DeVita and Schein (9) developed a set of basic principles of combination chemotherapy for cancer patients, and these are still the guiding principles today. Among the most important of these principles are the following: (a) All of the component drugs in a combination must have activity against the neoplasm being treated; (b) drugs must be administered at dosages close to the minimum effective dosage for each drug as a single agent, or beyond if possible (the higher the dosage of each drug is raised the more likely that beneficial results will be obtained); (c) drugs that interrupt the synthesis of cellular macromolecules at several sites can be combined for additive or synergistic effects on the various synthetic pathways; (d) drugs in combination should have as little cross-toxicity as possible; and (e) mechanisms of tumor cell resistance to two agents in combination must not be similar (9).

CLINICAL APPLICATIONS

An anticancer therapy always should be started for those types of cancers in which chemotherapeutic regimens have been proven effective. Conventionally, efficacy of chemotherapy is defined by an objective decrease in the radiographic size of the tumor [usually by computed tomography (CT)]. A so-called complete response (CR) represents total disappearance of all observable disease for a minimum of 1 to 3 months, depending on the criteria used (5,10,11 and 12), whereas a partial response (PR) represents a decrease in measurable tumor size of 50% or more. With the development of newer cytotoxic agents, many solid tumors display an objective response to specific chemotherapy. Although cure of most forms of cancers is still an elusive objective, current drug treatments produce good partial remission and even complete remission in some cancers, for which two decades ago only supportive therapy was available. As a general rule, the achievement of significant objective response [CR + PR = RR (response rate); i.e., some significant decrease in the size of the tumor radiographically] almost always translates into an improved survival of responders compared with nonresponders. It also translates into relief of pain related to the tumor mass—although pain relief from chemotherapy has rarely been the end point of clinical trials (Table 37B-2). Furthermore, in a fraction of patients with specific forms of cancers, such as pediatric tumors, lymphomas, testicular cancer, and ovarian cancer, complete remission of the neoplastic disease is followed by prolonged disease-free survival compatible with cure (3).

TABLE 37B-2. Efficacy of chemotherapy in relieving pain

There are, however, many patients whose tumor is resistant to chemotherapy. They have progressive disease either shortly after the completion of therapy or, in some cases, during the time of active therapy. The category that falls between an objective response and progressive disease, in which the tumor neither shrinks nor grows in the face of active anticancer therapy, is referred to as *stable disease*. Whether there is any analgesic benefit to the administration of chemotherapy in the setting of stable disease is largely unknown. Although there is speculation about the role of chemotherapy in altering peripheral sensory nerve function, thereby producing analgesia (1), as well as relieving pain by altering the “tumor-host milieu” (1), these hypotheses await clinical trials, with assessment of the analgesic outcomes as a primary end point of therapy. At the moment, one of the significant barriers to these studies is the lack of a universal language for a pain classification schema and staging system. Although such systems have been developed, they remain underused and underappreciated (13).

Thus, we are left with both the clinical impression and limited outcome data that generally support the claim that “systemically administered cytotoxic drugs do not relieve cancer pain in the absence of tumor regression” (1). It is therefore imperative to know the type of cancer that one is evaluating before initiating chemotherapy, paying particular attention to the histology (squamous cell carcinoma, adenocarcinoma, germ cell, lymphoma), the grade (high, intermediate, low) and the degree of differentiation (well differentiated, poorly differentiated), because these factors will give clues as to the likelihood of a response to chemotherapy. One must also follow the rapidly evolving literature on objective response rates for newer agents and various combination regimens on a given tumor type. Careful assessment of the overall performance status of patients will help to determine their ability to tolerate systemic chemotherapy and endure the likely associated toxicities.

In general, the more rapidly growing the tumor, the more frequent is cellular division and therefore the more responsive the cells are to cytotoxic therapy: Intervention can lead to increased pain control, long-term survival, and, potentially, cure. Ironically, the more rapid the cell division, the more aggressive the tumor and the more imminently life-threatening the tumor is if it is not responsive to cytotoxic therapy. Table 37B-3 summarizes the most common malignancies and their likelihood of response to chemotherapy. Of the most common solid tumors [lung, colorectal, prostate (men), and breast (women)], all except breast carcinoma are minimally responsive to current chemotherapeutic regimens. This and other evidence provides a basis for reviewing the palliative benefits of chemotherapy. However, most of the evidence describes the palliative use of chemotherapy as noncurative, or life prolonging, rather than for true subjective (palliative) benefit, in terms of either pain control or enhanced quality of life.

TABLE 37B-3. Effects of chemotherapy on various cancers

RESPONSE OF TUMORS TO CHEMOTHERAPY

Curable by Chemotherapy

The lymphomas, both Hodgkin's and non-Hodgkin's types, are considered “the cancers you want to get—if you have to get one.” They tend to respond better than most to combination chemotherapy. For Hodgkin's lymphoma, there are several active regimens, but the preferred treatment regimen, doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, is highly active and produces a complete remission rate that varies from 98% for early-stage disease (overall survival of more than 93% at 6 years) to 82% for advanced stage disease (overall survival of 73% at 6 years) (14,15). The therapeutic effect of this combination regimen is rapid, even in advanced cases, providing prompt pain relief in those patients who have pain (although this has never been a primary end point), with observed resolution of other symptoms and signs as well. In non-Hodgkin's lymphomas (NHL), there is a larger variability based on histology, with high-grade NHL being significantly more responsive to therapy than low-grade types. For high-grade NHL, treatment with a variety of combination chemotherapy regimens, including bleomycin, Adriamycin, cyclophosphamide, vincristine, and prednisone; cyclophosphamide, Adriamycin, vincristine, and prednisone; or others, produces a CR in 44% to 59% of cases, with overall survival of approximately 50% at 3 years (16). Again, no studies of NHL have examined pain as a primary end point. Similar results are also obtained in carcinoma of the testicle with platinum, etoposide, and bleomycin, in Wilms' tumor, and in the leukemias (especially the lymphoblastic types) (17).

Chemotherapy Has Significant Activity

In moderately chemosensitive tumors (see Table 37B-3), the results obtained with the various chemotherapeutic combinations are less favorable (30% to 60% response rates), and in general, the therapeutic effect is slower in onset. Small cell lung cancer, for example, tends to be quite aggressive, and combination chemotherapy regimens with cisplatin and etoposide or cytoxan, Adriamycin, and vincristine can induce an objective response in approximately 60% of cases, with CR occurring in approximately 10% (18). Again, this and other studies have not attempted to quantify analgesia or relief from dyspnea in small cell lung cancer.

The course of recurrent or metastatic breast cancer follows two dominant pathways: The hormone receptor–positive tumors tend to occur in older (postmenopausal) women and follow a more indolent course, with a predominance of bone as the metastatic site, and can be managed with hormone therapy, often for years; the hormone receptor–negative tumors tend to occur in younger (premenopausal) women and follow a more aggressive course, with visceral and soft tissue involvement that often necessitates the use of, and responds to, chemotherapy (19). Standard combination chemotherapy for advanced breast cancer has been cytoxan, methotrexate, and 5-fluorouracil (5-FU); this combination achieves response rates of approximately 50%, with CR of approximately 15%. This regimen impacts positively on quality of life and tumor-related symptoms (20). Subsequent studies have shown similar results for the combination of cyclophosphamide and Adriamycin, with both regimens achieving an improvement in quality of life and tumor-related symptoms, including pain (21). Yet again, it is interesting to note that “given the prevalence of recurrent breast cancer, it is intriguing that few studies have specifically addressed quality of life issues” (19) and that even fewer address symptomatic benefits of therapy.

Newer agents, especially the taxanes (paclitaxel and docetaxel) have demonstrated significant activity in breast cancer, with response rates of 60%. Early data suggest that the taxanes, probably in combination with some configuration of cyclophosphamide and Adriamycin, will likely become the treatment of choice for chemotherapy-appropriate patients with breast cancer (19). A British study evaluating patients with advanced breast cancer who received first-line palliative chemotherapy (a variety of regimens) did have primary palliative (subjective patient-centered) outcomes that were assessed by using the Rotterdam Symptom Checklist. In this study, one-fourth of the patients (26%) felt better after having received chemotherapy, with statistically significant decreases in psychological distress, pain, and improvement in lack of energy and sense of tiredness. As might be expected, feeling better correlated with disease response ($p = .03$) (21). Other studies have evaluated novel agents, including vinorelbine, which has been shown to have significant activity in breast cancer, with similar response rates as the taxanes of approximately 60%, but none has assessed symptoms as a primary end point (22). The role of vinorelbine in breast cancer remains to be determined.

Head and neck cancer is one of the most challenging disease sites to treat. However, recent advances in combined modality therapy with combined modality chemoradiation have revealed promising results: Haraf et al. (23) reported that patients with stage II and III head and neck cancer who were treated with older drugs (hydroxyurea and 5-FU) used in a novel fashion as radiosensitizing agents, in conjunction with hyperfractionated (twice a day) radiotherapy, had long-term disease-free survival consistent with cure (65% at 5 years) (23). This new approach with combined modality therapy has made a previously dreadful disease potentially curable. One of the primary concerns, however, is the subsequent short- and long-term toxicity of such aggressive therapy, and strategies aimed at reducing long-term toxicities are under study. Additional work with the taxanes is encouraging, with response rates of 42% in one study (24). Paclitaxel has been added to the above-mentioned combined modality protocol for patients with further advanced stage IV disease, with encouraging results (Merrill Kies, M.D., *personal communication*, 1999).

Finally, ovarian cancer is “among the most sensitive of all malignancies to cytotoxic chemotherapy” (25). Combination regimens in which a platinum-based agent (cisplatin or carboplatin) is used achieve overall response rates of 60% to 80%. Newer agents, most notably the taxanes, also have significant activity in ovarian cancer, with overall response rates of 20% to 40%. The combination of carboplatin and paclitaxel has demonstrated superior response rates and has become the standard of care for ovarian cancer amenable to chemotherapy (25). In one review, Patnaik et al. (26) commented that few studies have addressed palliative end points in ovarian cancer but that those that did showed that half of patients derived a palliative benefit from chemotherapy that was above the objective response rate. This brings to the fore the question of potential symptomatic benefits of chemotherapy in the absence of objective tumor regression.

Chemotherapy Has Minor Activity

In tumors with poor chemosensitivity, such as adenocarcinoma (lung, colorectal, esophageal, pancreatic, and prostate), malignant melanoma, malignant brain tumors, and sarcoma of bone and soft tissue, long-term alteration of the course of disease is rarely obtained with chemotherapeutic drugs. In this group of tumors, anticancer modalities are rarely effective in reducing the size of the tumor (achieving neither PR nor CR), and as a result, the associated pain and other symptoms, although not studied as primary end points, are unlikely to be affected significantly by chemotherapy. There are many factors responsible for the limited efficacy of chemotherapy in these tumors. First, the cellular biology of these solid tumors that often produce pain is such that they have limited response to current drug regimens. Second, the size of the tumor is inversely related to the incidence of satisfactory drug penetration into the mass. Thus, the larger the mass, the poorer is the cytotoxic response. Furthermore, given that these tumors generally do not exhibit long-term responses to first-line therapy, additional therapy with second- or third-line drug treatments often yields a minimal (usually less than primary therapy) response rate. Finally, in certain target sites (e.g., head and neck, pelvis) prior radical surgery and/ or prior radiation therapy impair the vascular supply to the tumor bed, thus interfering with delivery of an effective drug concentration to the target site.

This group therefore represents not only the most prevalent sites of malignancy, but also the most challenging for the medical oncologist to demonstrate objective response rates to chemotherapy. Interestingly, this would be the ideal patient population in which to demonstrate a palliative benefit of chemotherapy in the absence of an objective tumor response—with subjective decreases in pain, dyspnea, and fatigue and increases in performance status, appetite, and weight gain. A few investigators have pursued this notion, with intriguing results. The initial Food and Drug Administration approval of one of the newer chemotherapeutic agents, gemcitabine, was earned not by data showing its benefits on overall survival or objective response rate, but by improvements in pain control, weight gain, and performance status in patients with pancreatic cancer (27).

Non–small cell lung cancer represents the epitome of the challenge of medical oncology. It is the most prevalent cancer type, and it has required years of study requiring the synthesis of metaanalyses and new drug development to conclude that chemotherapy provides a modest survival and probable quality-of-life benefit in a significant number of patients when contrasted with best supportive care (28). Newer agents, including vinorelbine, gemcitabine, and paclitaxel, show response rates in the 11% to 25% range when combined with platinum-based therapy. No study has examined the effects of therapy on pain or dyspnea, although a few have evaluated improvements in performance status and weight gain (29).

In the realm of gastrointestinal malignancies, the role of chemotherapy “even as an adjuvant treatment, has a proven benefit in only a limited subset . . . of patients” (30). The fluoropyrimidines (5-FU and its derivatives) are the agents with demonstrated efficacy in gastrointestinal malignancies. 5-FU can be given in multiple doses and schedules with variable toxicities, yet all have resulted in disappointingly consistent response rates of approximately 20%. Leucovorin, a reduced folate analog, enhances 5-FU activity modestly, with combination therapy (5-FU/leucovorin) yielding response rates of approximately 30% in advanced colorectal cancer. In a large study of more than 400 patients conducted by the North Central Cancer Treatment Group (31), 70% of patients who received 5- FU/low-dose leucovorin had improvements in performance status and weight gain; there was no assessment of pain as a primary end point. In pancreatic cancer, there is promise that new drug developments will have clinical benefits. In 1995, some claimed that “there currently is no role for chemotherapy in the palliation of pancreatic cancer” (30), yet as mentioned earlier, the approval of gemcitabine for pancreatic cancer was based on the palliative end point of “clinical benefit” over the conventional 5-FU therapy. In

this study, clinical benefit was defined by a composite of pain, performance status, and weight gain (27). This was one of the first studies to directly assess the primary end point of pain via patient report of pain intensity together with analgesic consumption. An additional study from Sweden examined the primary end point of quality of life (using the European Organization for Research and Treatment of Cancer– QLQ-C30) in pancreatic cancer for patients treated with either chemotherapy (5-FU, leucovorin, and etoposide) or best supportive care, and it demonstrated that 36% of patients treated with chemotherapy had statistically significant improvement or prolongation of quality of life (32).

Prostate cancer is yet another prevalent disease that is poorly responsive to conventional chemotherapy. There is more palliative end- point evidence supporting the use of chemotherapy in prostate cancer than any other disease, in part because it is a slow-growing tumor that tends to cause significant pain and disability for a prolonged period of time. The most widely discussed study is Tannock's Canadian study, which used mitoxantrone and prednisone for hormone-refractory metastatic prostate cancer where the primary end point was pain relief (10). In this study, pain relief was again defined differently from previous studies as a “2-point decrease in pain as assessed by a six- point pain scale . . . without an increase in analgesic medication and maintained for two consecutive evaluations at least 3 weeks apart.” They found that this chemotherapy combination produced a positive effect in 29% of patients—above the benefit of prednisone alone, with a decrease of the analgesic medication by 50%. Other studies are suggesting the positive impact of estramustine-based chemotherapy either with vinblastine or paclitaxel on pain in hormone-refractory metastatic prostate cancer (Timothy Kuzel, M.D., *personal communication,* 1999).

Finally, soft tissue sarcomas demonstrate a response rate of approximately 35% to combination chemotherapy with doxorubicin and ifosfamide, with no studies assessing quality of life or symptomatic benefit from chemotherapy in this disease (11).

DECISION MAKING ABOUT CHEMOTHERAPY

The diagnosis of cancer is often quite traumatic for both the patient and the family. As Hippocrates said in 500 BCE, the goal of medicine is “to do all that is within my ability to cure illness, but above all things, at least, to do no harm.” On the one hand, the administration of chemotherapy is, by definition, cytotoxic—to malignant cells as well as normal host cells. On the other hand, the risks of not treating the disease are also quite significant. Given the fact that pain is a prevalent feature of both early- and advanced- stage cancer—present in nearly 50% of patients with early-stage disease and in 70% to 90% of cases of advanced cancer—one must strike a balance between giving enough therapy directed at eliminating tumor without reaching toxicities sufficient to eliminate the patient. Thus, it is imperative that an interdisciplinary team of clinicians with expertise in oncologic surgery, radiation therapy and medical oncology, nursing, and pharmacology evaluate patients to determine the treatment plan that is likely to provide the greatest cumulative benefit for the patient. If, as ought to be the ideal, the patient is always to be kept at the center of the decision-making process, then studies that assess patient-centered outcomes (pain, dyspnea, fatigue, appetite, weight loss, performance status, anxiety) for chemotherapy merit a higher priority. Although it is generally accepted that patients with a poor performance status do not usually benefit from systemic chemotherapy, it is not known whether patients with, for example, lung cancer have improvements in dyspnea as a result of chemotherapy.

An additional challenge for the medical oncologist is decision making after the first-line of chemotherapy has failed to control the tumor. For some disease types, there is clear objective benefit from the administration of second-line therapy. For many, however, second-line therapy is more likely to lead to enhanced cumulative toxicities rather than objective tumor response. A sensitive and thoughtful discussion with the patient and the family regarding the goals of care is needed. Emphasis must be placed on the ability to successfully manage the symptoms of progressive advanced disease with nonchemotherapeutic modalities.

As mentioned above, the beneficial effects of chemotherapy on pain is not often evaluated. Yet, it is interesting that the adverse effects of chemotherapy are well understood from monitoring in clinical trials in which nausea, vomiting, alopecia, neuropathy, and other symptoms are evaluated.

SIDE EFFECTS AND COMPLICATIONS

Toxicities and the predictable side effects of each of the chemotherapeutic agents are indicated in Table 37B-1. Perhaps the most common painful sequela of chemotherapy administration is a toxic peripheral neuropathy manifested as painful paresthesia, hyporeflexia, and, less frequently, sensory or motor loss or autonomic dysfunction (12). The drugs most commonly associated with this complication are the vinca alkaloids, especially vincristine; the taxanes, especially paclitaxel; vinorelbine, cisplatin, procarbazine; and less frequently misonidazole and hexamethylmelamine (19,33). In some cases, the painful peripheral neuropathy not only limits the dosing of anticancer therapy, but also can be more debilitating than the cancer itself and more difficult to treat than the more common nociceptive aspects of cancer pain.

Another painful complication of cancer and its therapy is acute herpes zoster and postherpetic neuralgia, which occur with increased frequency in patients with cancer—especially in those receiving chemotherapy or immunosuppressive drugs. Although the palliative benefits of glucocorticoids on mood, pain (as an antiinflammatory coanalgesic), and appetite are well known, chronic steroid therapy can cause myopathy, as well as necrosis of the femoral and humeral heads (34). Furthermore, one should be aware of the fact that withdrawal of glucocorticoids can cause a sense of decreased well-being, with increased pain, decreased energy, and apathy called *pseudorheumatism* (35).

ENDOCRINE THERAPY

In the 1890s, Beatson (36) was the first to demonstrate hormonal control of breast cancer when he induced regression of metastatic tumor by ovariectomy. In 1941, Huggins and Hodges (37) reported the successful use of exogenous estrogen administration for prostatic carcinoma. Since then, several other tumors have been shown to respond to hormonal manipulation, which is achieved either by ablating endocrine glands or by administration of an exogenous hormone or hormone antagonist.

Mechanism of Action

The mechanism of action of these agents has been clarified by the demonstration that receptors that bind with estrogen exist in the cytosol of normal and malignant cells (5). Hormones bind to receptors in the cytoplasm and sterically alter the shape of the receptive protein itself, which, after transport to the cell nucleus, interacts with DNA, and this results in altered messenger RNA production and protein synthesis (6). After this interaction, cytoplasmic receptor concentration is restored and the cycle can be repeated. Estrogen receptors can be quantitated as 8S and 4S proteins (6). Primary tumors in humans have estrogen receptor values that range from zero to almost 1,000 fmol per mg cytosol protein. Receptors also exist for progesterones and androgens, and receptors for corticosteroids have been identified in the cytosol of leukemic cells (6).

Hormonal ablation can be achieved by surgical means, as occurs with oophorectomy, adrenalectomy, and hypophysectomy; by irradiation of the ovaries or ablating the pituitary gland with the various radioactive compounds; by injecting alcohol; or by surgical extirpation (see Chapter 104 and Chapter 108). Medical adrenalectomy can be achieved by administering aminoglutethimide, a potent inhibitor of the conversion of cholesterol to pregnenolone in the adrenal gland (6). Hormone additive therapy is achieved by the administration of estrogens, progestins, androgens, antiestrogens, corticosteroids, and thyroid hormones. Table 37B-4 lists the hormonal agents used in the treatment of various cancers, their dosage ranges, and side effects. The dosages used generally produce plasma levels that are substantially higher than physiologic levels. Such hormone changes can cause complex endocrine effects, such as pituitary inhibition of luteinizing hormone, follicle-stimulating hormone, and prolactin, as well as changes in endogenous steroid hormone production (6).

TABLE 37B-4. Hormonally active agents in cancer treatment

Endocrine Therapy for Relief of Cancer Pain

Pannuti and associates (38,39) were among the first to point out that most reports containing results of anticancer treatment in patients with advanced malignant neoplasm are usually concerned only with measuring volume reduction of the tumor masses. Most writers have neglected, and often deliberately excluded, the assessment of subjective responses, including those related to pain, because this factor was not thought to be a reliable measure of the efficacy of treatment. Pannuti and colleagues further pointed out that there was no universally accepted rating system or qualification of pain relief on the part of oncologists, and this obviously led to heterogeneous results that could not be compared.

At the First International Symposium on Cancer Pain (38) and at another symposium held subsequently (39), Pannuti and colleagues presented a comprehensive summary of the results reported by a number of oncologists. Table 37B-5 contains mean data presented by Pannuti et al. (38,39) that provide an overview of the response to hormonal therapy of patients with four types of cancers. These reports were one of the first in which the efficacy of hormonal therapy on pain relief was correlated with the efficacy of these agents on tumor remission. Unfortunately, a significant number of reports had no data on the degrees of pain relief.

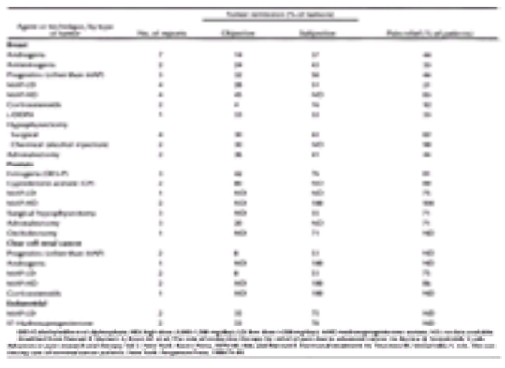

TABLE 37B-5. Results with hormonal therapy in advanced cancer

As can be noted in Table 37B-5, Pannuti et al. (38) gave progestin therapy in the form of high doses of injectable medroxyprogesterone acetate (MAP-HD) and noted pain relief in 83% of breast cancer patients with predominantly bone metastasis, although only 45% had objective evidence of tumor remission. In view of the corticosteroidlike side effects from these large doses of MAP-HD, it is possible that much of the subjective response was due to nonspecific steroid action. They also noted that hypophysectomy provided a high degree of pain relief. With regard to advanced cancer of the prostate, MAP-HD and hypophysectomy produced the highest degree of pain relief. For hypophysectomy, pain relief was twice as good as subjective tumor remission. With regard to renal carcinoma, androgens and progestins (particularly in the form of MAP-HD) provided pain relief and a subjective tumor remission in approximately 40% of the patients.

Although ovarian carcinoma contains steroid receptors, very little objective response to hormone has been demonstrated (38). Subjective response to the tumor occurred in some patients with progestin therapy, but no information is available concerning pain relief.

Well-differentiated papillary thyroid carcinoma, found particularly in women younger than the age of 40, is likely to be dependent on thyroid-stimulating hormone, and pituitary thyroid-stimulating hormone secretion can be suppressed by thyroxine administration, but no data are available concerning pain relief.

Side Effects

Endocrine therapy is generally much better tolerated than chemotherapy. None of these agents produces bone marrow suppression. Corticosteroids and high doses of medroxyprogesterone acetate (MPA), given for long periods of time, are associated with classic cushingoid side effects, and parenteral MPA can cause gluteal abscess (38).

Sex hormones, particularly estrogens, can cause intermittent uterine bleeding, which can be upsetting, especially for postmenopausal women. Androgens cause virilization and increased libido in some women. Estrogen given to men causes alopecia, testicular atrophy, gynecomastia, loss of libido, and impotence. Long-term administration of estrogen is also associated with a decrease in mortality from cardiac and cerebrovascular disease—presumably on the basis of favorable effects on lipoproteins—whereas androgens are thought to increase the risk of cardiovascular disease. Adrenalectomy causes side effects similar to those of estrogens, with the exception of the excess cardiovascular complications. Surgical adrenalectomy and hypophysectomy are both major operative procedures and carry a small but significant mortality risk. However, radiosurgical hypophysectomy using a gamma-knife is promising, as it has been reported to produce high incidences of pain relief with much less morbidity and virtually no mortality, although hormone replacement is required (40).

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CHAPTER 38

Oral Mucositis in Cancer Patients

Joel B. Epstein and Mark M. Schubert

Pain in cancer patients may be related to the cancer or therapy of the malignant disease or may be unrelated the cancer or the therapy (Table 38-1) (see Chapter 35, Chapter 36 and Chapter 37). Pain caused by oral mucositis occurs secondary to tissue damage that results in erythema and ulceration. Ulcerative mucositis is a painful, debilitating condition that at times represents a dose- and rate-limiting toxicity of cancer chemotherapy and therapeutic irradiation. Sequelae consist of severe pain, increased risk for local and systemic infection, compromised oral and pharyngeal function, and bleeding that affect quality of life and increase the costs of care. Because oral pain associated with mucositis is the most common pain condition requiring management in patients receiving cancer treatment, this chapter reviews current strategies for managing oral mucositis as a means of preventing pain. This chapter also addresses the current approaches for pain management associated with oral mucositis. Finally, current research that may lead to improved management and prevention of oral mucositis is reviewed. Pain associated with head and neck cancer is discussed in Chapter 53.

I. Acute
1. Caused by disease: invasion of bone, nerve, muscle, mucosal damage; tumor pressure
2. Caused by cancer therapy: surgery, radiation therapy, and chemotherapy
a. Oral/dental pain: mucositis, infection, and neuropathy
3. Unrelated conditions causing pain
II. Chronic
1. Caused by persisting/progressive disease
2. Caused by cancer therapy: surgery, radiation therapy, and chemotherapy
a. Mucosal atrophy/xerostomia
b. Mucosal infection
c. Neuropathy
d. Temporomandibular (myofascial) disorders
e. Dental caries
f. Osteoradionecrosis/mucosal necrosis
g. Postherpetic neuralgia
h. Unrelated conditions causing pain

TABLE 38-1. Orofacial pain in cancer patients

EPIDEMIOLOGY

Mucositis is the most common cause of oral pain during treatment of cancer (1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28 and 29) (Table 38-2). Oral mucositis is a common complication resulting from bone marrow transplant (BMT) conditioning and is virtually universal in patients treated with tumoricidal radiation therapy that includes the oropharynx. The increasing use of more aggressive therapy to improve cancer cure rates has markedly increased the frequency and severity of oral complications. Changes in medical management include increased use of combined radiation and chemotherapy, hyperfractionation of radiation therapy, and increasingly aggressive BMT protocols, all of which result in increased toxicity (1,3,4,6,9,12,14,17,22,29). The use of growth factors to speed the recovery of the hematopoietic compartment has led to the recognition that oral mucositis has become a significant treatment-limiting complication in cancer therapy (30,31 and 32). Oral mucositis may also be coincident with toxicity at other sites, including venoocclusive disease (29) and gastrointestinal toxicity (33). The potential for systemic infection caused by oral opportunistic and acquired flora associated with oral mucositis has been documented in several studies of leukemia and BMT patients (34,35,36,37 and 38).

Acute pain during treatment:	
Oropharyngeal mucositis	
Chemotherapy	40–70%
Bone marrow transplant	60–85%
Radiation therapy	Up to 100%
Postsurgical therapy	Up to 100%
Chronic pain following cancer therapy	
Mucosal pain	Up to 33%
Pain associated with mucosal infection	
Candidiasis	
After bone marrow transplant	Up to 50%
After radiation therapy	20–33%
Herpes simplex in seropositive bone marrow transplant patients	Up to 90%
Neuropathy	16%
TMD/myofascial (patients with head and neck squamous cell carcinoma)	25–30%
TMD, temporomandibular disorder.	

TABLE 38-2. Frequencies of oral pain associated with cancer therapy

PATHOGENESIS

Intense cytotoxic chemotherapy and radiation therapy directly affect the proliferation of epithelial cells resulting in thinning of the epithelium and ultimately to loss of the barrier (Fig. 38-1 and Table 38-3). Mucosal damage is primarily related to the rate of cell proliferation of the epithelium. Epidermal growth factor (EGF) may increase the risk of mucositis, and cytokines that reduce epithelial cell proliferation may decrease the severity of tissue damage. Interaction with cytokines produced in the connective tissue such as granulocyte-macrophage stimulating factor (GM-CSF), tumor necrosis factor, and others may affect tissue damage. The oral microflora may play a role in the cause and progression of the mucosal damage, as suggested in studies of gram-negative bacterial flora in radiation-induced mucositis. The role

of the oral flora in chemotherapy-associated mucositis is not clear. The outcomes of infection caused by mucosal damage are conditioned by the potential effect of systemic therapy on the hematopoietic system and local and systemic immune function. Resolution of mucositis may be dependent on white blood cell function and the production of pluripotential growth factors (12,30,31,32 and 33). During resolution, cytokines inducing epithelial cell proliferation and migration, and angiogenic growth factors may play a role (39,40,41,42,43 and 44). Pain associated with mucositis is dependent on the degree of tissue damage, sensitization of nociceptors, and elaboration of inflammatory and pain mediators. The rate of resolution of mucositis appears to depend on epithelial growth and repair, recovery of white cell counts, and reduction of microbial and physical irritation in the mouth and likely reflects the complex interaction of various growth factors.

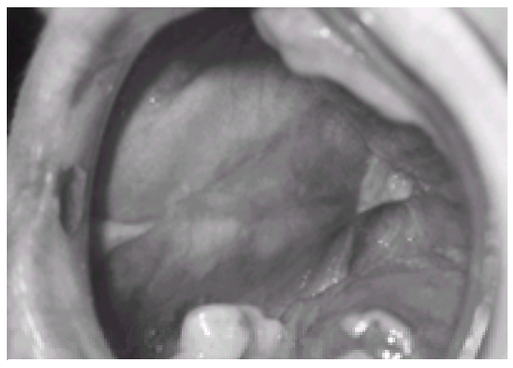

Figure 38-1. Mild mucositis with erythema and minor erosion of the cheek mucosa in a patient following autologous bone marrow transplant (at day +14). Mild mouth discomfort was reported.

Direct factors	Indirect factors
Radiation therapy	Myelosuppression
Dose/fraction	Immunosuppression
Total dose/days	T-cell loss/dysfunction
Chemotherapy	B-cell loss/dysfunction
Drug/dose/schedule	Reduced secretory IgA
Bone marrow transplant	Infections
Chemotherapy	Bacterial
Irradiation	Plaque control
Salivary gland dysfunction	Viral
Mucosal trauma	Herpes simplex
Physical	Varicella zoster
Chemical	Cytomegalovirus
Thermal	Other
Microbial flora	Fungal
Graft versus host disease	
Manifestations	
Prophylaxis	
Therapy	
Patient susceptibility	

TABLE 38-3. Factors contributing to oropharyngeal mucositis

ORAL MUCOSITIS

Bone Marrow Transplant

Ulcerative mucositis is the most common toxicity of BMT and treatment for hematologic cancer (14,15,20,22). Mucositis is more severe and of longer duration in patients with herpes simplex virus (HSV) reactivation and in those with poor oral hygiene (13,20,25,26). Reactivation of HSV is a contributor to severe ulcerative mucositis after BMT, especially in the first 30 days posttransplant (13,25,26). HSV prophylaxis has changed the frequency and severity of mucositis in BMT patients and represents an advance in prevention of ulcerative mucositis in at-risk patients. However, even in BMT patients provided acyclovir prophylaxis, oral ulcerative mucositis occurs in more than 75% of patients (15).

Mucositis begins at approximately 5 days after marrow infusion (day +5) with resolution in more than 90% of patients by day +15 when recovery of white cell count occurs (15). Damage to the mucosa most often presents in a bilateral pattern, primarily involving the cheeks, lip mucosa, lateral and ventral surfaces of the tongue, floor of the mouth, and soft palate. The mucosal reaction may begin shortly after exposure to the conditioning regimen and progress to erythema and ultimately ulceration (Fig. 38-2; see Fig. 38-1). Persistence of ulcers beyond day +15 occurs in patients who develop oral graft-versus-host disease and in patients who had more severe oral ulcerations. Increased mucosal toxicity is seen with the addition of total body irradiation (22,24,30). Mucositis is increased in BMT patients with xerostomia (23).

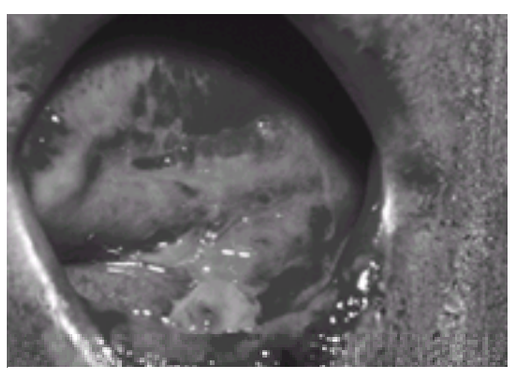

Figure 38-2. Severe ulcerated mucositis in a patient receiving an unrelated donor bone marrow transplant (day +14) requiring systemic opioid analgesic.

The influence of oral microflora and dental plaque on the severity of mucositis is increasingly clear (45,46,47,48,49,50 and 51). Intensive oral hygiene has been documented to reduce oral mucositis by 70% in BMT patients (45). The median time of onset of mucositis was delayed in the intensive oral care group (11 days versus 9 days) and the duration of moderate to severe mucositis was reduced. Septicemia was not increased in patients who continued intensive oral care (45). Immunoglobulins and other antimicrobial proteins in the saliva are dramatically decreased after BMT conditioning, which may be a factor in the increased risk of mucosal infection and in mucositis (33).

Radiation Therapy

Pain is commonly present at the time of diagnosis of head and neck and oral cancer (85%), although the pain is not severe (18,52). The presence and severity of pain are related to tumor stage, and pain is present in all cases with bone involvement (18). Pain occurs with treatment in all patients treated for oropharyngeal cancer and increases in severity throughout the course of radiation and persists after treatment (1,18,27,28) (see Chapter 37 and Chapter 53). Radiotherapy-related mucositis is the most frequent complication in patients submitted to irradiation for head and neck cancers (see Table 38-1). Mucositis affects the oral tissue involved in the primary treatment field, corresponding to the fields of irradiation and the dose of exposure, although considerable individual variability is seen (Fig. 38-3 and Fig. 38-4). Mucositis-related pain increases during radiation treatment, and typically resolves within 1 month. However, discomfort may continue for 6 to 12 months or longer, although the severity of pain decreases over time after treatment (18). Chronic complaints include mucosal sensitivity attributed to mucosal atrophy (33%), musculoskeletal syndromes (temporomandibular disorder) (25%), and neurologic syndromes attributed to deafferentation (16%) (18). In another study, the most

common persisting complaints after radiation treatment included xerostomia (57%), jaw pain involving the muscles of the jaw or joint pain (27%), and a 10% increased rate of dental caries (53). Pain may also be associated with other complications of radiation therapy including necrosis of bone and oral soft tissue. Chronic complications of radiation therapy were assessed in 676 head and neck cancer patients treated in a multicenter study (54). Eleven percent had severe complications (grade 3 or 4) involving the oral mucosa, bone, or muscle (54). Grade 3 mucosal change was defined as marked atrophy with complete dryness and ulceration; grade 3 muscle change was defined as severe induration and severe trismus; and grade 3 bone change was defined as pain or tenderness and bone exposure (54). These late complications were found to be related to total radiation dose; complications in bone were more common with large radiation fields, and complications in bone and muscle were related to fraction size. The severity of chronic mucosal damage may relate to severity of acute mucosal reaction.

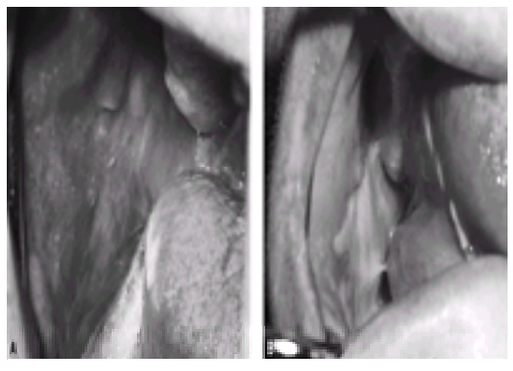

Figure 38-3. **A:** Initial tissue reaction in a patient receiving radiation therapy (dose received 1,400 cGy of planned 6,000 cGy) resulting in erythema and sensitivity of the right buccal mucosa. **B:** Late tissue reaction in the same patient receiving radiation therapy (total dose received 6,000 cGy) resulting in oral pain and mucosal ulceration within the radiation field.

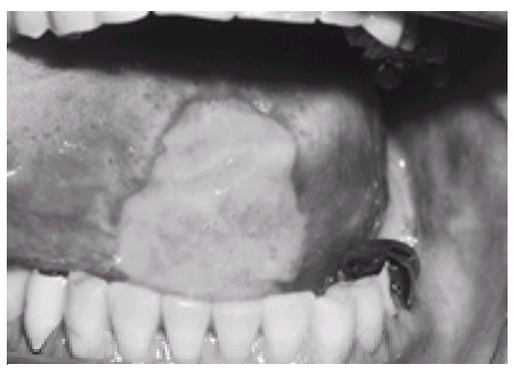

Figure 38-4. Localized ulcerative mucositis following brachytherapy for a squamous cell carcinoma of the middle portion of the lateral border of the tongue.

Combined Radiation Therapy with Surgery or Chemotherapy

Mucositis is a dose- and rate-limiting toxicity of the treatment for head and neck and oral cancer. The principal treatment-limiting side effect of head and neck cancer therapy is mucositis. Treatment of locally advanced head and neck carcinoma with surgery and radiotherapy is associated with significant treatment complications affecting oral function. Hyperfractionated radiotherapy and chemotherapy may improve survival, but treatment is frequently limited by the severity of oral toxicity (1,4,6,17,55,56). Severe oral mucositis occurs in all patients treated with accelerated fractionated irradiation for supraglottic cancer (1) and in those provided combined chemotherapy and radiation therapy (55,56). The primary factor limiting radiation treatment was severe mucositis, which caused considerable pain, limited oral intake, and required suspension of irradiation therapy (1,56). Changes in the delivery of radiotherapy including increasing total dose, hyperfractionation, and the combination of radiation therapy and chemotherapy have increased the severity of the resulting mucositis. Mucosal reactions in patients receiving radiation treatment for head and neck cancer are currently regarded as unavoidable side effects.

The importance of fungal colonization and infection in radiation mucositis is not clearly defined (57,58 and 59). In a group of patients receiving head and neck irradiation, patients on fluconazole developed one mycotic infection, and 14 nonscheduled breaks in radiation therapy occurred, compared with 19 fungal infections and 30 breaks in radiation therapy in those not on prophylaxis with fluconazole (57). However, others have not found an association between candidiasis or oral colonization and mucositis during cancer therapy (58,59).

PAIN ASSESSMENT

Most studies have used visual analogue scales or 5- or 10-point scales to assess oral pain (see Chapter 15 and Chapter 35). The McGill Pain Questionnaire has also been used (16,60). Approximately 90% of patients develop oral pain during BMT (16). The McGill Pain Questionnaire was compared with two different factor models in patients with oral mucositis pain after BMT, and it was recommended that a single pain rating may provide a better practical measurement (60). Clinically, patients may be unable or unwilling to complete lengthy questionnaires, particularly when their overall condition including pain is at its worst. Pain assessment may also be affected by use of systemic analgesics, which mask the pain experienced. Therefore, both pain and analgesic use need to be simultaneously assessed. Despite this, pain report is correlated with the severity of mucositis; most of the variance in pain report is explained by the severity of the mucositis rather than psychosocial variables (11).

MEDICAL MANAGEMENT OF ORAL MUCOSITIS

Most studies assessing management of oral mucositis involve small numbers of patients, and many suffer from use of outcome measures that are not validated and may lack sensitivity. Wide variation exists in quality of studies, making assessment of outcomes difficult and requiring reviewers to carefully assess the methods employed in the study. Guidelines for the use of outcome measures and approach to study design in management of mucositis may improve the value of many studies. Prevention and management of oral mucositis require an understanding of the multifactorial nature of the condition (Table 38-4).

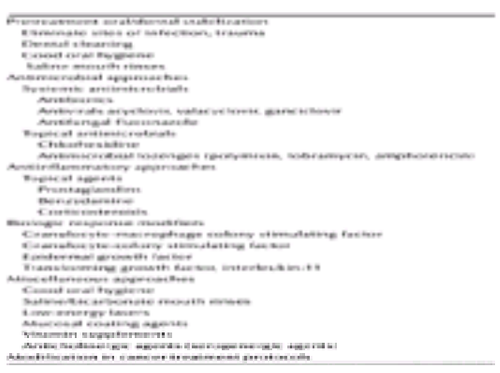

TABLE 38-4. Prevention and management of oral mucositis

Pain Management

Mucositis is the most common condition requiring the use of systemic analgesics during cancer therapy (5). Management of severe oropharyngeal mucositis often requires the use of systemic opioids. Guidelines are presented in Chapter 84.

Systemic analgesics should be prescribed following the World Health Organization analgesic ladder (21). These recommendations include the use of nonopioid analgesics alone, or in combination with opioids and adjunctive medications with increasing pain. In addition, analgesics should be provided on a time-contingent basis, with provision for management of breakthrough pain (see Chapter 83 and Chapter 84). In patients with oral mucositis pain, topical approaches should continue to be used in combination with systemic analgesics in order that the best pain management can be achieved with the least potent and lowest doses of systemic pain medications.

The equianalgesic dose of morphine and hydromorphone was evaluated in patient-controlled analgesia (PCA) in BMT patients with severe oral mucositis (61). A morphine to hydromorphone ratio of 3:1 was determined, which is different from doses in single- dose studies used in published dose equivalency recommendations (61). Another study assessed morphine or hydromorphone PCA use in preteen children during BMT (5). The median duration of PCA use was 19 days, depending on the severity of mucositis or other painful conditions. Ninety-five percent of children successfully mastered PCA to control pain associated with BMT. No instance of drug overdose or difficulty stopping the opioid was noted (5). Addiction is not a concern in oncology patients, rather the concern is with underuse and underdosing, leading to poor pain management (21). Another common concern is the lack of use of adjuvant analgesics and other methods of pain management in cancer patients (21).

Antimicrobial Approaches

Acyclovir prophylaxis in HSV-seropositive BMT patients is strongly supported in the literature. In HSV-seropositive BMT patients provided acyclovir prophylaxis, viral shedding was seen in 2.9% of patients, and one case of clinical HSV was diagnosed (62). Thus, acyclovir was confirmed as preventing HSV viral shedding in most cases. Oral ulcerations have been described caused by cytomegalovirus (CMV) in BMT (63). Acyclovir prophylaxis has also been shown to prevent shedding of CMV by one-half in BMT (64). In another study, shedding of CMV was detected in 13.3% of CMV-seropositive patients; however, no oral lesions consistent with CMV were identified. No correlation between severity of mucositis and serologic status of HSV or CMV was seen in patients provided acyclovir prophylaxis (62). Ganciclovir after engraftment in BMT has been shown effective in suppressing CMV infection (65).

Consecutive BMT recipients at risk of streptococcal bacteremia were treated for 5 days with clindamycin (900 mg intravenously three times a day) and ceftazidime (2 g three times a day) for the initial management of fever associated with severe oral mucositis (37). Bacteremia caused by *Viridans* streptococci occurred in 70% of patients when maximum mucositis was present, and culture results were positive a day before fever in approximately one-third of cases, indicating that mucosal ulceration predisposes to systemic infection by oral flora. Severe oral mucositis rather than infection appeared to induce fever, suggesting bacteremia caused by viridans streptococci may be a consequence of mucosal damage (37). These data indicate that rather than an antimicrobial approach, it may be more important to develop strategies that minimize mucosal damage in BMT (37).

In a series of patients with leukemia and BMT, fluconazole prophylaxis was compared with no prophylaxis (59). Although no differences in oropharyngeal or systemic candidiasis were seen, a trend to reduction in oropharyngeal colonization by *Candida albicans* was seen ($p = .07$). No relationship was seen between *Candida* species, antifungal prophylaxis, and mucositis, indicating that *Candida* was not involved in the etiology of mucosal damage in these patients (58). In a randomized controlled trial, fluconazole prevented systemic fungal infections (7% of fluconazole versus 18% of placebo patients) (66). The incidence of mucosal infection and oropharyngeal colonization by *C. albicans* was also significantly reduced. Fluconazole should be considered for prophylaxis of infection by *C. albicans* in BMT patients.

Antiinflammatory Approaches

Antiinflammatory approaches for prevention of mucositis have received preliminary study. Patients undergoing BMT received prostaglandin E_2 (Prostin E2, 0.5 mg per tablet) or placebo for prophylaxis of oral mucositis (67). The incidence, severity, and duration of oral mucositis were similar for both groups. However, the incidence of HSV infection was higher in patients receiving prostaglandin, and in these patients more severe oral mucositis was seen. These results indicate that prostaglandin E_2 is not a candidate for prophylaxis of mucositis in BMT recipients (67). Studies using other antiinflammatory medications or combinations with antiviral prophylaxis should be considered.

Pentoxifylline and methylprednisolone were provided to 12 BMT patients, and oral mucositis was assessed (7). The most common site of toxicity was the mouth (87.5%). Mucositis was less severe in patients receiving pentoxifylline and methylprednisolone, and pain medications were required less often in these patients (7). This trial could not determine if pentoxifylline or methylprednisolone or both may have had an effect on mucositis and further study is needed.

Xerostomia

Mucosal toxicity is dose limiting for patients on etoposide and may be related to direct effects of myoablative doses of etoposide on the mucosa that are secreted in saliva (19). Twelve patients received propantheline, 30 mg (an anticholinergic xerostomia-inducing agent), or placebo orally every 6 hours for six doses (19). Mucositis was less frequent and less severe ($p = .05$) in the propantheline arm. Another study investigated the effect of drug-induced xerostomia on mucositis during BMT by comparing patients with historic controls (68). Propantheline was found to significantly reduce oral mucositis, caused by high-dose etoposide, although no effect was seen in esophagitis and enteritis. Minor toxicities included constipation and asymptomatic tachycardia, and clinically significant toxicity was seen in two patients (tachycardia, urinary retention) (68). These studies suggest that for chemotherapeutics that are secreted in saliva, xerostomia may decrease the contact time of the chemotherapeutic to the mucosa and thereby reduce tissue damage.

Miscellaneous Approaches

Sixty-three patients with oral carcinoma treated with concomitant chemoradiotherapy were assigned to daily azelastine (2 mg) (69). Mucositis was mild in 21 patients and ulceration with severe pain was seen in 16 patients on azelastine, whereas, in the control group, mild reactions were observed in five cases, and severe mucositis occurred in 21 patients (69). Azelastine may suppress neutrophil respiratory burst activity by suppressing cytokine release from lymphocytes. Further study of azelastine for treatment of mucositis is indicated. An extensive analysis of the literature showed that external beam radiotherapy provided effective pain relief or substantial reduction of pain caused by skeletal metastases in nearly all cases (70). Systemic radiotherapy using radionuclides may be indicated for generalized skeletal pain in patients with metastatic disease (70,71). However, optimal doses and fractionation have not been established. Management of bone pain caused by metastatic disease has been assessed using strontium 89 and local radiation therapy (71). A common side effect of strontium 89 is bone marrow suppression, although this may not be clinically significant in patients with a pretreatment platelet count of more than 60,000 per µL and a white blood cell count of more than 2,400 per µL (71).

TOPICAL APPROACHES TO MANAGEMENT OF ORAL MUCOSITIS

Although no studies exist demonstrating the effectiveness of saline or bicarbonate rinses in decreasing mucositis, the use of frequent oral rinses is commonly included in oral care protocols. Also, because many institutions recommend frequent oral rinsing, these recommendations become incorporated into studies as a baseline oral care standard.

Forty patients undergoing radiotherapy to more than 50% of the oral cavity were randomized to an oral care protocol using either saline or hydrogen peroxide rinses (72). No significant differences were seen in mucositis, although oral sensitivity was greater in those using peroxide (72).

Topical tretinoin cream was assessed in six BMT patients beginning at day –7 and continuing until day +21 (73). This preliminary study showed a reduction in the severity of mucositis in those on tretinoin and fewer of these patients required systemic analgesics.

Topical Antimicrobials

Chlorhexidine has been assessed in BMT patients in a number of studies and conflicting results with the use of chlorhexidine in mucositis have been seen. The majority of studies do not demonstrate a prophylactic effect on mucositis, although a tendency to reduced oral colonization of *Candida* species has been seen in several studies (74). The effect of oral hygiene may represent a confounding factor in these studies. The effect of chlorhexidine rinsing on plaque levels, gingival inflammation, and caries risk have not been the primary end points in these studies, but may be valuable effects of chlorhexidine during cancer therapy.

Studies of an antimicrobial lozenge combining polymixin, tobramycin, and amphotericin B in head and neck radiation therapy have shown that ulcerative mucositis is prevented (75). The effect was attributed to a reduction in gram-negative bacteria. Double- blind studies are ongoing.

Miscellaneous Approaches

Coating agents used as oral rinses in patients with mucositis, such as milk of magnesia, liquid Amphojel, and loperamide (Kaopectate) have been recommended frequently, but have not been subjected to double-blind studies (21).

Sucralfate suspension has been studied in mucositis (76,77,78 and 79). Less severe mucositis has been reported with use of sucralfate (76,77 and 78), but not in all reports (79). A randomized prospective trial of sucralfate prophylaxis of oral mucositis during radiation therapy delivered with high daily fractions did not show a significant difference in mucositis (79). Less oral pain was reported early during radiation therapy in the sucralfate group (79). The lack of effect of sucralfate in this study may be caused by the large daily fractions of irradiation provided or the limited action of sucralfate in preventing oral mucositis. Another study showed reduced pain and a reduction in potentially pathogenic organisms (78). Taken together, the studies of sucralfate are inconclusive, and further studies are needed to determine if sucralfate reduces pain and mucosal damage during cancer therapy.

Lidocaine viscous is frequently recommended, although no studies are available that assess the benefit or the potential for toxicity with use in cancer patients (21). Lidocaine may result in burning with use, obtund taste, and the gag reflex, and may have cardiovascular and CNS effects. Other topical anesthetics also have been used including dyclonine HCl, which may be better accepted than lidocaine by patients. Benzydamine HCl (Tantrum rinse, 3M-Riker Canada; Difflam, 3M United Kingdom) has been shown to reduce mucositis and associated oral pain in radiation-induced mucositis (21,28). The mucosal effects include mild anesthesia and analgesia. Controlled studies of benzydamine rinse in chemotherapy-induced mucositis remain to be conducted. Local applications of topical anesthetic creams or gels may be useful for local painful mucosal ulcerations.

Topical capsaicin was assessed in a phase I study of mucositis pain (10). Oral capsaicin in a taffy-candy vehicle produced partial and temporary pain reduction in 11 patients with oral mucositis pain (10). The findings suggest that some of the pain of mucositis is mediated by substance P.

Radiation shields are often suggested during radiation therapy. The use of midline mucosa-sparing blocks for protection of the mucosa during radiation therapy resulted in less weight loss, fewer hospitalizations for nutritional support, and a trend toward fewer treatment interruptions ($p = .07$) than in control patients (8). Unfortunately, mucositis was not directly assessed.

Biological Response Modifiers and Cytokines

Studies have been conducted assessing the potential of growth factors to affect oral mucositis using a cheek pouch model of mucositis in Syrian Golden hamsters (39,40,41,42,43 and 44). The animal model yields mucositis in the hamster cheek pouch after infusion of 5-FU and local mucosa trauma. Outcome measures used in this model included assessment of severity of mucosal damage, weight loss, and survival. EGF was shown to increase the severity of mucosal damage when given concurrently with chemotherapy in the hamster model (80). Transforming growth factor-b_3 (TGF-b_3) given after chemotherapy has been shown to reduce the incidence, severity, and duration of mucositis, reduce weight loss, and increase survival of animals (41,43). Topical transforming growth factor (TGF) reduces the proliferation of oral epithelial cells *in vitro* and *in vivo* (41,43). The mechanism may be reduction in proliferation of the basal epithelial cells, as measured by proliferating cell nuclear antigen and DNA ploidy (41). Interleukin-11 (IL-11) has been shown to cause dose-dependent and statistically significant reduction in mucositis ($p < .05$) (39,40,44). Survival was 85% on IL-11 versus 46% in placebo, and less weight loss was seen in the IL-11 group. The lack of change in bone marrow cellularity suggests that the effects of IL-11 are caused by direct epithelial or connective tissue effects (39). A rat model of inflammatory bowel disease also showed reduction in gross and microscopic damage to the colon in animals treated with IL-11 (44).

EGF in saliva was assessed in patients receiving head and neck radiation therapy (42). The quantity of EGF in the oral environment decreased because of decreased volume of saliva and decreased in concentration per milliliter of saliva as mucositis increased throughout the course of radiation therapy (42). EGF may represent a marker for mucosal damage and has the potential to promote resolution of radiation-induced mucositis. Further study is required.

Several studies in humans have assessed the potential effect of GM-CSF on oral mucositis (30,31 and 32). In 20 patients treated for squamous cell carcinoma GM-CSF significantly reduced the incidence, duration, and severity of oral mucositis (81). An initial study of 14 head and neck cancer patients receiving radiotherapy treated with GM-CSF when mucositis developed showed that 79% of patients had reduction in severity of the reaction (82). In 26 children receiving BMT, the duration of mucositis was reduced in the GM-CSF group, although the severity of the mucosal reaction was not affected (30). Oral mucositis was improved in eight BMT patients who received topical GM-CSF compared with historic controls (32). A study of BMT for 22 patients provided granulocyte colony stimulating factor (G-CSF) versus 24 not given G-CSF found the most common toxicity was oral mucositis (38%) (12). Posttransplant G-CSF resulted in a trend toward a reduction in severity of mucositis ($p = .07$) (12). A multicenter controlled trial of G-CSF administration after BMT showed that G-CSF resulted in acceleration of neutrophil recovery. The length of stay in hospital was reduced; however, no difference in mucositis was seen (33). Further multicenter studies of GM-CSF and possibly G-CSF on prevention of oral mucositis appear warranted.

Miscellaneous Approaches

Low-energy lasers have been studied in the prevention and management of mucositis associated with BMT (83,84). The mechanism of action may be caused by effects of cytokine release caused by laser exposure of the tissue, but further study is needed. The helium-neon laser was assessed in 30 consecutive patients receiving peripheral stem cell BMT who received daily treatment from day -5 to day +1 (83). Reduced occurrence and duration of ulcerative mucositis as well as reduced oral pain and opioid use were seen. The requirement for parenteral nutrition was not reduced. Another study investigated unilateral application of helium-neon laser in 20 BMT patients (84). Oral mucositis and pain scores were significantly lower for the treated versus the untreated side (84). Further study is needed to determine the efficacy of low-energy laser in preventing mucositis.

COGNITIVE AND BEHAVIORAL INTERVENTIONS

There has been limited study of the use of these approaches to pain management (see Chapter 88, Chapter 89, Chapter 90, Chapter 91 and Chapter 92). Although relaxation, imagery, biofeedback, hypnosis, and transcutaneous electrical nerve stimulation have been employed in the management of cancer pain, few controlled studies have been conducted (21). The use of hypnosis also has been shown to be a valuable adjunct in cancer pain (85,86).

A survey of pediatric oncology and BMT centers was conducted to determine the cognitive behavioral interventions used (87). Interventions, such as providing information before procedures and positive reinforcement after procedures, were used more frequently than behavioral interventions, such as rhythmic breathing, distraction, and imagery, that require more time and training. Psychological services were primarily available on an as-needed basis and support groups were not generally offered. Increasing emphasis on psychological support and techniques for pain management may be useful for patients during BMT.

A controlled clinical trial of psychological interventions as adjuncts to medical treatment in cancer-related pain was conducted (88). This study assessed oral mucositis pain in 94 BMT patients in four groups: standard treatment, therapist support, relaxation and imagery training, and cognitive-behavioral coping skills combined with relaxation and imagery (88). It was shown that relaxation and imagery training reduces pain associated with oral mucositis and that adding cognitive-behavioral skills to relaxation and imagery did not improve pain relief (88).

SUMMARY

The study of pain management in oncology has focused on pain caused by oral mucositis because of the frequency of this complication, the effect oral symptoms have on patient quality of life, and the implications for medical management. Pain in the head and neck and oropharynx of cancer patients is a significant factor in the quality of life. Mucosal damage, particularly in the presence of immunosuppression and neutropenia, may result in risk of systemic infection (Fig. 38-5). Oropharyngeal pain in cancer patients frequently requires systemic analgesics, adjunctive medications, physical therapy, and psychological therapy, in addition to oral care and topical treatments (see Table 38-4). Good oral hygiene reduces the severity of oral mucositis and does not increase the risk of bacteremia.

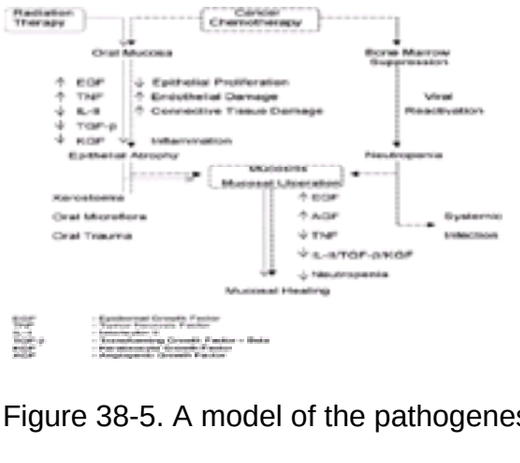

Figure 38-5. A model of the pathogenesis of oral mucositis.

Clinically apparent mucositis is the result of a number of toxicities and tissue damage and inflammation. The primary event is cell damage from chemotherapy, radiotherapy, or both. Secondary influences include indirect toxicities resulting in immunosuppression, neutropenia, reactivation of latent virus (herpes viruses), and opportunistic microbial (bacterial and fungal) infections. Salivary gland dysfunction caused by dehydration and direct effects of the cancer therapy on gland function may alter the local mucosal defenses. Because the etiology is multifactorial (see Table 38-3), approaches to prevention and treatment have been multifactorial (see Table 38-4). Effective prevention and management of mucositis affect the pain experienced during cancer treatment. When mucositis is present, symptomatic management is needed (Table 38-5).

Maintain good oral hygiene
Prevent mucosal damage (see Table 38-2)
Coating agents (milk of magnesia, aluminum hydroxide gel (Amphojel), sucralfate, loperamide (Kaopectate), and so forth)
Topical analgesic/antiinflammatory (benzydamine)
Topical anesthetics
Systemic analgesics
Adjuvant systemic medications
Adjuvant cognitive/psychological support
Physical therapy (rinsing, ice chips)
Miscellaneous agents

TABLE 38-5. Symptomatic management of pain of oral mucositis

Systemic analgesics are important in pain management, and continuing study has involved determination of dose and route of administration. Pain management approaches in addition to systemic analgesics of potential interest are agents that affect neurotransmitters of pain such as substance P. Research in topical analgesic and antiinflammatory agents is ongoing.

A number of approaches appear to be viable candidates for further study. Biological response modifiers offer the potential for prevention and to speed healing. Initial studies with G-CSF have been encouraging; however, the reports with GM-CSF have been less positive. Other cytokines will enter clinical trial in the near future and offer the potential for reduction of epithelial cell sensitivity to toxic effects of cancer therapy or to stimulate repair of the damaged tissue. Other approaches include the use of xerogenergic medications to reduce exposure of the oral mucosa to chemotherapeutic drugs that are secreted in saliva. Antimicrobial approaches have met with conflicting results, with little effect of chlorhexidine and systemic antimicrobials in preventing mucositis in radiation patients. In BMT and leukemic patients chlorhexidine may not prevent mucositis, although there may be an effect on *Candida* carriage. Initial studies of a topical antimicrobial lozenge (polymixin, tobramycin, and amphotericin B) have shown reduction in ulcerative mucositis during radiation therapy. Other approaches that require further study include low-energy lasers and antiinflammatory medications. These approaches to management have had initial study, but additional research is needed to determine effectiveness of newer approaches to prevention of mucositis and symptom management as well as to determine the appropriate dose and frequency of the intervention.

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CHAPTER 39

*Pain in Human Immunodeficiency Virus Disease**

William Breitbart

Studies conducted between 1990 and 1995 have documented that pain in individuals with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) is highly prevalent, diverse, and varied in syndromal presentation; associated with significant psychological and functional morbidity; and alarmingly undertreated (1,2,3,4,5,6,7,8,9,10 and 11). With the introduction of highly active antiretroviral therapies (i.e., combination therapies including protease inhibitors) the face of the AIDS epidemic, particularly for those who can avail themselves of and tolerate these new therapies, is indeed changing. Death rates from AIDS in the United States have dropped dramatically since 1997, and rates of serious opportunistic infections and cancers are declining. Despite these hopeful developments, the future is still unclear, and millions of patients with HIV worldwide continue to die of AIDS and suffer from the enormous burden of physical and psychological symptoms. Even with the advances in AIDS therapies, pain continues to be an issue in the care of patients with HIV. As the epidemiology of the AIDS epidemic changes in the United States, the challenge of managing pain in AIDS patients with a history of substance abuse is becoming an ever-growing challenge. Pain management needs to be more integrated into the total care of patients with HIV. This chapter describes the prevalence and types of pain syndromes encountered in patients with HIV, and discusses the effect of pain on quality of life. Principles of pain management in AIDS, including pharmacologic and nonpharmacologic interventions, are described. In addition, undertreatment of pain in AIDS, barriers to adequate pain treatment in this population, and guidelines for the management of pain in HIV-infected patients with a history of substance abuse are presented.

PREVALENCE OF PAIN IN HUMAN IMMUNODEFICIENCY DISEASE

Estimates of the prevalence of pain in HIV-infected individuals have been reported to range from 30% to over 90%, with the prevalence of pain increasing as the disease progresses (3,11,12,13,14 and 15), particularly in the latest stages of illness.

Studies suggest that approximately 30% of ambulatory HIV-infected patients in early stages of HIV (pre-AIDS; category A or B disease) experience clinically significant pain, and as many as 56% have had episodic painful symptoms of less clear clinical significance (4,6,11). In a prospective cross-sectional survey of 438 ambulatory AIDS patients in New York City, 63% reported “frequent or persistent pain of at least two weeks' duration” at the time of assessment (4). The prevalence of pain in this large sample increased significantly as HIV progressed, with 45% of AIDS patients with category A3 disease reporting pain, 55% of those with category B3, and 67% of those with category C1, 2, or 3 disease reporting pain. Patients in this sample of ambulatory AIDS patients also were more likely to report pain if they had other concurrent HIV-related symptoms (e.g., fatigue, wasting), had received treatment for an AIDS- related opportunistic infection, or if they had not been receiving antiretroviral medications [e.g., zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (D4T)].

In a study of pain in hospitalized patients with AIDS in a public hospital in New York City, over 50% of patients required treatment for pain, with pain being the presenting complaint in 30% and the second most common presenting problem after fever (7). In a French multicenter study, 62% of hospitalized patients with HIV had clinically significant pain (6). Schofferman and Brody (15) reported that 53% of patients with far advanced AIDS cared for in a hospice setting had pain, whereas Kimball and McCormack (13) reported that up to 93% of AIDS patients in their hospice experienced at least one 48-hour period of pain during the last 2 weeks of life.

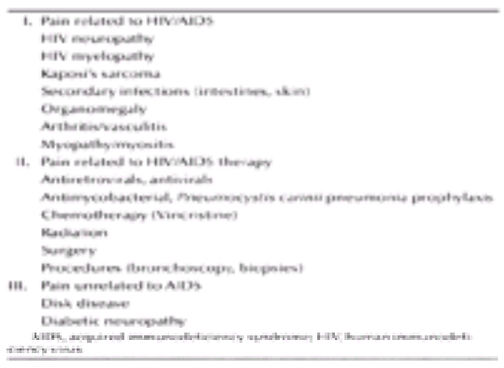
Larue and colleagues (14) demonstrated that patients with AIDS being cared for by hospice at home had prevalence rates and intensity ratings for pain that were comparable with, and even exceeded, those of cancer patients. Breitbart and colleagues (3) reported that ambulatory AIDS patients in their New York City sample reported a mean pain intensity “on average” of 5.4 (on the 0 to 10 numeric rating scale of the Brief Pain Inventory) and a mean pain “at its worst” of 7.4. In addition, as with pain prevalence, the intensity of pain experienced by patients with HIV increases significantly as disease progresses. AIDS patients with pain, like their counterparts with cancer pain, typically describe an average of 2.5 to 3.0 concurrent pains at a time (3,5).

PAIN SYNDROMES IN HUMAN IMMUNODEFICIENCY VIRUS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

Etiologies and Classification

Pain syndromes encountered in AIDS are diverse in nature and etiology. The most common pain syndromes reported in studies to date include painful sensory peripheral neuropathy, pain caused by extensive Kaposi's sarcoma, headache, oral and pharyngeal pain, abdominal pain, chest pain, arthralgias and myalgias, as well as painful dermatologic conditions (4,5,7,9,11,12,14,15 and 16). In a sample of 151 ambulatory AIDS patients who underwent a research assessment that included a clinical interview, neurologic examination, and review of medical records (5), the most common pain diagnoses included headaches (46% of patients, 17% of all pains), joint pains (arthritis, arthralgias, and so forth in 31% of patients; 12% of pains), painful polyneuropathy (distal symmetric polyneuropathy in 28% of patients, 10% of pains), and muscle pains (myalgia, myositis in 27% of patients; 12% of pains). Other common pain diagnoses included skin pain (Kaposi's sarcoma, infections in 25% of patients; 30% of homosexual men in the sample had pain from extensive Kaposi's sarcoma lesions), bone pain (20% of patients), abdominal pain (17% of patients), chest pain (13%), and painful radiculopathy (12%). Patients in this sample had a total of 405 pains (averaging three concurrent pains), with 46% of patients diagnosed with neuropathic-type pain, 71% with somatic pain, 29% with visceral pain, and 46% with headache (classified separately because of controversy as to pathophysiology). When pain type was classified by pains (as opposed to patients) 25% were neuropathic pains, 44% were nociceptive-somatic, 14% were nociceptive-visceral, and 17% were idiopathic-type pains. Patients in this study with lower $CD4^{+}$ cell counts were significantly more likely to be diagnosed with polyneuropathy and headache. Hewitt and colleagues (5) demonstrated that although pains of a neuropathic nature (e.g., polyneuropathies and radiculopathies) certainly make up a large proportion of pain syndromes encountered in AIDS patients, pains of a somatic nature, visceral nature, or both are also extremely common.

Pain syndromes seen in HIV can be categorized into three types (Table 39-1): (a) those directly related to HIV infection or consequences of immunosuppression; (b) those caused by AIDS therapies; and (c) those unrelated to AIDS or AIDS therapies (2,5). In studies to date, approximately 45% of pain syndromes encountered are directly related to HIV infection or consequences of immunosuppression; 15% to 30% are caused by therapies for HIV- or AIDS-related conditions, as well as diagnostic procedures; and the remaining 25% to 40% are unrelated to HIV or its therapies (5).



I.	Pain related to HIV/AIDS
	HIV neuropathy
	HIV myelopathy
	Kaposi's sarcoma
	Secondary infections (intestines, skin)
	Organomegaly
	Arthritis/vasculitis
	Myopathy/myositis
II.	Pain related to HIV/AIDS therapy
	Antiretrovirals, antivirals
	Antimycobacterial, *Pneumocystis carinii* pneumonia prophylaxis
	Chemotherapy (Vincristine)
	Radiation
	Surgery
	Procedures (bronchoscopy, biopsies)
III.	Pain unrelated to AIDS
	Disk disease
	Diabetic neuropathy

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

TABLE 39-1. Pain syndromes in acquired immunodeficiency syndrome

Our group at Memorial Sloan-Kettering has reported on the experience of pain in women with AIDS (5,16). Although preliminary in nature, our studies suggest that women with HIV experience pain more frequently than men with HIV and report somewhat higher levels of pain intensity. This may in part be a reflection of the fact that women with AIDS-related pain are twice as likely to be undertreated for their pain compared with men (3). Women with HIV have unique pain syndromes of a gynecologic nature specifically related to opportunistic infectious processes and cancers of the pelvis and genitourinary tract. Women with AIDS were significantly more likely to be diagnosed with radiculopathy and headache in one survey (5).

Children with HIV infection also experience pain (17). HIV-related conditions in children that are observed to cause pain include meningitis and sinusitis (headaches); otitis media; shingles; cellulitis and abscesses; severe *Candida* dermatitis; dental caries; intestinal infections, such as *Mycobacterium avium intracellulare* (MAI) and cryptosporidium; hepatosplenomegaly; oral and esophageal candidiasis; and spasticity associated with encephalopathy that causes painful muscle spasms.

Specific Pain Syndromes in Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

The following section reviews, in detail, the various painful manifestations of HIV. The author acknowledges the important review by O'Neill and Sherrard (9) that formed the basis of this section on specific pain syndromes in HIV.

Gastrointestinal Pain Syndromes

Many of the opportunistic infections and HIV-associated neoplasms may present as pain referable to the gastrointestinal tract. Generally, the pain is alleviated by specific treatment of the causative diseases. Adequate analgesia should be provided during diagnostic assessment (9).

Oropharyngeal Pain

Oral cavity and throat pain is common, accounting for approximately 20% of the pain syndromes encountered in one study (7,18,19) (see Chapter 38). The sources of oral cavity pain have been well described (9). Oropharyngeal candidiasis occurs in up to 75% of HIV- positive individuals and, although frequently asymptomatic, it is the most common cause of oral cavity pain. Bacterial infections are mainly seen as necrotizing gingivitis and can arise in HIV-positive patients in spite of maintaining a good standard of oral hygiene (9). Dental abscesses occur more commonly in HIV-infected individuals than in the general population. Oral ulcerations are extremely common and can be the result of herpes simplex virus, cytomegalovirus (CMV), Epstein-Barr virus, atypical and typical mycobacterial infection, cryptococcal infection, or histoplasmosis. Frequently, no infectious agent can be identified, and these painful aphthous ulcers are a clinically challenging problem (9). Up to 75% of patients with cutaneous Kaposi's sarcoma also have intraoral lesions, most commonly on the palate, although these seldom cause pain (9).

Esophageal Pain

Approximately one-third of patients with HIV experience esophageal symptoms such as dysphagia or pain on swallowing (odynophagia) often caused by esophageal candidiasis. Esophageal candidiasis occurs in as many as 75% of patients with HIV disease (20,21 and 22) and may present as dysphagia or odynophagia. Ulcerative esophagitis, which can be quite painful, is usually a result of CMV infection but can be idiopathic. Infectious causes of esophagitis include herpes simplex, Epstein-Barr virus, mycobacteria, *Cryptosporidium*, and *Pneumocystis carinii* (21,22,23,24, and 25). Kaposi's sarcoma and lymphoma both have been reported to invade the esophagus, resulting in dysphagia, pain, and ulceration (9). AZT has also been reported to be a cause of esophageal ulceration (26).

Abdominal Pain

Abdominal pain is the primary site of pain in 12% to 25% of patients with HIV (5,7,27). Infectious causes of abdominal pain predominate and include cryptosporidiosis, *Shigella*, *Salmonella*, and *Campylobacter* enteritis, CMV ileitis, and mycobacterial (MAI) infection. Perforation of the small and large intestine secondary to CMV infection has been described (27). Repeated intussusception of the small intestine has been seen in association with *Campylobacter* infection (27). Lymphoma in the gastrointestinal tract can present with abdominal pain and intestinal obstruction (28). Kaposi's sarcoma spreads to the gastrointestinal tract of 40% to 50% of AIDS patients with cutaneous lesions (29). Rarely, intestinal Kaposi's sarcoma may cause obstruction, bleeding, perforation, and diarrhea (30). Other causes of abdominal pain in HIV-positive patients (9) include ileus, organomegaly, spontaneous aseptic peritonitis, toxic shock, herpes zoster, and Fitz-Hugh-Curtis syndrome (perihepatitis in association with tubal gonococcal or chlamydia infection).

Biliary Tract and Pancreatic Pain

Cholecystitis may occur in HIV-infected patients as a result of opportunistic infection, CMV and cryptosporidiosis being the most common infectious agents. Extrahepatic biliary tract obstruction secondary to Kaposi's sarcoma or MAI infection has been reported (9). Sclerosing cholangitis (CMV, cryptosporidiosis), also known as AIDS cholangiopathy, is another cause of right upper quadrant or epigastric pain (31). Opportunistic liver infections (CMV, MAI, fungal infections) as well as drug-induced hepatic toxicities (ddI, pentamidine) are sources of hepatitis and abdominal or right upper quadrant pain (32).

Pancreatitis is often related to adverse effects of HIV-related therapies, in particular the antiretroviral agents ddI and ddC. Between 7% and 10% of patients on ddI develop pancreatitis, and lower rates are reported with other antiretrovirals. Intravenous pentamidine is also associated with pancreatitis. Infectious causes of pancreatitis include CMV infection, MAI infection, and cryptococcal infection (33). Rarely, lymphoma or Kaposi's sarcoma may involve the pancreas, resulting in pancreatitis.

Anorectal Pain

Painful anorectal diseases are common, occurring in approximately one-third of homosexual men with HIV. Infectious causes of anorectal pain include perirectal abscesses, CMV proctitis, fissure-in-ano, and herpes simplex virus infection. A small increase has been noted in anal and anorectal carcinoma in HIV-positive homosexual men (34).

Chest Pain Syndromes

Chest pain is a common complaint in patients with HIV, making up approximately 13% of the pain syndromes encountered in a sample of ambulatory AIDS patients (5). Sources of chest pain in patients with HIV are similar to those encountered in the general population (i.e., cardiac, esophageal, lung and pleura, and chest wall); the etiologies may be somewhat unique (i.e., opportunistic infections and cancers). In immunosuppressed patients, infectious causes of chest pain should be considered, particularly in the presence of fever and some localizing sign such as dysphagia, dyspnea, or cough. Infectious causes of chest pain include *Pneumocystis* pneumonia (with or without a pneumothorax), esophagitis (CMV, candidiasis, herpes simplex), pleuritis and pericarditis (viral, bacterial, tuberculous), and postherpetic neuralgia. Opportunistic cancers (Kaposi's sarcoma, lymphoma) invading the esophagus, pericardium, chest wall, lung, and pleura may be sources

of chest pain. Rarely, pulmonary embolus or bacterial endocarditis may be the cause of chest pain.

NEUROLOGIC PAIN SYNDROMES IN ACQUIRED IMMUNODEFICIENCY SYNDROME

Pain syndromes originating in the nervous system include headache, painful peripheral neuropathies, radiculopathies, and myelopathies. The HIV virus is highly neurotropic, invading central and peripheral nervous system structures early in the course of HIV. As many as 75% of patients with late-stage AIDS have a neurologic complication (35,36,37,38 and 39) either directly caused by HIV itself (e.g., AIDS dementia, HIV peripheral neuropathy, HIV myelopathy) or secondary to opportunistic infection [e.g., central nervous system (CNS) toxoplasmosis, CMV neuropathy], cancer (e.g., CNS lymphoma), or medication side effects (toxic neuropathies caused by ddI, ddC, D4T, or AZT-induced headache). Headache is a frequent symptom in HIV-infected patients and may be an important indication of disease of the CNS including opportunistic infections and cancers. Rarely, cerebrovascular events (e.g., thalamic stroke) occurring in hypercoagulable states can result in central pain syndromes.

Headache

Headache is extremely common, reported by 40% to 50% of patients with HIV disease, particularly in the later stages of illness (5,40). Headache poses a diagnostic dilemma for physicians in that the underlying cause may range from benign stress and tension to life-threatening CNS infection (9) (see Chapter 48). The differential diagnosis of headache in patients with HIV includes HIV encephalitis and atypical aseptic meningitis, opportunistic infections of the nervous system, AIDS-related CNS neoplasms, sinusitis, tension, migraine, and AZT-induced headache (41). Toxoplasmosis and cryptococcal meningitis are the two most commonly encountered opportunistic infections of the CNS in patients with HIV (37). Cerebral toxoplasmosis usually presents with persistent headache, sometimes associated with focal signs, change in mental status, or seizures. Diagnosis is based on radiologic imaging (magnetic resonance imaging is more sensitive than computed tomography) with a characteristic appearance of multiple deep ring-enhancing lesions and a clinical response to a trial of empiric treatment for toxoplasmosis. A brain biopsy is sometimes necessary to establish a definitive diagnosis and to differentiate cerebral toxoplasmosis from cerebral lymphoma. Cryptococcal meningitis usually presents with symptoms of headache, neck stiffness, and recurring fever, although focal neurologic signs may occur. Other opportunistic infections of the CNS that can present as headache in the AIDS patient include CMV, herpes simplex virus and herpes zoster, progressive multifocal leukoencephalopathy (papovavirus), *Candida albicans*, *Mycobacterium tuberculosis*, MAI, and neurosyphilis. Headache related to sinus infection is common in immunocompetent patients with HIV who present with headache, but have no focal neurologic signs. Opportunistic cancers of the CNS include CNS lymphoma, metastatic systemic lymphoma, and metastatic intracranial Kaposi's sarcoma. These can present, particularly in the immunocompromised patient with HIV, with signs of increased intracranial pressure with or without focal neurologic signs, as well as fever and meningismus. More benign causes of headache in the patient with HIV include AZT-induced headache, occurring in 15% to 30% of patients; tension headache; migraine with or without aura, and unclassifiable or idiopathic headache (41,42).

Neuropathies Encountered in Patients Infected with Human Immunodeficiency Virus

Pain syndromes of a neuropathic nature occur in approximately 40% of AIDS patients with pain (5) (see Chapter 19). Although several types of peripheral neuropathies have been described in patients with HIV and AIDS (Table 39-2), the most common painful neuropathy encountered is the predominantly sensory neuropathy of AIDS, affecting up to 30% of people with HIV infection. Other potentially painful neuropathies encountered in HIV and AIDS patients, however, can be caused by viral and nonviral infectious processes (mononeuritis multiplex, including polyneuritis cranialis, polyradiculopathy of the lower limbs, cauda equina syndrome, and plexopathies caused by CMV, herpes zoster virus, MAI), immune-mediated inflammatory demyelination (acute and chronic Guillain-Barré syndrome), a variety of medical conditions (diabetic neuropathy, postherpetic neuralgia, entrapment neuropathies), nutritional deficiencies (B_6, B_{12}), toxins (alcohol), and HIV-related therapies. Several antiretroviral drugs, such as ddI, ddC, and D4T; chemotherapy agents used to treat Kaposi's sarcoma (vincristine); as well as a number of medications used in the treatment of *Pneumocystis carinii* pneumonia, mycobacterial infection, and other HIV-associated infections can cause painful toxic neuropathy (9,43,44).

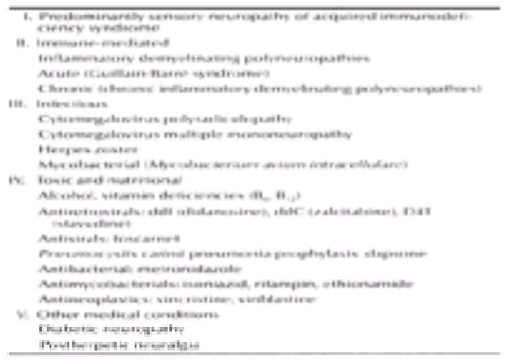

I. Predominantly sensory neuropathy of acquired immunodeficiency syndrome
II. Immune-mediated
Inflammatory demyelinating polyneuropathies
Acute (Guillain-Barré syndrome)
Chronic (chronic inflammatory demyelinating polyneuropathy)
III. Infectious
Cytomegalovirus polyradiculopathy
Cytomegalovirus multiple mononeuropathy
Herpes zoster
Mycobacterial (Mycobacterium avium intracellulare)
IV. Toxic and nutritional
Alcohol, vitamin deficiencies (B_6, B_{12})
Antiretrovirals: ddI (didanosine), ddC (zalcitabine), D4T (stavudine)
Antivirals: foscarnet
Pneumocystis carinii pneumonia prophylaxis: dapsone
Antibacterial: metronidazole
Antimycobacterials: isoniazid, rifampin, ethionamide
Antineoplastics: vincristine, vinblastine
V. Other medical conditions
Diabetic neuropathy
Postherpetic neuralgia

TABLE 39-2. Neuropathies encountered in human immunodeficiency virus disease

Predominantly Sensory Neuropathy of Acquired Immunodeficiency Syndrome

The most frequently encountered neuropathy is a symmetric predominantly sensory painful peripheral neuropathy. This is a late manifestation, occurring most often in patients with an AIDS-defining illness, but has been reported earlier in the course of the disease (36). Prevalence in hospice populations ranges from 19% to 26% (15,45,46). It is the only peripheral sensory neuropathy that has been postulated to be a direct result of HIV infection of the peripheral nervous system (36,47,48). The predominant symptom in approximately 60% of patients is pain in the soles of the feet. Paresthesia is frequent and usually involves the dorsum of the feet in addition to the soles. Most patients have signs of peripheral neuropathy (most commonly, absent or reduced ankle jerks and elevated thresholds to pain and vibration sense); and while the signs progress, the symptoms often remain confined to the feet (37,48,49). Although the patients' complaints are predominantly sensory, electrophysiologic studies demonstrate both sensory and motor involvement.

Immune-Mediated Neuropathies

Acute Guillain-Barré syndrome has been described in association with seroconversion (group I infection) but may occur at any time. Both acute and chronic inflammatory demyelinating polyneuropathies are predominantly motor, and sensory abnormalities are rare (42). Mononeuritis multiplex presents with sensory or motor deficits in the distribution of multiple spinal, cranial, or peripheral nerves (49) and may progress into a chronic inflammatory demyelinating polyneuropathy (42).

Infectious Neuropathies

Polyradiculopathies (associated with CMV infection) often present with radicular pain and follow a distinct course (50). The onset is usually subacute and the deficit initially confined to sacral and lumbar nerve roots. Both sensory and motor functions are involved, and usually early involvement of sphincters is seen. Progression is relentless (42).

Toxic and Nutritional Neuropathies

Toxic and nutritional neuropathies in patients with HIV have been reported with the following: alcohol; vitamin deficiencies (B_6 and B_{12}); antiretroviral drugs such as ddI, ddC, and D4T; antivirals such as foscarnet; *Pneumocystis carinii* pneumonia prophylaxis such as dapsone; antibacterial drugs such as metronidazole; antimycobacterial drugs such as INH, rifampin, and ethionamide; and antineoplastics such as vincristine and vinblastine (44,47).

Painful Neuropathies According to Stage of Human Immunodeficiency Virus Infection

The type of neuropathy varies with the stage of infection. The acute or seroconversion phase of HIV is associated with mononeuritides, brachial plexopathy, and acute

demyelinating polyneuropathy. The latent or asymptomatic phase ($CD4^+$ T lymphocytes greater than 500 per mL) is characterized by acute and chronic demyelinating polyneuropathies. The transition phase (200 to 500 $CD4^+$ cells) is characterized by herpes zoster (shingles) and mononeuritis multiplex. The late phase of HIV disease (less than 200 $CD4^+$ cells) is characterized by predominantly sensory HIV polyneuropathy, CMV polyneuropathy, mononeuritis multiplex, autonomic neuropathy, mononeuropathies secondary to meningeal disease, and antiretroviral-induced toxic neuropathies (44).

RHEUMATOLOGIC PAIN SYNDROMES

In studies conducted by the Memorial Sloan-Kettering group (15), over 50% of pain syndromes were classified as rheumatologic in nature, including various forms of arthritis, arthropathy, arthralgia, myopathy, myositis, and myalgias. In another study, 72% of patients with different stages of HIV infection had painful symptoms involving the musculoskeletal system (51).

Arthritis and Arthropathies

HIV disease has been associated with several types of painful arthritis and arthropathies, including nonspecific arthralgias, reactive arthritis, psoriatic arthritis, HIV-associated arthritis, and rarely aseptic arthritis (52,53) (see Chapter 27). The most frequently reported arthritis is a reactive arthritis or Reiter's syndrome (53,54 and 55), often unresponsive to nonsteroidal antiinflammatory drug (NSAID) therapy. Reiter's syndrome can present with persistent oligoarthritis primarily affecting the large joints of the lower limbs, sacroiliitis, urethritis, conjunctivitis, keratoderma blenorrhagica, circinate balanitis, and oral ulceration. Many patients have positive results for HLA-B27 antigen. Diarrhea is a common precipitating event. Nonspecific arthralgias are common (51,52 and 53). Acute HIV infection may present with a polyarthralgia in association with a mononucleosislike illness. A syndrome of acute severe and intermittent articular pain also exists, often referred to as HIV-associated painful articular syndrome, which commonly affects the large joints of the lower limbs and shoulders. Psoriasis and psoriatic arthritis have been reported in patients with HIV infection (56,57). The arthritis is typically seen in conjunction with the skin changes of psoriasis, and authors suggest it may follow a disease course that proves refractory to conventional therapy (9). An HIV-associated arthritis has also been described (58), which typically presents as an oligoarthritis affecting the joints of the lower limbs. Synovial fluid is noninflammatory, and biopsy shows a mild chronic synovitis. No associated infection exists to suggest a reactive arthritis, and the patients reported have had HLA-B27–negative results. It appears that this arthritis is caused by the HIV virus itself (52). Septic arthritis has been reported in patients with HIV, including arthritis caused by bacterial infections, and infections with *Cryptococcus neoformans* and *Sporothrix schenckii* (52,53).

Myopathy and Myositis

Muscle pain is common in patients with HIV. Several types of myopathies and myositis have been described in HIV-infected patients, including HIV-associated myopathy or polymyositis, necrotizing noninflammatory myopathy in association with AZT and without AZT, pyomyositis, and microsporidiosis myositis (49,59,60,61,62,63 and 64). Polymyositis may occur at any stage of HIV infection, is thought to be the result of direct viral infection of muscle cells (53), and may present with a subacute onset of proximal muscle weakness and myalgia (49). Electromyographic evidence of myopathy, a raised serum creatinine kinase level, and biopsy evidence of polymyositis are common in symptomatic patients. Drugs used in the treatment of HIV may also be associated with the development of myalgia (65) and myositis (59,66). AZT has been particularly implicated. In these patients symptoms frequently improve after discontinuation of AZT therapy (9).

EFFECT OF PAIN ON QUALITY OF LIFE

Pain, in patients with HIV disease, has a profound negative effect on physical and psychological functioning, as well as overall quality of life (6,10). In a study of the effect of pain on psychological functioning and quality of life in ambulatory AIDS patients (10), depression was significantly correlated with the presence of pain. In addition to being significantly more distressed, depressed, and hopeless, those with pain were twice as likely to have suicidal ideation (40%) as those without pain (20%). HIV-infected patients with pain were more functionally impaired (10). Such functional interference was highly correlated to levels of pain intensity and depression. Patients with pain were more likely to be unemployed or disabled and reported less social support. Larue and colleagues (6) reported that HIV-infected patients with pain intensities greater than 5 (on a 0 to 10 numeric rating scale) reported significantly poorer quality of life during the week preceding their survey than patients without pain. Pain intensity had an independent negative effect on HIV patients' quality of life, even after adjustment for treatment setting, stage of disease, fatigue, sadness, and depression. Singer and colleagues (11) also reported an association between the frequency of multiple pains, increased disability, and higher levels of depression. Psychological variables, such as the amount of control people believe they have over pain, emotional associations and memories of pain, fears of death, depression, anxiety, and hopelessness, contribute to the experience of pain in people with AIDS and can increase suffering (10,67). Our group also reported (68) that negative thoughts related to pain were associated with greater pain intensity, psychological distress, and disability in ambulatory patients with AIDS. Those AIDS patients who thought that pain represented a progression of their HIV reported more intense pain than those who did not see pain as a threat.

MANAGEMENT OF PAIN IN ACQUIRED IMMUNODEFICIENCY SYNDROME

Assessment Issues

The initial step in pain management is a comprehensive assessment of pain symptoms. The health professional working in the AIDS setting must have a working knowledge of the etiology and treatment of pain in AIDS. This would include an understanding of the different types of AIDS pain syndromes discussed previously, as well as a familiarity with the parameters of appropriate pharmacologic treatment. A close collaboration of the entire health care team is optimal when attempting to adequately manage pain in the AIDS patient. A careful history and physical examination may disclose an identifiable syndrome (e.g., herpes zoster, bacterial infection, or neuropathy) that can be treated in a standard fashion (69,70). A standard pain history (71,72) may provide valuable clues to the nature of the underlying process and indeed may disclose other treatable disorders. A description of the qualitative features of the pain, its time course, and any maneuvers that increase or decrease pain intensity should be obtained. Pain intensity (current, average, at best, at worst) should be assessed to determine the need for weak versus potent analgesics and as a means to serially evaluate the effectiveness of ongoing treatment. Pain descriptors (e.g., burning, shooting, dull, or sharp) help determine the mechanism of pain (somatic, nociceptive, visceral nociceptive, or neuropathic) and may suggest the likelihood of response to various classes of traditional and adjuvant analgesics (e.g., NSAIDs, opioids, antidepressants, anticonvulsants, oral local anesthetics, corticosteroids) (73,74). Additionally, detailed medical, neurologic, and psychosocial assessments (including a history of substance use or abuse) must be conducted. Where possible, family members or partners should be interviewed. During the assessment phase, pain should be aggressively treated while pain complaints and psychosocial issues are subject to an ongoing process of reevaluation (72). Federal guidelines developed by the Agency for Health Care Policy and Research for the management of cancer pain (74) also address the issue of management of pain in AIDS and state the following: “The principles of pain assessment and treatment in the patient with HIV positive/AIDS are not fundamentally different from those in the patient with cancer and should be followed for patients with HIV-positive/AIDS.” In contrast to pain in cancer, pain in HIV may more commonly have an underlying treatable cause (9).

Multimodal Approach

Optimal management of pain in AIDS is multimodal and requires pharmacologic, psychotherapeutic, cognitive-behavioral, anesthetic, neurosurgical, and rehabilitative approaches (75). A multidimensional model of AIDS pain that recognizes the interaction of cognitive, emotional, socioenvironmental, and nociceptive aspects of pain suggests a model for multimodal intervention.

Pharmacologic Interventions: The World Health Organization Analgesic Ladder

The World Health Organization (WHO) (76) has devised guidelines for analgesic management of cancer pain that the Agency for Health Care Policy and Research has endorsed for the management of pain related to cancer or AIDS (73). These guidelines, also known widely as the *WHO analgesic ladder*, have been well validated (75). This approach advocates selection of analgesics based on severity of pain, as well as the type of pain (i.e., neuropathic versus nonneuropathic pain). For mild to moderate severity pain, nonopioid analgesics, such as NSAIDs and acetaminophen, are recommended. For pain that is persistent and moderate to severe in intensity, opioid analgesics of increasing potency (e.g., morphine) should be used. Adjuvant agents, such as laxatives and psychostimulants, are useful in preventing as well as treating opioid side effects such as constipation or sedation, respectively. Adjuvant analgesic drugs, such as the antidepressant analgesics, are suggested, along with opioids and NSAIDs, in all stages of the analgesic ladder (mild, moderate, or severe pain), but have their most important clinical application in the management of neuropathic pain.

This WHO approach, although not yet validated in AIDS, has been recommended by the Agency for Health Care Policy and Research and clinical authorities in the field of pain management and AIDS (7,9,11,15,43,73,76). Clinical reports describing the successful application of the principles of the WHO analgesic ladder to the

management of pain in AIDS, with particular emphasis on the use of opioids, have also appeared in the literature (8,13,15,77,78,79,80 and 81).

Nonopioid Analgesics

The nonopioid analgesics (Table 39-3) are prescribed principally for mild to moderate pain or to augment the analgesic effects of opioid analgesics in the treatment of severe pain. The use of NSAIDs in patients with AIDS must be accompanied by heightened awareness of toxicity and adverse effects. NSAIDs are highly protein bound, and the free fraction of available drug is increased in AIDS patients who are cachectic, wasted, and hypoalbuminemic, often resulting in toxicities and adverse effects. Patients with AIDS are frequently hypovolemic, on concurrent nephrotoxic drugs, and experiencing HIV nephropathy and so are at increased risk for renal toxicity related to NSAIDs. The antipyretic effects of the NSAIDs may also interfere with early detection of infection in patients with AIDS.

TABLE 39-3. Oral analgesics for mild to moderate pain in human immunodeficiency virus disease

The major adverse effects associated with NSAIDs include gastric ulceration, renal failure, hepatic dysfunction, and bleeding. The nonacetylated salicylates, such as salsalate, sodium salicylate, and choline magnesium salicylate, theoretically have fewer gastrointestinal side effects and might be considered in cases in which gastrointestinal distress is an issue. Prophylaxis for NSAID- associated gastrointestinal symptoms includes H_2 antagonist drugs (cimetidine, 300 mg three or four times a day, or ranitidine, 150 mg twice a day); misoprostol, 200 mg four times a day; omeprazole, 20 mg every day; or an antacid. Patients should be informed of these symptoms, issued guaiac cards with reagent, and taught to check their stool weekly. NSAIDs affect kidney function and should be used with caution. NSAIDs can cause a decrease in glomerular filtration, acute and chronic renal failure, interstitial nephritis, papillary necrosis, and hyperkalemia (82). In patients with renal impairment, NSAIDs should be used with great caution, because many (i.e., ketoprofen, fenoprofen, naproxen, and caprofen) are highly dependent on renal function for clearance. The risk of renal dysfunction is greatest in patients with advanced age, preexisting renal impairment, hypovolemia, concomitant therapy with nephrotoxic drugs, and heart failure. Prostaglandins modulate vascular tone, and their inhibition by the NSAIDs can cause hypertension as well as interference with the pharmacologic control of hypertension (83). Caution should be used in patients receiving b-adrenergic antagonists, diuretics, or angiotensin-converting enzyme inhibitors. Several studies have suggested that a substantial biliary excretion of several NSAIDs occurs, including indomethacin and sulindac. In patients with hepatic dysfunction, these drugs should be used with caution. NSAIDs, with the exception of the nonacetylated salicylates (e.g., sodium salicylate, choline magnesium trisalicylate), produce inhibition of platelet aggregation (usually reversible, but irreversible with aspirin). NSAIDs should be used with extreme caution, or avoided, in patients who are thrombocytopenic or who have clotting impairment.

Opioid Analgesics

Opioid analgesics are the mainstay of pharmacotherapy of moderate to severe intensity pain in the patient with HIV (Table 39-4) (see Chapter 84). Several reports describing the safe and effective use of opioid drugs in the management of moderate to severe pain in populations of patients with HIV (including patients with a history of injection drug use as their HIV transmission factor) have begun to appear in the literature (13,77,78,79,80 and 81). Kaplan and colleagues (83) conducted a multicenter study in which 44 patients with moderate to severe AIDS-related pain were treated with sustained-release oral morphine in an open-label prospective study of patients treated for up to 18 days. Pain intensity decreased by 65% in the patients who completed the study, quality of life was good in 80%, acceptability of therapy was 96% in the patients who completed the study, 92% of side effects were resolved, and total morphine dose remained stable through the course of the study. In a pilot study, Lefkowitz and Newshan (80) reported similar findings on the effectiveness and safety of the transdermal fentanyl patch in a small sample of patients with AIDS-related pain.

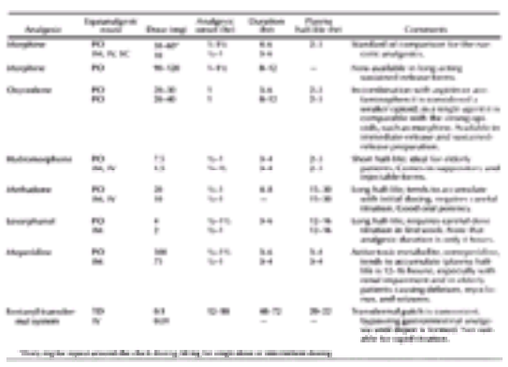


TABLE 39-4. Opioid analgesics for moderate to severe pain in human immunodeficiency virus disease

Principles that are useful in guiding the appropriate use of opioid analgesics for pain (74,76,84) include the following: (a) choose an appropriate drug; (b) start with lowest dose possible; (c) titrate dose; (d) use as-needed doses selectively; (e) use an appropriate route of administration; (f) be aware of equivalent analgesic doses; (g) use a combination of opioid, nonopioid, and adjuvant drugs; (h) be aware of tolerance; and (i) understand physical and psychological dependence. In choosing the appropriate opioid analgesic for cancer pain, Portenoy and Foley (73) highlight the following important considerations: (a) opioid class; (b) *weak* versus *strong* opioids; (c) pharmacokinetic characteristics; (d) duration of analgesic effect; (e) favorable prior response; and (f) opioid side effects.

Opioid analgesics are divided into two classes, the agonists and the agonist-antagonists, based on their affinity to opioid receptors. Pentazocine, butorphanol, and nalbuphine are examples of opioid analgesics with mixed agonist-antagonist properties. These drugs can reverse opioid effects and precipitate an opioid withdrawal syndrome in patients who are opioid tolerant or dependent. They are of limited use in the management of chronic pain in AIDS. Oxycodone (in combination with either aspirin or acetaminophen), hydrocodone, and codeine are the so-called weaker opioid analgesics and are indicated for use in step 2 of the WHO ladder for mild to moderate intensity pain. More severe pain is best managed with morphine or another of the stronger opioid analgesics, such as hydromorphone, methadone, levorphanol, or fentanyl. Oxycodone, as a single agent without aspirin or acetaminophen, is available in immediate and sustained-release forms and is considered a stronger opioid in these forms.

The oral route has often been described as the preferred route of administration of opioid analgesics from the perspectives of convenience and cost. However, the transdermal route of administration has gained rapid acceptance among clinicians and patients. Patients with HIV infection are burdened with the task of taking anywhere from 20 to 40 tablets of medication per day and often need to follow complicated regimens in which medication has to be taken on an empty stomach. In a study on patient-related barriers to pain management in AIDS patients (85), the vast majority of AIDS patients endorsed a preference to use a pain intervention that required a minimal number of additional pills (e.g., sustained-release preparations of oral opioids) or interventions that did not require taking pills at all (i.e., transdermal opioid system). Immediate-release oral morphine or hydromorphone preparations require that the drug be taken every 3 to 4 hours. Longer-acting, sustained-release oral morphine preparations and oxycodone preparations are available that provide up to 8 to 12 hours or more of analgesia, minimizing the number

of daily doses required for the control of persistent pain. Rescue doses of immediate-release, short-acting opioid are often necessary to supplement the use of sustained-release morphine or oxycodone, particularly during periods of titration or pain escalation. The transdermal fentanyl patch system (Duragesic) also has applications in the management of severe pain in AIDS (79,80). Each transdermal fentanyl patch contains a 48- to 72-hour supply of fentanyl that is absorbed from a depot in the skin. Levels in the plasma increase slowly over 12 to 18 hours after patch placement; so with the initial placement of a patch, alternative opioid analgesia (either oral, rectal, or parenteral) must be provided until adequate levels of fentanyl are attained. The elimination half-life of this dosage form of fentanyl is long (21 hours), and so it must be noted that significant levels of fentanyl remain in the plasma for approximately 24 hours after the removal of a transdermal patch. The transdermal system is not optimal for rapid dose titration of acutely exacerbated pain; however, a variety of dosage forms are available. As with sustained-release morphine preparations, all patients should be provided with oral or parenteral rapidly acting short-duration opioids to manage breakthrough pain. The transdermal system is convenient and can minimize the reminders of pain associated with repeated oral dosing of analgesics. In AIDS patients, it should be noted that the absorption of transdermal fentanyl can be increased with fever, resulting in increased plasma levels and shorter duration of analgesia from the patch.

It is important to note that opioids can be administered through a variety of routes: oral, rectal, transdermal, intravenous, subcutaneous, intraspinal, and even intraventricular (79). There are advantages and disadvantages, as well as indications for use of these various routes. Further discussion of such alternative delivery routes as the intraspinal route are beyond the scope of this chapter. Interested readers are directed to the Agency for Health Care Policy and Research Clinical Practice Guideline: Management of Cancer Pain (73), available free of charge through 1-800-4CANCER.

Opioid Side Effects

Although the opioids are extremely effective analgesics, their side effects are common and can be minimized if anticipated in advance. Sedation is a common CNS side effect, especially during the initiation of treatment. Sedation usually resolves after the patient has been maintained on a steady dosage. Persistent sedation can be alleviated with a psychostimulant, such as dextroamphetamine, pemoline, or methylphenidate. All are prescribed in divided doses in early morning and at noon. Additionally, psychostimulants can improve depressed mood and enhance analgesia (86,87). Delirium, of an either agitated or somnolent variety, can also occur while on opioid analgesics and is usually accompanied by attentional deficits, disorientation, and perceptual disturbances (visual hallucinations and more commonly illusions). Myoclonus and asterixis are often early signs of neurotoxicity that accompany the course of opioid-induced delirium. Meperidine (Demerol), when administered chronically in patients with renal impairment, can lead to a delirium caused by accumulation of the neuroexcitatory metabolite normeperidine (88). Opioid-induced delirium can be alleviated through the implementation of three possible strategies: (a) lowering the dose of the opioid drug presently in use; (b) changing to a different opioid; or (c) treating the delirium with low doses of high-potency neuroleptics, such as haloperidol. The third strategy is especially useful for agitation and clears the sensorium (89). For agitated states, intravenous haloperidol in doses starting at between 1 and 2 mg is useful, with rapid escalation of dose if no effect is noted. Gastrointestinal side effects of opioid analgesics are common. The most prevalent are nausea, vomiting, and constipation (74). Concomitant therapy with prochlorperazine for nausea is sometimes effective. Because all opioid analgesics are not tolerated in the same manner, switching to another opioid can be helpful if an antiemetic regimen fails to control nausea. Constipation caused by opioid effects on gut receptors is a problem frequently encountered, and it tends to be responsive to the regular use of senna derivatives. A careful review of medications is imperative, because anticholinergic drugs such as the tricyclic antidepressants can worsen opioid-induced constipation and can cause bowel obstruction. Respiratory depression is a worrisome but rare side effect of the opioid analgesics. Respiratory difficulties can almost always be avoided if two general principles are adhered to: (a) start opioid analgesics in low doses in opioid-naïve patients; and (b) be cognizant of relative potencies when switching opioid analgesics, routes of administration, or both.

Adjuvant Analgesics

Adjuvant analgesics are the third class of medications frequently prescribed for the treatment of chronic pain and have important applications in the management of pain in AIDS (Table 39-5). Adjuvant analgesic drugs are used to enhance the analgesic efficacy of opioids, treat concurrent symptoms that exacerbate pain, and provide independent analgesia (see Chapter 83). They may be used in all stages of the analgesic ladder. Commonly used adjuvant drugs include antidepressants, neuroleptics, psychostimulants, anticonvulsants, corticosteroids, and oral anesthetics (73,90,91).

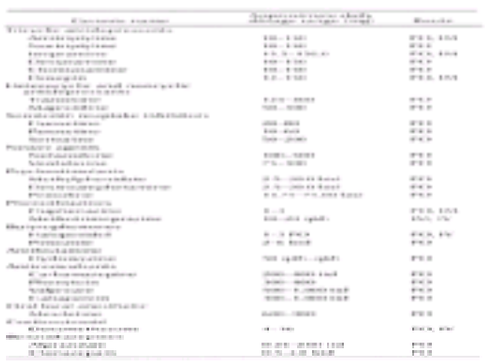


TABLE 39-5. Adjuvant analgesic drugs for pain in human immunodeficiency virus disease

Antidepressants

The current literature supports the use of antidepressants as adjuvant analgesic agents in the management of a wide variety of chronic pain syndromes, including cancer pain, postherpetic neuralgia, diabetic neuropathy, fibromyalgia, headache, and low back pain (92,93,94,95,96 and 97) (see Chapter 85). The antidepressants produce pain relief through a number of mechanisms that include antidepressant activity (93), potentiation or enhancement of opioid analgesia (94,98,99), and direct pain-relieving effects (100). The leading hypothesis suggests that both serotonergic and noradrenergic properties of the antidepressants are probably important and that variations among individuals in pain (as to the status of their own neurotransmitter systems) are an important variable (69). Other possible mechanisms of antidepressant pain-relieving activity that have been proposed include adrenergic and serotonin receptor effects (101), adenosinergic effects (102), antihistaminic effects (101), and direct neuronal effects, such as inhibition of paroxysmal neuronal discharge and decreasing sensitivity of adrenergic receptors on injured nerve sprouts (103).

Substantial evidence suggests that the tricyclic antidepressants in particular can relieve pain and are useful in the management of chronic neuropathic and nonneuropathic pain syndromes. Amitriptyline is the tricyclic antidepressant most studied and has been proved effective in a large number of clinical trials addressing a wide variety of chronic pain syndromes, including neuropathy, cancer pain, fibromyalgia, and others (69,93,94,104,105 and 106). Other tricyclics that have been shown to relieve pain include imipramine (107,108), desipramine (70,109,110 and 111), nortriptyline (112,113), doxepin (114), and clomipramine (113,115).

The heterocyclic and noncyclic antidepressant drugs, such as trazodone, mianserin, maprotiline, and the newer serotonin-specific reuptake inhibitors fluoxetine and paroxetine may also be useful as adjuvant analgesics for chronic pain syndromes (69,90,94,100,108,109,114,116,117 and 118). Fluoxetine, a potent antidepressant with specific serotonin reuptake inhibition activity (117), has been shown to have analgesic properties in experimental animal pain models (118) but failed to show analgesic effects in a clinical trial for neuropathy (109). Several case reports suggest fluoxetine may be a useful adjuvant analgesic in the management of headache and fibrositis (119). Paroxetine, a newer serotonin-specific reuptake inhibitor, is the first antidepressant of this class shown to be a highly effective analgesic in a controlled trial for the treatment of diabetic neuropathy (108). Newer antidepressants such as sertraline, venlafaxine, and nefazodone may also eventually prove to be clinically useful as adjuvant analgesics. Nefazodone, for instance, has been demonstrated to potentiate opioid analgesics in an animal model (120).

Given the diversity of clinical syndromes in which the antidepressants have been demonstrated to be analgesic, trials of these drugs can be justified in the treatment of virtually every type of chronic pain (91). The established benefit of several of the antidepressants in patients with neuropathic pains (105,108,109), however, suggests these drugs may be particularly useful in populations, such as cancer and AIDS patients, in which an underlying neuropathic component to the pain(s) often exists (91). Although studies of the analgesic efficacy of these drugs in HIV-related painful neuropathies have not yet been conducted, they are widely applied clinically using the model of diabetic and postherpetic neuropathies.

Although antidepressant drugs are analgesic in both neuropathic and nonneuropathic pain models, their clinical use is most commonly in combination with opioid

drugs, particularly for moderate to severe pain. Antidepressant adjuvant analgesics have their most broad application as *coanalgesics*, potentiating the analgesic effects of opioid drugs (73). The opioid-sparing effects of antidepressant analgesics have been demonstrated in a number of trials, especially in cancer populations with neuropathic, as well as nonneuropathic, pain syndromes (94,97).

The dose and time course of onset of analgesia for antidepressants when used as analgesics appears to be similar to their use as antidepressants. Compelling evidence exists that the therapeutic analgesic effects of amitriptyline are correlated with serum levels, as are the antidepressant effects, and that analgesic treatment failure is caused by low serum levels (105,109). A high-dose regimen of up to 150 mg of amitriptyline or higher is suggested. The proper analgesic dose for paroxetine is likely in the 40- to 60-mg range, with the major analgesic trial using a fixed dose of 40 mg (108). Anecdotal evidence suggests that the debilitated medically ill (cancer, AIDS patients) often respond (regarding depression or pain) to lower doses of antidepressant than are usually required in the physically healthy, probably because of impaired metabolism of these drugs (90). As to the time course of onset of analgesia, a biphasic process appears to occur. There are immediate or early analgesic effects that occur within hours or days, and these are probably mediated through inhibition of synaptic reuptake of catecholamines. In addition, there are later, longer analgesic effects that peak over a 2- to 4-week period that are probably caused by receptor effects of the antidepressants (104,105,109).

Neuroleptics and Benzodiazepines

Neuroleptic drugs, such as methotrimeprazine, fluphenazine, haloperidol, and pimozide, may play a role as adjuvant analgesics (111,121,122 and 123) in AIDS patients with pain; however, their use must be weighed against what appears to be an increased sensitivity to the extrapyramidal side effects of these drugs in AIDS patients with neurologic complications (124). Anxiolytics, such as alprazolam and clonazepam, may also be useful as adjuvant analgesics, particularly in the management of neuropathic pains (125,126 and 127).

Psychostimulants

Psychostimulants, such as dextroamphetamine, methylphenidate, and pemoline, may be useful antidepressants in patients with HIV infection or AIDS who are cognitively impaired (125). Psychostimulants enhance the analgesic effects of the opioid drugs (128). Psychostimulants are also useful in diminishing sedation secondary to opioid analgesics, and they are potent adjuvant analgesics. Bruera and colleagues (88) demonstrated that a regimen of 10 mg of methylphenidate with breakfast and 5 mg with lunch significantly decreased sedation and potentiated the effect of opioids in patients with cancer pain. Methylphenidate has also been demonstrated to improve functioning on a number of neuropsychological tests, including tests of memory, speed, and concentration, in patients receiving continuous infusions of opioids for cancer pain (88). Dextroamphetamine has also been reported to have additive analgesic effects when used with morphine in postoperative pain (129). In relatively low doses, psychostimulants stimulate appetite, promote a sense of well-being, and improve feelings of weakness and fatigue in cancer patients.

Pemoline is a unique alternative psychostimulant that is chemically unrelated to amphetamine but may have similar usefulness as an antidepressant and adjuvant analgesic in AIDS patients (87). Advantages of pemoline as a psychostimulant in AIDS pain patients include the lack of abuse potential, the lack of federal regulation through special triplicate prescriptions, the mild sympathomimetic effects, and the fact that it comes in a chewable tablet form that can be absorbed through the buccal mucosa and thus can be used by AIDS patients who have difficulty swallowing or who have intestinal obstruction. Clinically, pemoline is as effective as methylphenidate or dextroamphetamine in the treatment of depressive symptoms and in countering the sedating effects of opioid analgesics. No studies exist of pemoline's capacity to potentiate the analgesic properties of opioids. Pemoline should be used with caution in patients with liver impairment, and liver function tests should be monitored periodically with longer-term treatment.

Anticonvulsant Drugs

Selected anticonvulsant drugs appear to be analgesic for the lancinating dysesthesias that characterize diverse types of neuropathic pain (91) (see Chapter 86). Clinical experience also supports the use of these agents in patients with paroxysmal neuropathic pains that may not be lancinating, and to a far lesser extent, in those with neuropathic pains characterized solely by continuous dysesthesias. Although most practitioners prefer to begin with carbamazepine because of the extraordinarily good response rate observed in trigeminal neuralgia, this drug must be used cautiously in AIDS patients with thrombocytopenia, those at risk for marrow failure, and those whose blood counts must be monitored to determine disease status. If carbamazepine is used, a complete blood count should be obtained before the start of therapy, after 2 and 4 weeks, and then every 3 to 4 months thereafter. A leukocyte count below 4,000 is usually considered to be a contraindication to treatment, and a decline to less than 3,000, or an absolute neutrophil count of less than 1,500 during therapy, should prompt discontinuation of the drug. Other anticonvulsant drugs may be useful for managing neuropathic pain in AIDS patients, including phenytoin, clonazepam, valproate, and gabapentin (91).

Several newer anticonvulsants have been used in the treatment of neuropathic pain, particularly patients with reflex sympathetic dystrophy. These drugs include gabapentin, lamotrigine, and felbamate. Of these newer anticonvulsants, anecdotal experience has been most favorable with gabapentin, which is now being widely used by pain specialists to treat neuropathic pain of various types. Gabapentin has a relatively high degree of safety, including no known drug-drug interactions and a lack of hepatic metabolism (91). Treatment with gabapentin is usually initiated at a dose of 300 mg per day and then gradually increased to a dose range of 900 to 3,200 mg per day in three divided doses.

Corticosteroids

Corticosteroid drugs have analgesic potential in a variety of chronic pain syndromes, including neuropathic pains and pain syndromes resulting from inflammatory processes (91). Like other adjuvant analgesics, corticosteroids are usually added to an opioid regimen. In patients with advanced disease, these drugs may also improve appetite, nausea, malaise, and overall quality of life. Adverse effects include neuropsychiatric syndromes, gastrointestinal disturbances, and immunosuppression.

Baclofen

Baclofen is a gamma-aminobutyric acid agonist that has proven efficacy in the treatment of trigeminal neuralgia (130). On this basis, a trial of this drug is commonly used in the management of paroxysmal neuropathic pains of any type. Dosing is generally undertaken in a manner similar to the use of the drug for its primary indication, spasticity. A starting dose of 5 mg two to three times per day is gradually escalated to 30 to 90 mg per day, and sometimes higher if side effects do not occur. The most common adverse effects are sedation and confusion.

Oral Local Anesthetics

Local anesthetic drugs may be useful in the management of neuropathic pains characterized by either continuous or lancinating dysesthesias. Controlled trials have demonstrated the efficacy of tocainide (131) and mexiletine (132), and clinical evidence suggests similar effects from flecainide (133) and subcutaneous lidocaine (134). It is reasonable to undertake a trial with oral local anesthetic in patients with continuous dysesthesias who fail to respond adequately to, or who cannot tolerate, the tricyclic antidepressants, and with patients with lancinating pains refractory to trials of anticonvulsant drugs and baclofen. Mexiletine is preferred in the United States (91).

NONPHARMACOLOGIC INTERVENTIONS

A variety of physical and psychological therapies may also prove useful in the management of HIV-related pain (Table 39-6). Physical interventions range from bed rest and simple exercise programs to the application of cold packs or heat to affected sites. Other nonpharmacologic interventions include whirlpool baths, massage, the application of ultrasound, and transcutaneous electrical nerve stimulation. Increasing numbers of AIDS patients have resorted to acupuncture to relieve their pain, with anecdotal reports of efficacy.

Physical therapies
Cutaneous stimulation (superficial heat, cold, and massage)
Transcutaneous electrical nerve stimulation
Acupuncture
Bed rest
Psychological therapies
Relaxation, imagery, biofeedback, distraction, and reframing
Hypnosis
Patient education
Neurosurgical procedures
Nerve blocks
Cordotomy

TABLE 39-6. Nonpharmacologic interventions

Several psychological interventions have demonstrated potential efficacy in alleviating HIV-related pain, including hypnosis, relaxation, and distraction techniques such as biofeedback and imagery, and cognitive-behavioral techniques (see Part V, Section C). When nonpharmacologic and standard pharmacologic treatments fail, anesthetic and even neurosurgical procedures, such as nerve block, cordotomy, and spinal delivery of analgesics, are additional options available to the patient who appreciates the risks and limitations of these procedures (see Chapter 102, Chapter 103, Chapter 104, Chapter 105, Chapter 106 and Chapter 108).

UNDERTREATMENT OF PAIN IN ACQUIRED IMMUNODEFICIENCY SYNDROME

Reports of dramatic undertreatment of pain in AIDS patients have appeared in the literature (3,6,7 and 8). These studies suggest that all classes of analgesics, particularly opioid analgesics, are underused in the treatment of pain in AIDS. Our group has reported (3) that fewer than 8% of individuals in our cohort of ambulatory AIDS patients reporting pain in the severe range (8 to 10 on a numeric rating scale of pain intensity) received a strong opioid, such as morphine, as recommended by published guidelines (i.e., the WHO analgesic ladder). In addition, 18% of patients with severe pain were prescribed no analgesics whatsoever, 40% were prescribed a nonopioid analgesic (e.g., NSAID), and only 22% were prescribed a weak opioid (e.g., acetaminophen in combination with oxycodone). Using the Pain Management Index (PMI) (135), a measure of adequacy of analgesic therapy derived from the Brief Pain Inventory's record of pain intensity and strength of analgesia prescribed, we further examined adequacy of pain treatment. Only 15% of our sample received adequate analgesic therapy based on the PMI. This degree of undermedication of pain in AIDS (85%) far exceeds published reports of undermedication of pain (using the PMI) in cancer populations of 40%. Larue and colleagues (6) report that in France, 57% of patients with HIV reporting moderate to severe pain did not receive any analgesic treatment at all, and only 22% received a weak opioid.

Although opioid analgesics are underused, it is clear that adjuvant analgesic agents, such as the antidepressants, are also dramatically underused (3,6,7 and 8). Breitbart and colleagues (3) reported that less than 10% of AIDS patients reporting pain received an adjuvant analgesic drug (e.g., antidepressants, anticonvulsants), despite the fact that approximately 40% of the sample had neuropathic-type pain. This class of analgesic agents is a critical component of the WHO analgesic ladder, particularly in managing neuropathic pain, and is vastly underused in the management of HIV-related pain.

A number of different factors have been proposed as potential influences on the widespread undertreatment of pain in AIDS, including barriers related to patients, clinicians, and the health care system (3,85,136,137). Sociodemographic factors that have been reported to be associated with undertreatment of pain in AIDS include gender, education, and substance abuse history (3). Women, less educated patients, and patients who reported injection drug use as their HIV risk transmission factor are significantly more likely to receive inadequate analgesic therapy for HIV-related pain.

Breitbart and colleagues (85) surveyed 200 ambulatory AIDS patients using a modified version of the Barriers Questionnaire (BQ) (138), which assesses a variety of patient-related barriers to pain management (resulting in patient reluctance to report pain or take opioid analgesics). Results of this study demonstrated that patient-related barriers (as measured by BQ scores) were significantly correlated with undertreatment of pain (as measured by the PMI) in AIDS patients with pain. Additionally, BQ scores were significantly correlated with higher levels of psychological distress and depression, indicating that patient-related barriers contributed to undertreatment for pain and poorer quality of life. The most frequently endorsed BQ items were those concerning the addiction potential of opioids, side effects and discomfort related to opioid administration, and misconceptions about tolerance. Although no age, gender, or HIV risk transmission factors were associated with BQ scores, nonwhite and less educated patients scored higher on the BQ. Several additional AIDS-specific patient-related barriers examined (136,137) reveal that 66% of patients are trying to limit their overall intake of medications (i.e., pills) or use nonpharmacologic interventions for pain, 50% of patients cannot afford to fill a prescription for analgesics or have no access to pain specialists, and approximately 50% are reluctant to take opioids for pain out of a concern that family, friends, or physicians will assume they are misusing or abusing these drugs.

In a survey of approximately 500 AIDS care providers (85), clinicians (primarily physicians and nurses) rated the barriers to AIDS pain management they perceived to be the most important in the care of AIDS patients. The most frequently endorsed barriers were those regarding lack of knowledge about pain management or access to pain specialists and concerns regarding the use and addiction potential of opioid drugs in the AIDS population. The top five barriers endorsed by AIDS clinicians included lack of knowledge regarding pain management (51.8%); reluctance to prescribe opioids (51.5%); lack of access to pain specialists (50.9%); concern regarding drug addiction, abuse, or both (50.5%); and lack of psychological support or drug treatment services (43%). Patient reluctance to report pain and patient reluctance to take opioids were less commonly endorsed barriers, with approximately 24% of respondents endorsing those barriers. In contrast, past surveys of oncologists rated patient reluctance to report pain or take opioids as two of the top four barriers. Like AIDS care providers, oncologists also endorsed highly a reluctance to prescribe opioids, even to a population of cancer patients with a significantly lower prevalence of past or present substance abuse disorders. Both oncologists and AIDS care providers report they have inadequate knowledge of pain management and pain assessment skills.

Pain Management and Substance Abuse in Acquired Immunodeficiency Syndrome

Individuals who inject drugs are among the AIDS exposure categories with the highest rate of increase since 1994, especially in large urban centers. Pain management in the substance-abusing AIDS patient is perhaps the most challenging of clinical goals. Fears of addiction and concerns regarding drug abuse affect both patient compliance and physician management of pain and use of opioid analgesics, often leading to the undermedication of HIV-infected patients with pain.

Studies of patterns of chronic opioid analgesic use in patients with cancer, burns, and postoperative pain, however, have demonstrated that, although tolerance and physical dependence commonly occur, addictions (i.e., psychological dependence and drug abuse) are rare and almost never occur in individuals who do not have histories of drug abuse (139,140 and 141). More relevant to the clinical problem of pain management in AIDS patients, however, is the issue of managing pain in the growing segment of HIV-infected patients who have a history of substance abuse or who are actively abusing drugs. The use, specifically of opioids for pain control in patients with HIV infection and a history of substance abuse, raises several difficult pain treatment questions, including how to treat pain in people who have a high tolerance to opioid analgesics; how to mitigate this population's drug-seeking and potentially manipulative behavior; how to deal with patients who may offer unreliable medical histories or who may not comply with treatment recommendations; and how to counter the risk of patients' spreading HIV while high and disinhibited.

Perhaps of greatest concern to clinicians is the possibility that they are being lied to by substance-abusing AIDS patients complaining of pain. Clinicians must rely on a patient's subjective report, which is often the best or only indication of the presence and intensity of pain, as well as the degree of pain relief achieved by an intervention. Physicians who believe they are being manipulated by drug-seeking patients often hesitate to use appropriately high doses of opioid analgesics to control pain. The fear is that the clinician is being duped into prescribing narcotic analgesics that will then be abused or sold. Clinicians do not want to contribute to or help sustain addiction. This leads to an immediate defensiveness on the part of the clinician and an impulse to avoid prescribing opioids and even to avoid full assessment of a pain complaint.

Because concerns are often raised regarding the credibility of AIDS patients' reports of pain, particularly in cases in which a history of injection drug use exists, Breitbart and colleagues (142) conducted a study of 516 ambulatory AIDS patients, in which they compared the report of pain experience and the adequacy of pain management among patients with and without a history of substance abuse. This study found that there were no significant differences in the report of pain experience (i.e., pain prevalence, pain intensity, and pain-related functional interference) among patients who reported injection drug use as their HIV transmission risk factor and those who reported other transmission factors (non–injection drug use). Furthermore, no differences existed in the report of pain experience among patients who acknowledged current substance abuse, those in methadone maintenance, and those who were in drug-free recovery. The description of HIV-related

pain was comparable among injection drug use and non–injection drug use groups. What was different was the treatment received by these two groups. Patients in the injection drug use group were significantly more undermedicated for pain compared with the non–injection drug use group. In addition, clinicians did not distinguish among various types of patients in the injection drug use group (i.e., active users, those in drug-free recovery, and those in methadone maintenance), and withheld the use of opioids in all patients, resulting in only 8% to 10% of injection drug use patients' receiving adequate analgesia based on the PMI (143).

Unfortunately, the existence or severity of pain cannot be objectively proven. The clinician must accept and respect the report of pain in spite of the possibility of being duped and proceed in the evaluation, assessment, and management of pain. Experience from the cancer pain literature suggests that it is possible to adequately manage pain in substance abusers with life-threatening illness and to do so safely and responsibly using opioid analgesics and several sound principles of pain management outlined here (Table 39-7) (78,142,144,145). Most clinicians experienced in working with this population of patients recommend that practitioners set clear and direct limits. Although this is an important aspect of the care of intravenous drug-using people with HIV, it is by no means the whole answer. As much as possible, clinicians should attempt to eliminate the issue of drug abuse as an obstacle to pain management by dealing directly with the problems of opiate withdrawal and drug treatment. Clinicians should err on the side of believing patients when they complain of pain and should use knowledge of specific HIV-related pain syndromes to corroborate the report of a patient perceived as being unreliable.

Substance abusers with HIV deserve pain control: we have an obligation to treat pain and suffering in all of our patients.
Accept and respect the report of pain.
Be careful about the label *substance abuse*; distinguish between tolerance, physical dependence, and addiction (psychological dependence or drug abuse).
Not all substance abusers are the same; distinguish between active users, individuals in methadone maintenance, and those in recovery.
Individualize pain treatment plan.
Use the principles of pain management outlined for all patients with human immunodeficiency virus disease and pain (World Health Organization analgesic ladder).
Set clear goals and conditions for opioid therapy: set limits, recognize drug abuse behaviors, make consequences clear, use written contracts, and establish a single prescriber.
Use a multidimensional approach: pharmacologic and nonpharmacologic interventions, attention to psychosocial issues, team approach.

TABLE 39-7. Approach to pain management in substance abusers with human immunodeficiency virus disease

The clinician must be familiar with and understand the current terminology relevant to substance abuse and addiction. It is important to distinguish between the terms *tolerance*, *physical dependence*, and *addiction* or *abuse* (psychological dependence). Tolerance is a pharmacologic property of opioid drugs defined by the need for increasing doses to maintain an (analgesic) effect. Physical dependence is characterized by the onset of signs and symptoms of withdrawal if opioid analgesics are abruptly stopped or an opioid antagonist is administered. Tolerance usually occurs in association with physical dependence. Addiction or abuse (also often termed *psychological dependence*) is a psychological and behavioral syndrome in which drug craving, compulsive use (despite physical, psychological, or social harm to user), other aberrant drug-related behaviors, and relapse after abstinence occur (76). The term *pseudoaddiction* has been coined to describe the patient who exhibits behavior that clinicians associate with addiction, such as requests for higher doses of opioid, but in fact is caused by uncontrolled pain and inadequate pain management (146,147).

The clinician must also distinguish between the former addict who has been drug free for years, the addict in a methadone maintenance program, and the addict who is actively abusing illicit drugs, prescription drugs, or both. Actively using addicts and those on methadone maintenance with pain must be assumed to have some tolerance to opioids and may require higher starting and maintenance doses of opioids. Preventing withdrawal is an essential first step in managing pain in this population. In addition, active addicts with AIDS understandably require more in the way of psychosocial support and services to adequately deal with the distress of the pain and illness. Former addicts may pose the challenge of refusing opioids for pain because of fears of relapse. Such patients can be assured that opioids, when prescribed and monitored responsibly, may be an essential part of pain management, and the use of the drug for pain is quite different from its use when they were abusing similar drugs. Some authorities emphasize the importance of conducting a comprehensive pain assessment to define the pain syndrome. Specific pain syndromes often respond best to specific interventions (i.e., neuropathic pains respond well to antidepressants or anticonvulsants). Adequate assessment of the cause of pain is essential in all AIDS patients, and particularly in the substance abuser. It is critical that adequate analgesia be provided while diagnostic studies are under way. Often, treatments directed at the underlying disorder causing pain are effective as well. For example, headache from CNS toxoplasmosis responds well to primary treatments and corticosteroids.

When deciding on an appropriate pharmacologic intervention in the substance abuser, it is advisable to follow the WHO analgesic ladder. This approach advocates selection of analgesics based on severity of pain; however, clinicians also often take into account the nature of the pain syndrome in selecting analgesics. For mild to moderate pain, NSAIDs are indicated. The NSAIDs are continued with adjuvant analgesics (antidepressants, anticonvulsants, neuroleptics, corticosteroids) if a specific indication exists. Patients with moderate to severe pain or those who do not achieve relief from NSAIDs are treated with a weak opioid, often in combination with NSAIDs and adjuvant drugs, if indicated.

It has been pointed out that it is critical to apply appropriate pharmacologic principles for opioid use. One should avoid using agonist-antagonist opioid drugs. The use of as-needed dosing often leads to excessive drug-centered interactions with staff that are not productive. Although patients should not necessarily be given the specific drug or route they want, every effort should be made to give patients more of a sense of control and a sense of collaboration with the clinician. Often a patient's report of beneficial or adverse effects of a specific agent is useful to the clinician.

The management of pain in substance-abusing AIDS patients requires a team approach. Early involvement of pain specialists, psychiatric clinicians, and substance abuse specialists is critical. Nonpharmacologic pain interventions should be appropriately applied, not as a substitute for opioids, but as an important adjunct. Realistic goals for treatment must be set, and problems related to inappropriate behavior around the handling of prescription and interactions with staff should be anticipated.

Hospital staff must be educated and made aware that such difficult patients evoke feelings that if acted on could interfere with providing good care. Clear limit setting is helpful for both the patient and treating staff. Sometimes written rules about what behaviors are expected and what behaviors are not tolerated and the consequence should be provided. The use of urine toxicology monitoring, restrictions of visitors, and strict limits on amount of drug per prescription can all be useful. It is important to also remember that rehabilitation or detoxification from opioids is not appropriate during an acute medical crisis and should not be attempted at that time. Once more stable medical conditions exist, referral to a drug rehabilitation program may be useful. Constant assessment and reevaluation of the effects of pain interventions must also take place to optimize care. Special attention should be given to points in treatment when routes of administration are changed or when opioids are tapered. It must be made clear to patients what drugs, regimen, or both would be introduced to control pain when opioids are tapered or withdrawn, and what options are available if that nonopioid regimen is ineffective.

Finally, it is important to recognize that substance abusers with AIDS are quite likely to have comorbid psychiatric symptoms as well as multiple other physical symptoms that can all contribute to increased pain and suffering. Adequate attention must be paid to these physical and psychological symptoms for pain management to be optimized.

CONCLUSIONS

Pain in AIDS, even in this era of protease inhibitors and decreased AIDS death rates, is a clinically significant problem contributing greatly to psychological and functional morbidity. Pain can be adequately treated and so must be a focus of care in the AIDS patient. The principles of managing pain in HIV are similar to those principles that have been developed previously from the management of cancer pain. Substance abusers and women are a particularly undertreated segment of the AIDS pain population and need special attention.

Managing pain in AIDS patients with a history of substance abuse is a particularly challenging problem that pain specialists and AIDS care providers will be facing with increasing frequency. A multimodal, multidisciplinary approach for managing pain in HIV is optimal, particularly in the management of pain in AIDS patients with a

history of substance abuse.

*Dr. Breitbart's work is supported by National Institute of Mental Health Grant MH49034, National Cancer Institute Grant CA57790, the Faculty Scholars Program, Open Society Institute, Project on Death in America, and the Emily Davie and Joseph S. Kornfeld Foundation.

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CHAPTER 40

Palliative Care

Eduardo Bruera, Irene Higginson, and Catherine M. Neumann

More than 80% of patients with advanced cancer develop pain before death (1,2). During the last 10 years, there have been major advances in both the assessment and management of cancer pain that allow for adequate pain control in the great majority of cancer patients (see Chapter 35 and Chapter 36). Additional information can also be found in the *Oxford Textbook of Palliative Medicine* edited by Doyle, Hanks, and MacDonald (3).

During the terminal stages of the illness, patients with cancer pain present a number of unique challenges. Palliative care emerged during the 1960s as a response to the unmet needs of these patients and their families. It has been defined as “the active, total care offered to a patient with a progressive disease and their family when it is recognized that the illness is no longer curable, in order to concentrate on the quality of life and the alleviation of distressing symptoms within the framework of a coordinated service” (4). Physicians and other health professionals involved in the delivery of palliative cancer care need to modify the assessment and management of pain in order to meet some of these challenges.

The purpose of this chapter is to discuss these unique issues encountered in the delivery of palliative care. In most of the chapter, emphasis is on the management of patients with terminal cancer, because they are the majority of the palliative care population (1,2). However, most of these concepts are readily applicable to palliative care patients with pain caused by acquired immunodeficiency syndrome, neurologic disorders, and other terminal chronic illnesses (see Chapter 39).

EPIDEMIOLOGY AND ASSESSMENT OF PAIN AND OTHER SYMPTOMS IN PALLIATIVE CARE

Cancer pain is reported by approximately 50% of patients at all stages and by more than 70% of terminal cancer patients. This percentage varies by cancer type and stage. Pain is more prevalent in patients with advanced cancer of the gastrointestinal tract and bone, and less prevalent in hematologic malignancies (5). Table 40-1 summarizes the frequency of pain in patients with different primary tumors (6,7,8,9,10,11,12,13 and 14).

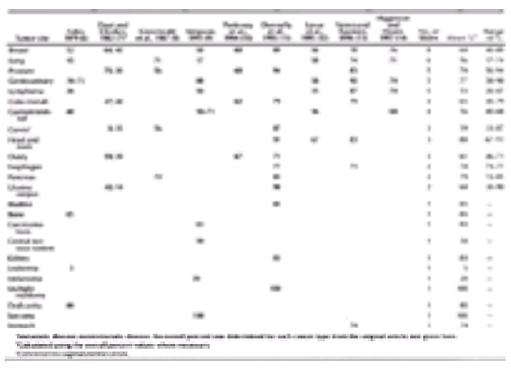

TABLE 40-1. Frequency of pain by primary tumor site (%)

In conjunction with mortality data, available data on the frequency of cancer pain imply that each year approximately 100,455 cancer patients in England and Wales, and 376,600 in the United States, potentially experience pain at the time of death (the total number of deaths is 143,500 in England and Wales and 538,000 in the United States).

Different studies report marked variations in the frequency of cancer pain. Study designs are often limited and not generalized. Pain has been studied in health care settings, rather than in communities, so prevalence pertains to a group of patients referred to a specific service such as a pain clinic. In addition, measures of pain are not constant between studies. Although pain severity and its effect on patient function are both crucial to assessment, severity is the main factor that determines the effect of pain (15). Failure to assess the severity of pain and the variety of methods used for its categorization (visual analog scales; ordinal scales; patient interviews; and physician, nurse, or patient assessments) compound the difficulties in assessment. Much more work is needed to develop systematic assessments of pain for use in routine care and epidemiologic monitoring.

In the great majority of patients with advanced cancer, pain is related to the presence of primary or metastatic cancer (1,2,15,16). However, a number of devastating psychosocial symptoms such as anxiety, depression, delirium, and spiritual or financial concerns can influence the expression of the intensity of pain (17,18 and 19). In palliative care, an appropriate multidimensional assessment is even more important than the assessment that takes place at earlier stages of cancer.

Pain is only one of the many symptoms experienced by cancer patients (20). It is important to assess pain within the context of other symptoms for several reasons. Pain may not necessarily be the symptom that is having the greatest effect on a patient's quality of life at a given point in time. The experience of pain may affect the perception and expression of other symptoms, and vice versa, resulting in misinterpretation and inappropriate management. Also, the treatment of pain may lead directly to a worsening of other highly prevalent symptoms in the terminally ill such as nausea, constipation, somatization, and delirium.

In the clinical situation, current knowledge of the interrelation between different factors indicate that different facets (physical, emotional, social, spiritual, and health care related) need to be assessed, particularly in patients who continue to express high levels of pain intensity in spite of otherwise appropriate treatment.

Table 40-2 summarizes some of the outcome and quality of life measures used or proposed for use in palliative care. Four criteria are important in choosing a clinical measure:

TABLE 40-2. Measures for assessing the outcome of palliative care for people with advanced cancer

- Validity: It is important to measure what you think you are measuring.
- Reliability: If staff changes, it is important that the measurement does not.
- Responsiveness: Clinically important changes should be detectable.
- Appropriateness: Patients, families, and staff should feel comfortable using the measure in this setting, should not be burdened by it, and should find it clinically useful.

By using these four criteria to conduct a systematic literature review that examined all measures identified from MEDLINE, PsychLit, and CancerLit data bases (21), 12 assessment systems were identified that could be used for the multidimensional assessment of pain in palliative care patients (22,23,24,25,26,27,28,29,30,31 and 32).

Unfortunately, at the present time, no gold standard exists. A number of studies are being conducted comparing simplified forms of these tools in different palliative care populations. It is hoped that as a result of this research, a smaller number of highly accepted tools will emerge.

CHARACTERISTICS OF PALLIATIVE CARE PATIENTS

Table 40-3 summarizes some of the main characteristics and therapeutic challenges in palliative care patients. In the following paragraphs, the main issues associated with these characteristics are discussed.

Multiple physical symptoms
Frequent psychosocial distress
Cachexia (decreased albumin level)
Low intravascular volume
Reduced glomerular filtration
Need for alternate opioid routes
Borderline cognition
Polypharmacy

TABLE 40-3. Characteristics of palliative care patients

Multiple Physical Symptoms

As discussed previously, pain in palliative care patients coexists with a number of severe physical symptoms, such as anorexia, chronic nausea, constipation, asthenia, and confusion (33,34). The coexistence of other physical symptoms with pain can significantly aggravate the overall sensation of well-being and increase the psychosocial distress in palliative care patients. Analgesic treatments may not improve and occasionally may even aggravate some of these coexisting symptoms, such as nausea, confusion, or constipation (34,35 and 36). Figure 40-1 summarizes some of the complex interactions between opioid treatment and some of the common symptoms in palliative care patients. These complex interactions necessitate multiple symptom analysis in palliative care.

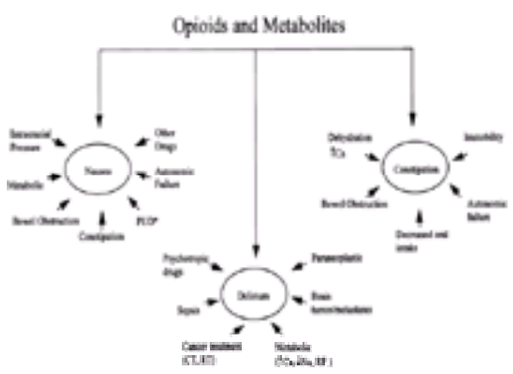

Figure 40-1. Complex interactions between opioid treatment and some of the common symptoms in palliative care patients. (CT, chemotherapy; PUD, peptic ulcer disease; RF, renal failure; RT, radiation therapy.)

Palliative care assessment tools differ from those used in earlier stages of cancer and those used for nonmalignant pain: They focus on multiple different symptoms simultaneously. The outcome and quality of life measures summarized in Table 40-2 cover anywhere from 5 to 34 different items. Regular monitoring of a variety of symptoms is of major relevance to palliative care.

Psychosocial Distress

Pain is only one component of the overall psychosocial distress at the end of life (37,38). Affective disorders including anxiety or depression are a frequent problem in terminally ill patients (37,38). Somatization is a frequent finding in cancer patients with affective symptoms (39). Therefore, the expression of pain intensity and other symptoms may be increased in terminally ill patients who have significant affective symptoms. Somatization is more likely to be a component of the pain intensity expression in those patients who have had either a history of psychiatric illness or who have displayed somatization as a coping strategy in the past (37,38,39 and 40). The presence of psychosocial distress and somatization has been identified as an independent poor prognostic factor for the control of cancer pain (41,42). The inability to recognize somatization as an expression of suffering in palliative care patients can lead to excessive opioid administration and opioid-induced neurotoxicity (35,43). A positive history of alcoholism, drug abuse, or both is a marker of chemical coping and an independent poor predictor for pain control in palliative care patients (41). However, appropriate screening, diagnosis, and multidisciplinary care result in similar levels of pain control and opioid use as compared with

nonalcoholics (44).

Regular monitoring of the level of affective symptoms, history of psychiatric disease, and coping strategy greatly assists palliative care teams in optimizing pharmacologic and nonpharmacologic interventions for pain control.

Cachexia, Low Intravascular Volume

Cachexia consists of progressive weight loss, lipolysis, loss of visceral and skeletal protein mass, and profound anorexia. The great majority of patients experience this devastating complication before dying of cancer and AIDS (45,46). Weight loss is an independent risk for poor survival, and cachectic patients have a higher incidence of complications after surgery, radiation therapy, and chemotherapy. In addition, cachexia aggravates weakness, is frequently associated with anorexia and chronic nausea, and is a source of psychological distress for patients and families because of the associated symptoms and the change in body image.

This syndrome was previously interpreted as a result of increased energy demand from the growing tumor mass. Research has demonstrated that cachexia occurs mostly as a result of major metabolic abnormalities, including profound lipolysis and loss of skeletal and visceral proteins caused by immune mediators, such as tumor necrosis factor and interleukin-6, as well as tumor by-products including lipolytic hormone (47). Anorexia is an almost universal component of cachexia and should be interpreted as a result of the metabolic abnormalities rather than the main cause of cachexia (45,46).

Chronic nausea and profound anorexia frequently lead to different levels of dehydration in cachectic patients (48). The presence of reduced body mass, decreased circulating albumin, and reduced intravascular volume has major implications for the pharmacologic management of pain. Drugs with a large volume of distribution, or those drugs that bind significantly to albumin should be used in reduced doses in terminally ill patients. This is particularly applicable to the use of nonsteroidal antiinflammatory drugs and methadone. In addition, cachectic patients frequently have reduced glomerular filtration. This may result in the accumulation of active opioid metabolites after chronic administration, after an increase in the dose of opioids, or in patients who receive a combination of opioids and nonsteroidal antiinflammatory drugs (35,43).

Alternating Opioid Routes

Because of the presence of cachexia, asthenia, muscle weakness, and chronic nausea, more than 80% of terminal cancer patients require alternate routes for the delivery of opioids (49,50). Ideally, the route and modality of administration should allow patients to be appropriately managed at home or in rural areas. Table 40-4 summarizes some of the alternate routes for opioid delivery in terminally ill patients.

Feature	Rectal	Intravenous	Sublingual[a]	Buccal[a]	Transdermal	Subcutaneous	Inhalatory[a]
Uremia, bowel obstruction, dysphagia	++	++	++	++	++	++	++
Cognitive failure, comatose patients	++	++	0	0	++	++	0
Diarrhea, colostomy, hemorrhoids	0	++	++	++	++	++	++
Coagulation disorders	++	+	++	++	++	0	++
Severe immunosuppression	++	+	++	++	++	0	++
Cerebral anal edema	++	++	++	++	0	++	++
Frequent dose changes, initial titration	++	++	++	++	0	++	++
Breakthrough pain	++	++	++	++	0	++	++
Home care	+	+	++	++	++	++	+
Rural areas, developing countries	++	0	++	++	0	0	0

[a]Not enough information available to recommend clinical use.
++, useful; +, partially useful; 0, not useful.

TABLE 40-4. Alternate routes for systemic opioid delivery in palliative care

The subcutaneous route is particularly useful in terminally ill patients. Because of cachexia as well as multiple intravenous therapies, peripheral vein access is usually difficult in these patients. In addition, peripheral intravenous routes need frequent changes, reduce the mobility of the upper limbs, and are generally more expensive than the subcutaneous route (50).

A subcutaneous needle can be left in place usually for periods of one week or more (51,52). The needle can usually be inserted under the skin of the thoracic or abdominal region, thereby allowing free use of the limbs. There is no need for anticoagulation of the site of infusion. The bioavailability of opioids administered subcutaneously is excellent and similar to that of intravenous opioids (53). The patients themselves or with the help of their relatives can frequently administer the opioid analgesics using preloaded syringes or low-cost infusion devices such as the Edmonton Injector (Auto Control Medical, Mississauga, Ontario) (50,54).

The rectal route also allows for safe and effective absorption of a number of opioid analgesics (55,56). One of the main limitations of this route is the discomfort associated with frequent opioid administration. Evidence suggests that slow-release morphine suppositories can be administered every 12 hours (57) and methadone can be administered every 8 to 12 hours (58). Preliminary evidence suggests that in some patients, rectal suppositories of slow-release morphine can be administered once a day (59).

Delirium

Delirium is the most frequent neuropsychiatric complication in patients with terminal cancer, and most patients die in delirium (57,60,61). Despite its high prevalence in patients with cancer and acquired immunodeficiency syndrome, delirium is frequently underdiagnosed (62). Patients with delirium present with combinations of cognitive failure, fluctuating levels of consciousness, changes in the sleep-wake cycle, variable severity of psychomotor agitation, hallucinations, delusions, and other perceptual abnormalities (62). Delirium is often a multicausal syndrome. Some of the most frequent causes are summarized in Figure 40-1. Although opioid toxicity is one of the most frequent causes (43,63), other possible causes include infection, dehydration, and metabolic abnormalities. Various drugs frequently administered to terminally ill patients, including benzodiazepines, tricyclic antidepressants, and drugs with a central anticholinergic effect are capable of causing or aggravating delirium. Figure 40-2 summarizes the clinical approach for the treatment of delirium in palliative care.

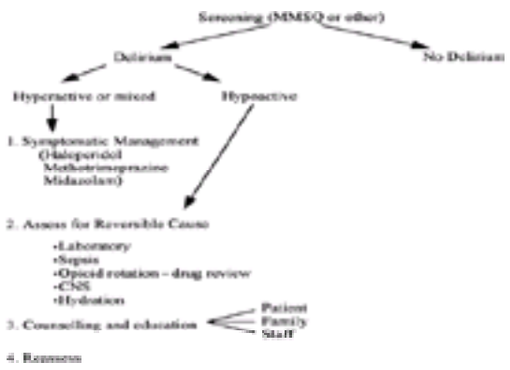

Figure 40-2. Clinical approach to delirium in palliative care. (CNS, central nervous system; MMSQ, Mini-Mental State Questionnaire.)

Approximately 30% of patients with cancer-related delirium experience complete improvement in cognition (64). The remaining patients usually continue in hypoactive delirium or progressively become hypoactive if they were in hyperactive or mixed delirium. A small minority of patients may remain in a state of chronic hyperactive or

mixed delirium and require chronic neuroleptic medication.

Haloperidol is indicated in the symptomatic management of patients presenting with hyperactive forms of delirium including psychomotor agitation, delusions, or hallucinations (65). Haloperidol should be considered a temporary measure while other strategies such as change in the type of opioid, hydration, or the management of metabolic or infectious complications are introduced. In most patients, the hyperactive symptoms improve within 3 to 5 days. If no response is observed within 24 to 48 hours, other, more sedating neuroleptics such as methotrimeprazine have been proposed as an alternative.

Patients who have failed to improve with at least two courses of neuroleptics may require aggressive sedation including the use of subcutaneous infusions of midazolam (43). This highly liposoluble benzodiazepine is potent with a short half-life, allowing for rapid titration. As in the case of other neuroleptics, the use of midazolam should normally be considered as a short-term measure, while other causes of reversible delirium are investigated and treated.

Delirium can be one of the most distressing syndromes for patients, health care professionals, and families. This is at least partially because the assessment of pain in these patients is extremely difficult. In patients with agitated delirium related to cancer, evidence exists that the patient's behavior was frequently misinterpreted by families and health care professionals as increased pain. This leads to increased use of extra opioid analgesics during the agitated period (66). In addition, conflict, defined as consistent expression of dissatisfaction with care of a family member, occurred in almost one-third of the families of patients with delirium as compared with only 5% of patients with no delirium (66). Both the interpretation of behaviors as pain and conflict appear to be observed only in those patients with hyperactive or mixed types of delirium. Unfortunately, no effective methods exist that might assist clinicians in the assessment of pain in patients with severe confusion, delirium, or dementia.

Polypharmacy

Because of the physical and psychosocial symptoms, palliative care patients are frequently receiving a large number of drugs. Analgesics are likely to interact with some of these drugs, particularly because of the presence of previously described characteristics, such as borderline cognition, cachexia, low intravascular volume, and reduced glomerular filtration. As a result, a complete drug review is required before the addition or modification in the dose of analgesic drugs.

Adjuvant analgesic drugs are commonly used in advanced cancer patients for multiple purposes including the enhancement of analgesia initiated by other medications (typically an opioid), their own analgesic effect, treatment of opioid-induced side effects, or all three. The use of adjuvant drugs was reported in approximately one-half of patients with cancer pain in 35 Italian oncology cancer centers (67). Increasing use of adjuvant drugs ranging from more than 50% to more than 66% of patients was reported in an American cancer center (68), an English hospital (69), and a Canadian cancer center (70). Table 40-5 summarizes the potential side effects of frequently used adjuvant drugs in combination with opioids. These effects are mostly manifested as autonomic (orthostatic hypotension, gastroparesis, urinary dysfunction) or central (sedation, delirium).

Drug	Interaction
Nonsteroidal antiinflammatory drugs	Risk of decreased glomerular filtration resulting in enhancement of opioid metabolite accumulation
Corticosteroids	Possible increased risk of organic mental disorders in cancer patients when combined with opioids
Psychotropic medications (e.g., tricyclic antidepressants, neuroleptics, benzodiazepines)	Autonomic dysfunction: gastric stasis, orthostatic hypotension, urinary dysfunction, sedation delirium

TABLE 40-5. Adjuvant drug interactions with opioids in terminally ill patients

One of the main pitfalls of adjuvant drug use in the terminally ill is its risk of general obtundation. Although the development of obtundation may not have initially been targeted as the desired outcome, its occurrence may be erroneously equated with having achieved adequate symptom management, particularly pain control and alleviation of distressing psychiatric symptoms such as agitated delirium or anxiety.

The *lytic cocktails*, which customarily combined a neuroleptic, opioid, and antihistamine, were originally designed during the 1950s as an acute treatment of shock and anesthesia. With time, lytic cocktails were applied to the treatment of pain in cancer patients (71). Lytic cocktails have been perceived by many physicians and patients as a type of disguised euthanasia based on their low potential for analgesia, high sedative properties, and possibility of acceleration of the dying process (72). The Brompton cocktail, a mixture of an opioid such as morphine, or diamorphine in the United Kingdom; cocaine; ethyl alcohol; chloroform water; and flavoring syrup, with a frequent addition of a phenothiazine, gained popularity in the 1960s and early 1970s (73,74). This cocktail has been criticized not only for its inability to provide improved analgesia above and beyond the use of an opioid alone, but for the increased adverse effects caused by the four substances accompanying the morphine, particularly the addition of cocaine. It was discovered that some patients, notably older ones, developed an agitated delirium with hallucinations when given morphine and cocaine, and their symptoms abated when the cocaine was withdrawn (75). An evaluation of the use of lytic cocktails in a French general hospital revealed that improved pain education resulted in an increase in the use of morphine and a decreased use of lytic cocktail practices (72).

Similar to the use of lytic cocktails, the use of combinations of psychotropics can also increase the risk of sedation, confusion, and general obtundation in terminal cancer patients. To prevent the development of excessive sedation and decline in cognition, routine monitoring of these symptoms is advisable. The latter can be accomplished by regular physician and nursing clinical bedside assessments, coupled with the screening detection methods such as the Mini-Mental State Questionnaire (76) or the confusional assessment methods (77). Table 40-6 summarizes some recommendations for the prevention of toxicity associated with polypharmacy in palliative care.

Identify opioids as the first-line treatment for the majority of cancer pain syndromes.
Remember opioid *responsiveness* when titrating dose (reach dose-limiting toxicity before adding another drug).
Add one adjuvant drug at a time to avoid combined or enhanced side effects.
If a decision is made to use an adjuvant drug, use an effective (high) dose.
Define outcome measures at the start of treatment.
Discontinue the adjuvant drug if ineffective.
Always monitor sedation and cognition.

TABLE 40-6. Preventing the toxicity of adjuvant drugs in palliative care

COMMUNICATION

Poor communication is one of the most common reasons for litigation and complaint in palliative care (78). Good verbal and nonverbal communication is viewed positively by patients, even in the most adverse situations, and can increase satisfaction with services and allow patients to make informed choices about their care. This includes information about the disease, procedures, treatment options and effects, and a realistic assessment of predicted outcome. Patients and families should

also be given information about sources of support and practical help. This information should be provided in appropriate forms and language for patients from ethnic minority groups.

One of the best predictors of patients' ability to adapt to the news that they have cancer and require treatment is that they should perceive the information they have been given as adequate for their specific needs (79). The information needs of patients may vary during the course of their illness. Therefore, it is important to establish what individuals' needs are, rather than to make assumptions about the kind of person they are and how much they want to be told (80). Doctors need to be aware that patients often find it difficult to take in or recall complex information given during a consultation, particularly after receiving bad news. Studies on patient preferences for the amount of information they receive report that up to 90% of patients wanted to know if their illness was cancer. Once patients are aware of their diagnosis, up to 97% have been reported as wanting to know about the treatments, investigations, and side effects (81), and 93% were opposed to their family's influencing the information they were given (82). The role of staff is to help individuals adjust to their terminal condition in the best way possible, taking into account their familial, cultural, and spiritual background. Staff who distance themselves, feeling that they can bring nothing but a lack of comprehension, do not realize that it is often the attempt to understand and to listen that aids the patient.

CONCLUSIONS

The majority of patients with advanced cancer and acquired immunodeficiency syndrome develop pain before death. Appropriate management of pain in these patients is the most important aspect of adequate palliative care. It has become evident that appropriate multidimensional assessment is the most important component of adequate palliative care delivery. A number of reliable assessment systems are available for research and clinical use.

Opioids remain the mainstay in the management of these patients. However, the special characteristics of palliative care patients make drug combinations difficult and increase the risk of opioid side effects. Unfortunately, there has been limited research on the appropriate use of opioids in these debilitated subgroups of patients. Increased emphasis on pharmacologic and nonpharmacologic studies is required in palliative care patients.

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CHAPTER 41

Postoperative Pain

Michael A. Ashburn and L. Brian Ready

In spite of the advances in the availability of acute pain management services, many individuals continue to endure pain during hospitalization (1,2 and 3). In one survey of 500 U.S. households, 57% of those who had surgery cited concern about pain after surgery as their primary fear experienced before surgery. Their fear appears to have been well founded, because the same survey reported that 77% of adults reported pain after surgery, with 80% of those experiencing moderate to extreme pain (4).

Pain after surgery occurs not only after major surgery, but is a problem even for relatively minor surgery. As the health care environment changes, increasing pressure is felt to complete operations in the ambulatory setting that would have traditionally been undertaken as an inpatient. As a result, physicians are challenged to provide aggressive pain control in new settings. Unfortunately, our current efforts have not been entirely effective. Although major morbidity is uncommon after ambulatory surgery, symptom distress and reduced functional status are common up to 7 days postoperatively (5). One in 20 patients reports severe pain after ambulatory surgery, some of whom required hospital admission only for pain control (6).

To provide acute pain management modalities to the surgical patients who might benefit from them, anesthesiology-based acute pain services (APS) have been developed. First described by Ready in 1988 (7), an APS can provide the interdisciplinary support necessary to safely and effectively manage severe postoperative pain. Originally found mainly in academic institutions, APSs are now found in the private hospital setting as well. In a survey by Ready and associates, nearly all hospitals in the United States with more than 100 beds had some form of patient-controlled analgesia (PCA) service available for use, and 73% had some form of anesthesiology-based APS (8). In another survey that included hospitals of all sizes, 42% of the hospitals had APSs, and an additional 13% had plans to establish such a service (4).

Many pain treatment modalities have become available that have been shown to provide superior analgesia when compared with intramuscular as-needed opioid administration. PCA provides excellent analgesia to patients in a variety of settings. Likewise, epidural and intrathecal opioids, as well as combinations of opioids with local anesthetics, have been shown to provide excellent analgesia (9,10 and 11). More recently, aggressive use of regional anesthetic techniques has become popular again, as has the concept of multimodal or balanced analgesic techniques. This chapter addresses current methods of treating postsurgical pain. In addition, we discuss some of the changes that are occurring in the way this care is provided in the perioperative setting.

BASIC CONSIDERATIONS

Surgical trauma and pain cause an endocrine response that increases the secretion of cortisol, catecholamines, and other stress hormones (12,13 and 14) (see Chapter 9). Tachycardia, hypertension, regional decreases in blood flow, alterations in immune response, hyperglycemia, lipolysis, and a negative nitrogen balance can occur as a result of these and other metabolic changes (15). The stress response may play a role in perioperative morbidity and mortality. Breslow and associates evaluated the effect epidural opioids may have in patients undergoing abdominal aortic surgery (16). In this study, patients received in a double-blind, randomized fashion either 5 mg of epidural morphine or 5 mL of epidural saline as a one-time dose after induction of general anesthesia, but before surgery. The patients were then followed postoperatively in the intensive care unit and data were collected on norepinephrine levels and opioid use, as well as the incidence and severity of hypertension and tachycardia. They found that patients who received epidural morphine had a decreased incidence of postoperative hypertension, used fewer doses of systemic morphine, had better pain control, and experienced lower norepinephrine levels as compared with the patients who received epidural saline (Fig. 41-1 and Fig. 41-2). These changes were attributed to an attenuation of sympathetic outflow, which was in part caused by improved analgesia experienced by the patients receiving epidural morphine.

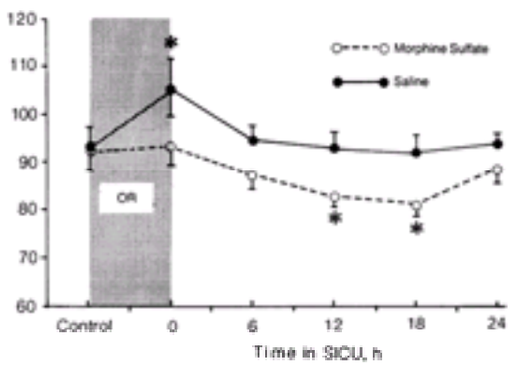

Figure 41-1. Mean arterial pressure before induction of anesthesia (control) and 0, 6, 12, 18, and 24 hours following aortic surgery. Surgical intensive care (SICU), operating room (OR, *shaded area*), and asterisk, $p < .05$ compared with preinduction value. Data are mean ± SE (*vertical bars*) of 12 patients per group. (Reprinted from Breslow MJ, Jordan DA, Christopherson R, et al. Epidural morphine decreases postoperative hypertension by attenuating sympathetic nervous system hyperactivity. *JAMA* 1989;261:3579, with permission.)

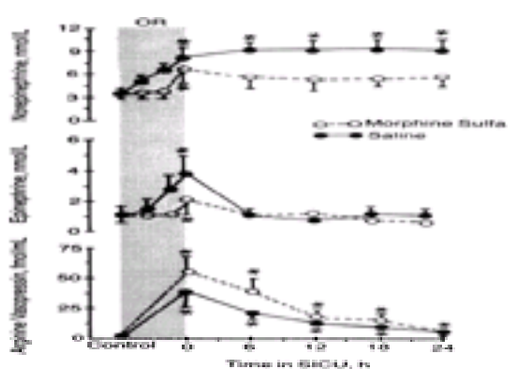

Figure 41-2. Arterial plasma concentrations of norepinephrine (top), epinephrine (center), and arginine vasopressin (bottom) before induction of anesthesia (control);

at two points during surgery; and 0, 6, 12, 18, and 24 hours following aortic surgery. Surgical intensive care (SICU), operating room (OR, *shaded area*), and asterisk, *p* <.05 compared with preinduction value. Data are mean ± SE (*vertical bars*). (Reprinted from Breslow MJ, Jordan DA, Christopherson R, et al. Epidural morphine decreases postoperative hypertension by attenuating sympathetic nervous system hyperactivity. *JAMA* 1989;261:3579, with permission.)

In another study, Yeager and associates evaluated the effect of combined general and epidural anesthesia followed by epidural morphine analgesia in high-risk surgical patients (17). Their prospective, randomized study compared the perioperative morbidity and mortality of high-risk surgical patients who had combined general and epidural anesthesia followed by epidural morphine analgesia with patients who had a routine general anesthetic followed by systemic morphine analgesia. They found a significant decrease in mortality, cardiovascular morbidity, and infection in the group that received combined general and epidural anesthesia followed by epidural morphine analgesia.

Brodner and associates reported results similar to those seen by Yeager. This study compared outcome in patients undergoing abdominothoracic esophagectomy receiving aggressive multimodal pain control versus historic controls (18). Both treatment groups had a thoracic epidural catheter placed before surgery. The control group (n = 49) received a general anesthetic for surgery followed by an epidural infusion of bupivacaine, 1.25 mg per mL, with sufentanil, 1 mg per mL. The treatment group (n = 42) received a preoperative bolus of bupivacaine, 2.5 mg per mL, with 20 to 30 mg of sufentanil, sufficient to obtain a T-4 sensory blockade. Patients then received a general anesthetic with perioperative infusion of bupivacaine with sufentanil for surgery. Postoperative pain in the treatment group was controlled with an epidural PCA using bupivacaine with sufentanil. When compared with the historic controls, the treatment group experienced superior pain relief, had improved nutritional status, had earlier tracheal extubation, had more rapid discharge from the intensive care unit, and met hospital discharge criteria earlier (Table 41-1).

	Group 1 (n = 49)		Group 2 (n = 42)	
	Mean	Standard deviation	Mean	Standard deviation
Extubation (hours after admission to the intensive care unit)	25.06	31.57	6.73*	3.03
first resting on the bedside (days after surgery)	1.57	1.71	1.02*	0.35
first time out of the bed (days after surgery)	1.94	2.26	1.17*	0.49
Intensive care discharge (days after surgery)	4.02	4.34	1.67*	1.95
Intermediate care discharge criteria (day after discharge)	6.37	3.95	4.86*	2.32

*Group 1 are historic controls receiving general anesthetic followed by thoracic epidural bupivacaine-sufentanil infusion. Group 2 patients received a preoperative T-4 local anesthetic block, epigastral anesthesia, followed by thoracic epidural patient-controlled analgesia with bupivacaine-sufentanil.
*p <.01 compared with group 1.
Modified from Brodner G, Pogatzki E, Adam M, et al. A multimodal approach to control postoperative pathophysiology and rehabilitation in patients undergoing abdominothoracic esophagectomy. Anesth Analg 1998;86:228-234.

TABLE 41-1. Postoperative recovery of patients undergoing abdominothoracic esophageal surgery [a]

A metaanalysis of randomized, controlled trials on the effect of postoperative analgesic techniques on pulmonary outcome has been completed (19). Ballantyne and associates evaluated the effect on pulmonary outcome of a variety of analgesic techniques, including epidural opioid, epidural local anesthetic, epidural opioid with local anesthetic, thoracic versus lumbar epidural opioid, intercostal nerve block, wound infiltration with local anesthetic, and intrapleural local anesthetic. The analysis failed to find improvements in pulmonary outcome for any modality studied other than epidural techniques. Compared with systemic opioids, epidural opioids decreased the incidence of atelectasis and had a tendency to reduce the incidence of pulmonary infections and pulmonary complications. Epidural local anesthetics decreased the incidence of pulmonary infections and pulmonary complications when compared with systemic opioids. The study concluded that postoperative epidural pain control can significantly decrease the incidence of pulmonary morbidity.

Surgery also leads to suppression of immune function in humans (20), and this suppression appears to be directly related to the invasiveness of surgery (21). Although limited data are available in humans, animal data suggest that this immune suppression can be attenuated by the administration of analgesics, potentially improving outcome (22,23).

Preemptive Analgesia

More recent studies document that even the timing of pain control can have an effect on patient care extending to months after surgery.

CLINICAL CONSIDERATIONS

Process of Acute Pain Management

In the early 1990s, the practice of pain management came under increased scrutiny. To foster continued improvement in acute pain management, the Agency for Health Care Policy and Research (AHCPR) published clinical practice guidelines for the management of acute pain (24). The stated goal of the guideline was to reduce the incidence and severity of patients' acute postoperative or posttraumatic pain, educate patients about the need to communicate unrelieved pain so they can receive prompt evaluation and effective treatment, enhance patient comfort and satisfaction, and contribute to fewer postoperative complications and, in some cases, shorter stays after surgical procedures.

AHCPR guidelines emphasized a collaborative, interdisciplinary approach to pain control. The guidelines advocated the inclusion of all members of the health care team in the process of pain management, with input from the patient and the patient's family, when appropriate. To accomplish this, the guidelines recommended a formal, institutional approach to the management of acute pain, with clear lines of responsibility. The institutional plan should include the use of an individualized, proactive pain control plan, developed preoperatively by patients and practitioners, frequent patient assessment, and the use of both drug and nondrug therapies to prevent and control pain.

Other organizations have also developed acute pain management guides or practice guidelines. These include the International Association for the Study of Pain (25) and the American Society of Anesthesiologists (26). It is believed by many that these guidelines have led to improved acute pain management. However, the effect acute pain guidelines have had on establishment and potential preservation of an APS in a particular institution is questionable. Decisions on the development, maintenance, or both of an APS appear to be made, to a large extent, on the financial viability of these programs. And, as a result, the survival of these programs is in doubt in many areas of the country.

Unfortunately, the increased interest in acute pain management by government and private organizations is not reflected by the establishment of a commitment by health care payers to pay for such services (27). Although the AHCPR guidelines advise that institutions should give the responsibility of acute pain management to those most knowledgeable, experienced, interested, and available to deal with patients' needs in a timely fashion, they offer no suggestions on how such services should be paid for (28).

For example, Medicare does not pay for pain consultation after surgery if PCA is used, with rare exception. Some private insurers have adopted this payment practice. Difficulties in obtaining reimbursement for professional services have led to variability in access to expert pain management. Some health policy experts are advocating that payment should be based on the medical necessity for the services, rather then eliminating payment based solely on the types of services provided. Unfortunately, denials for payment may be increasing in frequency. Medicare often argues that the management of postoperative pain is part of the global fee paid to the surgeon and has been slow to recognize that the intensity of pain management between *traditional* pain management (i.e., as needed, intramuscular opioids) and more modern techniques is large.

Health care reform has led to the development of health care alliances and the establishment of bundled fees for hospital-related services. In this environment, acute pain management may actually fare better than in the fee-for-service system. An APS can provide perioperative pain management in an efficient, cost-effective

manner, improving outcomes while holding down overall costs. However, it is essential to the future of acute pain management that we prove this to be true.

As was discussed earlier, AHCPR guidelines have advocated that health care institutions develop and implement an institutional plan for pain management. Since the publication of the AHCPR guidelines, other accrediting agencies in the United States have acknowledged the importance of pain management and have made an institutional pain management plan a part of their standards for acute care hospitals.

Although such an institutional plan is important in establishing an environment conducive to the appropriate management of pain for the hospitalized patient, evidence is lacking that the presence of such a plan improves pain management in hospitalized patients (29). In addition to an institutional plan establishing the need for adequate pain management, there needs to be a process to ensure that this care is being provided. In response to this perceived need, the American Pain Society's Quality of Care Committee published guidelines for a quality improvement plan to ensure adequate acute and cancer pain management in the hospitalized patient (30). This plan should contain several key elements that are outlined in Table 41-2.

Ensuring that a report of unrelieved pain raises a *red flag* that attracts clinicians' attention
Making information about analgesics convenient where orders are written
Promising patients responsive analgesic care and urging them to communicate pain
Implementing policies and safeguards for the use of modern analgesic technologies
Coordinating and assessing implementation of these measures

Reprinted from American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. JAMA 1995;274:1874–1880, with permission.

TABLE 41-2. Key elements in an institutional quality improvement plan for acute and cancer pain

Integrated Perioperative Care

Considerable interest exists in the development and use of utilization management and critical pathways (31). Critical pathways describe a course of care for patients with similar problems and treatments (32). A critical pathway should be an integrated interdisciplinary plan that leads to high-quality, cost-effective care (Table 41-3). Increasing amounts of data demonstrate that this model of care does lead to improved outcomes and reduced cost (33,34). This model of care for the hospitalized patient, which resembles the integrated interdisciplinary approach advocated for the chronic pain patient, may be an opportunity for the survival of APSs.

Standardize the course of events that lead to a successful outcome.
Interdisciplinary approach to patient care.
Include health care team education in the implementation of the plan.
Monitor the cost of care and patient outcome to ensure the pathway meets established goals.

TABLE 41-3. Critical aspects in the development of a critical pathway

In the case of acute pain management, it appears that gains in improving patient care could be obtained by exploring the use of the concepts seen in the creation of critical pathways for selected patient populations. A traditional APS often provides pain management in consultation with the primary care service by carving out pain management from the remainder of the patient's care. In the postoperative setting, interaction with the surgeon can be infrequent, and pain management may not be integrated with the overall care plan of the patient. In fact, the APS and the surgical service may only interact when a critical adverse event occurs, straining relationships between health care providers.

The development of a critical pathway for the surgical patient should begin with the decision to operate and extend to the moment of discharge. Although acute pain management would be a vital part of such a plan, other elements are equally important. For example, Fisher presented a model for a preoperative evaluation clinic that he believes provides high-quality, cost-effective care (35). Other investigators have shown that the selection of anesthetic technique has a direct effect on the quality of postoperative pain control (36). Many clinicians have emphasized that pain control at rest is not as important as pain control with movement, which allows the patient to participate in rehabilitation after surgery. Still others have shown that early effective postoperative pain control may reduce the chances for long-term chronic pain problems (37). All of these parts of the patient care experience have to be integrated into a seamless perioperative critical pathway for the surgical patient.

Some investigators have begun to integrate acute pain management into the postoperative rehabilitation of the surgical patient. Using a patient-focused approach similar to critical pathway development, pain management has been integrated into a global rehabilitation plan for the surgical patient (38). Although the role of the APS remains important, this care is not provided in isolation from other portions of the patient's care, but in the broader context of integrated rehabilitation of the patient (39). Early data indicate that this approach may lead to improved outcomes as well as earlier recovery and faster hospital discharge (40,41,42,43,44,45 and 46).

Participation in perioperative care by an organized APS can not only improve the quality of pain control, but should also decrease the incidence and severity of some adverse events. Pain therapy has risks, many of which can lead to patient harm. For example, although PCA therapy is considered to be safe, the potential for serious adverse outcome exists (47,48 and 49). Opioid administration is associated with alterations in ventilation (50). Life-threatening respiratory events associated with the use of PCA have been reported (48,51,52). These events are almost always associated with human error. Patient care through an APS may decrease the incidence and severity of these adverse events, thus improving outcomes and decreasing health care cost.

Other acute pain management modalities are also associated with the potential for serious adverse events. Neuraxial opioid therapy is associated with an incidence of respiratory depression of 1 per 1,000 to 1 per 1,300 (53,54,55,56,57,58,59,60,61,62,63,64 and 65). Although this therapy is considered to be safe in many patient care settings, it is clear that patients receiving neuraxial analgesics require monitoring by trained individuals who are immediately available to provide this care.

The APS has taken a leadership role in the establishment of monitoring standards and is often responsible for the training of nurses with regard to these standards. Changes in staffing of acute care hospitals may make it more difficult to ensure conformance with patient monitoring requirements in some settings. As hospital care evolves, it is vital that individuals expert in providing pain management maintain a leadership role to ensure adequate care to these individuals.

Although most APSs concentrate their services on behalf of individuals experiencing pain from surgery or trauma, other hospitalized patients frequently experience poorly controlled pain. For example, in a manuscript on the care of the dying patient, the Council on Scientific Affairs of the American Medical Association stated the following (57): “The current patient care delivery system is deficient in regard to the care of the terminally ill. Expertise in pain management is often not available to

patients, and comprehensive and enduring care is the exception.”

Clearly, this patient population can also benefit from the development of a critical pathway that integrates pain management into comprehensive care and ensures patients' access to experts in the field of pain management when indicated. A hospital- based APS can play a vital role in providing these necessary services.

Acute Pain Service

The goal of an APS is to improve postoperative pain management by applying effective methods of analgesic control (7). In addition, the APS provides education for residents and nursing staff and conducts research on the treatment of acute pain. In a university setting, the service is usually staffed by a pain management physician attending, an anesthesiology resident, a clinical nurse specialist, and a pharmacist. Staffing in a private practice setting varies with the available resources and pain treatment modalities offered.

The traditional APS patient care team is often composed of a pain management physician, advanced practice nurse, and pharmacist. Patients who are receiving care through the APS should be seen by the service at least daily. Evaluation of the quality of analgesia, side effects, medication dose, and inspection of the intravenous and epidural sites are completed. An APS physician should be available 24 hours a day for consultation and routine patient management problems.

A nurse specialist experienced in acute pain management is vital to the success of the service (58). The APS clinical nurse specialist ensures that the unit nurses have the special skills necessary to care for patients on the APS. Unit nurses are instructed on how to monitor patients receiving intrathecal or epidural medications, as well as patients receiving PCA for possible adverse reactions including inadequate analgesia, pruritus, nausea, or delayed respiratory depression. In addition, they are instructed on how to administer epidural medications and how to program and manage PCA devices. The APS clinical nurse specialist also acts as a liaison between the physician and nursing staff and functions as the quality control coordinator for the APS.

The pharmacist should also take an active role in the acute pain management. Frequently, the pharmacist can become aware of physician orders for drug combinations that could lead to an adverse event. In addition, the pharmacist should actively participate in the selection of standard analgesics to be used, including the establishment of standard concentrations and labeling practices. In many institutions, the pharmacist participates in acute pain team patient rounds, periodic team meetings, or both.

The APS is often responsible for establishing a pain treatment policy for the hospital. Such a policy should be in conformance with national guidelines and should emphasize that pain assessment and treatment are the responsibility of all health care providers. Pain care should be integrated into the patient's treatment plan, and pain assessment should be considered a fifth vital sign.

In addition to the institutional pain management policy, the APS often establishes policy for the use of available pain treatment modalities. For example, the University of Washington has established a process for credentialing physicians with appropriate training and experience to provide intravenous PCA. This process allows all qualified physicians to provide PCA therapy to *routine* patients, whereas patients who are not *routine* receive this care through the APS (Fig. 41-3 and Table 41-4). However, one study reported subtle differences in outcome when PCA therapy was provided by an APS compared with the primary surgeon. Stacey and associates reported that although pain scores were not different between patients cared for through the APS and the primary surgeon, APS patients had fewer side effects, were more likely to receive a loading dose, had their PCA settings adjusted more often, and used more opioid (59). Patients cared for by the primary surgeon also were more likely to receive intramuscular medications after PCA discontinuation. Whether these differences affect overall outcome has yet to be determined.

Definition of routine patient-controlled analgesia patient
Age <70 yr
No history of difficult pain management problems
No history of opioid tolerance (regular opioid use >1 mo), ethyl alcohol abuse, or ongoing substance abuse
No concomitant use of epidural local anesthetic infusions, epidural opioids, or intrathecal opioids or other analgesics
Definition of complex patient-controlled analgesia patient
Age >70 yr
Positive history of difficult pain management problems
Positive history of opioid tolerance (regular opioid use >1 mo), ethyl alcohol abuse, or ongoing substance abuse
Concomitant use of epidural local anesthetic infusions, epidural opioids, or intrathecal opioids or other analgesics

TABLE 41-4. Definitions of routine and complex patients for patient-controlled analgesia therapy

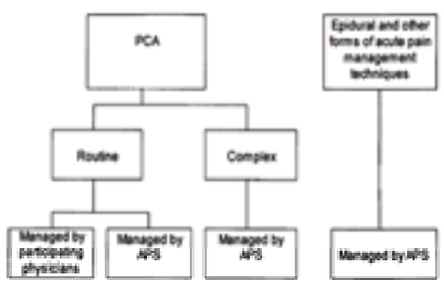

Figure 41-3. Process for provision of intravenous patient-controlled analgesia (PCA), as developed at the University of Washington. Patients meeting the definition of a routine PCA patient can receive intravenous PCA therapy by either a qualified participating physician or the acute pain service (APS). All other patients receive acute pain management by the APS.

The APS, in consultation with others, often establishes the drug formulary for PCA and other pain treatment modalities, which includes the establishment of drug concentrations to be used in selected drug delivery devices. The establishment of a limited number of drugs and drug concentrations decreases the risk of human error associated with device programming. Finally, the APS often is involved in the standardization of physician order forms for the provision of pain treatment modalities, which includes the use of standardized monitoring and treatment protocols, as seen in Figure 41-4 and Figure 41-5.

Figure 41-4. Standard preprinted patient-controlled analgesia orders used by the Acute Pain Service, University of Utah.

Figure 41-5. Standard preprinted epidural opioid orders used by the Acute Pain Service, University of Utah.

Pain assessment is the cornerstone of acute pain management (see Chapter 15). Assessment should be made using a valid measurement tool. Although the 0- to 10-cm visual analog scale is frequently used in clinical pain trials, it is less useful in a busy clinical setting. For older children and adults, the 0 to 10 verbal pain assessment tool, with 0 equal to *no pain* and 10 equal to *worst pain imaginable*, can be easily integrated into a busy clinical practice. Pain assessment tools appropriate to the developmental age of younger children should be used as indicated.

Pain assessment should be made for patients both at rest and with activity. Because activity is often an important part of the rehabilitation of the surgical patient, it is critical that one assess movement pain. Some studies have confirmed that some pain treatment modalities are more effective in controlling pain with movement when efficacy of pain control at rest is similar.

The incidence and severity of treatment-induced adverse side effects should be assessed frequently. Sedation, respiratory depression, pruritus, and nausea and vomiting are assessed in all patients. Additional treatment-related potential adverse side effects may be assessed, depending on the treatment modality used. A standardized method for documenting adverse side effects is important, so that this information can be collected and documented in a consistent manner. One method for assessment of adverse side effects is shown in Table 41-5. In addition, standardization of treatment of side effects, when present, improves efficacy of care and may lead to the selection of therapy that decreases costs. For example, droperidol has been shown to be as effective as ondansetron for the treatment of postoperative nausea and vomiting after ambulatory surgery (60).

0 Side effect not present
1 Side effect present, no treatment required
2 Side effect present, treatment required and effective
3 Side effect present, treatment required but not effective

TABLE 41-5. Assessment for adverse side effects

SPECIFIC TREATMENT MODALITIES

Nonsteroidal Antiinflammatory Drugs

In an effort to improve pain control and decrease the incidence and severity of drug-induced adverse side effects, many clinicians have introduced the use of nonsteroidal antiinflammatory drugs (NSAIDs) into the management of postoperative pain. In fact, the AHCPR guidelines suggest that NSAIDs should be the first-line drug for the treatment of mild to moderate pain and should be used in combination with opioids if not contraindicated for more severe pain.

Some investigators have reported that the combination of NSAIDs with opioids in this setting is more effective than either class of drug alone, and the use of NSAIDs with opioids decreases the necessary dose of the opioid and therefore decreases the incidence and severity of opioid-induced adverse side effects (61,62,63 and 64). Others have reported improved analgesia and reduced side effects when NSAIDs are used in combination with intrathecal opioids (65). However, NSAIDs alone and in combination with other medications can lead to adverse side effects, with some patients at increased risk. In this section, we review the use of NSAIDs for the management of postoperative pain (see Chapter 83).

The pain-reducing capacity of NSAIDs is attributed to their influence on the peripheral nervous system. This action is achieved through the partial inactivation of both cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2), which in turn inhibit prostaglandin biosynthesis (Fig. 41-6 and Fig. 41-7). The inactivation of these enzymes blocks sensitization and activation of peripheral nerve fibers and decreases the number of pain impulses delivered to the central nervous system.

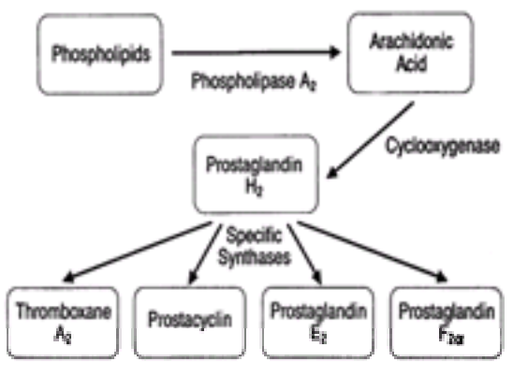

Figure 41-6. The cyclooxygenase pathway. [Reprinted from Lindgren JA. Overview of the physiology of COX-1 and COX-2 and selectivity of NSAIDs. *Am J Man Care* 1996;2(Suppl):S16–S17, with permission. All rights reserved.]

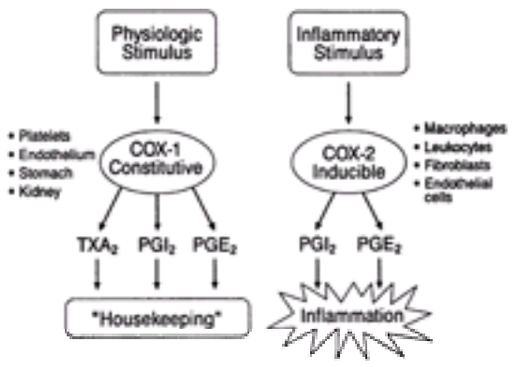

Figure 41-7. Role of COX-1 and COX-2. [Reprinted from Lindgren JA. Overview of the physiology of COX-1 and COX-2 and selectivity of NSAIDs. *Am J Man Care* 1996;2(Suppl):S16–S17, with permission. All rights reserved.]

COX-1 is present in a wide variety of cell types and influences the *housekeeping* functions of prostaglandins. This activity is particularly important in the gastrointestinal tract, kidney, and the circulatory system.

In the gastrointestinal tract, prostaglandin F_2 and prostacyclin maintain mucosal integrity by inhibiting acid secretion and stimulating bicarbonate and mucous secretion. The suppression of these cytoprotective functions by NSAIDs explains the gastrointestinal complications associated with the use of these drugs.

In the kidney, prostaglandins increase renal blood flow, which in turn elevates glomerular filtration and helps regulate both tubular salt and water resorption. Again, the suppression of these functions by NSAIDs explains the adverse effects on renal function seen with this class of drugs.

In the circulatory system, prostaglandins participate in maintaining vascular tone and are involved in control of platelet function. Administration of NSAIDs can adversely affect platelet function, resulting in clinically important bleeding disorders.

COX-2, on the other hand, is found in only a few cell types, especially macrophages and other leukocytes, fibroblasts, and endothelial cells, including those of the vascular system. COX-2 is involved in those aspects of the inflammatory process that are mediated by prostaglandins. Specifically, large volumes of prostaglandins are produced as an inflammatory response begins to build after tissue injury, such as a surgical incision. These prostaglandins potentiate other inflammatory mediators, including leukotrienes, histamine, and bradykinin, the last of which is the most powerful normal vasodilatory substance in human physiology. By potentiating vasodilatation and hyperalgesia, prostaglandins contribute to vascular permeability and, therefore, to edema.

NSAIDs do not cause the respiratory depression seen with opioids. In addition, NSAIDs do not interfere with either bowel or bladder function. However, that does not mean that they are devoid of potential adverse effects. The most common adverse side effects of NSAIDs are gastritis, peptic ulceration, and bleeding (66). In general, the incidence of these effects increases with increased daily dose of NSAID and increased duration of NSAID therapy. Individuals with a prior history of peptic ulcer disease appear to be at increased risk for these complications.

In the postoperative setting, considerable attention has been paid to the potential for NSAIDs to increase the likelihood of bleeding (67). NSAIDs lead to reversible inhibition of the platelet function. Postoperative administration of NSAIDs has been reported to lead to an increased incidence of bleeding (68). However, this is usually associated with selected patient populations, or in individuals who have received other anticoagulants in combination with the NSAID (69).

A rare but potentially serious complication is NSAID-induced depression of renal function (70). Individuals who suffer from chronic renal insufficiency, who are receiving concurrent diuretic therapy, or who are experiencing intravascular volume depletion are at increased risk for this adverse event. Usually, this complication is reversible with discontinuation of the NSAID, but long-term impairment of renal function has been reported.

The risk for adverse events associated with NSAID therapy is increased when some drugs are used in combination with NSAIDs. As stated previously, concurrent diuretic therapy increases the risk of renal complications. In addition, concurrent use of corticosteroids dramatically increases the risk of life-threatening gastrointestinal bleeding. Finally, the use of any other drug that impairs coagulation, such as coumadin or heparin, increases the likelihood of a clinically significant bleeding disorder.

Caution should be exercised when using NSAIDs during pregnancy. Analgesic therapy during pregnancy has been described in detail elsewhere (71).

Selected patients may also be at increased risk for NSAID-induced adverse events. Individuals with congestive heart failure, hepatic cirrhosis with ascites, systemic lupus erythematosus, and multiple myeloma are at increased risk for an adverse event. In addition, elderly persons with significant atherosclerotic disease are at elevated risk for such side effects (72). Care should be taken in these patient populations, dosing may need to be changed to decrease the potential for adverse events, and appropriate monitoring should be instituted when indicated (73). The recent clinical release of COX-2–specific drugs may reduce the side effects experienced with NSAIDs.

Patient-Controlled Analgesia

A PCA device consists of an electronic infusion pump that allows the patient to self-administer an analgesic medication. When the patient experiences pain, he or she pushes a button attached by a cord to the instrument. It then delivers a preset dose (interval dose) of medication via an indwelling intravenous catheter. The machine has a programmable period of time (lock-out time) after each interval dose administration during which it will not deliver another interval dose even when activated by the patient. This lock-out time is intended to prevent the patient from receiving an additional dose of the analgesic before the maximum effect of the previous dose is attained, thus decreasing the possibility of overmedication.

The use of as-needed intramuscular analgesia requires the patient to contact the nurse when he or she experiences pain. The nurse must then check the physician's orders, identify the analgesic, obtain the drug, prepare it for injection, and administer the medication. After drug administration, there is a period of time before the drug is systemically absorbed and reaches analgesic blood levels. Because high intramuscular doses are required to decrease the time to analgesia, there is often a period of high blood concentration and oversedation. The patient experiences analgesia for a relatively short period of time, and then the cycle repeats itself as the drug level decreases below analgesic levels (Fig. 41-8) (74).

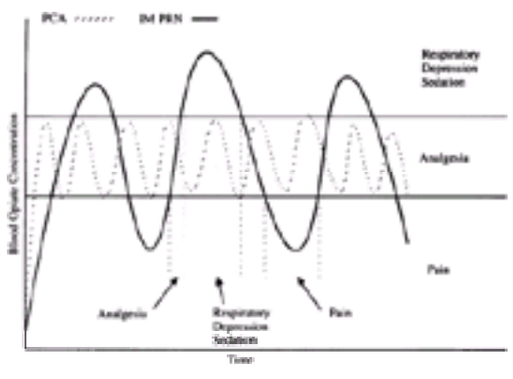

Figure 41-8. The difference in opioid levels between patient-controlled analgesia (PCA) and intramuscular routes of administration. (Reprinted from Ashburn M, Smith K. The management of postoperative pain. *Surg Rounds* 1991;14:129–134, with permission.)

PCA allows the patient to receive medication intravenously as soon as he or she begins to experience pain and eliminates the obligatory delays in drug administration and absorption seen with intramuscular dosing. The administration of smaller intravenous doses allows the patient to titrate the opioid to analgesic levels more accurately and decreases the risk of oversedation associated with intramuscular opioid dosing.

Although PCA devices have been in existence since the late 1960s, they have not met with widespread acceptance until more recently. This is caused, in part, by improved device technology, such as improved device memory and safety features. In addition, the introduction of anesthesiology-based APSs into clinical practice has made this treatment modality more widely available.

PCA therapy provides improved analgesia compared with as-needed intramuscular opioid administration in patients undergoing a variety of surgical procedures (75,76,77,78,79 and 80). Patients usually require less analgesic via the PCA device than those receiving equianalgesic doses of intramuscular opioids (81).

Approximately 85% of the patients who receive PCA for the management of acute pain experience good to excellent pain control (82). Many patient factors may influence the ability of PCA therapy to be successful, including the ability of the patient to understand the correct use of the device, the patient's prior pain experience, and other psychosocial factors (83,84,85 and 86). These factors must be taken into account when considering patients for this therapy, and when making decisions on the appropriateness of continuing therapy once begun.

Patient selection for PCA therapy is based on the patient's ability to understand the concept of PCA therapy and appropriately interact with the device. No arbitrary age limit is set, as PCA therapy has been proven to be effective in pediatric and adolescent age groups (80,87,88 and 89). Preoperative patient education on the use of the PCA device greatly enhances success.

The analgesic used in the PCA device is usually a potent opioid, such as morphine or hydromorphone (Dilaudid). Opioid antagonists, such as nalbuphine, have also been employed successfully (90), as have NSAIDs (91). Interval dose and lock-out time for the different agents are determined by the potency of the drug and the time necessary for maximum effect after intravenous administration (Table 41-6).

Drug	Bolus dose (mg)	Lock-out interval (min)
Agonist		
Morphine	0.5–3.0	5–20
Methadone	0.5–3.0	10–20
Hydromorphone	0.1–0.5	5–15
Oxymorphone	0.2–0.8	5–15
Meperidine	5–15	5–15
Fentanyl	0.015–0.075	5–10
Sufentanil	0.002–0.015	5–10
Agonist-antagonists		
Pentazocine	5–20	5–15
Nalbuphine	1–5	5–15
Buprenorphine	0.03–0.20	10–20

Reprinted from Joshi GP, White PF, Inc Ashburn MA, Rice LL eds. The management of pain New York: Churchill Livingstone, 1998:577–611, with permission.

TABLE 41-6. Guidelines regarding the bolus dosages and lock-out intervals for various parenteral analgesics when using a patient- controlled analgesia system

Meperidine is a commonly used opioid for intramuscular, as-needed analgesia. Many institutions continue to use this opioid for intravenous PCA analgesia. However, it should not be used as the first-line opioid for acute pain management. Meperidine has a short duration of action (2.5 to 3.5 hours), which necessitates frequent dosing. In addition, excessive use or decreased renal clearance can lead to the accumulation of normeperidine (6-desmethylmeperidine). This metabolite can accumulate because of its long half-life (24 to 36 hours), especially in elderly patients and patients with impaired renal function. It is a cerebral irritant that can cause effects ranging from mood irritability to grand mal seizures (92). As a result of the potential for these serious drug-specific side effects, many institutions are changing their acute pain processes to significantly limit the use of meperidine or are removing meperidine from their formulary entirely.

The use of a basal infusion with PCA opioids does not appear to increase the effectiveness of analgesia and may increase the incidence of adverse side effects in adult (93,94) and pediatric (95) patient populations. Others have noted that the addition of an infusion may increase the risk of programming error (49,51,96).

Although PCA therapy is considered to be safe, the potential for serious adverse outcome exists (Table 41-7) (47,48,52,97). Opioid administration is associated with alterations in ventilation (50). Life-threatening respiratory events associated with the use of PCA have been reported (48,49 and 50,52,98,99). The incidence of these events has recently been reported to be 0.01%, similar to that seen with intramuscular opioid administration or epidural morphine administration (51). These events are most often associated with human error, usually related to pump programming (see Table 41-7).

Operator errors
Misprogramming PCA device
Inappropriate drug, dose, or concentration
Inappropriate lock-out period
Inadvertent addition or deletion of a basal infusion
Failure to clamp or unclamp tubing while loading or unloading the drug reservoir
Improperly loading syringe or cartridge
Inability to respond to safety alarms
Misplacing PCA pump key
Patient errors
Failure to understand PCA therapy
Alterations in negative feedback loop
Misunderstanding PCA device
Intentional analgesic abuse
Mechanical errors
Failure to deliver on demand
Cracked drug reservoir
Defective one-way valve at Y-connector
Faulty alarm system
Malfunctions (e.g., leak)
Nonpatient delivery system
Block or kink in the intravenous catheter or tubing, leak, or disconnect

PCA, patient-controlled analgesia.
From Weiss H. Management of patient-controlled analgesia. Anesthesiology 1985;63, with permission.

TABLE 41-7. Summary of problems that may occur during patient- controlled analgesia therapy

Interdisciplinary acute pain management can be used to decrease the incidence and severity of adverse outcomes while providing the highest quality patient care possible. Acute pain management requires the involvement of the patient and family, primary care physician, pain management physician, primary nurse, pain management nurse, and pharmacist.

Although PCA is most commonly used for systemic delivery of potent opioids, it has also been used in other settings. PCA has been used for systemic delivery of nonopioid analgesics, such as NSAIDs (91). In addition, PCA has been used to administer epidural analgesia (100), which is discussed later in this chapter, as well as in the chapter on spinal opioids. Finally, PCA has also been used to deliver regional local anesthetics, such as patient-controlled interscalene analgesia (101).

In addition to the management of postoperative pain, PCA has been effectively used in other patient populations. PCA can be used to manage pain associated with acute medical illness, prolonged cancer therapy (102), and terminal illness. Newer designs of the PCA device have allowed it to be effectively used in the ambulatory setting. However, regardless of the setting, systemic administration of a potent analgesic can lead to serious adverse outcome. Therefore, prudent use of PCA in any setting must be accompanied by appropriate monitoring.

Spinal Opioids

Intrathecal and epidural administration of opioids is a relatively new technique first described in humans in 1979 (103). The technique gained rapid, widespread use because of the long duration of intense analgesia caused by opioids administered directly on the spinal axis (10). However, this enthusiasm was soon tempered by reports of side effects such as pruritus, urinary retention, nausea and vomiting, and delayed respiratory depression.

In contrast to the local anesthetics, which act at the spinal nerve root level, opioids act at receptor sites in the dorsal horn of the spinal cord. Because of this selective effect at opioid receptor sites, they do not lead to hypotension caused by sympathetic blockade. Opioids also do not cause any motor blockade that could lead to reduced patient mobility.

The onset and duration of analgesia of spinal opioids is closely related to their lipid solubility. Morphine, with a relatively low lipid solubility, has a slow onset time of approximately 45 minutes, but a long duration of action of up to 24 hours. Meperidine, on the other hand, is relatively lipid soluble, when compared with morphine, and has an onset time to analgesia of approximately 15 minutes, with an average duration of 2 to 6 hours (104,105,106 and 107). The relatively fast onset and intermediate duration of action of epidurally administered meperidine makes it a possible candidate for epidural PCA. Initial reports of its use in this setting have been promising (108,109).

Very lipid-soluble opioids, such as fentanyl and sufentanil, have a relatively short duration of action when administered intrathecally. Controversy exists, however, on the location of action (either systemic or spinal) after the epidural administration of fentanyl or sufentanil. Pharmacokinetic studies of epidural fentanyl reveal rapid absorption of fentanyl across the dura mater and into the cerebrospinal fluid (110). However, clinical studies fail to show a difference in the pain control provided by epidural versus intravenous fentanyl (111,112). Other relatively lipid-soluble opioids, such as meperidine and hydromorphone, have a spinal effect when administered epidurally (113). However, it appears that epidural fentanyl and sufentanil have their primary effect as a result of systemic absorption, rather than at the dorsal horn of the spinal column (114,115).

Intrathecal and epidural administration of opioids is associated with several potential adverse side effects. These include pruritus, nausea, vomiting, urinary retention, early- and late-onset respiratory depression, infection, and bleeding. Pruritus and urinary retention are common with the administration of spinal opioids, but are usually controllable and infrequently lead to discontinuation of drug administration. The incidence of nausea and vomiting associated with spinal opioid administration is similar to or less than that seen with intramuscular opioid administration. These side effects can be effectively managed with intravenous naloxone, usually without decreasing the effectiveness of pain relief. In spite of these potential side effects, numerous clinical trials have documented that 90% of the patients who receive either intrathecal or epidural opioids report excellent analgesia (116).

Both early and late respiratory depression has been seen with spinal opioid administration (117). Early respiratory depression is thought to be secondary to the effect of systemically absorbed drug, whereas late respiratory depression is thought to be secondary to the central effect of the drug that has flowed cephalad from the point of injection. Late-onset respiratory depression is usually associated with the administration of morphine and is rarely seen with the administration of the lipid-soluble opioids. Late-onset respiratory depression is most likely caused by rostral spread of the opioid to the respiratory centers of the brainstem (118) and appears to be dose related (Table 41-8 and Table 41-9) (119). Respiratory depression is usually associated with relatively high doses (epidural morphine more than 5 mg, intrathecal morphine more than 0.5 mg) and is seen more frequently in patients who are elderly, debilitated, or have received systemic opioids or benzodiazepines.

Result	Determined cause of error (no. of events): Misprogram PCA continuous infusion	Machine tampering	Family member activating PCA	Clinical judgment (MD, RN, or both)
No adverse outcome	7	1	1	1
Serious adverse outcome	1	4	2	2

[a] A critical event may have more than one cause.
From Ashburn MA, Love G, Pace NL. Respiratory-related critical events with patient-controlled analgesia. Clin J Pain 1994;10:[illegible], with permission.

TABLE 41-8. Respiratory-related critical events after patient-controlled analgesia (PCA) therapy in 3,785 patients (11,521 patient care days) [a]

Intrathecal morphine dose (mg)	SpO_2 <90%	SpO_2 <85%	Respiratory rate <8	Supplemental oxygen needed
0	0 (0)	0 (0)	0 (0)	0 (0)
0.2	40 (2)	0 (0)	40 (2)	0 (0)
0.4	60 (3)	40 (2)	20 (1)	20 (1)
0.6	80 (4)	80 (4)	20 (1)	80 (4)

SpO_2, peripheral oxygen saturation.
From [illegible], with permission.

TABLE 41-9. Percent (and number) of adult volunteers by intrathecal morphine dose experiencing one or more episodes of SpO2 less than 90% and less than 85%, respiratory rate less than 8, and requiring supplemental oxygen

Because of the risk of late respiratory depression, some investigators advocate aggressive monitoring of patients receiving spinal opioids or limiting their use to special nursing areas, such as the intensive care unit. However, when late respiratory depression does occur, it usually has a gradual onset and is associated with a gradual increase in somnolence. These drugs can be safely administered on any patient care unit in which the nursing staff caring for the patient has been instructed on the correct monitoring of these patients and where appropriate physician care is available (7).

Bernards and associates reported on the effect of needle puncture on morphine and lidocaine flux through the spinal meninges of the monkey (120). In an *in vitro* model, they demonstrated a significant increase in the flux of morphine through meningeal tissue after needle puncture. This has been confirmed in the animal model with morphine and sufentanil (121,122), and a case report of late-onset respiratory arrest after the use of the combined spinal-epidural technique has been published (123). As a result, some pain management physicians avoid the use of morphine in a patient who has had an inadvertent dural puncture with an epidural needle, followed by placement of an epidural catheter. Certainly, caution and careful monitoring for respiratory depression are indicated.

Opioids with Local Anesthetics

Local anesthetics have been used for years for spinal and epidural anesthesia and analgesia and can provide excellent analgesia. Investigators have documented in the animal model a synergistic effect when dilute local anesthetics are combined with opioids for epidural analgesia (124,125). Good analgesia has been reported with the use of continuous epidural infusions of bupivacaine and morphine (53), bupivacaine and fentanyl (56), and bupivacaine and sufentanil (126). Only a few studies have compared the efficacy of local anesthetics with morphine versus more lipid-soluble opioids. However, it appears that the use of the more lipid-soluble opioids, such as fentanyl, may be associated with similar analgesia and fewer side effects (127).

The use of epidural local anesthetics with opioids may allow for comparable or improved analgesia with fewer side effects when compared with using either agent alone. For example, Liu and associates evaluated the effects of various analgesic techniques on rate of recovery after colon surgery (43). They studied four analgesic techniques: epidural infusion of morphine, epidural infusion of bupivacaine, intravenous patient-controlled morphine, and an epidural infusion of bupivacaine with morphine. They reported superior analgesia with activity in the epidural bupivacaine and epidural bupivacaine-morphine groups. Both groups experienced more rapid recovery of gastrointestinal function and met hospital discharge criteria approximately 1.5 days earlier than the other study groups. However, the epidural bupivacaine-morphine group experienced fewer adverse side effects when compared with all other analgesic study groups.

When using dilute epidural local anesthetics with opioids, the catheter should be placed at a vertebral level corresponding to the dermatomal level of the surgical incision. As a result, more catheters will be placed at the high lumbar and thoracic levels. Although placement of the catheter at higher levels has been thought to lead to an increased risk of neurologic injury, reports refute this belief (128). The risk of neurologic injury associated with the placement of an epidural catheter appears to be 0.07% (129).

Even with dilute local anesthetic solutions, a risk of hypotension and motor block exists. The risk of motor block appears to be related to both the concentration of local anesthetic used as well as the position of the epidural catheter, with a low lumbar catheter having the highest risk of motor block compared with either a high lumbar or thoracic catheter (100,130).

Several investigators have reported on the use of patient-controlled epidural analgesia with opioids alone or local anesthetic- opioid mixtures. Early studies with relatively small numbers of patients report excellent analgesia in both obstetric (131,132) and surgical patients (133). When compared with continuous infusions, epidural PCA appears to provide comparable or improved analgesia with less medication (134). A more extensive surveillance study reported excellent analgesia in 1,030 surgical patients (100). Liu and associates reported on the use of patient-controlled bupivacaine 0.05% with fentanyl, 4 mg per mL. This technique provided excellent analgesia both at rest and with movement, with an acceptable adverse-event profile (Table 41-10).

Side effect	% Incidence (95% confidence interval)
Pruritus (patient request for antipruritic)	16.7 (14.7–18.7)
Nausea (patient request for antiemetic)	14.8 (12.8–16.8)
Sedation	
Mildly drowsy	11.7 (9.7–13.7)
Moderately drowsy	0.9 (0.3–1.5)
Very drowsy	0.5 (0.1–0.9)
Difficult to rouse	0.1 (0.0–0.2)
Hypotension (systolic blood pressure <90 mm Hg)	6.8 (5.0–9.0)
Motor block (inability to ambulate because of lower extremity weakness)	2.0 (1.0–3.0)
Respiratory depression (respiratory rate <8 breaths per minute)	0.3 (0.0–0.6)
Requiring naloxone	0.2 (0.0–0.4)

From Liu S, Allen H, Olsson G. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards. Anesthesiology 1998;88:693, with permission.

TABLE 41-10. Incidence and maximal risk of side effects associated with epidural patient-controlled analgesia using bupivacaine 0.05% with fentanyl, 4 µg per mL

As with other complex pain management modalities, standardization of therapy decreases the risk for human error. Liu and associates have published their recommendations for standard orders for epidural PCA therapy (Table 41-11), monitoring (Table 41-12), and treatment of adverse side effects (Table 41-13) (100). A survey of monitoring practices in the United States after epidural analgesics has also been published (135). It appears, however, that with appropriate monitoring these techniques can be safely used on the hospital ward (56).

1. Epidural analgesic solution is 0.05% bupivacaine with 4 µg/mL of fentanyl.
2. Set the background infusion rate to 4 mL/hr.
3. Set the loading dose to 5 mL.
4. Set 1-hour limit to 14 mL.
5. Set patient-controlled epidural analgesia bolus to 2 mL and lock-out to 10 minutes.
6. If analgesia is inadequate (verbal pain score >5 at rest or with activity), then administer a 5 mL loading dose, increase the infusion rate by 2 mL/hr, and increase the 1-hour limit to 24 mL.
7. If more than two adjustments to patient-controlled epidural analgesia are needed within a 24-hour period, then call the acute pain service.
8. No other analgesics or hypnotics are to be given without notifying the acute pain service.

Modified from Liu S, Allen H, Olsson G. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards. Anesthesiology 1998;88:693, with permission.

TABLE 41-11. Standing orders for patient-controlled epidural analgesia settings and analgesic therapy

1. Check respiratory rate, level of consciousness, and blood pressure/heart rate every 1 hour for 12 hours, then every 2 hours for 12 hours, then every 4 hours thereafter.
2. If systolic blood pressure is <90 mm Hg, call the acute pain service.
3. Check postural pressure on the morning of postoperative days 1 and 2.
4. Check the level of sensory block every 8 hours. Notify the acute pain service for T-4 block or increasing sensory level.
5. Maintain intravenous access for 2 hours after the epidural infusion is discontinued.

Modified from Liu S, Allen H, Olsson G. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards. Anesthesiology 1998;88:693, with permission.

TABLE 41-12. Standing orders for nursing monitoring for epidural patient-controlled analgesia

1. Respiratory depression.
   If respiratory rate is <8 breaths per minute and unable to arouse patient, then give 0.1 mg of naloxone intravenously STAT (may repeat 3 times). Call the acute pain service STAT.
   If respiratory rate is <10 breaths per minute, call the acute pain service.
2. For nausea and vomiting, administer 0.5 mg of droperidol intravenously every 4 hours as needed.
3. For pruritus, administer 25 to 50 mg of diphenhydramine intravenously or by mouth every 4 hours as needed.
4. If systolic blood pressure is <90 mm Hg, call the acute pain service.
5. Allow assisted ambulation only. Call the acute pain service for motor weakness.

Modified from Liu S, Allen H, Olsson G. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards. Anesthesiology 1998;88:693, with permission.

TABLE 41-13. Standing orders for the treatment of side effects associated with epidural patient-controlled analgesia

Placement of an epidural catheter is associated with a risk of infection. Surveillance studies report a low incidence of infection in both adults and children with epidural catheters used for short-term postoperative analgesia (136,137). However, life-threatening infections can occur (138). Appropriate monitoring for this potential complication should be completed.

A potentially serious complication of epidural analgesia is the development of an epidural hematoma, leading to severe neurologic injury. The occurrence of symptomatic hematomas after epidural catheter placement is rare (139). However, patients who are anticoagulated are at increased risk. Surgical patients are frequently placed on anticoagulants to avoid the development of thrombotic complications. Studies evaluating the risk of bleeding associated with epidural analgesia after oral anticoagulant prophylaxis revealed a low rate of bleeding (140). However, other investigators have documented a wide variation in response to anticoagulation therapy (141); the more anticoagulated a patient is, the higher the risk of bleeding. In addition, the use of other drugs that interfere with the coagulation process, such as NSAIDs, platelet inhibitors, or other anticoagulants, also increases the risk of bleeding.

Low-molecular-weight heparin compounds have been introduced into practice (142). Initial studies indicated that low-molecular-weight heparin, when administered at equivalent antithrombotic doses, caused less bleeding than standard heparin. However, there have been reports of spinal hematoma occurring spontaneously and in association with regional anesthesia in patients who have received low-molecular-weight heparin (143). The Food and Drug Administration published a public health advisory in December 1997 outlining the agency's concern over the use of regional anesthesia and analgesia in patients receiving low- molecular-weight heparin. The Food and Drug Administration cited 30 spontaneous safety reports describing patients who have developed epidural or spinal hematomas with concurrent use of enoxaparin sodium and spinal or epidural anesthesia or spinal puncture. The Food and Drug Administration reported that many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. The risk for serious bleeding appeared to be increased by traumatic or repeated epidural or spinal puncture.

Horlocker and Heit published guidelines for regional anesthetic management in patients receiving low-molecular-weight heparin (Table 41-14 and Table 41-15) (144). Clearly, the pain management physician should consider the risk for this and other rare but serious events when considering a regional analgesic technique. Appropriate monitoring is critical, especially with regard to risk of bleeding and infection, because prompt diagnosis and treatment of these complications are critical to avoid long-term neurologic injury (143).

TABLE 41-14. Guidelines for the management of regional anesthesia in patients receiving perioperative heparin [a]

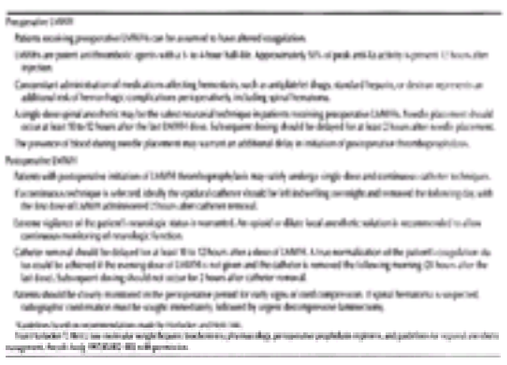

TABLE 41-15. Guidelines for the management of regional anesthesia in patients receiving perioperative low-molecular-weight heparin (LMWH) [a]

CONCLUSIONS

A goal of acute pain management programs is to ensure that individuals experiencing pain receive the best possible pain management. Anesthesiologists have had a significant effect on improving care to those suffering from pain and will continue to do so. Individuals who experience trauma and surgery will continue to experience pain and will require the care that anesthesiologists provide. However, the organizational structure through which acute pain care is provided will likely continue to evolve. It is vital that anesthesiologists continue to strive to meet the needs of the people we serve, and in doing so we will remain a vital part of an integrated, interdisciplinary system of care for the perioperative patient.

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CHAPTER 42

*Burn Pain**

David R. Patterson and Sam R. Sharar

If burn injuries in themselves are not the most painful type of trauma a person can sustain, then they likely reach this status once the nature of their treatment is considered. Treatment for burn injury involves a multitude of invasive procedures that may continue for months. Each intervention has the potential of inflicting more pain than that of the initial trauma. Burn injuries are pervasive in the United States and the world and tend to affect individuals across a wide demographic span. Estimates of burn incidence in the United States suggest 1.25 million episodes with 51,000 acute hospitalizations and 5,500 deaths annually (1). Substantial evidence suggests that pain from burn injuries is undertreated, particularly in children (2). This is unfortunate, because the pain from acute burns has physiologic effects that are likely to impede wound healing (3. Furthermore, pain correlates strongly with psychological outcome in this patient population. Thus, there are humane reasons to control burn pain in a better fashion, as well as practical, cost-effective ones.

NATURE OF BURN PAIN

Burn pain is an unpleasant form of suffering to treat, from the perspective of both the patient and the clinician. It is well known that a burn injury results in one of the most intense types of nociception imaginable. However, it is the treatment of a burn injury that creates the true challenge, for typical burn care involves a series of aggressive procedures that stimulate nociceptive afferent fibers on a daily basis for days, weeks, or months after the initial injury. In conventional care, a burn injury is assessed as to its depth and treated accordingly. Shallow burns are left to heal on their own, and full-thickness thermal injuries typically are excised and covered with a skin graft (4). Patients with burns of indeterminate depth in many burn centers undergo a series of wound debridements and dressing changes on a daily basis. The pain of a burn patient can be anticipated and treated, to a large degree, based on the phase of care in which he or she is involved. Wound cleaning, mobility, therapeutic stretching, and other medical procedures result in procedural pain, which is of high intensity, but limited duration. Patients who are between procedures, showing minimal activity, still experience resting pain that is of less intensity but almost constant duration. When pain control interventions fail to control resting pain, patients experience breakthrough pain. Finally, because surgical interventions are a frequent treatment for severe burn injuries, postoperative pain is an additional type of pain to be considered. Each of these types of pain has specific treatment strategies associated with them.

Although the nature of burn care provides some prediction as to the pain a patient will experience, the overall quality of a given individual's pain experience has proved to be extremely difficult to anticipate. The sensory and affective quality of burn pain has received scant attention in the literature, and almost no studies have addressed patterns over the course of hospitalization. Patients have been found to report their pain as severe or excruciating, despite receiving intravenous (IV) morphine (5). Pain from burn injuries has also been found to be linked to emotional factors, such as depression and posttraumatic stress disorder (6,7 and 8). Choiniere and colleagues (9) followed pain over the course of hospitalization and found that it varied substantially both within and across patients over time. They also reported that burn pain is not predicted well by social-demographic factors or burn size (the latter finding is contrary to the inaccurate assumptions of many clinicians treating burns). The unpredictable and often opioid-resistant nature of burn pain has been hypothetically linked to underlying sensory nerve damage (10,11).

The literature suggests that the times burn pain is at its worst can be anticipated, but only within broad parameters. Capturing the individual pain experience of a patient will likely continue to prove to be elusive. In spite of the challenge inherent in adequately treating burn pain, it remains important to continue to treat this problem aggressively. First of all, burn recovery, as is the case with any type of trauma, can be hindered by the presence of acute pain (3,12,13 and 14). Remarkably, burn pain has been reported to influence posthospitalization emotional recovery, more than the size of the burn, the length of hospitalization, or even the patient's preinjury mental health. Ptacek and colleagues (15) reported that pain scores correlated higher with 1-month distress and quality of life scores than other variables measured. A more recent study suggested that this relationship held at 1 year posthospitalization (16). Future studies will likely substantiate the practical utility of adequately treating burn pain.

PSYCHOLOGICAL FACTORS

As discussed previously, the pain experienced by burn patients is influenced by their emotional state. Unfortunately, a burn injury is a form of trauma that has dire emotional consequences for many survivors. Equally important, patients who sustain severe burn injuries often do so because of their predisposing psychological status. In considering psychological factors, then, it is important to consider the preinjury status of patients, as well as their emotional adjustment during and after hospitalization.

The estimates of preinjury psychological problems in some studies of burn patients are so high that injuries of this type should be considered to be, in part, a symptom of social ills (17). Estimated rates of psychiatric diagnoses in patients admitted for burn care have ranged from 25% to 75%, with the most prevalent diagnoses including depression, character disorder, and substance abuse (17). In addition, the nature in which the burn injury occurred is often cause for concern: suicide attempts, child and elder abuse (or neglect), adult batterings, and juvenile fire setting are all unfortunately common sources of injury. Psychological disturbances that predate the burn injury have the potential to increase complications, lengthen hospital stays, and lead to more serious long-term adjustment problems (18,19 and 20). A number of these preinjury complications have direct relevance to pain control. Patients with drug and alcohol histories may show lower pain tolerance, more drug-seeking behaviors, and greater tolerance to opioid analgesics. *Diagnostic and Statistical Manual*, fourth edition, axis II character disorders can present a particular challenge to clinicians. Patients with such personality predispositions may not only show drug-seeking but also dramatic acting out behaviors, manipulation, staff-splitting, and low frustration tolerance. Patients with borderline personality disorders, in particular, engage in parasuicide behavior and self-mutilation. The latter groups of patients can provide clinicians with notable behavioral challenges on top of already difficult pain control issues.

The nature of burn care, hospitalization, and the significance of sustaining a burn injury can cause psychological complications that complicate pain control. Patients with large unhealed burn areas or other significant medical complications are usually placed in intensive care units. In the intensive care unit, delirium and other psychotic reactions are common (20,21). Infections, alcohol withdrawal, and metabolic complications are the most frequent etiologies (22). Poor communications from altered mental status or endotracheal intubation may impede pain assessment. Anxiety can be particularly intense on the intensive care unit, which is particularly significant, given the cyclic interaction between anxiety and nociception (3). Anxiety, in fact, is a frequently reported psychological complication that persists into the acute phase of burn care. As hospitalization persists and patients show greater mental capacity, depression becomes increasingly common and is well known to interact with pain (23). Posttraumatic stress disorder is another complication that can affect pain control. Perry (24) warned against undermedicating such patients who are quiet and withdrawn as a function of their reaction to stress.

With pediatric burn patients, the interaction between psychological factors and pain control can be particularly notable. For children, the burn unit environment can be extremely strange and frightening. Little opportunity exists for the burn staff to prepare children psychologically for the repeated medical procedures they must endure, and conditioned anxiety to the stimuli associated with burn care can be expected. Children also often demonstrate regression and behavioral acting out in response to hospitalization, making pain control during procedures a particular challenge.

In the long-term rehabilitation phase of burn recovery, both acute pain and psychological symptoms are less common. However, patients may show persistent depression or posttraumatic stress disorder that interacts with pain control. Sleep problems are prevalent, frequently underaddressed in posthospitalization, and may reflect undertreatment for pain. When psychological or pain problems persist long after hospital discharge, the possibility of social or financial disincentives should be entertained. Although some patients certainly have internally generated psychological problems, for others, the issues persist because of such factors as litigation or the desire to avoid returning to an undesirable job.

GENERALIZED TREATMENT PARADIGM FOR BURN PAIN

Because burn pain is highly variable and cannot be reliably predicted by clinical assessment of the patient or the burn wound, we recommend a structured approach to burn analgesia that incorporates both pharmacologic and nonpharmacologic therapies, targets specific pain issues unique to the burn patient, and can be tailored to anticipated variations in patient need and institutional capability. One clear goal of such a paradigm is to avoid the undertreatment of burn pain, an unfortunate reality in the settings of adult (25) and pediatric (2,26) burn care, and more historically described for other acute pain settings (27). Perry and colleagues (28) noted that burn staff members failed to medicate patients adequately with opioids, despite education regarding the low risks for addictive and other side effects. These investigators offered a psychodynamic conceptualization of this issue, proposing that staff members required to perform repeated and painful procedures on these patients had a need for patients to demonstrate pain as a means to create a psychological distance between themselves and the realities of burn care. Alternatively, the fear of creating psychological dependence on opioids may explain the reluctance of some burn care staff to aggressively treat burn pain. However, currently no evidence exists that opioid addiction occurs more commonly in burn patients than in other populations requiring opioids for acute pain (approximately 1 in 3,000) (29).

In the generalized burn pain management paradigm, selection of an analgesic regimen is individualized and based on two broad categories: (a) the clinical need for analgesia (i.e., treatment of background versus procedural versus postoperative pain), and (b) limitations imposed by the patient (presence of IV access, endotracheal tube, or opioid tolerance) or by clinical facilities (available monitoring capabilities and personnel). The presence or absence of IV access directly influences analgesic drug choice, particularly in children in whom IV access may be problematic. Patients who are endotracheally intubated and ventilated are “protected” from the risk of opioid-induced respiratory depression; thus, opioids may be more generously administered in these individuals, as is often indicated for complex burn debridement procedures in patients with more extensive or severe burn injuries. Individual differences in opioid efficacy should be considered in all patients, including opioid tolerance in patients requiring prolonged opioid analgesic therapy or in those with preexisting substance abuse histories. Because of the development of drug tolerance with prolonged medical use (more than 2 weeks) or recreational abuse of opioids (both commonly seen in burn patients), opioid analgesic doses needed for burn analgesia may significantly exceed those recommended in standard dosing guidelines. One clinically relevant consequence of drug tolerance is the potential for opioid withdrawal to occur during inpatient burn treatment. Thus, the period of inpatient burn care is not an appropriate time to institute deliberate opioid withdrawal or detoxification measures in the substance-abusing patient, because such treatment ignores the real analgesic needs (background pain and wound care pain) of these patients. Similarly, when reductions in analgesic therapy are considered as burn wounds heal, reductions should occur by careful taper, in order to prevent acute opioid withdrawal syndrome.

Institutional capability to provide adequate monitoring (pulse oximetry, independent patient observer) as required for conscious sedation may also dictate which agents are used for procedural analgesia, as some of the more potent opioids (e.g., fentanyl) and agents such as ketamine may provide levels of sedation beyond those of mere analgesia. Obviously, this distinction between analgesia and conscious sedation is subjective and requires both individual and institutional interpretation to ensure safety and practicality in meeting proposed monitoring guidelines for conscious sedation. The use of potent opioids and anxiolytics should only occur in settings with adequate monitoring, personnel, and resuscitation equipment appropriate for the degree of sedation anticipated. For most wound debridement procedures, opioid analgesia with minimal sedation is sufficient, and no special monitoring is required. Larger or more potent doses of opioids, or the concurrent use of anxiolytic sedatives (e.g., benzodiazepines) may produce more pronounced sedation (deep sedation) in which patient-staff communication, consciousness, or both are lost. Current guidelines of the Joint Commission on Accreditation of Healthcare Organizations (30), as well as physician specialty professional organizations (31), dictate both general and specific levels of monitoring (e.g., continuous pulse oximetry, presence of an independent observer specifically responsible for monitoring ventilation and vital signs) for patients requiring this level of analgesia and sedation.

Because nociception at the burn site is the predominant mechanism of pain and suffering in these patients acutely, pharmacologic treatment with potent opioids, anxiolytics, and other agents (e.g., ketamine) is the first line of therapy. We believe that nonpharmacologic methods of treating burn pain are also extremely useful, although some nonpharmacologic pain control techniques should be second nature to the staff and integrated into standard care (e.g., minimizing the number and intrusiveness of dressing changes, limb elevation, brief educational approaches). Others are more practically implemented after a stable pharmacologic regimen is established (e.g., hypnosis). To reinforce a consistent approach to analgesic management, particularly in centers where house staff physicians, nursing staff, or both may rotate or change frequently, the establishment of succinct yet detailed institutional guidelines may help physicians and nurses with choosing and administering analgesics that target specific analgesic needs (32,33), as shown in Table 42-1. To maximize simplicity and utility, it is recommended that such guidelines be safe and effective over a broad range of ages, be explicit in their dosing recommendations, have a limited formulary to maximize staff familiarity, and allow the bedside nurse continuously to evaluate efficacy and safety (33). In addition, the regular use of a weight-based pediatric medication worksheet (placed at the bedside and in the patient record), containing all analgesic and resuscitation drugs likely to be administered, provides a supplemental safeguard against accidental overdose, particularly in the young pediatric age group (34).

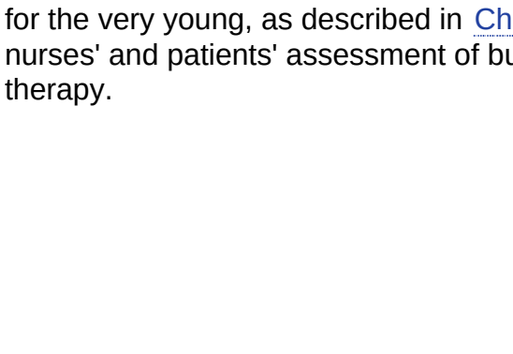

TABLE 42-1. Harborview Medical Center/University of Washington Burn Center burn analgesic guidelines for adults [a]

PHARMACOLOGIC APPROACHES

In describing pharmacologic approaches for burn analgesia, three consistent observations can be made. First, for patients with injuries extensive enough to require hospitalization, pain from the burn itself is severe. Thus, potent opioids form the cornerstone of pharmacologic pain control in these patients, leaving few indications for the mild to moderate analgesia provided by nonsteroidal antiinflammatory or acetaminophen, with notable exceptions of the rehabilitative phase of care and outpatient treatment. Second, because burn pain has well-defined components (e.g., background, procedural, and postoperative pain) pharmacologic choices for analgesia should target each pain pattern individually. Finally, because burn pain varies somewhat unpredictably throughout hospitalization because of surgical intervention, activity levels, and so forth, analgesic regimens should be continuously evaluated and reassessed to avoid problems of undermedication or overmedication. Pain assessment is facilitated by the regular use of standardized, self-report scales for adults and older children, and observational scoring systems for the very young, as described in Chapter 15. A reliance on nurse assessment of patients' burn pain can be problematic, however, as it is well documented that nurses' and patients' assessment of burn pain and analgesia are not always comparable (25,35,36), with nursing staff typically underestimating the need for analgesic therapy.

Opioids

Opioid agonists are the most commonly used analgesics in the treatment of burn pain, in part because (a) they are potent; (b) the benefits and risks of their use are familiar to the majority of care providers; and (c) they provide some dose-dependent degree of sedation that can be advantageous to both burn patients and staff, particularly during burn wound care procedures. The wide spectrum of opioids available for clinical use (see Chapter 84) provides dosing flexibility (i.e., variable routes of administration, variable duration of action) that is ideal for the targeted treatment of burn pain. The pharmacokinetics of opioids in burn patients are not consistently different from nonburn patients (37,38), although decreased volume of distribution and clearance, and increased elimination half-life have been reported for morphine in this population (39). Similarly, the pharmacodynamic potency of opioids has inconsistently been reported as increased (40) and decreased (39) in burn patients.

The route of opioid administration is an important issue in burn patients, with the principal choice between IV or oral administration dictated by the severity of burn (critically ill patients require IV access and may have abnormal gut function) and the high risk of burn patients for developing intravascular catheter-related sepsis (hence, physician reluctance to maintain long-term IV access) (41). Intramuscular opioid administration is avoided because of the need for repeated, painful injections, and because of variable vascular absorption caused by unpredictable compartmental fluid shifts and muscle perfusion in burn patients, particularly those undergoing acute, burn shock resuscitation. Patient-controlled analgesia (PCA) with IV opioids offers the burn patient a safe and efficient method of achieving more flexible analgesia. PCA also offers the patient some degree of control over his or her medical care, this often being a major issue for burn patients whose waking hours are often completely scheduled with care activities ranging from wound care to physical and rehabilitation therapy. Some studies comparing PCA opioid use to other routes of administration in the burn population have shown positive, but limited benefits of PCA (42,43), although others have shown that patients may prefer an attentive nurse and that the cost of this technology when used with burn patients may not be justified (44,45). The PCA administration of potent, short-acting opioids (e.g., alfentanil, remifentanil) for procedural analgesia may also have a useful role in burn analgesic management, but is yet to be investigated. Finally, oral transmucosal administration of opioids has been reported in burn patients (46) and appears to be particularly advantageous in those patients without IV access and in children.

Nonopioids

The list of nonopioid analgesics in widespread use for the treatment of burn pain is currently limited, although not without potential benefit. Oral nonsteroidal antiinflammatory drugs and acetaminophen, as outlined previously, are only mild analgesics that exhibit a ceiling effect in their dose-response relationship, rendering them unsuitable for the treatment of typical, severe burn pain. However, they are of benefit in treating minor burns, particularly in the outpatient setting. Topical applications of nonsteroidal antiinflammatory drugs on burn wounds can theoretically reduce nociception at the injury site with minimal systemic uptake (47), yet do not result in significant analgesia (48). The opioid agonist-antagonist drugs (e.g., nalbuphine, butorphanol) produce mixed actions at the opiate receptor level, theoretically providing analgesia (agonist property) with lesser side effects (antagonist properties), but also exhibit ceiling effects. Although studies have shown this class of drugs to be effective in treating burn pain (49), experience with them is both limited and suggestive of efficacy in patients with only relatively mild burn pain.

Antidepressants, anticonvulsants, and clonidine have been proposed as potential analgesic agents for burn pain (50) based on their known mechanisms of action in other pain states, yet have not been studied in the setting of burns. As neuropathic pain can occur in patients with healed burns (11), these agents may have specific application in this fortunately uncommon setting.

Anxiolytics

Current aggressive therapies for cutaneous burn wounds, together with the persistent and repetitive qualities of background and procedural pain, make burn care an experience that is likely to engender anxiety in both adult and pediatric patients. It is also recognized that anxiety can exacerbate acute pain (12). This has led to the common practice in U.S. burn centers of using anxiolytic drugs in combination with opioid analgesics (51). Intuitively, this practice is particularly useful in premedicating patients for wound care, because of the anticipatory anxiety experienced by these patients before and during debridement. Although previously shown that benzodiazepine therapy improves postoperative pain scores in nonburn settings (52), it has been recently reported that low-dose benzodiazepine administration significantly reduces burn wound care pain reports (53). It appears that the patients most likely to benefit from this therapy are not those with high trait (premorbid) anxiety, but rather those with high state (at the time of the procedure) anxiety or those with high baseline pain scores.

Anesthetics

Inhaled nitrous oxide is an analgesic agent safe for administration by nonanesthesia personnel. It provides safe and effective analgesia without loss of consciousness for moderately painful procedures in other health care settings and is also a commonly used, although less well-studied, agent for the treatment of burn pain (54,55). It is typically used as a 50% mixture in 50% oxygen and is self-administered by an awake, cooperative, spontaneously breathing patient via a mouthpiece or mask. A secondary benefit of nitrous oxide use, like that of PCA opioid administration, is the element of control given to the patient for his or her care. Nitrous oxide is less useful with critically ill or uncooperative patients. It has also been implicated in a small, but measurable, incidence of toxicity issues (e.g., spontaneous abortion, bone marrow suppression) to patients or staff exposed for prolonged periods (56,57), although not in the setting of burn pain treatment.

Although it is obvious that general anesthesia is required for the excision and grafting of deep burn wounds, a small population of patients requires specific wound care procedures on a scale well below that of surgical burn care, but that are difficult to perform on a conscious patient. These procedures include (a) the removal of hundreds of skin staples from recently grafted wounds; (b) meticulous wound care of recently grafted and often tenuous skin on the face or neck; and (c) wound care procedures in variably cooperative children. Historically, IV or intramuscular ketamine has been used for these procedures (58,59), and, more recently, oral ketamine use is described for pediatric burn patients (60). However, ketamine use is limited by the potential risk of associated emergence delirium reactions (5% to 30% incidence), particularly in the elderly.

The extension of full anesthetic care capabilities outside of the operating room and into the burn unit has been implemented in some specialized burn centers with apparent success (43,61). This has been facilitated by the introduction into clinical anesthetic practice of a variety of drugs with a rapid onset and short duration of action, a more rapid awakening and recovery, and fewer associated side effects, which are ideal qualities for agents to be used for procedural burn wound care. These agents include IV propofol and remifentanil and inhaled sevoflurane. Propofol is particularly advantageous and can be titrated to effect both in terms of level of consciousness and duration of action using continuous IV infusion techniques. The provision of brief, dense analgesia and anesthesia in a comprehensively monitored setting by individuals specifically trained to provide the service appears safe and efficient, both in terms of allowing wound care to proceed rapidly under ideal conditions for patient and nursing staff, and in terms of cost-effective use of the operating room only for true surgical burn care procedures.

Local anesthetics are of obvious use in regional blockade for wound care procedures, but have also been used for burn pain analgesia as a topical gel or IV infusion. Topical local anesthetic use on the burn wound is controversial. Prilocaine-lidocaine cream (EMLA) has no effect on burn pain in volunteers (62); however, topical 5% lidocaine applied at 1 mg per cm^2 offers analgesic benefit without associated side effects (63). Topical lidocaine use is significantly tempered by reports of local anesthetic- induced seizures caused by enhanced systemic absorption at the open wound site (64). The analgesic benefit of an IV lidocaine bolus (1 mg per kg) and 3-day continuous infusion (40 mg per kg per minute) has also been reported in acute burn injuries (65), although whether its mechanism is caused by antiinflammatory or analgesic actions is unclear (50). Neuraxial administration of local anesthetics (or opioids, or both) via epidural catheter would seem to be of benefit in patients with lower extremity burns, resulting in both analgesia (particularly during procedural burn care) and sympathectomy (of theoretical benefit to wound healing). However, such use has only been reported anecdotally (66). A major drawback of this technique is the use of an indwelling catheter in patients densely colonized with infectious organisms at the wound site, thus increasing the risk for epidural abscess formation (67).

Background Pain Management

Because background pain is relatively constant, it is best treated with mild to moderately potent analgesics administered so that plasma drug concentrations remain relatively constant throughout the day. Examples include the continuous IV infusion of fentanyl or morphine (with or without PCA), the oral administration of long-acting opioids with prolonged elimination (methadone) or prolonged enteral absorption (sustained-release morphine, sustained-release oxycodone), or oral administration on a regular schedule of short-acting oral analgesics (oxycodone, hydromorphone, codeine, acetaminophen). Background pain decreases with time as the burn wound (and associated donor sites) heals, so that analgesics can be slowly tapered (in the absence of significant analgesic tolerance).

Procedural Pain Management

In contrast to background pain, procedural pain is significantly more intense, but shorter in duration; therefore, analgesic regimens for procedural pain are best comprised of moderately to highly potent opioids that have a short duration of action. IV access is helpful in this setting, with ketamine and short-acting opioids (fentanyl, alfentanil) offering a potential advantage over longer-acting agents (morphine, hydromorphone). In the absence of IV access, orally administered opioids (morphine, hydromorphone, oxycodone, codeine) are commonly used, although their relatively long durations of action (2 to 6 hours) may potentially limit postprocedure recovery for other rehabilitative or nutritional activities. Oral ketamine (60), oral transmucosal fentanyl (46), and nitrous oxide (54,55) are agents of particular use when IV access is not present, because of their rapid onsets and short durations of action. Finally, when a particularly painful dressing change or one that requires extreme cooperation in a noncompliant patient (e.g., face debridement in a young child) is anticipated, the provision of brief general anesthesia in the burn unit setting has been shown to be safe and effective (44,61).

Postoperative Pain Management

Postoperative pain deserves special mention because of the increased analgesic needs that should be anticipated following burn excision and grafting. This is particularly true when donor sites have been harvested, as these are often the principal source of increased postoperative pain complaints, rather than the grafted burn. Typically, this increased analgesic need is limited to 1 to 4 days following surgery before returning to preoperative levels.

NONPHARMACOLOGIC APPROACHES

Cognitive Interventions

The application of cognitive-behavioral interventions has been reported more in chronic than acute pain (68,69). However, such techniques have been also applied to a number of types of acute pain, including that from rectal examinations (70), surgery (71), and dental work (72). Only a handful of studies have looked at the use of cognitive approaches with burn pain (72). Certainly, however, the work that has been done with other types of acute pain is applicable to patients with burn pain.

Patients vary in the manner in which they respond to stressful medical procedures. Whereas some patients seek out as much information as possible, others would just as soon leave their care to health care professionals (73,74). In applying cognitive interventions to burn patients, it behooves the clinician to be aware of how they cope with stressful medical procedures. Paramount to such thinking is whether the patient will approach procedures with a tendency toward cognitive avoidance, in which case they will distract or dissociate themselves from painful stimuli. This is in contrast to patients who tend to respond to acute pain by focusing on the procedures. Such patients may take a hypervigilant stance toward pain and may find distractions difficult.

Patients who tend to respond to acute pain with avoidance will likely benefit from distraction. In the burn unit, simple distraction is more likely to be of benefit with brief procedures, such as blood draws or line placements. Children at certain development levels may benefit by not seeing their wounds or by being engaged by the clinicians. Such distraction is less effective with older children or adults during the more extensive wound care procedures. In such instances, engaging patients in deep relaxation with distracting imagery will likely be more useful. Although a form of distraction, relaxation and imagery techniques are far more extensive and require substantially more training time for both patients and staff.

Patients who must focus their attention on medical procedures are usually poor candidates for distraction techniques. Such patients may benefit by reappraisal techniques. Rather than focusing away from pain, reappraisal techniques might encourage patients to attend to their nociception. They can then be encouraged to differentiate sensory from affective components of pain as well as evaluate the meaning of the sensation. As is the case with chronic pain, patients may benefit from being taught to differentiate “hurt from harm” with respect to their pain sensations (75). It is also useful to teach patients that increased pain sensation is usually a positive sign with respect to burn wound healing. Specifically, full-thickness burns often destroy nerve endings and the capacity for nociception. As burn wounds heal, skin buds emerge that are highly innervated and sensitive to pain and temperature. Teaching patients the latter two principles will likely be useful to them independent of their cognitive styles in response to acute pain.

Preparatory Information

Preparatory information involves providing patients with information about impending procedures as a way of mitigating pain and anxiety. Such interventions have been found to enhance pain control with acute pain from a variety of different procedures (76). Patients may be provided with preparatory information (what they can expect to occur mechanically during a procedure) or sensory information (what they will likely feel). The use of preparatory information has not been studied with burn patients, but evidence suggests that it can be useful with a variety of medical procedures such as cardiac catheterization, endoscopies, cast removal, and surgery (71,77,78 and 79). Unfortunately, burn injuries often do not lend themselves to such interventions. Certainly, it is not possible to anticipate that a burn injury will occur, and medical procedures are often performed quickly, and in an invasive matter. There is little time to prepare patients, and this can be particularly difficult for children.

At least two phenomena are associated with burn care that lend themselves well to preparatory information. First of all, nociceptive input often increases after the time of the initial burn injury. As mentioned earlier, full-thickness burn injuries may not be that painful, whereas healing injuries with new skin buds may be particularly sensitive. Patients can be warned accordingly. Also, patients often show periods of delirium on the intensive care unit, a clinical phenomenon that can be frightening to both patients and their family members. Letting them know in advance that such confusion is a common and usually benign occurrence can mitigate subsequent anxiety.

Irrational fears related to the use of opioid analgesics can also be minimized through preparatory information. Patients may believe that pain medications lead to addiction or are a sign of weakness. Information about the negligible rates of opioid addiction among burn patients can be useful in this regard. Also, it is useful to let the patients know that good analgesia likely promotes recovery. Our research indicates that high levels of pain are one of the most significant predictors of posthospital adjustment problems (15).

Behavioral Interventions

The application of behavioral principles to burn pain care can be divided into classical (stimulus) and operant (respondant) strategies. Stimulus conditioning applications have to do with the patient's state before wound care. Certainly, decreasing the patient's level of arousal through relaxation training, or any other means available, can minimize the ensuing cycle between anxiety and nociception. With children, the stimulus context of painful procedures can be particularly relevant. Children (and many adults) often show heightened anxiety and fear just by being exposed to the stimuli associated with painful procedures (e.g., nursing scrubs, procedures rooms, and so forth). If the threatening nature of the wound care environment can be reduced, pain control can be enhanced by virtue of stimulus-response principles. As an example, some children's hospitals have instituted the creative approach of having a magnetic resonance imaging scan tunnel appear as a cave in a jungle environment (rather than the morguelike drawer such equipment more typically seems to resemble).

Operant (reinforcement) principles can be applied to burn pain management in several ways. The first application has to do with medication scheduling. The tendency in many acute care settings is to medicate patients on an as-needed schedule. Certainly, the notion of waiting until the patient hurts does not make sense from a pharmacologic perspective (2). However, operant principles would also suggest that as-needed medication schedules reinforce patients for complaining of pain both in terms of the euphoria-producing properties of opioid analgesics and the attention received from caregivers. Providing opioid analgesics on a regular schedule that reflects their pharmacokinetic properties minimizes the potential for operant factors to exacerbate the pain problem.

The importance of a regular drug schedule is particularly salient to patients with substance abuse histories. Such patients may demonstrate frequent pain complaints or drug-seeking behaviors on the burn unit. The tendency of such patients to approach multiple caregivers for analgesics has the potential to create staff-splitting and resentment toward the patients. Furthermore, the burn unit staff may hold punitive attitudes about the patient's substance abuse history, the excessive nature of his or her pain complaints, or both. Regularly scheduled medications often minimize such problems. Also, channeling communications and negotiations about changing doses or types of medications through a single caregiver also serves to improve the behavior of such patients.

Occasionally, a patient's presentation might dictate that the burn staff abandon an acute care model in favor of an operant-based model of pain management. Effective burn team members are trained to be highly attentive to the pain complaints of their patients. However, occasional patients may show excessive complaints based on such factors as strong dependency needs or somatic tendencies. As in any case, it is important that such patients receive adequate doses of analgesics.

However, operant approaches, in which discussions of pain are minimized and patients are distracted from their complaints (75), may become the prominent intervention.

The quota system (80) represents another useful application of operant principles to burn care. The repeated, invasive nature of burn care has the potential to create a state of learned helplessness in patients (81). The quota system uses rest as a reinforcement for activity and keeps activity levels well within the patient's level of physical endurance. Ehde and colleagues have reported that with overwhelmed, seemingly unmotivated patients, it is useful to encourage the burn team to reduce their overall demands, take baseline behaviors, and *gradually* increase demands on what the patient's baseline behavior suggests is within the range of tolerance. It is hoped that such interventions create a sense of mastery in patients as they are able to see steady improvement in their activities.

A final application of operant principles is to avoid inappropriately rewarding escape behavior during procedures. With children, it is particularly essential to do all the interventions possible to enhance procedural pain control, such as adequate analgesics and anxiolytics, sufficient emotional preparation, optimizing the wound care environment, and including parents when appropriate. Children also do better if allowed to have control of their wound care procedures, perhaps by doing their own dressing removal (81). However, there are times when it is important to set firm limits during wound care by following through with procedures; otherwise, pain behaviors can be exacerbated. Establishing this balance can certainly be a challenge for caregivers.

Hypnosis

A surprising number of reports have been published on hypnosis and burn pain. In 1987, there were at least 14 papers published on this subject (82), and a number of new reports have appeared since then. Further, a number of additional reports have focused on the use of hypnosis to treat complications from burns other than pain. Although a number of reports have been published, the vast majority of them have been anecdotal. However, the controlled studies that have been published also support the efficacy of this intervention (82,83).

Patterson and colleagues (84) have proposed four reasons why burn patients appear to be such good candidates for hypnotic-based pain control interventions. First of all, because burn patients are in high levels of pain, they are motivated to engage in hypnosis, a technique that they might ordinarily resist. In support of this, patients with high levels of initial pain seem to show a better analgesic response to hypnosis (85,86). Second, patients in trauma care may be more cooperative because of the regression that might often be a normal reaction to trauma care (i.e., a willingness to allow others to take care of one). Third, the dissociation that may accompany a burn injury may also be a factor that moderates hypnotizability. Certainly, dissociative tendencies have been related to hypnosis (87). Finally, and on a more simplistic level, clinicians are able to predict that patients will show more pain during procedures, and hypnosis is nicely suited for preparing a patient for a future, adversive event.

Ewin (88,89) has published anecdotal data to suggest that hypnosis used early in burn care can not only enhance pain control, but might even facilitate wound healing. This work has received a great deal of attention as well as criticism because of the lack of controlled studies to support the underlying premise (90). It is hoped that the question of whether hypnosis can have such powerful effects when used early in care will be the subject of a controlled study. It would be of great utility to determine what effects aggressive pain interventions of any modality have when used early in the patient's care.

SUMMARY

Effective treatment of burn injuries requires an appreciation of the unique patterns of nociception caused by this trauma and their interaction with psychological factors. We recommend that aggressive use of opioid analgesics tailored to the nature of the pain (e.g., procedural, background, postoperative) serve as the cornerstone of a multifaceted approach to burn pain. Procedural pain often involves consideration of a variety of supplemental pharmacologic approaches, ranging from benzodiazepines to mild sedation. Nonpharmacologic approaches should be woven into the structure of burn care, with more time-consuming psychological approaches instituted with the failure of opioid analgesics. The undertreatment of burn pain remains an unfortunate reality, particularly because adequate analgesia may facilitate recovery, and posthospital adjustment, as well as represent a more humane course of treatment.

*Supported by grant GM 4275-06 from the National Institutes of Health.

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CHAPTER 43

Posttrauma Pain

W. Thomas Edwards

This chapter focuses on the issues of pain after major trauma. In some ways, the problems of pain after trauma are no different from other acute pain states (see Chapter 41 and Chapter 42). Tissue damage leads to nociception and thence pain and suffering. An easy intellectual connection is that greater tissue damage leads to greater pain. Although this is certainly true, as evidenced by correlation of the size of a burn with pain reports (1), we must keep in mind that pain is an *experience* (2), and the entirety of the pain experience occurs in the context of what is usually a catastrophic event to the individual who suffers major trauma. The patient who is injured brings to pain treatment all those issues that affect anyone undergoing *elective* surgery, including fear and anxiety about the events associated with the trauma, as well as concerns about the recovery and the ability to function after major trauma. There may be issues of guilt, loss of loved ones, and other issues that will play an important role in how effective pain management will be. A useful management plan requires an awareness of and sensitivity to these issues.

Pain will be a constant presence from the time of injury through correction of those injuries (often surgically) and through the time of rehabilitation to the restoration of normal function. In fact, a useful approach that we take to the categorization of pain and its treatment after trauma is according to the stages of trauma management (Table 43-1). Other categorizations may lead to different approaches and to subtly different understanding of the value of these approaches (Table 43-2 and Table 43-3). Categorization schemes are not mutually exclusive, and understanding a problem in pain management may turn on how one sees the problem in context. So, for example, the management of pain of chest wall trauma as an isolated injury will be very different depending on whether the patient is in the emergency or the acute phase of trauma management and on whether it is pain at rest (background pain) or pain associated with chest physiotherapy (incident pain).

Phase of trauma care	Time course of stage
Emergency	*Begins* at time of injury *Ends* when resuscitation and emergency stabilization of wounds and/or life-threatening injuries are complete
Acute or healing	*Begins* at completion of emergency stabilization *Ends* when all wounds are closed and surgical treatment of injuries is complete
Rehabilitation	*Begins* when surgical treatment of injuries is complete *Ends* with restoration of acceptable levels of functioning

TABLE 43-1. Pain categorization by phases of trauma care

Injury pattern	Description
Regionalized	Injuries are confined to one or a limited number of body regions (e.g., leg and knee).
Broadly regionalized	Peripheral injuries are bilateral or injuries involve trunk (chest and abdomen). Injuries may be widely separated but limited in number (e.g., scapula and pelvis fractures).
Generalized	Injuries involve large regions, are complex (e.g., large burn with blunt trauma), or involve the central nervous system.

TABLE 43-2. Pain categorization by injury pattern

Circumstance	Description
Background pain	Pain is always present or occurs with ordinary activity such as moving in bed.
Breakthrough pain	Pain appears spontaneously from a well-controlled background. Pain may be related to more vigorous ordinary activity such as walking or mild exercise.
Incident pain	Pain occurs associated with a specific activity such as wound manipulation or physical therapy.

TABLE 43-3. Pain categorization by circumstance

Both background and incident pain may be poorly localized when injuries are widespread (generalized pain), involving multiple organ systems or anatomic locations. Blunt trauma with an associated burn or chest, pelvic, and lower extremity fractures are good examples of clinical states leading to generalized pain states.

Pain may be well localized or at least confined to a limited region of the body (regionalized or broadly regionalized pain). Both background and incident pain under these circumstances may be managed by thoughtful application of the techniques of regional anesthesia (see Chapter 102).

PROBLEMS POSED BY TRAUMA IN DEVELOPING PAIN MANAGEMENT PLANS

Trauma poses particular problems in developing pain management plans, including the following:

- *Anatomic derangement may preclude certain approaches to pain treatment.* These might include such examples as four extremity fractures that prevent the patient from using a patient-controlled analgesia (PCA) demand switch, or burn or soft tissue loss over the back that would interfere with placement of an epidural catheter. Spinal column injury constitutes a special consideration and is covered separately later in this chapter.
- *Pain levels vary widely and are highly incident dependent.* Unstable fractures, for example, can cause high levels of pain over a perfectly well-controlled background pain when the patient is subject to routine nursing care such as turning from side to side. The need to manage open wounds with dressing changes or hydrotherapy (water pick) constitutes another of these types of problems.
- *Physiologic derangement may cause difficulty in pain management.* This problem is common in the emergency phase of trauma care, when resuscitation is taking place. Patients who are actively bleeding or whose intravascular volume status is uncertain present difficult challenges in pain management, especially when they are conscious. A patient who is sustaining blood pressure in part because his or her own intrinsic catecholamine output is high from high levels of pain may drop his or her blood pressure precipitously when pain is relieved.

PAIN MANAGEMENT AND THE PHASES OF TRAUMA CARE

The phases of trauma care describe the clinical course of a patient from the time of the injury until the return to normal function (see Table 43-2). Pain management plans need to be formulated to meet changing patient needs within each of these phases as well as during movement from one phase to the next. Movement through the phases may not be monotonic (i.e., patients may enter a later phase and then require additional surgery that sets them back to an earlier phase). Physiologic responses to treatment during movement among phases may be influenced by treatments used before (e.g., opioid tolerance). The phase of trauma care is a useful context in which to consider pain management plans as they are being formulated.

Emergency Phase

Pain during the emergency phase occurs in an extremely stressful situation and is caused by direct massive and prolonged nociceptive stimulation originating in damaged tissue. During this phase, the goal is always stabilization of the injured patient, and treatment is directed toward preservation of life and function. The duration of this phase is variable, and it persists until open wounds are stabilized and life-threatening injuries are controlled. Modalities of pain control are dependent on the physiologic condition of the patient and the experience of personnel in any given institution. Some pain relief is obtained by treating the underlying result of injury in this phase–for example, relieving a hemopneumothorax or stabilizing an unstable fracture. Often multiply injured patients require emergency major surgical intervention in this phase, and the issue of pain relief becomes moot in the face of need for a general anesthetic.

In managing pain during the emergency phase, anxiety and fear must be carefully assessed. Reassurance and information may help considerably in managing agitation often assumed to be a pain response during this phase. Often an uncooperative patient has consumed alcohol or some other mood-altering substance before trauma. Studies at the University of Washington Harborview Medical Center and the Maryland Shock Trauma Center found that 35% to 41% of all multiple trauma admissions to the emergency department were positive for alcohol (3), with a high percentage of these patients meeting criteria for alcohol dependence (4). A pattern of repeated injuries is strongly correlated with alcohol dependence (5). The presence of mood-altering drugs must be taken into account in planning any pain management scheme, as it may herald a difficult pain management course. Tolerance to opioids is likely to be a problem in this setting, and when substance abuse is part of the presenting history, planning for pain management must include prevention of drug withdrawal as well.

The provision of analgesia during the emergency phase of trauma care is not contraindicated once the urgent surgical and neurologic evaluations of the trauma patient are performed. The improved cooperation of the injured patient that can ensue from providing adequate pain relief may facilitate completion of the indicated examinations. Once the decision is made to treat the patient's pain, adequate monitoring of vital signs and adequacy of ventilation must be continued, especially if the patient is moved out of an emergency resuscitation area. A subtle decrease in intravascular volume can dramatically augment response to opioids. While patients undergo additional workup in radiology, computed tomography, or magnetic resonance imaging, for example, they should be attended by personnel able to detect, evaluate, and respond to a shifting level of alertness.

Systemic opioids and some regional anesthesia techniques will be the mainstay of pain therapy during the emergency phase of care. As much as possible, systemic therapy should be patient directed because of the widely varying pain levels experienced by patients after a given injury. For opioids, the intravenous route is best. Opioid loading to patient satisfaction requires attention, repeated evaluation of pain level, and repeated treatment. Once a satisfactory degree of pain relief is achieved, intravenous PCA will be useful in maintaining analgesia if the patient can interact with the PCA device (6). Although shorter-acting high-potency opioids such as fentanyl may have a place, especially during the early phase of emergency stabilization, more definitive therapy using morphine, hydromorphone, or meperidine will prove easier to manage. Long-acting opioids such as methadone or levorphanol have no routine place in this phase of care.

Most often during the emergency phase of care, particularly after multiple trauma, it is difficult to obtain definitive information on the integrity of the spine. This lack of “spine clearance” most often precludes the use of central conduction analgesia. Peripheral regional analgesia, however, can be very useful in selected patients (see Chapter 102). Those techniques include isolated peripheral nerve blocks [e.g., femoral nerve block for dislocated patella (7), intercostal blocks for a limited number of fractured ribs] and blocks of the major neural plexuses (brachial, lumbar) for more extensive unilateral limb injuries. Table 43-4 illustrates useful approaches to pain management during emergency care of the trauma patient. Breakthrough pain is usually not considered as a separate issue during this phase, and therapy is directed exclusively to background and incident pain.

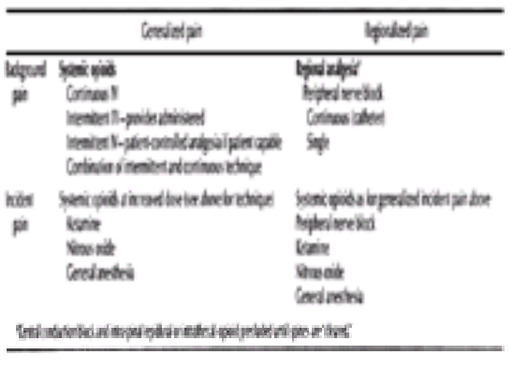

TABLE 43-4. Approaches to the management of pain in the posttrauma emergency phase

Acute or Healing Phase

The beginning and end of the healing phase of trauma care are set out in Table 43-1. It may very well begin while the patient is in the intensive care unit being ventilated. Pain management techniques for critically ill patients during this phase of trauma care may require imaginative approaches that combine regional and systemic analgesia techniques (8). This phase may continue for weeks or months, depending on the nature of the injuries. There are frequently multiple surgical procedures during this phase, especially to correct orthopedic injuries, and the problems of pain control change to considerations of postoperative pain during these periods. Approaches to pain management during the healing phase are most easily conceptualized by thinking of the time after all surgical procedures have been completed and before the period of rehabilitation begins.

One of the hallmarks of this phase of trauma care is background pain, often punctuated by breakthrough pain. Incident pain is most often procedure-related, frequently associated with mobilization procedures, and sometimes occurs more frequently than daily if twice or three times daily care of open wounds is necessary. One of the goals of therapy is the provision of adequate baseline analgesia by a technique or combination of techniques with adequate flexibility to treat breakthrough pain. A second equally important goal is to provide brief, intense analgesia for “incidents” that does not leave the patient oversedated and uncooperative for an

extended period afterward.

A gradual decrease in a patient's ability to tolerate procedures may develop, although the pain reports may not reflect this. This is the time to begin to help the patient deal with the emotional impact of the injury (9). It is important to be alert to the development of the early signs of posttraumatic stress disorder (see Chapter 26).

When behavioral issues such as failure to cooperate with scheduled treatments, acting out, or conflict with nursing staff develop, the advice and help of a behavioral specialist will be needed. Pharmacologic management should involve such techniques as non–pain-contingent timed administration of analgesics. Supportive psychotherapy is often valuable in helping patients deal with many aspects of trauma. Patients often need a route to uncovering their feelings about loss of a body part and alteration in body image. This therapy can be coupled with cognitive pain control and coping skills training, and even with techniques of hypnosis (10,11) (as described in Chapter 42, Chapter 91, and Chapter 92).

Longer-acting agents should be incorporated into the pharmacologic plan when the patient's opioid requirement has been established by use of a flexible demand technique such as intravenous PCA. This is the time when sustained-release opioids and long-acting agents become most useful in the management of background pain. Sustained-release opioids (morphine, oxycodone) and methadone or levorphanol are useful agents for oral administration during this phase. Analgesic agents with high bioavailability and short duration of action should be used for the management of incident pain. When intravenous administration is no longer the ideal approach, oral oxycodone or hydromorphone can be useful for incident pain management. Oral transmucosal fentanyl citrate provides another option for brief intense analgesia. Oral ketamine has been used successfully (12,13). Table 43-5 illustrates analgesic approaches that are useful during this phase.

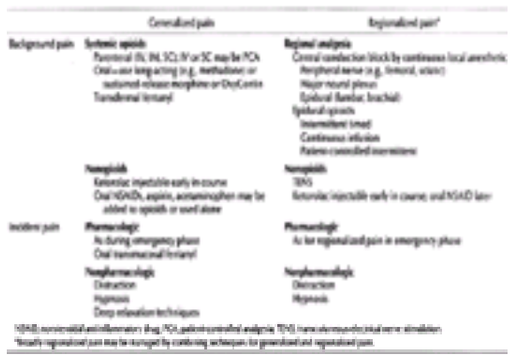

TABLE 43-5. Approaches to the management of pain in posttrauma healing phase

If regional analgesia techniques are used, they are best used early in this phase and after the multiple surgical procedures that occur during this period. It is not difficult to maintain thoracic or lumbar epidural catheters for extended periods in hospitalized patients (14), and the techniques of epidural opioid administration are effective for both background and incident pain when they are correctly applied (see Chapter 103).

Rehabilitation Phase

The length of the rehabilitation phase is indeterminate. Trauma patients will have been fully mobilized and in all cases will be out of an acute-care hospital setting. The character of the pain experienced during this phase is usually described as deep and aching, perhaps akin to the pain of arthritis. Pain tends to become progressively more regionalized during this phase and the problems of pain management more focused. Chronic pain states can begin to develop during this phase. Opioid therapy is rarely necessary for the entirety of this phase but may be necessary in the early part, especially for those patients whose prolonged use of opioids during the healing phase has rendered them physiologically dependent on opioids. Patients who had a problem of opioid dependency before their injury will need to have that problem addressed during this phase.

A weaning schedule from potent opioids is usually developed for patients with physiologic opioid dependencies during this phase. Time-contingent opioid administration using a long-acting agent on a gradually declining dosage scale can usually be developed. The time required for complete cessation of opioid administration varies depending on the starting dose. A step-down schedule of 10% every 3 to 4 days usually is tolerated reasonably well, but it is sometimes necessary to go more slowly, reducing the dose on a weekly schedule. Although it was not originally developed for this application, a pain cocktail strategy (blind dosing) can be used to allay patient anxiety about dose reduction. We routinely use methadone as the opioid in pain cocktails; anxiolytics can be added if necessary. Pain cocktails may also be helpful in the case of a preexisting substance abuse problem or to help in the management during this phase of some behavioral issues such as manipulative behavior.

Background pain management is best accomplished with nonsteroidal antiinflammatory agents, acetaminophen, or if necessary, a weak opioid such as codeine. Pain associated with procedures, physical therapy, joint manipulations and the like is treated exactly as it would be during the healing phase, with a short-acting agent such as oxycodone. The general approach is contained in Table 43-6.

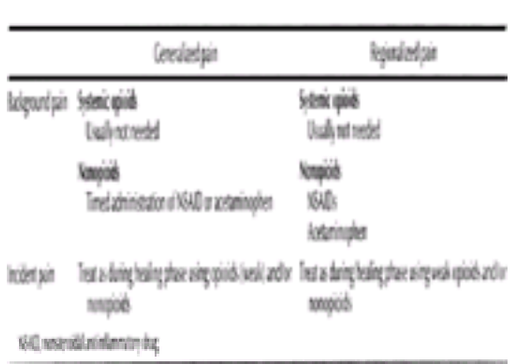

TABLE 43-6. Approaches to the management of pain in posttrauma rehabilitation phase

PROBLEM OF NEUROPATHIC PAIN

A particular type of background pain, often burning in nature, may be associated with trauma to some part of the nervous system, either peripheral or central. Various terms have been applied to this condition in the past– *deafferentation pain*, *dysesthetic pain*, and a whole range of terms meaning pain involving the sympathetic nervous system, such as *reflex sympathetic dystrophy.* We have generally chosen to use the more inclusive term– *neuropathic pain*. The problems and management of neuropathic pain and complex regional pain syndromes are covered in Chapter 19, Chapter 20, and Chapter 23.

In the setting of multiple traumas, neuropathic pain often presents early in the course but is usually delayed in onset by days or weeks after injury. It is important to distinguish this pain from pain arising in other damaged tissue (nociceptive pain), as neuropathic pain is frequently unresponsive to opioids. Management with tricyclic antidepressants (amitriptyline, nortriptyline, others), antiseizure medications (gabapentin, lamotrigine, carbamazepine, others), sodium channel–blocking agents (lidocaine, mexiletine), or combinations of these may be indicated (15,16) (see Chapter 85 and Chapter 86).

Some of these neuropathic pain states respond to transcutaneous electrical nerve stimulation (17,18 and 19). The perception of electrical stimulation is required to generate pain relief: An anesthetic region cannot be the site of stimulation. Long-term management of brachial plexus avulsion pain is a particularly vexing problem in

chronic pain management. A variety of neurosurgical procedures can be tried if pharmacologic techniques fail. Limb amputation never relieves this type of pain (20).

Although pain arising from tissue injury progresses through the three phases (emergency, healing, rehabilitation) described above, neuropathic pain does not. It frequently persists as a chronic pain state and is thus one of the points at which acute pain and chronic pain management may converge.

EPIDURAL ANALGESIA AFTER TRAUMA

A common request that comes from our surgical colleagues is to place an epidural catheter for a patient who has sustained multiple trauma, especially blunt trauma to the chest with simple multiple rib fractures or flail chest. Because it is perceived as being more specific than systemic analgesia, it is thought to be more desirable than systemic analgesia. It has often been our practice to optimize systemic analgesia before initiating epidural analgesia. Earlier invasive intervention really may be valuable, however, and some pain consultants have begun to be much more aggressive about epidural analgesia after trauma (21). There are data that indicate an improvement in outcome with epidural analgesia versus systemic analgesia in chest wall trauma (22,23 and 24). There are no data to indicate that epidural analgesia is preferable to any other form of regional analgesia, such as paravertebral (25) or intercostal (26) block, nor are there any data to indicate whether there is a critical number of fractured ribs or a size of a flail segment at which the benefits of epidural analgesia are specific to the technique. Epidural analgesia does appear to be superior to interpleural analgesia for blunt chest trauma (27).

Many different techniques can be used to provide analgesia, including continuous-infusion local anesthetic (18), continuous-infusion opioid (28), intermittent opioid by timed administration (18), and intermittent opioid by patient administration (29). Details of these administration techniques are covered in other chapters. Epidural techniques can be combined with one another, and continuous-infusion local anesthetic can be combined with systemic opioid analgesic techniques. Epidural opioid techniques should usually not be combined with systemic opioid techniques because of the risk of accentuating opioid central nervous system effects.

There are several common clinical scenarios wherein the request for epidural analgesia comes when chest trauma is part of the multiple trauma complex:

1. The patient has been extubated after emergency stabilization and is now showing increasing difficulty maintaining oxygenation because of inability to cough and clear secretions.
2. The patient is still intubated and is oxygenating well but cannot meet extubation criteria (vital capacity, inspiratory force, or both) because of pain of fractured ribs. Frequently these patients are judged to become excessively sedated with systemic opioids.
3. The patient is intubated and still requires ventilation but becomes excessively agitated when routine nursing care is attempted. This is thought by nurses and the primary team to be because of pain.

The algorithm presented in Table 43-7 provides the basis for decision making in each of these clinical situations.

TABLE 43-7. Indications for the use of epidural analgesia in critically ill patients after major trauma

Contraindications to the use of epidural analgesia after trauma are very similar to contraindications in other surgical settings. The following are the principal differences that are presented by the unique clinical setting of trauma:

A. *Lack of consent*. Initiation of epidural analgesia requires that consent be obtained. A patient's specific refusal of consent can never be overridden unless the patient is legally determined to be incompetent to give consent. A physician's judgment that the procedure is indicated in a circumstance in which the patient or his or her agent specifically declines consent for an invasive procedure cannot override the patient's wishes.
B. *Central nervous system trauma*
   1. Brain. Penetrating trauma to the brain or the brainstem, raised intracranial pressure, and bleeding into the cranial vault are all relative contraindications to instrumentation of the spinal epidural space because of both the risk of accidental dural tap and the fact that small changes in the volume of contents of the spinal canal may cause large changes in the intracranial pressure when intracranial compliance is low. Epidural analgesia has been used successfully and safely in the presence of closed-head injury when intracranial pressure is low (30).
   2. Spinal cord. Space-occupying lesions in the spinal canal such as epidural or intraparenchymal hemorrhage or the presence of localized swelling of the cord can be associated with sharp and prolonged rises in pressure in the spinal canal during injection of fluid and can result in markedly diminished blood flow to the spinal cord. Instrumentation of the spinal canal is contraindicated under these circumstances. The ability to judge that the spinal cord function is intact, or at least to define and document the degree of specific neurologic impairment, is necessary before such instrumentation.
C. *Spinal skeletal trauma present.* It is essential that the spinal column be documented to be intact before instrumentation of the spinal epidural space at any level. If trauma to the spinal column has occurred and it is the judgment of the consultant that the risk/benefit relationship is such that selective regional analgesia should be provided, that must be documented. The spinal canal should never be instrumented in the absence of documentation regarding trauma to the skeletal structures.
D. *Sepsis and infection.* Evidence of septicemia or apparent infection at the proposed epidural insertion site is usually considered an absolute contraindication. There may be a relative contraindication for patients with large, infected wounds because of the risk of bacterial showers into the circulation during wound manipulation (31). Fever otherwise unexplained in a multiple trauma victim is not necessarily a contraindication.
E. *Bleeding diatheses.* There are no absolutely incontrovertible data on when the risk of epidural hematoma associated with epidural analgesia is unacceptably high. Evidence of circulating anticoagulant present or severe dilution-based factor deficiency leading to prolongation of prothrombin time or partial thromboplastin time to greater than 1.5 times control is generally considered unacceptably high risk. Platelet counts commonly fall after trauma. Most clinicians would want to know that a falling platelet count had reached a nadir. A count of less than 40,000 may (but does not definitely) increase the risk of epidural hematoma formation. Many consultants believe the platelet count should be double this number to be safe. There is no documented correlation between bleeding time and the risk of clinical bleeding, but some prefer to know that the bleeding time is normal to assess adequacy of platelet function, particularly if the platelet count is below 75,000, the patient has received platelet transfusion within 24 hours, or both.

CONCLUSIONS

As with any other acute pain state or set of states, the management of pain after major trauma requires an understanding of the pathology of the nociception and attention to the patient's complaints. An understanding of the natural history of the problems involved in the particular set of injuries helps in the planning of pain treatment strategies to fit the position of the patient in the time course of trauma treatment. Treatment plans must take account of whether one is dealing with the emergency, acute, or rehabilitation phase of care. Management of background, breakthrough, and incident pain in each phase is different and makes use of different pharmacologic “tricks.” Treatment of pain should draw on different strategies of combining systemic and regional analgesia suited to the appropriate phase of trauma care.

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CHAPTER 44

Pain and Its Management in Children

Kenneth R. Goldschneider, Thomas J. Mancuso, and Charles B. Berde

> “Hurting isn't necessary.”
> Sarah Jaye, age 4

Few things stimulate a caregiver's helping instinct more than the pain cry of a child. Organized pain relief for children, however, historically has been hampered by societal and medical misinformation and by the slow and deliberate nature of good basic research. The fields of developmental biology, pain assessment, and treatment have seen tremendous gains. Progress is reflected in the fact that treatment for the pain of infants and children in both acute and chronic settings has become safe and effective. Assessment and measurement of pain in infants and preverbal children continue to be difficult. On the other hand, cognitive-behavioral treatments can be used quite effectively for children undergoing medical procedures as well as in the treatment of a range of acute and chronic pain problems. For many children, fear and anxiety dominate their thought processes regarding medical encounters. Making interactions in medical settings less terrifying for children therefore is an essential component of pediatric pain management. Although the pharmacopoeia of pain control is essentially the same for children as for adults, there are age-related differences in several pharmacokinetic and pharmacodynamic factors. Many of these age-related pharmacologic differences become less important after a year of age. Understanding what is unique and dynamic about the psychological, physiologic, and pharmacologic treatment of pediatric pain is critical to the safe and effective alleviation of pain and suffering in children.

UNDERTREATMENT OF PAIN IN CHILDREN

As recently as the mid-1980s, pediatric postoperative and trauma patients received greatly different pain treatment than did adults with comparable diagnoses (1). At the same time the great majority of physicians responding to a survey in the same geographic region expressed the belief that children felt pain similarly to adults by the age of 2 years (2). Despite this belief, 87% of children in one survey reported unrelieved pain during hospitalization (3).

Furthermore, a comparison of pediatric cardiac patients with adult patients undergoing cardiac surgery revealed a significant discrepancy in the amount of pain medications administered for postoperative analgesia (4).

As the data have accumulated in favor of improved outcomes (5), health care workers are being compelled to make the same use of pain control techniques for children as they do in adults. For example, in 1992, the Agency for Health Care Policy and Research published acute pain management guidelines for children (6). These clinical practice guidelines, titled *Acute Pain Management in Infants, Children and Adolescents: Operative and Medical Procedures and Trauma* , outline four general responsibilities for institutions (Table 44-1).

1. Children and families must be educated about pain relief and their role in assisting with assessment of comfort.
2. Pain assessment and management must be documented.
3. Each institution must adopt a standard of care for pain relief.
4. Institutional quality-improvement programs must include effectiveness of pain relief efforts.

TABLE 44-1. Institutional responsibilities for pain services

To provide care at the level suggested by these guidelines, it is important to understand the neurodevelopment of pain processing in children and infants and the methods by which the expression of pain are measured.

PAIN IN INFANCY

Developmental Neurobiology of Pain

The study of pain in infancy and of the longer-term implications of noxious stimuli has intensified over the past 20 years. Pain plays an important role in learning and neurologic development. Thus, it would be expected that the afferent pathways for pain sensation and perception would develop early in life.

At the time of birth, the nociceptive pathways and connections are well established. In fact, thalamocortical projections begin synapse formation with cortical neurons by 20 to 24 weeks' gestational age, and myelination of afferent pathways to the thalamus is generally complete by 30 weeks. Myelination of thalamocortical fibers is complete by roughly 37 weeks' gestational age. Although afferent nociceptive paths appear well developed by birth, descending control of pain is slower to develop (7).

Primary afferent nerve fibers project to peripheral targets midway through fetal life in rats and in humans. Infant rats show lower- impulse thresholds and more prolonged discharges in primary afferent C and A fibers when exposed to noxious stimuli than do adult rats. In addition, newborn rat pups respond to skin wound with extensive proliferation of A and C fibers in the region of the wound. Functionally, the rat pups display hyperalgesia manifested by decreased flexion withdrawal

thresholds (8). These behavioral and neuroanatomic responses appear to decrease in magnitude with advancing age.

The flexion withdrawal reflex is well developed in neonatal rats and human newborns. Interestingly, younger premature infants exhibit sensitization to repeated noxious stimuli (9). The closer the infants are to full-term gestational age, the more likely they are to habituate to the stimuli, a response characteristic of children and adults. Human newborns receiving repeated heel lancing for blood sampling develop secondary hyperalgesia, a manifestation of spinal plasticity (10).

In a number of studies, the protooncogene c-*fos* has been used as a marker of neuronal activity. In adult animals, noxious stimulation evokes c-*fos* expression in the superficial dorsal horn laminae. Jennings and Fitzgerald showed that even nonnoxious stimulation evokes prominent c-*fos* expression in laminae 1 and 2 in neonatal rats (11). This finding correlates with the findings of Coggeshall and coworkers that neonatal rats have A-fiber light-touch afferent projections to synaptic targets on lamina 1 and 2 dorsal horn neurons (12). The light-touch A-fiber afferents of the adult rat normally synapse in deeper laminae of the dorsal horn, not in the superficial laminae that receive projections from C- and A-delta-fiber afferent fibers that are involved in nociception. In addition, dorsal horn neurons in neonatal animals often show quite prolonged firing after noxious stimulation.

It is unclear how to interpret what the experiments regarding flexion withdrawal reflexes, c-*fos* expression, and A-fiber projection to superficial laminae mean in terms of pain *experience* in the neonate. It would be an overinterpretation to conclude that the neonate is inherently hyperalgesic.

Newborn rats respond with pain-specific behaviors (e.g., paw licking) to inflammatory stimuli, such as formalin. Such behaviors are ameliorated by morphine and appear to be inborn responses, not learned behaviors (13). The morphine-induced decrease in the response to pain is not due to sedation alone. Abbott and Guy found that both morphine and amphetamine produce analgesia, but pentobarbital produces sedation but not analgesia in this model (14). The reader is referred to a thorough review by Marsh and coworkers for a discussion of the ontogeny of opioid systems in newborns (15).

Overall, these results suggest that the neonatal nervous system is well equipped to process nociceptive input. In fact, the above- mentioned studies have been interpreted by some reviewers to suggest that the neonate may feel pain more intensely than older patients do. This finding has relevance to the manner in which we approach pain in the neonatal intensive care units. The relationship between pain and suffering, however, cannot be gleaned from data available at the present time. Comparatively little is known about the supraspinal processing of nociception in neonates, and even less is known about the affective aspect of their pain experiences. We will leave the discussion of the nature of suffering in newborns to others and turn to some of the studies of both short- and long-term consequences of pain in infancy and the role of anesthesia and analgesia for neonatal pain.

Outcome Studies

Short-Term Consequences of Pain in the Neonate

It is well known that opioids (16) and regional anesthesia can be used safely and effectively in neonates. Indeed, surgery performed on inadequately anesthetized newborns, whether premature or full-term, evokes dramatic hormonal and metabolic stress responses that have been associated with hemodynamic instability, catabolism, and poor postsurgical outcomes (17). In some cases, blunting of stress responses may improve outcomes in newborns as they do in adults. With proper expertise, neonates can be safely anesthetized for any type of surgery (18,19). No longer is the performance of surgery in neonates without adequate general and/or regional anesthesia justified.

Circumcision in newborns is often performed without anesthesia. Circumcision performed in this manner produces autonomic instability, manifested as increases in heart rate and blood pressure, hypoxemia, and sleep disturbances (20). Several methods have been studied to reduce the pain of circumcision. Kirya and Werthmann first studied dorsal penile nerve block (DPNB) for neonatal circumcision (21). Since then, the safety and efficacy of DPNBs have been confirmed (22). DPNB relieves the physiologic stress of circumcision in neonates (23). Topical anesthesia with a eutectic mixture of lidocaine and prilocaine (EMLA) appears to provide at least partial anesthesia for newborn circumcision (24). Lander and coworkers found that EMLA was more effective than placebo but less effective than DPNB or ring block (25). Nonpharmacologic measures, including use of a more comfortable papoose board and oral ingestion of sucrose (26), diminish but do not eliminate distress caused by circumcision. A multimodal approach may provide optimal comfort for this common, painful procedure.

Opioids and benzodiazepines are commonly used in neonatal intensive care units both for invasive procedures and to help patients tolerate mechanical ventilation. There is great variation in analgesic and sedative use among neonatal intensive care units (27). Outcome data are sparse and conflicting. A large, retrospective multicenter study focused on patterns of opioid administration in more than 1,000 low-birth-weight infants receiving mechanical ventilation in six different neonatal intensive care units (28). Mean opioid dosing varied 28-fold among units. The authors found minimal differences in outcomes, despite this wide variation. This study was retrospective and uncontrolled and did not examine long-term outcome measures. Thus, it is difficult to draw conclusions from this report regarding risks and benefits.

Potential Long-Term Consequences of Pain in Infants

Previously, a common rationalization for withholding opioids from newborns was that infants would not remember pain and that there were no long-term sequelae of untreated pain in infancy. There have been some recent forays into the long-term outcomes arena. Taddio and coworkers examined responses to intramuscular injections for immunization in cohorts of 4- to 6-month-old boys (29). Two of the study groups comprised infants who had participated as neonates in a randomized, blinded comparison of EMLA with placebo for circumcision. The control group comprised boys who were uncircumcised. Uncircumcised infants cried less and had lower pain ratings by blinded observers. For pain scores, but not cry duration or facial action score, the EMLA group had statistically lower pain ratings than the placebo group. Although these findings are suggestive, they should be interpreted cautiously in view of a potential for confounding factors.

Johnston et al. (30) examined responses to heel-stick procedures in two groups of infants at a gestational age of 32 weeks. The first group comprised relatively healthy babies born within that week. The second group included premature infants born at 28 weeks who had undergone a variety of invasive procedures. There were significant group differences in behavioral and physiologic parameters, both at baseline and after heel lancing. A history of multiple invasive procedures correlated inversely with the behavioral response to the heel-stick procedure. Whether these results reflect the neurocognitive deficits found in former premature infants (31) or a sense of “learned helplessness” is as yet unclear.

Overall, the long-term consequences of untreated pain in infancy remain difficult to quantify but merit further study. Safe and effective treatments are available for many forms of pain. In our opinion, the burden of proof lies with those who would withhold treatment, not with those who would treat pain aggressively.

PSYCHOLOGICAL AND DEVELOPMENTAL CONSIDERATIONS

One of the more challenging aspects of pediatric medicine is the need to adjust one's approach to meet the developmental needs of a particular child. A standard approach to children is insufficient at best and risks alienating both patient and family at a time when maximal cooperation is required. Several generalizations can be made, however, and are included in the following discussion of cognitive and emotional development.

The cognitive development of children was proposed by Piaget to proceed through four stages: sensorimotor, preoperational, concrete operational, and formal operational stages (32). The response to and understanding of pain by children have been discussed in detail elsewhere and are summarized in Table 44-2 (33,34 and 35). In brief, children younger than the age of approximately 2 years interact with their environment in a strict stimulus-response manner and have no sense of permanence, long-term anticipation, or cause and effect. The pretoddler will respond best to cuddling/swaddling, warm environments, soothing voices, and pharmacologic interventions. As the child becomes a toddler, a sense of permanence develops, and the child approaches the world in a strongly egocentric manner. Pain is seen by the child as a punishment, with the magnitude of pain correlating with how “bad” the child is. One must take care not to refer to the toddler as good or bad in the context of a painful procedure. Treatment often focuses on medicines, kissing/ rubbing the injury, and the “magic” Band-Aid. The child is still enmeshed in the ego strength of his or her parents and may benefit greatly from parental involvement. Due to the egocentricity and verbal capacity of the toddler, self-report becomes feasible as a measure of pain and intervention.

Age	Pain interpretation
0–3 mo	No apparent understanding of pain; memory likely but not conclusively demonstrated; responses are reflexive
3–6 mo	Pain response accompanied by sadness and anger response
6–18 mo	Develops fear of painful situations; localization of pain develops; words associated with pain (e.g., "owie," "booboo")
18–24 mo	Use of the word "hurt" to describe pain; noncognitive coping strategies
24–36 mo	Begins to describe pain and attribute an external cause to the pain
36–60 mo	Gives a gross indication of intensity of pain, use of descriptive adjectives; attaches emotional terms such as "sad" and "mad" to the pain
5–7 yr	Can more clearly differentiate levels of pain intensity; beginning to use cognitive coping strategies
7–10 yr	Can explain why pain hurts
11 yr	Can explain the value of pain

Adapted from McGrath PJ, McAlpine L. Psychologic perspectives on pediatric pain [review] [147 refs]. *J Pediatr* 1993;122:S2–S8.

TABLE 44-2. Developmental timeline of pain interpretation

As the child reaches school age, the concrete operations stage ensues. Pain can now be expressed in terms of affect. The child interacts with the world in simple, concrete ways; pain treatment focuses largely on medicine and physical interventions (e.g., rubbing). Pain is no longer viewed as a punishment (36). A sense of cause and effect develops, which is prerequisite for the use of patient- controlled analgesia (PCA) modalities. Young adolescents begin to master the skills of self-analysis, long-term anticipation, and delayed gratification. A sense of invulnerability also develops, leading to many of the risk-taking behaviors that bring the teenager to the hospital in the first place. Chronically ill adolescents, however, may report an increased negative quality to the sensations that accompany their disease. In the case of children with juvenile chronic arthritis, this has been suggested to result from increased appreciation of the pathophysiology of their disease (37). The teen may be treated in many ways like an adult; however, limited life experience, a strong sense of body image, and threats to the sense of invulnerability make the adolescent uniquely sensitive to the effects of disease and painful conditions. Independence from family has long been held to be a primary goal of adolescence (38); however, many teenagers still benefit from a hand to hold during procedures (39).

The stages of development are not attained immutably. Under stress, regression to earlier stages of cognitive and emotional development often occurs (34), necessitating use of therapeutic approaches geared to younger children. It is important not to address this apparent "immaturity" in a pejorative manner, but to accept it as the unique and dynamic part of pediatric development that it is.

The above discussion focuses on the normal, healthy child. Many mentally and physically handicapped children present for evaluation and treatment of painful conditions. The pain care of this set of patients can be extremely challenging, and new assessment tools are being evaluated (40).

PAIN ASSESSMENT

Assessment of pain in children, especially those in the preverbal age group, poses a particularly difficult problem. The reader is referred to an excellent series of discussions on measurement of pain in children and infants; the complexity of this topic precludes a full discussion here (41). Many health professionals report that adequate pain assessment is inconsistent and management is sporadic. In a national survey of pain practices in pediatric hospitals and residency programs (42), 60% of respondents stated that standard-of-care or pain protocols were present in their hospitals, but only 25% reported that the protocols were followed 80% or more of the time. Twenty-seven percent of respondents reported that they used none of the available pain assessment scales and 96% reported major obstacles to optimal pain management. Overall, it was believed that pain assessment and management were lower for infants and young children. A few of the many assessment tools that are available are displayed in Table 44-3,Table 44-4 and Table 44-5. The reader is referred to the Finley and McGrath monograph for a more comprehensive listing (41).

Age group	Assessment tool	Features
Infants	Neonatal infant pain scale	Good validation, multidimensional behaviors, can be done at bedside
	Premature infant pain profile	Good validation, multidimensional behaviors, can be done at bedside
	Neonatal facial coding	Good validation, original version required scoring from videos, although a rapid bedside version is now available (200)

Based on standardized observation of behaviors; facial activity most robust measure in infants.

Adapted from Lawrence J, Alcock D, McGrath PJ, et al. The development of a tool to assess neonatal pain. *Neonatal Network* 1993;12:59–66; and Stevens B, Johnston C, Petryshen P, et al. Premature infant pain profile: development and initial validation. *Clin J Pain* 1996;12:13–22.

TABLE 44-3. Assessment tools for infants

Age group	Assessment tool	Features
Children (verbal and nonverbal)	Children's Hospital of Eastern Ontario Pain Scale	Well validated for procedures, underestimates persistent pain
	Objective pain scale	Combines behaviors and blood pressure, little validation in original reports, converges to visual analog scale, convenient for a range of ages
	Toddler-preschooler postoperative pain scale	Easy to use, preliminary validation reported

Adapted from McGrath PJ, Johnson G, Goodman JT, et al. The CHEOPS: a behavioral scale to measure postoperative pain in children. In: Chapman J, Fields HL, Dubner R, Cervero F, eds. *Advances in pain research and therapy,* Vol 9. New York: Raven Press, 1985:395–402; Hannallah RS, Broadman LM, Belman AB, et al. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. *Anesthesiology* 1987;66:832–834; and Tarbell SE, Cohen IT, Marsh JL. The toddler-preschooler postoperative pain scale: an observational scale for measuring postoperative pain in children aged 1–5. Preliminary report. *Pain* 1992;50:273–280.

TABLE 44-4. Assessment tools for young children and nonverbal older children

Age group	Assessment tool	Features
Children (verbal)	Faces pain scale	Ages 4 and above Several different versions with drawings of faces Choice of anchors may modify results
	Oucher	Ages 4 and above
	Color analog scale	Ages 4 and above Converges to visual analog scale (VAS) in older children
	VAS	Ages 7 or 8 and above
	Poker chip tool	Ages 4 and above
	Douleur Echelle Gustave-Roussy	Ages 4 and above, specifically developed for cancer and other long-term pain conditions; theoretical attractiveness in describing affective dimension and impact on quality of life; some subjectivity in scoring

[illegible]

[illegible]

TABLE 44-5. Self-report tools

Several investigators have attempted to develop self-report measures that can be used reliably by children aged 3 to 8 years. Faces scales have been quite popular, and these scales differ in several respects, including number of faces presented, the way the faces are drawn or photographed (43), and the faces layout of the page (44). In general, severe pain is depicted as a crying face, with eyes closed, brow furrowed, and nasolabial folds deepened. Some scales feature a single child photographed through a continuum of facial expressions from happy to screaming. The accuracy of the tool is influenced by the gender and the ethnicity of both the patient and the child pictured on the scale. In one study, Chambers and Craig showed that the pain ratings differ according to the choice of anchors on the scale, particularly according to whether the “no pain” end of the scale shows a neutral face or a happy face (45). Some children seem to be confused regarding ranking of happiness or well-being as opposed to absence of pain. Color analog scales (more pain corresponds to more intensely red color) appear acceptable to most children aged 4 and older (46,47) and show convergent validity to visual analog scales in older children.

To assess preverbal children, behavioral scales have been developed. These scales are largely for use in the assessment of toddlers and preschool children undergoing brief, painful procedures or surgery (48,49) and in the assessment of neonates undergoing procedures or intensive care. Work by Grunau, Craig, and their colleagues showed that facial expressions appear useful and valid as indicators of pain in neonates of all postconceptual ages (50). Audiologic evaluation of crying responses to various stimuli has allowed characterization of the “pain cry” (51). Overall, facial expression measures appear more robust and sensitive than measures of crying (50,52).

Johnston et al. and Stevens et al. characterized differences in pain-related behaviors in premature babies through the full range of postconceptional and postnatal ages, both in terms of cry characteristics and facial action components (53,54). They developed multidimensional measures that adjust for developmental stage. These tools are useful for the study of pain in neonates of different postconceptional and postnatal ages (55).

Differentiating pain from other negative experiences on the basis of behavior can be a frustrating endeavor. Attempts have been made to separate pain from other causes of agitated behavior in the postoperative period and underscore the confounded nature of deriving pure behavioral assessment tools (56). Behavioral scales, such as the Children's Hospital of Eastern Ontario Pain Scale, may therefore signal fear or anxiety instead of pain in the setting of acute medical procedures. Conversely, behavioral measures developed for acute procedures may underrate persistent pain, such as postsurgical pain (57) or oncologic pain. Many children with persistent pain lie still in bed, close their eyes, and inhibit their movements, not because they are comfortable or narcotized, but because it hurts too much to move. Therefore, one should not consider a child to be comfortable solely on the grounds that he or she is lying quietly. Gauvain-Picard and others have developed measures for pediatric cancer patients that incorporate assessment of social involvement and inhibition of movement (58).

At first glance, assessment of pain via physiologic parameters may appear attractive because of their presumed objectivity. Pain evokes increases in heart rate, blood pressure, and respiratory rate. Unfortunately, these signs are influenced by factors such as underlying disease, volume status, emotional state, and medications. Indices of vagal tone have been used to measure stress and distress in neonates undergoing painful procedures (59,60). Analysis of these parameters may be confounded by factors unrelated to pain (61,62 and 63). McIntosh and coworkers have provided evidence that measures of variability in physiologic parameters, including heart rate, blood pressure, and end-tidal carbon dioxide, may indeed be more useful than absolute trends in these physiologic parameters in painful situations (64). Although such studies provide fascinating insights into the physiologic response to painful stimuli, issues of sensitivity and specificity remain, as do issues of practicality of use in clinical settings. We discourage clinical investigators from overinterpreting physiologic measures without correlating them with behavior and the overall clinical situation.

DEVELOPMENTAL PHARMACOLOGY

Overview

A number of pharmacokinetic and pharmacodynamic factors modify responses to analgesic medication in the newborn and young infant, as summarized in Table 44-6.

Factor	Implications
Immature ventilatory reflexes “Leaky” blood–brain barrier	Opioid-induced hypoventilation more likely.
Greater percentage of total body water	Altered volume of distribution compared to older children.
Immature hepatic enzymes	Diminished drug metabolism. Potential for accumulation of opioids and/or local anesthetics with repeated dosing or infusions.
Decreased glomerular filtration rate and renal tubular secretion capacity	Diminished renal excretion of opioid and opioid metabolites.
Decreased plasma concentration of albumin and alpha$_1$ acid glycoprotein	Greater free fraction of drugs in the serum for the same total serum level, especially with local anesthetics.

TABLE 44-6. Factors that affect drug activity in neonates

Analgesic Pharmacology

Aspirin (acetylsalicylic acid) is by far the oldest nonopioid analgesic and antiinflammatory, having been used since 1899, and it still has an important place in the pharmacologic treatment of pain. The use of aspirin as an antipyretic for children has been associated with the development of Reye's syndrome, and this must be borne in mind when using this drug. Nevertheless, aspirin is an effective analgesic, and due to its long history of use, its side effects and toxicities are well described. The drug is effective as a treatment for mild to moderate pain associated with inflammation. Peak blood levels are seen 90 to 120 minutes after oral administration. Toxicity is possible with repeated dosing or with excessive single doses. Its elimination is nonlinear so that at higher concentrations, it is eliminated more slowly than it is at lower concentrations. Aspirin inhibits prostaglandin synthesis and release. This effect is responsible for the drug's analgesic effect as well as its antiplatelet effect. Aspirin binds to platelets, irreversibly affecting their function, whereas the antiprostaglandin effects of aspirin are transient in all other tissues of the body (65). The mild to moderate gastrointestinal (GI) upset that is commonly seen with aspirin administration is likely due to local irritation and can be minimized by administration of the drug with milk or food. Hypersensitivity to aspirin, usually manifested as wheezing, is not generally seen in children but does occur.

Acetaminophen (paracetamol) is a paraaminophenol derivative that has analgesic properties similar to aspirin and is useful for treatment of both mild pain and fever. In contrast to aspirin, acetaminophen has little antiinflammatory effect. Fortunately, acetaminophen has virtually no antiplatelet effect. When given at the recommended doses, acetaminophen has few effects. GI upset is rare, as is allergy to the drug. The dose of acetaminophen varies according to the route of administration, in contrast to aspirin. Conservative daily dose limits based on available pharmacokinetic data are 90 mg per kg per day in children, 60 mg per kg per day in infants, and 45 mg per kg per day in premature infants (66). The dose of acetaminophen needed to achieve analgesic levels when the drug is given per rectum has not been firmly established. Doses ranging from 20 to 40 mg per kg have been studied. Doses at the higher end of that range appear to provide therapeutic levels more consistently (67). Clearance after rectal administration is slow (68). Therefore, after an initial dose of 35 to 45 mg per kg, subsequent doses should be given 6 to 8 hours after the rectal dose.

Oral doses of 150 mg per kg have been associated with liver damage, and children who ingest this amount or more require intervention. With chronic overdosing, a smaller dose may lead to toxicity. Clinically, toxicity begins with 24 to 48 hours of nausea, vomiting, and malaise and is followed by laboratory and clinical evidence of liver dysfunction. If untreated, liver failure is possible (69).

Propacetamol is an intravenous prodrug of acetaminophen that has been used in Europe for adults (70,71); some pediatric data are available as well (72). This medication may be useful in a few situations in which both oral and rectal routes are not feasible. Several cases of contact dermatitis have been reported in health care workers who handled this medication (73).

Nonsteroidal antiinflammatory drugs (NSAIDs) are useful for many forms of pain, including but not limited to postoperative pain, arthritis and other inflammatory conditions, and pain in sickle-cell disease (see Chapter 83). Dosing for some of the more common compounds is shown in Table 44-7. A large number of NSAIDs have been examined for perioperative use in children, including indomethacin (74), ibuprofen, diclofenac, and ketorolac (75). NSAIDs can be effectively administered via oral, intravenous, rectal, and intramuscular routes. Intramuscular injection should be discouraged for use in most children because it is painful and offers no advantage over other delivery routes. The intravenous route offers convenience for administration intraoperatively or postoperatively. There is little evidence that this route is uniquely more effective than oral or rectal dosing for NSAIDs (76). NSAIDs reduce the requirement for opioids in a number of pediatric postoperative studies. In some of these studies, this reduction results in a decrease in opioid-related side effects (77). There is little evidence for differences between NSAIDs in analgesic effectiveness, and many studies do not compare them at a range of doses that would permit proper comparison of analgesia and side effects.

TABLE 44-7. Dosing guidelines for nonopioid analgesics

In one study, when compared with aspirin in children with rheumatoid arthritis, ibuprofen appeared equally effective and better tolerated (78). Another study found that short-term use of ibuprofen in children in the pediatric office practice has a very low risk of gastric irritation or bleeding (79). Overall, the safety of NSAIDs in children seems quite good, although rare cases of GI bleeding and nephropathy have been reported. NSAIDs should be used with caution in types of surgery where bleeding is of major concern. Ketorolac is a very effective analgesic for a variety of outpatient surgeries in children (80). Conversely, NSAIDs should not be used as an excuse for withholding opioids for children having severe pain. Although ketorolac was initially studied and approved for intramuscular use, it is now approved for intravenous use as well, and there is little justification for the intramuscular route for any patient who has intravenous access. Given the problem with decreased platelet function seen with the use of ketorolac, it is not recommended for children at risk for bleeding (75). A retrospective study of children undergoing tonsillectomy reported an increased incidence of postoperative bleeding when ketorolac was used (81).

Other NSAID side effects, in addition to decreased platelet function, include GI distress and GI bleeding, acute renal failure, and interstitial nephritis. Routine use of ketorolac, as with all NSAIDs, should be avoided in patients who are at risk for GI bleeding or renal dysfunction. A retrospective cohort involving hospitalized adults found that the rate of renal failure was no different in the ketorolac group versus the group treated with opioids so long as treatment was for 5 days or less (82). The authors suggest that there may be a greater risk for renal failure when ketorolac therapy is extended beyond 5 days. A pediatric case of acute renal failure has been reported (83). The safety and efficacy of NSAID-based analgesia in newborns have not been established.

Few data are currently available regarding the cyclooxygenase 2–specific inhibitors in children. Available data in adults suggest that they will be useful and may reduce some of the side effects and complications of NSAIDs. The lack of impairment of coagulation may be especially useful for pediatric postoperative use and for children with cancer pain.

Opioids can be used for infants and children of all ages, with proper understanding of age-related changes in pharmacokinetics (84) and pharmacodynamics. A number of opioids have undergone pharmacokinetic study in infants and children, including morphine (85), fentanyl (86), and sufentanil (87). Opioid infusion rates in infants should not be directly extrapolated from recommended dosing in older children. Opioid clearances in the first months of life, normalized by body weight, are diminished compared with mature values and reach mature values over the first 3 to 12 months of age. Therefore, drug accumulation can occur, leading to delayed sedation and respiratory depression. The time course of maturation may further be affected by the newborn's medical condition. For example, infants undergoing noncardiac surgery tend to show mature morphine clearances by 1 to 3 months of age, whereas infants undergoing cardiac surgery show reduced clearances through the first 6 to 9 months of life (88). Recommended opioid dosing is shown in Table 44-8.

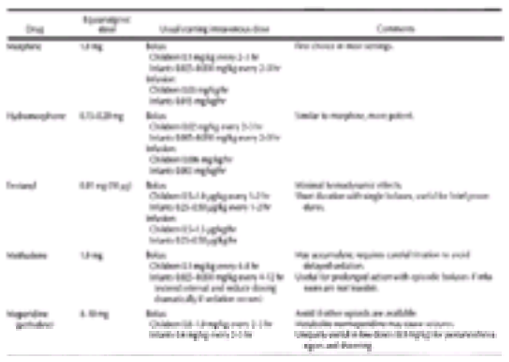

TABLE 44-8A. Intravenous opioid dosing guidelines

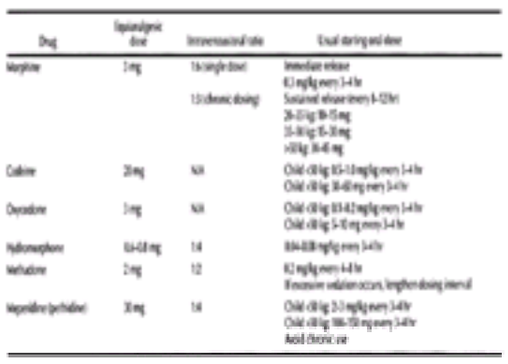

TABLE 44-8B. Oral opioid dosing guidelines

For many years, the issue of the pharmacodynamic respiratory sensitivity of neonates has been debated. Early observations by Way and others suggested that neonates had greater respiratory depression than older children and adults and that morphine may be more depressant than meperidine (89). Ventilatory reflexes to hypoxia and hypercarbia are indeed immature in human newborns and mature over the first weeks of life (90). Investigators have examined respiratory sensitivity in neonates by a number of methods, including carbon dioxide response curves, continuous oximetry, and impedance plethysmography. Healthy infants aged 3 months and older in these predominantly postoperative studies have similar analgesic responses and similar degrees of respiratory depression as adults at similar plasma

opioid concentrations (91). Opioid infusions have been used extensively for children with good efficacy and safety. Haberkern and colleagues, in a comparative trial, reconfirmed that both intravenous morphine and epidural morphine produce good analgesia but with a fairly high incidence of side effects, including itching, nausea, ileus, and urinary retention (92). Both routes of morphine administration resulted in reductions of approximately 50% in the slopes of the patients' carbon dioxide response curves.

Overall, opioid infusions in younger infants are useful and generally safe, but their dosing and titration require expertise and vigilance. Because pain assessment in infants is imprecise, titration to clinical effect is more troublesome. In the absence of conclusive evidence, there is debate over which forms of electronic monitoring are most useful for detecting hypoxemia or hypoventilation. Impedance apnea monitoring is widely available on hospital wards, with telemetry alarms that can ring in a hallway or nurses' station. There are case reports of significant hypoxemia in infants receiving opioids despite normal respiratory rates (93). For this reason, some clinicians have advocated continuous pulse oximetry as a method of monitoring. A false sense of security arises because remote telemetry of pulse oximeters is not widely available. Oximeter alarms may go undetected in a hospital room, defeating the purpose of continuous monitoring. These monitors also have practical limitations related to motion artifact. Convenient, low-cost, motion-insensitive oximetry with telemetry to a central site on a ward would be remarkably useful. No amount of technologic surveillance substitutes for clinical assessment and understanding of factors that modify opioid needs and risks.

MANAGEMENT OF SPECIFIC TYPES OF PAIN IN CHILDREN

Postoperative Pain

Overview

Amelioration of postoperative pain is best accomplished by coordinated efforts among parents, pediatricians, surgeons, anesthesiologists, nurses, pharmacists, child-life specialists, and others involved in perioperative care. Anxiety and fear, which can amplify pain, can be reduced with proper preoperative preparation. Children should receive explanations that are appropriate to their developmental stage. Preoperative education programs are now available at many pediatric centers, and these may be helpful in this process. Techniques of anesthetic induction should strive to be atraumatic. Parental presence for mask induction may reduce distress for many children. Use of EMLA or other topical anesthetics may reduce the distress of intravenous induction. Oral premedication can also reduce anxiety for many children.

Kehlet (94) and others have sponsored the concept of multimodal analgesia for adults undergoing surgery. It is likely that this concept applies for children as well. Combinations of opioids, local anesthetics, and NSAIDs may be ideal in many settings.

Acute pain services can provide patient advocacy and ensure that pain management is a priority. In many pediatric centers, these services have been developed and appear to provide extremely useful services. Standardized protocols are useful to ensure prompt and consistent management of both pain and side effects. Decimal point errors are common in pediatric hospitals. Provision of dosing protocols facilitates cross-checking for erroneous orders. If children are to be cared for in general hospitals, it is ideal to have pediatric specialists involved in the creation of specific pain management protocols for children. There are a variety of models for pain treatment services, and the choice of participants and specialists may depend on local expertise and availability.

Patient-Controlled Analgesia

PCA has been used for children for the past 10 years, with excellent safety, good efficacy, and excellent patient acceptance. In comparison with nurse-administered bolus dosing, PCA use results in better pain scores and better patient acceptance, without increasing opioid use or side effects (95). Compared with continuous opioid infusions, PCA provides either equivalent or improved pain scores, with a reduction of opioid use and side effects (96). PCA is generally well used by children aged 6 and older. Dosing parameters have been studied by Doyle and coworkers (98). Short lockout intervals (e.g., 7 to 8 minutes) are safe and allow more rapid “catch-up” in the setting of unrelieved pain. Basal infusions should be individualized according to medical risk factors, as well as psychological factors (97). Although basal infusions may increase patient satisfaction (98), they may also result in more episodes of nighttime oxygen desaturation (99).

There exist a variety of opioids from which to choose for PCA use. We use morphine most commonly, in a standard concentration of 1 mg per mL. In cases in which the patient has side effects from morphine, hydromorphone is prepared in a concentration of 0.5 mg per mL and dosed at a ratio of 1 to 5 with morphine (100). Fentanyl and meperidine are also used for selected patients. Meperidine has been associated with seizures in cases of renal insufficiency (101) and also in a healthy adolescent (102).

There is some controversy surrounding nurse-controlled and parent-controlled analgesia for children. Standard PCA is inherently safe because when patients become narcotized, they fall asleep. The plasma concentrations then fall, keeping the patients safe. Studies suggest good safety when nurses use the PCA pump for infants and children unable to dose themselves (103). There is similarly a very good experience with home dosing of PCA pumps by parents for infants and children in palliative care. Problems can arise when parents push the button for opioid-naïve children, particularly in a postoperative setting. Without specific training and monitoring, on rare occasions, well-meaning efforts may lead to overdose. We are aware of several cases around the world in which this has occurred, with disastrous consequences. The argument in favor of parental dosing is that parents are the children's primary caregivers and are in an ideal position to assess their needs. Pending further study, we recommend that if parent-controlled analgesia is to be used in nonpalliative situations, there should be a formal program of parent education and an increased level of patient observation.

Regional Anesthesia

Regional anesthesia in infants and children can be performed by specific modifications of techniques used in adults. The reader is referred to Dalens' excellent textbook for an illustrated, detailed discussion (104). A variety of peripheral nerve blocks can provide analgesia after surgery and have an excellent safety and side effect profile (105,106 and 107). Regional anesthesia is generally performed with the child anesthetized, as a method of providing postoperative analgesia. In general, the same range of peripheral blocks is available in the pediatric group as in adults. However, several factors limit the execution of pediatric regional blockade to practitioners especially familiar with pediatric anesthesia. Landmarks are often less well defined, proximity to neurovascular structures is greater, and the patients are usually anesthetized. Many of the blocks can be modified to provide prolonged analgesia via continuous infusions of local anesthetic.

Excessive doses of local anesthetics cause convulsions, arrhythmias, and cardiac depression that can be very difficult to treat. Kohane, Hu, and coworkers in our group recently demonstrated that rat pups have a narrower therapeutic index for local anesthetics than adult animals on the basis of scaling factors (107). The effective dose to block nerves scales comparatively weakly with body size. Toxic doses, on the other hand, scale more directly with body size (108). Recommended maximum doses for a single injection are displayed in Table 44-9.

Drug	Single bolus (mg/kg)		Continuous infusion (mg/kg/hr)
Birth to roughly 6–12 mo of age			
Lidocaine	4	5 with epi	0.8
Bupivacaine	1.5–2.0	2 with epi	0.2
Chloroprocaine	30	30 with epi	30
1 yr and older			
Lidocaine	5	7 with epi	1.6
Bupivacaine	2	2.5 with epi	0.4
Chloroprocaine	30	30 with epi	30

epi epinephrine

TABLE 44-9. Dosing guidelines for local anesthetics

Epidural Analgesia

Epidural analgesia can provide outstanding analgesia for major thoracic, abdominal, pelvic, and lower extremity operations. When optimally managed, epidural analgesia may facilitate recovery of high-risk patients (109,110). Combinations of opioids and local anesthetics have excellent efficacy and are particularly effective when the catheter tip can be placed at the dermatomal level of the surgery. This goal can be achieved either by direct placement in older children or by cephalad advancement of a caudal catheter in younger children (111). Dosing for epidural infusions is displayed in Table 44-10.

Solution	Age <6 mo mL/kg/hr	Age >6 mo mL/kg/hr
Bupivacaine 0.1% with fentanyl 2 μg/mL	0.2-0.4	0.1-0.2
Bupivacaine 0.1% with fentanyl 2 μg/mL and clonidine 0.8 μg/mL	0.2-0.3	0.1-0.15
Bupivacaine 0.1% with hydromorphone 10 μg/mL[a]	0.2-0.3	0.05-0.15[b]
Chloroprocaine 1.2% with clonidine 0.1 μg/mL	Rarely used	0.4-0.8

[a] Apnea monitoring is recommended.
[b] Use with caution; may highly constrict urinary

TABLE 44-10. Recommended epidural infusion dosing guidelines

Epidural catheter placement is generally performed while children are receiving general anesthesia (112). Test dosing for intravascular placement is not entirely reliable. Incremental dosing and ECG monitoring are recommended. Fluoroscopic guidance or radiographic confirmation of catheter positioning may be useful in certain circumstances.

Single-shot caudal blockade with local anesthetics is generally safe and effective. Caudal analgesia is most often provided for analgesia after minor procedures below the umbilicus. a_2-Adrenergic agents, such as clonidine, prolong local anesthetic action and have received promising study in children (113,114).

Cancer and Palliative Care

Few areas of medicine are more emotionally challenging than the care of the child with cancer or of the terminally ill child. Many of the principles outlined in adult palliative care apply to children (115,116 and 117). Pharmacologic management by the World Health Organization analgesic ladder is effective for most children with pain due to widespread cancer (118). Some of the differences in the approach to palliative care for children involve consideration of the child's emotional and cognitive development (*vide supra*) and the family's roles in support and palliative care (119).

One of the great challenges of palliative care of children is the topic of dying, *per se*. Often the family is reluctant to discuss death with the child and to make the transition from curative therapy to palliation. The emotional angst suffered by the family is natural and understandable and must be handled compassionately and honestly. How one discusses palliative care with the patient depends largely on the progress family members are making in their own psychological journey. The child's concept of death, however, often develops much earlier than either the family or the health care team appreciates (120). As one 3-year-old stated about dying, “Mommy would be sad because there would be no more [me],” which at least partially reflects the concepts of loss, grief, and permanence inherent in an adult's concept of death. Often child-life workers, nurses, and behavioral medicine specialists can be invaluable allies in situations of terminal illness.

Brief Diagnostic and Therapeutic Procedures

Overview and General Approach

Needle procedures are a significant source of distress for children. Immunizations and blood draws are sources of medical pain for healthy children. Children with acute and chronic illness may in addition receive more frequent procedures, including intravenous cannulation, lumbar puncture, and bone marrow aspiration.

Several principles are crucial in managing acute procedure-related pain. First, never lie to the child about the discomfort she or he will experience. It is often very difficult to inform children that what is about to be done will cause discomfort, but denying the reality of the pain makes it unlikely that the child will trust the caregivers. Because both family members and caregivers would prefer that the child not be uncomfortable, it may occur that these individuals, whom the child looks to for comfort, actually begin to deny the child's complaints. Principle number two is therefore the following: Do not ignore, invalidate, minimize, or disbelieve the child's complaint of pain. The children must feel that they are worth listening to and that their complaints are important. When treating procedure-related pain with analgesics and sedatives, the American Academy of Pediatrics guidelines for monitoring children undergoing sedation and analgesia should be followed (121).

Approaches to these procedures must be individualized according to the child's age, cognitive development, coping style, and health status. Appropriate explanation and support can be helpful. Topical cooling may be beneficial for some children. As noted above, oral sucrose has been used for infants receiving distressing procedures (26) and appears safe and partially effective. Transcutaneous electrical nerve stimulation (TENS) has also been investigated in the context of procedural pain (122).

Cognitive-behavioral techniques, including guided imagery, hypnosis, and relaxation, can diminish the distress of these procedures for many children (123,124,125,126 and 127). There is some evidence suggesting that girls' distress ratings are higher than those of boys (128); it is not clear if this reflects cultural expectations on pain reporting. The various techniques are used very widely and can be taught to most children aged 5 to 7 and older. Some experts use them for children aged 3 to 5 as well (123).

Children often anticipate painful procedures with varying amounts of fear and anxiety. Children who have experienced blood draws anticipate their next procedure with greater anxiety than those children having their first blood draw (129). Providing either amnesia or a pleasant first experience, therefore, is extremely important. There is considerable debate over the logistics and ethics of “conscious sedation” versus general anesthesia for children undergoing a variety of noxious procedures. Conscious sedation, deep sedation, and general anesthesia represent a continuum, and the same doses of sedatives may leave one patient conscious but render another deeply unresponsive (130). More cooperative patients often do well with benzodiazepines (131) in combination with either opioid analgesics or low-dose ketamine (132). For higher-risk or highly uncooperative children or for more extensive procedures, general anesthesia may be a more effective alternative.

Local and Regional Anesthesia

Topical administration of local anesthetics is widely used for relieving the pain of needle procedures, laceration repairs, and removal of skin lesions. For intact skin, the most widely used preparation is EMLA (133), which has proved to be extremely safe in all age groups. The cream requires at least an hour for adequate cutaneous analgesia in most situations. Although high systemic concentrations of prilocaine can produce methemoglobinemia, this has not been a significant clinical problem in widespread use, even with repeated or prolonged dosing in younger infants. Iontophoretic transcutaneous delivery of lidocaine has been used effectively for placement of intravenous lines in children (134). Effective analgesia can be obtained in as little as 10 minutes. There have been several cases of cutaneous burns from the electrical devices; however, current devices appear to reduce this risk.

For application to cut skin, especially for suture of lacerations, combinations of local anesthetics with vasoconstrictors are widely used. The combination of tetracaine with epinephrine (adrenaline) and cocaine is known as TAC. Several studies have shown that these preparations are effective when used in emergency departments for repair of lacerations (135). TAC should be avoided in the vicinity of end arteries because ischemic complications have occurred. Rapid absorption of the tetracaine and cocaine with larger doses applied to mucosal surfaces has produced convulsions and death. More recent studies have found equivalent effectiveness using

preparations with the cocaine omitted, and combinations of tetracaine and phenylephrine appear useful in this setting (136).

Chronic “Benign” Pains of Childhood

Overview

The large majority of pain complaints in children are the result of benign processes, as they are in adults. Chronic and recurrent pains in children, however, have a different epidemiology from those in adults. Back and neck pains are less common in children. School avoidance issues replace work avoidance issues. Children commonly experience recurrent pains of the head, chest, abdomen, and limbs. These conditions typically involve painful episodes alternating with pain-free times in a child who is otherwise healthy. These conditions are very common, and population-based surveys suggest that between 4% and 10% of children experience these symptoms with some regularity (137,138,139,140 and 141).

Most children presenting with these benign complaints will be determined to be medically well. Despite this fact, complaints such as chest pain evoke fears of life-threatening illness in the minds of adolescents (142) and their parents. The primary pediatrician or general practitioner needs to develop a screening approach that emphasizes a sensitive medical history and physical exam that detects the small subset of patients who need further evaluation (143). Extensive laboratory and radiologic testing is rarely warranted, and unfocused laboratory testing should be deemphasized. Lifestyle interventions may be helpful, and questions should be included regarding family and school circumstances, diet, sleep, sports, and the child's daily and social activities.

Physical therapeutic approaches are extremely helpful for many chronic painful conditions in children. Physical therapists should be integral participants in multidisciplinary chronic pain programs for children. Aerobic conditioning and strength training may have specific, localized benefits—for example, for an adolescent with myofascial pain—and also have more generalized beneficial effects on mood, sleep, and general well-being. The following discussion focuses on a few of the more common problems that are seen in a pediatric pain clinic.

Neuropathic Pains

Neuropathic pain in children can be a source of considerable distress and suffering (144). The causes we see most frequently are complex regional pain syndrome type 1 (CRPS I)/reflex sympathetic dystrophy (RSD), postsurgical/posttraumatic peripheral CRPS II/causalgia metabolic neuropathies, spinal cord injuries, and cancer. Phantom pain after amputation is more common than once thought and can be prolonged and severe (112,145). In the absence of randomized controlled trials in children, we commonly extrapolate approaches used in adults. Tricyclic antidepressants and anticonvulsants form the mainstay of pharmacologic therapy, with cognitive-behavioral strategies and TENS technology completing the therapeutic triumvirate. We prescribe amitriptyline or nortriptyline after obtaining a baseline electrocardiogram, at 10 mg qhs. Starting at 5 to 7 days, the dose is elevated in 10-mg increments every several days to effect or as limited by side effects. The patient should be told that although the effect on sleep is immediate, the analgesic effects might take 1 to 3 weeks. Unacceptable side effects at any time or lack of clinical effect after a few weeks are reasons for switching to a different antidepressant. Side effects of the tricyclic antidepressants include dysrhythmias, dry mouth, constipation, urinary retention, and blurred vision. Even among patients for whom pain is not improved, the beneficial effect of a tricyclic on sleep may make them worthwhile.

Anticonvulsants have been used frequently in adults, with the best data supporting phenytoin and carbamazepine (see Chapter 86). Recently, gabapentin has become popular for the treatment of various neuropathic pains (146,147). Gabapentin has the benefits of the lack of hematologic or hepatic toxicities, minimal protein binding, and the lack of interactions with hepatic enzyme systems (148). Some adult studies suggest efficacy for several neuropathic pain conditions; pediatric experience is limited (149) and no pediatric controlled trials are available at this time. Although side effects have been a minor problem in our practice, there have been children for whom behavioral side effects have been problematic. Many of these children had preexisting neurologic or neuropsychiatric problems, and the prevalence of adverse behavioral effects may be lower in patients with chronic pain (150).

CRPS I/RSD in children and adolescents differs from that in adults in several ways (151). Pediatric CRPS I has a marked female predominance (roughly 6 to 1); a marked lower extremity predominance (roughly 6 to 1); and an apparently high association with competitive sports (152), gymnastics, and dance (153). The reasons for this association are unclear. Some clinicians regard this as a psychogenic condition (154), although evidence of causation, as opposed to association, is weak. The syndrome rarely progresses to the third of the three stages seen in adults: acute, dystrophic, and atrophic. Even when CRPS I in children is relatively advanced, prognosis for recovery is generally good, although many patients have recurrent episodes and a small percentage have persistent pain and limb dysfunction. Approaches to treatment of CRPS I/RSD have been extremely varied, ranging from rehabilitative (155) to more interventionist. A prospective controlled trial of physical therapy in the treatment of CRPS I is in progress. In our view, the major role for neural blockade in pediatric CRPS I/RSD is to facilitate aggressive physical therapy.

Sickle Cell Anemia

Sickle-cell disease refers to series of related hemoglobinopathies occurring predominantly in those of African and Middle Eastern descent. Sickling of red blood cells occurs when the abnormal hemoglobin molecules polymerize under certain conditions, including hypoxemia, acidosis, hypothermia, and erythrocyte cell water loss. Reduced deformability of the cell ensues, leading to impaired rheology in small vessels, vasoocclusion, and ischemic pain. Pain in sickle-cell disease is extremely variable in its frequency and severity (156). The majority of patients manage their persistent and episodic pains as outpatients, using oral hydration, NSAIDs, and oral opioids. Some patients may be on hydroxyurea, a medication used to promote hemoglobin F production, which results in fewer painful crises (157). A subgroup of patients has more severe episodes of vasoocclusive pain that require hospitalization. Opioids should be given as needed to provide comfort (158). Often, hospitalization occurs to provide intravenous opioids.

Some patients arriving for hospital care are opioid-tolerant secondary to their home opioid management. It is important to take their baseline opioid requirement into account when formulating an inpatient regimen. Often, a basal infusion at an equianalgesic amount will suffice. Use of a PCA with the basal infusion allows provision of adequate amount of opioid without the need for the patient to use the bolus doses frequently. Given the intensity of ischemic pain and the baseline opioid exposure, relatively large doses of opioid are required and should be prescribed. As the patient's total requirements become known (usually after a couple of days), conversion to a combination of long- and immediate-release opioid can be arranged. Opioid titration may require some additional care because hypoxemia and hypercarbia further exacerbate sickling of erythrocytes. Use of pulse oximetry (apnea monitoring in selected cases) adds a layer of safety. The opioid-sparing effect of ketorolac makes this drug especially useful for vasoocclusive crises, if renal function is normal (159). Epidural analgesia has been used safely in the setting of acute vasoocclusive crisis (160). For the potentially lethal “chest crisis,” a thoracic epidural should be considered early in the clinical course to facilitate chest physiotherapy and effective coughing and to promote full chest excursion.

Some studies evaluating aggressive oral opioid use suggest that decreased hospital admission rates can result (161,162). There is an increasing emphasis on home management (163), oral opioid dosing, avoidance of a “crisis” model, and teaching cognitive- behavioral techniques (164,165). Gil et al. suggest that the earlier adaptive coping skills are learned, the more likely they are to become a routine part of the sickle cell patients' armamentarium against the pain of their disease (166).

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Human immunodeficiency virus (HIV) disease in children is now most commonly acquired by congenital infection (see Chapter 39). The natural history of HIV in infants has improved greatly in developed countries in recent years with multidrug treatment regimens. On the other hand, what was a relatively time-limited, fatal illness has become a longer-term chronic illness. Children with HIV undergo a large number of painful diagnostic and therapeutic procedures (167). Infants with encephalopathy and severe developmental delay sometimes present with persistent irritability and screaming of unclear etiology. Many of these infants respond to opioids. For other such children, anticonvulsants may be helpful, even when clinical seizures are not evident.

Headache

Both migraine and tension-type headaches increase in prevalence during the school-age years and into adolescence (168,169). Although the vast majority of headaches are benign in origin, the fear of brain tumors is prevalent, being seen in children as young as 5 to 7 years (170). Such fears can often be assuaged after careful history and physical and by a direct and honest discussion with the child. Certainly, any child with persistent early-morning headache accompanied by vomiting or who has focal neurologic signs deserves intracranial imaging.

There have been some recent clinical trials of analgesic treatment or prophylaxis of migraine pain in children, using trazodone (171), tricyclic antidepressants (172), and calcium channel blockers (173). Sumatriptan, which is effective in interrupting adult migraine attacks, has appeared less impressive in one pediatric trial (174). Similarly, propranolol appears less effective for migraine prophylaxis in children (175). There is a need for more controlled trials of a range of analgesics in children, especially in the setting of chronic or recurrent pain.

Before initiation of tricyclic antidepressants, we obtain an electrocardiogram to rule out conduction disturbances, including preexcitation syndromes or prolonged Q-T syndromes; there is a suggestion that patients with preexisting conduction abnormalities have a risk of developing atrioventricular block secondary to tricyclic antidepressant use (176). We start with nortriptyline at 10 mg nightly for adolescents or 5 mg nightly for school-aged children and escalate in 5- to 10-mg increments every 3 days until a response is obtained, until side effects arise, or until the daily dose escalates to 1.0 to 1.5 mg per kg per day. The side effects seen in children mirror those seen in adults. For patients who will benefit from nighttime sedating effects but who find peripheral anticholinergic effects bothersome, trazodone can be started at low doses (25 mg) at bedtime and escalated over a period of a few weeks to 50 to 100 mg nightly.

Behavioral medicine plays a prominent role in the prophylaxis of both muscle tension–type headaches (177) and pediatric migraine (178). In addition, TENS is also an effective adjunct for the treatment of tension headache (179). Acupuncture is beginning to receive attention for the management of pediatric headache and may prove to be a useful adjunctive treatment.

A common and very difficult headache type is the chronic daily headache, or mixed-type headache, most commonly presenting in mid-life (180). This type of daily headache originates in childhood and adolescence in almost 13% of respondents (181). Future investigations may lead to effective early treatment of these challenging headaches early in their development.

Others forms of head and facial pain occur less frequently. Trigeminal neuralgia is extraordinarily rare in children, and herpes zoster is much less likely to produce postherpetic neuralgia. Other unusual causes for head pain seen in the pediatric age group include headaches resulting from either high or low intracranial pressure as a result of interventions for hydrocephalus. Slit ventricle syndrome can be challenging to evaluate and treat (182), especially in children who are neurologically impaired, nonverbal, and prone to agitated behaviors at baseline. In this situation, close communication with the parents, careful titration of medications, and frequent reevaluation are the keys to success. There is some evidence for a relationship between facial pain and sexual or physical abuse (183), and pertinent histories should be obtained.

Abdominal Pain

Children commonly present to their pediatrician's office with a complaint of recurrent abdominal pain and, frequently, persistent school absenteeism. Although the majority of recurrent abdominal pain in children is “functional,” or nonorganic, indicators of potentially dangerous pathology should always be sought (Table 44-11). Such pathology should be dealt with as appropriate. Certainly, modifications of diet may have considerable benefit in some situations. For example, a subgroup of children with recurrent abdominal pain may improve by treating constipation or by treating lactose intolerance with oral lactase enzyme replacement or avoidance of milk products (184).

Focal pain (away from umbilicus)
Fever
Weight loss
Guaiac-positive stool
Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) concentration
Dysuria
Pain-induced night wakening
Anemia

TABLE 44-11. Signs of organic abdominal pain

Often, the patient has undergone an extensive workup before his or her arrival in the pain clinic. The initial approach should be to assure the patient and parents that the workup has been inclusive to the extent that no dangerous pathology has been missed. Attention then can be turned (often against great resistance) to demedicalizing the situation. In most of these patients, behavioral psychologists can help the patient learn coping and adaptive behaviors (185,186). Under some conditions, diagnostic and therapeutic epidural or celiac plexus blockade can be conducted. Only under extreme circumstances should a lytic block be performed for these nononcologic conditions. The more devastating complications of a lytic celiac plexus block include intravascular, intrathecal, or intrarenal injection of phenol or alcohol; retroperitoneal fibrosis with repeated blocks; and disruption of a major blood vessel.

The pattern of back pain differs from that of adults. Discogenic pain has been found in 11% and muscle tendon strain in 6% of an adolescent population presenting to a pediatric sports medicine clinic. Forty-seven percent of this study population has pain arising from spondylolysis stress fractures of the pars interarticularis, whereas only 5% of adults are found to have such an etiology for their pain (187). In our clinic, the numbers of spondylolysis versus discogenic disease are more even, although referral bias plays a role. For spondylolysis pain, back bracing with graded physical therapy along with a course of nonsteroidal antiinflammatory agents and often a tricyclic antidepressant are the cornerstones of treatment. Sciatica secondary to disk protrusion responds to selected use of epidural steroids, physical therapy, and NSAIDs, as it does in adults. The need for surgery is unusual.

Pelvic Pain

We have seen an increasing number of young women presenting to our clinic for pelvic pain (see Chapter 72). The pain may or may not be related to the menstrual cycle. Sometimes, defecation or urination worsens the pain. The patients often have missed moderate to large amounts of school and can be extremely disabled, although this is highly variable. Often the pain is secondary to endometriosis. In our gynecology clinic, patients not responding to oral contraceptives and NSAIDs were found on laparoscopic exam to have endometriosis approximately 70% of the time, with stage 1 and 2 disease being most prevalent (188). Very similar results have been found elsewhere (189). Owing to the high rate of pelvic inflammatory disease in the adolescent population (190) a thorough sexual history must be taken, and referrals to a gynecologist for cultures made in select cases. Psoas muscle abscesses, musculoskeletal injury, ovarian cysts, and constipation make up the large portion of nonendometriosis pain in adolescent women with pelvic pain.

If endometriosis is found at laparoscopy, the initial approach taken by our gynecologists is laser ablation along with oral contraceptives. Although gonadotropin-releasing hormone inhibitors are effective in suppressing endometriosis-related pain, their use is limited for short term in women older than age 16. We have seen several cases of osteopenia in young women treated for longer periods of time. Tricyclic antidepressants, prostaglandin inhibitors, behavioral medicine, physical therapy, and TENS form the multimodal therapy for the majority of pelvic pains.

“Functional” and Somatoform Pain in Children

A number of the recurrent benign pains of childhood have been commonly regarded as psychogenic. The evidence that most children with these symptoms have psychiatric illnesses is generally weak (191,192). Many children and adolescents with these symptoms, in fact, are well adjusted and cope fairly well. Infrequently, a patient will present with a conversion pain disorder, in which there is no organic disease, and the pain results from psychic conflict. The somatoform or psychosomatic disorders feature minor organic disease with significant psychological or stress components. Symptoms may be limited to pain but often accompany other complaints. Oberlander, Rappaport, and others have argued against dichotomizing these conditions as purely “psychogenic” or purely “organic” (193). The term “functional” has been used to describe these pains that may arise from variations in normal functioning but are related neither to a specific disease nor to psychopathology. From the behaviorist's standpoint, therapy is directed against the pain behaviors more than an underlying psychological process. The distinction among these entities is often

blurred and may be of more theoretical significance than functional importance. For a few children, intensive psychiatric therapy or family therapy is indicated.

Psychiatric Disorders

A small subgroup of children presenting to pediatric pain clinics do have more severe psychiatric illness. A number are depressed, even suicidal. Some have true conversion disorders. Some have a range of posttraumatic stress conditions or a history of physical or sexual abuse. The history taken from any young person in chronic pain should include screening questions for suicidal attempts and ideation. Drug and alcohol use histories should be sought. Munchausen's syndrome by proxy is a condition in which symptoms and signs are generated by parental actions. In many cases, the parents have a strong need for attention and establish a perverse role in relation to the health care team, simultaneously harming the child and appearing to be a perfect, caring parent (194). This disorder has a spectrum of presentations and can be regarded as a form of child abuse.

BEHAVIORAL AND EMOTIONAL CONSIDERATIONS

School Absenteeism and Disability

In adults, chronic pain is a major social, economic, and political problem because it produces suffering and because it is an enormous cause of disability. The child's and adolescent's main “occupation” is school. Questions about school attendance and performance are invaluable in assessing the level of functioning of a pediatric patient. School absenteeism and school avoidance are extremely common among patients referred to our pediatric pain clinic. In our view, it is helpful to regard school avoidance in many (but not all) cases as a disability syndrome with analogies to work absenteeism in adults with chronic pain. Just as the workers' compensation system in adult pain patients may serve to reinforce disability, home-tutoring programs for pediatric pain patients may facilitate a sick role away from the mainstream of life in a school setting. In the future, multidisciplinary programs for pain management in children will need to address more proactively the process of return to school (195).

Biobehavioral Therapy

Behavioral medicine techniques have proven to be useful in the treatment of many pediatric pain syndromes. These therapies can be grouped into four categories: relaxation therapies, including hypnosis; biofeedback (both electromyographic and thermal); operant (or contingency) pain behavior management; and a more general category of cognitive-behavioral techniques using self- monitoring, coping strategies, and environmental modification. There is strong evidence for the efficacy of biobehavioral intervention for recurrent abdominal pain (185), pediatric migraine (178), and juvenile rheumatoid arthritis (196). There is also some evidence that biobehavioral treatment techniques are useful for neuropathic pain (197) and pain associated with sickle-cell disease (198). Conversion disorder can also be treated with a biobehavioral approach (199).

CONCLUSIONS

Early in the development of pediatric pain clinics, a need for multimodal therapy was seen. The interplay between psychology and physiology is strong and changes with the growth of the child. In addition, the patients' fear of needles and the technical challenge of nerve blocks in young patients prevented the development of an overreliance on a single modality of therapy. We have observed that outcomes are better when physical therapy and behavioral medicine are combined with the standard allopathic medical approach, even though this is labor intensive (200). Pain treatment in children and adolescents can influence the function of an individual for a lifetime. Even in these times of managed care and enforced cost cutting, we must emphasize that the children do best when the multidisciplinary approach is taken. Pediatric pain clinics ideally comprise facilities that allow evaluation and intervention by medical doctors, physical therapists, and psychologists, with consultation of orthopedic surgeons, neurologists, and rheumatologists on an as- needed basis.

Unrelieved pain continues to be a major problem in the care of our youngest patients. The cognitive, emotional, and physiologic dynamism of the child can seem quite daunting at first glance. With a thoughtful, multidisciplinary approach that takes advantage of the expertise of pediatric physical therapists and psychologists as well as that of the pain physician, assessing and treating the pediatric pain patient can be an extremely rewarding endeavor. There is still a tremendous amount to be learned about the proper evaluation and treatment of many pediatric pain syndromes; randomized controlled trials of therapeutic modalities clearly are needed.

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CHAPTER 45

Aging and Pain

Stephen W. Harkins

> Senescence is not universal in nature, not even common. Most creatures out in the wild die off, or are killed off, at the first loss of physical or mental power. In a real sense, aging, real aging, the continuation of living through the whole long period of senescence, is a human invention, and perhaps a relative recent one at that (1).

This chapter reviews the effects of aging in the later years of life on pain sensation, perception, and behavior. A commonly accepted definition of being “old” is attaining an age of 65 years. This is artificial. The choice of 65 years of age for retirement and eligibility for Social Security in the United States was adopted in the 1930s from social policy of von Bismark's Germany during the 1880s. Such a definition of being old is subject to change based on epidemiologic, demographic, and political factors, as is illustrated by recent changes in retirement eligibility for Social Security.

There is need for a definition that allows more specific indication of the effects of chronologic time and individual differences on psychophysiologic integrity and homeostasis. In biogerontology, the term *senescence* serves this purpose and replaces *aging*. The Oxford English Dictionary (2) defines *aging* as a process without reference to any specific chronologic period. Aging, in this definition, begins at conception and continues across the life span without reference to specific developmental periods. In contrast, *senescence* in multicellular animals begins at some point post-maturity. Senescence is species specific, universal, and irreversible and results in reduced ability to withstand stress with an increase in probability of death. It is detrimental to the individual. Its value to the species is only now being explored but likely lies in aspects related to somatic cellular mutation or failure, telomere and telomerase activity during mitosis, and accumulated damage (particularly oxidative damage) in fixed postmitotic cells, following sexual maturity. In this regard, it is unclear whether senescence is independent of the selective process of evolution because organisms in nature seldom, as indicated by Lewis Thomas, live long enough to “senesce” (1). *Aging* in this chapter refers to developmental changes that occur during senescence.

Pain is a major force in quality of life for persons of all ages but is particularly so in those more dependent. Pain control in neonates and infants has received substantial attention in the past three decades, in contrast to pain and its control in the frail elderly individual. Critchley (3), in a highly influential paper on neurology of old age, stated that old people tolerate “minor” surgical and dental procedures with little or no “pain or discomfort.” This is certainly wrong, even though it is currently accepted by some in the health care community and by many elders as a “natural” part of “growing old.”

Although literature exists supporting no or at most minimal generalized impact of age, *per se*, on pain perception, there do appear to be very specific age differences in pain sensibilities. These may have important clinical significance in the diagnosis of specific disorders. Reviewing this literature reveals that, although the effect of aging on pain as a sensory/perceptual process differs from its effect on most other senses, another issue is more important for older persons: the impact of pain on successful aging. The major practical clinical concern may well be not whether loss of pain perception occurs with otherwise “normal” aging, but rather that considerable unnecessary suffering occurs from undertreatment of pain in the old. This is particularly true for the frail elderly and those with compromised cognitive capacity.

The purposes of this chapter are to provide the following:

- A summary of demographic changes over the recent past that has fueled awareness of the importance of understanding pain in the aged
- A definition of *presbyalgos* (*presby*, meaning old; *algos*, meaning pain)
- Evidence that the impact of pain on successful aging and maintenance of a quality life is more important to the older person than the impact of old age on pain perception

THE “GRAYING” OF AMERICA: THE COMPRESSION OF MORTALITY AND MORBIDITY

At the beginning of the “age of Social Security,” John Dewey wrote “In the United States, with decrease of birth-rate and the limitation of immigration (which had been mainly of the young and vigorous) we now have an unprecedented situation. Over one- third of the total population will soon be over fifty years of age. In 1980 the number of persons over sixty-five will be more than double that today” (4). Dewey was less than correct. The population has exceeded his projections from some two score and 10 years ago. This presents serious challenges to national imperatives, not the least of which include the solvency of Social Security, funding of health care in hospitals and skilled nursing facilities (Medicare), and home care for the frail elderly. From a demographic perspective, the change in the population has resulted in a compression of mortality into the later years of human life expectancy.

Compression of Mortality

Over the twentieth century in the United States, life expectancy from birth has increased from approximately 48 years to more than 76 years. This increase comes from substantial reductions in mortality early in life and not from an addition of years later in life; it has led to an increasing number of persons surviving into the seventh, eighth, or even ninth decades of life. In fact, those 85 years of age and older represent the fastest-growing segment, percentage-wise, of the total population. The number of persons 85 years of age and older is important because of the increased levels of disability in this group of older adults. For example, in community-dwelling individuals 85 years of age and older, one study estimates that 47% meet clinical criteria for probable Alzheimer's disease (AD) (5).

Numeric Growth

In 1900 there were approximately 3 million individuals aged 65 and older in the United States (approximately 4.1% of the total population). By 1994, the number of those 65 years of age and older increased to more than 33.2 million (approximately 12.5% of the population). Over the next decade (2000 to 2009), the growth in the elderly population will be moderate. Between 2010 and 2030, however, the number of older adults will increase. Individuals born between 1946 and 1964, the “baby boomer” generation, will begin entering a new “over-65 generation” in 2011. By 2030 those 65 years of age and older will number some 70 to 78 million (based on different mortality, fertility, and migration assumptions) and will comprise between 19% and 21% of the total population. Whereas in 1900 one in 25 was age 65 or older, by 2030 the most likely demographic scenarios project that one in five in the U.S. population will be 65 and older. This density of one to five will likely characterize the population from 2030 to 2050 (6). Substantial policy implications result from this broad shift in population structure, including a need for focusing clinical practice on identification and treatment of pain in the old. The baby boomer generation will have considerably different experiences with the health care system than previous generations of the “young-old,” and it is likely that they will place greater demand on pain control compared with their parents and grandparents (today's “old-old” and “oldest-old”).

Compressing mortality into the practical upper limit of human life expectancy (approximately 85 years of life) is not just an academic issue for gerontologists and demographers. The U.S. Congressional Budget Office estimates that in 1998 Social Security and Medicare spending was approximately 6% of the national gross domestic product of the United States. This is projected to rise to approximately 14% by 2060, a time when baby boomers will be entering the ranks of the oldest-old.

To fund Social Security and Medicare/Medicaid at current levels will require a reduction for defense, law enforcement, education, and other federal government spending from 13% of the gross national product to approximately 5% (7).

Numbers, however, do not tell the whole story. Increased individual variability is a major characteristic of the old. Focusing solely on the growth of the elderly population, no matter how dramatic, misses the fact that as a group they are characterized by greater social, psychological, and physiologic diversity than younger adults. “An increasingly numerous and diverse older population is destined to change our social landscape in ways we can only imagine” (8).

Compression of Morbidity

“Graying” of the more developed countries is due to a compression of mortality into the later years of the human life span. The aging of these populations will continue for another 50 years. This compression of mortality is a fact of history. In contrast, a critical question that is only now being answered with quality empirical information is whether new cohorts of elders will be healthier than past cohorts. The possibility of increasing health until the upper limit of the human life span essentially means the compression of morbidity into the upper limit of the human life span. It has been suggested that, presumably, generalized improvements in quality of life and health status in future generations of elders will result in future savings in health care and social support costs. No studies to date, unfortunately, have included pain as a factor influencing possible compression of morbidity or successful aging into the practical upper limits of the human life span.

The diversity and variability in the elderly as a group stem not only from social history but also from dynamic patterns of morbidity in the old. Patterns of illness in the elderly, particularly the frail elderly, are characterized by multiplicity, duplicity, and chronicity. This complicates identification of the specific etiology of pain problems.

One example of age-related changes in acute clinical pain is absence of pain associated with myocardial infarction (MI) in some older patients. Silent MI is more common in elderly than younger patients. In one study of MI occurring in residential care patients, 40% did not report pain as their major complaint, and 56% had atypical presentation (9). The high incidence of atypical MI in residential care patients may well reflect the inability of such patients to communicate their pain accurately or even the indifference to pain that some patients with frontal-cortical dementia manifest (see below). Dementia, aphasia, and significant depression are common problems in the nursing home and clearly influence the ability of the patient to accurately report presence of pain. Nevertheless, increased frequency of silent MIs also occurs in community-dwelling elderly. In a survey of 1,000 community-dwelling middle-aged and elderly MI patients presenting at the emergency room, 30% of the elderly and 23% of the middle-aged patients presented with the primary complaint being other than pain (10). The 7% difference between the middle-aged and old patients was significant.

Referred pain associated with cardiac ischemia apparently presents atypically in the old more frequently than in the young. This likely reflects some impairment of nociceptive transmission. As discussed in Chapter 61, pain consequent to MI develops when sufficient levels of afferent impulses are reached and when an appropriate activation of central ascending pathways has been established. In patients with silent MI, such levels are apparently not reached, perhaps because of insufficient stimulation by the myocardium, decreased capacity for cephalad transmission, altered age-related changes of mechanisms subserving referred pain at the level of the spinal cord (see Chapter 4), or for other unknown pathophysiologic reasons. This suggests a need for enhanced vigilance when evaluating older patients who may have suffered an MI.

Young-Old, Old-Old, and Oldest-Old

Because of the great variability between individuals in the older population, gerontologists have made several attempts to identify subgroups of elderly. One such grouping is based on chronologic age and identifies three groups: young-old, old-old, and oldest-old. The young-old consist of those between 65 and 75 years of age. This group is generally healthy and active with sufficient social and financial resources. The young-old as a group place limited strain on supportive and health care services. The old-old consist of those 76 to 90 years of age. This group is characterized by increasing morbidity, reduced independence, and decreasing social and financial resources. Demand for supportive services in their activities of daily living is increased compared to the young-old. The oldest-old consists of those older than 90 years of age and represents a group growing substantially in number. There is a high level of morbidity in this group, and a new uncontrolled or difficult-to-control pain problem will, for many of the oldest-old, represent a high probability of mortality in a short time interval after onset of the pain problem.

Currently there is no systematic research concerning pain in the oldest-old and only limited information on the old-old. The bulk of the laboratory and clinical research on age differences in pain perception is limited to the young-old.

Laboratory Studies of Pain in the Young-Old

What is the impact of aging on pain? Can pain studied in the psychophysics laboratory answer this important question? It is currently impossible to answer this question for a number of reasons, only one of which is the limited information on the old-old. Experimental pain, as studied in the laboratory, focuses on pain intensity and in a few studies on the immediate unpleasantness of nociceptive stimuli. For obvious reasons, laboratory and clinical studies of pain must not involve suffering, yet suffering is the hallmark of chronic pain.

Experimental pain involves primarily assessment of sensory processes. Change in sensory systems is a widely accepted part of the aging processes. As documented by well-controlled longitudinal studies, age-related changes in vision and audition mark the onset of old age for the eye and ear. No longitudinal studies of the effects of aging on pain perception exist. All laboratory studies of pain to date are cross-sectional in design, representing a contrast of younger and older individuals who differ not only chronologically but also in sociocultural history. Cross-sectional studies allow inferences concerning age difference, not age change. Table 45-1 summarizes a number of laboratory studies of human pain (11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31 and 32). It appears that the findings of these studies are at best inconclusive.

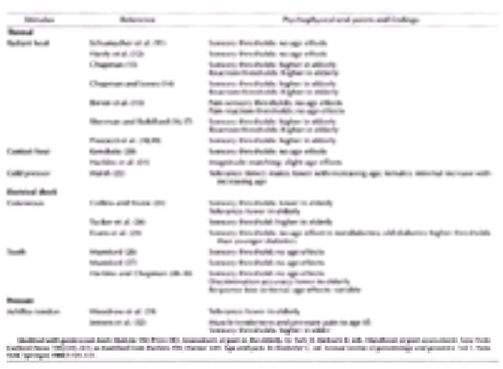

TABLE 45-1. Laboratory studies of the effect of age on psychophysical indices of pain sensitivity

Chronic Pain in the Old versus Young: Are There Differences?

General health status is a major factor in successfully coping with a chronic pain problem in any adult and may become paramount in the frail elderly with multiple-system disorders. The frailty of this population makes it particularly difficult to diagnosis a specific etiology of pain disorders and is thus a treatment challenge. There is, however, no question that chronic musculoskeletal pain complaints increase in both prevalence and incidence with aging. It is also clear that these conditions produce considerable morbidity. Figure 45-1 presents summary results from a stratified random sampling of community-dwelling individuals in the United States.

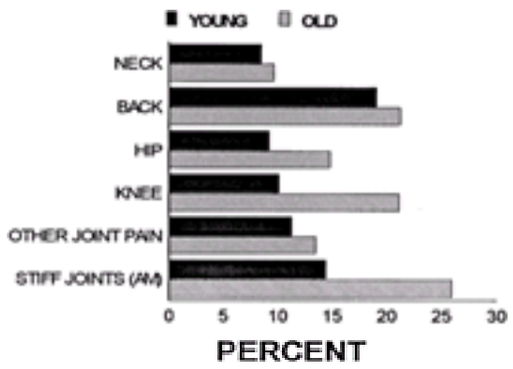

Figure 45-1. Prevalence of selected pains lasting at least 1 month and present during the past week in 5,659 community-dwelling individuals. Note that pain prevalence (percent) is greater in older [mean age, 75; standard deviation (sd) = 5.5 years; n = 2,863] compared with younger (mean age, 40; sd = 3.3 years; n = 2,796) respondents. [Data redrawn from Harkins et al. (40) based on original tabulations compiled from the National Health and Nutrition Follow-Up survey (33).] Significant group differences in pain prevalence were obtained for back pain (p <.05); hip pain (p <.001); knee pain (p <.0001); other joint pain (p <.01) and stiff joints on awakening (p <.0001). Knee pain associated with activities of daily living is likely to have a major impact on quality of life of the older adult.

As shown in Figure 45-1, prevalence of musculoskeletal and joint pain of the neck, back, hip, and knee and stiff joints on awakening is greater in older (mean age, 75; n = 2,836) compared with younger persons [mean age, 40; n = 2,796; original data tabulations from the National Health Nutrition Survey I Epidemiologic Follow-Up Study, 1982–1984 (33)] (see Table 45-1). Importantly, even in cases in which the prevalence of pain was not higher in the older group, pain intensity was reported as more severe (Fig. 45-2), as were symptoms associated with depression and limitations in activities of daily living (Fig. 45-3 and Fig. 45-4, respectively). Musculoskeletal pain in the old probably has an impact equal to or greater than that seen in the younger adult.

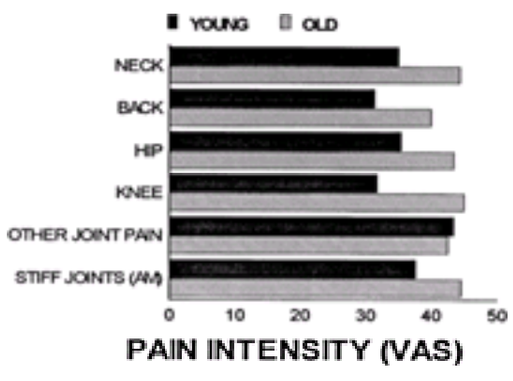

Figure 45-2. Pain intensity (visual analog scale) ratings for respondents shown in Figure 45-1. Pain intensity was assessed by visual analog scale rating of pain over the past week. Older respondents reported significantly higher pain intensity for all pain locations. This finding contrasts with laboratory findings that generally report decreased sensitivity in the elderly or no age differences (see Table 45-1 and Fig. 45-7 and Fig. 45-8). [Data redrawn from Harkins et al. (40) based on original tabulations compiled from the National Health and Nutrition Follow-Up survey (33).]

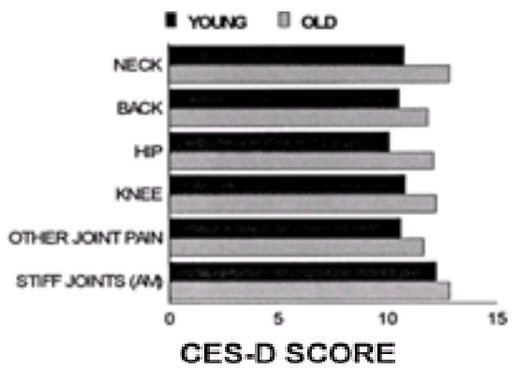

Figure 45-3. Negative affect (depressed mood over the past week) as assessed by the Center for Epidemiology Studies—Depression Inventory (Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychological Measurement* 1977;1:385). Although CES-D scores were consistently higher in older compared with the younger respondents, the magnitude of this difference exceeded p <.05 for neck, back, and hip pains only. (AM, morning.) [Data redrawn from Harkins et al. (40) based on original tabulations compiled from the National Health and Nutrition Follow-Up survey (33).]

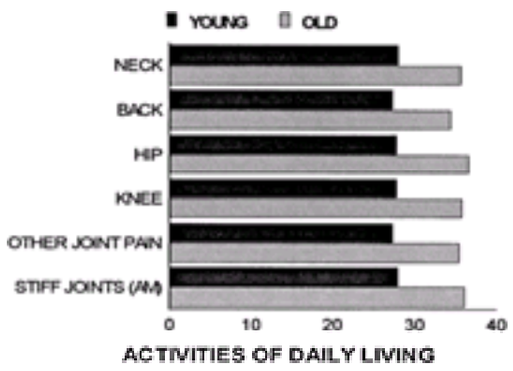

Figure 45-4. Age, pain, and limitations in activities of daily living (Lawton MP, Brody EM. Assessment of older people: self maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179). Note age is associated with a greater limitation in activities. It is currently unclear the degree to which pain, *per se*, contributes to the greater limitation in activities in the elderly (all differences significant at p <.001). [Data redrawn from Harkins et al. (40) based on original tabulations compiled from the National Health and Nutrition Follow-Up survey (33).]

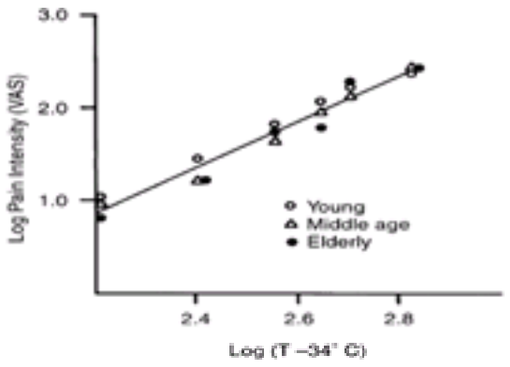

Figure 45-7. Effect of age on perceived intensity of thermal stimuli delivered to skin of the forearm in healthy young (mean, 25 years; range, 20 to 36), middle-aged (mean, 53 years; range, 45 to 60), and elderly (mean, 72.5 years; range, 65 to 80). Stimuli consisted of brief (5-second) heat pulses delivered to hairy skin of the forearm from an adapting temperature of 34°C to six intensities (43°C, 45°C, 47°C, 48°C, 49°C, and 51°C). Stimuli were presented twice randomly, and individuals reported pain intensity on a 150-mm visual analog scale (VAS). Care was taken to avoid stimulation of the same location more than once. Data are shown as log-log psychophysical functions. A significant main effect of age was observed (p = .05) and was due to older individuals rating lower intensity stimuli as less intense compared with younger individuals. At the higher stimulus intensities no age effects were statistically significant. This may represent age differences in response bias (cautiousness) rather than age differences in nociception. (From Harkins SW, Price DD, Martelli M. Effects of age on pain perception: thermonociception. *J Gerontol* 1986;41:58–63, with permission.)

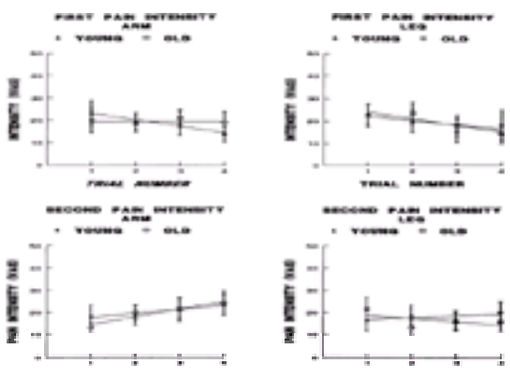

Figure 45-8. Suppression of first and slow temporal summation of second pain in relation to age (young mean, 26; range, 21 to 34; older mean, 65; range, 53 to 75). Top panels: visual analog scale (VAS) rating of very brief (0.7 seconds) 51°C (from an adapting temperature of 39°C) across four repeated stimuli (trial number) delivered to the same location on the arm and leg. First pain intensity decreased across repeated stimuli (interstimulus interval of 5 seconds). No age differences in pain intensity ratings were observed. Bottom panels: As in top panels but with interstimulus interval of 2.7 seconds. Slow temporal summation of second pain was observed at the arm for both younger and older subjects and no age effect was observed. For the leg a significant age effect was observed and was due to failure of the older group to show evidence of slow temporal summation of second pain. (From Harkins SW, Davis MD, Bush FM, et al. Suppression of first pain and slow temporal summation of second pain in relation to age. *J Gerontol A Biol Sci Med Sci* 1996;51:M260–265, with permission.)

The impact of specific types of pain on the quality of life of the older adult has not been systematically studied. Osteoarthritis is one of the most common joint disorders in the elderly (34) and has considerable impact on illness behavior and suffering. Radiographic severity of osteoarthritis of the knee is associated with symptomatology, morbidity, and psychological distress (35). Figure 45-5 shows prevalence of knee pain in different age groups as a function of age and expands the findings shown in Figure 45-1. Prevalence of knee pain increases to approximately 65 years of age and remains relatively stable in one in five adults aged 65 and older. As shown in Figure 45-6, prevalence of knee pain is considerably elevated in older women compared with older men. This interaction of age and gender is likely due to a combination of physiologic, psychological, and social factors. There is no systematic research of the interactions of age, gender, and specific musculoskeletal pains in relation to quality of life and well-being.

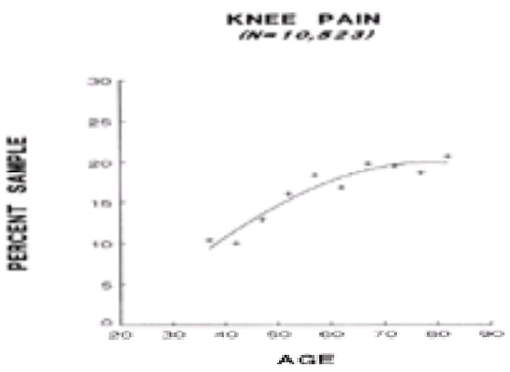

Figure 45-5. Knee pain in the general population in different age groups. Knee pain increases in prevalence to approximately the early 60s. Data as in Figure 45-1 but for age intervals between 37 and 89 years of age. Original tabulations from the National Health and Nutrition Survey I Epidemiologic Follow-Up Study (33).

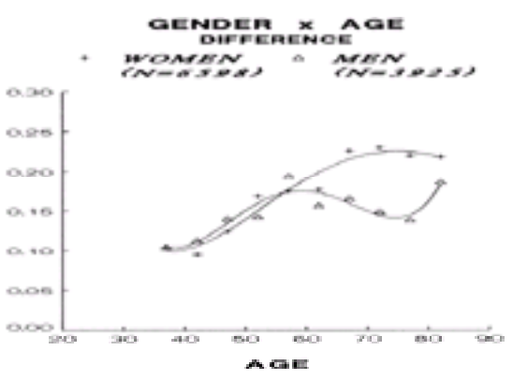

Figure 45-6. Age and gender on knee pain in the general population. Data as in Figure 45-5. Report of knee pain increases in women and decreases in men after 60 years of age. The degree to which this impacts on quality of life and activities of daily living and represents a sociocultural or physiological phenomenon is unclear. Stability of these descriptive prevalences estimated above age 80 is suspect due to the small sample size but may represent the fact that individuals who survive into their 80s and who reside in the community represent a special subpopulation of healthy, successfully aging individuals. Original data tabulations from National Health and Nutrition Survey I Epidemiologic Follow-Up Survery (33).

The Untidy Current State of Affairs

Age differences in pain perception appear to be study dependent (36,37,38,39,40,41,42,43 and 44). The findings are at best untidy. Some indicate a reduction in pain sensitivity, others an increase in pain sensitivity, and some no age differences in pain sensitivity. Findings from laboratory studies (see Table 45-1) contrast with findings from surveys on pain in the old (see Fig. 45-2). This variability in findings concerning pain sensitivity and aging reflects substantive differences in study design, psychophysical end points, pain-induction methods, subject selection criteria, practice on the psychophysical task, and instructions. Currently, the most parsimonious suggestion is that age differences in the perceived intensity of experimentally induced pain are minimal and likely reflect birth cohort effects and resulting psychosocial history more than the effects of time on the sensory processes of nociception. In turn, clinical studies are subject to biases in sample screening and selection. This is particularly true of studies based in the clinic, where selection biases include both self-referral bias and bias on the part of the primary health care provider. The recent and dramatic changes in the American health care system will likely further bias comparison of past and future clinical studies of pain in the frail elderly person.

PRESBYALGOS

Age in the later years of life systematically influencing pain sensitivity and perception is termed *presbyalgos*. Interestingly, there is no term parallel to *presbyopia* or *presbycusis* in the literature that summarizes age changes in the somatic senses, although there are well-documented age differences in vibrotactile sensitivity (45) proprioception and touch (46). Presbyalgos is limited to age effects on pain.

Presbyopia is defined as an age-related loss of ability to focus the lens at varying distances, but particularly in terms of near- point vision (loss of visual accommodation). The need for corrective lenses for near-point vision, so critical to reading and close work, is nearly universal by age 55 and marks the onset of old age for the eye. Additional age changes occur that degrade the visual image. These include increasing lens opaqueness and yellowing, resulting in decreases in light and its spectral properties reaching the retina (47). The major feature of presbyopia, the loss of accommodation, is due primarily to increased rigidity of the lens with age (sclerosis) and secondarily to decreased strength of the ciliary muscles.

Presbycusis refers to the progressive loss of higher-frequency sounds that is irreversible, progressive, and greater in men than women. The major clinical psychophysical feature of presbycusis is an increase in pure tone thresholds. Associated psychophysical findings include decreased temporal discrimination of tones and, more important, decreased speech recognition, particularly in noisy acoustic settings. Presbycusis is due, for the most part, to peripheral changes in the labyrinth and thus reflects the impact of changes over the life span on transduction processes (damage to outer hair cells particularly in the basal or high-frequency portion of the cochlea) (48). Thus, age changes in vision and hearing result more from accumulation of damage to mechanisms involving transduction of stimuli rather than from changes in central mechanisms of sensation and perception of light and sound.

Five components should be considered in the definition of presbyalgos: (a) age-dependent loss of receptors for pain (nociceptors); (b) changes in primary nociceptive afferents; (c) changes in more central mechanisms subserving pain sensation and perception; (d) changes in descending pain control mechanisms; and (e) birth cohort differences in social and cultural history that influence the meaning of pain.

Evidence for age changes or differences in density of nociceptors and primary nociceptive afferents is essentially nonexistent. Changes in nociceptor and primary nociceptive afferent density and function could result in age-related decreases in pain sensibilities. Although this would provide a blessing to those with chronic pain conditions, it would also confound the use of the symptom of pain as a diagnostic tool. Currently, inferences concerning the impact of old age on pain sensation are limited to clinical observations and psychophysical studies.

Most studies on age differences in pain sensitivity have used thermal stimuli in the nociceptive range and traditional psychophysical end points of pain threshold, pain reaction, and pain tolerance (see Table 45-1). More interesting are studies using multiple stimulus intensities and thus multiple levels of pain combined with subject reports of pain intensity by magnitude-matching procedures. Figure 45-7 presents results from an early study in our laboratory using contact thermal stimuli delivered to hairy skin in younger, middle-aged, and older adults (21). Although a significant age effect was observed, the explained variance due to age was very small (less than 0.1% of total variance). The age effect was due to lower levels of pain estimation at lower levels of stimulation in the elderly group. There were no age effects at the most intense levels of pain. These results suggest a response bias effect on the part of the old (elevated response criterion for lower level sensations) and not an age difference in pain sensitivity *per se*.

Several early studies from the 1940s and 1950s reported no age effect on thermal pain sensitivity when the subjects were well instructed and practiced and when the psychophysical end point was specifically defined as the pricking pain threshold (11,12,15). This is important not only for the emphasis on instructions and practice in the minimization of response biases, but also because the psychophysical end point, the pricking pain threshold, represents a specific sensation associated with so-called first pain. First pain sensation is mediated by A-d type II nociceptors that have an anatomic distribution mainly in hairy skin. A sharp, pricking sensation associated with first pain is absent from glabrous skin, which is innervated predominately by A-d type I and C fibers that are associated with the sensation of second pain (49) (see Chapter 3).

Thermal stimuli delivered to hairy skin of the arms or legs can produce a sensation of two distinct pains. The first is a brief, well- localized, sharp or pricking pain sensation that seldom outlasts the stimulus. This sensation is associated, as noted above, with activity in A-d type II mechano-heat afferents. These fibers are small (1 to 5 µm) and lightly myelinated, with a conduction velocity between 10 and 30 meters per second.

Under appropriate conditions, the sensation of first pain is followed by a painless period of up to 1 second, after which a second pain emerges. This second pain is characterized as a diffuse and poorly localized burning sensation that frequently outlasts the stimulus. This second sensation to thermal stimulation of hairy skin is associated with activation of “slow nociceptive” afferents or C fibers. This class of nociceptive afferents consists of small (0.05 to 2.00 µm) unmyelinated fibers with a conduction velocity of 0.5 to 2.0 meters per second. The differences in the sensory qualities of these two classes of nociceptors, including sensation onset times, allows evaluation of the selective effects of age on each. Several studies using fast rise–time thermal stimuli delivered to hairy skin have suggested that the elderly use information from C fibers more than type II A-d fibers (50,51).

Figure 45-8 shows pain intensity ratings of first and second pains in younger and older adults. No statistically significant group differences were obtained for previously unstimulated skin. The findings shown in Figure 45-7 and Figure 45-8 suggest that intensity of acute pain to thermal stimuli delivered to hairy skin is quite similar in younger and older adults, particularly for stimuli in the frankly painful range. It is this level of experimental pain that is relevant to an understanding of clinical pain, and not sensations that are near pain threshold.

Although the perceived intensity of frankly painful thermal stimuli delivered to hairy skin in the laboratory setting does not differ among age groups, there is increasing evidence that the quality of these sensations does change. We have observed that older adults do not describe brief thermal stimuli as sharp or pricking as frequently as do younger subjects. Rather, they tend to describe the sensations as burning. This suggests a greater reliance on second than first pain in older compared with younger persons. This possibility gains support from work by Helme's group (51), who report a greater use of second pain compared with first pain in older versus younger subjects in response to laser-produced radiant heat. A selective effect of age on first pain compared with second pain is also supported by recent age differences in response times to first and second pain (50).

Response time slowing is one of the most well-documented changes that occur with aging (52). One study, using thermal stimuli delivered to hairy skin of the arm and leg in healthy subjects, reported pain response time differences with age for onset of first pain but not for onset of second pain. Figure 45-9 summarizes these results. In this study, older subjects had longer reactions times to sensation onset to first pain from the leg compared with younger subjects. In contrast, there were no age group differences in onset to the sensation of second pain elicited from either arm or leg. Investigations interpreted these findings to indicate an age- dependent change in conduction properties of A-d type II nociceptive fibers, consistent with an age-related small-fiber peripheral neuropathy.

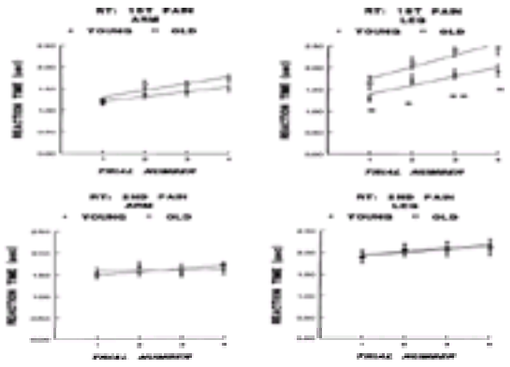

Figure 45-9. Effect of age on first and second pain onset (reaction time) to thermal stimuli delivered to arm and leg. Note that pain onset is delayed in elderly compared with younger individuals from the leg but not the arm for first pain but not second pain. These findings suggest that pain onset under well-controlled conditions may be of value in the study of small fiber peripheral neuropathy. Stimuli as in Figure 45-8. Response slowing with age is one of the more well-documented phenomena in the aging literature (52). The absence of any age differences for second pain suggests that the peripheral and, more important, the central components of generalized slowing do not apply to frankly noxious nociceptive stimuli delivered to hairy skin. Future research should focus on possible response slowing to similar stimuli delivered to glabrous skin. (From Harkins SW, Davis MD, Bush FM, et al. Suppression of first pain and slow temporal summation of second pain in relation to age. *J Gerontol A Biol Sci Med Sci* 1996;51:M260–265, with permission.)

There is growing evidence of subtle age-related differences in thermal pain sensitivity from hairy skin. This seems mainly related to changes in sensory qualities associated with first pain and thus changes in A-d type II mechano-heat nociceptors. There is less evidence that aging influences properties associated with the perception of second pain. Note that aging does not result in a marked reduction in pain intensity and thus the effects of aging on pain, at least from skin, do not parallel the effects of aging on many other senses. This should not be surprising. Age-related changes in sensory process are likely to be greater in systems with more complex transducer and receptor processes. Thus, changes with age in hearing (presbycusis) and vision (presbyopia) are due to loss of hair cells subserving audition and changes in the ability of the lens to accommodate for near-point vision and reflect effects of time on complex energy transduction and receptor mechanisms. The comparative simplicity of nociceptive afferents and their receptors suggests that “normal” aging will have minimal impact on pain sensation *per se*.

No studies to date have addressed possible age changes in central mechanisms of pain control in humans. This is an area in need of creative and well-conducted experiments. The fact that some individuals with Alzheimer's type dementia evidence altered reactions to painful events suggests that these illnesses may influence mechanisms subserving both pain sensitivity and responsivity. This is discussed below.

A few studies have indirectly addressed the possible influence of birth cohort effects on pain responses. Figure 45-7 summarizes one of these studies and suggests that the older adult reports less pain compared with younger pain patients. This probably reflects age differences in the meaning of chronic pain to different age groups (43).

Table 45-2 summarizes major characteristics of presbyalgos. As new information comes forth over time, this table is likely to change substantially. Note that the issues addressed in this definition of presbyalgos stress relations to sensory processes. This is consistent with earlier definitions of sensory changes with age. Nevertheless, it is critical in future research, clinical practice, and education to focus less on the sensory/perceptual changes (if any) in nociceptive processes with normal aging and more on the impact of recurrent and chronic pain on the older person. Although normal aging does not bring about major changes in the sensory/perceptual process subserving appreciation of pain, age-related cerebral disorders may directly influence pain and its expression. A special issue, as noted above, is that of dementia of the Alzheimer's type.

TABLE 45-2. Characteristics of presbyalgos

SPECIAL ISSUE

The impact of dementia on pain sensibilities and expression is unclear. AD is the most prevalent form of dementia in the older adult. Given the wide distribution of cerebral degeneration, loss of communicative and cognitive skills, as well as eventual failure of basic reflexes (e.g., gag reflex) critical to survival in the later stages of AD, altered pain expression in these patients would not seem surprising.

Early clinical reports suggested reduced pain sensibilities in some moderately demented AD patients (38). Pain reactions following what would normally be painful seem obtunded in these patients, and although this pain indifference appeared to be more obvious in more demented individuals, it was also present in some AD patients with mild to moderate dementia (53). These findings may stem from the increased “apathy” in some AD patients. In this case, apathy represents a state characterized by loss of interest and response to events that is independent of depression or depressed mood and affect (54).

Future research needs to be directed at identification of AD patients with pain indifference. It is likely that AD is a heterogeneous disorder with different etiologies but with a final common pathway that includes major cognitive symptoms. Subtle differences in natural history, including apathy and indifference to painful conditions may well have implications for identification of one or more subgroups of AD patients.

This is relevant to the study of pain because that specific cerebral pathology in subgroups of patients with AD may illuminate the mechanisms underlying selective properties of pain. The levels of emotional distress and apparent suffering due to chronic pain may be reduced in patients with AD. This would be consistent with loss of integrative cognitive ability, working and semantic memories that characterize this form of dementia. Helme suggests that chronic pain in AD patients is more like acute pain in nondemented individuals because the history of the pain is progressively lost (*personal communication*, R. Helme, 1997). This fits observed reduction in pain-related symptoms in AD patients with arthritis, frozen shoulder, Raynaud's disease, and osteoporosis (53). Additionally, the “I don't like this sensation” or the anhedonic and suffering dimension of pain is selectively reduced in a subgroup of AD patients.

The affective and sensory discriminative components of pain have different cortical representations. The sensory dimension, including aspects of pain quality, location, and intensity, is well represented at cortical areas SI and SII, with integration of pain, visceral, and limbic input at the insula (55). Insular volume appears to be relatively stable between 40 and 70 years of age in normal individuals and decreased in patients with a clinical diagnosis of AD (56).

It may also be that the natural history of pain perception, particularly pain affect and behavior, is different in patients with classic AD versus patients with frontotemporal dementia. Asymmetric frontal and anterior temporal atrophy is a distinctive finding thought to distinguish these two forms of dementia (57). Higher-order pain responses involving affect, emotion, and memory of pain appear well represented in prefrontal cortex (55). It may well be that patients with different

forms of later-life dementia react differently to pain as a direct result of the disease process.

Pain assessment in these dementia patients may allow more precise definition of the natural history of these various disorders. Given that new pharmacologic agents for the symptomatic treatment of dementia are becoming available, pain assessment could aid in identifying patients most likely to respond positively to such treatment. A better understanding of the relations among pain behavior and subforms of later-life dementia could also provide insight into cortical and subcortical representations of pain sensation and pain affect.

Pain perception that is obtunded or characterized by indifference and apathy in a subgroup of AD patients opens considerable care management and even legal issues. Fisher-Morris and Gellatly (53) report several cases of pain indifference in AD patients. One of these involved a nursing home resident who sustained a fractured femur sometime before death. Failure to diagnose the fracture was “primarily because she had not complained of any pain and has continued to ambulate without any apparent discomfort.” The coroner's inquiry noted that she must have died an “agonizing death” and pointed out that “as the man in the street feels pain, so should an elderly demented lady with a fracture.” Failure to recognize pain in AD patients is for the most part a failure to look. There may well, however, be a subgroup of older demented patients who are truly pain indifferent. This is an area in need of immediate and concerted attention.

CONCLUSIONS

An expanding literature has now begun to address issues related to geriatric pain assessment. Health care providers need to recognize certain principles for optimal care of the elderly patient. These include, as Ferrell (58) has pointed out, sensitivity to functional status in the face of limited potential for dramatic recovery. “Defining and treating pathologic entities [in the older adult] is often less complicated than intervening in the discomfort and disability of patients, but the latter is what truly constitutes the art of geriatric care.” Pain has a greater impact on successful aging and quality of life in the older adult than age has on pain sensitivity. Thus, presbyalgos differs from the other “presbys,” which by their very nature produce sensory loss and potential isolation and limitations in daily activities. The future in geriatric pain care should be less concerned with the psychophysics of sensory changes and more with the most efficient methods to clinically assess and treat pain in the frail elderly adult. In this regard, pain specialists need to educate care providers who are in daily contact with dependent elders. Table 45-3 summarizes several special considerations in geriatric pain assessment.

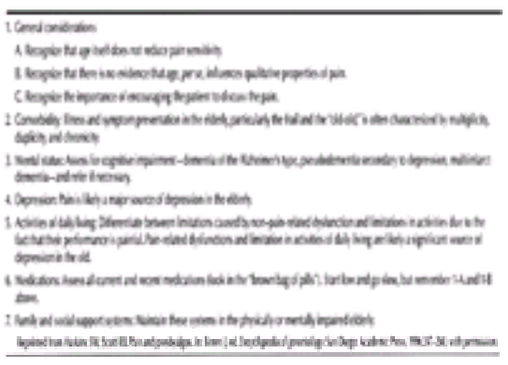

TABLE 45-3. Special considerations in geriatric pain assessment

It has been more than 20 years since the first modern review of geriatric pain (36), which was concerned primarily with sensory changes in pain with aging. The elderly, particularly the frail elderly, are now seen as a population that can be well served by recognition of the importance of pain control on activities of daily living and quality of life. This is a beneficial change in our understanding of pain in the elderly.

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CHAPTER 46

General Considerations of Pain in the Head

John J. Bonica and John D. Loeser

ANATOMIC AND PHYSIOLOGIC BASIS

The nerve supply to various structures of the head is presented in this section. For obvious reasons, emphasis is placed on sensory (nociceptive) pathways, and, as discussed in Chapter 4, these are found in cranial nerves V, VII, VIII, and IX, and in the second and third cervical dorsal roots and the autonomic innervation to the head is summarized. This discussion is based on the first edition of this book (1) and *Gray's Anatomy* (2).

Trigeminal Nerve

The trigeminal nerve, the largest of the cranial nerves, is a mixed somatic nerve consisting of a large sensory and, usually, two small motor roots. It is short, extending from the ventrolateral surface of the pons in an anterolateral direction to the apex of the petrous portion of the temporal bone, in which it expands into the gasserian (trigeminal, semilunar) ganglion located in Meckel's cave (Fig. 46-1 and Fig. 46-2). This is an outpouching of dura from the posterior fossa that lies under the dura of the middle fossa. The sensory root, which is composed of the central branches of the unipolar cells contained in the ganglion, conducts sensation from the face and anterior two-thirds of the head. The motor root, the fibers of which originate in the motor nucleus of the trigeminal nerve located in the pons, courses beneath and medial to the sensory root and then beneath the semilunar ganglion in Meckel's cave to pass through the foramen ovale, in which it joins and becomes part of the mandibular division to supply motor fibers to the muscles of mastication. The distal processes of sensory neurons divide into the three major divisions: the ophthalmic, maxillary, and mandibular nerves (Fig. 46-3; see Fig. 46-2). (Chapter 4 provides a detailed discussion of the anatomy and physiology of the trigeminal system in the brainstem and its homologies with the spinal sensory systems.)

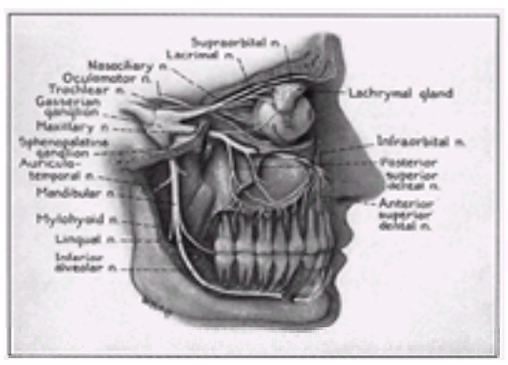

Figure 46-1. Anatomy of the trigeminal nerve and its three major divisions and their branches.

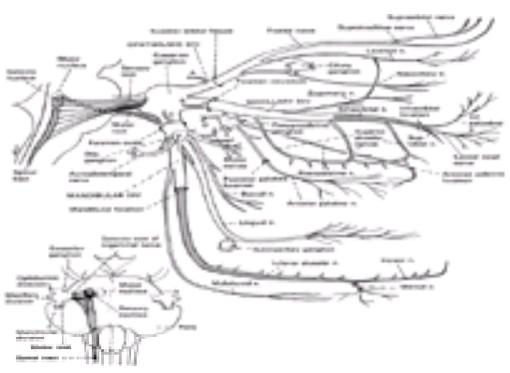

Figure 46-2. Schematic depiction of the trigeminal nerve and its branches. Also shown is its sensory root, composed of central branches of neurons in the gasserian ganglion that synapse with the main sensory nucleus and the descending tract and nucleus of the trigeminal nerve, as well as the origin of the motor root and its origin in the motor nucleus. Below is the anterior view showing the relationship of these nuclei and the gasserian ganglion. Recurrent branches of the major division of the trigeminal nerve that supply sensory fibers to the meningeal arteries and dura mater (*A*, *B*, and *C*). Nerve to the pterygoid canal (vidian nerve) (*D*). Middle and posterior palatine nerves and the pharyngeal branch from the pterygopalatine ganglion (*E*).

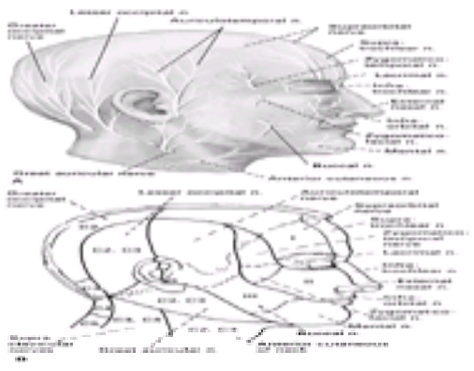

Figure 46-3. Cutaneous sensory supply to the head. **A:**Major cutaneous nerves. **B:** Border of the territory of each nerve.

Ophthalmic Nerve

The ophthalmic, the first and smallest division of the trigeminal nerve, is a short, somewhat flattened nerve approximately 2 cm long that arises from the anteromedial part of the gasserian ganglion (see Fig. 46-1 and Fig. 46-2). From this point the nerve proceeds in an anterior and slightly superior direction to pass through the lateral wall of the cavernous sinus and through the superior orbital fissure to reach the orbit (Fig. 46-4; see Fig. 46-2). It is solely sensory, conducting all somatic sensations from the eye and its adnexa, including the conjunctivae, lacrimal gland, part of the mucous membranes of the nose and paranasal sinuses, and the skin of the forehead, eyelids, and nose. Before passing through the fissure it gives off a recurrent branch to the tentorium cerebelli, a connecting filament to the oculomotor, trochlear, and abducens nerves, and it receives sympathetic filaments from the carotid plexus. In the superior orbital fissure it divides into three terminal branches: the lacrimal, frontal, and nasociliary nerves.

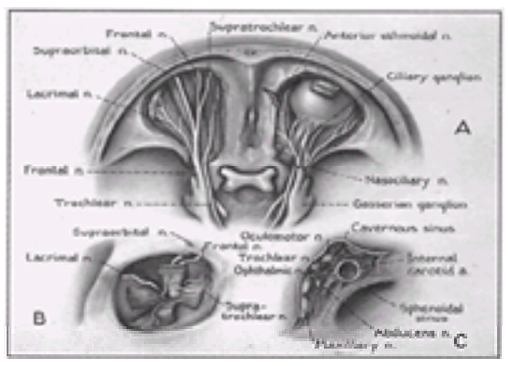

Figure 46-4. Ophthalmic division of the trigeminal nerve and its branches. **A:** The roof of the orbit has been removed and the nerves are viewed from the top. The main nerves are on the left; on the right these and the underlying muscles have been removed to show the course of the nasociliary nerve and the relationships of the ciliary ganglion. **B:** The eyeball of the right orbital cavity has been removed to show the relationships and courses of the branches of the ophthalmic division. **C:** Relationships of the ophthalmic and other nerves in the cavernous sinus.

Lacrimal Nerve. The lacrimal nerve, the smallest of the three branches of the ophthalmic nerve, passes into the orbit through the anterolateral part of the fissure above the ocular muscles, proceeds forward between the periosteum and the orbital contents to pass through the lacrimal gland, and finally pierces the orbital septum to end in the skin around the external canthus. Whereas it supplies filaments to the lacrimal gland and conjunctiva in the orbit and connects with the zygomatic branch of the maxillary nerve, in the subcutaneous tissues outside of the orbit it connects with branches of the facial nerve. In the orbit, through its connection with the zygomatic branch of the maxillary nerve, it receives postganglionic parasympathetic fibers that have their cell bodies in the pterygopalatine ganglion and are the secretomotor motor fibers to the lacrimal gland (see Autonomic Innervation of the Head, later in this chapter; also see Fig. 46-11).

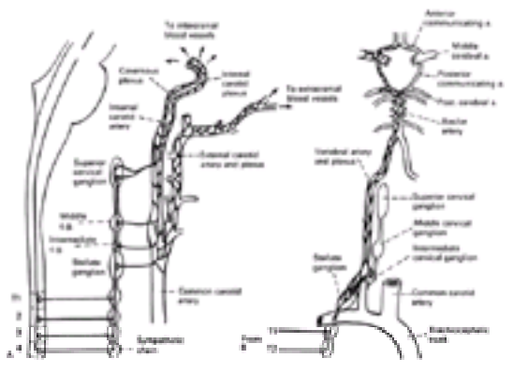

Figure 46-11. The sympathetic nerve supply to the head. **A:** Sympathetic supply through the carotid and cavernous plexuses. Preganglionic fibers originate in the first, second, third, and, frequently, the fourth thoracic segments of the spinal cord, pass through the white rami communicantes and from there to the paravertebral sympathetic chain to synapse in superior, middle, intermediate, and inferior cervical ganglia, in which they synapse with postganglionic neurons. The axons of the latter make up the internal carotid nerve, which passes to the internal carotid artery and soon divides into a lateral branch; this breaks up into the internal carotid plexus and a medial branch that forms the cavernous plexus. Both plexuses continue as subsidiary plexuses to supply all the branches of the internal carotid artery. The postganglionic fibers that make up the external carotid nerves arise primarily in the stellate ganglion but also in the middle and superior cervical ganglia, and then pass to the common carotid and the external carotid arteries. The external carotid nerves break up into intricate plexuses that continue as subsidiary plexuses to all the branches of this artery to supply the extracranial blood vessels as well as the middle and accessory meningeal arteries (a branch of the maxillary, which in turn is a branch of the external carotid artery). In addition to supplying blood vessels, sweat glands, and the arrector pili muscles, these plexuses also provide sympathetic nerves to intrinsic muscles of the eye and to the lacrimal, parotid, submandibular, sublingual, and parotid glands. **B:** Sympathetic supply to the vertebral artery and circle of Willis. Preganglionic neurons are located in the first and second thoracic segments, pass to the sympathetic chain, and ascend to the stellate ganglion and the middle and intermediate cervical ganglia, in which they synapse with postganglionic neurons. The axons of postganglionic neurons make up the vertebral nerve, consisting of two major branches that arise from the stellate ganglion and a minor branch that arises from the middle or intermediate cervical ganglion. On reaching the vertebral artery, the vertebral nerve breaks up into the vertebral plexus, which continues as a plexus around the basilar artery, the circle of Willis, and all its branches.

Frontal Nerve. The frontal nerve, the largest branch of the ophthalmic nerve, enters the orbit through the superior orbital fissure just medial to the lacrimal gland and then proceeds anteriorly and rostrally between the periosteum and levator palpebrae superioris muscle for approximately two-thirds the length of the orbital cavity, where it divides into a larger lateral branch, the supraorbital nerve, and a smaller medial branch, the supratrochlear nerve (Fig. 46-5; see Fig. 46-4). Both of these nerves continue their forward paths and finally leave the orbit by curving around the superior orbital margin to reach and supply the skin of the forehead, the anterior two-thirds of the scalp, and the underlying pericranium.

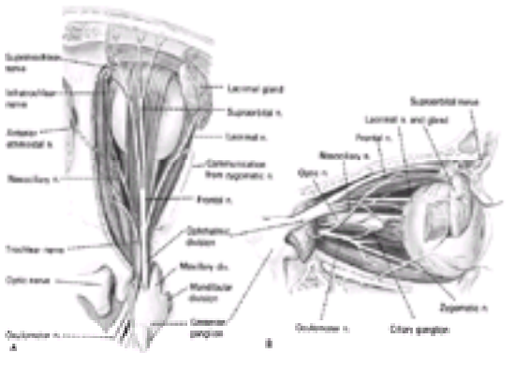

Figure 46-5. Anatomy of the ophthalmic nerve and its branches and relationship to other cranial nerves that supply the eye and lacrimal gland. **A:** Superior view. **B:** Lateral view. (Modified from Clemente CD, ed. *Gray's anatomy*, 30th Am. ed. Philadelphia: Lea & Febiger, 1985.)

Supratrochlear Nerve. The supratrochlear nerve within the orbit bends medially to pass above the pulley of the superior oblique muscle and gives off a filament that communicates with the infratrochlear branch of the nasociliary nerve. It pierces the orbital fascia and sends filaments to the conjunctiva and the skin of the medial part of the upper eyelid. It then curves around the supraorbital margin approximately 2 cm from the midline, passing deep to the corrugator and frontalis muscles, gives filaments to the pericranium, and divides into branches that pierce the muscles to supply the skin of the mesial lower part of the forehead (see Fig. 46-5).

Supraorbital Nerve. The supraorbital nerve, a continuation of the frontal nerve, leaves the orbit through the supraorbital foramen or notch, which is approximately 2.5 cm from the midline. In the notch it gives off a small filament that supplies the mucous membrane of the frontal sinus and also gives off filaments that supply the upper lid. The nerve then continues on the forehead beneath the frontalis muscle and divides into two branches. The smaller *medial branch,* often called the *frontal branch*, pierces the muscle and supplies the scalp as far back as the parietal bone. The larger *lateral branch* pierces the aponeurotica and supplies the scalp as far posteriorly as the lambdoidal suture.

Nasociliary Nerve. The nasociliary nerve is intermediate in size between the frontal and lacrimal nerves and is medially placed in the orbit (see Fig. 46-4 and Fig. 46-5). It enters the orbit through the medialmost portion of the superior orbital fissure, passes through the annulus of Zinn and between the two heads of the rectus lateralis, and proceeds obliquely in an anteromedial direction, crossing above the optic nerve to reach the anterior ethmoidal foramen on the medial wall of the orbit, where it is known as the *anterior ethmoidal nerve.* Through this foramen it passes into the anterior cranial fossa and immediately leaves by way of the nasal fissure of the cribiform plate to enter the nasal cavity where it divides into internal and external nasal branches. The nasociliary nerve gives off four important groups of branches while in the orbital cavity.

Long (Sensory) Root of the Ciliary Ganglion. The long root of the ciliary ganglion arises from the nasociliary nerve between the two heads of rectus lateralis muscles, runs anteriorly on the lateral side of the optic nerve, and enters the posterosuperior angle of the ciliary ganglion. It contains sensory fibers that pass through the ganglion without synapsing and continues on to the globe by way of the short ciliary nerves.

Long Ciliary Nerves. The long ciliary nerves, usually two or three, emerge from the parent nerve as it crosses the optic nerve and accompany the short ciliary nerves from the ciliary ganglion. They then pierce the posterior part of the sclera and proceed anteriorly between it and the choroid to become distributed to the iris and cornea. In addition to afferent fibers the long ciliary nerves contain sympathetic fibers from the superior cervical ganglion to the dilator pupillary muscles.

Infratrochlear Nerve. The infratrochlear nerve is given off from the nasociliary nerve just before the latter enters the anterior ethmoidal foramen and proceeds anteriorly along the superior border of the rectus medialis muscle near the pulley of the oblicus superior, where it is joined by the filament from the trochlear nerve. It then passes to the medial angle of the eye and supplies the skin of the eyelid, side of the nose, conjunctiva, lacrimal sac, and caruncula lacrimalis.

Ethmoidal Branches. The ethmoidal branches supply the mucous membrane of the sinuses. The *posterior ethmoidal nerve* leaves the orbit through the posterior ethmoidal foramen and supplies the posterior ethmoidal and sphenoidal sinuses. The *anterior ethmoidal branches* are filaments that are given off as the nerve passes through the anterior ethmoidal foramen and supply the anterior ethmoidal and frontal sinuses.

Nasal Branches. The internal nasal branch supplies the mucous membrane of the anterior part of the septum and the lateral wall of the nasal cavity. The external nasal branch emerges between the nasal bone and the lateral nasal cartilage, passes deep to the nasalis muscle, and supplies the skin of the ala and the apex of the nose (Fig. 46-6).

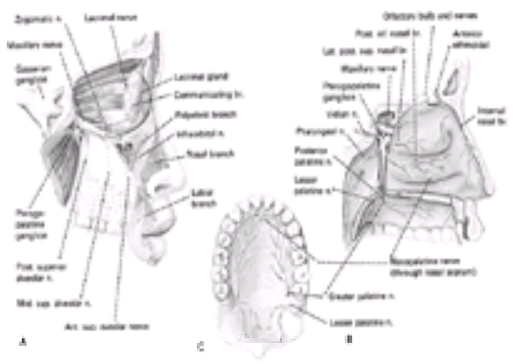

Figure 46-6. **A:** Anatomy of the maxillary nerve and its branches and the structures they supply. **B:** Sagittal section depicting the relationship of the pterygopalatine ganglion to the maxillary nerve and to the branches of the ganglion that supply the nasal cavity and the hard and soft palates. **C:** View of the inferior surface of the palate depicting distribution of the nerves to the structure. The nasopalatine nerves emerge through the anterior palatine foramina, the greater palatine nerves emerge through the greater palatine foramina, and the lesser palatine nerves emerge through the lesser palatine foramina.

Maxillary Nerve

The maxillary nerve, the second division of the trigeminal nerve, arises from the anterior border of the gasserian ganglion between the ophthalmic and mandibular nerves (see Fig. 46-1 and Fig. 46-2). Like the ophthalmic nerve, the maxillary nerve is entirely sensory, supplying the skin of the middle portion of the face, lower eyelid, side of the nose, and upper lip and the mucous membranes of the nasopharynx, maxillary sinus, soft palate, tonsil, and roof of the mouth, upper gums, and teeth. From its point of origin it proceeds anteriorly beneath the dura mater, passing first through the lateral wall of the cavernous sinus and then through the foramen rotundum, by which it leaves the cranial cavity to reach the pterygopalatine fossa. At its origin it gives off the *middle meningeal nerve,* which accompanies the ipsilateral middle meningeal artery and supplies this artery and its branches as well as the dura mater and other pain-sensitive structures within the cranium (see Chapter 48).

The maxillary nerve traverses the outer part of the pterygopalatine fossa in an anterior and slightly lateral direction and enters the orbit through the inferior orbital fissure to become the infraorbital nerve. Within the pterygopalatine fossa the maxillary nerve gives off the zygomatic nerve, pterygopalatine nerves, and posterior superior orbital branches. The nerve continues its anterior course, first occupying the infraorbital groove and canal in the floor of the orbit, in which it gives off the middle superior alveolar and anterior superior alveolar branches. It then passes through the infraorbital foramen to emerge on the face, where it immediately divides into its terminal branches, the inferior palpebral, lateral nasal, and superior labial nerves (see Fig. 46-6).

Zygomatic Nerve

Like its parent, the zygomatic nerve passes through the inferior orbital fissure and enters the orbit, where it gives off a filament that connects with the lacrimal nerve and then divides into the zygomaticotemporal and zygomaticofacial nerves (see Fig. 46-6A).

Zygomaticotemporal Nerve. The zygomaticotemporal nerve runs along the lateral wall of the orbit in a groove in the zygomatic bone, passes through a small foramen or suture, and enters the temporal fossa, in which it runs cephalad between the bone and the substance of the temporalis muscle. Approximately 2.5 cm above the zygomatic arch the nerve pierces the temporal fascia and becomes distributed to the skin of the side of the forehead; it usually communicates with the facial nerve and with the auriculotemporal branch of the mandibular nerve.

Zygomaticofacial Nerve. The zygomaticofacial (or malar) nerve passes along the inferior lateral angle of the orbit and through the zygomatic bone by way of the zygomaticoorbitale and zygomaticofacial foramina, emerges on the face, perforates the orbicularis oculi muscle, and supplies the skin on the prominence of the cheek. It also joins with the facial nerve and with the inferior palpebral branch of the infraorbital nerve.

Pterygopalatine (Sphenopalatine) Nerves. The pterygopalatine (sphenopalatine) nerves, formerly called the *sensory roots* of the pterygopalatine ganglion, connect

with preganglionic parasympathetic secretomotor fibers and pass through the ganglion without synapsing to become distributed into four groups: orbital branches, greater palatine nerves, posterior superior nasal branches, and pharyngeal branches (see Fig. 46-6B).

Orbital (Ascending) Branches. The orbital branches enter the orbit through the inferior orbital fissure to supply the periosteum and also give off filaments that pass through foramina in the frontal ethmoidal suture to supply the mucous membranes of the posterior ethmoidal and sphenoidal sinuses.

Greater (Anterior) Palatine Nerve. The greater (anterior) palatine nerve passes through the pterygopalatine canal, emerges on the hard palate through the greater palatine foramen, and divides into several branches, the longest of which passes anteriorly in a groove in the hard palate nearly as far as the incisor teeth. It also supplies the gums and mucous membranes of the hard palate and the adjacent part of the soft palate and communicates with the terminal filaments of the nasopalatine nerve. The *posterior inferior nasal branches* leave the greater palatine nerve while it is in the canal, enter the nasal cavity through the opening in the palatine bone, and ramify over the inferior concha and middle and inferior meatuses. The *lesser* (*middle and posterior*) *palatine nerves* emerge through the lesser palatine foramina and distribute branches to the soft palate, uvula, and tonsil and also join with the tonsillar branches across the pharyngeal nerve to form a plexus around the tonsil (circulus tonsillaris).

Posterior Superior Nasal Branches. The posterior superior nasal branches of the pterygopalatine nerve enter the posterior part of the nasal cavity by the sphenopalatine foramen, supply the mucous membrane covering the superior and middle conchae, the lining of the posterior ethmoidal sinus, and the posterior part of the septum, and give off the nasopalatine nerve. The latter passes across the roof of the nasal cavity inferior to the ostium of the sphenoidal sinus to reach the septum. The nasopalatine nerve proceeds anteriorly and caudad, lying between the mucous membrane and periosteum of the septum to reach and pass through the incisive canal, in which it communicates with the corresponding nerve of the opposite side and with the greater palatine nerve (see Fig. 46-6B and Fig. 46-6C).

Pharyngeal Branch. The pharyngeal branch of the pterygopalatine nerve emerges from the posterior part of the ganglion and, along with the pharyngeal branch of the maxillary artery, passes through the pharyngeal canal to become distributed to the mucous membrane of the nasal part of the pharynx, posterior to the auditory tube.

Posterior Superior Alveolar Nerves

The posterior superior alveolar (dental) branches, usually two, but occasionally only one, arise from the trunk of the maxillary nerve just before they enter the infraorbital groove. The branches arise and descend on the posterior surface of the maxilla, give off several twigs to the gums and neighboring parts of the mucous membrane of the cheek, and enter the posterior alveolar canals on the infratemporal surface of the maxilla (see Fig. 46-6).

They pass anteriorly in the substance of the bone, communicate with the middle superior alveolar nerve, and then give off branches to the lining membrane of the maxillary sinus and three twigs to each molar tooth, with each twig entering the foramen at the apex of the tooth (see Fig. 46-1, Fig 50-2, and Fig 51-4).

Middle and Anterior Superior Alveolar Branches

The middle superior alveolar (dental) branch of the maxillary nerve is given off in the posterior part of the infraorbital canal and proceeds caudad and anteriorly in a canal in the lateral wall of the maxillary sinus to supply the two premolar teeth. Filaments from these branches join with those of the anterior and posterior superior alveolar branches to form the *superior dental plexus*.

The large anterior superior alveolar (dental) branch is given off from the maxillary nerve just before its exit from the infraorbital foramen (see Fig. 46-6A). It courses in a canal in the anterior wall of the maxillary sinus and divides into branches that supply the incisor and the canine teeth. It gives off filaments that communicate with the middle superior alveolar branch, angles off a nasal branch that passes through the lateral wall of the inferior meatus, and supplies the mucous membrane of the anterior part of the inferior meatus and the floor of the nasal cavity.

Infraorbital Nerve

The infraorbital nerve is the terminal cutaneous branch of the maxillary nerve, which divides into three groups of branches (see Fig. 46-3 and Fig. 46-6A). The *inferior palpebral branches* pass cephalad deep through the orbicularis oculi muscle to supply the skin and conjunctiva of the lower eyelid and, at the lateral angle of the orbit, join with the facial and zygomaticofacial nerves. The *external nasal branches* supply the skin of the side of the nose and of the septum mobile nasi and also join with the terminal twigs of the nasociliary nerves. The *superior labial branches* pass deep to the levator labii superioris muscle and are distributed to the skin of the upper teeth, mucous membrane of the mouth, and labial glands.

Mandibular Nerve

The mandibular nerve is the third and only mixed division of the trigeminal nerve and is formed by the union of a large sensory root and a small motor root. The former arises from the anterolateral portion of the gasserian ganglion (see Fig. 46-1 and Fig. 46-2), whereas the latter arises from the pons and passes beneath the gasserian ganglion to reach the foramen ovale, through which it leaves the cranial cavity, together with the sensory root. The sensory fibers supply the skin of the temple region; auricula; external meatus; cheek, lower lip, and lower part of the face; the mucous membrane of the cheek, tongue, and mastoid air cells; the lower teeth and gums; the mandible and temporomandibular joint; and part of the dura mater and skull. The motor fibers supply the muscles of mastication (masseter, temporalis, pterygoids), the mylohyoid and anterior belly of the digastric muscles, and the tensores tympani and veli palatini.

Within or immediately outside the foramen ovale, the two roots fuse into a single short (2 to 3 mm) trunk, which lies just anterior to the middle meningeal artery, lateral to the otic ganglion and internal pterygoid muscle, and medial to the extensor pterygoid, masseter and temporal muscles, and ramus of the mandible. Soon after it is formed the nerve gives off two small branches, the *nervus spinosus*, which reenters the cranial cavity along with the middle meningeal artery to supply the anterior and posterior divisions of the artery and the dura mater, and the *medial pterygoid nerve*, which penetrates the otic ganglion, enters the deep surface of the medial (internal) pterygoid muscle, and ends in two branches, the nerve to the tensor veli palatini and the nerve to the tensor tympani. The trunk then divides into a small anterior trunk and a large posterior trunk.

Anterior Trunk

The anterior trunk (Fig. 46-7), composed mostly of motor fibers, promptly divides into the masseteric nerve, the deep anterior and posterior deep temporal nerves, and the external pterygoid nerve, which supply the aforementioned muscles of mastication. The anterior trunk also gives off a small sensory branch, the buccal (buccinator) nerve, which penetrates the pterygoid, temporalis, and masseter muscles and ramifies on the surface of the buccinator muscle, forming a plexus of communications with the buccal branches of the facial nerve. It supplies the skin of the cheek over this muscle and sends penetrating branches to supply the mucous membranes of the mouth and of part of the gums in the same area.

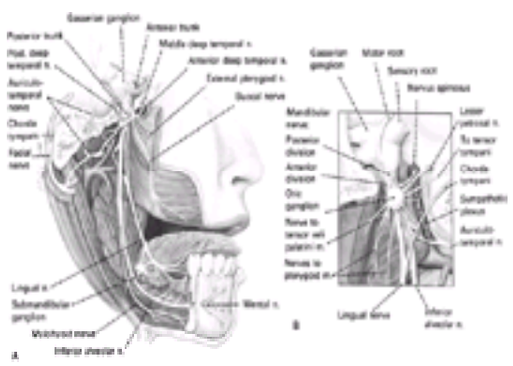

Figure 46-7. **A:** Anatomy of the right mandibular nerve and its branches and the structures they supply. **B:** Medial view of the right mandibular nerve showing its major branches and its relationship to the otic ganglion and its root (the lesser petrosal nerve), as well as its branches (see text for details).

Posterior Trunk

The large posterior trunk is composed mostly of sensory fibers and a small motor component. After a short course it divides into the auriculotemporal nerve, lingual nerve, and inferior alveolar nerve (see Fig. 46-7A).

Auriculotemporal Nerve

The auriculotemporal nerve arises by two roots from the posterior aspect of the trunk that encircles the middle meningeal artery close to the foramen spinosum and immediately runs posterolaterally beneath the external pterygoid muscle to reach the medial side of the neck of the mandible. Here it turns sharply cephalad to ascend between the anterior border of the auricle and the condyle of the mandible under cover of the parotid gland, finally reaching the subcutaneous tissue overlying the zygomatic arch in which it divides into five branches and communicates with the facial nerve and the otic ganglion.

The *anterior auricular branches*, usually two, supply the skin of the anterior superior part of the auricula, principally the helix and tragus. The two branches to the external acoustic meatus enter the meatus between its bony and cartilaginous portions and supply the skin lining it, the upper branch sending a filament to the tympanic membrane. The articular branches consist of one or two twigs that enter the posterior part of the temporomandibular joint. The parotid branches supply the parotid gland, carrying the parasympathetic postganglionic fibers transmitted by the communication between the auriculotemporal nerve and the otic ganglion. The superficial temporal branches accompany the superficial temporal artery to the vertex of the skull, supply the skin of the temporal region, and communicate with the facial and zygomaticotemporal nerve.

Inferior Alveolar Nerve

The inferior alveolar (dental) nerve accompanies the inferior alveolar artery, at first deep to the lateral pterygoid muscle and then between the sphenomandibular ligament and the ramus of the mandible, and enters the mandibular foramen (see Fig. 46-7A). Just before entering the foramen the inferior alveolar nerve gives off the mylohyoid branch that proceeds inferiorly and anteriorly in a groove on the deep surface of the ramus of the mandible to reach and supply the mylohyoid muscles and the anterior belly of the digastric muscle. On entering the mandibular foramen, the inferior alveolar nerve proceeds inferiorly and anteriorly within the mandibular canal until it reaches the mental foramen, in which it divides into two terminal branches: the incisor nerve, which continues its course through the bone to the midline to supply the incisor and canine teeth; and the mental nerve, which emerges out of the bone through the mental foramen to divide into several branches that supply the lower lip. While in the mandibular canal it gives off dental branches that form a plexus within the bone and supply the molar and premolar teeth. Filaments enter the pulp canal of each root through the apical foramen and supply the pulp of the tooth (see Chapter 50).

Lingual Nerve

The lingual nerve emerges from the medial aspect of the large posterior trunk and proceeds inferiorly, at first deep to the lateral pterygoid muscles, running parallel with the inferior alveolar nerve until the latter reaches the mandibular foramen. At this point the lingual nerve diverges anteromedially to reach the posterolateral portion of the tongue and courses along the undersurface of the tongue, lying immediately beneath the mucous membrane until it terminates in the tip of the tongue. The lingual nerve supplies sensory fibers to the anterior two-thirds of the tongue and to the mucous membranes on the inside wall and floor of the mouth and the sublingual gland. As it lies inferior to the external pterygoid muscle the lingual nerve is joined by the chorda tympani (Fig. 46-8; see Fig. 46-7A), a branch of the facial nerve that carries special sensory fibers of taste and parasympathetic preganglionic fibers for the submandibular ganglion (see Autonomic Innervation of the Head, later in this chapter). Both nerves take part in forming the roots of the submandibular ganglion, which appears to be suspended on the lingual nerve. The proximal nerves carry the preganglionic parasympathetic fibers communicated to the lingual nerve by the chorda tympani, while the distal branches contain postganglionic parasympathetic fibers for distribution to the submandibular, sublingual, lingual, and neighboring small salivary glands.

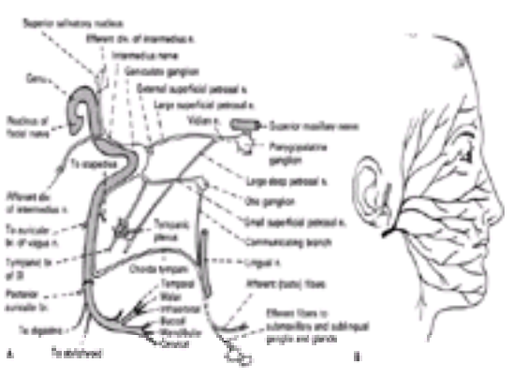

Figure 46-8. Anatomy of the facial nerve and its branches. **A:** Intracranial and extracranial portions of the motor portion of the nerve, nervus intermedius, geniculate ganglion, and chorda tympani and their connections with other nerves. **B:** Distribution of the branches of the facial nerve to the face. (**A** modified from Clemente CD, ed. *Gray's anatomy*, 30th Am. ed. Philadelphia: Lea & Febiger, 1985.)

Facial Nerve

The facial is a mixed cranial nerve composed of a large motor and a smaller sensory component and some parasympathetic fibers. The motor fibers arise from the motor nucleus of cranial nerve VII in the caudal portion of the pons, loop around the nucleus of the abducens (internal genu), and eventually terminate to supply the stapedius muscles of the middle ear, the muscles of facial expression, including those of the scalp and platysma, and the posterior belly of the digastric and stylohyoid muscles (see Fig. 46-8). The sensory fibers arise from the unipolar cells in the geniculate ganglion and immediately divide into central and peripheral branches. The central branches pass through the nervus intermedius (nerve of Wrisberg) to the nucleus of the tractus solitarius, whereas the peripheral branches pass distally through different courses to provide special and general sensation to various structures. Those that comprise most of the chorda tympani provide special taste fibers to the anterior two-thirds of the tongue. Other fibers convey general sensation (including pain) from the tympanic membrane, external auditory meatus, soft palate, and adjacent pharynx, whereas still others pass distally to supply the parotid gland by passing through the otic ganglion. The parasympathetic fibers originate from the superior salivatory nucleus and pass through the nervus intermedius, greater superficial petrosal nerve, and pterygopalatine (sphenopalatine) ganglion to the mucous membranes and glands of the pharynx, palate, paranasal sinuses, nasopharynx, and nasal cavity. Other parasympathetic fibers pass through the chorda tympani, lingual nerve, and submandibular ganglion to the submandibular and sublingual glands.

The facial nerve emerges from the posterolateral angle of the pons and proceeds laterally to enter the internal auditory meatus, which it traverses until it reaches the medial wall of the epitympanic recess where it suddenly curves posteriorly and inferiorly and travels within the facial canal to exit from the skull by way of the stylomastoid foramen. While the nerve is within the facial canal, approximately 0.5 cm above the stylomastoid foramen, it gives off the chorda tympani, which eventually reaches the lingual nerve to follow it to the anterior two-thirds of the tongue.

Glossopharyngeal Nerve

The glossopharyngeal nerve (cranial nerve IX) is a mixed nerve that contains visceral and somatic sensory fibers and somatic and autonomic (parasympathetic) motor fibers. The somatic sensory fibers arise from the unipolar cells in the superior and inferior petrosal ganglia and divide into central and peripheral branches. The former terminate in the tractus solitarius and its nucleus in the pons, whereas the latter are distributed to the pharynx, soft palate, posterior surface of the tongue, palatine tonsils, eustachian tube, and tympanic cavity to subserve general sensation to these parts. In addition, special sensory fibers form the carotid sinus nerve, which has special receptors in the carotid body and in the carotid sinus concerned with reflex control of respiration, blood pressure, and heart rate. The glossopharyngeal nerve also contains special visceral afferent fibers that supply the taste buds of the posterior third of the tongue.

The motor fibers arise from the nucleus ambiguous to terminate in the stylopharyngeus muscle. The parasympathetic fibers arise from the inferior salivatory nucleus to pass through the glossopharyngeal nerve by way of the tympanic plexus, Jacobson's nerve, and small superficial petrosal nerve to the otic ganglion, from which postganglionic fibers terminate in the parotid gland to convey secretory impulses.

The glossopharyngeal nerve emerges from the medulla at its posterolateral sulcus between the olive and peduncle in the form of three or four roots that soon fuse to form the nerve trunk (Fig. 46-9). After its formation, the trunk passes laterally to reach the central portion of the jugular foramen, through which it leaves the skull invested by a separate sheath of dura mater. Within the foramen it is situated anterolateral to the vagus and the accessory nerves, separated from both by the inferior petrosal sinus. After its emergence from the skull it passes anteriorly between the internal jugular vein and internal carotid artery and descends anteriorly to the latter vessel, medial to the styloid process and its attached muscles, and lateral to the vagus and accessory nerves to reach and wind around the lower border of the stylopharyngeus muscle. It curves anteriorly between the internal and external carotid arteries to form an arch on the side of the neck, lying first on the stylopharyngeus and medial constrictor muscles and then medial to the hyoglossus muscle to become distributed to the mucous membranes of the pharynx, palatine tonsils, and posterior third of the tongue.

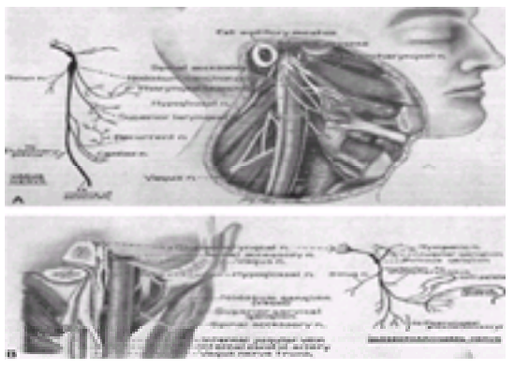

Figure 46-9. Deep dissection of the head and neck to show the anatomy of the ninth, tenth, eleventh, and twelfth cranial nerves. **A:** Lateral view. **B:** Posteroanterior view. Note especially the relationship of the glossopharyngeal and vagus nerves, shown schematically. The upper ganglion of the glossopharyngeal nerve should be labeled the *superior ganglion* and the upper ganglion of the vagus the *jugular ganglion*.

Vagus Nerve

The vagus is a mixed cranial nerve (cranial nerve X) and is composed of motor, parasympathetic, somatic, and visceral sensory fibers. The motor fibers of the vagus, together with the motor fibers of the glossopharyngeal and spinal accessory nerves, arise from the nucleus ambiguus and terminate in the muscles of the soft palate, pharynx, and larynx. The parasympathetic fibers originate in the dorsal motor nucleus of the vagus and terminate in the abdominal and thoracic terminal ganglia, from which postganglionic fibers arise to be distributed to the viscera.

The somatic sensory fibers arise from the unipolar cells of the jugular ganglion and soon divide into central and peripheral branches. The former terminate in the spinal tract of the trigeminal and its nucleus, whereas the latter ends in the external auditory meatus and ear by way of its auricular branch, and in the dura mater by way of its recurrent meningeal branch. The visceral sensory fibers, on the other hand, arise from the unipolar cells of the ganglion nodosum and also divide into central and peripheral branches. The central branches terminate in the tractus solitarius and its nucleus, whereas the peripheral branches terminate in the pharynx, larynx, trachea, esophagus, thoracic, and abdominal viscera. Somatic sensory fibers, which contribute to the pharyngeal, bronchial, pulmonary, and esophageal plexuses and to the superior laryngeal nerve, convey general sensations, including pain, from the mucous membranes of the pharynx, larynx, tracheobronchial tree, and upper part of the esophagus. Sensory fibers that supply viscera below the diaphragm do not convey thermal or mechanical nociceptive information but conduct the sensations of distension and nausea and impulses concerned with the regulation of respiration and blood pressure.

The vagus nerve trunk is formed by the fusion of 8 to 10 filaments that are attached to the medulla in its posterolateral groove between the olive and inferior cerebellar peduncle just caudad to the glossopharyngeal nerve. After it is formed, the flat cordlike nerve passes beneath the flocculus to reach the midportion of the jugular foramen, through which it leaves the skull within the same dural sheath as the spinal accessory nerve (cranial nerve XI). As it passes through the foramen it enlarges into the jugular ganglion, to which the accessory nerve is connected by one or two filaments. After the vagus emerges from the skull it is joined by the cranial portion of the spinal accessory nerve and enlarges into the ganglion nodosum, through which the accessory nerve fibers pass to be distributed uninterruptedly with the pharyngeal, superior laryngeal, and recurrent laryngeal branches of the vagus. In the neck the vagus proceeds caudad, lying within the carotid sheath between the internal jugular vein and internal carotid artery and slightly dorsal to both vessels as far as the thyroid cartilage. At the upper border of this cartilage it comes to lie between and behind the internal jugular vein and common carotid artery. It is still in this position when it leaves the neck at the superior thoracic aperture. Its distribution within the chest and abdomen is described in Chapter 60 and Chapter 65.

Pharyngeal Branches

The pharyngeal branches of the vagus, usually two, arise at the upper part of the inferior ganglion and contain sensory fibers from the ganglion and motor fibers from the communication with the accessory nerve. The branches pass distally and at the superior border of the constrictor pharyngis medius divide into several branches. These join glossopharyngeal, sympathetic, and external branches of the superior laryngeal nerve to form the pharyngeal plexus, which contributes sensory fibers to the mucous membrane and motor fibers to the muscles of the pharynx.

Superior Laryngeal Nerve

The superior laryngeal nerve arises from the lower pole of the ganglion nodosum and proceeds inferiorly (caudad) and medially behind and medial to the carotid arteries to reach the lateral side of the larynx. During its course the nerve receives a filament from the superior cervical sympathetic ganglion and communicates with the pharyngeal plexus by several branches. At a point 1 cm anterior and slightly inferior to the great cornu of the hyoid bone the nerve divides into a smaller external and larger internal branch (Fig. 46-10). The external branch descends on the lateral side of the thyroid cartilage between the inferior pharyngeal constrictor and sternothyroid muscles, and finally enters the cricothyroid muscle. It also contributes twigs to the inferior pharyngeal constrictor muscle. The internal branch proceeds inferiorly and medially for a short distance and then pierces the thyrohyoid membrane to enter the hypopharynx, in which it divides into an upper and a lower branch that supply the mucous membranes of the base of the tongue, pharynx, epiglottis, and larynx above the vocal cords, and perhaps send a few motor filaments to the arytenoideus muscle.

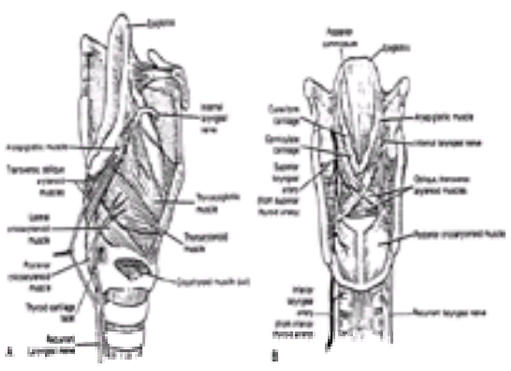

Figure 46-10. Anatomy and distribution of the superior and inferior laryngeal nerves. **A:** Lateral view of laryngeal muscles and nerves (half of thyroid cartilage and hyoid bone removed). **B:** Posterior view of laryngeal muscles, nerves, and arteries. (Reprinted from Graney DO. Anatomy. In: Cummings CW, ed.

Otolaryngology—head and neck surgery, 3rd ed. St. Louis: Mosby, 1998, with permission.)

Autonomic Innervation of the Head

Like other regions of the body, the head is supplied by sympathetic and parasympathetic nerves summarized in Table 8-6 and Figure 46-11, Figure 46-12, and Figure 46-13. These, together with the sensory nerves, supply the somatic and visceral structures in the head as well as the lacrimal, parotid, and submaxillary glands. The following briefly summarizes the course and distribution of sympathetic and parasympathetic nerves.

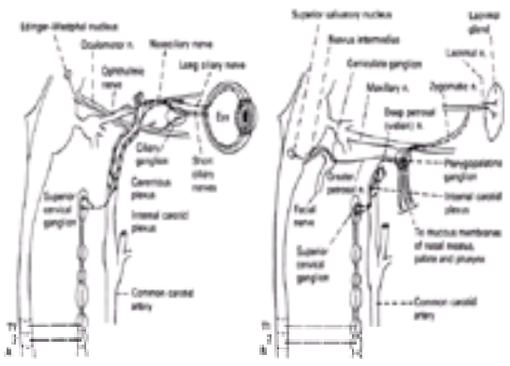

Figure 46-12. **A:** Autonomic nerve supply to the eye. The parasympathetic fibers arise in the Edinger-Westphal nucleus, which is part of the oculomotor nucleus, and traverse the ocular nerve and its inferior division. The fibers leave the oculomotor nerves to give rise to the short motor root of the ciliary ganglion. Within the ganglion they synapse with postganglionic neurons, whose axons pass to the eye by way of the short ciliary nerves. The cell bodies of the sympathetic preganglionic fibers are located in the upper two and frequently the third thoracic spinal cord segments; their axons pass to the sympathetic chain and ascend to end in the superior cervical ganglion, in which they synapse with postganglionic neurons. The axons of postganglionic neurons become part of the internal carotid plexus and eventually reach the eye by one of two courses; some of these are derived directly from the cavernous plexus and pass through the ciliary ganglion without synapsing, thus passing through the short ciliary nerves to reach the eye. Most sympathetic fibers course through the internal carotid plexus for a short distance, deviate into the middle ear accompanied by the caroticotympanic fibers, leave the middle ear, and pass through the base of the cranium lateral to the nerve of the pterygoid canal. They then become associated with the cavernous plexus, join the nasociliary nerve, and finally pass to the eye through the long ciliary nerves. **B:** Autonomic nerve supply to the lacrimal gland. The parasympathetic preganglionic fibers originate in the superior salivatory nucleus; their axons make up the efferent part of the nervus intermedius, which passes sequentially through the geniculate ganglion, the greater petrosal nerve, and the nerve of the pterygoid canal (vidian nerve) to end in the pterygopalatine ganglion, in which it synapses with postganglionic fibers. The latter then pass through the maxillary nerve, its zygomatic and zygomaticotemporal branches, and through fibers that connect these branches with the lacrimal nerve to end in the gland. The sympathetic preganglionic fibers originate in the upper two thoracic ganglia, pass through the paravertebral sympathetic chain, and travel cephalad from there to end in the superior cervical ganglion, in which they synapse with postganglionic fibers. These pass through the internal carotid plexus and leave the plexus as the deep petrosal nerve, which joins the greater petrosal nerve to form the nerve of the pterygoid canal. The postganglionic sympathetic fibers then pass through the pterygopalatine ganglion without synapsing, and thus have the same course as the parasympathetic fibers to reach the lacrimal gland. It can also be seen that both parasympathetic and sympathetic postganglionic fibers supply the mucous membranes of the nasal meatuses, palate, and pharynx through the various branches of the pterygopalatine ganglion (see text for details).

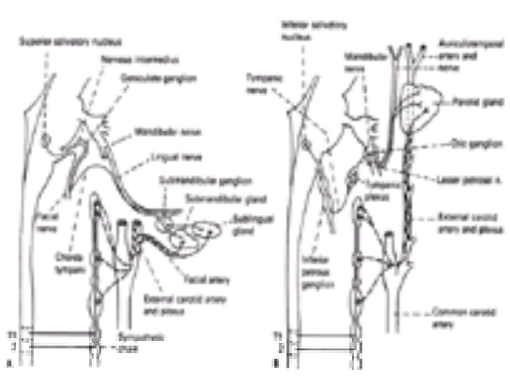

Figure 46-13. **A:** Autonomic nerve supply of the submandibular and sublingual glands. The parasympathetic preganglionic fibers originate in the superior salivatory nucleus and pass through the nervus intermedius, chorda tympani, and lingual nerves to end in the submandibular ganglion, in which they synapse with postganglionic fibers that pass to the submandibular and sublingual glands. The sympathetic preganglionic fibers have their cell bodies in the upper two thoracic segments, pass through the sympathetic chain, and ascend to end in the cervical sympathetic ganglia, in which they synapse with postganglionic fibers. These pass from the superior, middle, and inferior (stellate) cervical ganglia as the common carotid and external carotid nerves, which reach the arteries and break up into the common carotid and external carotid plexuses. The external carotid plexus continues and passes through the facial artery and its glandular branches to become distributed to the submandibular and sublingual glands. **B:** Autonomic nerve supply of the parotid gland. The parasympathetic preganglionic fibers have their cell bodies in the inferior salivatory nucleus and pass through the roots of the glossopharyngeal nerve and its inferior (petrous) ganglion from which they leave as the tympanic nerve. The tympanic nerve passes through the petrous portion of the temporal bone and enters the tympanic cavity, in which it joins with the caroticotympanic nerves to make up the tympanic plexus. Parasympathetic fibers then pass through the plexus to continue as a lesser petrosal nerve, terminating in the otic ganglion in which they synapse with postganglionic fibers. These pass from the otic ganglion into the auriculotemporal nerve and through its parotid branches to supply the parotid gland. The sympathetic preganglionic neurons have their cell bodies in the upper two thoracic spinal cord segments, pass to the sympathetic chain, and ascend to end in the cervical sympathetic ganglia, in which they synapse with postganglionic fibers. These pass as the external and common carotid nerves that break up into plexuses and proceed cephalad. The fibers pass through the plexus that surrounds the auriculotemporal artery and its transverse facial branch to reach and supply the parotid gland.

Sympathetic Nerves

The preganglionic neuron cell bodies are located in the intermediolateral column of the T-1 to T-2 segments for those destined for the brain, meninges, and related arteries, whereas those that supply the blood vessels of the face and neck are located in the T- 2 to T-4 segments of the spinal cord. As discussed in detail in Chapter 8, these cell bodies receive descending input from diencephalic autonomic centers through various descending pathways (see Fig. 46-11). The axons of these neurons pass through the anterior roots of the upper four thoracic spinal nerves and corresponding white rami communicantes to reach the sympathetic trunk. Here they ascend to terminate in the cervical ganglia, in which they synapse with cell bodies of postganglionic neurons. The axons of the latter pass cephalad as *nerves* and plexuses that come to surround the common carotid, external carotid, and internal carotid arteries and the vertebral and basilar arteries.

Internal Carotid Nerve. The internal carotid nerve is derived from the superior cervical sympathetic ganglion and accompanies the internal carotid artery as far as the carotid canal in the temporal bone, at which point it divides into a large branch that ramifies to become the internal carotid plexus and into a smaller branch that breaks up to become the cavernous plexus (see Fig. 46-11 and Fig. 46-12).

Internal Carotid Plexus. The internal carotid plexus ascends on the lateral side of the internal carotid artery and, within the cranial cavity, communicates with the gasserian ganglion and abducens nerve and gives off two branches, the deep petrosal and corticotympanic nerves. The deep petrosal nerve, comprised of postganglionic sympathetic fibers, joins the greater petrosal nerve to form the vidian nerve, which passes to the pterygopalatine ganglion and through the palatine nerves to supply the glands and blood vessels of the pharynx, nasal cavity, and palate, while some fibers that pass through the zygomatic nerve end in the lacrimal

gland. The corticotympanic nerve contributes to the tympanic plexus.

Cavernous Plexus. The cavernous plexus is situated just inferomedial to the internal carotid artery. As it passes through the cavernous sinus it communicates with the oculomotor, trochlear, ophthalmic, and abducens nerves and contributes the sympathetic root of the ciliary ganglion. The internal carotid and cavernous plexuses continue as subsidiary plexuses around the anterior and middle cerebral and ophthalmic arteries. Fibers on the cerebral arteries can be traced to the pia mater, whereas those on the ophthalmic artery accompany all its branches into the orbit. The filaments on the anterior communicating artery can connect the sympathetic nerves of the right and left sides.

Jugular Nerve. The jugular nerve arises from the superior pole of the superior cervical sympathetic ganglion, although in some cases it can arise from the internal carotid nerve. The jugular nerve ascends behind the internal carotid artery and hypoglossal nerve and reaches the base of the skull, in which it divides into two filaments, one joining the jugular ganglion of the vagus and the other joining the petrosal ganglion of the glossopharyngeal nerve.

External Carotid Nerves. The external carotid nerves containing postganglionic fibers from the cervical sympathetic ganglia pass to and break up into the plexuses that surround the external carotid artery and all its branches, giving off filaments along its course. The filaments on the facial artery join the submandibular ganglion and supply the submandibular and probably the sublingual glands. The network of filaments on the middle meningeal artery (which is usually a branch of the maxillary artery derived from the external carotid artery) gives off the small deep petrosal nerve that passes through the otic ganglion and accompanies the auriculotemporal nerve to the parotid gland. Other filaments form the external superficial petrosal nerve, which communicates with the geniculate ganglion. Filaments on the facial, superficial temporal, and other arteries that distribute to the skin supply vasomotor fibers as well as the arrectores pilorum muscles and sweat glands of the face.

Vertebral Nerve. The vertebral nerve, usually formed by two roots arising from the superior border of the superior cervical sympathetic ganglion, ascends along the posterior aspect of the vertebral artery within the vertebral canal and ramifies into several branches, some of which make up the vertebral plexus, which also receives a small filament from the intermediate cervical ganglion. The vertebral plexus follows the artery cephalad and continues on the basilar, posterior cerebral, and cerebellar arteries to contribute to the sympathetic innervation of the intracranial arteries and meninges.

Parasympathetic Nerves

The cranial outflow of the parasympathetic nervous system includes fibers in the oculomotor, facial, and glossopharyngeal nerves.

Oculomotor Nerve. The oculomotor nerve contains parasympathetic efferent fibers for the nonstriated muscle making up the ciliaris and sphincter pupillae muscles of the eyeball (see Fig. 46-12A). The preganglionic fibers arise from the cells in the Edinger-Westphal nucleus located in the anterior part of the oculomotor nucleus in the tegmentum of the midbrain. These fibers run in the inferior division of the oculomotor nerve to the ciliary ganglion, in which they synapse with cell bodies of postganglionic neurons. The axons of the latter proceed in the short ciliary nerves to the eyeball and penetrate the sclera to reach the aforementioned muscles.

Facial Nerve. The facial nerve contains parasympathetic fibers for the lacrimal, submandibular, and sublingual glands and for the many small glands in the mucous membranes of the nasal cavity, palate, and tongue. The cell bodies of the preganglionic fibers arise from cells in the superior salivatory nucleus and leave the brain in the nervus intermedius. Some axons of preganglionic fibers pass through the geniculate ganglion and the greater superficial petrosal nerve and end in the pterygopalatine (sphenopalatine) ganglion, in which they synapse with postganglionic fibers. Some of these postganglionic fibers reach the lacrimal gland by way of the maxillary, zygomatic, and lacrimal nerves (see Fig. 46-12B). Other postganglionic fibers accompany the branches of the maxillary nerve to the glands and mucous membranes of the nasal cavity and nasopharynx, and still others accompany the palatine nerves to supply the glands of the soft palate, tonsils, uvula, roof of the mouth, and upper lip. Other preganglionic fibers leave the facial nerve in the chorda tympani and with it join the lingual nerve to reach the submandibular ganglion in which they synapse with postganglionic fibers that become the secretomotor nerve supply to the submandibular and sublingual glands (Fig. 46-13A).

Glossopharyngeal Nerve. The glossopharyngeal nerve contains efferent parasympathetic fibers for the parotid gland and for small glands in the mucous membranes of the tongue and floor of the mouth. The cell bodies of the preganglionic neurons arise in the inferior salivatory nucleus in the medulla oblongata, traverse the tympanic and lesser superficial petrosal nerve, and end in the otic ganglion, in which they synapse with postganglionic fibers that supply the parotid gland (see Fig. 46-13B).

SUMMARY OF HISTORY AND PHYSICAL EXAMINATION

It is obvious from Table 46-1 that the diagnosis of head pain requires a detailed history and comprehensive physical examination, as discussed in Chapter 12 and in the book by de Jong (3). The characteristics of the pain must be ascertained in great detail by the history, including circumstances that precipitated the pain; character of onset (sudden or gradual); location; character (sharp or dull, lancinating, throbbing, or pulsating); severity; temporal characteristics (constant or intermittent; time of day, week, month, or season); duration (seconds, minutes, hours); character of termination (sudden or gradual); factors that reproduce, aggravate, or relieve it; and associated signs and symptoms. The latter include sensory changes (hyperalgesia or hypoalgesia), motor disturbances (tremors, weakness), autonomic dysfunction (e.g., hyperhidrosis, lacrimation), and any tinnitus, dizziness, syncope, or other nervous system dysfunction.

TABLE 46-1. Pain in the head (including headache): summary of etiology and differential diagnosis

The examination should include a general inspection, particularly of the facial expression; position of the head; color of the skin; and contour of the face, head, neck, eyes, nose, ears, lips, teeth, tongue, cheeks, pharynx, and larynx; and muscular expression and phonation. Palpation is carried out to determine the presence of trigger areas or zones, tenderness, and swelling or induration. The function of the muscles of the neck is examined in regard to flexion, extension, and lateral rotation and flexion for both right and left sides. The effect of head compression (Spurling's test) and head traction on the pain should be ascertained.

The patient who complains of face or head pain requires a detailed evaluation of the cranial nerves, the upper three cervical nerves, and sympathetic innervation of the head. Careful assessment of the extraocular muscles by testing for conjugate eye movements, nystagmus, and intraocular muscle function in response to light and near vision is required. Light touch and pinprick sensation of the scalp and of each of the three divisions of the trigeminal nerve should be assessed, over both lateral and anterior aspects of the face. Corneal sensation should be tested with a fine wisp of cotton. Taste (e.g., of sugar or salt) on the anterior tongue is important to evaluate.

The patient with face pain should have all facets of trigeminal function assessed, including the muscles of mastication. The facial nerves should be tested by asking the patient to whistle and then blow out the cheeks. The symmetry of the nasolabial folds and mouth movements should be noted. Strength of the orbicularis oculi muscles is assessed by asking the patient to keep the eyes shut while the examiner tries to open them. Although hearing can be crudely measured by testing with a watch or rubbing the fingers, a tuning fork permits one to ascertain that air conduction is greater than bone conduction and that a tuning fork applied to the forehead is heard equally in both ears. Audiometry is a much more precise method of evaluating hearing.

Testing for glossopharyngeal and vagal function is difficult. Taste over the posterior third of the tongue and pharynx is mediated by the glossopharyngeal nerve. A

cotton applicator stick moistened and coated with sugar or salt is an effective stimulus. The gag response should be elicited from each tonsillar fossa, and the elevation of the uvula in the midline should be noted. Accessory nerve function is tested by asking the patient to rotate the head against resistance while palpating the sternocleidomastoid muscle and by pressing down on the shoulders while the patient attempts to elevate them. Hypoglossal nerve function is assessed by observing the tongue for fasciculations and by testing strength and range of tongue motion.

Testing cranial nerve function is not time consuming and often indicates a structural lesion when abnormalities are found. Local tenderness in the regions of the paranasal sinuses and over the temporal arteries or the scalp can indicate the site of a pain-causing lesion. Skull tenderness to percussion can indicate a subjacent mass lesion, such as a tumor or subdural hematoma. Skin temperature and sweating, lacrimation, salivation, rhinitis, and pupillary size and reaction can be abnormal with lesions affecting parasympathetic or sympathetic innervation.

CHAPTER REFERENCES

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2. Clemente CD, ed. *Gray's anatomy*, 30th Am. ed. Philadelphia: Lea & Febiger, 1985:1158–1189.
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CHAPTER 47

Cranial Neuralgias

John D. Loeser

The classification of neuralgias of the face, head, and neck is difficult, and it is based more on opinion than on an understanding of the mechanisms or pathogenesis. Nonetheless, it is essential to impose some organization on this confusing area of chronic pain. Similar sentiments were expressed in the first edition of this book; little progress has been made in the understanding of the genesis of facial neuralgias, although new medications and surgical procedures have improved treatment efficacy. Headaches are discussed in detail in Chapter 48 and are not discussed here. Table 47-1 lists the pain syndromes that must be differentiated from cranial and facial neuralgias as well as the chapters in which a discussion of each is located.

Disorder	Chapter no.
Cranial neuralgias	47
Atypical facial pain	47
Temporomandibular joint pain	49
Myofascial pain of masticatory muscles	49
Temporal arteritis	49
Sinusitis	52
Tolosa-Hunt syndrome	51
Dental, gingival, and osseous pain	50
Migraine	48
Cluster headaches	48
Paratrigeminal syndrome of Raeder	52
Cancer of head and neck	53
Traumatic neuropathies	47
Muscle-tension headaches	48, 49
Occipital neuralgia	47
Eagle's syndrome	52

TABLE 47-1. Pain syndromes of the face, cranium, and upper neck

An old nomenclature is superimposed on advancing knowledge, and no scheme for categorizing neuralgias is perfect. In this chapter the term *typical neuralgia* refers to a pain syndrome restricted to the distribution of a specific cranial nerve or its branch. It can occur in any cranial nerve that has somatic afferent fibers—the trigeminal, facial (nervus intermedius), glossopharyngeal, and vagus—and is rarely seen in the uppermost cervical dorsal roots (C-2 and C-3). The most common typical neuralgia is tic douloureux, often called “classic trigeminal neuralgia' or “major trigeminal neuralgia.”

Other neuralgias occur in the cranial nerves but are continuous, may be associated with significant sensory loss, are usually described as burning or aching, perhaps with superimposed jabs, often not triggered, and are unilateral. Atypical neuralgias are frequently, but not always, associated with trauma to a nerve, chronic infection, or occult neoplasm in the face or base of the skull. These pains were formerly called “minor” the International Association for the Study of Pain (IASP) taxonomy system labels them as “secondary' neuralgias, but they are no more secondary than tic douloureux, which is almost always caused by vascular compression of the intracranial trigeminal nerve.

Herpes zoster can lead to both acute and chronic trigeminal and nervus intermedius pain syndromes. The pain can precede the vesicular eruption, and diagnosis can

be quite difficult at first.

The atypical neuralgias form a diverse group of facial pains. Some are not restricted to a specific cranial nerve distribution; can be bilateral, intraoral, or facial; and can extend into the neck. They are continuous, usually with little or no sensory deficit, are not triggered, and often occur in patients with significant psychopathology. The likelihood of establishing an etiology for this type of atypical facial pain is exceedingly small. Clinical studies have shown that the textbook distinctions among atypical facial pain, vascular headaches, and muscle tension headaches are not respected by all patients—that is, the borders of every syndrome are indistinct. Table 47-2 presents the characteristics of the major pain syndromes discussed in this chapter.

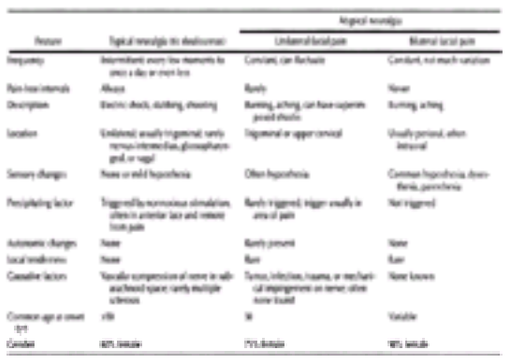

TABLE 47-2. Characteristics of facial pain syndromes

Correct diagnosis is mandatory with chronic facial pain because effective treatment strategies are available for some of the pains in this region. It is important to recognize the primary features of each of the facial neuralgias, and their differential diagnosis from pain of specific structural cause has relevance for the prompt implementation of effective care.

This chapter is organized around the specific types of neuralgias and commences with typical trigeminal neuralgia, or tic douloureux. A discussion of the other typical neuralgias follows; attention is then focused to the atypical neuralgias, unilateral and bilateral. The emphasis of this section is on diagnosis and the development of a logical management plan (1). More detailed descriptions of the cranial neuralgias and their management can be found elsewhere (2,3 and 4).

TRIGEMINAL NEURALGIA (TIC DOULOUREUX) (II-1)

The clinician must be able to identify a patient with tic douloureux, or classic trigeminal neuralgia, because this most severe pain syndrome can almost always be controlled by medication or surgery. Trigeminal neuralgia has long been recognized in the medical literature. It is believed that sixteenth-century stone carvings in Wells Cathedral depict the pain of trigeminal neuralgia (5). The first written description was ascribed to Johannes Bausch in 1672. André first used the term *tic douloureux* in 1756, and Fothergill provided a vivid description of this pain syndrome in 1773. Early medical therapies were without benefit; the first effective treatment was probably trichloroethylene inhalation, which was initiated in the 1920s.

Effective surgical procedures that injured the trigeminal nerve were developed in the early eighteenth century, although it was noted that Maréschal, surgeon to King Louis XIV, of France, cut the peripheral branches of the trigeminal nerve for pain (5). It was not until the studies of Bell and Magendie in the early nineteenth century that the different functions of the trigeminal and facial nerves were recognized. Mears, in 1884, discussed surgical extirpation of the gasserian ganglion; several surgeons undertook this procedure. A major step forward was Sir Victor Horsley's subtemporal retrogasserian neurotomy, first performed in 1891. Both Hartley and Krause developed similar operative approaches, and in 1900 Harvey Cushing described a simplified approach. Suboccipital retrogasserian neurotomy was developed by Fraser in 1901. Sjoqvist (6) described trigeminal medullary tractotomy in 1937. The history of neurosurgical treatments for facial pain has been reviewed by Walker and others (2,5).

Epidemiology

Tic douloureux is a disease of the elderly, but it does occur uncommonly in young adults (Fig. 47-1). The peak incidence is between ages 50 and 70. Although the early literature indicated a strong preponderance of women among patients with tic douloureux, current data suggest that only 60% of the patients are female (7). An earlier onset of tic douloureux is rarely a sign of multiple sclerosis; it does the patient a disservice to invoke the terrors of such a diagnosis when the only finding is tic pain. I have operated on a patient whose tic began when she was 17; she had a kinked superior cerebellar artery compressing the trigeminal root. There is no known racial or ethnic factor in the incidence of tic douloureux.

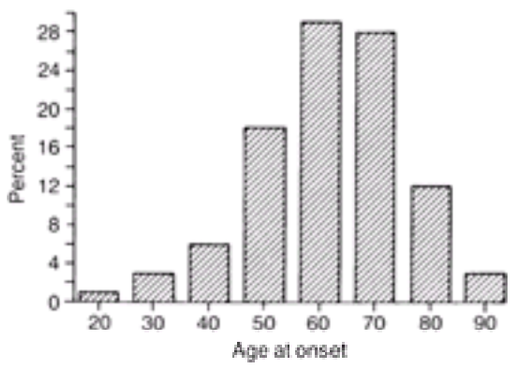

Figure 47-1. Distribution of age of onset of tic douloureux.

Etiology

Neither the etiology nor the pathophysiology of tic douloureux has been adequately explained. Certainly, the observations made by Dandy (7) and those of Jannetta (8) and other neurologic surgeons have made it apparent that the vast majority of patients with classic tic douloureux have mechanical compression of the trigeminal nerve as it leaves the pons and traverses the subarachnoid space toward Meckel's cave (see Chapter 107). The most common finding is cross-compression by a major artery, usually the superior cerebellar, but occasionally the posterior inferior cerebellar, vertebral, or anterior inferior cerebellar artery is involved. A few patients have been found to have a vein running across or even through the nerve, and a small incidence of arteriovenous malformation or tumors has also been reported (see Chapter 107).

The region of impingement of the blood vessel on the trigeminal root correlates with the region of face pain. When the pain is perceived in the second or third trigeminal division, the usual finding is compression of the rostral and anterior portion of the nerve by the superior cerebellar artery. If first-division pain is present, the most frequent finding is cross-compression of the trigeminal root in its caudal and posterior portion, most often by the anterior inferior cerebellar artery.

A small percentage of the patients with tic douloureux have multiple sclerosis as an underlying disease. The autopsy findings on these patients, which have been confirmed in a small number of surgical observations, include a demyelinating plaque in the trigeminal posterior root (9). It is well known, however, that plaques are frequently found in the descending trigeminal tract and in the lemniscal systems; it is not now possible to argue that a plaque in the trigeminal root is either necessary

or sufficient to cause tic douloureux. A patient with multiple sclerosis could also have arterial cross-compression of the trigeminal root.

Another theory has been described in the dental literature. Ratner et al. (10) and Shaber et al. (11) hypothesized that tic douloureux is caused by foci of abscess and bone resorption with irritation of the trigeminal nerve in the maxilla or mandible, but this theory is not widely accepted, even among dentists. Similar cavities are seen in the jaws of people with no pain or history of pain. The treatment of such cavities does not lead to symptom abatement uniformly and quickly. Some patients with tic douloureux cannot be shown to have these cavities. Even if the cause of the disease does not lie in the jaws, few would disagree that abscesses and other pathologic processes in the orofacial structures can act as the triggering stimulus for tic. Yet, this concept persists in the dental literature (12,13).

Pathophysiology

How a demyelinating plaque, infection in the jaw, or artery or tumor pressing on the trigeminal nerve can cause a unique pain such as tic douloureux is unknown. No animal model for a pain syndrome such as tic has been developed—only some theoretic explanations based on clinical information.

Two generic schemes for the explanation of tic douloureux can be identified, the “centralist' and “peripheralist.' The former is based on the similarities of tic douloureux to focal epilepsy and emphasizes the role of deafferentation in the genesis of neuronal hyperactivity (14). Epileptogenic agents injected into the trigeminal nucleus can cause neuronal hyperactivity and a pain syndrome in cats and monkeys (15). Changes in dorsal root reflexes and synaptic function in the trigeminal system have also been described (16). The peripheralist concept notes that changes in the trigeminal nerve myelin and axons can lead to altered peripheral nerve sensitivity to chemical and mechanical stimuli and ties the pain syndrome to suspected peripheral causes (17,18,19 and 20). Other theories based on ephaptic connections, reverberating circuits, and altered central connectivity caused by deafferentation have also been proposed (21,22).

Calvin and colleagues (23) concluded that both peripheral and central mechanisms are required for the production of tic douloureux. Fromm and associates (24) proposed a similar mechanism. Their studies indicated that a peripheral nerve lesion (in the trigeminal root or distal) is the first event in a process that leads to central synaptic changes. The response of the central synapses to altered peripheral events leads to the development of tic douloureux. Such a complex theory is required to explain many of the phenomena seen in tic douloureux: triggering by nonnoxious stimuli, separation of the trigger area from the painful region, sudden onset and cessation of pain, and response to anticonvulsant medications.

Symptoms and Signs

Even though the classification of pain syndromes of the face and head is often unclear, it should be possible to differentiate tic douloureux from any other type of pain (see Table 47-2). Tic is characterized by the following: electric shock–like stabbing pains; unilateral pain during any one episode; abrupt onset and termination of pain; pain-free intervals between attacks; nonnoxious stimulation triggering the pain, which is often in a different area of the face; minimal or no sensory loss in the region of pain; and pain restricted to the trigeminal nerve (1). Deviations from this typical picture can occur, but the more unusual features the patient manifests, the less likely is a favorable response either to medication or surgery.

The history of bilateral tic pain can be elicited in approximately 3% of patients. Rarely does a patient have bilateral tic pain during one episode; usually an interval of years separates the occurrence of pains on the two sides.

Surgical or anesthetic procedures that damage the trigeminal nerve can produce changes in the findings and in the patient's symptoms—it is essential to ascertain what the symptoms were before such an operation. Nerve damage can lead to a burning component of the pain that is uncommon in patients without nerve injury. Significant sensory loss mandates a thorough search for structural pathology such as tumor or infection that is damaging the trigeminal nerve.

Triggering

The average patient with tic douloureux describes a specific triggering stimulus, touching the face or chewing, talking, or swallowing. Many patients report that exposure of the face to cold triggers their pain. The cutaneous trigger is always a nonnoxious stimulus and is usually located in the anterior face (21) (Fig. 47-2).

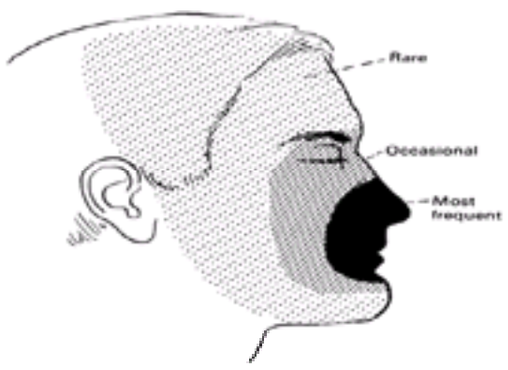

Figure 47-2. The most likely sites of triggering for tic douloureux are in the anterior face.

The trigger area is always ipsilateral to the pain but can be in the same or a different division of the trigeminal nerve. Rarely, the patient reports a trigger area outside the trigeminal territory, usually in the upper cervical dermatomes. Patients with triggering from the scalp often refuse to wash or brush their hair; shaving can be impossible for a man with triggering from the upper lip or face, and oral hygiene is often impossible when the triggering is from the teeth or gingivae. When swallowing or chewing triggers the pain, the patient may develop inadequate caloric intake or dehydration.

Distribution of the Pain

In the overwhelming majority of patients with tic douloureux the pain is restricted to the trigeminal dermatomes. A small number have pain both in the trigeminal areas and in the territory of the nervus intermedius (cranial nerve VII), glossopharyngeal nerve (cranial nerve IX), or vagus nerve (cranial nerve X) (25). The pains of tic douloureux can also be experienced exclusively in one of these areas (see below). The most common site of tic pain is the combination of the second and third divisions; the rarest site is the combination of the first and third divisions. Figure 47-3 depicts the distribution of pain from approximately 8,500 patients reported in the literature. Another way of analyzing these data is shown in Figure 47-4 —some pain is perceived in the second division in more than 44% of patients, the third division has some pain in 36% of patients, and the first division in 20% of patients. Thus, the malar area is the most likely to be involved in the patient with tic. This pain syndrome can and does occur, however, in every area of the face and anterior scalp, and all combinations of painful sites have been reported (4,26).

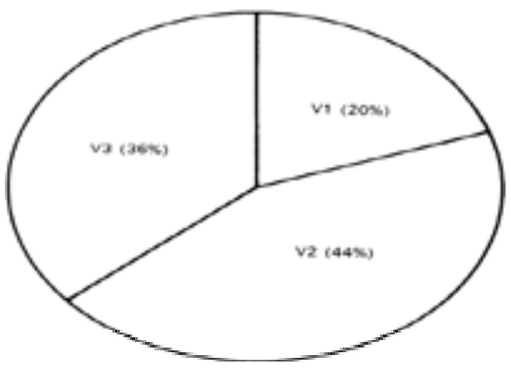

Figure 47-3. Distribution of pain among divisions of the trigeminal nerve in patients with tic douloureux.

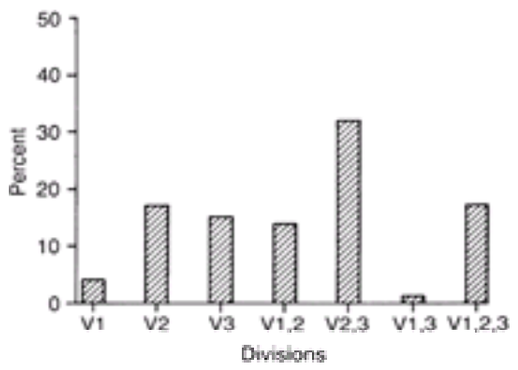

Figure 47-4. Trigeminal divisions involved in tic douloureux.

Chronology

Tic douloureux is often an intermittent disease. Many patients report intervals of months or even years between flurries of attacks. Recurrences are almost always in the same area of the face, but the painful areas tend to spread. It is common for intervals between attacks to decrease and episodes of severe pain to occur more often. Some patients never experience remission once their disease starts. Patients often report nonnoxious minor jabs in their painful areas between episodes of severe pain. Emotional and physical stress do appear to increase the likelihood of severe pain in the patient who has tic, but no evidence has been found to indicate that stress plays a causative role in this disease.

Diagnosis

Tic douloureux must be distinguished from all other face pains. The criteria already discussed suffice to establish the diagnosis. No diagnostic studies are available to confirm the presence of tic douloureux. Tic should be discriminated from a similar syndrome occurring in one of the other cranial sensory nerves (see below). This is readily accomplished by taking a careful history from the patient and by ascertaining the exact triggering stimulus and site of pain during the physical examination (see Table 46-1 for differential diagnosis of pain in the face and head).

The disease must also be distinguished from atypical facial pain of the unilateral variety (see Table 47-2). Atypical facial pains are discussed in detail below; they are characterized by continuous burning pain not like electric shock, that often is not triggered, and that often escapes the trigeminal territory. Atypical face pains are most common in younger women.

Myofascial pains involving the muscles of mastication and temporomandibular joint pain can be difficult to differentiate from each other but should not be confused with tic douloureux. These syndromes consist of pain that is predominantly in the lateral face, described as aching, burning, or cramping, is often associated with using the jaw or its muscles and with tenderness to palpation of the involved muscles and can radiate into the scalp or neck. Myofascial and temporomandibular facial pains are discussed in detail in Chapter 49.

Cluster headache and facial pains are a confusing group of pain syndromes (see Chapter 48). These are usually intermittent burning or throbbing dysesthetic pains that occur in clear-cut episodes and are frequently associated with autonomic signs, such as lacrimation, rhinitis, facial sweating, and facial flushing. The attacks can be random or clustered and have numerous variants that are often described by an eponym.

Local pathologic processes in the paranasal sinuses, jaws, teeth, pharynx, or base of the skull can lead to severe pain. This type of facial pain is usually constant and is described as aching, throbbing, or burning but rarely as shocklike. The pain is not triggered by nonnoxious stimulation remote from the painful area, and if a branch of the nerve is involved in the disease, sensory loss can occur. Physical examination and the appropriate diagnostic studies usually reveal the pathology (Chapter 52).

Pharmacologic Treatment

The primary treatment of tic douloureux is first pharmacologic, but, if this fails, surgical therapy is indicated.

The mainstays of the pharmacologic management of tic douloureux are the anticonvulsant medications carbamazepine and phenytoin (Table 47-3). Baclofen, gabapentin, and lamotrigine have more recently been introduced and can be helpful. Other drugs are sometimes useful but are not indicated as primary medication. Scattered reports of the efficacy of other anticonvulsants have appeared but have not been corroborated with appropriately controlled studies (27).

Generic name	Brand name	Pill size (mg)	Usual daily dose	Common side effects
Phenytoin	Dilantin, Eigamin, Phenytek	100	300–300 mg	Nausea, dizziness, unsteadiness, ataxia, dermatitis
Carbamazepine	Tegretol	200	600–1,600 mg	Nausea, dizziness, unsteadiness, hepatic and hematopoietic dysfunction
Lioresal	Baclofen	10	40–80 mg	Nausea, dizziness, confusion, drowsiness
Chlorpromazine	Thorazine	100	300–1,200 mg	Dizziness, unsteadiness
Amphetamine	Adderall, Dexedrine	30	5–15 g	Dizziness, nausea
Gabapentin	Neurontin	100, 300	1,200–4,800 mg	Dizziness, nausea
Lamotrigine	Lamictal	100	400 mg	Dizziness, nausea, unsteadiness

TABLE 47-3. Medications useful for typical neuralgias

Carbamazepine

Carbamazepine (Tegretol) is the most likely drug to control tic douloureux; approximately two-thirds of patients report symptomatic improvement (28). This drug should be started on a daily dosage of 100 mg (½ tablet); the dose is increased by increments of 100 mg every 2 days until a daily dosage of 600 mg is reached. Of course, if pain relief occurs on a lower dosage, the amount taken should not be increased. After 1 week at 600 mg per day, if no pain relief is seen, the daily dosage should be increased to 800 mg for 1 week. This process can be repeated until a total daily dosage of 1,800 mg is reached. Higher doses have not been more effective. Carbamazepine should be administered at least every 8 hours to maintain stable blood levels. A sustained-release form of this drug is now available.

Carbamazepine is a gastric irritant in some patients and should be taken with food or fluid. Some patients develop central nervous system side effects that render the drug intolerable. A small incidence of hematosuppression and liver dysfunction has been reported (29). Because of the gravity of this complication, a complete blood

count should be obtained monthly for the first year and quarterly thereafter. Most patients have some lowering of the white blood cell count; it is not necessary to stop this drug unless the white blood cell count falls below 3,500 cells per mL. The treatment strategy for this drug is to push the dosage until either pain relief or toxicity occurs. Serum levels have not been reliable predictors of either pain relief or toxicity. Because approximately 25% of patients find the side effects of carbamazepine unacceptable, it produces successful relief of symptoms without unacceptable side effects in approximately 50% of patients. Carbamazepine interacts with many other drugs and this must be carefully monitored (30).

Phenytoin

Phenytoin (Dilantin) is the second choice of medication for patients with tic douloureux. Approximately 25% of patients obtain satisfactory pain relief with serum levels of 15 to 25 g per mL. The strategy is to attain adequate serum levels for 3 weeks; if no relief of pain is seen, the drug should be discontinued because higher doses only lead to toxicity. The usual requirement for reaching the optimal serum level is 300 to 400 mg per day given in two doses. If the patient is having severe pain it is prudent to give a 1,000-mg loading dose to achieve rapid blood levels. Central nervous system side effects are usually related to toxic levels, but some patients cannot tolerate even low levels of this drug.

Other Drugs

Baclofen (Lioresal) is a drug that was developed for the treatment of spasticity but was found by Fromm and colleagues (31) to be effective in some patients with tic douloureux. It must be started gradually—5 mg is given, and the dose is increased by 5 mg every 2 days until either pain relief or toxicity occurs. The maximum dosage is 80 mg per day. The drug should be tapered and not suddenly discontinued, especially in the elderly (31,32). Gabapentin is a relatively recently developed anticonvulsant that may be effective for tic douloureux. The initial dose should be 100 mg for 3 days; if this is tolerated the dose can be immediately increased to 300 mg four times a day. If this is tolerated after 1 week, the dose can be increased gradually to a maximum of 4,800 mg per day. This drug is much more expensive than other anticonvulsants and good clinical trials are not yet available. Lamotrigine has also been shown to be effective in a small trial (33).

Chlorphenesin and mephenesin are no longer commonly used.

Nerve Blocks

Local Anesthetic Block

A local anesthetic injected either into the trigger area or painful site temporarily stops the pain of tic douloureux. Rarely, the patient reports pain relief that outlasts the expected duration of the local anesthetic. Nerve blocks can also be used to show the patient the effects of a planned neurectomy or total rhizotomy, but these are not optimal primary surgical procedures. Local anesthesia with a few milliliters of a long-acting agent such as bupivacaine can provide the patient with some peace while adequate serum levels of an anticonvulsant are being obtained or planned surgery is undertaken.

Neurolytic Block

Alcohol blocks of the peripheral branches of the trigeminal nerve or of the gasserian ganglion have a long history in the management of tic douloureux (26). Experienced operators have reported good results, but in most physicians' hands the long-term outcome is not favorable. Alcohol blocks rarely last longer than 1 year, and repeated blocks have a lower success rate and an increased morbidity rate. The amount of hypalgesia and anesthesia has been difficult to control except in the hands of experts (34,35). Alcohol blocks are less satisfactory than gangliolysis and are no longer standard therapy when modern technology is available. The technique of glycerol gangliolysis is actually a neurolytic block, but it is discussed below in conjunction with radiofrequency gangliolysis. When an experienced practitioner of gangliolysis is not available, an alcohol block might be the best alternative.

Dental Procedures

Physicians, dentists, and patients often believe that something must be wrong where it hurts, and this belief has led to the extraction of numerous healthy teeth and to extensive endodontic procedures. It is worth noting that tic douloureux perceived in the nose never results in surgical excision of that structure, whereas tic in the teeth often results in extraction. This is a commentary on the socially determined propriety of therapies, not on an understanding of pathophysiology. Similarly, surgical procedures on the paranasal sinuses are ineffective.

Surgical Therapies

The list of surgical treatments for tic douloureux extends from the peripheral nerve to the brainstem. The following are the commonly used surgical procedures:

Peripheral neurectomy
Peripheral radiofrequency or cryoprobe lesions
Gangliolysis (radiofrequency, mechanical, or glycerol)
Compression/decompression of the gasserian ganglion
Subtemporal retrogasserian neurotomy
Suboccipital retrogasserian neurotomy
Trigeminal tractotomy
Microvascular decompression of the trigeminal nerve
Stereotactic radiosurgery

No surgical procedure is warranted unless pharmacologic therapy has failed, either because of inadequate pain relief or unacceptable side effects. Currently, the two primary surgical treatments for tic douloureux are gangliolysis and microvascular decompression of the trigeminal nerve by a suboccipital craniectomy (8,36,37). These and other less frequently used operations are discussed in Chapter 107.

Gangliolysis

Gangliolysis is the most recent development in the long history of destructive procedures for tic douloureux (38). The goal is to produce the least neurologic deficit that will control the patient's pain. Gangliolysis is performed by placing a needle through the cheek and into the foramen ovale and then into the rootlets behind the gasserian ganglion (see Chapter 107). The placement of the needle is confirmed by roentgenography or fluoroscopy. Three methods are used for making a lesion: a thermally controlled radiofrequency current to heat and destroy anatomically selected portions of the posterior rootlets (37,38 and 39), injection of glycerol into the cistern of the trigeminal ganglion (37,40), and inflation of a balloon in Meckel's cave (41). Gangliolysis offers an 80% chance of 1 year of pain relief and a 60% chance of 5 years' success; the complication rate is less than 0.5% (3,40,42). Gangliolysis is particularly useful in the debilitated or elderly patient who would be at risk from a major surgical procedure. A detailed discussion of the techniques and results of various authors can be found in Chapter 107.

Microvascular Decompression

The popularity of microvascular decompression stems from the studies of Jannetta (8). It is performed under general anesthesia, with a suboccipital craniectomy, using a microscope to visualize the trigeminal nerve as it leaves the pons. Compression by a vascular structure is relieved by repositioning the offending artery or by coagulating a vein. This operation offers an approximately 85% 5-year success rate and does not lead to any sensory loss. The morbidity rate is approximately 5%, and the mortality rate is 0.5%. Chapter 107 contains a thorough discussion of this operative procedure.

Retrogasserian Neurotomy

Sectioning the trigeminal root between the gasserian ganglion and the pons was the standard intracranial procedure for the first half of the twentieth century (43). This operation is indicated when no compression of the trigeminal nerve is discovered during suboccipital craniectomy or if microvascular decompression fails to provide long-term pain relief. It is wisest to perform a partial rhizotomy, because this lessens the probability of inducing anesthesia dolorosa and reduces the morbidity of a

totally numb face. The standard approach today is by the posterior fossa; the subtemporal approach is seldom used. Chapter 107 provides a detailed discussion of this operation and its results and complications.

Peripheral Neurectomy

Peripheral neurectomy is indicated only when gangliolysis has failed and the patient cannot or will not tolerate a suboccipital craniectomy with microvascular decompression. It produces dense numbness and rarely provides more than a year of pain relief. Repeat avulsions of peripheral branches of the trigeminal nerve are even less likely to succeed. Peripheral cranial neurectomies are discussed in Chapter 107.

Compression or Decompression of the Gasserian Ganglion

Compression or decompression procedures were popular before the development of microvascular decompression and gangliolysis. They probably were effective because of minor damage to the trigeminal nerve, ganglion, or rootlets and require a craniotomy by way of the middle fossa. These procedures are not currently indicated.

Trigeminal Tractotomy

Section of the descending trigeminal tract in the medulla produces loss of pain and temperature sensation in the ipsilateral face and pharynx (6). It does not alter touch sensation. The operation is indicated when rhizotomy has failed to alleviate the patient's pain and when all other measures have failed. It is carried out through a small suboccipital craniectomy and laminectomy of C-1 and C-2. The surgical morbidity rate is high if the surgeon is inexperienced and does not use both anatomic and physiologic localization techniques. This operation can be used for tic pain that involves the territories of the nervus intermedius and glossopharyngeal and vagal nerves. Kunc (44) showed that the pain and temperature fibers for all three of the nerves travel in the medial aspect of the descending trigeminal tract. A detailed discussion of the anatomy of this region of the medulla can be found in Chapter 3; the surgical procedure is discussed in Chapter 107.

Stereotactic Radiosurgery

Using either a linear accelerator or a gamma knife, it is possible to place a radiosurgical lesion in the trigeminal root without damaging surrounding brain or vascular structures. The therapeutic effects of this single radiation treatment take weeks to a few months to be noted and there are no data available on the results after 5 years. The short-term results are as good as any other surgical treatment of tic douloureux, and this procedure is likely to have much more widespread use in the years to come (45).

SECONDARY TRIGEMINAL NEURALGIA (II-2)

Although no obvious reason for such a dichotomy is known, it is customary to separate tic douloureux associated with multiple sclerosis, brain tumor, or other recognized diseases from that which we now know to be caused by vascular compression of the trigeminal nerve (Table 47-4). As mentioned above, all trigeminal neuralgia appears to be secondary to a lesion of the trigeminal sensory system.

Neoplasms
Neurinoma of trigeminal nerve
Meningioma
Acoustic neurinoma
Brainstem glioma
Nasopharyngeal carcinoma
Metastatic tumor
Vascular lesions
Aneurysm of circle of Willis
Arteriovenous malformation
Ectatic basilar artery or branches
Arnold-Chiari malformation
Syringobulbia
Pseudotumor cerebri
Amyloidosis
Sarcoidosis
Syphilis
Dejerine-Sottas disease
Acromegaly
Paget's disease of skull
Scleroderma

TABLE 47-4. Identified causes of secondary trigeminal neuralgia

Multiple Sclerosis

Patients with multiple sclerosis can have classic trigeminal neuralgia, or they can have variants that resemble atypical facial pain. The number of patients with multiple sclerosis in any reported series of patients with trigeminal neuralgia is subject to various selection biases. The literature suggests that less than 0.5% of patients with tic douloureux have multiple sclerosis (2). Females younger than age 45 are the most likely to have tic due to multiple sclerosis. This diagnosis requires the identification of nervous system lesions disseminated in both time and space; if the patient's only symptom is tic douloureux, the diagnosis of multiple sclerosis should not be proposed, regardless of the patient's age.

Neoplasm

It is uncommon for a neoplasm to lead to classic trigeminal neuralgia. A constant pain associated with sensory loss, properly diagnosed as atypical facial pain, is much more common. A small fraction of patients with trigeminal neuralgia have a small benign neoplasm impinging on the trigeminal nerve in the subarachnoid space between the brainstem and Meckel's cave. These are usually meningioma, neurinoma, or cholesteatoma.

Neoplasms intrinsic to the trigeminal nerve or those that impinge on it in Meckel's cavity or further peripherally rarely produce classic trigeminal neuralgia. They are much more likely to lead to a constant, aching pain that is associated with sensory loss and to other cranial nerve involvement.

HERPES ZOSTER AND POSTHERPETIC NEURALGIA (II-4, II-5)

Herpes zoster can involve the trigeminal nerve and can lead to a painful neuropathy. Facial or deep ear pain often precedes the vesicular eruption, and this can lead to a diagnostic enigma for a day or so. If the pain persists after the eruption has healed, the diagnosis of postherpetic neuralgia can be made. This is a trying pain syndrome for both the patient and physician. It is fully discussed in Chapter 22. Ramsay-Hunt syndrome (IASP group II-6) follows herpes zoster infection of the geniculate ganglion. The vesicular eruption occurs on the ear, and the pain is felt within the ear or posterior pharynx.

Anesthesia dolorosa is the neurosurgeon's most dreaded complication of ablative lesions of the trigeminal nerve or its branches. A similar pain syndrome is occasionally seen after spinal rhizotomy, but it is seen more frequently in the trigeminal distribution. The term refers to the complaint of pain in an anesthetic region. It is most commonly noted after surgery for atypical facial pain, but it can occur after surgery for tic douloureux or after traumatic nerve injury. It is rarely reported after ablative lesions for cancer pain in the face. The patient complains bitterly of painful numbness, which can also have burning, stabbing, or aching components. The pain is not triggered and is constant.

Anesthesia dolorosa is more common after lesions that totally denervate a region of the face; partial rhizotomy or careful gangliolysis are much less likely to lead to this complaint than complete rhizotomy or dense sensory loss caused by gangliolysis.

No pharmacologic or ablative surgical treatment is effective for anesthesia dolorosa. Sporadic case reports of success are difficult to corroborate. Electrical stimulation of the thalamus-internal capsule has produced a few good results (see Chapter 101).

NERVUS INTERMEDIUS (GENICULATE) NEURALGIA (II-6)

Nervus intermedius neuralgia is an extremely uncommon pain syndrome in which the patient reports shocklike pains in the distribution of the nervus intermedius, which is the somatic sensory branch of cranial nerve VII. The pain is in every way similar to that of tic douloureux except for its location. Few cases have been reported since the original report by Clark and Taylor in 1909 (46,47).

Etiology

It is presumed that the etiology of nervus intermedius tic is analogous to that of trigeminal tic: cross-compression of the nerve at its central-peripheral myelin junction, a few millimeters from the lateral pons. Jannetta (8) described such a finding and the beneficial results produced by moving the offending vessel.

Symptoms and Signs

The patient complains of intermittent, stabbing, electric shock–like pain deep in the ear. The pain can be triggered by nonnoxious stimulation of the ear canal or can follow swallowing or talking. The patient is pain-free between attacks. Neurologic deficits are absent. The syndrome is always unilateral. Some patients have reported salivation, bitter taste, tinnitus, and vertigo during the pain attacks; perhaps this indicates involvement of central connections of the nervus intermedius or irritation of other components of cranial nerves VII and VIII. Rarely, patients with pain in the trigeminal distribution also have pain in the nervus intermedius territory.

Diagnosis

Geniculate neuralgia can also be caused by herpes zoster (see Chapter 22). The patient with geniculate neuralgia usually has a vesicular eruption on the eardrum and external canal that follows the onset of the pain by 1 or 2 days. The pain is constant and burning and can be readily discriminated from the intermittent stabbing pain of nervus intermedius tic.

Treatment

The medical management of nervus intermedius neuralgia is identical to that of tic douloureux (see Table 47-2). When medications do not control the pain, a surgical procedure is warranted. It is impossible to block the nervus intermedius with local anesthetics, but they can be injected into the glossopharyngeal or trigeminal nerve to establish the fact that these two nerves are not responsible for the pain, leaving, by subtraction, the nervus intermedius as the culprit. When medical management fails, suboccipital craniectomy with exploration of the nervus intermedius is indicated. If an offending vessel is found, it can be mobilized. If no vessel can be identified, the nervus intermedius should be sectioned. This procedure is highly likely to relieve the pain permanently, but when it does not, section of the medial aspect of the descending trigeminal tract is indicated (48).

GLOSSOPHARYNGEAL NEURALGIA (II-7)

Glossopharyngeal neuralgia is characterized by shocklike pains in the territory of the glossopharyngeal nerve. It is in every way similar to tic douloureux except for the distribution of the pain and the customary site of the triggering stimulus (48,49).

Etiology

The vast majority of patients with glossopharyngeal neuralgia are thought to have an artery compressing the nerve as it exits from the medulla and travels through the subarachnoid space to the jugular foramen (50). This syndrome can be seen in patients with multiple sclerosis, but it is rare.

Symptoms and Signs

Glossopharyngeal neuralgia is characterized by excruciating shocklike pain in the region of the tonsillar fossa, pharynx, or base of the tongue. It can radiate to the ear or the angle of the jaw or into the upper lateral neck. The trigger zone is often in the same area, and patients frequently report that swallowing, yawning, clearing the throat, or talking is the precipitating stimulus. The pain often appears to be spontaneous. Chewing or touching the face does not precipitate an attack. Glossopharyngeal neuralgia is much less common than tic douloureux—the incidence ratio is approximately 1 to 100 (49,50).

Diagnosis

The nature of the pain, its description by the patient, and the chronology of the attacks are identical to those of tic douloureux of the trigeminal nerve. Indeed, glossopharyngeal tic is sometimes mistaken for mandibular division trigeminal tic douloureux. Involvement of the glossopharyngeal nerve can be demonstrated by localizing the triggering stimulus to the pharyngeal structures that it innervates. Blocking the trigger area with local anesthetic can confirm the site of the trigger and nerve involvement. This is unsuccessful in some patients because the vagus nerve can contain the involved sensory fibers (35,51). The role of the glossopharyngeal nerve in the regulation of heart rate and blood pressure is thought to be why some patients with glossopharyngeal neuralgia have profound cardiac arrhythmias and even asystole with the attack of pain. The presence of such phenomena guarantees that the pain syndrome involves this nerve. The diagnosis can be confirmed by the cessation of pain when this nerve is blocked at the jugular foramen or when topical anesthesia of the pharynx stops the pain (35).

Treatment

The pharmacologic management is the same as that for tic douloureux of the trigeminal nerve (see Table 47-3). When medical management fails, suboccipital craniectomy with exploration of the glossopharyngeal nerve is indicated. If a compressing blood vessel is found it can be mobilized, and the pain usually stops without any loss of nerve function. When no structural pathology can be identified, the glossopharyngeal nerve should be sectioned. In such a case it is wise to section the upper fibers of the vagus nerve as well, because they can also be involved in the pain syndrome. When rhizotomy is unsuccessful, which happens rarely, the medial aspect of the descending tract of the trigeminal nerve can be sectioned to produce loss of pain and temperature sensation in the pharynx (44).

A percutaneous technique of glossopharyngeal neurolysis has been described, but it has not been widely used because of cardiovascular and laryngeal complications (52,53).

VAGAL AND SUPERIOR LARYNGEAL NEURALGIA (II-8)

The two somatic sensory branches of the vagus nerve, the auricular branch and the superior laryngeal nerve, can also be the site of a pain syndrome that resembles that of tic douloureux. This syndrome is rare (54).

Etiology

It is thought that compression of the upper fibers of the vagal nerve as they leave the brainstem and traverse the subarachnoid space to the jugular foramen is the cause of vagal neuralgia.

Symptoms and Signs

Vagus nerve neuralgia is characterized by paroxysms of shocklike pain in the side of the thyroid cartilage, pyriform sinus, angle of the jaw, and, rarely, in the ear (55). Occasionally the pain radiates into the upper thorax or up into the jaw. The trigger zone is usually in the larynx; attacks are precipitated by talking, swallowing, yawning, or coughing. When other portions of the vagus nerve are involved, the patient might have hiccups, inspiratory stridor, excessive salivation, or coughing. The pain is in every way typical of tic douloureux except for its location. The combination of glossopharyngeal and vagal as well as trigeminal pain has been reported.

Diagnosis

The diagnosis is established by the history and by identifying the site of the trigger zone. Associated vagal nerve findings, as described above, also pinpoint this nerve as the site of the pain. Laryngeal topical anesthesia or blockade of the superior laryngeal nerve stops the pain and is a useful diagnostic and prognostic procedure (35) (see Chapter 102).

Treatment

The pharmacologic treatment of vagal neuralgia is identical to that of tic douloureux (see Table 47-3). When medications do not control the pain, suboccipital craniectomy with decompression of the upper fibers of the vagus nerve is warranted. If no lesion is seen, the upper vagal and glossopharyngeal nerves should be sectioned. This procedure is usually successful, but when it is not, section of the medial portion of the descending trigeminal tract can be beneficial (44).

UNILATERAL ATYPICAL FACIAL NEURALGIA

Unilateral atypical facial neuralgia represents a diverse group of facial pain problems that have common symptoms and signs but varied causes. It is more frequent in females and seems to be a disease of young adults. The pain is rarely as severe as that of tic douloureux. The evidence for successful treatment is sparse; the literature is littered with unsubstantiated hypotheses of etiology and treatment schemes that lack any demonstrable efficacy. Part of the problem is the heterogeneity of this group of patients.

Etiology and Pathophysiology

No uniform etiology of unilateral atypical facial pain has been identified. Some patients are found to have an infection of the paranasal sinuses, jaws, or base of the skull; it is possible that the infectious and inflammatory processes can lead to nerve irritation and damage and thus be the originating factor for the pain. How such a process can lead to a pain syndrome that far outlasts the active phase of the disease process is unclear. A small number of patients are found to have a malignant neoplasm invading the base of the skull and traumatizing branches of the trigeminal nerve at their cranial foramina. Rarely, a benign tumor of the trigeminal nerve or the meninges can lead to atypical facial pain (56). Some neurosurgeons believe that vascular compression of the trigeminal nerve distal to the central-peripheral myelin junction (the site of the compression that seems to cause tic douloureux) can lead to atypical facial pain.

Some patients who sustain clear-cut trauma to the peripheral branches of the trigeminal nerve through facial lacerations and contusions develop an atypical pain syndrome in the territory of the damaged nerve. This type of pain can persist even after the sensory loss disappears.

The vast majority of patients with atypical facial pain do not have any discernible etiologic factors. Interestingly, almost all those in this latter group are young women and seem to have significant psychopathology (57). Many are reported to commit suicide.

Symptoms and Signs

Atypical facial pain differs from classic tic douloureux in every respect. The pain is reported as continuous but can fluctuate in intensity. Pain-free intervals are rarely reported. The pain is usually described as burning, aching, or cramping and not like electric shock, but the occasional patient has some shocks superimposed on the constant pain. The distribution of the pain is often within the trigeminal territory, but it can extend into the upper neck or posterior scalp. The patient frequently reports significant hypesthesia in the area of the pain and can also have allodynia or dysesthesia. The pains are not triggered by remote stimuli but can be intensified by stimulation of the painful area itself. Autonomic phenomena are rarely seen.

Diagnosis

The diagnosis of unilateral atypical facial pain is established when the patient complains of unilateral pain that meets the criteria described above. Unfortunately, not all patients present with such a clear-cut set of symptoms as described here. A few patients have a pain syndrome that combines some features of tic douloureux with some of those of atypical facial pain. An increasing number of reports describe patients with pain syndromes that have some features of cluster headaches or muscle-tension headaches with atypical facial pain. The most accurate diagnosis might actually be a combination of two or more of these syndromes. When a patient presents with unilateral atypical facial pain, the physician must undertake the search for a treatable causative lesion. This entails roentgenograms of the skull, computed tomography scan with particular attention to the skull base, magnetic resonance imaging scan, careful dental and otolaryngologic evaluation, and thorough neurologic examination.

Treatment

Atypical facial pain is difficult to manage, and there are few proven therapies. Because a small percentage of the patients will have a treatable structural lesion, the first step is always the search for pathology. This will usually be fruitless, but does at least reassure the patient that there is no major disease causing the pain. If no lesion can be found, the treatment is symptomatic. Antidepressants are of proven value (58,59). The combination of a tricyclic antidepressant and a phenothiazine has helped some patients (60). The standard dose is amitriptyline, 75 mg at bedtime, and fluphenazine, 1 mg four times a day. The risk of tardive dyskinesia has greatly reduced the use of phenothiazines, however. Other patients might respond to anticonvulsant medications, especially when their pain complaints contain some features of tic douloureux. Table 47-3 lists the commonly used anticonvulsants. One study revealed sumatriptan to be of no clinical value (61); another found negative results for calcitonin (62). Responses to almost every type of drug and nostrum have been reported, but little evidence exists to support the use of vitamins, amino acids, or physical therapies.

Psychotherapy for atypical facial pain has been extensively discussed in the psychiatric and psychological literature. Controlled studies cannot be found, however, and it is difficult to evaluate the role of these types of treatments. Certainly, if the patient has significant psychopathology in addition to the face pain, it is reasonable to use whatever form of psychotherapy that seems most appropriate.

Surgical treatments for atypical facial pain do not have a good track record. Operations that further damage the trigeminal nerve are unsuccessful in most patients and often lead to increased complaints of pain and numbness; a contrary opinion was offered by Ziccardi et al. in a relatively weak study (63). A few reports of the efficacy of trigeminal tractotomy and other ablative lesions of the midbrain, thalamus, and brainstem can be found (64,65). Other reports suggest some success with implanted stimulators of the trigeminal ganglion or thalamus (66). Some successes have also been noted with decompression of the trigeminal nerve in the subarachnoid space distal to the site of cross compression found in tic douloureux. Retrograde suicide axonal transport of doxorubicin (Adriamycin) has been reported to be a successful way of treating atypical facial pain in two patients (67). Generally, patients with unilateral atypical facial pain should not be offered destructive surgical procedures.

BILATERAL ATYPICAL FACIAL PAIN

Bilateral atypical facial pain is a disease with no known etiology. The patient is usually an older female but can be of any age. The pain is described as constant and burning and is not triggered. Sensory examination is either unremarkable or slight hypesthesia, paresthesia, allodynia, or dysesthesia can be found. Identical pains are seen by physicians on the face and intraorally by dentists (“burning mouth syndrome”). Indeed, a similar constant burning pain in the rectal area is also well known. None of these bilateral burning pains has been associated with any structural or physiologic pathology identified to date, and they do not usually respond to any drug, physical treatment, or surgical procedure (61). To the extent that allodynia is present, it is possible that brainstem function has been altered, resulting in abnormal responses to nonnoxious stimuli. There is some evidence that anticonvulsant medications may be helpful in a fraction of the patients (58). The patient often has significant emotional stressors and psychopathology, but how these relate to the pain is unclear (68,69). Psychologic therapies can be useful, but the most important thing the pain management specialist can do is to prevent the patient from undergoing inappropriate drug therapy or surgical procedures. Some have argued that there are specific causes of burning mouth syndrome or bilateral atypical facial pain, but the evidence is weak (70,71).

OCCIPITAL NEURALGIA (II-9)

Occipital neuralgia is characterized by pain in the suboccipital region and in the back of the head. A large number of patients have muscle-tension headaches in the

same distribution, but few of these patients have a true neuralgic pain. Muscle-tension headaches are discussed in Chapter 48.

Etiology

The two broad groupings of patients with occipital neuralgia include those with structural pathology and those with no apparent etiology. Known causes of neuralgic pains in this area include trauma to the greater or lesser occipital nerves, compression of these nerves or the upper cervical roots by arthritic changes in the spine, and tumors involving the second and third cervical dorsal roots. Most patients with occipital neuropathy do not have discernible lesions.

Symptoms and Signs

Occipital neuralgia is characterized by continuous aching and throbbing pain on which shocklike jabs can be superimposed. The pain starts in the suboccipital region and radiates over the posterior scalp and sometimes across the lateral scalp. Retroorbital pain is common in a severe attack. The pain is not triggered, but pressure over the occipital nerves can lead to an exacerbation. Both physical and emotional tension are common precipitating factors. Although textbooks usually distinguish between neuralgic and vascular pains, some patients have a pain syndrome that combines features of both types of pains. Patients with occipital neuralgia can have migrainelike symptoms and can develop autonomic changes similar to those seen in cluster headaches. When the pain is severe, the patient might note hypesthesia or dysesthesia in the posterior scalp.

Diagnosis

The region of the pain clearly establishes the diagnosis; the difficult task is determining whether the nerve lesion is primary or secondary. Vascular pains (migraine in the posterior scalp or cluster headaches in the anterior scalp and face) are usually characterized by discrete attacks of throbbing pain, often associated with nausea and vomiting and other autonomic phenomena. Migraine is often terminated by ergot alkaloids or sumatriptan; neuralgic pains are not.

Muscle tension headaches are a variant of myofascial pain syndrome and are common. They are clearly stress related. The patient usually has a long history of such headaches, which wax and wane over the years. Tender areas in the suboccipital muscles are frequently located by palpation.

Positive findings from neurologic examination lead to the suspicion of a structural lesion; roentgenography, computed tomography scan, or magnetic resonance imaging scan assists in the diagnosis.

Treatment

Obviously, when occipital neuralgia has a structural basis, surgical treatment may be aimed at the cause. In most patients, however, treatment is symptomatic. If the pains resemble those of tic douloureux, a trial of anticonvulsants (see Table 47-3) might be worthwhile. If they resemble those of atypical facial pain, a tricyclic antidepressant can be tried. Local nerve blocks can help to establish the diagnosis and sometimes provide even longer relief than the duration of the agent used. Some have advocated the injection of local anesthetics and steroids, but controlled studies of the outcomes of such treatments have not been undertaken.

Neurosurgeons have advocated decompression or sectioning of the second and third cervical roots as well as the greater and lesser occipital nerves (72). Information on the efficacy of these procedures is lacking; the vast majority of patients do not appear to require a surgical procedure.

SLUDER'S NEURALGIA

Sluder's neuralgia, also known as Sluder's syndrome, sphenopalatine ganglion neuralgia, lower half headache, and lower facial neuralgia, was first described by Sluder (73) in 1908 and later redefined by Eagle (74). This clinical entity is rare (if it exists at all) and is characterized by unilateral facial pain that never extends above the level of the eye and the ear. It is probably a variant of cluster headache and is further discussed in Chapter 48 (75).

Etiology

Sluder (73) suggested that this condition results from spread of paranasal infection, with consequent vasoconstriction, whereas Eagle (74) found swelling of the nasal mucosa and other intranasal pathology that he believed to cause stimulation of the pterygopalatine ganglion. Others have suggested a reflex vasomotor change, and still others believe it is a vasodilator syndrome (73,76,77).

Symptoms and Signs

Pain is said to begin in the root of the nose and to spread to the orbit, causing extreme soreness of the eyeball, nose, upper teeth, zygoma, palate, and pharynx, and even the shoulder and arm. Rhinorrhea, lacrimation, sneezing, photophobia, and salivation often occur, but no trigger point is found. The distribution and duration of pain vary and can simulate those of chronic paroxysmal hemicrania (Horton's histaminic syndrome).

Diagnosis

Eagle (74) believed that the diagnosis was conclusive if the symptoms and signs are relieved by anesthesia of the sphenopalatine (pterygopalatine) ganglion on the affected side. This can be achieved by application of 4% cocaine for 3 minutes or by injection of the pterygopalatine ganglion. The latter is achieved either through the nose or by inserting a needle bent to a 100-degree angle through the greater palatine foramen and then advancing it in a superior and slightly posterior direction along the pterygopalatine canal to a depth of 3.5 to 4.0 cm (47). Repeated blocks can be used to control recurrent attacks. Sluder (73) used alcohol injection to produce prolonged relief, whereas others have advocated resection of the ganglion for the same purpose (47).

Although a number of clinicians still believe that Sluder's neuralgia occurs and use the injection technique for its treatment, many investigators have denied that this syndrome exists as a distinct clinical entity and believe that it is probably a variant of atypical facial neuralgia.

VIDIAN NEURALGIA

Vidian neuralgia, also known as *Vail's syndrome*, was first described by Vail (78) in 1932. It is characterized by severe attacks of unilateral pain in the nose, face, eye, ear, head, neck, and shoulder, which often occur at night. The condition predominates in females. It too may be a variant of cluster headache (75).

Etiology and Pathophysiology

Vail (78) believed that this syndrome is caused by irritation or inflammation of the vidian nerve (nerve to the pterygoid canal) along its course in the pterygoid canal, secondary to infection of the sphenoid sinus. He theorized that this condition is the same as sphenopalatine neuralgia because the irritation of the nerve could extend forward to the pterygopalatine ganglion as well as backward to the geniculate ganglion (facial nerve) through the greater superficial petrosal nerve and from there to the sympathetic plexus around the internal carotid artery.

Diagnosis

A diagnosis should entail a thorough examination to determine if infection of the sinus is present. Block of the pterygopalatine ganglion by application of cocaine or through injection with another local anesthetic is a useful diagnostic and prognostic procedure.

Treatment

If at least four or five prognostic blocks produce complete relief of pain, alcohol injection of the pterygopalatine ganglion can be considered and has been reported to provide prolonged relief in some cases. Obviously, drainage of the sphenoid sinus should be carried out if infection is present. Vail (78) believed that this is essential

for permanent relief. Like sphenopalatine neuralgia, the existence of vidian neuralgia has been questioned by many clinicians.

PETROSAL NEURALGIA

Approximately four decades ago Gardner and associates (79) suggested that abnormal activity of the greater superficial petrosal nerve caused unilateral head pain, lacrimation, edema, rhinorrhea, and other symptoms and signs typical of cluster headache, in some patients. They based this observation on the fact that the greater superficial petrosal nerve contains parasympathetic secretory fibers for the lacrimal gland; vasodilator fibers to the nasal mucosa and cerebral hemisphere; and afferent fibers from the dura mater, internal carotid artery, and pterygopalatine ganglion. Gardner and colleagues (79) sectioned this nerve in 26 patients with the above signs and symptoms and noted excellent results (complete relief) in 25% of patients, fair to good relief in 50%, and failure in 25%.

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CHAPTER 48

Headache

K. M. A. Welch

Headache is the most common human malady. Ample evidence exists that the subject was a topic of discussion and a focus of therapy of physicians in ancient Sumer, Babylonia, Egypt, Greece, and Rome (see references 1,2,3 and 4 for reviews of the history of headache). The Ebers Papyrus, written approximately 1550 bc, includes an early Egyptian pharmacopeia that contains a prescription for a mixture of opium to treat Ra's headache. Egyptians also used trephine of the skull to relieve headache. Discussions of headache can be found in the writings of Hippocrates and other Greek physicians, of Celus, Aretaeus, Galen, and other early Roman physicians, of the Arabian physician Abulcasis, and Avicenna during the Middle Ages, and of Paracelsus, Mondini, Vesalius, and others during the Renaissance.

In this chapter, the term *headache* is used for pain felt in or around the cranial vault and includes pain behind the eyes and at the junction between the neck and back of the head. Although pain located in the eyes, nose, face, or jaws often spreads to the head, pain in these areas is discussed in Chapter 49, Chapter 50, Chapter 51, Chapter 52 and Chapter 53.

CLASSIFICATION OF HEADACHE

Before 1988 the classification proposed by the Ad Hoc Committee of the National Institutes of Health in 1962 (5) was the most widely used. These definitions were not operational, but instead short descriptions of the clinical features of each syndrome. The classification and definition system of the International Headache Society (IHS) listed in Table 48-1 (6), although not perfect, now is accepted, at least for research purposes. This classification will be revised early in the twenty-first century.

TABLE 48-1. Classification of headache disorders, cranial neuralgias, and facial pain

Epidemiology

Subsequent to the IHS classification, epidemiologic studies have focused on specific headache types. Consequently, contemporary epidemiologic studies are discussed under the sections dealing with specific headache diagnoses. Most studies before 1988 and the IHS classification suffer from lack of accepted definition of headache diagnosis but remain of general interest related to unclassified headache. Some of these studies are briefly reviewed.

In 1985, *The Nuprin Pain Report*(7) provided a mass of data on the prevalence and severity of headache, the demographic characteristics of headache sufferers, the effect on their lives and work, and how they cope with headache. Table 48-2 is a summary of the data. Among those surveyed, headache occurred 1 to 5 days a year in 30%, 6 to 10 days in 14%, 11 to 30 days in 16%, 31 to 100 days in 8%, and 100 days or longer in 5%. Among those who had headache, nearly one-fifth had it for 6 to 10 days, 22% for 11 to 30 days, 11% for 31 to 100 days, and 7% for 101 or more days. The overall prevalence among the American women (78%) was similar to that among Welsh women (79%) reported by Waters and O'Connor (8), whereas the prevalence was significantly higher among American men and women than among the Finnish population reported by Nikiforow and Hokkanen (9,10). As in both the Welsh and the Finnish findings, the prevalence of headache was lower among those older than 60 years. By a 10% margin, women reported headache more frequently than men. Those with a college education had headache more frequently than those with a high school education, working mothers and advertising executives had headache more frequently than homemakers and those in other occupations, and retired persons had the lowest incidence. No difference in the prevalence of headache was seen between those living in urban and rural areas. Table 48-3 summarizes the profiles of those who had headaches 6 days or more and their ratings of its intensity. Among adults with headache, 638 million workdays were lost among all adults and a total of 157 million workdays among all adults employed full- time. Using 1985 figures, the total cost of headache to the American people likely exceeded $17 billion for that year.

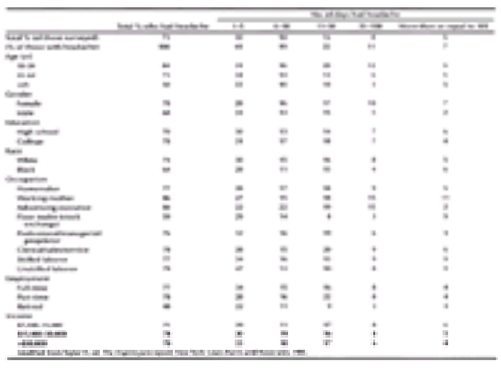

TABLE 48-2. Headache in Americans in 1985

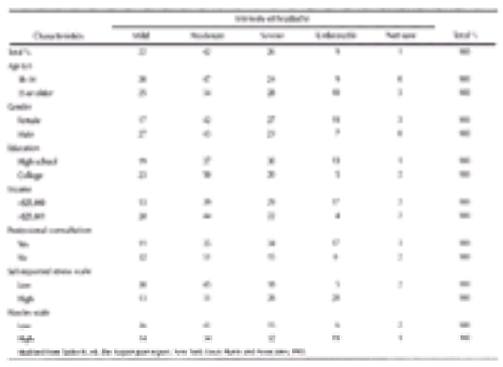

TABLE 48-3. Profiles of Americans who experienced headache in 1985 by intensity (in % of those who experience headache 6 days or more)

ANATOMY AND GENERAL PATHOPHYSIOLOGY

Innervation of the Cranium and Its Contents

Investigations on humans undergoing intracranial surgery under local anesthesia (11,12) have shown that the following structures are pain sensitive: (a) all of the extracranial structures, especially the arteries; (b) the great venous sinuses and their tributaries from the surface of the brain; (c) parts of the dura at the base of the brain; (d) the meningeal arteries and big cerebral arteries at the base of the brain; and (e) the fifth, ninth, and tenth cranial nerves and the upper three cervical nerves. The cranium (including the diploic and emissary veins), the parenchyma of the brain, some of the dura, almost all of the piaarachnoid, and the ependymal lining of the ventricles and the choroid plexus are insensitive to mechanical, thermal, electrical, or chemical stimuli (13).

Stimulation of pain-sensitive structures on or above the superior surface of the tentorium cerebelli causes pain in parts of the head anterior to a line drawn from the ears across the top of the head, whereas stimulation of structures on or below the inferior surface of the tentorium cerebelli generally causes pain behind the aforementioned line, but certain sites may project to the brow or behind the eyes (14). It has been further demonstrated that nociception from the supratentorial structures is mediated by the trigeminal nerve, whereas nociceptive impulses from stimulation of the infratentorial structures are transmitted by afferent fibers in the fifth, ninth, and tenth cranial nerves and the upper three cervical nerves.

The intracranial vessels also are supplied by afferent fibers, which run in the ophthalmic division of the trigeminal nerve and terminate in the trigeminal ganglion. In addition, the arteries are surrounded by dense networks of nerves containing a variety of neuropeptides.

Cranial bones are not pain sensitive, but stretch or other sensation of the periosteum, which surrounds them, evokes pain locally. The scalp, of course, is pain sensitive, as are the arteries that supply it (i.e., the supraorbital, frontal, superficial temporal, posterior auricular, and occipital arteries). The first three arteries are supplied by the trigeminal nerve, whereas the posterior auricular and occipital arteries are supplied by branches of the upper cervical nerves. The external carotid artery and its branches are also supplied by afferent fibers that are a part of the nerve plexuses surrounding these vessels and eventually reach the spinal dorsal horn or the trigeminal nucleus caudalis via the sensory roots of the upper four thoracic spinal nerves or the trigeminal nerve. The nerve fibers containing neuropeptides play a role both in nociception and in the regulation of vascular tone

Reference of Pain

Figure 48-1, Figure 48-2, and Figure 48-3 depict the site of reference of pain on stimulation of various intracranial and extracranial structures. Stimulation of the dura in the anterior fossa (supplied by a recurrent branch of the ophthalmic division of the trigeminal nerve) is referred to the ipsilateral eye, orbital region, and anterior part of the head (see Fig. 48-1). Stimulation of the dura in the middle cranial fossa, or the middle meningeal artery, which is supplied by the second and third division of the trigeminal nerve, causes pain to be referred to the ipsilateral supraorbital region and primarily to the temples and the ipsilateral aspect of the top of the head (see Fig. 48-1 and Fig. 48-2). Stimulation of the dura and the arteries of the posterior cranial fossa (supplied by recurrent branches of the glossopharyngeal and vagus nerves and the upper three cervical nerves) is referred to the ipsilateral ear, posterior auricular region, occiput, and suboccipital region. As noted in Figure 48-3, stimulation of the arteries of the scalp causes pain localized to that region. Pain from the eye, nasal sinuses, and teeth is felt locally at first, but then may be referred to the appropriate division of the trigeminal nerve, with some overflow to adjacent divisions if the nociceptive stimulation is intense.

Figure 48-1. Pain sensitivity of the dural floor of the skull, the tentorium cerebelli, and the adjacent venous sinuses and venous tributaries. *Circles* indicate points of stimulation that do not cause pain. *Black circles* indicate points of stimulation that cause pain. The diagrams show the area of pain after stimulation of (1 to 8) the dura of the floor of the anterior fossa; (9 and 17) the middle meningeal artery; (10 to 12) the dura of the floor of the posterior fossa; (13) the inferior wall of the transverse sinus; (14) the superior wall of the torcular Herophili; (15) the superior wall of the transverse sinus and upper surface of the tentorium cerebelli; and (16) the inferior cerebral veins. (From Wolff HG. *Headache and other pain*, 6th ed. New York: Oxford University Press, 1993, with permission.)

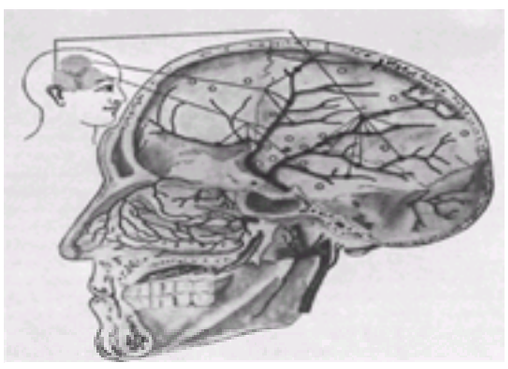

Figure 48-2. Pain sensitivity of the middle meningeal artery. *Open circles* indicate points of stimulation of the dura that do not cause pain. *Black circles* indicate points of stimulation that cause pain. The diagram shows three overlapping areas of pain in the parietotemporal region resulting from stimulation of different portions of the artery and its branches. (From Wolff HG. *Headache and other pain*, 6th ed. New York: Oxford University Press, 1993, with permission.)

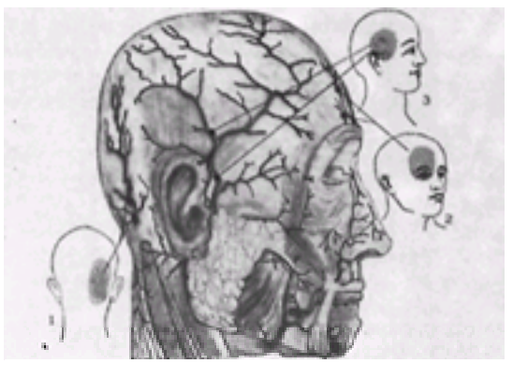

Figure 48-3. Pain sensitivity of the arteries of the scalp. *Black circles* indicate points of stimulation that cause pain. The diagrams show areas of pain following stimulation of (1) the occipital arteries; (2) the supraorbital and frontal arteries; and (3) the superficial temporal artery. (From Wolff HG. *Headache and other pain*, 6th ed. New York: Oxford University Press, 1993, with permission.)

Sympathetic Supply

The preganglionic neuron cell bodies are located in the intermediolateral column of T-1 to T-4 spinal cord segments, inclusively. Their axons course through the anterior nerve root of the upper four thoracic nerves, the white rami communicantes, and join the sympathetic trunk (see Fig. 46-11). Some of these end in the stellate ganglion, whereas others ascend to, and course through, the cervical sympathetic trunk to end in the superior cervical ganglion. The cerebral arteries are supplied exclusively by fibers from the superior cervical ganglion, whereas the extracerebral arteries are supplied partly from the stellate ganglion and partly from the superior cervical ganglion. Although neural control of the cerebral circulation remains controversial, evidence exists that, in some species, sympathetic fibers exert a mild constrictor effect on the cranial arteries that is greater in the external carotid than the internal carotid arterial system. This effect is weakest in the vertebral basilar arteries (14,15).

Parasympathetic Fibers

The parasympathetic fibers have their cell bodies in the midbrain, and their axons course through the facial and greater superficial petrosal nerve to end in ganglia located in the proximity of the anastomosis of the greater superficial petrosal and the internal carotid nerves (see Fig. 46-8, Fig. 46-12, and Fig. 46-13). Here they synapse with postganglionic neurons, the axons of which join and accompany the plexus that surrounds the internal carotid artery to reach and surround the cerebral arteries as far as the small arteries of the pia. Some evidence suggests that these are the efferent pathways for a vasodilator reflex with the trigeminal nerve as its afferent limb (4). This reflex may be responsible for some of the increases in cerebral and extracranial blood flow in painful conditions such as migraine (4).

General Headache Mechanisms

Human studies suggest that headaches can be brought about by (a) displacement, distension, and inflammation of cranial vascular structures including the branches of the external carotid artery and the intracranial arteries; (b) sustained contraction of muscles of the head and neck; and (c) direct pressure on the cranial and upper cervical nerves. Wolff and associates (11,12,14) suggested six basic mechanisms of headaches that arise from intracranial sources: (a) traction on the veins that pass to the venous sinuses from the surface of the brain and displacement of the great venous sinuses; (b) traction on the middle meningeal arteries; (c) traction on the large arteries at the base of the brain and their branches; (d) distension and dilatation of the intracranial arteries; (e) inflammation in or about any of the pain-sensitive structures of the head; and (f) direct pressure by tumors. Often, more than one of these mechanisms is involved in headaches of intracranial origin. Headache from extracranial sources may involve tender muscles of the head and neck, distension or inflammation of extracranial arteries, and pain referred from diseases of the eye, sinuses, and teeth.

EVALUATION OF THE HEADACHE PATIENT

History

To elicit a relevant history from an uncomfortable patient with a severe headache is a challenging task. A quiet, dark room usually helps in this situation. Because most patients with headache do not manifest positive neurologic findings on physical examination, history taking is essential to establish a diagnosis. The clinician may find it of help to ask four key questions in the following order: “How long have you had the headache?' “What do you think caused it?' “Where is the headache located?' and “What is it like?”

Duration, Onset, and Frequency of Headache

Among sufferers who present to a physician with the complaint of headache, three broad categories can be recognized: (a) patients coming to the emergency room with a first-time severe headache with no previous evaluation (they are a high-risk group for serious intracranial pathology); (b) patients with a history of chronic headache but change in the frequency, character, or intensity of the headache; and (c) patients with a chronic paroxysmal headache (e.g., migraine) in attacks occurring at regular intervals.

Information about onset of the headache provides further clues to its possible cause. *Thunderclap* onset may indicate a subarachnoid hemorrhage. If the patient survived, or had more than one such event, this is termed *sentinel headache*. Failure to recognize a sentinel headache should be the fear of every physician. A headache of onset 5 to 6 weeks before the consultation with increasing severity may point to raised intracranial pressure, for example, caused by a brain neoplasm. Awakening with a headache indicates an organic cause and may occur in conditions as varied as obstructive sleep apnea, cluster headache, migraine, hypertension, and cerebrovascular disease. Migraine and tension headaches almost always begin before the fourth decade of life. Before attributing a first-time headache in an elderly person to migraine or tension, more serious conditions should be excluded.

Cause

Knowledge about the precipitating factors of headache is most valuable in focusing the physician toward a particular diagnosis. Headache related to stress, fatigue, hunger, concentration, excitement, ingestion of chocolate, and the use of contraceptive pills or estrogens may support a diagnosis of migraine. Any recent head or neck trauma is an obvious cause for headache. Headache precipitated by activity, straining, blood pressure increase, and sudden head turning may indicate increased intracranial pressure. A first and worst headache during sexual intercourse should alert the physician to the possibility of subarachnoid hemorrhage. A history of fever, ingestion of toxins, caffeine, alcohol, tobacco, or nitrates suggests headache of infectious, chemical, toxic, or metabolic origin. Carbon monoxide poisoning must be considered when several patients from the same location present with a headache.

Location

Headache caused by infratentorial disease is most often localized to the occipital region. Supratentorial pathology usually produces pain in the frontal region. Remember, however, that pain from infratentorial structures may be referred to frontal regions and vice versa. Structural lesions obstructing the flow of cerebrospinal fluid (CSF) circulation in the infratentorial ventricular system also can produce frontal headache secondary to hydrocephalus of the lateral ventricles. Approximately two-thirds of migraine attacks are unilateral, although the location may vary with different attacks. Chronic pain experienced over the vertex or in a bandlike distribution around the head may suggest tension-type headache. A severe, pulsatile, retroorbital pain may suggest cluster headache, inflammatory lesions of the orbital structures, or an expanding aneurysm around the circle of Willis. Some other considerations concerning headache localization are listed here: (a) A headache that presents unilaterally and progresses over time to become bilateral may be caused by increasing intracranial pressure. (b) Lesions that cause traction on the falx or midline structures may cause pain in either eye. (c) Cerebellopontine angle tumors produce pain behind the ear and lesions involving the lateral sinus result in pain

deep in the ear.

Character

The character and intensity of pain are qualitative judgments made by the patient and are only occasionally helpful in making the diagnosis. In this regard, specific information on the increasing or decreasing severity of the headache becomes important. A steady, generalized pain increasing over several weeks may indicate increased intracranial pressure. Bending, stooping, coughing, defecation, or sexual intercourse enhances this type of headache. Headache of a pulsatile nature (corresponding to the radial/carotid pulse) is highly suggestive of vascular origin, whereas a throbbing pain is less specific. Sharp, lancinating, or a deep boring pain, when localized behind the eye, may suggest cluster headache. A stabbing, ice pick–like pain in the distribution of the fifth cranial nerve indicates trigeminal neuralgia. A constant vicelike gripping pain, or a dull pressure pain, may indicate muscle contraction headache.

Associated Symptoms

A sudden, severe headache with loss or alteration in consciousness or a drop attack should be taken as a sign of potentially serious intracranial pathology. Symptoms of paresis, paralysis, ataxia, or sensory disturbance associated with a headache indicate structural lesions. Visual symptoms are frequently associated with an acute headache and are helpful in formulating a differential diagnosis. A scintillating scotoma, photophobia, hemianopsia, and teichopsia occur as a part of the migraine aura. Raised intracranial pressure associated with a headache and papilledema may manifest as a rapid and progressive loss of vision with a centrocecal scotoma. Persistent field defects are a serious complication of temporal arteritis. Extracranial cerebrovascular disease may present with a headache and amaurosis fugax. Vomiting may accompany a severe migraine headache and may occasionally alleviate it. Projectile vomiting is classically associated with increased intracranial pressure. Vomiting may be a symptom of other systemic conditions likely to be associated with headache, such as fever, heat-related illness, and allergic reactions.

Physical Examination

Although history contributes greatly to diagnosing the cause of a headache, positive findings on the physical examination can make the difference between initiating emergent treatment versus nonemergent, routine outpatient workup. Examination should start with a review of the vital signs. Fever always mandates a search for meningitis, encephalitis, or brain abscess. Mild increases in blood pressure and heart rate are a normal physiologic response to pain. True hypertensive headache does not occur until the diastolic blood pressure is above 130 mm Hg. Blood pressure is often elevated as a secondary mechanism in cases of cerebral edema or acute stroke. Tachypnea may be present in conditions such as an exacerbation of chronic obstructive pulmonary disease and severe anemia.

Next, a general impression of the patient should be obtained through his or her appearance and response to pain. Most patients with headache lie still with eyes closed, unwilling to talk or move. Patients with meningeal irritation from any cause may exhibit extreme restlessness. Signs of any external trauma and head injury may be visible at first sight. Most pain-sensitive structures of the head and neck can be viewed directly or palpated. Palpating or tapping can easily discover local sources for pain over sinuses, teeth, and neck musculature. Tenderness overlying the superficial temporal artery is the hallmark of temporal arteritis. Tenderness of the internal carotid artery occurs in carotidynia. Infections in the head and neck often cause tender lymphadenopathy. An enlarging lymph node in the region of the occipital canal may entrap the occipital nerve and cause severe ipsilateral hemicranial pain. Tolosa-Hunt syndrome or painful ophthalmoplegia may be linked to enlarged tubercular nodes in the neck. In a patient with trauma, a boggy mass under the temporalis muscle is the site of a ruptured middle meningeal artery and an intracranial, extradural hematoma. Trapezius muscle spasm may be the primary cause of a muscle contraction headache or occur secondarily as a result of severe head pain of a different etiology. Always test for nuchal rigidity. It indicates meningismus caused by meningitis, encephalitis, severe cervical spondylosis, or a subarachnoid hemorrhage.

Ophthalmologic examination should seek the presence of redness, corneal clouding, and ciliary flush of iritis seen in glaucoma. A Tono-Pen can be used to easily measure the intraocular pressure. If untreated, glaucoma can rapidly progress to blindness. Errors of refraction rarely cause a headache. In the ear, look for signs of infection or cholesteatoma, which may erode intracranially, causing a brain abscess. Presence of hemotympanum or blood in the external auditory meatus suggests a basilar skull fracture as a result of head trauma. Listen over the carotid arteries for bruits of atherosclerotic origin and over the eyes and head for bruits of arteriovenous malformations. Dermatologic examination should look for the typical skin lesions of herpes zoster. The skin over the temporal arteries may be swollen or inflamed. Look for needle tracks or skin popping as evidence of intravenous drug abuse.

Neurologic Examination

Every patient with a headache should have a complete neurologic examination. Start by assessing the higher cortical functions and conscious state. Altered mentation and confusion are signs of serious intracranial pathology. Cranial nerve abnormalities are most frequently encountered in the ocular systems. Funduscopic examination should look for spontaneous venous pulsations, which suggest normal intracranial pressure. The pupil should not be dilated because this can either mask preexistent anisocoria or precipitate angle closure glaucoma in patients with a narrow angle. Papilledema, when present, is usually bilateral and points to increased intracranial pressure. With hypertensive emergencies, the fundus may show acute hemorrhages and exudates. Retinal and subhyaloid hemorrhages are virtually diagnostic of subarachnoid hemorrhage. Scotomas of hemianopic field defects may indicate less common causes of headache, such as a brain tumor, arteriovenous malformation, or expanding aneurysm. Bitemporal field defect in a patient with severe frontotemporal headache can be caused by an expanding pituitary adenoma. Unilateral ophthalmoplegia with sensory loss in the first division of the fifth cranial nerve in association with unilateral retroorbital headache may be caused by a superior orbital fissure syndrome, painful ophthalmoplegia, or Tolosa-Hunt syndrome. Ophthalmoplegic migraine is a rare syndrome. Unilateral third nerve or bilateral sixth nerve palsies are frequently related to aneurysms of the cerebral vasculature or increased intracranial pressure. Unilateral Horner's syndrome and headache may indicate carotid arterial dissection. Miosis together with excessive sweating may indicate posttraumatic dysautonomic cephalgia. Ischemic or hemorrhagic cerebrovascular disease may present with a headache, visual field defects, and motor weakness.

Diagnostic Evaluation

In the vast majority of headache patients the diagnosis can be made without a laboratory examination. When the history and physical examination lead to suspicion of disease, further neurodiagnostic tests are indicated. Laboratory studies (e.g., complete blood count, electrolyte profile) depend on underlying medical problems or search for secondary causes of headache. For example, in all patients over the age of 50 years in whom the diagnosis of temporal arteritis is suspected, an erythrocyte sedimentation rate should be ordered. As another example, carbon monoxide level or toxicology screen may be ordered in an emergency room setting. In the absence of focal neurologic deficits or papilledema it is safe to directly proceed to a lumbar puncture. Computed tomography (CT) scanning is commonly used in diagnosis, especially in the evaluation of headache in the emergency setting. Magnetic resonance imaging (MRI) is the most sensitive to structural disease causing secondary headache.

PRIMARY HEADACHES

Migraine

Migraine is the most important type of headache because of its frequency and severity. The term *migraine* evolved from the original Greek *hemikranios*, which the Romans translated into Latin as *hemicranium*. Galen introduced the term *hemicrania* to describe this type of headache. The term *hemicrania* remained in use throughout the Middle Ages and Renaissance and was used as a title of several books; in 1660, Van der Linden published a monograph *De Hemicrania Menstrua*, and a century later, Fordyce published *De Hemicrania*. Subsequently, the term was corrupted into lower Latin as *hemigranea* and *migranea*, which was translated into old English *mygrane* or *megrim*. This term was used by Liveing in his comprehensive treatise *On Megrim, Sick Headache and Some Allied Disorders*, published in 1873 and containing summaries of reports on the etiology, symptoms and signs, and therapy of headache reported by numerous other writers (16). In this book Liveing continued the debate as to whether migraine was vascular or neurogenic by stating that migraine was analogous to epilepsy and that the circulatory phenomena that occurred during the attacks were secondary to CNS discharges or “nerve storms,' views shared by Jackson and Gowers. The French term *migraine* gained widespread acceptance in the eighteenth century and has been used ever since. The term *migraineur*, derived from the French *migraineux*, denoting a migraine sufferer, is also common.

Classification

The classification adopted by the IHS has replaced classic migraine with the term *migraine with aura* and common migraine with the term *migraine without aura*. Migraine without aura is an idiopathic chronic headache disorder manifesting in attacks lasting 4 to 72 hours and characterized by headache that is unilateral, has a

pulsating quality, is of moderate or severe intensity, is associated with nausea or photophobia or phonophobia, and is aggravated by physical activity. In migraine with aura (classic migraine) these symptoms are accompanied by attacks of neurologic symptoms localized to the cerebral cortex or brainstem. The neurologic symptoms usually develop gradually over 5 to 20 minutes and last less than 60 minutes. Headache, nausea, photophobia, and phonophobia usually follow the neurologic aura directly or after a headache-free interval usually less than 1 hour. In some instances the headache phase might be completely absent (*migraine sine hemicrania*). As noted in Table 48-1, migraine with aura is further classified into subgroups including migraine with typical aura, migraine with prolonged aura, basilar migraine, migraine aura without headache, and migraine with acute onset aura. The classification also distinguishes the aforementioned types of migraines from ophthalmoplegic migraine, retinal migraine, migraines associated with intracranial disorders, and the group labeled possible precursors of migraine. Specific diagnostic criteria are also included in the IHS classification.

Epidemiology

Epidemiologic studies have provided estimates that, in the United States, migraine occurs in up to 18% of women and 6% of men; one-third is severely disabled or require bed rest during an attack (17). The peak prevalence occurs between the ages of 30 to 45, after which the prevalence declines. In children, the prevalence is 2.5% (7 to 9 years), 4.6% (10 to 12 years), and 5.3% (13 to 15 years). The overall prevalence of migraine with aura is approximately 4%, distinctly less than the prevalence of migraine without aura in women and approximately equal in men (18). Because of the sex differential, migraine is uncommon after the age of 45 in men, but remains common in women into the menopausal years and beyond. Although long thought to be a disorder of the highly intelligent or the upper social classes, migraine is in fact more prevalent in lower income groups (17). Possibly, this is caused by poor diet, stress, inadequate medical care, or else disabling migraine results in low income groups by disrupting education and occupation. Eight percent of male subjects and 14% of female subjects may miss all or part of a day of work or school in any 1 month (19). The estimates of cost of lost productivity in the United States range from $1.2 to $17.2 billion (19). Fifty percent of migraine sufferers account for 90% of the work lost (20).

Pathophysiology

The mechanisms of migraine remain to be determined. We review the relevant evidence and general hypotheses for the aura and migraine susceptibility, culminating in a synthesis of contemporary views.

Migraine Attack

Aura-Cerebral Vasospasm. Migraine, according to the theory of Wolff (21), was a primary defect of CNS vasculature. He postulated that the neurologic features of the aura were caused by vasospasm producing ischemia. Subsequently, brain acidosis caused cerebral vasodilation, which was painful. Points put forward in favor of the vascular concept were that the headache associated with migraine has a pulsating quality similar to the headaches secondary to stroke, arteritis, and hypertension. Also, blood vessels are predominantly the pain-sensitive structures in the brain. The drugs used to treat migraine produce vasoconstriction (e.g., ergotamines). Vasodilation (e.g., 10% carbon dioxide and 90% oxygen) was considered to prevent headache and abort the aura by increasing blood to brain regions undergoing vasospasm. Methysergide, a serotonin antagonist, prevents vasospasm induced by serotonin; because it is highly effective in preventing migraine, this linked serotonin release to triggering the attacks of vasospasm and hence aura.

This model of vasospasm giving way to vasodilation to explain both the aura and headache still has its supporters. Cerebral blood flow (CBF) measurements performed by earlier methods certainly supported this notion, and a critical appraisal of more recent CBF studies argues in favor of a primary ischemic basis for the aura (22). Nevertheless, the clinical features of the aura are distinctly unlike those of acute ischemia caused by cerebral vascular disease. For this and other reasons discussed later, this hypothesis is currently less favored than others.

Aura-Spreading Depression. In 1944, Leao reported an experimental phenomenon in rodent brain and retina that has come to be known as spreading depression (SD) (23), although it could also be termed spreading activation. Neuronal depolarization is followed by suppression of neuronal activity in a wave that spreads slowly across the surface of the brain. Two mechanisms have been proposed for SD, one based on the release of K^+ from neural tissue (24) and the other on release of the excitatory amino acid glutamate (25). Neural tissue may possess both mechanisms. Glutamate release from dendrites or soma of neurons depolarizes adjacent neurons that release additional glutamate, thus propagating SD. An increase of extracellular K^+ produces a similar train of events. Glutamate-induced SD is blocked by Mg^{2+} (25). The glutamate-induced Mg^{2+}-sensitive SD apparently propagates twice as fast as the K^+-induced Mg^{2+}-insensitive SD. Glutamate SD can be blocked by competitive and noncompetitive *N*-methyl-d-aspartate receptor antagonists.

The migraine aura, exemplified by an expanding visual scotoma (a suppressive, negative symptom) with preceding peripheral scintillations (a stimulative, positive symptom), was proposed as the clinical counterpart of SD years ago (26). Based on clinical observations and investigative studies, SD is now considered by most as a plausible explanation for the migraine aura (27). Investigation of this model in humans, however, remains far from complete and has not yet served to establish SD as the mechanism of aura. Most investigations have been limited to the indirect measure of blood flow, facilitated in migraine subjects by the development of noninvasive imaging techniques. CBF decreases, but only to oligemic values in posterior regions of the cortex in some patients during attacks of migraine with aura (28). During these studies it was also noted that the regional hypoperfusion developed before and outlasted the focal symptoms. Focal hyperemia, possibly related to neuronal depolarization, was also seen initially, followed by spreading oligemia (29). The oligemia was thought to be secondary to neuronal suppression, which progressively involved larger areas of the brain spreading at a rate similar to experimental SD (30). For the most part these CBF changes have been demonstrated in migraine with aura and not in migraine without aura. Also, these early studies were performed on migraine induced by cerebral arteriography.

One well-studied case report of dynamic blood flow measurements with positron-emission tomography and oxygen-15– labeled water demonstrated bilateral hypoperfusion that started in the occipital lobes and spread anteriorly (31). In this case, the patient had migraine without aura, suffering only minor visual blurring well into the attack of headache when CBF reduction was well established. This illustrated that migraine with and without aura could share a similar pathophysiology. Patients with spontaneous migraine with aura imaged with diffusion-weighted and perfusion-weighted MRI during the aura phase and during the headache phase had (20% to 37%) decreases in regional perfusion and (1.5% to 15%) regional cerebral blood volume (32). They had no change on diffusion-weighted imaging. Headache phase imaging did not reveal any consistent perfusion abnormalities. This supported the concept that the hypoperfusion seen in migraine aura may not be secondary to ischemia but to primary neuronal dysfunction. Most recently, Cao and associates (33) documented spreading suppression of neuronal activation during the early minutes of the aura and headache, made possible for the first time by using functional MRI.

Why, then, are some migraines not preceded by focal neurologic symptoms (i.e., migraine without aura) (34)? Although CBF is decreased in a spreading fashion in both migraine subtypes, it may require a certain threshold to produce symptoms in migraine with aura but not migraine without aura. (This is problematic to prove with CBF measures alone.) Alternative explanations include uncoupling of CBF from neuronal metabolism in some cases, spreading endothelial constriction, or spreading glial dysfunction with secondary neuronal dysfunction and consequent CBF reduction.

The most appropriate techniques to indicate SD are electrophysiologic, but because of limitations of EEG techniques, spontaneous SD has not been recorded previously in migraine sufferers. Okada and colleagues (35) reported biphasic, slow magnetic waves outside flattened isolated turtle cerebellum in which SD was produced by electrical stimulation and confirmed by electrocorticography. We have now used this technology to determine whether similar magnetic activity arises spontaneously in the migraine brain. We believe that DC magnetoencephalographic activity that we have observed supports SD occurring during an attack (36). Long-duration DC shifts and suppression of neuronal signals occur during the migraine aura and headache that were not found in patients with other forms of headache or in normal subjects. The DC shifts and neuronal symptoms are consistent with SD measured by electrocorticography and magnetoencephalography in experimental animals (37).

Headache, Trigeminovascular

The first, most convincing animal model of head pain was developed by Moskowitz in the rodent. This preparation involves electrical stimulation of the trigeminal ganglion with measurement of CBF or plasma extravasation in the dura mater. The resultant local release of peptides from sensory axons (involving an axon reflex) of the trigeminal nerve supply to certain extracranial arteries, meningeal tissues, dural arteries, and the dural sinuses sets up a pain-sensitive state (neurogenic inflammation) and promotes local vasodilatation, a state postulated to resemble that in pain-sensitive cranial structures during headache of the migraine attack (38). In support of this model, calcitonin-gene–related peptide is released into jugular venous blood during a migraine attack (39), and this release is blocked by sumatriptan (40). Sumatriptan is a selective agonist of the D subtype of 5-HT_1 receptors located on peripheral trigeminal nerve terminals that supply pain-sensitive vascular and meningeal structures. It has the same degree of affinity and selectivity for the subtype of 5-HT_1 receptors located on intracranial vessels, where it mediates contraction, particularly of large arteries. In the model, sumatriptan, acting presynaptically, blocks the neuropeptide-mediated inflammatory response after trigeminal

stimulation and may also block transmission in trigeminal neurons (38). The direct vasoconstrictive action of sumatriptan may be another mechanism by which this drug alleviates headache (41). A good deal of interest in this model attempts to find antimigraine drugs that are more selective, either on the 5-HT $_{1D_a}$ (predominantly neural) or 5-HT$_{1D_b}$ (predominantly vascular) receptor subtypes in the hope of avoiding vasoconstrictor side effects of the drugs. This should also provide insight into the critical mechanism for head pain, vasodilation or neuronal. Similarly, the 5-HT $_{1F}$ receptor is selectively distributed on neurons. Although agonists of the receptor have been in clinical trial, no published data support the effectiveness of this therapeutic approach, which if positive would substantiate the predominate neural origin of migraine pain.

Headache, Sagittal Sinus/Brainstem

A refinement of the trigeminovascular model involves a more specific stimulus to the sagittal sinus in the cat (42). This model allows electrophysiologic monitoring of activated neurons in the brainstem as well as identifying the same neurons by the c- *fos* technique. The model was validated by monitoring the increase of calcitonin gene-related peptide into the cranial circulation during sagittal sinus stimulation. The value of this model has been accentuated by a need to understand the function of brainstem nuclei that process nociceptive stimuli. Several observations have stimulated this approach. First is the observation that dihydroergotamine, a 5- HT $_{1D}$ agonist that is effective against migraine pain, passes the blood–brain barrier and binds to brainstem nuclei especially the dorsal raphe (43). Second, Weiller and colleagues (44) investigated whether the activation of brainstem nuclei could be visualized with positron emission tomography during acute attacks. Nine patients suffering from migraine without aura were studied within 6 hours of the onset of untreated migraine symptoms. Three regional CBF measurements were taken: (a) during the attack; (b) after relief of symptoms with sumatriptan subcutaneously; and (c) during the headache-free interval. During the acute migraine attack compared with the headache-free interval, regional CBF was greater in medial brainstem structures. This increase in regional CBF persisted even after complete symptom relief. This finding indicates that the change in regional CBF is not caused by pain or activity of the endogenous antinociceptive system but may be inherent to the migraine attack itself, possibly reflecting a brainstem headache generator. The identification of discrete brainstem nuclei was beyond the resolution of the positron emission tomography camera. However, the area of maximum increase coincided in the Talairach atlas, with the anatomic location of the dorsal raphe nuclei and locus coeruleus. Those areas are involved in antinociception and intracerebral vascular control, making them likely candidate foci for the many facets of migraine.

In sum, the SD model appears the most plausible to account for the aura and that the trigeminovascular and the sagittal sinus/ brainstem models complement and extend each other as headache models. The challenge is to establish how the mechanisms of the aura and the headache are linked.

Interictal Mechanisms

The concept that the migraine attack originates in brain and can be triggered by various factors under various conditions argues in favor of a threshold that governs the triggering of attacks. The nature of this final common pathway with which these factors interact probably constitutes the true cause of migraine.

Brain Hyperexcitability

Previous neurophysiologic, CBF, and brain metabolic measures have suggested neuronal and neurovascular instability between migraine attacks and have been reviewed elsewhere (45). Enhanced excitability of occipital cortex neurons has been proposed as the basis for the spontaneous or triggered onset of the migraine aura (46). Clinical studies of visual discrimination demonstrated that migraine sufferers had a greater sensitivity for low-level visual processing between attacks (47). But, to date, neurophysiologic evidence for hyperexcitability of occipital cortex between attacks is both limited and controversial. For instance, some studies have demonstrated differences in the amplitude of the visual-evoked responses in migraineurs compared with controls (48,49 and 50), whereas others found no abnormalities (51,52). The development of transcranial magnetic stimulation, however, has provided a new opportunity to noninvasively and more directly investigate brain cortex physiology and excitability (53,54 and 55). Indeed, migraineurs already have been investigated using transcranial magnetic stimulation, although only the motor cortex was examined (56,57). All three studies reported a lowered threshold for motor-evoked potentials in migraineurs compared with healthy subjects, supporting an increase in excitability of the motor cortex. We have used transcranial magnetic stimulation to evaluate occipital cortex excitability in migraine with aura. Our results confirmed that the threshold for observing phosphenes in migraine with aura subjects was lower than in controls (58). Furthermore, one patient who developed aura had the lowest stimulation threshold for eliciting sensory experiences among all subjects. To the best of our knowledge, this is the first, most direct neurophysiologic evidence confirming that the excitability threshold of the occipital cortex in migraine sufferers is low compared with healthy subjects, thus strongly indicating that the occipital cortex neurons can be hyperexcitable in this condition.

Abnormalities have been reported in migraine sufferers that could account, alone or in combination, for neuronal hyperexcitability. These are reviewed in the following sections. They include mitochondrial defect, disturbance in magnesium metabolism, and a calcium channelopathy.

Mitochondrial Defect. Migrainelike attacks occur in patients with mitochondrial encephalomyelopathies [mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome (MELAS)] in which disordered cellular energy metabolism is caused by a defect in mitochondrial metabolism. Dvorkin and colleagues (59) have described cases that they considered to be closely related to mitochondrial encephalomyelopathy with migrainelike episodes (usually with aura), seizures (benign at first, progressing to malignant), and stroke, particularly in the posterior cerebral artery territory. The authors postulated that a brain and generalized mitochondrial abnormality might be present in all cases and in vascular smooth muscle to account for the strokelike findings in their cases. MELAS also has been reported without stroke in a large family who had members with frequent migraine attacks (60). Mosewich and colleagues (60) described 12 patients from three generations in a family carrying the tRNA Leu (UUR) point mutation at position 3243 in mitochondrial DNA, known to be associated with MELAS. The family members had various combinations of sensorineural hearing loss, retinal pigmentary degeneration, migraine, hypothalamic hypogonadism, and mild myopathy. It was not stated whether the headaches were with or without aura or if they fulfilled IHS criteria. There was significant overlap between the MELAS and other forms of mitochondrial myopathy (e.g., Kearns-Sayre syndrome, myoclonus epilepsy with ragged red fibers, and progressive external ophthalmoplegia). In this family, migraine represented a common symptom of the underlying disease process that plagued successive generations. Although the exact relationship between migraine, stroke, and seizures in MELAS is unclear, the presence of the same point mutation in every affected member strongly suggests an association of these features with the mitochondrial defect.

Mitochondrial DNA analysis from a patient with recurrent migraine-related strokes revealed a DNA deletion (61) previously known to be associated with mitochondrial dysfunction. This patient also had evidence of brain cortical energy metabolic defect. Furthermore, in the family with MELAS and migraine who were referred to earlier (60), 6 of 12 had evidence of mutant mitochondrial DNA in blood or muscle or both.

Investigative studies using ^{31}phosphorous magnetic resonance spectroscopy (^{31}P MRS) have provided evidence of mitochondrial abnormality in platelets and muscle and have shown disordered cerebral cortex energy metabolism in migraine with aura subjects (62,63 and 64). The most recent studies of 12 migraine with aura subjects reported by Barbirolli and colleagues (63) have documented low brain phosphocreatine content in all subjects between attacks in the presence of high adenosine diphosphate, high Vmax for adenosine triphosphate (ATP), and a low phosphorylation potential, all features of unstable cerebral energy metabolism. Nine of the 12 patients also had abnormal muscle energy metabolism, considered to reflect mitochondrial dysfunction. We had previously reported a decreased phosphocreatine to inorganic phosphate ratio (an index of phosphorylation potential) and elevated inorganic phosphate in brain cortex between attacks in nine migraine patients with and without aura (62). Thus, two separate laboratories now have provided evidence for disordered energy metabolism between attacks of migraine, possibly caused by mitochondrial dysfunction. A study by Uncini and colleagues (65) also demonstrated altered energy metabolism in extraneural (muscle) and neural tissue via MRS in a kindred of familial hemiplegic migraineurs, suggesting a multisystems disorder of mitochondrial function.

Imaging metabolism during migraine attacks has been carried out only infrequently. Welch and colleagues (62) used ^{31}P-MRS to determine pH during migraine attacks. ^{31}P-MRS reliably determines pH *in vivo*, and some theories of pathogenesis implicate brain ischemia as the metabolic factor causing the neurologic deficits during the migraine attack. No significant differences in brain pH were found among healthy controls, migraineurs during the headache attack, and between attacks. It was concluded that without a shift of brain pH to acidosis, brain ischemia was excluded as a pathogenic event of the migraine attack. The studies demonstrated ictal loss of high- energy phosphates in the setting of normal pH, however, indicating energy failure in the brain not resultant from altered CBF but possibly from SD.

A primary disorder of mitochondria leads to cellular ionic inhomeostasis by impairment of the Mg^{2+}-sensitive Na^+/K^+ ATPase, which controls the active sodium pump, and by dysfunction of the Mg^{2+}-sensitive ATP-dependent Ca^{2+} pump. Mitochondrial membrane permeability itself further increases cytosolic Ca^{2+} (66) and secondarily increases the permeability of plasma membranes. Cells become loaded with Ca^{2+} and Na^+ and lose K^+ and phosphorous to cause relative depolarization of cell membranes. Thus, brain neurons may become primed for the triggered depolarization that may initiate SD and migraine aura.

Magnesium. A mitochondrial metabolic defect, if it is important in migraine, could be primary or secondary. Magnesium is among a number of systemic metabolic factors that influence mitochondrial function and is discussed here. An increasing body of evidence supports systemic and brain Mg^{2+} deficiency in migraine sufferers

(45). During a migraine attack, there is an approximately 20% decrease in brain Mg^{2+} that we have reasoned must be the case before the onset of the attack (67). However, with the exception of cases of familial hemiplegic migraine (FHM), we have been unable to document low free Mg^{2+} in brain cortex between attacks. This is not unexpected or incompatible with a low magnesium state. The CSF and brain are well buffered from fluctuations in the systemic concentrations of Mg^{2+} by the blood–brain barrier and blood–CSF barrier. CSF Mg^{2+} levels are maintained within narrow limits by an active transport system that moves Mg^{2+} from the plasma to the CSF. The carrier acts at well-below-normal levels of plasma Mg^{2+} but may desaturate after prolonged hypomagnesemia, presumably because it can no longer replenish losses. Thus, a threshold must exist whereupon a sudden further decrease in systemic Mg^{2+} levels (e.g., during acute stress) (68), superimposed on marginal systemic Mg^{2+} deficit, could deplete brain Mg^{2+} levels. As noted previously, we have reported a low occipital cortex Mg^{2+} in subjects with FHM (69).

Magnesium is among a number of systemic metabolic factors that influence energy metabolism and mitochondrial function and an integral part of the structure of cellular and subcellular membranes with the major function of providing membrane stability. Thus, Mg^{2+} deficit can (a) result in abnormality of mitochondrial oxidative phosphorylation; and (b) cause an instability of neuronal polarization, two features that appear to be characteristic of migraine. Neuronal hyperexcitability could be the result of Mg^{2+} deficiency or a defect in mitochondrial metabolism, or both, and could predispose the brain to the spontaneous initiation of SD or its activation by migraine trigger factors.

Channelopathy. From patients with FHM, Ophoff and colleagues (70) have isolated, on chromosome 19p13.1, a gene encoding the a_1-subunit of a brain-specific voltage-gated P/Q-type neuronal calcium channel (CACNL1A4). Four different missense mutations were identified in five unrelated FHM families. The investigators also detected premature stop mutations predicted to disrupt the reading frame of CACNL1A4 in two unrelated patients with episodic ataxia type 2. Thus, FHM and episodic ataxia type 2 can be considered as allelic channelopathies but of differing molecular mechanism, the former involving a gain of function variant of the Ca^{2+} channel subunit and the latter a decrease in channel density. The mutation in the gene for this particular Ca^{2+} channel in FHM is exciting because it is brain specific. The finding has served to place at least one form of migraine alongside other episodic disorders such as episodic ataxia type 2, hyperkalemic periodic paralysis, and episodic myotonias that are now identified as ion channel disorders.

The breakthrough in establishing the cause of FHM was achieved during the clinical investigation of CADASIL (cerebral autosomal dominant arteriopathy with subcortical leukoencephalopathy and stroke) (71). This disease is inherited in an autosomal dominant pattern and is characterized by recurring small deep infarcts, dementia, and leukoencephalopathy (71). Some patients also experience recurrent attacks of severe migrainelike headache with aura symptoms that include transient hemiparesis. Joutel and colleagues (72) published a report of two large family pedigrees of FHM, one with cerebellar signs and the other without. Linkage analysis was performed with a set of DNA markers spanning the most probable location for CADASIL, which was mapped previously by them to the short arm of chromosome 19. FHM did indeed map to chromosome 19, the location for the gene being a 30-cM interval between D19S216 and D19S215, which encompassed the probable position of the CADASIL locus.

Since this report, the same French group identified ten different missense mutations in the *Notch 3* genes of 14 unrelated families with CADASIL (73). The *Notch* genes are intimately involved in intercellular signaling during development. Proteins belonging to the *Notch* family are transmembrane receptors. Nine of the ten mutations either added or mutated a cysteine residue in one of the epidermal growth factor–like repeats; epidermal growth factor–like motifs are to be found in the extracellular domain. It is likely that this mutation strongly affects protein conformation, although how this leads to CADASIL remains to be established. Possibly, though, membrane instability and abnormality of cell signaling could be the underlying basis of the migraine attacks in this disorder. Thus, both appear to have mutations that could result in abnormal neuronal excitability. Missense mutations in the gene encoding the a_1- subunit of the presynaptic voltage gated P/Q type neuronal calcium channel (CACNL1A4), perhaps involving a gain of function variant of the Ca^{2+} channel subunit, would likely influence presynaptic neurotransmitter release, possibly of excitatory amino acid systems or inhibitory serotonergic systems (74), leading to postsynaptic neuronal excitability. The calcium channel abnormality also may explain our ^{31}P-MRS observations of low free Mg^{2+} in the occipital cortex, because Mg^{2+} may be fixed in the receptor that it gates for voltage-dependent Ca^{2+} permeability.

It remains to be seen if these findings can be extended to other subtypes of migraine, which would establish yet another episodic neurologic disorder as a channelopathy. It must be noted that cases of non-FHM studied by Ophoff and colleagues failed to show mutations. Also, the same group has suggested that chromosome 19 is the locus for migraine with and without aura (75), but review of other studies suggests that this may be controversial (76). Furthermore, the distribution of the abnormal calcium channel identified is densely cerebellar (77), a structure not obviously involved in the initiation of a migraine attack. This point is of interest, nevertheless, in view of the occurrence of cerebellar atrophy in a small number of FHM families (78). It is tempting to speculate that cerebellar atrophy might be explained by abnormal release of excitatory amino acids such as glutamate, which has cytotoxic consequences. It is also interesting to consider whether the episodic nature of migraine can be explained purely by the abnormal channel's providing a continuous background of neuronal instability or whether some unknown factor can precipitate an attack by directly switching the abnormal channel on or off. Were this to occur on the central pain-modulating serotonergic system, where apparently these aberrant channels may be found (74), it might support a central origin for the headache and offer a pharmacotherapeutic target.

Synthesis

A migraine attack is a response of the brain and its blood vessels to some trigger, often external. The brain is the target organ wherein the migraine attack originates; disordered neurogenic control of the intrinsic and extrinsic circulation is a secondary accompaniment of the attack. A neuroelectric event resembling the SD of Leao appears to be the basis of the aura. How the aura activates the headache remains to be determined. The period of time from the onset of the aura to the headache, usually up to 30 minutes, might be accounted for by the time it takes for the depolarizing wave of SD to pass from its site of origin into those parts of the cerebral cortex that are supplied by pain-sensitive arteries. On the other hand, brainstem centers for pain are influenced by the cortical event of SD as evidenced by the associated generation of c-*fos* in trigeminal ganglia (42). Activation of the central noradrenergic and serotonergic systems may secondarily initiate the events of neurogenic inflammation in the trigeminovascular system and modulate the transduction of pain via the same system. The evidence of continued activity in these central systems after pain has subsided, provided by the study by Weiller and colleagues (44), might also support the contention that these centers are the primary initiators of the attack, and would also explain the often-observed coincidence of the onset of aura with headache, as well as aura appearing well into the headache phase.

Assuming that the threshold for migraine is related to increased excitability of central neurons, how a migraine attack is triggered remains to be determined. This must involve those events leading from the postulated increased sensitivity for neuronal depolarization to the development of SD. The initiation of SD may be related to shifts in extracellular potassium or may involve glutamate release. The possibility that Ca^{2+} ion channels are abnormal in migraine may explain neuronal hyperexcitability, and the propagation of depolarization and prolonged recovery from depolarization that characterizes SD.

Finally, migraine patients may manifest all three states of migraine with and without aura and aura without headache at any time during their natural history. But these may not be different. Instead, pathophysiologic differences may have been recorded because patients were studied at different mechanistic points in the spectrum of the same disorder; the lack of a clear-cut aura of neurologic deficit in common migraine may mislead investigators. Alternatively, migraine without aura may originate in relatively silent brain areas (e.g., frontal, limbic, or visual association cortex), or perhaps, as some hemodynamic studies indicate, a dissociation occurs between neurologic symptoms and the underlying neurovascular event.

Symptoms and Signs

Clinical Syndromes of Migraine

The most frequently encountered migraine syndromes include typical headache without aura of neurologic deficit (previously termed *common migraine*) and headache associated with aura of neurologic deficit (previously termed *classic migraine*). Patients can have migraine headache both with and without neurologic aura at any time during the natural history of their disorder. They may also suffer neurologic deficit of migraine type without headache (migraine sine hemicrania).

In migraine with aura, visual disturbances account for well over one-half of the transient neurologic manifestations. Most often, these disturbances consist of positive phenomena, such as stars, sparks, photopsia, complex geometric patterns, and fortification spectra. These positive phenomena may leave in their wake negative phenomena, such as scotoma or hemianopsia. The symptoms are characteristically slow in onset and progression; however, onset can occasionally be abrupt. Visual symptoms sometimes progress to visual distortion or misperception, such as micropsia or dysmetropsia. The patterns of symptoms indicate the spread of neurologic dysfunction from the occipital cortex into the contiguous regions of the temporal or parietal lobes.

Somatosensory symptoms are the second most common manifestations and are characteristically distributed around the hand and lower face. Less frequently, the

symptoms include aphasia, hemiparesis, or clumsiness on one side. In most cases, a slow, marching progression is characteristic. The anatomic distribution of the neurologic deficit often overrides vascular boundaries. Some patients experience visual distortions of body image (i.e., metamorphopsia) and other visual illusions that occur in the Alice in Wonderland syndrome. Transient global amnesia can occur as a migraine aura, but only in rare instances. The aura usually lasts approximately 30 minutes before subsiding and is followed by a brief interlude of normality before the onset of headache that is unilateral or bilateral, pulsating, moderate to severe in intensity, and exacerbated by physical activity. In some instances, the aura continues into the headache phase. The headache may subside in as little as 6 hours or may last as long as 3 days. The longer duration is more typical of the headache of migraine without aura, which has similar features to migraine with aura but is characteristically moderate to severe in intensity and more prolonged in duration.

Migraine with Prolonged Aura (International Headache Society 1.2.2). This condition is characterized by one or more aura symptoms that last more than 60 minutes but with full recovery within 3 weeks and normal late CT scan results. Before attacks of migraine both with and without aura, a prodrome of behavioral changes may occur, which may include depression, anxiety, elation, increased sensitivity to external stimuli, and increased or decreased libido. In many instances, the characteristics of a person's prodrome are stereotypical, producing similar changes before each attack. Associated symptoms of both types of migraines include nausea, vomiting, photophobia, and phonophobia. In the 24 hours after the attack subsides, a spectrum of behavioral changes may arise, ranging from depression to exhilaration.

Migraine attacks both with and without aura may have characteristic triggers, including certain foods (e.g., chocolate, blue cheese, and alcohol), erratic mealtimes, sleep loss, acute stress, exercise, atmospheric pressure change, and the use of certain drugs, such as nitroglycerin and oral contraceptives. Menstruation is a common trigger. When migraine occurs only at the time of menses, it is termed *menstrual migraine*. Such patients may also suffer ovulatory migraine, and they are more likely to have experienced their first migraine in the year of menarche and to cease having attacks during pregnancy. Menopause is often a time of severe and frequent migraine attacks, which later resolve. It is helpful in the management of the disorder to distinguish between triggers that are time locked to a single attack and triggers that increase the frequency and severity of attacks. As an example of the latter, use of oral contraceptives may precipitate migraine for the first time, increase the frequency of attacks, and even convert migraine without aura to migraine with aura.

Hemiplegic Migraine. Transient hemiparesis associated with a migraine attack was first described by Liveing in 1873 (16). In 1910, Clarke published the first report of hemiplegic migraine occurring in a family (79). Hemiplegic migraine also has been described in children (80). The IHS classifies hemiplegic migraine under migraine with typical aura or migraine with prolonged aura. FHM is also classified as a subgroup of migraine with aura; the working definition includes the criteria for migraine with aura with hemiplegic features that may be prolonged, along with at least one first-degree relative having identical attacks.

Attacks are characterized by episodic hemiparesis or hemiplegia. In most attacks, the arm and leg are involved, often combined with face and hand paresis. Isolated facial and arm paresis occurs less often. The progression of the motor deficit is slow, with a spreading or marching quality. In most cases, symptoms are accompanied by homolateral sensory disturbance, particularly of hand and lower face, also with a slowly spreading or marching quality. Infrequently, the hemiparesis may alternate from side to side, even during an attack. Myoclonic jerks have been reported but are rare. Visual disturbance taking the form of hemianopic loss or typical visual aura is common, but homolateral or contralateral localization of the visual disturbance is uncertain. When dysphasia occurs, it is more often expressive than receptive. The neurologic symptoms last 30 to 60 minutes and are followed by severe pulsating headache that affects one or both sides of the head. Nausea, vomiting, photophobia, and phonophobia are associated features. In severe cases, the aura persists throughout the headache phase. Uncommon manifestations of severe hemiplegic migraine attacks include fever, drowsiness, confusion, and coma, all of which may be prolonged (i.e., from days to weeks).

FHM, which has an autosomal dominant inheritance pattern, is characterized by the same neurologic features as the nonfamilial form, with identical features occurring in at least one other first-degree relative. Additional neurologic deficits described with the disorder include a syndrome of progressive cerebellar disturbance, dysarthria, nystagmus, and ataxia (81). Retinitis pigmentosa, sensory neural deafness, tremor, dizziness, and oculomotor disturbances with nystagmus have also been described (82). These neurologic deficits are present between attacks and are not part of the aura.

The complications of hemiplegic migraine, although rare, can be serious. True migraine-induced stroke occurs when a typical migraine aura with hemiparesis persists after the attack; imaging studies of the brain show cerebral infarction appropriate to the neurologic deficit. In rare instances, severe hemiplegic migraine leads to persistent minor neurologic disorders; the cumulative effects of repeated attacks may produce profound multifocal neurologic damage or even dementia.

As noted previously, from patients with FHM, Ophoff and colleagues (70) have isolated, on chromosome 19p13.1, a gene encoding the a_1-subunit of a brain-specific voltage gated P/Q type neuronal calcium channel (CACNL1A4).

Basilar Artery Migraine. The concept of basilar artery migraine was first proposed by Bickerstaff (83). He later wrote how his attention was drawn to the syndrome when he saw, within a short period of time, two patients with identical symptoms explicable only on the basis of an abnormality of basilar artery circulation (84). One of these cases was a boy of 14 years whose symptoms lasted a few hours and were repeated on numerous occasions. The other was an elderly man whose symptoms progressed rapidly to coma and death and in whom infarction of the brainstem and occipital cortex was caused by thrombotic occlusion of the basilar artery demonstrated at autopsy. So it was by clinical analogy with the structural lesion in the basilar artery and the symptoms of basilar artery territory ischemia that the syndrome basilar artery migraine first was described.

No specific information exists on the prevalence of basilar migraine except that it is rare. Longitudinal studies are needed of the natural history of these serious migraine subtypes.

Classification. The IHS (85) classified this disorder as basilar migraine (IHS 1.2.4). The classification committee suggested that this term replace basilar artery migraine and other terms such as *Bickerstaff's migraine* and *syncopal migraine*. The diagnostic criteria include those for migraine with aura (IHS 1.2) plus two or more aura symptoms of the following types: visual symptoms in both the temporal and nasal fields of both eyes, dysarthria, vertigo, tinnitus, decreased hearing, double vision, ataxia, bilateral paresthesias, bilateral paresis, and decreased level of consciousness. The absence of consistent evidence for basilar artery spasm during migraine attacks and uncertainty about the origin of the mechanisms of the symptoms prompted the IHS classification committee to remove the word *artery* from the terminology. Further investigative studies were called for to definitively establish or disprove the existence of migraine aura originating in the brainstem.

Pathogenesis. Few studies have been made specifically of basilar migraine, and it has to be assumed that the pathogenetic mechanisms are the same as those of more clearly lateralized migrainous auras and headaches. Frequin and colleagues (86) describe a patient with recurrent prolonged coma in whom angiography showed profound narrowing of the basilar artery; they attribute this to vasospasm, although it remains possible that this appearance was actually produced by an inflammatory swelling of the vessel wall. In a transcranial Doppler study, La Spina and colleagues showed an increase in mean flow velocity in both posterior cerebral arteries, again consistent with narrowing of these vessels (87). It remains to be determined whether these changes are the cause of, the consequence of, or entirely unrelated to the aura symptoms.

Clinical Features. Of the 34 patients in Bickerstaff's original series, all were aged less than 35 years, and 32 were under the age of 23 years (83). Twenty-six of the 34 were female, and 28 gave a family history of migraine. A definite association existed with the menarche, and attacks were often then linked to the menstrual period. The attacks were infrequent although often interspersed with more typical migrainous attacks with aura. In Bickerstaff's series the headache was bilateral and occipital and was preceded by visual disturbances affecting both sides of the visual field, diplopia, bilateral circumoral or limb paresthesiae, dysarthria, bilateral ataxia, vertigo, and tinnitus, often lasting for 20 to 30 minutes and clearly resembling intoxication. The attacks were relieved by sleep. Bickerstaff himself noted that the attacks tended to become more typically migrainous as the patients grew older.

Several large series of such patients have been published more recently, and these give a breakdown of the proportion of patients with each type of aura symptom (88,89). More than one-third of subjects have their first attack in the second decade, and two-thirds have the first attack in their second or third decade. The condition also occurs frequently in children. A small number of cases, however, present for the first time over the age of 50 years. The condition may occur in combination with other forms of migraine, although basilar migraine remains the dominant problem in over 75%.

At first, Bickerstaff noted a predominance of teenage girls in his basilar artery migraine population, but subsequent experience revealed a female incidence that is similar to other forms of migraine (83). The highest gender ratio, approximately 3:1, is to be found when basilar migraine presents for the first time in the second decade of life (89). Not uncommonly, when basilar artery migraine starts in the teens the frequency of attacks diminishes, to be replaced in adult life by other forms of migraine (83).

Patients who suffer from basilar migraine identify trigger factors that are similar to those for other forms of migraine. Precipitating factors were identified by as many as

71% of subjects. Emotion, stress, menstruation, and weather change were the predominant triggers, but head injury, foodstuffs, and contraceptive drugs were also common. Of note, vascular risk factors were present in 41% of sufferers, including smoking, oral contraceptives, and diabetes mellitus.

In the majority of cases, the aura lasts between 5 and 60 minutes, but can extend up to 3 days. Visual symptoms commonly occur first, predominantly in the temporal and nasal fields of vision. The visual disturbance may consist of blurred vision, teichopsia, scintillating scotoma, graying of vision, or total loss of vision. The features may start in one visual field and then spread to become bilateral. Bickerstaff (84) pointed out that when vision is not completely obscured, diplopia may occur, usually sixth nerve weakness. Some form of diplopia occurs in up to 16% of cases.

Vertigo and gait ataxia are the next most common symptoms. Fenichel described a series of patients with isolated “benign recurrent vertigo,' which later evolved into migraine (90). This entity, first described by Basser (91), usually starts in preschoolers and progresses into the teens. Abrupt attacks of rotational sensation occur lasting seconds to minutes, accompanied by loss of balance, pallor, and vomiting. The disorder is self-limiting but may be a precursor to migraine or a migraine equivalent because many sufferers subsequently develop migraine with and without aura.

Ataxia can occur independently of vertigo. Tinnitus may accompany vertigo. Dysarthria is as common as ataxia and vertigo. Tingling and numbness, in the typical cheirooral spreading pattern seen in migraine with aura, occurs in over 60% of cases. This is usually bilateral and symmetric, but may alternate sides with a hemidistribution. Occasionally, dysesthesias extend to the trunk. Bilateral motor weakness occurs in over 50% of cases.

Impairment of consciousness in some form is common. Bickerstaff noted in his early work that patients enter a state of impaired consciousness that resembles sleep from which they may be easily aroused by stimulation, only to return to the same state. Rarely, this progresses to stupor and prolonged coma (92,93). Other forms of altered consciousness include amnesia and syncope. Drop attacks with transient loss of consciousness may occur as part of the full clinical syndrome, but this is rare.

Headache occurs in almost all patients. It has an occipital location in the majority and a throbbing, pounding quality and is accompanied by severe nausea and vomiting. It is unusual for the headache to be unilateral or localized to the more anterior parts of the cranium. Photophobia and phonophobia occur in one-third to one-half of the patients. As with other forms of migraine, the symptoms may occur without headache, but this is usually in no more than 4% of cases.

Seizures have been observed in association with basilar migraine (91,94). Eight percent of Sturzenegger et al.'s patients had overt seizures (89). Electroencephalographic (EEG) changes, without seizures, occurring with attacks of typical basilar artery migraine, also have been described (95). These cases are said to have a good response to anticonvulsants (95,96,97,98 and 99). Camfield and colleagues described a syndrome of basilar migraine and unilateral or bilateral temporal occipital EEG abnormality suppressed by opening the eyes. The epileptic seizures were either focal or generalized after the migraine aura (96). In all, EEG abnormalities are detected in less than one-fifth of cases with basilar migraine and are mostly independent of any clinical manifestation of the disorder (100). The EEG findings between attacks are usually spike wave or spike–slow wave complexes. During an attack, diffuse high-voltage slow waves occur and associated spikes with sharp waves and diffuse beta activity. In a long-term follow-up (8 to 16 years) of seven children affected by basilar migraine (101), who had EEG findings of occipital spike and wave complexes, basilar migraine resolved and the EEG became normal in all subjects. In one patient basilar migraine ceased and tonic-clonic seizures occurred 5 years after; these seizures also resolved. Four patients in this series later developed migraine with typical aura, two of whom had migraine aura associated with seizures that were partial with secondary generalization.

The prognosis of basilar migraine is generally good. The disorder declines in frequency as patients enter their 20s and 30s. Rarely, basilar migraine is complicated by stroke, which most often involves the posterior cerebral artery (84,102), although other terminal arteries may be involved (103).

Migraine Aura without Headache (International Headache Society Code 1.2.5). This condition is characterized by typical aura symptoms unaccompanied by headache, but it fulfills the criteria for migraine with aura. In many patients this condition develops as the individual gets older; the headaches might disappear completely, but the auras continue. Less commonly, this condition is present from the onset, usually after the age of 40.

Migraine with Acute Onset (International Headache Society Code 1.2.6). This condition is characterized by migraine with aura except that the neurologic symptoms develop suddenly (less than 4 minutes) and headache lasts 4 to 72 hours (untreated or unsuccessfully treated) and is associated with at least nausea, vomiting, or both and photophobia and phonophobia. In this condition intracranial lesions must be ruled out by neuroimaging procedures, and thromboembolic transient ischemic attacks are ruled out by angiography, cardiologic examination, and blood tests.

Other Types of Migraines

Ophthalmoplegic Migraine (International Headache Society Code 1.3). An attack of migraine headache can be accompanied by third, fourth, or sixth cranial nerve paresis ipsilateral to the side of the headache, beginning either as an aura or during the headache phase. In most cases, the ocular palsy involves the third nerve; the sixth and fourth nerves are involved only in rare instances. The ophthalmoplegia is at first transient, but after repeated episodes, it can become permanent. The mechanisms involved in the production of ophthalmoplegic migraine remain speculative. The major differential diagnosis is aneurysmal dilatation of the cerebral arteries, particularly the internal carotid artery or the posterior communicating artery. As a strict rule, all cases should be promptly evaluated. The diagnosis of ophthalmoplegic migraine has become an even greater rarity since brain imaging has become available, which suggests that many earlier cases were misdiagnosed.

Retinal Migraine. Retinal migraine occurs more frequently than ophthalmoplegic migraine (i.e., approximately one in 200 migraine sufferers). However, persons who experience homonymous field defects are often diagnosed with monocular migraine because the temporal hemifields of vision are larger than the nasal hemifields. The term *anterior visual pathway migraine* is actually preferred, because the disorder is not limited to the retina. Typically, visual disturbances identical to migraine with aura occur in a monocular distribution, which may include complete monocular visual loss. Often a previous history of migraine exists, with or without aura. Headache may or may not follow. Episodes can be precipitated by postural change or exercise.

The mechanism of anterior visual pathway migraine is uncertain, but retinal vasospasm has been observed in certain cases. Although permanent visual field loss is unusual, persons who experience frequent episodes of anterior visual pathway migraine should probably receive prophylactic therapy. The diagnosis of this disorder should be one of exclusion because the condition is relatively rare, and monocular visual loss can be a presenting syndrome of serious vascular or other structural disease.

Childhood Migraine. Migraine prevalence gradually increases from the age of 7 and reaches the adult level at puberty. The characteristics are similar to those of adult migraine, with the following differences: It occurs more frequently in boys than in girls; the attacks tend to be shorter in duration; lateralization and visual symptoms occur less frequently; and vertigo, motion sickness, and lightheadedness are common.

Complications of Migraine (International Headache Society Code 1.7). Migraine is associated with an increased risk of stroke between and during attacks (102). Various syndromes of migraine may mimic cerebrovascular syndromes, including migraine with aura of different types, retinal or ocular migraine, ophthalmoplegic migraine, hemiplegic migraine, and basilar artery migraine (104,105,106 and 107). If the deficit of a migraine attack remains, *migraine-induced stroke* should be suspected.

Head pain also occurs in various forms of acute ischemic stroke (108,109), particularly in posterior territory stroke. Headache usually occurs at the onset, although in some cases headache is premonitory or accompanied by transient ischemic attacks (110,111,112,113,114 and 115). Overall, the frequency of headache was 31% in carotid and 42% in vertebrobasilar disease. Mitsias and Ramadan have extensively reviewed the literature on this topic up to 1997 (108,109). The possible mechanisms of headache caused by ischemia remain to be determined (109).

The relationship of migraine and stroke is complex, and the opportunities for diagnostic confusion are multiple. This calls into question much of the published work before contemporary methods of investigation. Furthermore, working criteria for headache classification became available only recently, and even these do not address the classification of migraine-related stroke in a comprehensive fashion.

Epidemiology. Many of the hospital and population-based studies, even some in the 1980s, are severely flawed for reasons of classification and diagnosis. Many did not use contemporary epidemiologic methods. The data must therefore be interpreted with extreme caution.

A review of hospital-based studies conducted before 1989, most uncontrolled, showed that in patients younger than 50 years of age carrying a diagnosis of stroke, between 1% and 17% were attributed to migraine. In two-thirds of these the diagnosis was made in 1% to 8% of patients and 11% to 17% in one-third (116). A

compilation of studies up to the same time revealed a prevalence of 4% attributed to migraine in 448 total stroke patients, 31% of whom had an unknown cause. In clinical studies, stroke was reported as more common in patients with migraine with aura (117,118) and in patients with posterior cerebral artery strokes (119). No differences in stroke risk factors were found in migraine sufferers compared with controls without stroke, although those with migraine were more likely to have recurrent stroke, supporting migraine as an independent stroke risk factor (see following discussion) (118). Another study of migraine with aura reported that 91% of patients who had stroke during an attack had no arterial lesions, as opposed to 9% of migraine with aura patients who suffered stroke remote from a migraine attack and 18% of patients with stroke without a migraine history (120). In some instances, however, stroke risk factors increased stroke risk in migraine with aura.

The overall incidence of *migrainous infarction* has been estimated at 3.36 per 100,000 population per year (95% confidence interval, 0.87 to 4.8) but in the absence of other stroke risk factors becomes 1.44 per 100,000 population per year (95% confidence interval, 0.00 to 3.07)(121). This rate is similar to that reported later in subjects younger than 50 years (119); migrainous infarction accounted for 25% of cerebral infarcts. To place these data in context, the overall incidence of ischemic stroke under age 50 ranges from 6.5 per 100,000 (73) to 22.8 per 100,000 (122,123).

Controlled epidemiologic studies have been few. In a retrospective study of parents of migraine sufferers, no increased risk of stroke was found, but the frequency of hypertension was 1.7 times greater in persons with migraine than in those without (124). In an inconclusive study, the Collaborative Group for the Study of Stroke in Young Women found that the relative risk of thrombotic stroke was twofold higher, and greater for women with migraine compared with neighbor but not hospital controls (125). A hospital-based controlled study of 89 cases found that ischemic stroke was increased more than twofold in patients with migraine with aura (126), but when stroke risk factors were excluded in this group, there was no longer a statistically significant association.

Two cohort studies reported a twofold increased risk of stroke in migraine sufferers (125,126). Both studies have major diagnostic shortcomings. The most consistent studies of migraine as a stroke risk have been case controlled. Tzourio and colleagues showed no overall association between migraine and ischemic stroke, but among women aged less than 45, migraine and stroke were significantly associated; there was approximately a fourfold increased risk, more so in women who smoked (127). When this study was extended to a larger population, the results were confirmed and strengthened (128). The risk of stroke was three times control for migraine without aura and six times the risk of controls for migraine with aura. Furthermore, young women with migraine who smoked increased their stroke risk to approximately ten times control, more than three times greater than young women without migraine who smoked. For young women with migraine on oral contraceptives, the risk of stroke was 14 times control, and four times the risk of stroke and the dose of estrogen: The odds ratio was 4.8 for pills containing 50mg of estrogen, 2.7 for 30 to 40mg, 1.7 for 20mg, and 1mg for progesterone. In none of these cases was the stroke induced by the migraine attack.

Similar risk of stroke in women aged 15 to 44 years, close to three times, was confirmed in a questionnaire survey of 692 female subjects (107). In a later case-controlled study of 308 patients with either transient ischemic attacks or stroke, a history of migraine was more frequent than in controls (14.9% versus 9.1%) (129). Migraine was the only significant risk factor (odds ratio, 3.7) in women younger than 35 years of age. Although these risk figures appear startlingly high in both studies, it must be remembered that the absolute risk of stroke for this patient population translates to approximately 19 per 100,000 per year, which is a low rate.

The most recently published study was hospital based and case controlled involving five European centers. Two hundred ninety-one women aged 20 to 44 years with ischemic, hemorrhagic, or unclassified arterial stroke were compared with 736 age- and hospital- matched controls (105). Adjusted odds ratios associated with a personal history of migraine were 1.78 (95% confidence intervals, 1.14 to 2.77), 3.54 (1.30 to 9.61), and 1.10 (0.63 to 1.94) for all stroke, ischemic stroke, and hemorrhagic stroke, respectively. Odds ratios for ischemic stroke were similar for migraine with aura (3.81, 1.26 to 11.5) and migraine without aura (2.97, 0.66 to 13.5). A family history of migraine, irrespective of personal history, was also associated with increased odds ratios, not only for ischemic stroke but also hemorrhagic stroke. Use of oral contraceptives or a history of high blood pressure or smoking had greater than multiplicative effects on the odds ratios for ischemic stroke associated with migraine alone, although only smoking was statistically significant. Change in the frequency or type of migraine on using oral contraceptives did not predict subsequent stroke. Between 20% and 40% of strokes were possibly induced during a migraine attack. This study should be interpreted with particular caution on the basis of the methods, working criteria for the classification, and questionnaire used. Concerns are raised by the higher numbers of migraine with aura as compared with those without aura, and the difficulty in diagnosing migraine by questionnaire in family members. Also, clinical experience would not support the high incidence of true migraine-induced stroke.

In summation, based especially on case-controlled studies, an association between migraine and stroke appears confirmed. The risk increases threefold in young women. Common risk factors for stroke in general increase this risk. The studies emphasize that oral contraceptives should not be prescribed without the caution of stroke risk and migraine sufferers should not smoke.

Epilepsy. The reported frequency of migraine among patients with epilepsy varies from 8.4% to 23.0%. The frequency of epilepsy among patients with migraine ranges from 1% to 17%. Such data suggest that no conclusive evidence exists of any relation between the two disorders other than random coincidence. Nevertheless, in one study, 3% of a cohort of adult patients with epilepsy experienced seizures during or immediately after migraine (130). Furthermore, the genetic relation between migraine and epilepsy (which has always been controversial) was clarified in a 1993 study by Ottman and colleagues (131), who collected data on the prevalence of migraine in patients with epilepsy and in relatives with and without epilepsy. Of the probands, 24% had a migraine history; 26% of relatives with epilepsy had a migraine history. However, 15% of relatives who did not have epilepsy had a migraine history. The cumulative incidence of migraine was also higher in patients with epilepsy (24%) and relatives with epilepsy (23%), compared with relatives without epilepsy; and the risk of migraine for the first two groups was twice as high as that for the third group. There also appears to be a high incidence of migraine in persons with certain forms of epilepsies, such as benign rolandic epilepsy, benign occipital epilepsy, and corticoreticular epilepsy with absence.

Psychiatric Disorders and Personality Traits. A high incidence of neuroticism occurs in migraine sufferers. However, the stereotype of the rigid, obsessive migraine personality could well be a selection bias of a migraine subtype seen more frequently in the clinical population. A few studies have been made of migraine and psychiatric disorders. Epidemiologic studies have shown a major comorbidity with depression (132). Although this association with depression may represent a psychological reaction to frequent and disabling migraine attacks, depression carries with it a major risk for migraine, raising the possibility that there is a shared genetic or environmental risk between the disorders. A common abnormality of brain function may be responsible (e.g., dysregulation of the central serotoninergic system). Increased risk for episodes of mania, anxiety, and panic disorder have also been reported, together with an increased prevalence of illicit drug use and nicotine dependence. Perhaps the most disturbing feature of this report was the increased lifetime prevalence of suicidal ideation and suicide attempts independent of depression (133).

Chronic Daily Headache. Chronic daily headache (CDH) is best classified under the tension-type headaches and headaches associated with drug overuse, but is dealt with under the migraine section, because some consider this condition as an evolution of migraine.

Controversy abounds with this subject, however. Definitions are arbitrary and classifications vary without universal acceptance. Agreement exists on one issue. For headache specialists and neurologists this is an important clinical problem.

The first and only notable population-based study conducted found that 0.5% of 20,468 subjects reported daily severe headache (134). Daily headaches are rare in the population. In contrast, headache clinic population studies observe up to 30% of patients complaining of daily or almost daily headache.

The definitions of this disorder are based on clinical features, but clinical features also depend on definition. The history of confusion began with the writings of Sicuteri on the topic of *essential headache* (135), a term used to imply a state of “central dysnociception,' that apparently differed from tension-type headache but that was never convincingly delineated or understood clinically. The impetus for controversy came with Mathew and colleagues' pointing out that patients with episodic migraine at the outset of their illness later develop daily headache (136). The implication in the title of the paper was that migraine was *transformed* to this state. Here lay the apparent heresy. Before this time we only had recognized *mixed* or *combined* episodic migraine and tension-type headache. (In retrospect, such classification was not rigorously analyzed in terms of precise clinical features.) Furthermore, Mathew and colleagues implied in their paper that there were certain factors that contributed to the transformation, namely medication, stress, hypertension, and disturbed psychological status. This work was uncontrolled, retrospective, observational, and without statistical analysis. But in the light of subsequent papers evoked by this study [and with the usual caveat that in fact the observation had been made before (137)], it was a seminal paper that changed the way we think about daily headaches.

Some authorities believe that, until proven otherwise, the classification of CDH is incorporated in the currently most widely accepted classification of primary headache by the IHS. Others believe that the headache disorder is an entity worthy of separate classification. The latter view is supported by a headache clinic's retrospective studies of patients with almost daily headache that up to 30% of their subjects could not be categorized using IHS criteria for the primary tension-type, migraine, or other headaches (138). This also addressed the criticism that subjects can suffer two or more separate primary headache disorders occurring in close temporal proximity. In essence its detractors believe the IHS classification problems are created by a primarily cross-sectional analysis of clinical features, with

insufficient emphasis on temporal patterns to refine the clinical impression.

To add to the confusion, one study suggested that episodic tension-type headache could precede an unclassifiable daily headache syndrome (139). Alternatively, then, repeated attacks of the primary migraine and, less commonly, episodic tension-type headaches, under certain circumstances might induce a secondary headache syndrome, the nature of which remains to be determined.

Mindful that the IHS classification was created with the intention to stimulate nosologic and epidemiologic research, classification schemes have been proposed that recognize daily headache that fails to meet existing working criteria. More than 15 days a month with headache for at least 6 months (some expect a year) has been used to define this term. This liberality has been qualified by those who prefer *daily* or *near daily*. Daily headache may also be continuous or episodic and allow treatment resolution.

No specific diagnostic features of CDH have been described despite multiple studies. In general, the headache resembles features of migraine headache during the less severe phases of pain. Intriguingly, Mathew and colleagues described a minor preponderance of headache on the same side as the hemicrania of the now transformed episodic migraine, or at the same head locations as the prior episodic head pain (136). This observation has not been followed up or rigorously replicated.

CDH patients have a family history of migraine. Triggers are common, in particular menses. This is despite inconsistencies between studies on gender prevalence. In addition to tension-type headache and migraine without aura, migraine with aura can precede CDH, although the prevalence is low and variable. In sum, the clinical syndrome of CDH is not uniform.

Associated and Possibly Comorbid Factors

Drug Abuse. In most CDH series, drug overuse figures prominently. There are a number of issues with this association that evoke controversy. Can drug overuse itself cause headache? Is the use of drugs the factor in transforming episodic migraine or tension-type headache to CDH? Diener has reviewed the topic with clarity (140). He used individual studies and metaanalysis to evaluate working criteria of the IHS classification.

In almost all cases of CDH a history of primary headache exists; approximately two-thirds suffered migraine and one-third tension- type headache. Other headaches such as cluster rarely were involved. The time intervals for CDH to develop were approximately 5 years of exposure to medication and a history of primary headache for 10 years before that. No single drug induces headache exclusively. To develop CDH, a critical dose of a single drug or a combination of drugs used below the critical level of each is required. With the exception of codeine, narcotic induction of CDH is unusual. Acute withdrawal worsens headache. Treatment for the primary headache complaint fails if the drugs are not terminated. The effectiveness of treatment does not appear to be dependent on effective migraine or tension-type headache prevention, although blinded controlled studies have not been carried out. Up to 75% of cases improve. Headache usually remains, although less severe and less frequent.

It remains curious that similar drugs that are associated with CDH do not cause headache in subjects without primary headache. This emphasizes the importance of a history of prolonged primary headache increasing the susceptibility to CDH and drug-induced CDH and may provide some clues to pathogenesis.

The question of whether drugs are factors in transforming migraine to CDH in susceptible individuals remains to be answered. Transformed migraine occurs without drug exposure, however, in convincing numbers of subjects.

Depression and Psychological Factors. Depression and other psychiatric and psychological disturbances are comorbid with migraine (141). In the tested case of depression this appears caused by a common brain state. Depression occurs both before the start of migraine attacks as well as for the first time subsequent to migraine onset. The association of depression with CDH is unsurprising in view of the susceptibility to CDH that the primary headache induces.

Although several factors, as well as psychiatric factors, have been invoked to play a role in transforming migraine (e.g., stress and hypertension) (136), based on study design these cannot be treated as anything other than associations rather than the claimed causative role.

Mechanisms. The mechanisms of CDH have rarely been studied and remain to be determined. Past theories include a low serotonin state with receptor upregulation (142), central hyperexcitability of pain systems (143) or *N*-methyl-d-aspartate receptor dysfunction (144), low b-endorphin and opioid state (145), and a postviral syndrome (146). Platelet membrane studies in CDH related to drug overuse found evidence of abnormal signal transduction that recovered after successful drug withdrawal (147).

Treatment

The goals of migraine treatment are alleviation of the symptoms of an acute attack and prevention of further attacks, either by behavioral or pharmacologic means. The behavioral approach commonly involves regular sleep and meals and avoidance of initiating factors. Family-related or work-related stresses and emotional problems are often unavoidable and are best managed by stress coping or relaxation techniques. Pharmacologic treatments for migraine are available (Table 48-4).

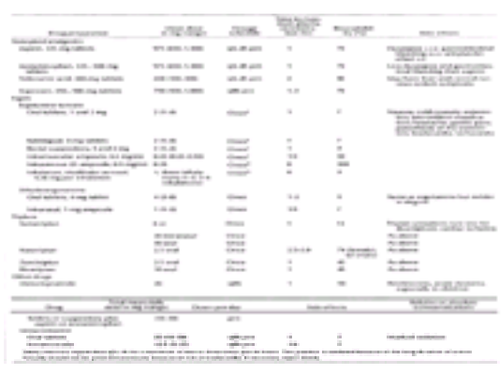

TABLE 48-4. Drug treatment for migraine attacks

Analgesic Drugs. During prolonged, severe attacks of migraine, the patient's judgment may be impaired, with consequent uncertainties as to the type of drug to be used or the amount to be taken. Family or friends should be instructed in the use of medications for acute cases of migraine. Mild or moderate attacks should be treated with simple analgesic drugs or nonsteroidal antiinflammatory drugs (NSAIDs). Aspirin, acetaminophen, propoxyphene, codeine, and certain NSAIDs are all superior to placebo in relieving the pain of migraine. Effervescent formulations are more effective because they are absorbed more rapidly. Because gastric stasis often accompanies migraine attacks, metoclopramide, a drug that increases gut motility and promotes gastric emptying, enhances the effectiveness of analgesic drugs. However, metoclopramide should be used sparingly in adults and should not be used at all in young patients, because it can cause dystonia. When nausea and vomiting are prominent, suppository preparations of analgesic and antiemetic drugs can be given. The most frequently used antiemetic drugs are perphenazine, prochlorperazine, and chlorpromazine.

Ergot Preparations. For many years, ergotamine tartrate was the drug of choice for treatment of moderate to severe acute migraine attacks. However, controlled trials have proved that ergotamine is effective in only one-half of patients when given orally, sublingually, rectally, or nasally. The addition of caffeine enhances the absorption and possibly the vasoconstrictive activity of ergotamine. Because absorption of ergotamine and related drugs is variable, the drug should be given by a route acceptable to the patient, and the dosages should be increased to find a single, effective dose as early as possible for subsequent attacks. Ergotamine is best absorbed rectally. An antiemetic drug (best given by suppository) may be needed together with ergotamine. Dihydroergotamine, which is available for parenteral administration in the United States, is also effective in migraine attacks. Patients can be instructed to self-administer dihydroergotamine subcutaneously. Dihydroergotamine is available in a nasal spray, enhancing the convenience of delivery. Probably because the drug has a prolonged dissociation with its receptors,

the drug is particularly useful in those patients who have prolonged attacks or a high recurrence rate with use of the triptan group of drugs to be discussed next. Ergot preparations are vasoconstrictors and should not be given to patients with vascular disease.

Sumatriptan. Sumatriptan is a serotonin receptor agonist that has proved to be effective in migraine. Sumatriptan is effective when administered subcutaneously during an attack of migraine. Subcutaneous administration of 6 mg of sumatriptan reduces migraine within 2 hours in up to 86% of patients (148). Nausea and vomiting are effectively relieved in most patients. Unfortunately, headache can recur in up to 46% of patients within 24 hours, probably because of the short half-life of the drug.

When sumatriptan is given orally in a dose of up to 100 mg, headache and associated symptoms are relieved within 4 hours in 75% of patients (149). The usual dose is 50 mg at the outset of the attack. As with subcutaneous administration, headache recurrence is a problem. Nasal spray is also available, the standard dose being 20 mg. Patients should be instructed to deliver the spray with the head bent forward because the taste of the drug is unpleasant. This preparation is useful when a more rapid action of the drug is required than can be obtained by the oral route, or for patients who find the injection unacceptable but require more rapid pain relief. The practitioner should attempt to characterize first the severity and rapidity of pain onset as well as monitor response to the modes of drug delivery and customize the drug regimen to the needs of the individual patient.

The side effects of subcutaneous and oral sumatriptan are similar. Most of the side effects are mild to moderate in intensity, are short lived, resolve spontaneously, and do not change with repeated use of sumatriptan. The most common side effects are injection site reaction after subcutaneous administration; sensations of flushing, heat, and tingling; and neck pain with stiffness. Three percent to 5% of patients experience chest tightness, heaviness, pressure, tingling, and pain. The cause of the chest symptoms is unknown, but in rare instances, coronary vasospasm has undoubtedly occurred. For patients who are likely to have unrecognized coronary artery disease (e.g., postmenopausal women, men older than 40 years, and patients with risk factors for coronary artery disease), the first dose of sumatriptan should be given under medical supervision. Sumatriptan is contraindicated in patients with a history of myocardial infarction, symptomatic ischemic heart disease, Prinzmetal's angina, and hypertension.

Newer members of the triptan class of drugs are now available. Zolmitriptan, naratriptan, and rizatriptan are in the formulary, and the release of eletriptan is expected. Zolmitriptan (149,150,151,152,153,154,155,156,157,158 and 159) was the second triptan to be marketed in the United States (150,151,152,153,154,155,156,157,158,159,160 and 161). It is available only in oral form, and the recommended dose is 2.5 mg, repeated if needed in 1 hour (150). Higher doses do not appear to increase efficacy, but increase side effects. Zolmitriptan varies from sumatriptan in both site of action and pharmacokinetics, which appear to provide limited advantages over oral sumatriptan (151). In addition to the peripheral effects of vasoconstriction and inhibition of neurogenic inflammation, common to both drugs, unlike sumatriptan, zolmitriptan penetrates the blood–brain barrier. Zolmitriptan also shows higher bioavailability (42%) when compared with sumatriptan (14%). Clinically, zolmitriptan has a more rapid onset of action when compared with oral sumatriptan (18% therapeutic gain at 1 hour versus only 10% for sumatriptan, 100 mg). After this initial gain, however, zolmitriptan's advantage is lost; the number of patients who are pain free 2 hours after treatment is nearly identical for both drugs (17% and 18%, respectively). Nausea, vomiting, and photophonophobia are also effectively treated. Zolmitriptan is effective regardless of time taken during the headache and has equal efficacy across headache types (migraine with aura, migraine without aura, menstrual migraine). A high response rate (81%) is maintained throughout multiple attacks. Headache recurrence appears to be lower for zolmitriptan as compared with oral sumatriptan. The side-effect profiles of the drugs remain similar, and despite the central penetration of the zolmitriptan, adverse CNS effects do not occur at a higher rate than sumatriptan. Most adverse events are mild and well tolerated, with onset in 20 to 45 minutes. The duration is typically less than 30 minutes, but symptoms may last up to 2 hours. Adverse events are similar to those of sumatriptan, including nausea, dizziness, somnolence, paresthesias, and tightness of the throat or chest. Contraindications to use remain the same as for sumatriptan, including its use in those with known or suspected cardiac disease. The use of vasoconstrictors, such as ergotamines, dihydroergotamine, and other triptans, is contraindicated within 24 hours.

Naratriptan is available only in oral form. The recommended dose is 2.5 mg, and the same contraindications and precautions apply as with other triptans (162). Naratriptan is not more effective than sumatriptan, rizatriptan, or zolmitriptan in either pain relief or pain-free responses (158,161,162). Adverse events occur overall at a lower rate than sumatriptan (0.1% when corrected for placebo), and the drug appears to be better tolerated. Headache recurrence after treatment with naratriptan may be lowest of all the triptan drugs.

Rizatriptan was most recently released for clinical use. It is available in 5- and 10-mg tablets, with a recommended dose of 10 mg in a single dose (163,164). Bioavailability (45%) is comparable with zolmitriptan (42%) (150,155,156), higher than sumatriptan (14%), but lower than naratriptan (74% for women, 63% for men). Like sumatriptan, rizatriptan does not cross the blood–brain barrier in significant amounts. The onset of action is comparable with oral sumatriptan and slower than zolmitriptan. Rizatriptan may prove more rapidly effective than other triptans, but this remains to be established. However, a substantial decrease in efficacy occurs 4 hours after treatment compared with sumatriptan. The rate of headache recurrence (44%) (163) is higher than that of oral sumatriptan (36%). Rizatriptan is effective against nausea, photophobia, and phonophobia. Adverse reactions are similar to those of the other triptans (163), although experimentally rizatriptan may have fewer constrictor effects on coronary arteries than sumatriptan (165,166). Nevertheless, the same cautions should be exerted when using this drug as with other triptans. Propranolol at doses typically higher than those used for headache prophylaxis (240 mg) may increase serum concentrations of rizatriptan.

Symptomatic Treatment in the Emergency Department. Migraine attacks that are severe, prolonged, and unresponsive to self- administered medication may be treated in the clinic or emergency department. Patients with such attacks should be treated with dihydroergotamine given intravenously or intramuscularly or with sumatriptan given subcutaneously. If these drugs fail, the preferred regimens are metoclopramide (10 mg intravenously), prochlorperazine (10 mg intravenously), or chlorpromazine administered in three intravenous injections of 0.1 mg per kg given 15 minutes apart. In addition to dystonia and tardive dyskinesia, the side effects of the three drugs are drowsiness, nausea, vomiting, dizziness, and hypotension, all of which are infrequent. The mechanism by which these dopamine antagonists relieve headache remains to be determined.

Major Narcotic Analgesic Drugs. Major narcotic analgesic drugs, particularly meperidine, are used in the emergency treatment of migraine attacks. The use of meperidine should be limited to patients who have attacks that do not respond to antimigraine preparations and patients in whom antimigraine drugs are contraindicated (e.g., those with peripheral vascular or coronary artery disease and pregnant women).

Acute attacks may be so frequent and the patient's pain so severe and continuous that hospitalization is needed. In these patients, it may be effective to administer dihydroergotamine intravenously for three to four days, discontinue all other drugs, and administer intravenous fluids (167).

Preventive Treatment

Preventive treatment should be considered only when attacks of migraine occur more than two or three times a month, when the attacks are severe and limit normal activity, when the patient is unable to cope with the attacks, when symptomatic therapies have failed or have had serious side effects, and when attempts at nonpharmacologic prevention have failed. Several points should be considered before preventive therapy is initiated. Some form of contraception, preferably barrier contraception rather than an oral contraceptive that may trigger headache, should be advised in women of child-bearing age. Costs of drugs should always be considered because prolonged treatment may be required.

Each medication should be given for a period adequate for its effectiveness to be determined. In patients with frequent migraine, this is usually 2 to 3 months. Preventive treatment is usually continued for 6 months or longer and gradually withdrawn after the frequency of headaches diminishes. Serotonin-influencing drugs were the first to be used effectively for migraine prevention (Table 48-5). Methysergide is more effective than amitriptyline but is not used much in the United States, because it can cause retroperitoneal, cardiac valvular, and pleural fibrosis. Methysergide is contraindicated in patients with vascular disease because of its vasoconstricting action. Amitriptyline is a useful drug for preventing migraine, especially in patients with depression or tension-type headaches, although its beneficial effect in migraine is independent of its antidepressant activity. Nortriptyline may also prove effective and, because it causes less weight gain, may be preferred by some patients.

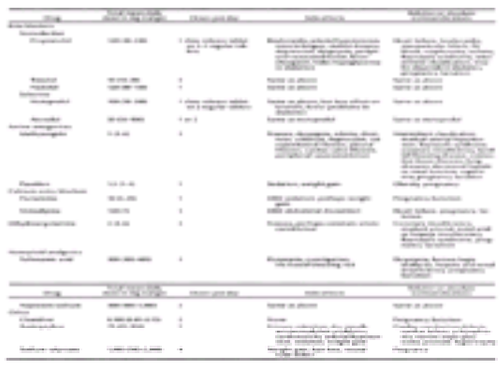

TABLE 48-5. Drug prophylaxis of migraine

b_2-Adrenergic antagonist drugs have proved effective in preventing migraine in numerous clinical trials. They should be considered the treatment of choice for preventing migraine, especially in patients with stress-related attacks. However, these drugs are effective in only up to 65% of treated patients and are contraindicated in patients with bronchospasm, congestive heart failure, cardiac arrhythmias, and a history of depression. b $_2$-Receptor antagonists with partial agonist activity are ineffective.

Despite initial enthusiasm for the use of calcium channel blocking agents to prevent migraine, their effect has been unimpressive. Verapamil is probably used the most. In general, the calcium channel blockers may decrease the frequency of attacks, but they have little effect on their severity. It may take weeks to months before an effect is noted, which reduces patient compliance. The vasodilatory action of calcium channel blockers sometimes causes severe headache that is indistinguishable from migraine.

NSAIDs have been used in satisfactorily controlled trials. Aspirin is also effective in preventing migraine. However, because of gastrointestinal ulceration and hemorrhage, prolonged prophylaxis with NSAIDs should be avoided. No comparison has been made of the relative effectiveness of the various classes of NSAIDs, but it is reasonable to change to another class if one has proved ineffective.

Valproic acid was introduced as preventive therapy for migraine, but it is only moderately effective in preventing migraine and reducing the frequency, severity, and duration of severe attacks. The mechanism of action of valproic acid is not known.

Menstrual migraine (i.e., an attack occurring only in association with menses) is frequently refractory to treatment. Women with menstrual migraine may benefit from preventive treatment limited to the period of menses. If they are already receiving prophylactic treatment, an increased dose at the time of menses may be beneficial. The use of percutaneous estradiol gel applied just before and throughout menses may reduce the frequency of headache (168). Patients already taking oral contraceptives who continue taking them throughout the menstrual cycle may experience fewer attacks. Bromocriptine, a dopamine D $_2$-receptor agonist that suppresses prolactin release, may be given during the luteal phase with some effect. Finally, Lupron, the gonadotropin-releasing hormone analog that suppresses ovulation, can be tried but has not been subjected to controlled trials. The menopause is often a time of severe and frequent migraine attacks. Those already taking estrogen who have frequent migraine attacks may improve if the hormone is either stopped or increased.

The mechanisms by which ovarian hormones influence migraine remain to be determined, but an abrupt decrease in serum estrogen concentrations before the onset of an attack appears to be a critical factor (169). The currently used low-dose estrogen oral contraceptive formulations are associated with a haphazard occurrence of attacks during the cycle, probably because of fluctuating serum estrogen concentrations. Thus, treatment strategies are aimed at preventing either a decrease or a substantial fluctuation in serum estrogen levels. Women already taking estrogen who have frequent migraine attacks may improve if the hormone is either stopped or increased.

A condition of near-daily or daily migrainelike headaches, with repeated therapeutic failure, multiple analgesic use and abuse of drugs such as codeine and barbiturate, and depression, can develop in migraine sufferers. This is among the most frequent of the headache disorders that present to specialized headache clinics, and a major management problem because the headache is commonly intractable. Management should be to withdraw the overused drug and consider a preventive approach with the standard drugs used for migraine. Sodium valproate is popularly regarded as most effective in these cases, although this remains to be established. Hospital admission and the use of intravenous dihydroergotamine may be indicated in intractable cases.

Cluster Headache

Cluster headache is a disorder that occurs six times more often in men than in women, usually beginning in the third or fourth decade of life. Attacks occur during defined periods that may last weeks to months and may return within a span of 1 or more years. Not infrequently, the cluster periods resume according to well-defined cycles that may be associated with seasons. As time passes, the cluster periods become longer and merge into one another as the duration of remission shortens, so that subjects enter a stage termed *chronic cluster headache*, clearly a misnomer. When headaches occur in a cluster, there are usually several clear-cut triggers of an attack (the most common being alcohol and nitroglycerin), all of which appear to have vasodilator properties.

Pathophysiology. The causes of cluster headache remain to be determined. Paresis of the sympathetic nerve fibers that traverse the cavernous sinus to innervate orbital and retroorbital structures appears to play an important role. Indeed, after severe and frequent attacks, persons may be left with permanent sympathetic palsy. In addition, the trigeminal system must transmit the pain, which probably originates in dilated and sensitized arteries and veins. A relapsing and remitting venous inflammatory process of unknown cause has been suggested as the underlying basis of cluster headache. Positron emission data have shown that hypothalamic centers are activated during a cluster attack, although the significance of this finding remains to be determined. The same center appears to be structurally different in cluster patients than normal controls.

Clinical Features. Cluster headache attacks are characteristically unilateral and periocular, although they may also occur in frontal, temporal, or maxillary locations. The pain is almost always excruciating and is usually described as boring, knifelike, or burning. The pain is accompanied by conjunctival injection, lacrimation, rhinorrhea, and miosis. The attacks are relatively short, lasting from 15 minutes to 3 hours. They may recur numerous times during the day but usually only two or three times. Cluster headache attacks often wake the patient during the night. These clinical features of cluster headache are so stereotypical that the diagnosis can be made on their basis alone without resorting to other investigations.

Cluster headache sufferers do not search for a quiet environment to relax. They tend to pace the floor and bang their heads against hard surfaces, hoping to relieve the excruciating pain. In rare instances, patients with cluster headache are photophobic, phonophobic, or both and require a dark room to alleviate the pain.

Treatment. One hundred percent oxygen is effective in approximately 70% of patients when it is delivered in a tight-fitting face mask at 7 L per minute for 10 minutes. Ergotamine nasal spray may provide rapid benefit. Dihydroergotamine given subcutaneously or intranasally may also be effective. Two percent lidocaine intranasal drops (or occasionally lidocaine gel) are sometimes beneficial in acute cluster attacks. The patient's head should be kept back and tilted toward the side of the headache when the lidocaine anesthetic is applied. Subcutaneous administration of sumatriptan is effective in treatment of acute episodes of cluster headache. Sumatriptan has a rapid onset of action, making it ideal for the treatment of severe cluster headaches of short duration. The availability of the sumatriptan nasal spray offers an alternative approach to rapidly deliver the drug. If treatment fails or medications are contraindicated, acute intravenous glucocorticoids or intramuscular meperidine may be indicated. Finally, hospital admission and the use of intravenous dihydroergotamine may be indicated in intractable cases.

Preventive Treatment. Prevention of attacks during the cluster period is almost always indicated because of the severity of pain. Preventive treatment is probably best achieved by a short course of glucocorticoids (e.g., prednisone, 60 mg per day), usually for 2 weeks and then tapered over 10 days. However, this strategy cannot be repeated regularly. Verapamil (up to 80 mg four times a day) or lithium carbonate (300 mg three times a day) can be given. Alternatively, 0.5 to 1.0 mg of ergotamine may be given in suppository form at night and may be effective. No published experience exists of the use of sumatriptan as a preventive treatment of cluster headache. Although it may have a similar action to ergotamine, it has a much shorter half-life and may have less utility for this purpose.

Chronic Paroxysmal Hemicrania

Chronic paroxysmal hemicrania is a primary headache so rare that it will probably never be diagnosed in a nonspecialist setting, but it demands mention because it resembles aspects of cluster headache. The pain is similar in intensity and location to cluster headache, but the attacks are short (rarely longer than 30 minutes) and frequent (up to 30 times a day). The disorder is also distinct from cluster headache because it rarely occurs in men and is entirely resolved by use of indomethacin. The condition also needs to be differentiated from other rare headache forms that occur around the eye, such as the cluster-tic syndrome and the SUNCT syndrome (short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing). Hemicrania continua, a controversial primary headache, is also selectively responsive to indomethacin.

Tension-Type Headache

Tension-type headache is typically pressing or tightening in quality, mild to moderate in intensity, and bilateral in location and does not worsen with physical activity. Phonophobia, photophobia, or both are occasionally present, but nausea is absent. An attack may last hours to days. If tension-type headache occurs more than 15 days a month for 6 months, the condition is termed chronic as opposed to episodic tension-type headache. Whereas almost 60% of the population may suffer episodic tension-type headache in any 1 year, the chronic form is present in fewer than 3% (170).

Pathophysiology. The mechanisms of tension-type headache remain to be determined. The previous term for this disorder, *tension headache*, was coined because the pericranial and pericervical muscles were thought to be involved (i.e., muscle contraction headache). Indeed, this may still be the cause in some cases. Neurophysiologic studies have found an abnormality of a temporalis muscle reflex that indicates a brainstem origin of disinhibited muscle contraction.

Differential Diagnosis. Episodic tension-type headache can pose a problem in differential diagnosis. Some authorities consider that the distinction between episodic tension-type headache and migraine without aura is unwarranted, whereas others disagree. The distinction is even more difficult in the context of the so-called mixed headaches, in which attacks of migraine with aura occur against a background of chronic tension-type headache. Contemporary headache specialists call this CDH, with the hallmark of the condition being its development over time (maturational migraine) from an earlier and unequivocal diagnosis of episodic migraine (see previous discussion). So-called CDH, as yet unrecognized in the IHS classification, is compounded by the frequent use of analgesic and sedative medications, which some experts consider to be instigators of the condition.

Treatment. An exacerbation of episodic tension-type headache is best treated by bed rest and complete relaxation. Precipitating factors should be sought, and reassurance and psychological support should be provided for the patient. Gentle massage of the head and neck area and application of hot packs to these areas are physical maneuvers that may be helpful in alleviating some of the pain. In view of the risk of analgesic addiction in patients with chronic headache, only minor analgesics should be used. If the patient has consistently used scheduled analgesics, such as codeine, the pain of an acute exacerbation of severe muscle contraction headache may not respond to anything but parenteral narcotics. Accordingly, instead of pursuing this line of treatment, it is preferable to treat the patient with tranquilizers that are also neuromuscular relaxants, such as diazepam, which may have the added beneficial effect of causing drowsiness and sleep. Muscle relaxants are occasionally effective in acute exacerbations. NSAIDs, such as naproxen and ibuprofen, are useful alternative analgesics that are effective in some patients.

For the management of chronic tension-type headache, a similar pain strategy is used. In this instance, it is better to avoid tranquilizers and to try preventive measures with pharmacotherapy, but only if behavioral measures, such as regular sleep and effective stress coping, have failed. The tricyclic antidepressants, such as amitriptyline, are the most effective preventive drugs.

Conversion Headache

Conversion headache is one of the most difficult forms of headache to diagnose; indeed, a long delay in diagnosis is almost a diagnostic feature. Most cases have an abrupt onset followed by exacerbations and remission. The incidence in men and that in women are nearly identical. Conversion headache occurs predominantly in adults 18 to 30 years of age, but it can be observed at all ages. The character of conversion headache often cannot be differentiated from that of other types of headaches. In addition, major abnormalities in mental status are seldom found in patients with conversion reaction. Laboratory, electrophysiologic, and radiologic studies are normal. The usual duration is from months to years, but in most cases, diagnosis is made within 1 year of initial presentation. Conversion headache is rarely relieved by medication.

On examination, the major abnormalities are behavioral in nature. Patients may have a total indifference to their symptomatology despite bitter complaints of pain. In addition, symptoms may be overdramatized, particularly when they are of an unusual description. Patients may exhibit extreme passivity or express hostile denials when they are asked about possible emotional problems. The psychiatric examination rarely reveals serious psychiatric disease, but the personality profile may indicate that the patient is an immature, dependent person.

Miscellaneous Headaches

The IHS has classified miscellaneous headaches under primary headaches even though less is known about the mechanisms of miscellaneous headaches than about the other primary headache syndromes. Notable characteristics of the miscellaneous headaches include a resemblance of the head pain to that of serious structural disorders; thus, miscellaneous headaches require special mention and, often, good clinical judgment as to the extent into which they are investigated.

Idiopathic Stabbing Pain. Idiopathic stabbing pain includes the syndromes of so-called ice pick headache and so-called jabs and jolts. Transient stabs or series of stabs of head pain lasting fractions of a second occur at irregular intervals of hours to days. Patients with migraine, cluster headache, and chronic paroxysmal hemicrania are predisposed to this condition (see previous discussions). An important differential diagnosis is the sentinel headache of subarachnoid hemorrhage, which most often can be discriminated from idiopathic stabbing pains by a history of past events in the case of subarachnoid hemorrhage.

External Compression Headache. External compression headache is a constant pain resulting from external pressure applied to the site from which it originates, usually by stimuli such as swim goggles. The pain is mediated by the trigeminal or occipital nerves.

Cold Stimulus Headache. As the name implies, cold stimulus headache results from exposure of the head to low temperatures. This includes a generalized headache from exposure of the bare head to subzero weather or from diving into cold water. Ingestion of a cold stimulus, best typified by ice cream headache, produces a more focused and more severe pain, usually frontal or retropharyngeal in location.

Benign Cough Headache. Benign cough headache is a bilateral headache of sudden onset lasting less than a minute that is precipitated by coughing. It can be diagnosed only after structural lesions, especially posterior fossa space-occupying lesions, have been excluded.

Benign Exertional Headache. In contrast to the benign cough headache, benign exertional headache is brought on by physical effort, lasts minutes, and has a throbbing, pounding quality. It too has the important differential diagnosis of intracranial mass.

Headache Associated with Sexual Activity. Headache associated with sexual activity, which is often known as *benign coital cephalalgia*, can take three forms. In one form, the headache has a sudden onset precisely at the time of orgasm. In another form, the headache can begin gradually during sexual excitement and then intensify at the time of orgasm. The headache of sudden onset is explosive in character, and the headache of gradual onset is a dull ache. In both headaches, but more commonly in the one of sudden onset, the headache occurs at the time of masturbation, a historic feature that may be helpful in distinguishing it from subarachnoid hemorrhage. Curiously, these headaches may occur with a clusterlike periodicity. The third type of headache associated with sexual activity is postural headache, resembling intracranial hypotension. Unlike the other types, which are short lived, the postural headache may persist for days. The mechanisms of these headaches remain to be determined. The conditions usually spontaneously remit; however, if preventive management is desired, propranolol may be tried. Propranolol has been successful in some cases, perhaps by preventing an increase in blood pressure at orgasm.

Headaches with Sudden Onset

Subarachnoid Hemorrhage (International Headache Society Code 6.3). Subarachnoid hemorrhage results from ruptured berry aneurysm, trauma, or an arteriovenous malformation (171). Most cases of subarachnoid hemorrhage occur between the ages of 20 and 40 years. An expanding aneurysm gives rise to intermittent headache in the same location. Almost 40% of patients describe a premonitory sentinel bleed before their major subarachnoid hemorrhage. The incidence of headache in a ruptured aneurysm approaches 100%. The leading symptom is the so-called *thunderclap headache*, which is present in approximately 80% of patients. The acute onset of headache is caused by a ruptured aneurysm and the entrance of blood into the subarachnoid space, rapidly causing meningeal irritation and clinical signs of meningismus, neck pain, and stiffness. Hemorrhagic CSF also causes varying degrees of cerebral vasoconstriction that causes alteration of consciousness ranging in spectrum from mild confusion to coma. Nausea, vomiting, diaphoresis, photophobia, neck pain, tachypnea, tachycardia, and hypertension are common associated symptoms and signs.

A third-generation CT scanner can accurately detect subarachnoid hemorrhage in up to 95% of cases; however, sensitivity decreases to 74% after 3 days (172). A lumbar puncture is mandatory if no blood is detected on CT. The remainder of the cases can be detected on lumbar puncture by the presence of red blood cells that do not clear in four samples of CSF. Subarachnoid hemorrhage can be distinguished from a traumatic tap by the presence of xanthochromia in the CSF sample. Once the diagnosis of subarachnoid hemorrhage is confirmed, prompt neurosurgical consultation is required to determine if the patient qualifies for arteriography and surgical clipping. Aneurysms are best confirmed by four-vessel catheter angiography. Patients in deep coma are managed conservatively. Medical management includes intravenous hydration, control of hypertension, and nimodipine therapy to reduce vasospasm. In most countries surgery is recommended within 72 hours after the headache onset, depending on the grade of the disease. For the appropriate neurosurgical management, Hunt and Hess (173) established a ranking scale ranging from headache plus nuchal pain (I°) until deep coma (V°). Overall mortality from subarachnoid hemorrhage is approximately 50%.

Cerebral Venous Thrombosis (International Headache Society Code 6.7). Cerebral sinus or venous thrombosis is the most important differential diagnosis of subarachnoid hemorrhage, because the leading symptom in cerebral venous thrombosis is headache (more than 80%). *Thunderclap headache* is the first symptom in approximately 25% (20). In other cases the headache is dull and waxing and waning. Cerebral sinus or venous thrombosis is most often accompanied by additional signs, especially epileptic seizures (50%) and drowsiness, somnolence, or coma (50%). Motor deficits occur in approximately one-third of the patients. In almost 50% of patients papilledema can be detected. A contrast-enhanced CT scan usually shows nonspecific signs of elevated intracranial pressure, such as small ventricles or diminished sulci. In certain circumstances the specific delta sign is observed (174), a contrast-sparing region within the occipital part of the superior sagittal sinus or the confluence of sinuses. If the CT scan is suspicious for cerebral venous thrombosis, the diagnosis can be confirmed by MR angiography, or digital subtraction angiography when the former is unavailable. Early diagnosis is essential because heparin therapy may improve consciousness and resolve neurologic function. Recently, tissue plasminogen activator has been used with anecdotal success. Patients with cerebral venous thrombosis should be monitored carefully, because of secondary complications such as infarction, intraparenchymal bleeding, hydrocephalus, and seizures. An antiepileptic strategy should be initiated on the first day.

Headache Caused by Dissection of Carotid or Vertebral Arteries (International Headache Society Code 6.6.1). The onset of pain is usually acute and of moderately severe intensity, often with pulsating character. The pain might be referred to the cranium or face or may be located in the neck. The most frequent associated signs are those of cerebral ischemia. Ischemic signs may be delayed up to 1 month after the onset of pain and may be caused by embolism from the site of dissection (175). The combination of cervical pain, headache, and ischemic signs is characteristic and provides a strong clue to the diagnosis. One of the most common features of carotid dissection is ipsilateral Horner's syndrome (40% to 60%), followed by tinnitus, hemiparesis, and cervical pain. Whether there is increased frequency of carotid or vertebral dissection in migraineurs remains controversial (176). Nevertheless, when ischemic signs occur in migraineurs, the differential diagnosis of dissection must always be considered. Doppler and duplex sonography are sensitive tests for dissection, but MR angiography is the preferred investigation, or catheter angiography if this is not available. Anticoagulant therapy to prevent embolism is given for up to 6 months, unless the dissection extends intracranially.

Hypertensive Headache. Acute, severe headache is a prominent symptom of hypertensive encephalopathy, which occurs when sustained elevation in blood pressure exceeds the upper limits of cerebral autoregulation. The rate of blood pressure increase is more important than the absolute value; nonetheless most patients have a blood pressure that is in the range of 250/150. Other symptoms of hypertensive encephalopathy include nausea, vomiting, visual disturbances, seizures, confusion, and coma. Evidence of other end- organ damage (e.g., proteinuria and azotemia), focal neurologic deficits, retinal hemorrhages, and papilledema may also be present.

One percent to 2% of patients with essential hypertension progress to hypertensive emergency for unknown reasons. Arteriolar distension and interstitial extravasation produce focal vasogenic edema that often shows as nonspecific bilateral abnormalities in the occipital lobes and subcortical white matter (177). The therapeutic goal in the treatment of hypertensive emergency is reduction of the mean arterial pressure by 15% to 25% in the first 48 hours. Intravenous nitroprusside is the drug of choice because it can be rapidly titrated and has a high efficacy. Invasive blood pressure monitoring should be done through an arterial line while infusing nitroprusside. Use of oral nifedipine has fallen out of favor because of its potential for causing a steep decrease in blood pressure and precipitating ischemic stroke.

Ischemic and Hemorrhagic Stroke. Headache is three times more common in intraparenchymal hemorrhage than in ischemic stroke (171). The headache is usually focal, mild to moderate in severity, and ipsilateral to the stroke. The character of the headache may vary widely depending on the location and extent of the hemorrhage. In general, the severity of the headache does not correlate well with the size of the stroke or cortical involvement (178). Headache was lateralized in only 46% of patients; of those cases, 68% of headaches were ipsilateral to the stroke. When a patient presents with a headache and lateralized findings, a CT scan without contrast is the initial investigation of choice (179).

Acute Posttraumatic Headache Associated with or without Epidural Hematoma (International Headache Society Codes 5.1, 6.2.3). After head trauma, headache is common. For example, headache is always present in epidural hematoma caused by ruptured meningeal arteries involved in skull fracture. Depending on the size of the hematoma, the patient appears to be normal during the first minutes or hours after the head injury. During this *lucid interval* only headache might be present. Subsequent symptoms and signs include anisocoria, deterioration of headache, nausea, and rapid loss of consciousness. If skull fracture is suspected, CT scan is the diagnostic procedure of choice. Epidural hematoma is a neurosurgical emergency (180).

Central Nervous System Infections. Patients with CNS infections such as bacterial and viral meningitis, encephalitis, brain abscess, and human immunodeficiency virus (HIV) disease often present to the emergency room with acute severe headache. Untreated bacterial meningitis has a high mortality. Fever (95%), neck stiffness (88%), and altered consciousness (80%) are the common associated findings in meningitis (181). A CSF protein of greater than 220 mg per 100 mL, cell count above 2,000 per mL and a CSF to serum glucose ratio of less than 0.23 are 99% specific for bacterial meningitis. Antibiotic therapy should not be delayed while waiting for a CT scan or a lumbar puncture result. Ceftriaxone or cefotaxime should be given as soon as possible. Ampicillin is added if infection with *Listeria* is suspected. Children with presumptive *Haemophilus influenzae* meningitis should also receive dexamethasone, 0.15 mg per kg every 6 hours for 2 to 4 days. Untreated herpes encephalitis has a 70% mortality, even though it accounts for only 3% of all cases of viral encephalitis (182). Associated symptoms and signs include headache, low-grade fever, altered consciousness, vomiting, seizures, and focal neurologic deficits. A contrast-enhanced CT is only 60% sensitive in diagnosing herpes encephalitis, and MRI with gadolinium is the neuroimaging study of choice. A definitive diagnosis may require temporal lobe biopsy. Herpes simplex encephalitis requires immediate treatment with intravenous acyclovir, 10 mg per kg every 8 hours for at least 10 days. Of all the patients with HIV who visit the emergency room, 20% do so with complaints of headache, and 82% of these headaches are from secondary causes (183).

Cryptococcal meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy, HIV encephalitis, undiagnosed mass lesions, sepsis, and drug reactions are some of the common causes of headache in an HIV patient (184). All new headaches in patients with HIV should be evaluated with a neuroimaging study such as MRI and a lumbar puncture.

Acute Glaucoma. Patients with acute angle closure glaucoma usually present with severe pain localized to the eye and radiating to the ear, sinuses, teeth, or forehead. Accompanying signs are blurred vision, dilated unresponsive pupil, and ciliary injection. Nausea and vomiting are less common. Diagnosis is made by measuring intraocular pressure. Treatment is with miotics (b-receptor blocking eye drops, pilocarpine, or systemic acetazolamide).

Exercise Headache and Headache Associated with Sexual Activity (International Headache Society Codes 4.5 and 4.6). Recurrent headache associated with sexual activity is termed *coital cephalalgia*. It is categorized as explosive, similar to the thunderclap headache of subarachnoid hemorrhage. The differential diagnosis from the latter can be established if a series, even a cluster, of headache attacks under identical circumstances is reported. Often the diagnosis is helped when the headache is time locked with orgasm (orgasmic cephalalgia).

Exercise headache is also explosive in character and time locked with strenuous activity. Again, subarachnoid hemorrhage figures prominently in the differential diagnosis. Often the complaint is recurrent. All such patients should have an MRI scan of the head with particular attention to the posterior fossa structures, although

rarely is an abnormality found to explain the headache.

Subacute and Chronic Headache of High Intensity. In these cases, focal or generalized neurologic symptoms and signs, rather than the headache itself, usually cause the patient to present to an emergency room. Most of the diseases that cause acute secondary headaches discussed previously also may on occasion present with subacute headache (e.g., cerebral venous thrombosis). In the diseases discussed here, headache is subacute in onset with growing intensity during days or weeks.

Arteritis Cranialis (Headache Associated with Giant Cell Arteritis; International Headache Society Code 6.5.1). Headache is the leading symptom of giant cell arteritis, being present in approximately 80% to 90% of patients. It is described variably as unilateral or bilateral temporal headache, forehead pain, or diffuse headache. Occipital headache is rare, although occasionally patients complain about neck pain (185). Often the pain is severe and pulsating in nature and can be localized to the artery of involvement. Giant cell arteritis is associated with polymyalgia rheumatica. Additional symptoms include visual symptoms, especially transient or permanent unilateral or bilateral vision loss. An almost pathognomonic symptom is jaw or masticatory claudication. Furthermore, some patients present with tongue pain or tongue infarction. The disorder occurs in patients older than 60 years. Neurologic examination may reveal prominent, tender, nonpulsatile temporal arteries, although both temporal arteries might be normal. Funduscopy may reveal pale, swollen optic disks, indicating visual dysfunction. In the emergency room, the most rapid investigative information can be obtained from the erythrocyte sedimentation rate or C-reactive protein tests. The erythrocyte sedimentation rate might be as high as 100 mm, but may be normal. The sensitivity of this test decreases with the patient's age. Biopsy of the temporal artery is the investigation of choice, but the result may be negative if the arterial segment involved is limited in extent. Symptoms and signs respond rapidly to corticosteroids, usually 100 mg of oral prednisolone. To avoid visual loss, treatment with corticosteroids should be started urgently as soon as the diagnosis is suspected and before arterial biopsy.

Chronic Posttraumatic Headache Associated with or without Subdural Hematoma (International Headache Society Codes 5.2, 6.2.2). Subdural hematomas result from tearing of bridging veins. A history of trauma, presence of a CSF shunt catheter, or anticoagulation therapy should raise the suspicion of a subdural hematoma. Elderly persons are at high risk. Headache associated with subdural hematoma may present within as short a time as 6 hours or as long as 6 months. It may be a mild to moderate dull daily headache, without neurologic symptoms and only subtle neurologic signs. On the other hand, some patients report dizziness, drowsiness, disorientation, delusion, or personality changes, together with focal neurologic signs. A contrast-enhanced CT scan is the method of choice, if subdural hematoma is suspected. The management of a subdural hematoma, either conservative or surgical drainage, depends on its size and clinical signs.

Intracranial Infection (International Headache Society Code 7.3). Acute, severe secondary headaches associated with intracranial infections were discussed previously. Certain intracranial infections and encephalitides present with more indolent forms of headache, however.

Meningitis caused by *Mycobacterium tuberculosis* may take a chronic course of weeks to months. Immunosuppressed patients, patients with a history of pulmonary tuberculosis, or a history of tuberculosis in the neighborhood are at particular risk. Characteristically, CSF has a pleocytosis of less than 100 lymphocytes per milliliter, and an elevated protein of 100 mg per 100 mL. It may also be hemorrhagic. The CSF glucose level is moderately decreased to between 20 to 40 mg per 100 mL. Ziehl-Neelsen staining is negative in most cases. The sensitivity and specificity of diagnostic procedures for tuberculosis have been markedly improved by polymerase chain reaction. Indolent headache and clinical course are also features of cryptococcal meningitis and borreliosi *s*. The neurologic complications are much less severe in the former. CSF India ink or antigen tests may identify the *Cryptococcus*. Testing CSF for *Borrelia* produces variable positivity.

A specific virus is identified in less than one-half the cases of encephalitis; the most common virus identified is herpes simplex. No precise data exist on headache duration and localization in this disorder, but patient history can be short, lasting from hours to a few days. Occasionally, the headache and clinical presentation take an indolent course. Headache may be accompanied by meningism and fever (186). Other characteristic symptoms are fever, epileptic seizures, somnolence, coma, confusion, and focal neurologic deficits that localize to frontotemporal regions of brain cortex. MRI is the first-line diagnostic investigation. Mass lesions of necrotic tissue, usually in frontal or temporal cortex, can cause elevated intracranial pressure and shift of brain structures. Lumbar puncture should be performed immediately after scanning, mass effect permitting. CSF study may reveal a predominately lymphocytic pleocytosis of up to 300 per mm (186), a slightly elevated protein, higher if the CSF is hemorrhagic, and a moderately decreased glucose level. EEG may indicate a temporal focus. Treatment is with intravenous acyclovir.

Nasal and Sinus Headaches. Acute sinus infection often presents with moderate to severe headache and facial pain (see Chapter 52). Localization of the head pain corresponds to the affected sinus (e.g., retroorbital or temporal in ethmoid sinusitis or frontal in frontal sinusitis). Pain is often alleviated by an upright position (187). Sinusitis is typically associated with nasal obstruction, fever, and localized tenderness. Investigation with sinus radiography or CT scanning is diagnostic. To avoid intracranial complications, immediate antibiotic and anticongestant therapy is mandatory. Severe infections and pain may be relieved by sinus drainage if appropriate (e.g., maxillary sinusitis).

Headache Caused by Brain Tumor or Other Causes of Elevated Intracranial Pressure. Headache is the leading symptom in brain tumors, present in 48% of patients (188), or other conditions that elevate intracranial pressure. In brain tumors, headache usually takes a course of weeks to months, being of crescendo intensity. Initially, it may present only on wakening, before becoming continuous. Headache may reflect the tumor locus (e.g., posterior with cerebellar lesions) by involving contiguous pain- sensitive intracranial structures, later becoming generalized when intracranial pressure becomes elevated. Characteristically, the headache is briefly accentuated by behaviors that increase intracranial pressure such as coughing, sneezing, bending, defecation, and sexual intercourse. Patients with brain neoplasia usually present to the emergency room because of neurologic complications such as seizures, confusion, and paresis. A history of headache described previously and seizures in an emergency room patient require contrast-enhanced CT scanning to confirm the diagnosis and to estimate the degree of any mass shift and secondary hydrocephalus.

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CHAPTER 49

Facial and Head Pain Caused by Myofascial and Temporomandibular Disorders

Edmond L. Truelove, Samuel F. Dworkin, Jeffrey A. Burgess, and John J. Bonica

This chapter presents a detailed discussion of temporomandibular disorders (TMD) that produce orofacial pain. It primarily deals with painful myofascial conditions involving the muscles of mastication, internal derangements (ID) of the contents of the temporomandibular joint (TMJ) space, degenerative and other changes of the condyle and other osseous components of the joint, and fractures, infections, and tumors of the joint. Myofascial pain syndromes produce orofacial and other head pain and contribute significantly to headache. Because myofascial pain syndromes with trigger points affect various parts of the body, the subject is discussed in detail in Chapter 28 and Chapter 29. Some of the myofascial syndromes cause referred pain to the TMJ and other oral and facial structures and are undoubtedly similar to those discussed elsewhere in the text, and although similarities in the pathophysiology, symptoms, and signs between myofascial pain of the muscles of mastication and other areas exist, the causative factors between the two groups can be somewhat different.

TMDs and myofascial pain of the muscles of mastication are the most common cause of pain in the face, cranial vault, and other parts of the head. Facial pain is of particular importance because it has special psychological meaning to the patient and because its frequency, variable etiology, and complex nature commonly cause both medical and dental professionals to be involved collaboratively in its diagnosis and management. Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) have become available as a reliable taxonomic system for diagnosing and classifying the subtypes of TMD (1). This classification system contains reliable criteria and examination methods, consensually validated by expert panels, for diagnosing the most common forms of TMD. They are addressed in the bulk of the content of this chapter. The RDC/TMD uses a dual-axis system, also referred to in this chapter, to allow simultaneous consideration of physical diagnosis (axis I) and psychosocial assessment (axis II). As with virtually all chronic pain conditions discussed throughout this text, chronic orofacial pain is associated for a significant minority of TMD clinic cases with psychological and psychosocial morbidity, chiefly in the form of depression and dysfunctional chronic pain behaviors such as excessive treatment seeking and use of analgesic medications. A graded chronic pain scale, incorporated into axis II of the RDC/TMD, indicates, for example, that approximately 20% to 30% of clinic cases may present with significant psychological disturbance in the form of elevated symptoms of depression, anxiety, and somatization. These forms of psychological dysfunction tend to occur with other chronic pain complaints. Multiple health care visits and prolonged reliance on pain medications are common. Taken together, these data support the view that TMD is best understood as a chronic pain condition often associated with appreciable pain intensity and periodic limitations in mandibular function while it shares, in common with the most prevalent pain conditions, namely persistent back pain and chronic headache, the risk for appreciable psychological and psychosocial disturbance.

TEMPOROMANDIBULAR DISORDERS (III-3)

Disorders of the TMJ and associated muscles of mastication are collectively classified as TMDs and are recognized as the major source of nondental chronic orofacial pain. It is useful to view TMD as a cluster of related disorders that have many common features. The most important and by far the most common presenting symptom is pain localized at the TMJ, in the preauricular area, or in the muscles of mastication. In addition to complaints of pain, patients with TMDs typically also present with findings of limited or asymmetric patterns of jaw opening and joint sounds usually described as clicking, popping, grating, or crepitus.

The pathophysiology of TMD is confusing because the site of pain does not always coincide with the site of pathology or dysfunction. Patients with persistent TMDs are at risk for increasingly aggressive treatment, with a focus on surgical and dental reconstruction. Scientific studies have not clearly identified the specific causes of TMD and therefore some of the treatments advocated are empiric and without scientific foundation. Furthermore, these procedures are invasive and costly and often have irreversible consequences. A recent National Institute of Health Technology Consensus Conference on the management of temporomandibular disorders (2) concluded that irreversible surgical procedures such as occlusal, or bite, adjustment and surgery of the TMJ are not indicated as early or initial treatments for this condition.

Wide differences of opinion regarding the etiology, pathophysiology, diagnosis, and treatment of TMD caused the American Dental Association to review the scientific literature about TMD and to prepare a Presidential Report meant to assist clinicians in understanding which of the many concepts regarding TMD were based on sound scientific principles and supported by valid research findings (3). The American Dental Association report continues to represent an excellent summary of current standards regarding the diagnosis and management of TMD, and the discussion of TMD that follows in this chapter is consistent with the outline and recommendations of that American Dental Association report and the National Institute of Health Technology Consensus Conference cited previously. More detailed information can be found elsewhere (4,5 and 6).

Basic Considerations

Epidemiology

Increased numbers of reliable epidemiologic studies assessing the prevalence of TMD related pain are available and show surprising agreement when comparable definitions and methods are used. Table 49-1 summarizes findings from several of those studies, as compiled by LeResche (7). In general, agreement exists that women report TMD pain on average approximately twice as frequently as men, with the population-based (as opposed to clinically based) prevalence rates varying from approximately 3% to 10% for male subjects and approximately 9% to 18% for female subjects, across all ages. These studies also agree that the modal age in the population for TMD-related pain occurs in women during their reproductive years, with the rate of TMD falling for both men and women after age 45 years.

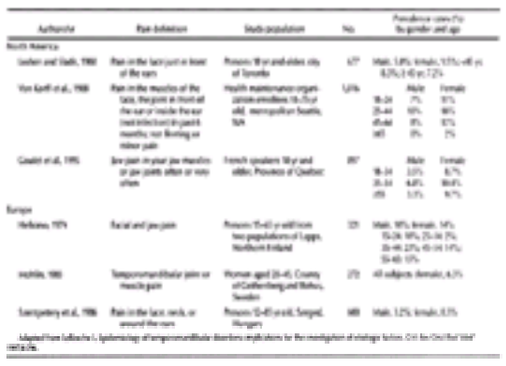

TABLE 49-1. Pain in the temporomandibular region: findings from population-based prevalence studies

The available epidemiologic data also support the conclusion that the presence of at least one sign or symptom of TMD, other than pain, is quite common (Table 49-2). Joint sounds elicited during functional excursions of the TMJ, for example, may be present in as much as 25% of an otherwise asymptomatic population (8).

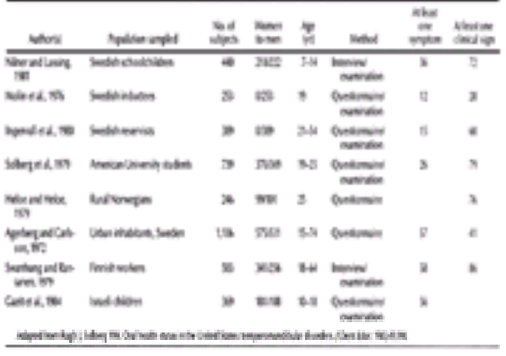

TABLE 49-2. Percentage of temporomandibular signs and symptoms in selected populations

We carried out a survey in a probability sample of 1,265 adults (aged 18 to 75 years) and of 320,000 enrollees of a large health maintenance organization, to which 1,060 persons responded (9). Analysis of the data indicated a 6-month prevalence of 12.1% for TMD pain in those enrolled in the study. The community cases showed a female-to-male ratio of 2:1, with approximately a 6:1 female-to-male ratio among clinic cases. As a major symptom compelling treatment, pain seems to diminish markedly in prevalence by the sixth decade of life. Our data indicated that only 2% of those aged 65 years or older had reported TMD pain in the prior 6 months. Only 23% of those who had pain sought health care. This lends support to the consensus that those seeking treatment are in an appreciably smaller group than those reporting symptoms. Some authors have suggested that painful TMD is even more prevalent than studies indicate, often being misdiagnosed as other forms of head and neck pain.

Anatomic and Physiologic Bases*

To appreciate the various painful disorders that are caused by pathophysiologic factors involving the TMJ, it is essential to understand the anatomy and function of the joint as well as the muscles of mastication.

Anatomy of the Temporomandibular Joint. Each TMJ is generally considered to be an ellipsoid synovial joint divided into upper and lower synovial cavities by a complete fibrous articular disk (5,10). Structures that make up the joint on each side are the anterior part of the mandibular fossa and the articular tubercle of the temporal bone above, and the condyle of the mandible below. Figure 49-1 depicts the ligaments of the joint.

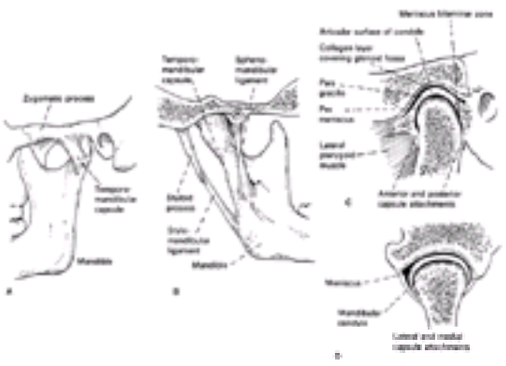

Figure 49-1. Anatomy of the left temporomandibular joint. **A:** Lateral view. **B:** Medial view. **C:** Sagittal section through the joint. **D:** Frontal section.

The articular capsule is a thin fibrous envelope attached above to the circumference of the mandibular fossa and the articular tubercle and below to the neck of the condyle of the mandible. The fibrous disk attaches to the inner surface of the articular capsule. The capsule is loose above the attachment to allow the disk to slide easily along the temporal bone, whereas below the disk the capsule is stretched more tautly.

The lateral ligament (formally called the temporomandibular ligament) strengthens the anterolateral aspect of the fibrous capsule. It is a rather short and narrow fibrous band attached superiorly to the lower lateral border of the zygomatic process of the temporal bone, with its fibers passing obliquely downward and backward to the lateral surface and posterior border of the neck of the mandible. It is covered by the parotid gland and by the integument.

The sphenomandibular ligament is a flat thin band of fibrous tissue attached to the spine of the sphenoid bone, becoming broader as it descends. It is fixed inferiorly to the lingula of the mandibular foramen. It lies medial to the capsule of the joint, and its upper lateral surface is in relation to the lateral pterygoid muscle and the auriculotemporal nerve. The stylomandibular ligament is a specialized band of the cervical fascia that extends from near the apex of the styloid process of the temporal bone to the angle and posterior border of the ramus of the mandible between the masseter and medial pterygoid muscles. This ligament separates the parotid from the submandibular gland.

The *articular disk* (see Fig. 49-1C) is formed of fibrous tissue; it is a thin oval plate placed between the condyle of the mandible and the mandibular fossa. Its circumference is connected to the articular capsule and anteriorly it attaches to the tendon of the lateral pterygoid muscles. The articular disk divides the joint into two cavities, each of which is lined by a synovial membrane. The upper cavity is above and the lower cavity below the articular disk. The upper cavity, the larger and looser of the two, continues from the margin of the cartilage covering the mandibular fossa and the articular tubercle onto the superior surface of the disk. The lower cavity passes from the undersurface of the disk to the neck of the condyle and is prolonged somewhat further inferiorly behind than in front.

The *synovial tissues* that line the periphery of the superior cavity appear as villi in sagittal section of the joint. The posterior villi are actually folds of synovial

membrane that are attached to the temporal bone and to the superior surface of the pars posterior of the meniscus. These folds allow the meniscus to translate as far as 2 cm forward by unfolding into a sheet when the jaws open. The synovial tissues of the inferior cavity are also folded into villi. The meniscus actually projects into the villi at the anterior portion of the cavity to form a heellike process of tissue. This pliable heel allows the meniscus to rotate posteriorly as the condyle translates forward.

Nerve Supply. The nerve supply of the TMJ is derived from branches of the mandibular nerve. The medial posterior lateral and lateral half of the anterior wall of the capsule are innervated by a large branch of the auriculotemporal nerve as it crosses posteriorly to the neck of the condylar process. The posterior temporal nerves innervate the lateral-anterior corner of the capsule, whereas the masseteric nerves supply the medial anterior corner. These nerves contain both large A and b fibers associated with pacinian, Ruffini, and Golgi proprioceptive endings and also contain small A- d and unmyelinated fibers. All these nerve endings supply the periphery of the meniscus where it attaches to the bone through the superior belly of the lateral pterygoid muscle.

Physiology of the Temporomandibular Joint. The muscles of mastication permit the movement of the mandible to be depressed (jaw opening) or elevated (jaw closing) (Fig. 49-2). Only the mandible moves because the maxilla is firmly articulated by sutures to the other bones of the skull and, when the mandible is at rest, the maxillary and mandibular teeth are slightly separated. On contact, the teeth assume their occlusal position. In addition to depression and elevation, the joint allows protrusion or retraction of the mandible as well as lateral displacement and some rotation. The two parts of the temporomandibular articulation are the one between the condyle and the articular disk and the other between the disk and the mandibular fossa. When the jaw is depressed or elevated (the mouth is open or closed), motion takes place in both parts. The disk glides anteriorly on the articular tubercle and the condyle moves on the disk like a hinge, causing the mandible to rotate around a horizontal access whose center of suspension traverses the rami of the mandible near their middle (4,5,10). Near this accidental lingula, which is adjacent to the mandibular foramen, is the attachment of the sphenomandibular ligament and the sling formed by the masseter and medial pterygoid muscles. When the jaw is open, the angle of the mandible moves posteriorly while the condyle glides forward as the short arm of a lever; the chin is the long arm of the lever and describes a wide arc. The motion between the condyle and articular disk is largely one of accommodation to the change of position. When the jaw is closed, some of the force is applied to the condyle as a fulcrum, especially when biting with the incisors. When chewing with the molars, however, pressure is applied more directly between the teeth, and the condyle acts more as a guide than as a fulcrum. In protrusion of the mandible both disks glide forward in the mandibular fossa, whereas during lateral displacement one disk glides forward and the other remains in place. During grinding or chewing the mandible is first displaced laterally by the forward movement of the one condyle, and the mandible is then brought back into place by the action of the closing muscles and the meshing of the teeth.

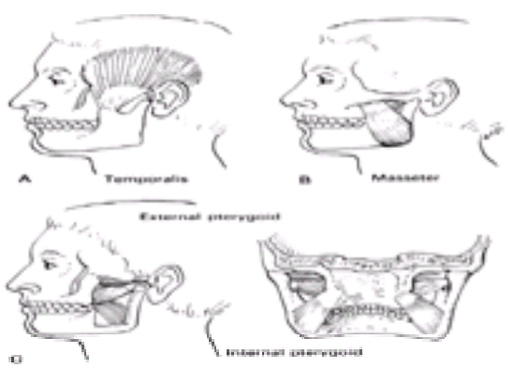

Figure 49-2. Anatomy of the muscles of mastication. **A:** The temporalis muscle is supplied by anterior and posterior deep temporal nerves from the anterior trunk of the mandibular division of the trigeminal nerve. **B:** The masseter muscle is supplied by the masseteric branch of the mandibular division. **C:** Lateral and medial pterygoid muscles. The medial pterygoid muscle is supplied by the medial pterygoid branch of the mandibular nerve, whereas the lateral is supplied by the lateral pterygoid nerve from the same nerve. (See text for function of each of these muscles.)

The mandible is depressed and the mouth is thereby opened by the lateral pterygoid muscles, which are assisted by the digastric mylohyoid and the geniohyoid muscles. Elevation of the mandible to close the mouth is accomplished by the masseter, medial pterygoid, and temporalis muscles. Protrusion of the mandible is effected by the simultaneous action of the lateral pterygoid muscles of both sides and by the synergistic action of the closing muscles. The mandible is retracted by the action of the posterior fibers of the temporalis, whereas lateral displacement is achieved by the action of the opposite lateral pterygoid muscle.

Clinical Considerations

The most common forms of TMD are most usefully divided following the RDC/TMD approach (1) into three major groups, depending on the presumed site of pathophysiology: Group I is disorders of the muscles of mastication [commonly referred to as *myofascial pain dysfunction* (MPD)] and which may or may not be associated with limitations in vertical range of mandibular motion; group II is ID of the contents of the joint space, commonly further classified depending on whether the articular disk reduces (returns to a functional position) after mandibular opening and excursions, and whether ID conditions are associated with limitations in ability to open or close the jaws (so-called closed-locking conditions of the mandible), the latter condition occurs with a low prevalence as data from our own population-based studies show and as confirmed by studies of clinical populations in Sweden, using the RDC/TMD (11); group III represents degenerative joint disorders (commonly labeled DJD) and other changes of the condyle associated with arthralgia of the TMJ (painful TMJ), a fairly prevalent condition among TMD clinic cases, degenerative changes consistent with diagnoses of TMJ arthritis and arthroses, which occur with low prevalences of less than 5% when RDC/TMD criteria are applied, or both conditions. In addition, other clinical conditions diagnosed as subtypes of TMD, but occurring rarely, include pain subsequent to mandibular or TMJ fractures, infections, and tumors of the joint.

The following discussion presents the etiology, clinical signs and symptoms, diagnosis, and treatment for MPD, ID, and DJD. The last category is included for completeness, but this far-ranging and much less prevalent miscellaneous category is discussed in less detail than the other groups.

Disorders of the Muscles of Mastication (III-3)

Myofascial pain (MPD) is a common pain complaint. It is generally chronic and the mechanisms associated with the etiology of the condition are poorly understood. No specific pathophysiologic process has been identified either peripherally or centrally and, at present, MPD is seen as a nonspecific pain condition of the muscular structures of the face, neck, and back. In severe cases, dysfunction occurs along with pain. The diagnosis of MPD is usually restricted to cases in which no underlying organic pathology can be detected and in cases of trauma when pain and muscle tenderness persist after normal healing. MPD is a common form of chronic musculoskeletal pain and accounts for significant treatment seeking, but only modest progress has been made in furthering our knowledge of the pathophysiology, etiology, or definitive treatment for the condition. Patients with MPD usually present with complaints of static facial pain that increases during or after jaw function. Stress and tension can also trigger episodes as can physical activities that strain the muscles of mastication. Mandibular opening may be limited because of muscle tightness. Frequently, pain is referred to adjacent sites including the dentition and the TMJ.

Etiology and Pathophysiology. The etiology of disorders of the muscles of mastication (MPD) has been the subject of much controversy, in part because several tissues are involved, and because separation of physical, behavioral, habitual, traumatic, and psychophysiologic factors is difficult. The following list includes the more common etiologic factors thought to be associated with the onset of MPD symptoms:

- Psychophysiologic factors (stress, tension, depression), traumatic dental occlusion (premature contact of teeth)
- Malalignment of the jaws (upper or lower jaw in a forward or retruded position)
- Incorrect position of the internal components of the joint space, resulting in muscular fatigue (displacement of the meniscus)
- Incorrect position of the joint in the fossa
- Excessive vertical spacing between the maxilla and mandible
- Habitual parafunction of the jaws (clenching and grinding of the teeth, fingernail biting, jaw posturing)
- Muscle splinting and posturing to limit movement of injured or inflamed joint
- Central deregulation of muscle activity

In some cases, however, the connection between the proposed cause and confirmation through controlled research findings are lacking. Peripheral and central theories of etiology compete to explain the pain and dysfunction of the muscles of mastication and other TMD categories. Hypotheses of peripheral pathophysiologic processes focus on the *occlusion* (i.e., how the teeth and jaws function in relation to each other) and on pathologic muscle function, arising mostly from hyperactivity. The extent to which malocclusion and malposition of the jaws play a role in the evolution of muscle dysfunction is unproved. Although a few studies indicated a causative role for dental malocclusion (12), several others showed no relationship between occlusion and MPD or the broader category of TMD (13,14 and 15). One study compared two sets of patients with malocclusion: One-half received orthodontic treatment, whereas the others were untreated (16). A 10-year follow-up failed to identify a difference in the incidence of TMD in either group, suggesting that malocclusion does not predispose to TMD and also that orthodontic treatment neither protects nor increases the risk of TMD, as suggested by some investigators and clinicians. In fact, the strikingly high prevalence of TMD in young women and the reduction in symptoms with age appear to argue against a major mechanical jaw position defect as the primary cause in the development of TMD (14,15), especially because malocclusion is equally common in both genders. Studies of the role of occlusions in all forms of TMD are technically complex; further studies might identify a relationship between occlusion and TMD in general, but at present one must proceed carefully in suggesting that malocclusion is a major causative factor (17).

Central Hypotheses. Central etiologic hypotheses for TMD give preeminence to psychosocial and psychophysiologic factors that burden the patient excessively and result in abnormal use of the muscles of mastication, as seen in excessive jaw clenching and tooth grinding (bruxism) (18). The presence of pain behaviors, stress responses, and other psychophysiologic factors appears to be better documented and investigated than other psychological factors such as overt psychopathology or clear-cut personality disorders. In general, studies suggest that, whereas the level of psychopathology is no greater in patients than in controls, MPD patients appear to respond less adequately to stressful stimuli than others (19). Also those with MPD have a greater tendency to contract the muscles of mastication and engage in parafunctional mandibular habits (e.g., clenching and bruxism) in response to stressful stimuli.

Many features of MPD are similar to overuse injuries seen in other soft tissues of the body, and several studies confirm that those with MPD have a greater frequency of tooth contact and clenching than those in control populations. Although the incidence of nocturnal bruxism has been investigated and found to be greater in MPD and ID cases (20,21), other studies have also confirmed an increased frequency of tooth contact during awake periods in some patients (22).

The primary factor associated with an increased rate of bruxism and clenching is observable stress leading to maladaptive and behavioral change. Contrary to widespread opinion, little evidence exists to link increased rates of jaw parafunction (bruxism and clenching) with malocclusion (tooth and jaw relationships) or traumatic occlusion (dental bite) (23,24 and 25).

Symptoms and Signs. The signs and symptoms of TMD depend to a degree on whether the muscles or joints are primarily affected. As with musculoskeletal disorders of other regions, however, a significant overlap in clinical findings and involvement of several structures frequently results in patients presenting with both joint and muscle symptoms. The major findings that occur in all forms of TMD are presented:

- Unilateral or bilateral pain in the ear, TMJ, side of face, temples, mandible, and preauricular region
- Report of limited mouth opening (less than 40 mm)
- Report of deviation of jaw laterally during opening
- Facial pain while chewing
- Clicking of the joint with function
- Report of periodic or continuous locking during attempted function
- Tinnitus or other vague ear symptoms
- Sensation of a change in the bite
- Recurrent headache with increase in pain on awaking and with stress
- Report of nocturnal clenching or bruxism
- Crepitus in joint during function
- Spasticity in the muscles of mastication with prolonged chewing
- Diffuse jaw pain in the presence of no dental pathology
- Associated complaint of neck pain and stiffness
- Swelling in the preauricular region
- Difficulty in chewing
- Rapid development of an open bite with loss of contact of the anterior maxillary and mandibular teeth
- Report of recent change in occlusion (bite)

Certain symptoms predominate in muscle disorders of the facial region, whereas others are primarily associated with IDs or degenerative changes of the joint. Later discussion attempts to separate the differences for each diagnosis.

A triad of symptoms (i.e., muscle pain, joint sounds, and limitation in jaw opening), uncomplicated by degenerative or inflammatory changes in the joint itself, makes up the most commonly encountered chronic orofacial pain syndrome. The term MPD has been given to this uncomplicated myogenic pain syndrome. Of those who seek treatment for MPD, women predominate over men by a ratio greater than 5:1. The mean age of onset for pain is the third decade of life (3,26).

Pain. Pain primarily arising from muscle is usually of moderate intensity and frequently bilateral. The pain is described as a persistent dull ache, often with a boring or gnawing quality. The regions of the masseter, temporalis, and preauricular areas are most often involved. The pain usually responds to mild analgesics such as aspirin, nonsteroidal antiinflammatory drugs, or acetaminophen. With progressive involvement the muscle pain becomes more severe and is associated with muscle trismus that fails to respond to nonnarcotic analgesics.

Adjacent sites of the head and neck are prone to referral of pain complaints that are often vague and diffuse (27). Patients frequently report deep ear pain and pain radiating throughout the maxilla and mandible. In persistent cases, patients typically seek diagnostic and treatment assistance from dentists and otolaryngologists, ascribing their symptoms to dental infection or middle ear pathology.

Pain is spontaneous and persistent, but remissions of varying duration do occur. Pain can frequently be elicited by palpation of the muscles of mastication but the clinical significance of pain elicited by palpation is not completely understood.

Changes in Jaw Function. Whether primarily of muscle or joint origin, changes in jaw function are a common occurrence. Reduction in mandibular opening can result from muscle spasm and fatigue, but can also occur in the presence of a displacement of the joint meniscus sometimes associated with inflammation of the joint contents. Inability to open the jaw can range from mild restriction of a few millimeters to total inability to separate the teeth.

Joint Sounds. MPD is frequently associated with joint sounds, most typically clicking of the joint with function. The true clinical significance of joint sounds is not well understood and, because joint sounds occur frequently in the general population, for this group of MPD patients such joints sounds are not viewed as particularly contributory (8,28). In some patients the clicking indicates the presence of both a muscle and joint disorder, but all clicking within the TMJ does not come from a displacement of the meniscus.

Clenching and Jaw Parafunction. If questioned, most patients with MPD and ID disorders report an increased incidence of waking or nocturnal bruxism (gnashing) or clenching of the teeth. When first questioned, patients might initially deny such activities but, after instructed to monitor the actions of their orofacial musculature, most report some level of parafunction. Other oral habits, including nail biting, frequent gum chewing, and cheek biting are contributing factors that require assessment when a diagnosis of TMD is suspected (29,30 and 31).

Behavioral and Psychological Factors. Most of those presenting with symptoms of both MPD and ID of longer than 1 month's duration experience an increase in stress or other adverse emotional reactions (29,30,31,32,33 and 34). They can report changes in sleep patterns, fatigue, and other signs of psychophysiologic dysfunction. Almost all studies consistently indicate that behavioral, emotional, and psychosocial issues are important contributing components in MPD and are frequently present in patients diagnosed with ID as well. The most frequently reported psychological concomitants of MPD are anxiety, depression, decreased interest or ability to cope with work and family responsibilities, and related illness and pain behaviors, including increased medical and dental treatment-seeking activities.

Hormonal Factors in Temporomandibular Disorders and Myofascial Pain Dysfunction. TMD and MPD are significantly more prevalent in female than male subjects,

and female sex hormones have been suggested to play a role in either susceptibility or persistence of chronic musculoskeletal facial pain. A community-based study of several thousand women over 40 years of age found hormones to be a risk factor for TMD, with a 30% excess risk of developing TMD if estrogen replacement was used (35). The study also analyzed data from more than 7,000 women between the ages of 15 and 35 and found a 20% higher risk for developing TMD or MPD if oral conceptives were used.

Diagnosis. Because TMDs frequently affect both the muscles and joint, clinical findings often overlap and make a firm diagnosis difficult. Correct diagnosis is most often based on history and clinical findings and is frequently assisted by the results of radiographic examinations. Less frequently, laboratory tests are needed. In complex cases special procedures such as arthrography and computed tomographic (CT) scans are required. Frequently, pathobiological changes (e.g., muscle or joint inflammation) and psychological distress (e.g., stress responses) factors must be identified and managed if all aspects of the patient's symptoms are to be treated successfully.

Clinical Findings. The following list presents the major clinical findings common in MPD:

- Spontaneous report of pain, usually not at the joint, but described as muscle ache, tenderness, or tired jaw; muscle tenderness with palpation (masseter, temporalis, lateral pterygoid, digastric, sternomastoid, and neck muscles)
- Muscle trigger points with pain referred to other sites
- Muscle pain with function (pain with prolonged contraction or stretching of the muscles)
- Deviation of the mandible or an asymmetric pattern of jaw movement during opening (deviation can be corrected at full opening or can remain)
- Restricted opening (restriction can be minor or moderate; less than 40 mm of opening considered restricted)
- Joint clicking during opening, closing, or both
- Percussion tenderness in several teeth (secondary to prolonged clenching or bruxism)
- Elevation of electromyographic levels (not a consistent finding but sometimes present)
- Pain reduction or elimination with ice or cooling spray to the affected muscles
- Pain elimination with local anesthetic infiltration of the affected muscle
- Evidence of tooth wear from clenching and bruxism (similar patterns can be seen without pain)
- Recent history of contributing behavioral factors (including stress, tension, anxiety), often stemming from psychosocial areas, such as family, work, or school

Several clinical findings and symptoms are usually encountered simultaneously and occur in both muscle and joint disorders. Fractures and degenerative changes of the joint can produce many secondary changes that are easily confused with primary muscle dysfunction or IDs. Differential diagnostic considerations are presented in the final section of this chapter and summarized in Table 49-3.

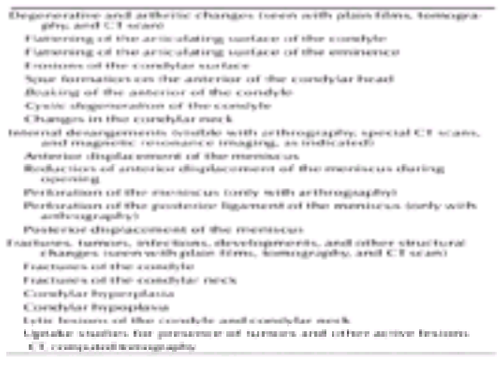

TABLE 49-3. Radiographic findings in temporomandibular disorders

Laboratory Findings. Laboratory studies for MPD are generally not required. They are usually limited to patients suspected of having orofacial symptoms secondary to generalized arthritic changes caused by such systemic disorders as rheumatoid arthritis and lupus erythematosus. Studies of chemical changes within the joint during acute and chronic TMD episodes have revealed differences between control subjects and patients with symptomatic joints. Interleukin-1 b levels in synovial fluid of the TMJ have been found to be associated with pain and hyperalgesia of the TMJ and also associated with anterior open bite, suggesting that elevated levels predict tissue damage and destruction within the joint (36).

Radiographic Findings. Radiographic findings are negative for MPD and extensive radiographic investigation is not warranted for this myogenic disorder. Radiography is potentially valuable, however, in establishing a diagnosis of arthritis and IDs. The timing and selection of radiography are important. Furthermore, the limitations of radiography should be considered in establishing a diagnosis.

Psychological and Behavioral Findings. As already mentioned, all chronic pain conditions are associated with appreciable morbidity for psychological and psychosocial dysfunction. For the majority of these patients, such negative affective and cognitive states appear to be transient and associated with the onset or exacerbation of jaw-related pain. However, studies repeatedly confirm that clinic populations dependably contain numbers of patients whose psychological disturbance meets criteria for major affective disorders, principally depression and elevated somatization. Somatization—the predisposition to identify nonspecific physical sensations as troubling symptoms and often associated with health care visits—has emerged as an important clinical consideration because it seems a reliable predictor of poor treatment outcome. In this regard, the presence of physical symptoms need not be so elevated as to meet formal (e.g., *Diagnostic and Statistical Manual*, fourth edition) criteria for a somatoform disorder; rather, an emerging clinical consensus views as problematic the presence of four to five nonspecific symptoms, such as tremors, night sweats, and heart palpitations, in the absence of confirming pathobiology. This relationship among psychological conditions of depression, anxiety, and somatization is probably not limited to TMD sufferers, but may be associated with a variety of conditions in which so-called chronic benign pain is a predominant feature, including headache, back pain, irritable bowel syndrome, and fibromyalgia.

Methods for assessing these psychological and psychosocial factors are included, for example, in the RDC/axis II assessment protocols, but a wide variety of measures have been used to support the finding that TMD clinic cases are at risk for important psychological disturbance. Some of the better-known measures for which an appreciable literature exists, even relevant to TMD, include use of the Minnesota Multiphasic Personality Inventory (MMPI), the Beck Depression Inventory, the Symptom-Checklist 90 (Revised), and the Multidimensional Pain Inventory developed by Turk and colleagues. The experienced clinician-interviewer—physician or dentist—can frequently obtain an excellent assessment of behavioral factors by the routine use of these measures, together with a structured psychosocial interview. Because family- and work-related stress can contribute significantly to the onset of symptoms, careful history-taking methods should be used to determine if psychosocial stressors, especially those related to career, family, and social factors, are important to the patient's current personal and interpersonal functioning.

Treatment. The treatment of all forms of TMD, including MPD, incorporates both general components used in treating all TMD patients and specific approaches limited to treatments applied only to particular forms of the problem. The functional nature of TMD furthermore requires that factors that might allow continued trauma to muscle and joint components be identified and eliminated. Although not always possible, therapy should first be directed toward removing causative factors, if known, to prevent continued damage and persistent symptoms (see following discussion).

Control of Causative Factors. The development of muscle pain is generally the result of overuse of the muscles of mastication, sometimes consciously. This typically occurs through the development of learned habits that allow muscle response to proceed outside of awareness. Control of muscle overuse requires several steps: counseling the patient to reduce the frequency of tooth contact caused by clenching, bruxing, and oral habits; reduction of stress through identification of behavioral factors that lead to clenching and muscle pain; and relaxation strategies or biofeedback to reduce muscle activity and produce physical relaxation (37,38).

Physiotherapy. Physiotherapy includes the use of ice packs on tender muscles, injection of muscle trigger points, passive or active stretching of the muscles of mastication, and general physical exercise to reduce the focus on excessive use of the jaw muscles (see Chapter 88 and Chapter 89). Interest has increased in the use of external energy sources such as laser, diathermy, and ultrasound in the treatment of TMD, but randomized trials have not shown significant differences in these approaches (39). Injection of trigger points has been a common treatment modality in MPD and TMD, with variable results reported in short- and long-term

outcomes. A number of preexisting nonphysical factors appear to influence the outcome of trigger point therapy including unemployment caused by pain, constant pain, and lack of relief with analgesic medications (40). Comparisons between use of dry needling, injection of sterile water, saline, and local anesthetics to treat trigger points have generally not demonstrated different results except for decreased postoperative discomfort with use of local anesthetics (41,42).

Drug Therapy. Drug therapy can include the use of skeletal muscle relaxants, sedative-hypnotics to ensure a good night's sleep, nonopioid analgesics, and opioids to relieve transient moderate to severe pain. Medications may be useful in the early stages of MPD and may be necessary to provide muscle relaxation and pain control at levels that improve patient function (43). It is essential to avoid prescribing opioids and other dependency-producing medications for long-term chronic nonmalignant pain unless all other treatment modalities have failed and the patient is enrolled in a chronic pain management program with careful monitoring of medications and regular follow-up. Diazepam is an effective muscle relaxant but shares the same risks for dependency seen in patients using opioids. Patients who have vegetative signs and symptoms of depression should be given a trial of antidepressants (44,45) (see Chapter 83, Chapter 84 and Chapter 85).

Appliances. Splints, bite guards, and habit control appliances, such as nonmandibular repositioning bite splints to alleviate jaw movement habits and reduce the frequency of nocturnal and waking clenching, have been shown to be effective. Comparisons of active versus placebo splints and splints worn for only a few minutes each day versus longer periods of use have shown little difference in treatment outcomes with placebo and brief splint use as effective as more aggressive splint therapy (46). Simple inexpensive splints that are made chair side or by the patient have been shown to provide equivalent pain reduction as more costly custom-made appliances (47). These findings and findings demonstrating nonsplint therapy as effective as splint therapy (47) raise questions about common current approaches to TMD treatment.

Occlusal Equilibration. Bite adjustment should *not* be used as the first line of treatment and is not indicated in most cases of MPD or TMD. Equilibration has been determined to be an irreversible procedure and should be avoided unless clearly indicated (3). A minor spot bite adjustment, however, can be useful in those patients in whom minor occlusal discrepancies have become a focus for parafunctional habits. Care should be exercised before initiating even small adjustments in the bite when the patient appears to be extremely focused on or obsessed with the discrepancy. In such cases behavioral evaluation should precede any irreversible treatment including bite adjustment.

Surgical Management. No surgical treatment is indicated for patients with MPD.

Psychological and Psychiatric Treatment. Studies have demonstrated a strong relationship between long-standing myofascial pain and emotional and behavioral changes (1,32,33). Some patients benefit from stress management or other forms of focused, brief counseling, whereas others justifiably require more definitive psychotherapy. It seems reasonable to assert that most TMD patients require less intensive forms of assistance in managing life stressors and psychosocial components of their problem. The patient should be given complete information regarding probable causative factors, the rationale for conservative reversible therapies, as outlined previously, and the benign noninvasive course of the problem. This often provides enough reassurance to preclude development of persistent treatment-seeking behavior.

Exacerbating conditions that provoke persistent anxiety and depression should be identified and discussed with the patient. In extreme cases, inquiry into suicidal ideation is appropriate and necessary, and consultation or referral to a mental health practitioner is often indicated, both for further psychological evaluation and cognitive-behavioral or psychodynamic psychotherapy. In general, psychological therapies that favor cognitive-behavioral approaches are more readily accepted by these often somatically focused patients. Psychophysiologic therapies that incorporate biofeedback and relaxation have proven helpful to many patients (48,49 and 50). A trend too recent to be validated with empirical data has been to consider tailoring biobehavioral therapies for specific TMD (and other chronic pain) patients based on their axis II level of psychological and psychosocial functioning and to do so cutting across their axis I or physical diagnosis (51,52). In summary, cognitive-behavioral therapies are the most commonly invoked for chronic pain patients with significant psychological and psychosocial disturbance. These cognitive-behavioral therapies emphasize relaxation and self-management strategies to alter patterns of negative thoughts and dysfunctional attitudes. This therapeutic approach incorporates education, skills acquisition, cognitive and behavioral rehearsal, and strategies for generalization and maintenance. A National Institute of Health Technology Assessment Conference (53) concluded that such approaches were usefully integrated into the treatment of chronic pain and many chapters of this text are devoted to the specific components of cognitive-behavioral therapies that can be applied across chronic pain conditions. Cognitive-behavioral therapies are the modal form of biobehavioral treatment provided by well-respected multidisciplinary pain centers.

INTERNAL DERANGEMENTS OF THE JOINT SPACE CONTENTS

Etiology and Pathophysiology

ID of the components of the joint space refer primarily to abnormalities in the functioning relations of the articular disk and the bony articular surfaces of the TMJ, articular fossa of the temporal bone, and articular surface of the condyle of the mandible (54,55). ID disorders can be initiated either by a traumatic blow to the mandible, producing relatively rapid, usually self-reversible, changes within the joint spaces, or by more slowly occurring changes produced by chronic pathologic patterns of muscle hyperactivity, restriction in condylar movement imposed by malocclusion, or, rarely, developmental defects or predisposition to derangement. Few data are available, however, to support the contention that malocclusion and ID are related causally.

In ID, the articular disk and the condylar surfaces acquire a maladaptive functional pattern that can cause the disk to be displaced in one of several directions. Sometimes, the displacement is not entirely self-correcting, provoking pain and dysfunctional patterns of jaw movement (55,56 and 57).

In general, the same role given to psychophysiologic, psychological, and psychosocial factors in the etiology of MPD that can lead to ID is also thought to apply to many ID syndromes. (See previous discussion of the role of anxiety, depression, stress, and psychosocial issues in the etiology of MPD.)

Symptoms and Signs

Pain

Pain may or may not be associated with ID. Nonpainful ID is likely to represent a nondisease adaptation phenomenon. When pain is a predominant symptom for ID patients, it is usually localized to the joint itself, but can also be referred to the preauricular area immediately in front of the joint or to the ear. Pain that occurs during function and movement is often described as sharp or shooting and of brief duration, with residual aching that can last for a considerable time. With ID, mild pain can usually be elicited by palpation of the joint.

Changes in Jaw Function

Joint pathology and IDs of the meniscus or its attachment usually affect one joint. In such cases the patient's symptoms, including pain and deviation on opening, are localized to the affected side. Deviation of the mandible from the midline as the jaw opens can vary from subtle to several millimeters. Anterior displacement of the meniscus with its self-reduction to normal position is associated with a return of the jaw to midline at full opening. More significant deviation without correction at full opening in association with severe jaw opening limitation in acute cases may suggest the presence of an anterior disk displacement without reduction.

Joint Sounds

Clicking sounds during function might indicate an ID of the meniscus, usually an anterior displacement. If the patient reports a prior pattern of clicking with cessation of clicking immediately before the onset of pain, accompanied by limited opening and deviation to the affected side with opening, a diagnosis of anterior displacement of the meniscus *without reduction* should be suspected.

Clicking alone should be used only in the most general way to assist in the determination of pathologic ID of the TMJ, because approximately 35% to 40% of adults surveyed have clicking sounds in the TMJ without other evidence of pathology (28,58). Several studies have reported a high incidence of clicking in patients presenting for TMD treatment, with approximately 35% to 40% continuing to experience clicking after pain and other signs of dysfunction have been eliminated. Such a high rate of clicking in normal populations and *cured* TMD patients suggests that clicking be used only as a secondary diagnostic criterion of TMD (3,28,59), and unless joint pain or significant physical dysfunction (catching or episodic locking) occurs, clicking should be considered an adaptive process.

Joint Pain and Swelling

The onset of actual joint pain and swelling suggests the presence either of acute inflammation, infection, or recent trauma with effusion within the joint. In such cases the changes are usually unilateral unless the inflammation is the result of immune system pathology, such as that encountered in lupus erythematosus and rheumatoid arthritis (see Chapter 27).

Rapid Changes in Dental Occlusion (Bite)

In normal adult populations the bite, or occlusion, is remarkably stable. A sudden change in the occlusion, particularly an anterior open bite with loss of contact between the anterior maxillary and mandibular teeth, indicates an aggressive change in the structures of the joint. Patients with preexisting malocclusion often report changes in their bite, but these tend to be subtle. For those with previously stable bites a sudden change in occlusion indicates the need for further clinical and radiographic evaluation.

Parafunction and Behavioral Factors

As mentioned previously, muscle hyperactivity in the form of clenching and bruxism, as well as behavioral and psychological factors, are present in patients with ID, as they are in MPD patients. Some tentative evidence has shown that patients with true joint pathology might not demonstrate maladaptive stress and related behaviors to the same extent as MPD patients, but further exploration of this distinction is necessary (60).

Diagnosis

The following major clinical findings contribute to the diagnosis of ID of the TMJ:

- Joint clicking during opening, closing, or both occurs with anterior displacement of the meniscus, with reduction of the meniscus to normal position during function
- Deviation of the mandible during opening and correction to midline at full opening (anterior displacement with reduction to normal position during opening)
- Significant deviation of the mandible to the affected side during opening without correction to midline at full opening (anterior displacement without reduction during function)
- Intermittent catching or locking necessitating manipulation of the mandible to effect full opening or closing
- Limited opening, frequently less than 30 mm
- Assisted opening of less than 40 mm
- Joint pain during function and movement
- Joint pain during palpation (mild)
- Elimination of joint click when opening and closing the mandible in a protruded (anterior) position (anterior displacement of the meniscus with reduction during function)
- Soft tissue crepitus in the joint during function (present in some IDs and with irregularities in the tissue lining of the joint)

As already noted, clinical findings for ID and MPD overlap, and the differential diagnosis can be difficult. The presence of both muscle and joint symptoms or findings usually suggests the presence of multiple TMD disorders with both muscular and joint problems. Frequently, locking of the jaws with inability to open more than 20 to 30 mm also indicates an anterior displacement of the meniscus without reduction (i.e., the anteriorly displaced meniscus cannot return to its initial position unassisted). If few muscle symptoms are present, the diagnosis of anterior displacement of the meniscus is even more probable. Another confounding factor in the diagnosis of TMD is the presence of otherwise asymptomatic clicking (anterior displacement of the meniscus with reduction) in a patient with severe myofascial pain. The presence of pain and joint sounds often leads the clinician to assume that the problem resides in the joint when symptoms are arising from muscle rather than joint dysfunction.

Laboratory Findings

Laboratory findings are of limited value for patients with ID unless concurrent local or systemic pathology affecting the joint is present. When laboratory studies for TMD are considered, they are usually limited to patients suspected of having orofacial symptoms secondary to generalized arthritic changes caused by such systemic disorders as rheumatoid arthritis and lupus erythematosus. As stated earlier, studies of chemical changes within the joint during episodes of joint pain have revealed higher levels of interleukin-1 b in synovial fluid that are associated with pain and hyperalgesia of the TMJ. Actual joint changes are also associated with these chemical findings, suggesting that elevated levels predict tissue damage and destruction within the joint (36).

Radiographic Findings

A substantial number of reports have been published regarding the value of radiographic findings and their reliability in the diagnosis of ID and degenerative disorders of the TMJ (61). Currently, radiography is of little value in determining correct condylar position, and CT scanning is the method of choice for visualizing the osseous contour of the joint and for identifying arthritic changes. Screening films such as transcranial views of the joint are of limited value, especially because they only allow assessment of the lateral aspect of the joint and are only two dimensional (61,62).

If an ID of the meniscus is suspected and previous therapy has failed to resolve symptoms, arthrography or magnetic resonance imaging studies of the joint to evaluate the disk and its attachment should be considered. Because arthrography is an invasive procedure with potential complications, it should be reserved for cases that are being considered for surgical intervention in which perforation of the disk is suspected. Many clinical centers have selected magnetic resonance imaging as the major imaging modality for detection of IDs of the TMJ (63,64). Magnetic resonance imaging is considerably less invasive than arthrography and provides dynamic images of the joint and capsule without artificially altering joint dynamics. Table 49-3 presents major findings of both standard and special radiography of the joint.

Certain considerations should be noted regarding radiography of the joint. Several methods of treatment for ID and DJDs are based on the concept that the joint is displaced in the fossa and requires repositioning with either surgical, orthodontic, or dental procedures. Clinicians who use these treatments use radiography to determine joint position, but studies conducted in several centers suggest that most radiographic techniques are unreliable in identifying the true position of the joint in the fossa. Therefore, radiography should be used with caution in suggesting either diagnosis or choice of therapy for ID (61,62,64,65). Arthrography, CT scans, and magnetic resonance imaging can provide such information, but the true role of disk displacement as a causative factor in chronic TMD pain is unresolved (66,67,68,69,70 and 71).

Psychological and Behavioral Findings

The psychological and behavioral factors for ID closely parallel those observed with MPD patients except, as previously noted, some reports indicate that ID patients might be better adjusted psychologically and be less maladaptive to stressful situations. The evidence is conflicting on this view and it may simply be that the ID group includes a smaller percentage of patients who exhibit pain or illness behaviors as compared with the percentage for those in the MPD and other pain groups, such as patients with chronic back pain.

Treatment

As with MPD, treatment should first seek to control causative factors that can be clearly identified and should proceed conservatively.

Control of Causative Factors

Avoidance of initial and repeated overt joint trauma such as a motor vehicle accident, sports injury, assault, or prolonged dental or medical treatment is important. Once joint function has been compromised from prior trauma or low-grade repetitive injury, the joint should be protected from additional injury during sports or medical

or dental treatment. Also, reduction in clenching and parafunctional habits (the same factors present in myofascial disorders) is essential. Posturing habits of the mandible, tensing the jaw either in an anterior or posterior position, and mechanical restriction of the mandible in a posterior position or habitual popping of the joint must be controlled to minimize repeated injury.

Nonsurgical Management

Nonsurgical management should include jaw habit control and home-based physiotherapy such as ice packs and passive opening exercises. If the disk is displaced and opening is restricted, it can sometimes be repositioned with gentle manipulation of the mandible while the joint is distracted from the fossa by using a *few* pounds of pressure. Nonsteroidal antiinflammatory drugs (Table 49-4) are frequently helpful in reducing joint symptoms.

Drug	Suggested dose
Aspirin	650–1,000 mg every 4–6 hr
Ibuprofen	600–800 mg every 6 hr
Naproxen	250–375 mg every 6–8 hr
Oxaprozin	600 mg every 12–24 hr
Sulindac	200 mg every 12 hr
Piroxicam	20 mg every 24 hr
Prednisone	10–30 mg every 24 hr

TABLE 49-4. Nonsteroidal antiinflammatory drugs used to treat internal derangements

Muscle relaxants are of value if the ID is accompanied by MPD (see previous discussion). Analgesics are frequently required and those recommended for myofascial pain are usually acceptable, except during episodes of moderate to severe pain when opioids may be required.

Splints and bite guards that are nonrepositioning and are designed to reduce habitual clenching and parafunction of the mandible are helpful. A repositioning splint to recapture the disk and prevent repeated disk displacement may be required if the patient repeatedly experiences mandibular locking. Repositioning splints might not improve joint function permanently and should be used conservatively, because their use can lead to irreversible changes in the joint and bite (5,9,24,72,73).

Surgical Therapy

Surgical therapy, including disk repositioning and plication of the ligament in cases in which the disk remains displaced and pain continues, is indicated (74,75). The most common and successful surgical procedure is arthroscopic rather than an open joint approach. In more chronic cases disk removal might be required, especially if the disk is perforated or extensively damaged (76). Some surgeons advocate implantation of an artificial meniscus, but that procedure has met with frequent complications and is rarely advocated (77). Rejection of implant material has been widely reported (78). Overall, the long-term prognosis for TMJ surgery is unclear and currently it should be advised with great caution (79).

Psychological and Psychiatric Treatment

If required, psychological and psychiatric treatment is carried out (as described previously; see Disorders of the Muscles of Mastication). Patients with organic disease of the TMJ may also have concurrent psychological or behavioral problems that reduce tolerance and coping or even generate additional symptoms. Considering any patient with chronic pain on both a physical and behavioral axis is important in planning and providing therapy.

DEGENERATIVE JOINT DISEASE OF THE CONDYLE AND OTHER OSSEOUS COMPONENTS OF THE TEMPOROMANDIBULAR JOINT (III-4,5)

Etiology

Evidence has shown that in some cases IDs appear to increase the risk for degenerative changes of the condyle and bony surface of the fossa, suggesting that the meniscus serves a protective role for the articulating osseous components of the joint (64,66,67). The relationship between arthritic TMD and coexisting systemic metabolic or autoimmune forms of arthritis seems to be clearly identifiable as a special causative factor in DJD. In specific cases, DJD can be clearly associated with elderly patients, in whom the few principal degenerative diseases are osteoarthritis and rheumatoid disease. The following etiologic factors are seen in DJD:

- Fractures of the condyle, condylar neck, and fossa
- Degenerative changes (secondary to overt jaw trauma or blunt impact, aging, adaptive remodeling)
- Nonreducing ID of the meniscus
- Autoimmune arthritis (rheumatoid arthritis, lupus erythematosus)
- Idiopathic condyliasis (condylar resorption)

Emotional and behavioral factors have been implicated as potential causative factors. According to some, prolonged parafunctional misuse of the muscles of mastication can result in pathologic remodeling of the condylar head (55). The proposed mechanism suggests that ID of the meniscus associated with excessive parafunction allows destructive forces to be applied directly to the osseous surface of the condyle, leading to condylar remodeling. The evidence for so-called pathologic remodeling under these conditions, however, is largely speculative.

Symptoms and Signs

Pain

The location and pattern of clinical pain symptoms of DJD closely resemble those reported with IDs of the joint. Pain is typically localized to the joint, ear, and preauricular area, with minimal radiation or referral to the surrounding regions. Painful symptoms include stiffness of the joint, which tends to develop gradually. Acute onset of pain is rare unless associated with trauma superimposed on underlying disease. Pain is generally dull in character and tends to be mild in intensity. Pain occurs during function and can be severe, and joint palpation results in localized joint pain.

Changes in Jaw Function

Jaw opening can be unimpaired or only slightly affected, yet major restriction in ability to open the jaw can be found when severe inflammation of the joint is present. If only one side is affected, deviation in the opening pattern to the affected side without correction (i.e., return to midline) at full opening can be observed. If the degenerative process triggers ankylosis of the condyle, jaw mobility is dramatically restricted and surgical intervention may be required.

Joint Sounds

The onset of crepitus, as opposed to discrete clicking and popping joint sounds, is a firm sign of degenerative arthritic changes in the articulating osseous surfaces of the joint and indicates loss or damage to the soft tissue articulating components, such as the meniscus. A change from soft tissue crepitus to hard bony grating signals a progressive degenerative process. Crepitus, however, is not invariably present in every patient.

Emotional and Behavioral Changes

Psychological factors cited for MPD can also present in this group of patients, but the clinical impression and some research findings suggest that those in the DJD group have less psychological disturbance than those in groups already discussed.

Diagnosis

Clinical Findings

Clinical findings associated with degenerative changes of the TMJ are presented:

- Joint pain during function
- Joint pain during palpation of the joint
- Joint crepitus during function (soft or hard tissue crepitus)
- Limited opening (major restriction with severe inflammation of the joint and ankylosis)
- Deviation to the affected side during opening (deviation without correction at full opening)
- Development of an anterior open bite (caused by posterior and superior shift of the mandible)
- Presence or absence of muscle pain and spasm
- Pain, swelling, or both in other joints indicative of systemic disease

Especially in the elderly, symptoms tend to be aggravated by cold and general poor health. Usually, the patient with rheumatoid disease is easily recognizable, because this generalized condition first presents itself in the TMJ only rarely. By contrast, osteoarthrosis associated with ID is probably of a secondary type, occurring as a result of altered disk anatomy and function. This secondary type of osteoarthrosis occurs in a localized area, generally in the absence of systemic involvement. Therefore, diagnosis in such a case would be based on local findings of the presence of joint pain, crepitus, restricted joint movement, and radiographic findings.

Laboratory Findings

Detailed discussion of all laboratory tests and their significance in systemic joint pathology are beyond the scope of this discussion. Those laboratory tests most frequently useful in the diagnosis of DJD are sedimentation rate, rheumatoid factor, and antinuclear antibody (they are helpful in lupus erythematosus and other immune system dysfunctions). Laboratory studies to identify gout or psoriatic arthritis are of infrequent value in DJD unless other findings indicate that disease. Newer laboratory studies are under investigation using synovial fluid aspirated from the joint, and although differences are seen in inflammatory mediators in healthy and TMJ patients, the value of these findings in the routine management of TMDs has not been established.

Radiographic Findings

Given the caveats concerning radiographic interpretation of the TMJ (see Internal Derangement of the Joint Space Contents, previously in this chapter), the diagnosis of DJD is more dependably associated with radiographic findings than are the other categories of temporomandibular disturbance. CT and newer imaging methods reveal osseous changes in both the condylar contour and, less frequently, in the articular cortical plate (66,67,80). These changes can appear as loss of continuity of the cortical area and as erosion of the bony surfaces, resulting in marked degenerative flattening of the condyle in particular and osteophyte formation on the peripheral joint surfaces. Although changes can occur with both osteoarthritic and rheumatoid disease, condylar destruction is more severe in cases of rheumatoid involvement.

Treatment

Because the specific nature of degenerative arthritic changes is not well understood, treatment directed toward causative factors is generally not available except for those patients with autoimmune forms of arthritis in whom antiinflammatory medications might slow or stop the damage caused by the inflammatory process. The extent to which the degenerative process can be controlled is unknown.

Nonsurgical Management

Nonsurgical treatment can include the use of physiotherapy, muscle relaxants, and analgesics, as for myofascial pain. Antiinflammatory medications can be helpful, as for IDs, except higher dosages are often required. Splints can be used as for myofascial pain, but not in the same way as for IDs. It is not thought that repositioning appliances are of value.

Surgical Therapy

Some patients with severe arthritis may benefit from surgical management of the joint including arthrocentesis or arthroscopy to remove osteophytes and irregularities caused by the degenerative process (74,75,79). In severe cases the placement of a prosthetic joint may be indicated. If the degenerative process has produced a severe open bite or malocclusion, orthognathic surgery can also be necessary to restore mandibular function.

FRACTURES, INFECTIONS, AND TUMORS OF THE JOINT

It is well beyond the scope of this chapter to present the etiologic and symptomatic picture, diagnosis, and treatment of such varying clinical conditions as jaw fracture and neoplastic or metastatic diseases of the TMJ. A full discussion of these conditions has been presented by Okeson (81).

Etiology

Except for traumatic or disease-related fractures of the condyle, condylar neck, or fossa (82), infections and tumors of the joint occur rarely, have not been systematically studied, and are managed on a case-by-case basis. Proposed causative factors for this category of TMD include gonococcal arthritis, streptococcal arthritis, local benign and malignant tumors, metastatic cancer, and trauma. Whiplash trauma to the TMJ has become an increasingly popular etiology that is advocated as the cause for chronic headache and facial pain after rear-end motor vehicle accidents, but analysis of data related to the role of whiplash in TMJ pain and dysfunction has failed to demonstrate that soft tissue trauma to the joint during vehicle collisions is a high risk factor (83).

Symptoms and Signs

Clinical and laboratory findings can vary greatly across these different disease categories. A number of endocrine and hormonal assays are helpful in monitoring the patient with a history of secreting tumors that can metastasize to the joint. The occurrence of such metastases is infrequent, and such tests are usually unwarranted. Nevertheless, these studies deserve consideration in patients with a history of malignancy. Description of atypical symptoms (e.g., numbness, tingling, dysesthesia) and unresponsiveness to appropriate biomedical and biobehavioral treatments coupled with increasing physical disability suggests the need for additional evaluation including imaging studies. The following are clinical findings relevant to infections and neoplasms of the joint and to trauma and fractures of the joint region.

- Infections and neoplasms of the joint: joint pain at rest and during function; joint pain during palpation; joint swelling; limited opening (can be severe); deviation of the mandible during opening; unilateral posterior open bite; joint pain during contact of posterior teeth; spontaneous fracture of the condyle or condylar neck; neurologic and neurosensory changes on the affected side (e.g., paresthesia, anesthesia, and muscle wasting secondary to damage to cranial nerves); drainage from preauricular region; fever (present in infection); inability to retrude mandible; mandible displaced to unaffected side
- Trauma and fractures of the joint region: sudden development of cross-bite; deviation of mandible to affected side; limited opening; joint swelling; sudden development of bite changes or open bite

Treatment

Treatment for this group of pain-producing TMJ problems is, of course, as diverse as the conditions themselves and is clearly beyond our purposes here. It should be appreciated that many non-TMD neoplastic conditions can affect jaw function and mimic TMD (e.g., nasopharyngeal tumor, parotid neoplasm, developmental cysts). Obviously, the potential risk from neoplasms and infections requires careful monitoring and aggressive treatment. High-dosage antibiotic therapy with penicillin or other appropriate antibiotics is essential, and establishment of drainage through incision is required if the infection remains uncontrolled. The presence of infection requires culturing of the joint fluid, if possible.

Surgical management of tumors is generally required unless they have metastasized from other sites. Radiotherapy is usually attempted in such cases for palliation and local control. Fractures of the condyle and condylar neck can require fixation, depending on the degree of displacement of the components.

FINAL COMMENT ON DIAGNOSIS AND TREATMENT

Establishing the most appropriate diagnosis is complicated in TMD because a significant percentage of patients have both muscle and joint involvement. Table 49-5 identifies factors involved in its differential diagnosis.

Finding	Myofascial pain	Internal derangement	Degenerative diseases
Limited opening	±	+	+
Deviation during opening	+	+	+
Joint pain	–	+	+
Clicking	±	±	±
Crepitus	–	–	+
Joint swelling	–	–	±
Muscle tenderness	+	±	±
Bite changes	–	–	±
Joint locking	–	+	–
Clenching	+	±	±
Pain	+	±	+

+, usually present; –, usually absent; ±, variable

TABLE 49-5. Differential diagnosis of temporomandibular disorders

The treatment of TMD entails many of the same risks and complications encountered in the management of other forms of musculoskeletal disorders and arthritis (84). Drug side effects include gastrointestinal symptoms, allergies, and blood dyscrasias. Those agents used to control pain, muscle spasm, anxiety, and behavioral changes can lead to chemical or psychological dependence or both. The use of oral appliances can produce changes in the bite and alignment of the jaws. Surgery can lead to open bite and skeletal changes in addition to the usual risks involved with general anesthesia and surgery.

Because the results of most studies clearly suggest that managing the overwhelming majority of TMDs with conservative and reversible therapies offers an excellent chance for success, the clinician is encouraged to limit the use of invasive procedures to those patients who have failed conservative treatment and in whom behavioral factors appear to be of limited contributing value (2,5).

The role of stress and psychological issues has been so well documented for the major categories of TMD discussed here that an important therapeutic focus should be to control those issues and their resultant parafunctional habits and muscle dysfunction (3,37,52,53). Failure to do so can contribute to the development of sufferers who manifest resistant chronic pain and illness behaviors.

*This section on anatomy and physiology was contributed by John J. Bonica.

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CHAPTER 50

Pain of Dental and Intraoral Origin

Margaret R. Byers and Jeffrey A. Burgess

Overwhelming clinical evidence suggests that the most commonly experienced orofacial pain is toothache (1,2). During the past several decades there has been progress in many areas throughout the world in controlling tooth decay through fluoridation programs, the educational efforts of the World Health Organization, and increased access to dental services. However, poverty and social inequalities in both developed and undeveloped countries, lack of health care, neglect, and other social problems have allowed dental caries and other causes of oral and dental pain to continue to be major health problems.

Toothache varies considerably in expression and as a result is easily confused with other pains that occur in the orofacial region (3,4). Dental pain can originate from nociceptive endings inside teeth (activated by stimuli to dentin or pulp) for which dental caries, pulpitis, and dentin exposure are the principal causative agents, or from periodontal tissues, especially periapical ligament around the tooth root apex. Intraoral pain may also arise in the mucosal tissues surrounding the teeth and covering the hard and soft tissues of the oral cavity. Pain of mucosal origin can originate as a consequence of trauma (e.g., tooth eruption) or can represent the first sign of local infection or systemic diseases as varied as measles, herpes simplex, immune system dysfunction, and malignancy. Although much of the sensory and autonomic nerve activity in oral mucosa and dental tissues is similar to that found elsewhere, oral mucosa has special functions (detection of material entering the mouth; reflexes related to mastication, swallowing, or speech), as do teeth (dentin production, enamel support, regulation of fluid dynamics in a noncompliant chamber, production of reparative dentin during wound healing) that affect the specific types of sensory innervation and the pain characteristics of these tissues.

In this chapter we present a survey of the odontogenic and mucosal conditions frequently associated with orofacial pain in two major sections: Basic Considerations consists of summaries of the normal neurobiology, pathologic reactions, and plasticity of sensory nerves in oral mucosa, teeth, and periodontium, as well as far-reaching changes in trigeminal ganglion and the central nervous system (CNS). The reader is referred to reviews that provide much more information about these topics (5,6,7,8,9,10,11,12,13 and 14). The section Clinical Considerations consists of a discussion of pain of odontogenic and of mucosal origins. Where relevant, we have used the terminology consistent with the diagnostic nosology prepared by the International Association for the Study of Pain (IASP) (15). For the most frequently encountered pains of odontogenic and mucosal origin we present the etiology, clinical signs and symptoms, diagnosis, and therapeutic procedures. Other reviews of orofacial pain mechanisms and their relationship to clinical diagnosis and pain provide additional information and are highly recommended (2,16,17,18,19,20 and 21). In the concluding section of this chapter, we summarize key issues in current research and clinical management of dental and oral pain. A detailed discussion of the management of oral mucositis pain can be found in Chapter 38.

BASIC CONSIDERATIONS

Pain Mechanisms in Oral Mucosa and Dental Tissues

An overview of the nerve supply of the head, distribution of the trigeminal nerve, general considerations of pain in the head, and the sensory innervation of teeth and oral mucosa via the maxillary and mandibular nerves has already been given in Chapter 46 and the basic pain mechanisms for trigeminal systems are discussed in Chapter 3, Chapter 4 and Chapter 5. Here the sensory and autonomic nerve supply to these regions is depicted in more detail (Fig. 50-1, Fig. 50-2 and Fig. 50-3). As discussed in Chapter 3, all tissues have specific A-b, A-d, and C nociceptive fibers that respond to acute injury or threat of injury, as well as A-d and C polymodal receptors and A-d and C silent nociceptors, and these also occur in teeth and oral mucosa (14,22,23). The cervical sympathetic ganglia supply vasomotor innervation, and parasympathetic innervation comes from the sphenopalatine ganglion, and probably also the otic ganglion. Smaller parasympathetic ganglia also exist (e.g., in the tongue) (24) that contribute to innervation of orofacial tissues and to some pain conditions (25). In the oral mucosa and periodontium, the vasoconstriction functions of sympathetic fibers are opposed by sensory neuropeptides and by parasympathetic agents, but pulpal vasoregulation depends only on sympathetic vasoconstriction and sensory neuropeptide vasodilation (10,11).

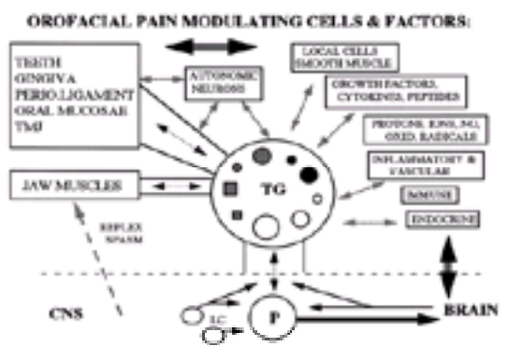

Figure 50-1. Schematic diagram showing the cells and factors that affect the flow of information in sensory nerves from tissues through the trigeminal ganglion (TG) and into the CNS. Modulating actions (*gray arrows*) that affect pain perceptions can occur at the nerve endings, along the nerve, in the TG, and at the central terminals. The intraneural dotted arrows are bidirectional because conduction and axonal transport can be bidirectional and because efferent release of neural factors affects the peripheral modulators and tissues. Neuronal types that affect pain are indicated in the TG by small circles for C fibers, medium size for A-d, and large for A-b. They are represented as black filled for nociceptive-specific; gray circles for polymodal; gray squares for *silent* nociceptors; and open circles for mechanoreceptive, thermoreceptive, or both kinds of neurons that have altered cytochemistry and activity in inflamed tissue. Whether a projection neuron (P) in the brainstem sends signals to the brain depends on the rate and intensity and combination of the incoming signals, and those depend on the variety of peripheral interactions and the modulations in the ganglion and dorsal horn. Each P neuron is modulated by local circuit (LC) neurons and by descending input from supraspinal centers, both of which can also affect the afferent presynaptic endings. Nociception-induced reflex spasms in jaw muscles (*dashed-line arrow*) may exacerbate pain conditions, possibly causing additional injury to the muscle and tendons, generating additional nociceptive signals. The endocrine and immune systems have additional important effects on the brain (*large arrow*) in addition to their peripheral actions. The peripheral modulation system has different properties in normal tissues compared with inflamed tissues, and both of those differ from neuropathic damage to the nerves.

Figure 50-1 depicts the main cellular interactions that affect the flow of afferent nociceptive information into the CNS. Information is conveyed by action potentials in milliseconds to seconds, primarily in the afferent direction through the ganglion to the CNS, but under some conditions, such as axon reflex or ganglion signal generation, the action potentials move out to the tissues where they cause the release of neurochemical agents such as substance P. In addition, a much slower system (many hours) carries molecular signals such as nerve growth factor via retrograde axonal transport from the peripheral endings to the cell body in the ganglion and delivers neuropeptides via anterograde transport to tissues for vasoregulatory and homeostatic functions. In some cases the transported signals move from the

peripheral endings all the way to the central endings (26) and into subsequent neurons (27), and also bidirectional transport occurs between the central endings and sensory cell body. For further details, see Chapter 3.

Depending on the rate of action potentials and the composition of the retrogradely transported material, the sensory neuronal cell body and neurons in trigeminal brainstem nuclei *know* whether peripheral tissues are normal, stressed, acutely injured, inflamed, necrotic, or healing. For example, nociceptor functions (including those of teeth and oral mucosa) are affected by (a) factors released from the damaged tissue such as protons, adenosine triphosphate, kinins, serotonin, prostaglandins, neuropeptides; (b) growth factors from injured local cells such as nerve growth factor; (c) inducible enzymes such as nitric oxide synthase and cyclooxygenase 2; (d) vascular factors such as platelet-derived growth factor and nerve growth factor; (e) neural agents such as substance P, calcitonin gene-related peptide, neurokinin A, excitatory amino acids, noradrenalin; and (f) cytokines or other signals from immune cells such as interleukin-1b, interleukin-6, interleukin-8, tumor necrosis factor-a, nerve growth factor, and opioid peptides (see Fig. 50-1). These agents interact with specific molecular receptors to initiate altered neuronal expression of membrane receptors, growth factors, neuropeptides, enzymes, and ion channels, as well as altered activity levels for those molecules (28,29,30 and 31). An additional set of agents such as galanin, neuropeptide Y, somatostatin, and opioid peptides appear to protect the nociceptive neurons from excessive reactions to neuroinflammatory conditions (32).

Once a tissue is injured and becomes inflamed, the complex cascade of cellular interactions in the periphery causes sensitization of the acute nociceptive physiology and of the polymodal receptors, specific efferent secretion of neuropeptides by sensory endings to cause neurogenic inflammation, altered sympathetic activity, altered tissue chemistry and signals (e.g., nerve growth factor, cytokines, inflammatory mediators), addition of some A-b fibers to the response, and activation of silent nociceptors. These features of peripheral neuroplasticity related to pain are discussed in greater detail in Chapter 3, and their effects on central neural function and pain perception are discussed in Chapter 4 and Chapter 5.

Given the extensive alteration of nociceptive functions and central mechanisms in response to inflammation, it should not be surprising that analgesics that are effective for inhibiting a healthy nerve may not work if inflammation or neuropathic injury is present, as appears to be the case for difficult anesthesia of inflamed teeth (*hot tooth* syndrome). Now that the mechanisms driving alteration of sensory phenotypes are becoming known, a major effort has been undertaken to develop new drugs to inhibit their inflammation-driven or neuropathic conditions, as suggested in analyses of tetrodotoxin-resistant sodium channels (33,34) and discussed further in Chapter 3. A number of clinical pain studies have used microdialysis of third molar extraction sockets in awake humans to correlate pain levels with the effects of nonsteroidal antiinflammatory agents on tissue levels of prostaglandin E_2 (35), gender differences in opioid mechanisms (36), and efficacy of preemptive analgesia on duration of postoperative pain (37). This is an important model system that will make fundamental contributions to our knowledge of mechanisms and to developing additional types of treatments, both for specific dental problems and for pain in general.

Oral Mucosa

The oral mucosa is extensively innervated by nociceptive, polymodal, mechanoreceptive, thermosensitive, and chemosensitive sensory fibers to provide a wealth of sensory information about material entering the mouth, and for sensory components of oral functions and reflexes. The innervation is regionally specialized so that each distinctive oral epithelium (e.g., palate, lip, cheek, tongue, buccal mucosa, gingiva, junctional epithelium) has its own pattern of sensory innervation (see Fig. 50-2). Within the oral cavity there is an anteroposterior gradient of sensory innervation density. Intraepithelial innervation consists of free endings, Merkel-neurite mechanoreceptive complexes, and chemosensory corpuscles (taste buds). Subepithelial receptors include various mechanosensory corpuscles, unencapsulated Ruffinilike receptors, and numerous free endings in subepithelial plexuses. In addition, sensory and autonomic innervation of the mucosal vasculature exists. Use of immunostains such as protein gene product 9.5 has enabled detailed studies of the sensory innervation of biopsies of human oral tissues (38); for example, showing reductions in innervation patterns of edentulous gingiva compared with focal increases in areas contacted by implant-retained dentures (39).

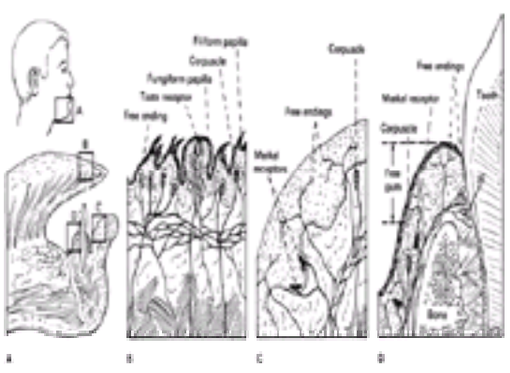

Figure 50-2. Oral mucosa. **A:** Sensory innervation has different components and patterns in different regions of the oral mucosa. **B:** Near the tip of the tongue numerous subepithelial corpuscles form a network of fine fibers beneath the epithelium with thin intraepithelial free endings in each filiform papilla. The larger fungiform papilla has a different epithelial structure, a taste receptor, and numerous fine fibers. **C:** In mucosa lining the inside of the lip, the epithelium is thicker, nonkeratinized, and less innervated than other regions. Fine intraepithelial fibers are found, as well as intraepithelial Merkel's receptors, subepithelial corpuscles, and fine fibers. **D:** The gum adjacent to the teeth has three different regions: junctional epithelium (JE), free gingiva extending above the alveolar bone, and attached gingiva next to the bone. The junctional epithelium has many free intraepithelial fibers. Free gingiva has fewer endings, most of which are in the crest. The attached gingiva has intraepithelial free endings above the dermal papillae, intraepithelial Merkel's receptors, and subepithelial mechanoreceptors, corpuscular endings, and a network of free fibers. Oral mucosa is also characterized by innervation of many blood vessels by fine sensory fibers.

Many of the thin fibers of oral mucosae are neuropeptide-rich, capsaicin-sensitive polymodal receptors that cause burning pain. These fibers promote neurogenic inflammation (40), and they play key roles in many mucosal pain syndromes. Some of them have widely dispersed branches to different dental regions, so that neurogenic inflammation and blood flow changes can be induced at distant sites, such as in gingiva, lip, buccal mucosa, tongue, and palate after stimulation of a maxillary tooth (10). These regional vasoregulatory reflexes involve interactions between the polymodal sensory fibers and the autonomic innervation (41).

Although oral mucosae are surface-covering tissues, their innervation differs from skin in some important ways. The elegantly detailed, receptor-specific neurotrophic and neuropeptide features of somatosensory innervation (42), do not hold true for all oral innervation. For example, in mice that do not produce the low-affinity p75 neurotrophin receptor molecule, the teeth and gingiva have dense neuropeptide-rich sensory innervation, whereas skin of those mice is only sparsely innervated (43,44). Also, calbindin D-28-K immunoreactivity characterizes the mechanoreceptive and thin fibers of oral mucosa (and is typical of viscerosensory fibers) but is not common in cutaneous innervation (45). The causes for special pain problems of the oral mucosae, such as burning mouth syndrome or other complex regional pains, must depend to some extent on its specialized neural cytochemistry, conditions of epithelial maintenance for the rapidly renewing mucosal epithelia, and responses of both the mucosa and nerve fibers to physiologic and pathologic stimuli, as discussed in this chapter (see Clinical Considerations) and in Chapter 38.

Teeth and Periodontium

The sensory nerve fibers in tooth pulp, dentin, gingiva, and periodontal ligament are specialized to contribute different kinds of somatosensory information needed for normal tooth use, tissue preservation, and injury responses. For example, warm and cold sensations from teeth depend on innervation in the adjacent gingiva, whereas information about tooth contact and movement during chewing, speech, jaw reflexes, and injury reactions depends on mechanoreceptors and nociceptors located outside the tooth in the periodontal ligament. Neuroanatomic and physiologic studies have shown that these receptors are concentrated in the apical third of the ligament and are mostly unencapsulated Ruffinilike mechanoreceptors with occasional corpuscular endings (see Fig. 50-3). The periodontal Ruffini endings from the trigeminal ganglion elicit conscious sensations of dental touch, whereas the mesencephalic trigeminal neurons provide the periodontal receptors for unconscious proprioceptive reflexes (46,47). The ligament is also supplied with acute nociceptive and polymodal A-d and C fibers that end in association with blood vessels and within the ligament bundles (48). The periodontal nerve fibers outside the roots react to pulpal inflammation and contribute to dental pain by becoming sensitized and undergoing extensive sprouting and altered cytochemistry (14,49).

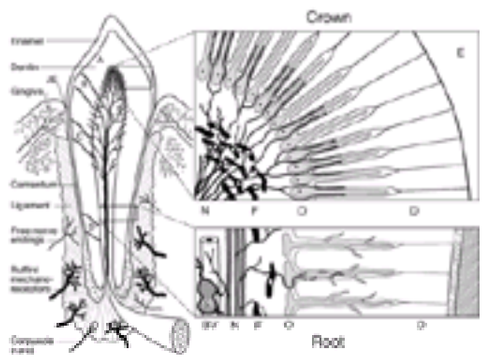

Figure 50-3. Schematic diagram of a mature erupted tooth and its dentinal, pulpal, and periodontal sensory innervation. The labeled dentinal zones were found by previous work to have more than 40% of the dentinal tubules innervated (A) compared with decreasing percentages in zones B (4% to 8%), C (0.2% to 1.0%), and D (0.02% to 0.2%). The higher magnification panels of crown and root compare their nerve (N) incidence, pulpal fibroblasts (F), odontoblast morphology (O), dentin (D), and enamel (E). Neither the odontoblasts (*stippled*) nor the sensory innervation of dentin reach the dentin-enamel junction. Perivascular immunocompetent dendritic cells (dc), and vascular innervation (BV) are shown in the root diagram. Periodontal innervation is primarily by large- or medium-sized branched Ruffini mechanoreceptors and thin-branched nociceptors, with rare encapsulated endings. For details of gingiva and junctional epithelium (JE) nerves, see Figure 50-2. (Modified from Byers MR, Närhi MVO. Dental injury models: experimental tools for understanding neuroinflammatory interactions and polymodal nociceptor functions. *Crit Rev Oral Biol Med* 1999;10:4–39.)

Pain is the predominant sensation that is perceived from within injured or inflamed teeth, regardless of whether the stimulus is electrical, thermal, mechanical, osmotic, or chemical. As a result, teeth have been one of the most useful tissues in which to analyze nociceptive functions. They have two different qualities of pain: sharp focal pain and diffuse toothache. The latter can cause diagnostic difficulty and confusion with other orofacial pain conditions because of its diffuse nature. That blurred location is caused by both widely dispersed endings in the brainstem (26) and wide branching in the periphery, between different teeth, or even with branches and vasodynamic reflexes between teeth and supporting tissues (10,50). In addition, inflammation causes large changes in receptive fields of sensory and central neurons (13,23). As long as teeth are not damaged significantly by stimuli, the pain sensations are brief.

The intradental sensory nerve fibers mostly terminate in the crown pulp and associated dentin in extensively branched endings that are close to the odontoblasts, but not in synaptic or gap junction contact with them (see Fig. 50-3). Extensive studies of dental pain in human subjects in the 1960s and 1970s demonstrated that fluid movement in dentin occurs whenever stimuli (heat, mechanical, osmotic, and so forth) cause rapid outflow of the interstitial fluid, as is common when dentinal tubules have become exposed in cervical roots or along coronal cracks (51,52 and 53). Single fiber studies in animals have shown that the acute sensation of dental sharp pain correlates with A- d innervation of dentin, and brief, dull ache depends on capsaicin-sensitive slow A-d and C fibers in pulp (54,55,56 and 57) (Table 50-1). Inflammation-driven nociceptors that are *silent* or *sleeping* in normal teeth are also present (23) and become active once tissue damage and inflammation have occurred. The A-b fibers have similar properties to the A-d fibers under most experimental conditions and cause brief prepain sensations at low stimulus intensities (58), although purely mechanoreceptive A-b activities have been found in cats when recordings were made from the trigeminal ganglion cell (59,60).

		Conduction velocity (m/s)		
Group	No.	Extrapulpal	Intrapulpal	Capsaicin response
A-β	21	42.5 ± 8.2	15.8 ± 3.2	0/11
A-δ fast	38	22.0 ± 4.1	7.1 ± 3.4	0/26
A-δ slow	43	5.0 ± 2.1	1.5 ± 0.3	6/25
C	37	1.7 ± 0.2	0.9 ± 0.2	10/20
Fiber total	139			

[a]Conduction and capsaicin (1- to 100-nM dose).
Data from Ikeda H, Tokita Y, Suda H. Capsaicin-sensitive A delta fibers in cat tooth pulp. J Dent Res 1990;76:1345–1349.

TABLE 50-1. Dental nerve fiber conduction velocities and capsaicin response [a]

Sensory receptor mechanisms in normal dentin involve fluid movement that activates distant A-d and A-b nerve endings in inner portions of dentinal tubules or near the pulp border using hydrodynamic mechanisms (51,53,55,61). For much of this century, it has been popular to also attribute sensory activity to odontoblasts, because of the sharp sensitivity of the dentin-enamel junction and the presumed presence of odontoblast processes there. It is now known that neither odontoblast processes nor nerve endings reach the dentin- enamel junction (61,62). Thus, the sensitivity of the dentin-enamel junction must be caused by transfer of extracellular changes from that site to the sensory receptors in inner dentin and peripheral pulp. The sensory endings do not form synaptic or gap junctions with the odontoblasts, but some of the largest fibers do form adhesivelike junctions with the odontoblast cell body, most likely as a way of anchoring their endings near the openings to the dentinal tubules (9,14,53,63). Pulpal damage leads to activation of A-d and C fibers that are chemosensitive, polymodal, or both, with different receptor mechanisms from those of the dentinal sensory apparatus.

Teeth contain numerous sensory C and A-d fibers as well as some A-b axons and some unmyelinated sympathetic axons. However, estimates of their relative proportions are difficult because parent axons have often subdivided into smaller preterminal branches far away from endings, often branching before entry into the tooth, as shown by the faster conduction velocities outside the tooth (see Table 50-1) (50,57).

Most of the time teeth do not hurt, but that does not mean that their extensive innervation is inactive. Sensory nerves in teeth have many paracrine interactions (local cytochemical signaling) with pulp cells such as (a) orientation of the dentinal sensory endings in the regions with greatest production of nerve growth factor by coronal fibroblasts (64), (b) transfer of anterogradely transported tracers from trigeminal axons to the odontoblasts (65), and (c) efferent delivery of neuropeptides to the pulp for vasoregulation (10,66,67). During development, neurotrophin factors and receptors are expressed by different dental cell groups at different stages (68,69) that affect the distribution of arriving innervation and local nonneuronal interactions. During aging, as dentin thickens and pulp volume shrinks, the innervation shifts location and is correspondingly reduced (63,70). This suggests that dental innervation can shift the sensory apparatus volume and cytochemistry in relation to local growth factors and other paracrine signals concerning pulp and dentin status.

Although the sensory nerves of teeth have many nonsensory functions (vasoregulation, pulpal regulation), those nerve fibers, as all dental patients can testify, are ready to signal brief or acute noxious events via sharp pain as soon as dentin is injured (i.e., as soon as the drill breaks through the dentin-enamel junction) or via ache sensations for pulpal inflammation. Once pulpal inflammation has begun, there are complex cascades of changes in neural function, structure, cytochemistry, axonal transport, ganglionic gene expression, and central connections, so that normally nondetectable stimuli become algesic and the receptive fields for dental neurons expand (13,23,56). Neural cytochemistry and function change again as healing progresses to patterns that are relevant to the healing conditions (71) (Fig. 50-4), or if damage becomes irreversible in the tooth and its nerves. These phenotypic alterations in the structure, function, and chemistry of the nociceptive system must be considered when seeking to understand and treat the various types of dental and oral pains.

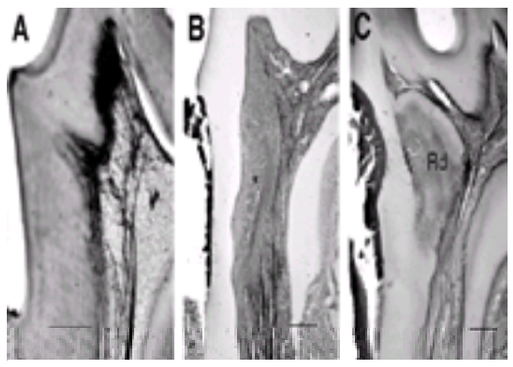

Figure 50-4. Comparison of rat molars and their calcitonin gene-related peptide–immunoreactive sensory innervation for **(A)** normal conditions with sensory endings concentrated in coronal pulp and dentin, **(B)** at 4 days after injury with nerve sprouting near a pulp abscess (*), and **(C)** at 3 weeks after injury when much reparative dentin (Rd) has been made. The sensory innervation has completely different anatomic distribution and calcitonin gene–related peptide intensity for each condition. Scales: 0.2 mm. (Reprinted from Taylor PE, Byers MR. An immunocytochemical study of the morphological reaction of nerves containing calcitonin gene-related peptide to microabscess formation and healing in rat molars. *Arch Oral Biol* 1990;35:629–638, with permission.)

Dental Injury Models and Neuroinflammatory Interactions

Tooth injury models are useful for correlating the degree of peripheral injury with inflammatory reactions, immune responses, healing mechanisms, and neural reactions (in tooth, ganglion, and CNS), because the depth, location, and duration of injury can be controlled (14,53,64,72). For example, a pulp exposure in rat or mouse molars causes a continuous acute inflammation that gradually destroys the pulp and spreads into periodontal tissues (49) and has been a useful way to induce experimental lesions in the periapex (73). Less extensive injuries allow production of different depths of dentin cavity for analyses of local pulpal injury, neural reactions, and rates of healing (see Fig. 50-4) (71,74). In previous studies, specific pulpal reactions, such as the rapid production of nerve growth factor by injured fibroblasts (64) and invasion of monocytes (8,11), were found to precede the local sprouting of pulpal sensory terminals that begins by 1 day and becomes profuse 2 to 3 days after injury. Ganglionic upregulation of glial fibrillary acidic protein in satellite cells was only found for pulp exposure injuries but not dentin cavities (75), even though both types of injuries cause increased expression of the trkA, trkB, and p75 neurotrophin receptors and brain-derived neurotrophin in dental neurons of the trigeminal ganglion (76). Finally, useful comparisons have been made between injury models at teeth, skin, and temporomandibular joint for understanding central plasticity reactions (13,74,75).

Most of the dental injury models have been in animals, but the studies of third molar extraction sites using pain testing, pharmacology, and microdialysis probes have correlated pain levels with specific inflammatory mediators such as prostaglandin E_2 (35) (Fig. 50-5) in the injury sockets, and demonstrated reduced postoperative pain when nociceptive signals during and just after oral surgery are inhibited by long-acting analgesia (37). This is a valuable clinical experimental model in which to develop better analgesics, antiinflammatory drugs, and overall pain management.

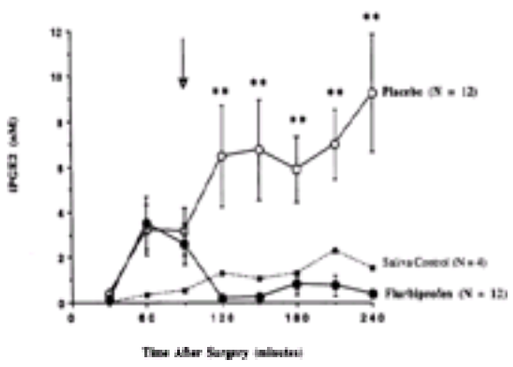

Figure 50-5. Tissue levels of immunoreactive prostaglandin E_2 ($iPGE_2$) from the surgical wound (third molar extraction) in patients receiving either 200 mg of flurbiprofen or placebo at postoperative pain onset. A separate group of patients served as negative controls in whom microdialysis probes were placed into the buccal vestibule, away from the sites of surgery, to evaluate salivary levels of $iPGE_2$. Wound dialysate samples were collected at 30-minute intervals, frozen, and analyzed for $iPGE_2$ with a previously validated enzyme immunoassay. Data are presented as the mean plus or minus standard error of the mean, corrected for percent recovery of $iPGE_2$. The arrow represents the mean time of drug administration for both treatment groups. $^{**}P < .001$ flurbiprofen versus placebo. [Reprinted from Roszkowski MT, Swift JQ, Hargreaves KM. Effect of nonsteroidal antiinflammatory agents administration on tissue levels of immunoreactive prostaglandin E_2, leukotriene B_4, and (S)-flurbiprofen following extraction of impacted third molars. *Pain* 1997;73: 339–345, with permission.]

Trigeminal Brainstem Mechanisms

Hyperexcitation of neurons in central pain pathways (indicated by expanded receptive fields and decreased thresholds) is a fundamental aspect of neuropathic and inflammation pain mechanisms in spinal cord and brainstem (13,79,80). Electrophysiologic studies have shown that orofacial nociceptive information is processed primarily in trigeminal nucleus caudalis, but there is also important input from C fibers and capsaicin-sensitive afferents to the main sensory nucleus and subnucleus oralis (12,81,82 and 83), and the caudal zone of nucleus interpolaris has important processing of nociceptive inputs (84,85). Those studies show that both subnormal and excessive activity of nociceptive fibers affect the functions of wide dynamic range and low-threshold mechanoreceptive neurons in those areas. Neuroanatomic mapping of central endings from dental afferents shows that they branch and end throughout the trigeminal region from the cervical dorsal horn to the main sensory nucleus (26). However, the endings in nucleus caudalis may have more direct effects on pain pathways than other regions where the terminals may be masked. It has been proposed that serotonin-mediated rapid activation of masked nociceptive endings is an important central mechanism that affects brainstem neuron functions within seconds (86). Similarly, antagonism of the excitatory *N*-methyl-d-aspartate channels rapidly reverses the expansion of receptive fields in nucleus caudalis that was induced by capsaicin depletion of C fibers (83,86). These studies show the kind of work that is in progress to correlate specific features of brief, acute transient and chronic persistent pain with molecular mechanisms in the CNS.

Activation of transcription factors such as c-*fos* in central neurons has been found to be a useful marker of *N*-methyl-d-aspartate–driven central plasticity (87), and there have been several studies of c-*fos* expression in brainstem trigeminal subnuclei after various tooth or mucosal injuries. By 2 to 4 hours after acute injury to teeth of rats, cats, or ferrets (a), the *fos* response in the periobex regions of nucleus caudalis is maximal, (b) the number and location of *fos* responding neurons depend on the type of stimulus, (c) the expression of *fos* in trigeminal nuclei is independent of altered motor reflex responses, and (d) there is greater rostrocaudal response when more teeth are involved (88,89 and 90). Analysis of chronic pulp exposure injury to rat molars (91) has shown that there is transient expression of *fos* at 1 week in large ipsilateral neurons of dorsomedial nucleus oralis and adjacent reticular zone, and persistent *fos* for at least 4 weeks in dynorphin-rich regions (lateral solitary nucleus, periobex nucleus caudalis, interstitial cells of the trigeminal tract, and medial superficial neurons of the cervical dorsal horn).

These persistent *fos*-reactive neurons are only a small proportion of the entire set that receive dental afferent terminations, so that most dental central endings do not induce *fos*-driven plasticity in the brainstem after dental or oral injuries. Similarly, the efficacy of synapses from orofacial nociceptive endings may vary in different trigeminal subregions and be under different regulatory control. The rapid regulation of afferent central terminal efficacy in relation to central plasticity of pain mechanisms and the subspecializations within the nociceptive afferent termination zones are important current areas of investigation (83,85,86). For further details see Chapter 4 and Chapter 5.

CLINICAL CONSIDERATIONS

A correct diagnosis of pain in the teeth and surrounding structures requires knowledge of the anatomy as well as a systematic approach for obtaining information and carrying out appropriate physical, laboratory, and radiographic examinations.

The general approach is similar to that described in Chapter 12. Obviously, the history and description of the pain are the first and perhaps the most important parts of the patient's evaluation. The patient should be encouraged to provide a detailed description of the characteristics of the pain when first experienced, during the interval, and at the time of the examination. Detailed information must be obtained about the site and distribution of the pain as well as about its quality, intensity, frequency, periodicity, and duration. If the pain is not constant, information must be obtained about the time of day the bouts of pain occur, the provoking factor(s), and that which relieves the pain. In addition to general examination of the mouth, the response elicited by tooth percussion, application of heat (by means of heated gutta-percha), or cold (by means of a CO_2 ice pencil or as cold water, ice, or cold air, or by a cotton pledget saturated with ethyl chloride applied directly to the tooth) should be ascertained. It is important to make a comparison between corresponding teeth on the opposite side of the midline. To evaluate pain location some practitioners use response of the pulp to electrical stimulation and the effect of local infiltration anesthesia on the pain. In addition, roentgenography is an essential part of the examination.

Pain of Odontogenic Origin

Dental pain, termed *odontalgia*, has been associated with pulpal and periodontal pathology, exposed dentin or cementum, cracked teeth, parafunctional jaw behavior (e.g., bruxism), or iatrogenic causation such as trauma related to osmotic change or placement of dental restorations. Tooth pain not associated with readily identified disease has been termed *atypical odontalgia*. These conditions, presented in the following section, are summarized in Table 50-2. In cases of pulpal or periapical pathology, dental caries are typically the principal causative agent.

Condition	Etiology	Clinical signs and symptoms
Pulpitis	Caries	Pain poorly localized; referred to the opposite arch, etc; characterized as throbbing or burning; intermittent, exacerbated by touch, pressure, sweet, heat, cold; clinical signs: caries
Periodontitis	Periapical infection	Pain easily localized; throbbing, long lasting; hours; exacerbated by heat; clinical signs: percussion sensitivity, tissue erythema and swelling; sometimes radiographic periapical change evident
Cracked tooth syndrome	Fractured cusp or crest	Pain intermittent, brief, sharp, or dullAche; eccentric (lateral) biting, chewing, percussion increases pain; radiography not beneficial except for horizontal root fractures
Dentinal and cementum pain	Hydrodynamic stimulation of pulp dentin (tubular) axon	Pain poorly localized; intermittent, sharp; follows mechanical, thermal, or chemical (sweet) stimulation; clinical signs: exposed dentin or root surface (cementum)
Bruxism pain	Pulpal or periapical inflammation	Pain poorly localized; involving the maxillary and mandibular teeth on both sides of the mouth; dull ache; clinical signs: tooth facets
Iatrogenic pain	Pulpal or periapical inflammation	Pain fairly well localized; intermittent, shooting (barometric) pain perceived during pressure changes occurring in flight; contact of metal with teeth causes galvanic pain

TABLE 50-2. Pain of odontogenic origin

Dental Caries

Etiology. Caries represents a complex pathologic process involving microbial infection of the organic component of the inorganic matrix of the tooth, resulting in biochemical changes that cause loss of the calcified material protecting the pulpal tissue (16). Caries progression appears to be mediated by several factors, including host resistance (e.g., enamel structure including fluoride content, saliva composition, or functional properties), species of microflora and local environment, the types and amounts of food substrates available to the bacteria (e.g., dietary sugar), and the quality and quantity of oral hygiene behaviors.

Pathophysiology. Fortunately, the carious process typically proceeds slowly in enamel (92), and pulpal tissue often has time to form secondary dentin as a protective barrier to microbial encroachment. Without interventions such as antimicrobial therapy, diet control, fluoride or sealant application, or removal of caries and tooth restoration, the eventual sequelae are typically invasion of the dentinal tubules by bacteria, pulpal inflammation, and necrosis, with spread of infection into the periapical ligament space and alveolar bone (20). Pain might or might not be experienced during the progression of these pathologic events. Nonetheless, even though only slight correlation has been demonstrated between pain characteristics and the histopathologic status of the pulp (93), pain remains a good predictor of carious extension into the dentin (94). Pain conditions associated with teeth, including those arising from caries, are categorized according to the IASP criteria as acute pulpitis, acute periapical inflammation, cracked tooth syndrome, dentin and cementum pain, atypical odontalgia, and pain of bruxism. Alternative nomenclature includes Ingle and Glick's taxonomy, which lists categories such as hyperreactive pulpalgia, acute pulpalgia, chronic pulpalgia, hyperplastic pulpitis, necrotic pulp, internal resorption, traumatic occlusion, and incomplete fracture. For additional information regarding this nomenclature, the reader is referred to the previously cited literature and to Ingle (2).

Odontalgia: Acute Pulpitis (IV-3) (Code 031.X2c) and Toothache Caused by Dentinoenamel Defects (IV-2; Code 034.X2b)

Etiology. Caries progression and infusion of microflora into the dentinal tubules cause intrapulpal arteriole and capillary dilation, increased vessel permeability, fluid extrusion and edema, increases in polymorphonuclear leukocytes, and an increase in intrapulpal pressure, cell lysis, and the release of algogenic agents. As previously discussed, physical (fluid pressure) and chemically mediated neural stimulation is thought to be to the primary cause of acute pulpitis (inflammation) pain (95).

Symptoms and Signs. Pain of pulpal origin is often poorly localized within the teeth, jaws, or face (18). Although pain is usually confined to one side and does not cross the midline (the exception is pain associated with the central incisors), it is not uncommon for pain emanating from a tooth in one arch (e.g., the maxilla) to be perceived as arising from a tooth in the opposite arch. In such cases, however, one class of tooth (e.g., molar, bicuspid) usually refers pain to the same class of tooth in the opposing arch. Pain can also be referred to adjacent mandibular, maxillary, or both kinds of teeth or, in cases of posterior teeth, to the ear, cheek, or temporomandibular joint.

Pulpitis can occur without apparent stimulation or can be activated (or exacerbated) by various stimuli such as touch, chewing pressure, and contact with sweet, hot, or cold foods. The degree of pulpal pathology does not appear to be highly correlated with pain experienced in response to stimulation (95). When severe, pain is described as throbbing or burning and can occur in paroxysms that are quite debilitating. The more usual course is for pain to be intermittent in nature, lasting a few minutes to hours.

In mild cases of acute pulpitis clinical signs might not be readily observed. Recurrent caries under old restorations or crowns is often difficult to detect by visual, tactile, or radiographic examination. The application of cold, heat, or electrical stimulation and probing, however, often (but not always) induces pain in the involved teeth. Tooth percussion is not typically a finding associated with mild pulpitis but is present if inflammation is severe. In addition, with severe pulpitis, visual and radiographic examination of the uncrowned tooth usually reveals dental caries extending into the dentin and in some cases the pulpal tissue (Fig. 50-6).

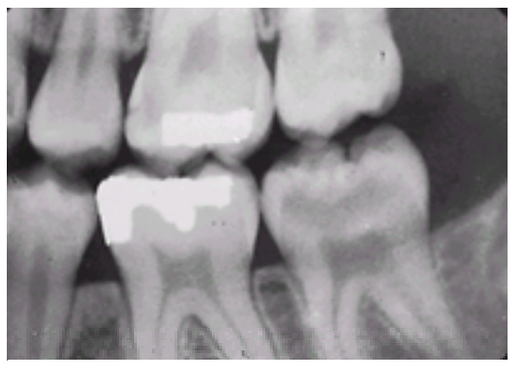

Figure 50-6. Bite-wing radiograph of posterior teeth showing multiple carious sites, as evidenced by radiolucencies between the teeth and extensive coronal radiolucency within the mandibular second molar. (Courtesy of H. Rumberg, Department of Oral Medicine, University of Washington.)

Differential Diagnosis. Acute pulpitis should be differentiated from pain of periapical origin such as acute periapical inflammation (see following discussion), acute periodontal pain, middle ear infection, sinusitis, metastatic cancer, and local neoplasm. It should be appreciated that persistent toothachelike pain has been associated with thoracic pathology including mediastinal lymphoma (96), lung cancer (97), and cardiac disease (98), as well as occipital neuralgia (99) and central neoplasm. Pain perceived in the teeth may also be referred from the masticatory musculature (100).

Brief shocklike pain has been described by Ingle and attributed to hyperreactive pulpalgia (2). This tooth pain problem, because it is associated with a trigger, may be confused with trigeminal neuralgia. Both types of pains are often initiated by intraoral stimulation. Unlike neuralgia, however, pulpalgia is not set off by light touch of the external face (e.g., showering, application of makeup, shaving), and this serves to differentiate the two conditions. Secondary trigeminal neuralgia arising from central neoplasm may also cause tooth pain mimicking pulpalgia. The presence of concomitant paresthesia or anesthesia differentiates this condition from pain of dental etiology. In the latter case, blocking the involved peripheral nerve with local anesthetic does not eliminate pain referred from central pathology.

Treatment. In some cases of slow caries progression, the pulpal tissue can successfully wall off and contain the inflammation (i.e., within a pulpal horn), thus preventing additional pathology. In such cases treatment includes caries removal, the application of a sedative base (e.g., zinc oxide and eugenol or calcium hydroxide), and tooth restoration (101). When caries extends into the pulp, as in cases of moderate to severe pulpitis without periapical involvement, partial (i.e., pulpotomy) or complete (i.e., pulpectomy) extirpation of the pulpal tissue might be necessary (1). Tooth extraction is the treatment of last resort.

Many patients are quite proficient at self-prescribing various “home remedies” for acute pulpitis pain. Several *toothache* solutions designed to be placed in the carious lesion, essentially containing eugenol, are also available as retail preparations. In general, mild pulpitis pain is managed with analgesics such as acetaminophen, acetylsalicylic acid, or other nonsteroidal antiinflammatory medications (e.g., ibuprofen). For moderate pain, a mild narcotic may be helpful. Also important is dental restoration. Promising research provides support for the development of a caries vaccine and therapy based on genetic manipulation.

Acute Periapical Inflammation (IV-4; Code 031.X2d)

Etiology. Acute periapical abscess is the most prevalent consequence of untreated caries-induced acute pulpitis. Infusion of bacteria through the root apex into the periodontal ligament space and alveolar bone is thought to contribute to this more generalized orofacial inflammatory process.

Symptoms and Signs. Pain produced by infection of the periodontium and alveolar bone is similar in quality and duration to pain of pulpal origin. In contrast to the pain of acute pulpitis, however, periapical inflammatory pain is typically severe, unremitting, and throbbing; lasts for hours; and awakens the patient from sleep. Generally, the infected tooth is more easily located by the patient. Intensity varies depending on the severity of the inflammatory process, cellular destruction, degree of pus production, and containment of infection. When intrapulpal necrosis occurs in association with gas-producing microorganisms, heat applied to the tooth often causes severe exacerbation of the pain. Ice water often ameliorates the pain temporarily.

A predominant feature of periapical inflammation is tooth percussion sensitivity. In addition, the patient might report that the offending tooth feels as though it has been displaced into supraocclusion so that closing the mouth becomes painful because of premature tooth contact. Depending on the severity of periapical pathology, associated symptoms can include localized tissue erythema, local or diffuse cellulitis, trismus, and lymphadenitis. In severe cases the patient can be febrile and appears quite ill.

Persistent (greater than 10 days) periapical inflammation can be associated with discernible radiographic bone loss (Fig. 50-7). Immediate radiographic examination is useful for establishing baseline data (i.e., the initial bone density) and, in cases of diffuse cellulitis, for defining the extent of associated fascial space involvement (102). Generally, however, radiographic findings have not been found to be highly correlated with clinical symptoms of pain (103).

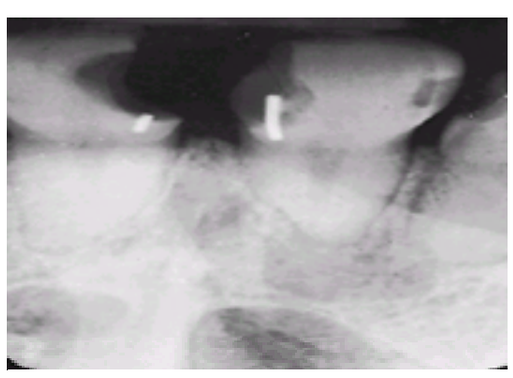

Figure 50-7. Periapical radiograph of a maxillary central incisor. The pin restoration was associated with pulpal necrosis and apical radiolucency. (Courtesy of H. Rumberg, Department of Oral Medicine, University of Washington.)

In more severe cases, diffuse parapharyngeal and carotid space cellulitis can result in life-threatening complications with potential airway obstruction, CNS involvement with cerebral abscess, or endocardial inflammation (104). Hematologic, histopathologic, and microbiological laboratory testing is, in these uncommon instances, a necessary component of diagnosis and treatment.

Differential Diagnosis. In the differential diagnosis, it should be determined whether other odontogenic infections are present, such as infection associated with apical cysts, or whether there is nonodontogenic infection or neoplasia (e.g., external periosteal or intrabony metastatic lesions). Sinusitis must also be considered for maxillary pain. Chronic pain associated with odontogenic infection, osteitis, or osteomyelitis of the mandible may result in additional myofascial abnormality that causes a more generalized unilateral or bilateral facial pain or headache.

Treatment. Occasionally, for some untreated patients, localized cellulitis occurring within the buccal vestibule of the maxilla and mandible, or the palate, is followed by the formation of an intraoral or extraoral sinus tract that allows drainage of the purulent material and produces an associated reduction in facial pain. In cases of localized cellulitis without sinus tract drainage, dramatic relief of pain can be gained by simply opening the pulpal chamber and extirpating the pulp; occasionally (in cases in which drainage does not occur) this intervention might need to be augmented by incision and drainage, analgesics, and judicious use of antibiotics. Incision and drainage procedures should be followed by therapy that includes either root canal filling and tooth restoration, or tooth extraction (21).

Patients with diffuse cellulitis warrant careful diagnosis and therapeutic evaluation. Infection involving the mentalis, submental, sublingual, submandibular, buccal, submasseteric, deep temporal, and superficial temporal fascial spaces has a relatively low risk for spread to other fascial planes. Culture for sensitivity testing followed by conservative management with oral antibiotics, such as penicillin V, 500 mg four times a day, can be sufficient for pain relief. Moderate to severe pain associated with diffuse cellulitis is usually managed with acetylsalicylic acid and codeine, oxycodone, or meperidine HCl.

Failure to obtain pain resolution or reduction of swelling with oral antibiotics, coupled with spread of infection to the pharyngeal (e.g., infratemporal, parotid, pterygomandibular), parapharyngeal (e.g., lateral or retropharyngeal, peritonsillar, cervical), or periorbital spaces, can produce a life-threatening medical emergency. In these cases hospitalization with appropriate parenteral or intravenous antibiotic coverage, airway or fluid support, and appropriate incision and drainage should be instituted promptly.

Cracked Tooth Syndrome (IV-7; Code 034.X1)

Etiology. As the term *cracked tooth syndrome* implies, this type of odontogenic pain is associated with cracked teeth. Teeth that have been weakened by caries, restoration, or root canal treatment, and unrestored teeth subject to traumatic loading (e.g., clenching or bruxism), are susceptible to cracking and fracture (Fig. 50-8). It is speculated that pain is produced in vital teeth from hydrodynamic events (51) or from mild pulpal inflammation caused by the infusion or oral fluids and microorganisms through the defect, and in nonvital teeth from irritation of the periodontal ligament.

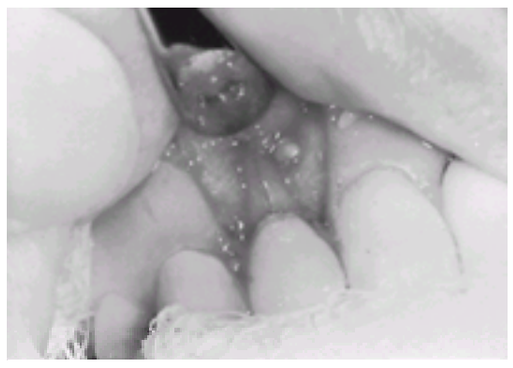

Figure 50-8. Peridontal flap procedure demonstrates vertical root fracture in incisor tooth associated with slight discomfort. The pain followed compacting of root canal material. (Courtesy of G. Harrington, Department of Endodontics, University of Washington.)

Symptoms and Signs. Pain is intermittent, of brief duration, and described as sharp or shocklike. Eccentric (lateral) biting or chewing often exacerbates the pain (105). Percussion of the involved cusp during examination can recreate the pain experience. Coronal cracking is difficult to detect, and radiographs are not usually beneficial; in some cases of horizontal root fractures the abnormality can be detected by dental radiographic evaluation. Staining solutions designed to assist in locating surface enamel defects are available. It is important to note, however, that many normal teeth demonstrate signs of coronal cracks so the presence of this feature alone is not enough to define the diagnosis.

Differential Diagnosis. Pain resulting from a cracked tooth should be differentiated from other forms of pain of pulpal origin (e.g., early pulpitis, periapical abscess) and iatrogenic pain (e.g., loose restorations, failing root canal treatment), and neuropathic pain (e.g., neuralgia).

Treatment. Immediate pain reduction usually results from removal of the fractured portion of the tooth and conservative restorative treatment of the defect. Occasionally, the placement of a crown eliminates pain. Root fractures generally necessitate tooth extraction.

Dentin and Cementum Pain (IV-9; Code 034.X8f)

Etiology. Sensitivity in otherwise healthy teeth is thought to be the result of hydrodynamic stimulation of neural processes in the inner portions of the exposed dentinal tubules (51,106), as the external dentin and cementum are (as previously reviewed) not innervated (63).

Symptoms and Signs. Sharp intermittent pain often follows mechanical, thermal, or chemical (sweet) stimulation. Localization of the pain by the patient can be difficult. Examination may reveal exposed dentin or root surface (cementum) in a vital tooth that may also be eroded or abraded.

Differential Diagnosis. The differential diagnosis includes other forms of toothache, particularly cracked tooth syndrome and acute pulpitis.

Treatment. The application of strontium chloride solution, fluoride paste, or oxalate-containing compounds, or iontophoresis with fluoride (107) is generally an adequate pain control intervention for most patients. Sealing the exposed dentin with resins or tooth restoration (i.e., filling) is sometimes necessary in cases of persistent pain.

Bruxism Pain (IV-9; Code 34.X8f)

Etiology. It is presumed that bruxism or clenching pain is the result of prolonged trauma to the periodontium, which results in periodontal ligament or pulpal inflammation.

Symptoms and Signs. Periodontal pain resulting from trauma is described as a generalized dull ache involving the maxillary and mandibular teeth on one or both sides of the mouth.

Differential Diagnosis. This generalized oral orofacial pain that often accompanies a masticatory myofascial abnormality must be distinguished from this condition (see Chapter 29).

Treatment. Behavioral measures designed to eliminate daytime clenching may be all the management that is necessary for this problem. Experimental data suggest that appliances covering either the maxillary or mandibular teeth may be helpful in reducing nocturnal tooth clenching or gnashing (bruxism). Daytime parafunctional behaviors are typically more difficult to control in these cases (see Chapter 49). Appropriate habit modification can be coupled with a low-dose tricyclic antidepressant medication.

Iatrogenic Pain (IV-9; Code 03X.X8d)

Etiology. Infrequently, odontogenic pain results from restorative procedures. In such cases it is speculated that tenderness results from the following: thermal sensitivity secondary to deep caries removal or placement of an inadequate protective base or, in cases of plastic restoration, sensitivity to chemical components of the material; improper tooth preparation techniques resulting in hyperoccluding fillings or open margins; galvanism (formation of an intraoral electrical cell) associated with adjacent placement of dissimilar restorative metals, such as gold and silver amalgam; osmotic change related to defective and leaking restorations; or barodontalgia associated with the inclusion of fluid or air under a restoration (20). Toothache may also result from traumatic nerve injury associated with a variety of procedures (orthognathic surgery, dental implants, anesthesia, or root canal therapy).

Symptoms and Signs. These intermittent pains are typically described as sharp or shooting. Pain associated with barodontalgia is usually perceived during pressure changes occurring in flight. Galvanic pain can occur when metal, such as a stainless steel fork or aluminum foil, comes into contact with the involved teeth. Pain

associated with traumatic nerve injury can occur as paroxysms of electrical or sharp jabs or may be described as a persistent burning.

Differential Diagnosis. Iatrogenic pain should be differentiated from pain of pulpal or periapical origin, bruxism pain, and the pain of cracked tooth syndrome.

Treatment. These pains are generally self-limiting. Pain related to galvanism can be controlled temporarily by dental treatment including the coating of the offending tooth with protective varnish. In severe cases of postoperative pain, galvanism, or barodontalgia, removal of the offending filling, placement of a sedative pulpal dressing, and replacement of the restoration might be necessary.

Atypical Odontalgia (IV-5; Code 034.x8b)

Etiology. The underlying cause of atypical odontalgia is unknown. Given the lack of obvious underlying disease, it has been speculated that this chronic pain perceived in the teeth or gingiva may be of neuropathic origin (108) and possibly sympathetically maintained (109). Other factors historically linked to atypical odontalgia include vascular change, psychological factors such as depression (110), stress (111), and phantom (i.e., central) phenomenology. The possibility of interaction between preexisting vascular abnormality and deafferentation pain has also been reported (112).

Symptoms and Signs. The pain of atypical odontalgia persists for hours as a continuous mild to moderate or severe ache or throb. Duration ranges from months to years. Pain can be focal but is often diffuse, radiating, and migrating. It is frequently precipitated by a dental procedure such as crown placement, periodontal therapy, or dental surgery. It may move to a different adjacent site following tooth extraction. Although the epidemiologic research on orofacial pains is generally limited, and data for atypical odontalgia are virtually nonexistent, the condition is acknowledged to occur more frequently in women. Associated symptoms include psychological distress and other orofacial and head pain complaints (e.g., temporomandibular disorders). The history and examination are with inconsistent hot and cold sensitivity. Even though organic pathology is not identified, patients with atypical odontalgia are at great risk for unnecessary dental treatment such as root canal therapy and surgery.

Differential Diagnosis. Atypical odontalgia should be differentiated from pain of pathologic origin including pulpitis, periodontitis and abscess, cracked tooth syndrome, maxillary sinusitis, atypical facial migraine, intracranial pathology, neoplasm, and myofascial abnormality.

Treatment. Tricyclic antidepressants have demonstrated the greatest potential for pain control in this cohort of orofacial pain patients. Given pain chronicity, potential for overtreatment, and psychological distress, appropriate intervention should also include counseling and other biobehavioral strategies useful in the management of pain refractory to medical treatment. Additional therapeutic strategies that can be useful include topical application of analgesic (lidocaine patch or gel) or capsaicin, sympathetic blockade (stellate block or phentolamine infusion), or systemic lidocaine (mexiletine) (109).

Pain of Mucosal Origin

Pain can originate from the intraoral mucosa as a consequence of trauma (e.g., tooth eruption), infection or systemic disease, allergy, or tumor. Mucosal burning pain not associated with pathology has been termed *burning mouth syndrome* or *glossodynia* . Medical conditions associated with painful oral mucosal ulceration are listed in Table 50-3. Although pain intensity has been included as an outcome variable in therapeutic trials involving mucosal disease (113), the descriptive characteristics of pain associated with mucosal disease remains largely unstudied. Nonetheless, empirical evidence suggests that intraoral ulceration pain is, in most cases, well localized to the lesion site. It can vary considerably in presentation, however, depending on the extent of tissue involvement. The quality of pain is typically described as a dull ache or as a burning sensation. Discomfort is most frequently intermittent but, depending on the condition, can be quite persistent. Although mucosal pain is not typically paroxysmal, a trigeminal neuralgialike pain has been associated with mixed connective tissue disease with intraoral *lichenoid* mucosal lesions (114).

Blood dyscrasias: pancytopenia; cyclic neutropenia; sickle cell anemia
Infection: viral (primary herpes, herpangina, measles, herpes zoster); bacterial (acute necrotizing ulcerative gingivitis; gingivitis, periodontitis); fungal (candidiasis, actinomycosis in the immunosuppressed patient)
Allergy: stomatitis medicamentosa (erythema multiforme, Stevens-Johnson syndrome, Behçet's syndrome); contact stomatitis
Nutritional deficiencies: anemia; niacin deficiency (pellagra)
Exanthematous disease: migratory glossitis (psoriasis)
Pemphigus (vulgaris)
Benign mucous membrane pemphigoid
Lupus erythematosus
Erosive lichen planus
Diabetes
Neoplasm: squamous cell carcinoma; lymphosarcoma; metastatic tumor; acute leukemia
Acquired immunodeficiency syndrome
Recurrent aphthous ulcer: major; minor; herpetiform
Trauma: self-induced; iatrogenic; traumatized tumors (salivary gland tumors, minor gland; odontogenic tumors; metastatic tumors)
Wegener's granulomatosis

TABLE 50-3. Systemic and local mucosal conditions associated with intraoral pain

In this section, pain of mucosal origin is divided into pain associated with tissue attached to alveolar bone (e.g., gingiva of the palate), unattached tissue (e.g., buccal mucosa and soft palate), and the tongue. A comprehensive discussion of the etiology, clinical signs and symptoms, and treatment of all conditions causing intraoral pain is not within the scope of this chapter. The following discussion focuses on the important clinical pain characteristics and pain interventions for the most common intraoral conditions that cause pain of mucosal origin.

Gingival Pain

Etiology. Gingival mucosal tissues cover alveolar or palatal and mandibular bone surfaces that surround and support the teeth. Gingival pain can arise in these tissues as a result of trauma (e.g., self-mutilation, abrasion associated with tooth brushing or flossing habits, food impaction), chemical burns (e.g., aspirin, restorative materials), inflammation associated with teething or third molar eruption, infections caused by viral organisms (e.g., herpes), bacterial organisms (e.g., pericoronitis or acute necrotizing ulcerative gingivitis, Vincent's infection), fungal organisms (e.g., atrophic candidiasis), contact allergy (e.g., from toothpaste, mouthwash dental materials), or as a feature of a chronic dermatologic or other systemic disease process [e.g., benign mucous membrane pemphigoid (BMMP), pemphigus vulgaris, lichen planus, Wegener's granulomatosis, acquired immunodeficiency syndrome, leukemia].

Symptoms and Signs

Traumatic Pain. Pain resulting from trauma is usually characterized as a dull ache, and in cases of food impaction, there may be a sensation of pressure between the teeth. If infection occurs secondary to impaction, the pain often has a throbbing character. This type of pain presentation is also reported in cases of inflammation and infection of the pericoronal flap of tissue covering erupting teeth (particularly third molars) in which, in addition, the patient can be prevented from biting because of edematous enlargement and ulceration of the tissue.

Pain associated with chemical burns, if reported, is usually of a stinging or burning quality (115). Teething pain can occur along with slightly elevated temperature, intense agitation, and sleep disturbance.

Infection. Pain that results from primary ulcerative herpetic infection is often excruciating and accompanied by malaise, irritability, headache, and fever. Discomfort related to inflammation and ulceration of the buccal mucosa, lips, and attached gingiva (which serves to help differentiate this condition from herpetiform aphthous, occurring primarily on nongingival tissue) can prevent the patient from ingesting adequate fluids or nutrition (116).

Pain arising from bacterial conditions is usually perceived in the attached gingiva around the teeth. In gingivitis and periodontal disease pain is not usually present unless the condition includes development of giant cell granuloma (pyogenic granuloma), superimposed infection, or periapical (pulpal) abscess.

Acute necrotizing ulcerative gingivitis, characterized by erosive lesions localized to the interdental papilla and fetor oris, causes pain that is exacerbated by contact

with food or tooth brushing. Secondary symptoms frequently include malaise, but rarely is fever an associated finding (117). A rare variant of acute necrotizing ulcerative gingivitis, diffuse gangrenous stomatitis, can occur in patients with severe debilitating disease (e.g., advanced leukemia, malnutrition) (118).

Candidal infections produce pain of the gingiva, palate, or tongue that is characterized as burning in nature. Associated symptoms can include the presence of a metallic taste and dryness or sialorrhea.

Contact Allergy. Pain is not a frequent finding associated with intraoral allergy, unless it includes mucosal ulceration. If present, it is described as a mildly burning sensation.

Dermatologic Disease. Considerable oral discomfort is often associated with the generalized gingival and tissue ulceration and sloughing that occurs consequent to oral lesions of BMMP (cicatricial) (Fig. 50-9) or pemphigus vulgaris (Fig. 50-10). Pain, felt as a stinging or aching sensation, can be intensified by eating or drinking (especially alcohol).

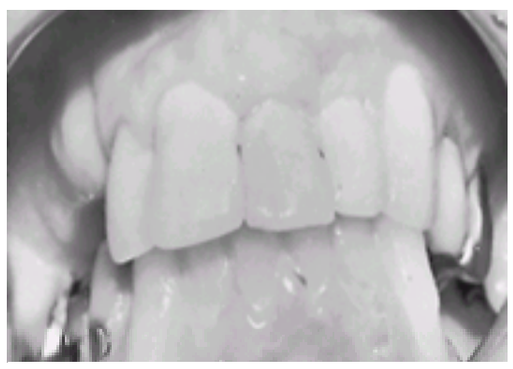

Figure 50-9. Generalized gingival erythema with frank ulceration and slough observed adjacent to lower lateral incisors in patients with benign mucous membrane pemphigoid.

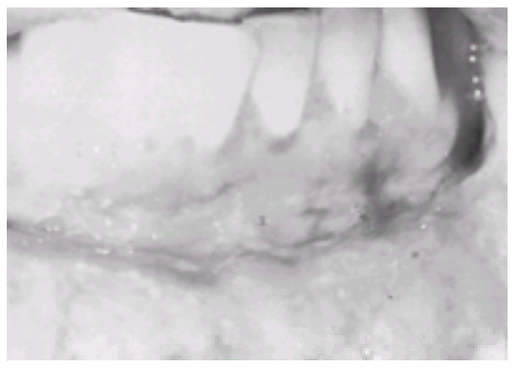

Figure 50-10. Ulceration of attached gingiva adjacent to lower incisors and ulceration of mucosa of buccal vestibule associated with pemphigus. (Courtesy of E. Sommers, Department of Oral Medicine, University of Washington.)

In pemphigus vulgaris, which has been reported to occur initially in the oral cavity in 50% to 60% of patients with the disease (119), associated symptoms can include weight loss and sore throat related to the pemphigus vulgaris lesions. In BMMP, which is considered to be a disease of the elderly but has been reported in children, ulceration can also involve the eyes, urethra, vagina, and rectum. Cutaneous lesions occur in approximately 25% of BMMP cases.

Ulceration identified with lichen planus occurs in approximately 33% of cases (in a random survey of 20,323 Swedish individuals, 1.9% were found to have oral lichen planus and, of these, approximately 33%, 134, had atrophic and ulcerative tissue changes) (120), but in contrast to BMMP and pemphigus vulgaris, it is usually limited to one or a few discrete lesion sites (Fig. 50-11). As a result, pain, described as a dull aching sensation, is relatively less severe. Patients might also complain of dryness of the oral mucosa (121). Malignant transformation of lichen planus lesions has been reported (122), but review of the literature suggests that this might be a relatively rare phenomenon (123).

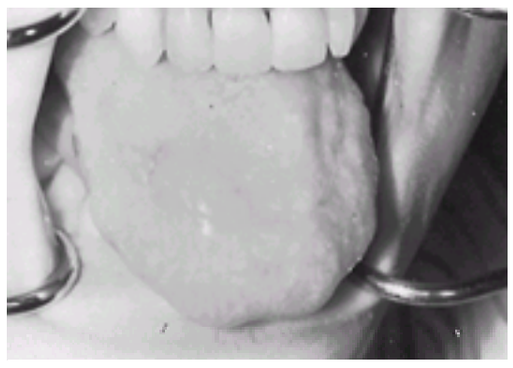

Figure 50-11. Atrophic and lichenoid mucosa on dorsal tongue with ulceration of right lateral border in a patient with lichen planus. (Courtesy of B. Gandara, Department of Oral Medicine, University of Washington.)

Systemic Disease. Wegener's granulomatosis, a rare necrotizing granulomatous vasculitis involving the kidneys and respiratory tract, can initially present as a gingival lesion associated with considerable discomfort (124). Pain is usually described as a persistent dull ache. Development of oral gingival lesions of Kaposi's sarcoma related to advanced acquired immunodeficiency syndrome has been reported to cause severe pain (125).

Treatment

Traumatic Pain. Management of pain associated with trauma includes behavior modification if the condition is self-inflicted; removal of the foreign body, offending restoration, or broken portion of tooth if these structures are contributing to the pathology; and tissue excision in cases of pericoronitis. Several over-the-counter anesthetic solutions are available for teething pain, although simply allowing the child to suck on a chilled object (e.g., teething ring or flavored Popsicle) often provides more than adequate relief. Teething pain that inhibits sleep can often be managed with a prebedtime administration of acetaminophen.

Infection. Pain associated with acute herpetic ulceration, particularly in cases in which fluid and food intake is being compromised, can be reasonably managed before eating or drinking through application of a topical anesthetic rinse such as dyclonine hydrochloride, 0.5%, or in situations in which this is not available, a rinse of a mixture of 5 mL of diphenhydramine hydrochloride (10 mg per 5 mL as oral elixir) and 5 mL of milk of magnesia (117). Any surgical procedure aimed at the trigeminal

nerve or ganglion can lead to the activation of latent herpes virus and severe pain.

Paradoxically (because the procedure can cause considerable immediate pain), the most effective approach for managing pain resulting from acute necrotizing ulcerative gingivitis is repeated curettage and lavage of the tissues, reinforced by frequent brushing and rinses of 3% hydrogen peroxide (126).

Interventions for burning pain are discussed in the following section, Pain of Unattached Tissue and the Tongue.

Other Problems. Ulcerative pain resulting from allergy, dermatologic disorders, or systemic diseases of unknown cause can often be managed effectively by topical application of a low-potency (e.g., hydrocortisone 1% or methylprednisolone 0.25%), moderate-potency [e.g., triamcinolone acetonide 0.1% (Kenalog, Aristocort); fluocinonide 0.01%, as a gel], or high-potency (e.g., betamethasone dipropionate 0.05%, triamcinolone acetonide 0.5%) corticosteroid. In cases in which ulceration is severe, systemic corticosteroid therapy can be a more useful intervention. The therapeutic goal of a systemic corticosteroid therapy is to suppress lesion development and prevent scarring. This is best accomplished by an initial starting dose of 20 to 32 mg per day, tapered to 0 mg over 7 to 10 days (127).

In cases in which candidiasis is suspected of complicating the clinical course of the ulcerative process, use of topical nystatin rinses or antifungal troches can be helpful. Secondary bacterial infection and pain can be minimized by tooth brushing and flossing, oral hygiene techniques designed to eliminate dental plaque.

Patients with allergy may benefit from nutritional management. If trauma (e.g., from poor dental fillings or sharp tooth cusps) is suspected of contributing to ulcer formation, dental restorative treatment is appropriate (128).

Pain of Cheek, Tongue, and Soft Palate

Etiology. Pain identified with the buccal mucosa, tongue, and soft palate results primarily from ulceration associated with trauma (e.g., cheek or tongue biting, chemical burns) (Fig. 50-12); infection (e.g., primary herpes, herpangina); aphthous ulcers (major, minor, and herpetiform); systemic conditions such as erythema multiforme (Stevens-Johnson syndrome), Behçet's syndrome, lupus erythematosus, pemphigus, BMMP, lichen planus, diabetes, exanthematous disease (e.g., migratory glossitis associated with psoriasis), nutritional deficiency (e.g., anemia), or blood dyscrasia (e.g., cyclic neutropenia); and neoplasm (e.g., squamous cell carcinoma, lymphosarcoma, acute leukemia).

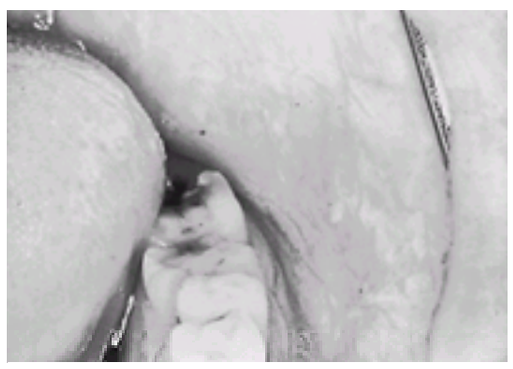

Figure 50-12. Ulceration and slough of the buccal mucosa in the left cheek adjacent to the lower molars following prolonged aspirin contact. (Courtesy of T. Morton, Department of Oral Pathology, University of Washington.)

The cause of perioral burning pain and glossodynia (burning tongue) is not presently understood. The condition has been associated with local irritation, chronic fungal infection (candidiasis), systemic nutritional deficiencies (primarily of vitamin B_{12} but also of vitamins B_1, B_2, and B_6), and xerostomia (129). In addition, depression has also been identified as contributing significantly to the condition (see Chapter 26).

Burning pain connected with numbness of the tongue has been reported following development of adenoid cystic carcinoma (a rare disease) in the floor of the mouth (130).

Symptoms and Signs. Depending on the extent of ulceration, mucosal ulcer pain is typically described as a mild to severe dull ache or burning. Whereas it is generally intermittent in presentation, ulceration associated with conditions such as bullous pemphigoid and its variants (e.g., pemphigus vulgaris), lupus erythematosus and its variants (e.g., chronic discoid lupus), neutropenia, periadenitis mucosa necrotica recurrens (major aphthous ulcer), and Behçet's syndrome can persist over weeks, months, or years. Typically, aggravation of ulcerated mucosal tissue by sour spicy food, alcohol, and superinfection increases pain severity.

Additional clinical features associated with erythema multiforme include hemorrhagic crusting of the lips and *target* or *iris* lesions on the skin. In Behçet's syndrome, ocular inflammation (conjunctivitis) and genital ulcers may also be evident. Erythematous cutaneous lesions occurring on the cheeks and bridge of the nose (in a butterfly pattern) are a characteristic clinical feature of chronic discoid lupus erythematosus, with oral lesions observed in approximately 20% to 25% of these cases. Oral ulceration is a more frequent finding with systemic lupus erythematosus (seen in 40% of cases), a disease that is also characterized by multiple signs and symptoms including arthritis, fever, renal involvement, cardiopulmonary abnormalities, and neurologic changes.

Historically, oral cancer (e.g., squamous cell carcinoma) has not been thought of as causing pain, although mild mucosal discomfort usually leads the patient to seek medical care (131). In some case reports, intraoral mucosal neoplasm is reported to cause pain that is shooting, stabbing, or radiating (132). Although only 3.2% of all neoplasms in patients in the United States are located intraorally (with 90% of these being squamous cell carcinoma), the increasing use of snuff might have a significant effect on future incidence of cancer pain (133). An observed intraoral feature of advanced acute leukemia is painful deep ulceration of the gingival and nongingival mucosa.

Patient description of the burning pain of the buccal mucosa, tongue, and soft palate is similar to that of gingival burning pain. It can also be combined with altered taste (metallic) and mouth dryness. Frequently, distinct intraoral pathologic findings are absent.

Treatment. As previously described, treatment of oral ulceration is primarily symptomatic, with adequate pain control generally obtained through the use of analgesics and topical or, in severe cases, systemic corticosteroids. Evidence has shown that for major aphthous ulcers the duration of painful episodes can be reduced with pharmacologic intervention consisting of immune stimulations such as levamisole (in a dosage as low as 150 mg a week) (134) or thalidomide (135).

Soft tissue wounds caused by trauma (e.g., by dental instruments, pencils) should be irrigated thoroughly with sterile saline solution. Tetanus immunization should always be considered. Pain resulting from secondary bacterial infection can be reduced by application of 3% H_2O_2 (on a cotton swab) and an emollient (Orabase) to the ulcer(s) (rinsing with 3% H_2O_2 can cause additional ulceration), by use of an oral rinse of 1% chlorhexidine gluconate (three times a day), or by vigorous rinsing with a suspension of tetracycline (e.g., Minocin, 100 mg every 12 hours or Achromycin V oral suspension) or Achrostatin V (a combination of tetracycline HCl, 125 mg per 5 mL, and nystatin, 125,000 U per 5 mL) followed by expectoration. A 5% paste of amlexanox has been reported to significantly affect healing time and pain resolution (136). Surgery and grafting might be necessary to control the nonresolving deep ulceration of a major aphthous.

Mucosal pain related to extensive infiltration of squamous cell carcinoma or to lymphosarcoma often required narcotic analgesics along with radiation, surgery, and chemotherapy. Adjunctive oral therapy in the management of mucositis from treatment of leukemia, covered in Chapter 38, include frequent saline rinses and appropriate antibiotic, viral, or fungal coverage.

Although the research is limited, pain resulting from persistent oral mucosal ulceration associated with conditions acknowledged to be highly stress related (e.g., BMMP, lichen planus, lupus erythematosus, aphthous ulcers) can benefit from psychological and behavioral strategies (i.e., interventions intended to managed stress, disability, and suffering), which have been found to be useful in managing other chronic pain and disease states. Dental treatment (e.g., restoration or a maxillary

splint) might be necessary if cheek biting is contributing to ulcer formation or maintenance.

Burning pain associated with candidiasis is most effectively managed with topical antifungal troches (e.g., clotrimazole or nystatin), because delivery of the drug in this fashion allows for prolonged dispersal. Burning pain associated with vitamin deficiency can be treated with appropriate replacement therapy.

Other recommended therapies for gingival, tongue, or mucosal burning include dental intervention (e.g., remaking of old dentures or bridges) management of xerostomia (e.g., artificial saliva, medication change), medication (e.g., Librium, 15 to 30 mg per day), and psychological management. The efficacy of antidepressants and major (e.g., Stelazine) or minor (e.g., Valium) tranquilizer use has not been thoroughly studied, although empiric evidence shows that these medications can be helpful in reducing perceived burning pain with or without associated disease (137).

CONCLUSIONS AND FUTURE DIRECTIONS

Clinical terminology in this chapter was chosen because of its consistency with nomenclature proposed by the IASP Subcommittee on Taxonomy. It should be appreciated, however, that the IASP classification system represents only a first step in the establishment of scientifically valid clinical criteria for defining odontogenic and mucosal problems causing facial pain. Future clinical research must focus on assessing the reliability, validity, and relative predictive values for the varied pain factors, signs, laboratory findings (if any), and radiologic findings associated with conditions causing odontogenic and mucosal pain. Future revision of the IASP taxonomy will also benefit from inclusion of a distinct diagnostic category for pain of mucosal origin associated with disease, which was neglected in the initial treatise (15). Given that chronic orofacial pain of odontogenic and mucosal origin may be associated with emergence of psychological and behavioral factors that can confound patient presentation and management, there is a need for research that not only elucidates biological disease issues but also enlightens with respect to the many potential biobehavioral factors effecting disease, chronicity, and management.

Advances during the 1990s, especially in the molecular neurobiology of pain, are bringing us into a new era of pain management using new and innovative pharmacologic tools. Current research should further improve our understanding of the special problems associated with orofacial pain in the young and elderly and the social problems of delivery of proven therapeutics to underserved world populations. In 1990 the use of tricyclic antidepressants was just beginning for complex regional pains including those in the orofacial area. Now that strategy is widespread and of proven efficacy. The information presented in this chapter suggests that there will be similar important advances in many areas including the following areas in the near future:

- Targeting of specific pharmacologic drugs to specific nociceptive mechanisms (138), as with the current efforts to develop nonsteroidal antiinflammatory agents that inhibit the inducible cyclooxygenase 2 enzyme without side effects from inhibition of cyclooxygenase 1 systems (139,140 and 141)
- Development of a new set of topical analgesics, such as capsaicin, for which clinical research has provided some intriguing data that should become firmly established soon (131,142)
- Introduction of centrally acting receptor antagonists such as the *N* -methyl-d-aspartate receptor antagonist or neurokinin receptor antagonists, as well as new generations of more specifically targeted drugs (143)
- Cellular engineering for delivery into the CNS of transplantable cells that make inhibitory agents for persistent pain problems of cancer or neuropathic injury (144,145)
- Human and animal genomic information to pinpoint the genes responsible for specific pain mechanisms, allowing more selective diagnosis and therapies (146,147)
- Better outcome analyses and educational efforts so that our present knowledge about orofacial pain management or prophylaxis can bring more effective care to underserved populations (148)

These potentially important strategies, coupled with continued international cooperation and efforts in providing improved access to service in developed as well as underdeveloped countries (via subsidization of care, improvement of socioeconomic status and elimination of gross social inequality, education with respect to diet and behavioral modification, and the implementation of fluoridation) should contribute significantly to a decline in worldwide caries and other oral infection problems and associated pain and suffering in the near future.

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CHAPTER 51

Ocular and Periocular Pain

James C. Orcutt

Pain in and about the eyes is remarkable for its intensity and its ability to provoke anxiety. Second only to the fear of death, the fear of blindness aroused by ocular pain often leads to emotional responses on the part of both the patient and the physician that can hinder proper diagnosis and treatment. Systemic symptoms of eye disease including nausea, vomiting, and prostration in an anxious patient, on more than one occasion, have led the unwary physician astray in the diagnostic quest. Similarly, the fear generated by ocular pain can lead the patient to overemphasize the symptom. The nature of the pain (e.g., location, intensity, variability, tenderness) is an often underused clinical symptom. Although most ocular or periocular pain is not related to eye disease, specific indicators should be noted that increase the likelihood of eye disease (1). A specific example is the patient presenting with oculosympathetic paresis (Horner's syndrome), tearing and intense headache localized around the right eye (Fig. 51-1). The diagnosis of cluster headache was made; however, the unrelenting nature of the pain suggested another cause. Carotid arteriogram disclosed a dissection of the carotid artery. The differential symptom in this case was the temporal nature of the pain.

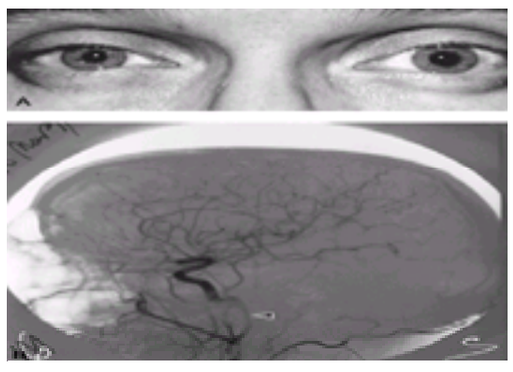

Figure 51-1. **A:** A 35-year-old man developed right-sided severe headaches 2 weeks after falling off a roof. The pain was constant, always right–sided, and associated with a small right pupil and mild ptosis (Horner's syndrome). **B:** Autography was ordered because of relentless pain, which disclosed a carotid artery dissection (*arrowhead*). (Reprinted from Orcutt JC. Neuro-ophthalmic aspects of orbital disease. In: Duane TD, ed. *Duane's clinical ophthalmology* . Vol 2. Philadelphia: Lippincott, 1992:20, with permission.)

Prompt attention to ocular pain is important not only for the relief and reassurance of the patient, but also to prevent vision loss caused by disorders such as angle closure glaucoma, in which the extent of structural and functional damage to the eye is directly related to the duration of the attack. The physician must guard against complacency when approaching the patient with ocular pain because of the great frequency of complaints of facial and head pain unrelated to potentially damaging organic disease. In contrast, pain is not a feature of the major blinding eye diseases (e.g., cataract, open angle glaucoma, and retinal diseases); attention to signs and symptoms other than pain, together with regular screening examinations, is required for accurate diagnosis.

This chapter is organized in three sections: anatomy; clinical signs and symptoms of ocular, periorbital, and functional pain; and management. The clinical section describes the signs and symptoms of the six types of ocular and periocular pains (i.e., ocular pain, pain with eye movement, deep orbital pain, tenderness, referred pain, and functional pain). Following the description of each type of pain, common clinical examples are described.

The reader is referred to the work of Tang and Pardo (2). Additional reviews of pain include those by Miller (3), Atkinson (4), Orcutt (5), Sires and Orcutt (6), Rootman (7), and Dalessio and Silberstein (8).

ANATOMY

Anatomy of Ocular and Orbital Pain

The primary sensory supply to the eye, orbit, and ocular adnexa is the ophthalmic division (V1) of the trigeminal nerve, although the maxillary division (V2) supplies most of the lower eyelid and the temporal aspect of the orbit (Fig. 51-2). The sensory (nociceptive) distribution, primarily through the nasociliary branch, does not parallel the visual sensory function because the ocular structures responsible for the sensation of light, the retina and optic nerve, are totally devoid of pain and touch sense. Conversely, the cornea has as many pain endings as any tissue in the body. The great sensitivity of the cornea to pain presumably serves to initiate avoidance behavior and the blink reflex serves to protect the eye. The cornea has a dual sensory input, an anterior subepithelial plexus, and a midstromal plexus (9).

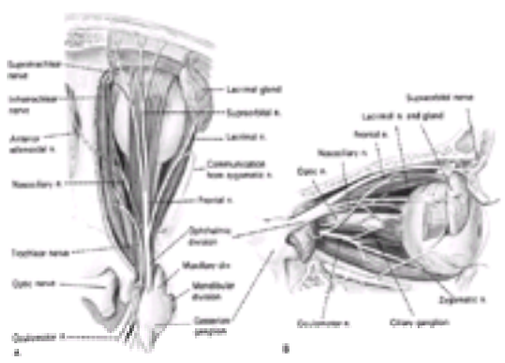

Figure 51-2. Anatomy of the nerves to the eye. **A:** Superior view. **B:** Lateral view.

In addition to many naked nerve endings mediating pain in the epithelium of the cornea and conjunctiva, receptors for touch and cold, and probably also for heat, are found. Photophobia can be induced by corneal epithelial erosion, intraocular inflammation, or even occipital injury (1). Unlike the cornea, the conjunctiva has many fewer nerves, resulting in only mild pain when irritated.

The uveal tract, especially the iris, contains abundant nociceptors, as demonstrated by the response of the patient undergoing surgical iridectomy when the previously placed retrobulbar block is inadequate. The iris also has heat receptors, because pain can be produced by laser burns of sufficient intensity (1).

Within the orbit, nociceptive endings within the extraocular muscles, the dural sheath of the optic nerve, and the periorbita are responsible for the sensation of pain when they are stretched (10). Tumor invasion of sensory nerves is occasionally responsible for periocular pain. Tenon's capsule surrounds the posterior globe, much like the synovial membrane in joints. As in inflammation in joints, inflammation of Tenon's capsule (i.e., scleritis) results in severe pain and tenderness.

Anatomy of Referred Orbital Pain

Without regard for the site at which the neural pathway of the trigeminal nerve in its course from the face to the cortex is stimulated, the sensation produced is interpreted by the patient to have originated from the location of the receptors for that sensation. The branches of the ophthalmic division (V1) include the nasociliary, frontal, lacrimal, and meningeal. The nasociliary branch of V1 supplies the globe as was described in the previous section on ocular pain. In addition, the nasociliary branch receives input from the ethmoid sinuses, nasal mucosa, skin on the tip of the nose, and medial eyelids. The meningeal branches of V1 innervate the cavernous sinus and meninges surrounding the cavernous sinus, including the cerebellar tentorium, falx cerebri, cribriform plate, and sphenoid wing. The lacrimal branch receives sensation from the lateral canthus and temporal conjunctiva. The sensory distribution of the lacrimal nerve may be manifest during cataract surgery when retrobulbar anesthesia is used. The temporal conjunctiva retains sensation because the lacrimal nerve is outside the muscle cone and is not blocked with the retrobulbar anesthetic. The frontal nerve innervates the forehead, medial upper eyelid, and the frontal sinus mucosa.

The maxillary division (V2) innervates the orbit and periocular structures through the zygomatic and infraorbital branches. The zygomatic branch innervates the lateral eyelids and temporal skin through its zygomaticotemporal and zygomaticofacial branches (Fig. 51-3). The parasympathetic fibers supplying the lacrimal gland traverse the zygomatic nerve in its course from the sphenopalatine ganglion to the lacrimal gland. Damage to the zygomatic nerve in the orbit may result in decreased ipsilateral reflex tearing. The infraorbital division supplies sensation to the upper teeth, oral mucosa, and the skin from the lower eyelid to the upper lip. Intracranial branches supply the dura of the middle cranial fossa.

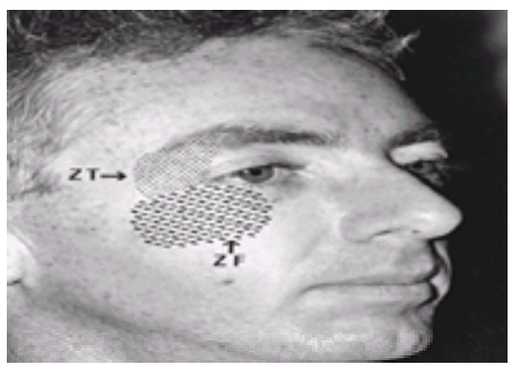

Figure 51-3. Peripheral distribution of the zygomaticotemporal (ZT) and zygomaticofacial (ZF) nerves.

Irritation of any of these branches by inflammation, or occasionally by tumors, can result in pain referred to the globe. Examples include such diverse diagnoses as postherpetic neuralgia, sphenopalatine tumors, cavernous sinus aneurysms, sinus inflammation, neurotropic lacrimal gland tumors, and tension headaches.

The nucleus caudalis of the trigeminal complex extends into the upper cervical spinal cord (11). Nociceptive input from C-1 and C-2 (12) can result in pain sensation around the orbit, perhaps because of the medullary anatomy. Greater occipital neuralgia, trapezius muscle spasm, or cervical arthritis commonly result in referred ocular or periocular pain (2). Local injection of local anesthetic and corticosteroid may result in improvement of pain (13) (see Chapter 29).

SYMPTOMS AND SIGNS OF OCULAR AND PERIOCULAR PAIN

Ocular and periocular pain can be divided into three groups: ocular, orbital, and functional pain. Specific facial pain syndromes that may be distributed in the periocular region, such as temporomandibular joint syndrome, temporal arteritis, dental pain, sinusitis, and tic douloureux, are discussed in Chapter 46, Chapter 47, Chapter 48, Chapter 49 and Chapter 50, Chapter 52, and Chapter 53. The description of ocular pain provided by the patient is often graphic and complete, because it has occupied all the patient's attention for the preceding hours or days. The localization of the pain by the patient is often erroneous. Some knowledge of differential symptoms and signs allows the physician to direct the examination properly as well as to make preliminary decisions regarding the urgency to which the problem must be addressed.

Ocular Pain

Foreign Body Sensation

We have all experienced a foreign body sensation when a grain of sand or a hair gets into our eye and we blink violently to remove it. This sensation of a foreign body on the surface of the eye arises from interruption of the surface epithelium and from mechanical stimulation of the subepithelial plexus of nerves. Most commonly, the corneal epithelium has been abraded by trauma, exposing the pain fibers, and no foreign body is present in spite of the patient's insistence (Fig. 51-4). A thorough search should be made for a foreign body, but symptoms often exist in its absence. The patient localizes the foreign body under the upper eyelid, regardless of the actual site of the epithelial injury. This is because of Bell's phenomenon; every time the patient closes the eye, the cornea moves upward under the upper eyelid. Foreign body sensation usually causes the patient to seek attention promptly but rarely indicates a disorder likely to cause severe vision loss.

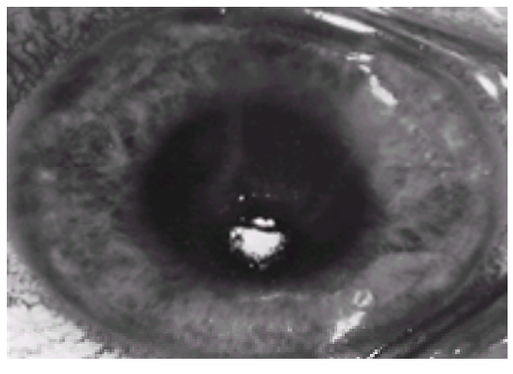

Figure 51-4. Corneal abrasion. A twig had brushed the cornea 6 hours previously. The patient localized a foreign body sensation under the upper lid. Increasing tearing and photophobia ensued. No foreign body was found. Fluorescein placed in the tear film stained the abrasion. Patching and cycloplegia with 5% homatropine

drops led to healing in 24 hours.

Aching Ocular Pain

Deep aching ocular pain originates from the uveal tract, especially the iris. The pain is caused by traction or stretching resulting either from acutely increased intraocular pressure or from the inflammation of anterior uveitis, often with secondary irritative spasm of the intraocular muscles. The pain can be referred to other ipsilateral parts of the face, especially the teeth. Systemic responses may include nausea, vomiting, and prostration and can overshadow the ocular disease. Laparotomy has been considered and in some cases performed before the proper ocular diagnosis was made. Systemic side effects can be caused in part by reflex vagal stimulation (14). Severe aching ocular pain indicates a disorder that requires prompt and effective therapy to prevent vision loss.

Pain with Use of the Eyes

A specific type of aching ocular pain deserves discussion, asthenopia, or *eye strain*. Pain syndromes, especially headaches, fatigue, and even vision loss, frequently have been attributed to the overuse of the eyes. The eyes are often blamed, particularly in the presence of a motor or refractive anomaly of the eyes that would have been considered trivial in the absence of the pain syndrome. Visual tasks require eye movements and alignment by the extraocular muscles as well as contraction or relaxation of the ciliary muscle to allow changes in focus. The muscles involved possess a contractile force many times greater than that which they are called on to exert and, because of their rich blood supply and other physiologic factors, they can contract actively for long periods of time without fatigue (15). Although it is true that, during a task such as reading, both the extraocular and intraocular muscles are in a nearly constant state of activity, no evidence has been found suggesting that these are not requirements of which they are easily capable or that such activity should result directly in pain or fatigue.

Too much importance has been attached to the correction of minor refractive errors, small degrees of eye muscle imbalance, and assorted other insignificant ocular variations. Headache, fatigue, and other discomfort frequently follow extensive use of the eyes, but these symptoms are related to the demands of the task itself, such as head posture or squinting, and are not mediated through the eyes. Therefore, it should not be expected that these mechanisms are influenced by spectacles or ocular alignment, and any benefits claimed for such treatments must be attributed to nonspecific effects (see Chapter 81). Similarly, no grounds exist for the popular belief that use of the eyes, especially under conditions of stress or when associated with headache and fatigue, leads to vision loss or permanent ocular damage.

Signs and Symptoms Associated with Ocular Pain

Photophobia or light-induced pain usually increases the pain associated with a corneal epithelial defect or the aching ocular pain associated with intraocular inflammation. Patients generally prefer to have the eye covered or use sunglasses to reduce photophobia. Paralyzing the ciliary muscle with a topical cycloplegic agent, such as atropine, reduces photophobia associated with intraocular inflammation.

The conjunctiva is often injected (conjunctivitis) and edematous (chemosis) when inflammation is the etiology of ocular pain. Typically, the injection is most intense around the edges of the cornea (ciliary flush) when the inflammation is intraocular. If the inflammation is anterior in the globe, the cornea commonly becomes edematous as well, resulting in decreased vision and halos around lights. Any of these symptoms associated with ocular pain should alert the clinician about the potential of vision-threatening intraocular inflammation.

Common Painful Ocular Diseases

Uveitis. Inflammatory disorders of the iris (iritis) or ciliary body (cyclitis) are collectively called *anterior uveitis* and can be exquisitely painful (16). Posterior uveal inflammations (choroiditis) are usually painless. Most nontraumatic inflammations of the uveal tract are idiopathic. Treatment directed at suppression of inflammation is often effective in the absence of specific therapy. Corticosteroids may be administered topically or by periocular injection (17). Oral corticosteroids are useful for short-term control of uveitis but should be replaced by topical or locally injectable preparations when possible to avoid undesirable effects with prolonged systemic use. Local and occasionally systemic corticosteroid therapy can produce glaucoma in susceptible persons, and periodic tonometry is indicated (18).

Although corticosteroids administered as described previously are important in the treatment of uveitis, the associated acute pain of anterior uveitis, especially the pain with light exposure, is caused by spasm of the irritated muscles of the iris and ciliary body. Prompt relief of the aching and photophobia is obtained by use of a cycloplegic drug such as atropine (Table 51-1). Cycloplegia should be maintained until all signs of inflammation have subsided.

Agent	Commonly used ophthalmic concentrations (%)	Duration of action	Indications
Cyclopentolate	1	6–48 hr	Diagnostic procedure; corneal abrasion
Homatropine	2–5	12–72 hr	Corneal abrasion; mild inflammation
Scopolamine	0.25	48 hr to 7 days	Inflammation
Atropine	1.0	5–14 days	Severe inflammation

TABLE 51-1. Cycloplegic drugs

Herpes zoster affecting the ophthalmic division of the trigeminal nerve can lead to a particularly recalcitrant uveitis associated with secondary glaucoma or hyphema (16,19). Whereas severe pain can precede cutaneous signs that lead to a diagnosis, uveitis usually appears after the disease is well established. The uveitis can occur alone or in association with corneal involvement. Treatment includes prolonged use of atropine and, if necessary, topical corticosteroids, together with acetazolamide to control secondary glaucoma. Chronic pain is usually not caused by uveitis but by postherpetic neuralgia (see Chapter 22).

Occasionally, recalcitrant intraocular inflammation may necessitate the use of systemic immunosuppression. Agents such as cyclosporin, azathioprine (Imuran), and methotrexate have been used in specific cases (20). The use of these agents requires monitoring for possible systemic side effects, such as immunosuppression and renal failure. Ideally, management of such cases can be facilitated by a team composed of ophthalmologists and rheumatologists, immunologists, or oncologists.

Corneal Diseases. Any interruption of the continuity of the corneal epithelium results in pain, tearing, and photophobia. Such symptoms are most often provoked by an obvious cause such as trauma (e.g., foreign body) or chronic abuse (e.g., contact lens overwearing). Apart from mechanical trauma to the cornea and infections, several corneal disorders are notable because of the prominence of pain as a symptom.

The use of prolonged topical anesthetics can lead to corneal epithelial breakdown. The patient might desire the drug for pain relief. Supervisors of workers who are exposed to such insults, particularly welders, have been known to provide eye drops that allow the injured person to continue working. This practice ultimately prolongs healing and results in more time loss than would be required for appropriate therapy. Nonsteroidal antiinflammatory drugs (NSAIDs) may provide some pain relief and do not carry the risk of corneal toxicity.

Ultraviolet Keratitis (Photophthalmia). Wavelengths of light between 314 and 250 nm (ultraviolet) are absorbed by proteins of the corneal epithelium and lead to cell death (21). Common sources of damaging ultraviolet radiation include arc welders, sunlamps, and reflected sunlight from snow or sand. The onset of symptoms, occurring 6 to 8 hours after exposure, is explosive, progressing rapidly from foreign body sensation to severe pain and photophobia with blepharospasm. Examination

after application of topical anesthetic shows diffuse corneal epithelial edema.

Treatment consists primarily of patching and cycloplegia, as with any corneal epithelial disturbance. NSAIDs and a bandage contact lens may be alternatives. Frequently, pain is severe enough to warrant the use of narcotic analgesia, a requirement that should be anticipated before allowing the patient to return home, where the effects of the diagnostic drop of topical anesthetic soon end. Healing is usually complete in 24 to 48 hours (22).

Recurrent Corneal Erosion. Recurrent episodes of pain, tearing, and foreign body sensation in one eye, usually on awaking in the morning, are typical symptoms associated with recurrent corneal erosion (23,24). Examination shows a corneal epithelial defect, often minute, in the same location with each episode. Frequently, a traumatic corneal abrasion has preceded the onset of the erosion by weeks or months. A deficiency of attachment of the regenerated epithelium to the basement membrane has been implicated as a causative factor (25,26). Each episode is treated in the same manner as a traumatic corneal abrasion by patching and cycloplegia, and recurrences eventually cease. A bland ophthalmic ointment can reduce the risk of recurrence if used before retiring each night. Dehydrating drops or ointment with sodium chloride may reduce the frequency of recurrence. Soft contact lenses are useful in some cases. Severe, recurrent erosions can be treated by micropuncture of the cornea (27) or phototherapeutic keratectomy with an excimer laser (28).

Bullous Keratopathy. The posterior layer of the cornea, the endothelium, functions to dehydrate the cornea against the hydrostatic effects of intraocular pressure (29). If the endothelium fails, either because of intrinsic disease or increased intraocular pressure, fluid accumulates throughout the cornea, especially within and beneath the basal layer of corneal epithelium. If severe, and particularly when chronic, corneal edema can elevate the corneal epithelium in blisters leading to bullous keratopathy. The bullae frequently rupture, resulting each time in an acute episode of pain and tearing.

Acute treatment of ruptured corneal epithelial bullae must promote healing through the use of patching, cycloplegia, and lubricating solutions, but healing is slow in a diseased cornea. More definitive treatment includes lowering of intraocular pressure, even if not originally elevated to levels usually considered pathologic, and replacement of the diseased cornea and its endothelium by corneal transplantation. Chronic dehydration of the edematous cornea by frequent topical application of hypertonic saline solution or ointment can be tried but is often unsuccessful because of failure to dehydrate sufficiently or because of irritation. Bandage and soft contact lenses can provide pain relief for patients for whom medical therapy has failed and surgery is not warranted (30,31).

Glaucoma

Angle Closure Glaucoma Angle closure glaucoma occurs in middle-aged and elderly persons who are anatomically predisposed because of developmental crowding of the anterior segment (32,33). The onset is sudden and often accompanied by nausea, vomiting, and prostration (34). The eye is injected, and the cornea is gray with edema. The pupil is middilated and fixed (Fig. 51-5). A few patients might have repeated subacute attacks of angle closure that terminate spontaneously but produce permanent anatomic damage to the anterior segment. The pain of angle closure is initially controlled medically by lowering the intraocular pressure (34) (Table 51-2). Historically, surgical iridotomy was performed through a small corneal incision; however, with the advent of laser technology, iridotomy can be performed with either the argon or yttrium-aluminum-garnet laser as a rapid clinical surgical procedure (35). Chronic pain control should not be required (34). The diagnosis of acutely elevated intraocular pressure must be made by tonometry, never by palpation of the globe or by history alone.

Drug	Suggested dosage
Pilocarpine, 1–4%	One drop to affected eye every 5 minutes x3
Diamox	250–500 mg PO or IV
Glycerol	0.7–1.5 mL (50% solution) per kg body weight PO
or	
Mannitol	1.0–2.0 g/kg body weight IV

TABLE 51-2. Emergency medical therapy of angle closure glaucoma

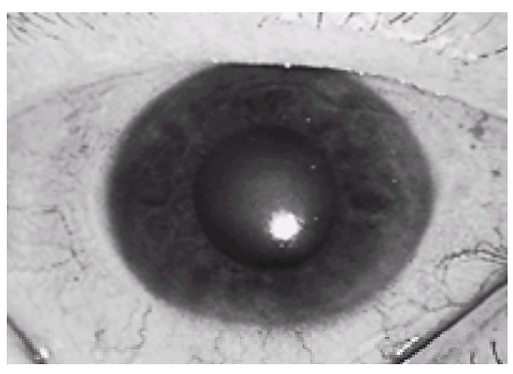

Figure 51-5. Angle closure glaucoma. The eye is acutely congested, with a hazy cornea. The pupil is middilated and fixed to light. The intraocular pressure is 50 mm Hg. Medical management (see Table 51-2) resulted in normal pressure, and laser iridectomy was performed 48 hours later.

Neovascular Glaucoma. Neovascular glaucoma is a form of glaucoma that is particularly difficult to control (35). It occurs most often in the eyes of diabetics, usually in combination with severe proliferative retinopathy. Neovascular glaucoma can also occur after occlusion of the central retinal vein, retinal vasculitis, or following trauma or ocular inflammatory disease (36,37). Rarely does neovascularization occur after central retinal artery occlusion. A fibrovascular membrane develops in the angle of the anterior chamber and on the surface of the iris, which leads to angle closure (36) (Fig. 51-6). The aqueous has no avenue for drainage. Repeated hemorrhage into the anterior chamber (hyphema) can occur. Pain is often severe and accompanied by vomiting and dehydration, a particularly serious management problem in the diabetic.

Figure 51-6. Histopathology of neovascular glaucoma. The iris root and filtration angle are shown. New vessels are present (*arrow*); they have caused closure of the filtration angle (*). (Hematoxylin and eosin stain, ×40.)

The angle closure of neovascular glaucoma is not relieved by iridectomy, and other conventional glaucoma operations often yield disappointing results. Procedures designed to decrease aqueous production by partial destruction of the ciliary body (e.g., cyclodiathermy, cyclocryotherapy) are often used, but these tend to be unpredictable, and often the result is a chronically agonizingly painful eye (32).

The medical therapy of neovascular glaucoma is designed to decrease intraocular pressure and control pain (37). The usual treatment of glaucoma must often be modified because acetazolamide and especially osmotic agents result in metabolic changes that might be unacceptable in the diabetic patient. Topically applied miotics are routinely used in the medical management of open angle glaucoma, but use of these agents in neovascular glaucoma produces a marked *increase* in pain with little or no effect on intraocular pressure.

Most often, the physician is faced with control of pain in an eye hopelessly affected by neovascular glaucoma. Although enucleation is the usual final result, such eyes with elevated intraocular pressure can usually be made comfortable for a time with the use of topical cycloplegics (see Table 51-1) and corticosteroids (prednisolone acetate 1%), perhaps combined with acetazolamide (250 mg four times a day), topical epinephrine solution (1%), or a topical b-blocker. Retrobulbar alcohol injection can also control pain, at least temporarily, and is especially indicated if useful vision remains (38,39). Thermocoagulation of the trigeminal ganglion can also provide pain relief in these patients.

Hyphema. Hemorrhage into the anterior chamber (hyphema) can occur following blunt trauma to the eye (Fig. 51-7). Most hyphemas clear spontaneously with rest. Rebleeding can occur, however, and the anterior chamber might become filled with blood, resulting in symptoms similar to those of angle closure glaucoma. Medical measures such as those described for angle closure glaucoma are usually sufficient to control the pressure and pain (40). Aminocaproic acid has been shown to be beneficial in decreasing the incidence of secondary hemorrhage (41). Occasionally, surgical removal of the hyphema is necessary to control the pressure (42).

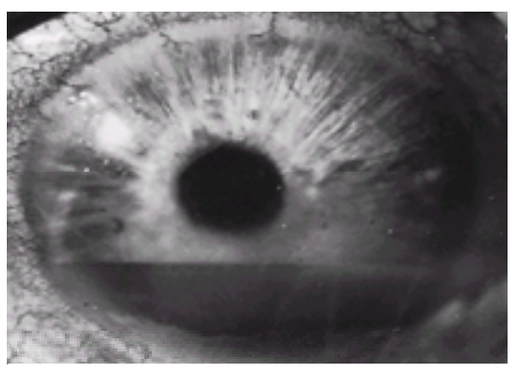

Figure 51-7. Forty percent hyphema following a handball injury. The eye was injected and mildly painful. The blood cleared over the next 5 days on a regimen of limited activity, eye protection, and aminocaproic acid.

Refractive Surgery. Refractive surgery is becoming a commonly performed surgical procedure to correct myopia or astigmatism. Commonly used procedures include radial keratotomy, photorefractive keratotomy, and laser *in situ* keratomileusis. Patients report mild to moderate pain for a few days following the procedure, more pronounced with radial keratotomy than the other procedures (43,44). Blurred vision, photophobia, halos, and glare are commonly reported, but usually clear several days to weeks after the procedure. The pain is usually managed with the use of a topical anesthetic, topical NSAIDs (e.g., indomethacin, diflorinac), and a bandage contact lens (45,46).

Accommodative Spasm. Accommodative spasm may accompany closed head injury or more commonly is functional. Typically, the patient presents with accommodative myopia caused by contraction of the ciliary body, meiosis, and esotropia (27). When prolonged, the patient may experience asthenopic or eye strain symptoms. Management consists of the use of cycloplegic agents (e.g., atropine, homatropine, scopolamine) and bifocals for several months.

Orbital and Periorbital Pain

Structures in the orbit with pain receptors include the optic nerve sheath, fascial sheath surrounding the globe (Tenon's capsule), periorbita, and sheaths of the extraocular muscles. When any of these structures is inflamed, pain is localized to the orbit. In addition, pain may be referred to the orbit from nerves with common innervation (i.e., referred pain). Typically, when orbital structures are involved, the associated orbital and periorbital pain presents in one of four scenarios: pain with eye movement, deep orbital pain, tenderness, and referred pain (47).

Pain with Movement of the Eyes

Approximately 80% to 92% of patients with optic neuritis complain at some time of pain intensified by movement of the eye (48,49). The pain usually lasts for approximately 1 week and improves as visual acuity improves. The pain is generally not overwhelmingly severe and presumably is caused by stretching of the inflamed pain-sensitive sheaths of the pain-insensitive optic nerve.

Anterior sinusitis can also present with pain on eye movement (10). This symptom is probably a result of inflammation of the adjacent periorbita or extraocular muscles that are mechanically stimulated with eye movement. Idiopathic inflammation of the orbit may also be localized to extraocular muscles (i.e., myositis). Movement of the eye with associated muscular contraction results in pain caused by mechanical stimulation of the muscular septa.

Deep Orbital Pain

Pain secondary to orbital disease is uncommon (Table 51-3); however, when present, it is useful diagnostically. Pain caused by orbital disease is generally moderate to severe, commonly keeps the patient awake at night or wakens him or her from sleep, is exquisitely localized directly behind the globe, is commonly associated with motor dysfunction (i.e., ptosis or diplopia), is deep and boring in nature, and is generally not in question by either the patient or physician (Fig. 51-8).

Orbital diseases commonly painful	Orbital diseases uncommonly painful
Idiopathic orbital inflammation (pseudotumor)	Metastatic disease to the orbit
Adenocystic carcinoma of the lacrimal gland	Lymphoma
Acute orbital hemorrhage	Orbital abscess
Cellulitis	Cavernous hemangioma
	Thyroid eye disease

TABLE 51-3. Pain caused by orbital disease

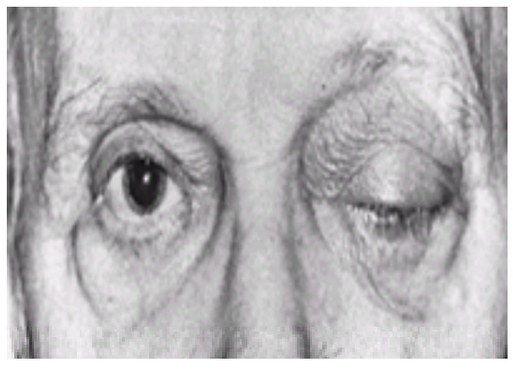

Figure 51-8. Patient presented with acute, severe, boring pain centered behind the left eye. Erythema, ptosis, and limited eye movement were present. Idiopathic orbital inflammation (pseudotumor) was diagnosed and responded to oral corticosteroids.

Orbital Inflammatory Pseudotumor. Pain is a common presenting symptom of idiopathic orbital pseudotumor, especially if onset is acute (48,50,51,52). Eyelid edema, proptosis, and diplopia commonly accompany the pain and can mimic signs of an intraorbital tumor. Most lesions respond to systemic corticosteroids (52,53). Occasionally, radiotherapy is required (51,54). Lesions unresponsive to corticosteroid therapy, especially if chronic, require biopsy to rule out the presence of a tumor.

Orbital Tumors. Primary and secondary orbital tumors are usually painless. The main exception is some malignant lacrimal gland tumors (55), primarily adenoid cystic carcinomas (56), and squamous cell carcinomas (57). The pain and often-accompanying decreased sensation are caused by the perineural invasion typical of these tumors (48,55,57). Decreased sensation in the distribution of the involved nerve is often associated (47).

Acute Orbital Hemorrhage. Trauma leads to most orbital hemorrhages, and the diagnosis is usually clear. Spontaneous orbital hemorrhages can produce sudden pain, proptosis, and nausea, commonly accompanied by vomiting (56). Most patients with spontaneous orbital hemorrhages have preexisting venous anomalies, but atherosclerosis, hypertension, blood dyscrasias, anemia, and obstetric labor have been associated (56).

Orbital Cellulitis. Orbital cellulitis is usually secondary to contiguous sinusitis. Proptosis, pain, chemosis, and ophthalmoplegia are diagnostic hallmarks. Institution of systemic antibiotics and sinus drainage usually produce resolution (58). Occasionally, orbital abscesses form and must be drained (59).

Tenderness

Tenderness implies that one of the pain-sensitive structures of the orbit anterior enough to be palpated must be inflamed. Typically the inflamed structures are either the fascia surrounding the globe or the anterior periorbita. Scleritis is inflammation of the visceral surface of the fascia surrounding the globe. Scleritis may be associated with chemosis, conjunctival inflammation, and occasionally with serous detachment of the retina. Ultrasound can be useful in the diagnosis, as fluid can be seen underlying the fascia (Fig. 51-9). The lacrimal sac is surrounded by periorbita. When obstruction of the lacrimal drainage system occurs, a secondary abscess may form in the lacrimal sac (dacryocystitis). Dacryocystitis causes pain because of inflammation of the surrounding periorbita, which generally increases significantly when the area is palpated.

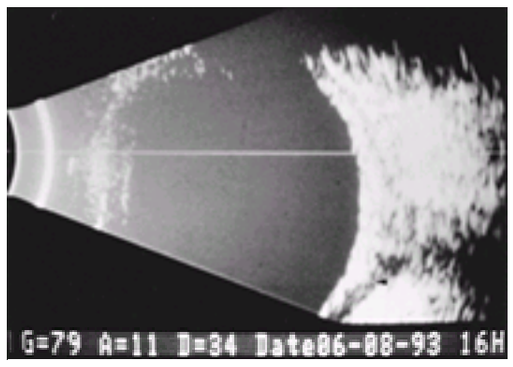

Figure 51-9. Orbital ultrasound of a patient with globe tenderness, erythema, and conjunctival swelling. Fluid collection is present outside the sclera (*arrowhead*). Posterior scleritis was responsive to oral corticosteroids.

Referred Pain

Referred pain is the most common etiology of orbital pain. Referred pain is diffusely represented around the orbit (Fig. 51-10). The pain is usually mild to moderate, rarely awakens the patient from sleep, and may be associated with other general symptoms such as cervical disease.

Figure 51-10. Typical clinical presentation of a patient with referred orbital pain.

Headache. Headache is the most common pain complaint to confront the practitioner, and the eyes are often suspected, if not blamed, as a contributing source (see Chapter 48). Most frequently, the physician must cope with the patient who appears to be entirely well and whose eyes appear normal and who has normal visual acuity, yet complains of chronic or recurrent headache. Usually chronic or recurrent headache is related to anxiety and muscular tension, without direct ocular implications. Many important causes of headache do have ocular manifestations (e.g., ischemic optic neuropathy with giant cell arteritis, papilledema with increased intracranial pressure, lid vesicles with herpes zoster, scintillating scotomata with classic migraine), but risking oversimplification, it can be said that headache in patients without ocular or periocular findings is never caused by primary ocular disorders. The eyes frequently are used extensively in anxiety-provoking or tension-producing pursuits, and it is not surprising, therefore, that the patient assumes a causal relationship when the true relationship is only coincidental.

The importance of migraine as a pain syndrome with ocular signs is so great as to warrant separate discussion. This well-known pain entity classically occurs in adults with a family history of the disorder and consists of unilateral head pain often associated with nausea and vomiting and terminates after hours or days. The onset of

headache frequently is preceded by a brief aura, most commonly visual. The visual aura can take many forms, ranging from diplopia to complete loss of vision, but most often consists of a hemianopic distribution of scintillating, often colored, jagged lines that persist for approximately 20 minutes, although less prominent visual field changes can last much longer. The spectacular aura can greatly alarm both the patient and physician, and the eyes can be further implicated in the syndrome because many patients suffer from photophobia during the period of headache. (See Chapter 48 for a more detailed discussion of migraine.)

When the migraine syndrome is complete, diagnosis is rarely difficult. Little appreciated, however, is the multiplicity of manifestations of migraine that often form an incomplete syndrome in which the diagnosis is not readily apparent. Probably the most common of the isolated manifestations of migraine is the scintillating scotoma, which often occurs in the absence of a subsequent headache. Full awareness of the characteristics and the benign nature of this superficially alarming symptom is necessary to avoid unnecessary and potentially hazardous diagnostic procedures in otherwise healthy persons.

Migrainous neuralgia (cluster headache) and Raeder's paratrigeminal neuralgia are headache syndromes that manifest with oculosympathetic findings. Migrainous neuralgia and Raeder's neuralgia can be accompanied by lacrimation and oculosympathetic palsy with ptosis, miosis, and anhydrosis (10,60,61) (see Chapter 47).

A diagnosis occasionally confused with cluster headache is dissection of the carotid artery. Dissection of the carotid may present days to weeks after a sudden deceleration trauma (e.g., falling off a roof). The patient commonly presents with ipsilateral headache and periocular pain associated with meiosis and ptosis (62).

Orbital Apex Syndrome. Inflammatory diseases located at the apex of the orbit, referred to as *orbital apex syndrome* , can inflame the frontal or nasociliary divisions of the trigeminal nerve, or both, leading to pain referred to the face or eye. Stretching or inflammation of the optic nerve sheath can also result in pain and vision loss. Inflammation can inhibit action potentials in the cranial nerves III and VI, and occasionally in the cranial nerve IV, resulting in ophthalmoplegia. Therefore, the combination of sensory loss, pain, ophthalmoplegia, and unilateral vision loss can indicate an orbital apex syndrome. Inflammation is usually caused either by orbital pseudotumor or infection (63). Rarely do tumors or vascular diseases in this area present with pain.

Parasellar Syndrome. Lesions involving the cavernous sinus lateral to the sella turcica, which can be accompanied by pain, ophthalmoplegia, and trigeminal sensory loss, include laterally expanding pituitary adenomas, intracavernous aneurysms, and nasopharyngeal carcinomas (31,64,65,66 and 67). Cavernous sinus thrombosis that follows petrositis can be accompanied by similar pain.

Fleeting Ocular Pain. Fleeting sharp ocular or periocular pain lasting 1 to 5 seconds is a common presenting complaint, sometimes called *ice-pick pain* . The pain occurs randomly, as a shooting, sharp, severe pain often described as going through the eye out the back of the head. In the face of a negative ocular history and a normal eye examination, however, these pains are unassociated with pathology (see Chapter 48).

Cervical Spine Disease. Cervical spine disease can lead to referred orbital pain. Greater occipital neuralgia, or neuritis, presents as occipital pain that spreads over the occiput to involve the periorbital region. Typically, the pain may be exacerbated by palpation of the occipital region in the distribution of the greater occipital nerve. Inflammation, arthritis, or compression of the nerve results in pain. Attacks commonly occur at night and may be associated with tearing, dizziness, and narrowing of the ipsilateral nasal passages (2,13). Initially, pain control is provided by local heat, massage, aspirin, and NSAIDs. However, if control is not obtained, local injection with anesthetic or corticosteroid is often helpful (2,13).

Other pain syndromes may result in referred pain. Temporomandibular joint syndrome, giant cell arteritis, sinusitis, and dental pain may have orbital or periorbital pain as part of the symptomatology. Trigeminal neuralgia (tic douloureux), herpes zoster, Raeder's paratrigeminal neuralgia, myofascial pain syndrome, nasopharyngeal tumors, and otalgia may also result in periorbital pain. These syndromes are covered specifically in Chapter 47, Chapter 49, Chapter 50, and Chapter 52.

Pain of Psychological Origin

Nonorganic pain syndromes are diagnoses of exclusion. A cause for ocular or orbital pain must be diligently evaluated in every patient. Only when no etiology can be found should the clinician entertain the diagnosis of functional pain. Emotional and psychological factors must be considered in the patient's response. Hypochondriasis, conversion reaction, hysteria, or other somatization disorders may be involved in the patient's report of pain. Secondary gain should also be evaluated; litigation and disability claims may be in process. It is often difficult for the physician to evaluate all the possible aspects of functional pain; assistance should be sought by psychological consultation when nonorganic factors seem to be involved in the complaint of pain.

MANAGEMENT

Topical Anesthetics and Analgesics

Instillation of 1 or 2 drops (0.05 to 0.10 mL) of a topical anesthetic solution (proparacaine hydrochloride 0.5%) immediately anesthetizes the surface of the globe and provides dramatic relief, lasting at least 15 minutes, from surface ocular pain. The patient might have been in agony moments before because of the pain and foreign body sensation of a mechanical, chemical, or photic injury to the corneal epithelium, but now rests comfortably. Use of a topical anesthetic to facilitate diagnosis is always permissible and allows thorough examination of the eye and institution of definitive therapy. The pain gradually returns, and the patient might beg for a prescription of the *miracle drug* , but topical anesthetics should *never* be prescribed for repeated instillation by the patient. All such agents are toxic to the corneal epithelium and can cause loss of the remaining corneal epithelium through their toxic effects and by acceleration of the breakup time of the lacrimal film, with resultant corneal drying (68).

Topical NSAIDs are available for ocular use (diclofenac 0.1%, flurbiprofen 0.03%, ketorolac 0.5%, and suprofen 1%). Diclofenac and suprofen are used to inhibit miosis during intraocular surgery. Some of these agents are also useful for seasonal allergies and postoperative inflammation. Reports have shown that topical NSAIDs may be useful in the management of pain associated with corneal abrasions and corneal surgery. Although patching is a useful technique in the management of corneal abrasions, studies show that management of corneal abrasions with topical NSAIDs and a bandage contact lens allows the patient to return to normal function more rapidly and therefore may be more acceptable to the patient (69,70 and 71). Laser refractive surgery is becoming commonplace; postoperative pain may be mild to moderate. Use of topical NSAIDs and a bandage contact lens has been shown to reduce the severity of postoperative pain (43,44 and 45).

Patching

Corneal epithelial defects are repaired by a combination of two mechanisms: sliding of cells from the periphery of the wound and division of neighboring cells (29). Frequent blinking delays the healing of the defect and contributes to the patient's discomfort. Presumably the delicate sliding of new cells is mechanically impeded or the cells are removed by the action of the eyelids.

The aim of a properly applied patch is forcible immobilization of the eyelids. The desired result is not accomplished by a quick application of a single eye pad with a strip of tape, but requires placement of at least two eye pads or other bulky dressing over the involved eye, secured with multiple strips of tape applied diagonally from the center of the forehead toward the angle of the mandible (Fig. 51-11). Successive tightly stretched layers of tape are added to increase the pressure on the dressing until the patient cannot open the eyelids voluntarily. Tincture of benzoin improves adherence of the tape to the skin. Because the eye under the patch moves with the unpatched eye, the patient is usually most comfortable with the unpatched eye closed, except for essential tasks, during the healing period, and is best advised to remain quiet.

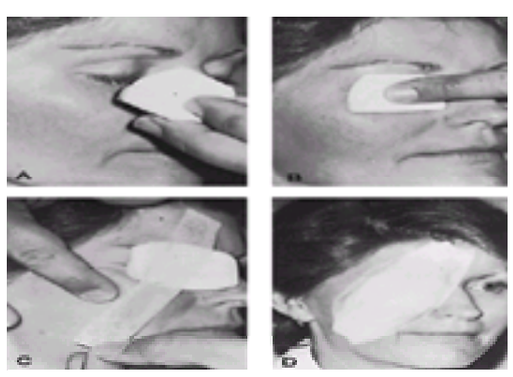

Figure 51-11. Patching. **A:** The first patch is folded to add bulk. **B:** The eye pads are applied while both eyes are closed. **C:** The tape is applied tightly over two patches from forehead to cheek. Addition of tincture of benzoin ensures adherence of the tape. **D:** Several strips of tape have been applied. Opening the unpatched eye should not allow the patched eye to open. If the patient reports that the eye has opened under the pad, it should be reapplied.

The corneal epithelium heals remarkably fast; all but the largest abrasions heal functionally within the first 48 hours. Patching, properly performed, is the most important single factor in promoting healing and relieving pain in any disorder in which the continuity of the corneal epithelium is interrupted. Patching raises the temperature of the cornea and conjunctival sac and provides an ideal milieu for bacterial growth. Therefore, antibiotics such as sulfacetamide 10%, gentamicin 0.3%, or tobramycin 0.3% should be instilled in the conjunctival sac before patching. Patching is contraindicated in bacterial corneal ulcers and conjunctivitis, in which incubation of the organisms would be expedited.

The cornea may be patched effectively with the use of bandage contact lenses. Bandage lenses may be either hydrogel lenses similar to normal soft contact lenses or collagen shields that dissolve over time (Fig. 51-12). These lenses protect the cornea from exposure to eyelid movement or the environment, allowing healing of the corneal epithelium. They are also clear and allow the patient some vision while the cornea is healing, often leading to more patient acceptance than the formal patching described previously.

Figure 51-12. Collagen corneal shield (Bausch and Lomb, Clearwater, FL).

Cycloplegic Agents

Inflammatory and traumatic disorders of the anterior segment of the globe frequently induce spastic contraction of the muscles of the ciliary body and iris, thereby inducing an aching pain. The pupil becomes miotic, and a large area of the posterior surface of the iris is in contact with the lens where, in the presence of inflammation, it can become permanently and undesirably adherent (posterior synechiae). Instillation of a cycloplegic (parasympatholytic) agent relieves the pain of ciliary spasm and dilates the pupil, preventing posterior synechiae.

The cycloplegic agent should be chosen according to the desired duration of action (see Table 51-1). Obviously, atropine is inappropriate for a corneal abrasion expected to be healed within 24 hours, because its duration of action lasts up to 14 days. Heavily pigmented eyes are generally less responsive to cycloplegic agents than are lightly pigmented eyes. The pupil can also be dilated for diagnostic purposes by the use of sympathomimetic drugs (e.g., phenylephrine), but such agents are not indicated for chronic therapeutic use because they do not relieve the ciliary spasm and can increase the inflammatory response.

Analgesics

Proper patching and use of cycloplegic agents, as described, markedly reduce or eliminate the requirement for systemic analgesics. The predisposition of ocular pain to provoke nausea and vomiting should be remembered, and drugs should be avoided that are likely to contribute to nausea or vomiting, either through irritation of the gastric mucosa or through systemic effects. Codeine or meperidine is usually satisfactory for short-term pain relief, but the parenteral route must be used if nausea exists.

Chronic administration of a narcotic agent is rarely, if ever, indicated for relief of ocular pain. Chronic ocular pain usually indicates a need for definitive treatment of the basic disorder or for enucleation of the eye if no hope exists for recovery of vision.

Retrobulbar Anesthetics and Alcohol

Blind, painful eyes are usually treated by surgical enucleation because they are disfiguring or because of the possibility that they harbor malignancy. Certain eyes that are painful as a result of chronic ocular disease, however, retain limited vision or some potential for future recovery of vision, but at present, clinical judgment dictates against definitive surgical therapy. The pain of such eyes can be relieved by retrobulbar injection of 1 to 2 mL of 20% to 95% alcohol (38,39). Palsies of extraocular muscles are common but transient; their risk of occurrence can be reduced by avoiding the deeper portion of the muscle cone with the injection. The immediate consequences of the injection, which should be preceded by injection of 1 to 2 mL of 2% lidocaine through the same needle left in place, are pain, proptosis, and chemosis, which subside over several days. The optic nerve resists the effects of alcohol because of its thick sheath; cases of vision loss caused by needles *properly placed* for retrobulbar alcohol injections have not been reported. Sharp disposable needles should be avoided to minimize the risk of direct injection of the optic nerve or blood vessels.

Surgery

Surgery can play a role in the control of ocular or periocular pain. Corneal pain, if not responsive to the usual therapy, can improve with a conjunctival flap, tarsorrhaphy (surgical eyelid adhesion), or corneal transplantation. Certain types of glaucomas, such as angle closure or neovascular glaucoma, can require surgery such as a peripheral iridectomy, laser surgery, or cryotherapy for pain relief. Orbital tumors or hemorrhage can require removal for pain relief. Chronic ocular or trigeminal pain can respond to thermocoagulation of the gasserian ganglion (72). Finally, when eye pain is chronic and severe and the visual potential is nil, enucleation is indicated for comfort.

Radiotherapy

Occasional patients have chronic pain caused by infiltrating tumors of the orbit or by orbital pseudotumor. Radiotherapy can be beneficial for pain relief in such cases if the pain is unresponsive to conventional therapy.

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CHAPTER 52

Pain in the Ear, Midface, and Aerodigestive Tract

Todd G. Dray and Ernest A. Weymuller, Jr.

Pain in the ear, midface, and aerodigestive tract is concerning to the patient, both as a harbinger of significant illness and in regard to the emotional ramifications of having pain in an area that is at once so important and so little understood by the layperson.

One characteristic feature of disorders in the head and neck is the frequent occurrence of referred pain. Pain in the ear, for instance, in the absence of visible ear pathology, should alert the clinician to the possibility of disease in the oropharynx or hypopharynx. Pathology in and around the vocal cords can present early with hoarseness, but pathology elsewhere in the upper aerodigestive tract can be silent until a significant airway problem develops. The hypopharynx and deep neck structures are difficult for the clinician to examine, making a high index of suspicion vital in this area.

Epidemiologic studies suggest that more than 50% of office visits to general practitioners are related to symptoms in the ear, midface, and aerodigestive tract. More than two-thirds of office visits to general pediatricians are for symptoms in these areas. Billions of dollars are spent in the United States each year on symptomatic relief of pain, infection, or allergy relating to this region of the body. Although most disorders in this area are self-limited or of little significance in regard to long-term disability, it is difficult to differentiate between insignificant and significant disorders on symptoms alone. Recognition of the characteristics of painful disorders and an understanding of pain referral patterns can greatly facilitate early diagnosis.

Table 52-1 lists disorders in this region of the body that have pain as a prominent symptom. Disorders notable for not being associated with pain are presented in Table 52-2. This chapter consists of three sections that discuss pain in the ear, midface, and upper aerodigestive tract. Some of the disorders in these anatomic regions are also discussed in other sections of this book. More comprehensive discussions have been presented by Senturia and colleagues (1), Shambaugh and Glasscock (2), and Schuknecht (3) regarding pain in the ear, by Alling and Mahan (4) regarding pain in the midface, and by Cummings and associates (5) regarding surgical therapy of these regions.

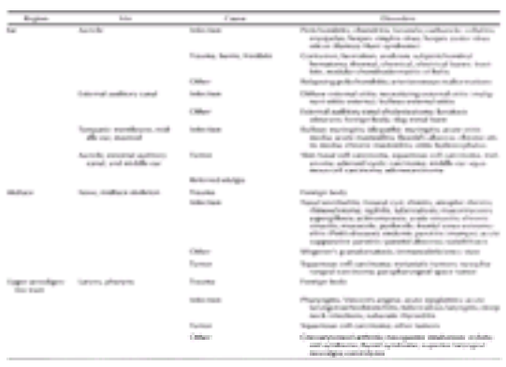

TABLE 52-1. Disorders that have pain as a prominent symptom

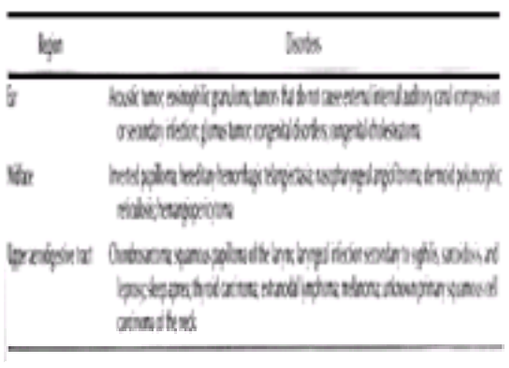

TABLE 52-2. Disorders in which pain is not a prominent symptom

PAIN IN THE EAR

Basic Considerations

Anatomy and Nerve Supply

The auricle is an exposed, irregular disk-shaped structure composed of cartilage and skin, with little subcutaneous tissue. The external auditory canal is a curved, skin-lined tube approximately 2.5 cm long that extends medially to the tympanic membrane. The lateral half is cartilaginous, whereas the medial half is bony. The

bony canal is an intact ring, but the cartilaginous portion is broken by several vertical fissures of Santorini along the anterior wall. Subcutaneous tissue is present in the cartilaginous portion but is nonexistent in the bony segment, contributing the extreme sensitivity of the canal skin in this area. The tympanic membrane forms the closed, skin-lined medial end of the external auditory canal. The middle ear is an air-containing space between the tympanic membrane, bony cochlea, eustachian tube, and mastoid air cells. The mastoid is bordered superiorly and posteriorly by intracranial structures. The bony labyrinth is located medially.

The ear is supplied by several cutaneous branches of the spinal and cranial nerves (Fig. 52-1). The auricle is innervated by the greater auricular and the lesser occipital nerves, which are derived from the cervical plexus and ascend from the neck along the sternocleidomastoid muscle; by the auricular branch of the vagus nerve, which travels laterally along the posterior aspect of the external auditory canal; and by the auriculotemporal branch of the mandibular nerve. The posterior and inferior aspects of the tympanic membrane receive their nerve supply from the auriculotemporal branch of the mandibular nerve, auricular branch of the vagus nerve, and tympanic branch of the glossopharyngeal nerve (Jacobson's nerve). The tympanic branch of the glossopharyngeal nerve, together with the caroticotympanic nerves (derived from the carotid sympathetic plexus) and the smaller superficial petrosal nerve, supply the other parts of the middle ear. The external auditory canal is also supplied by branches of the facial and glossopharyngeal nerves.

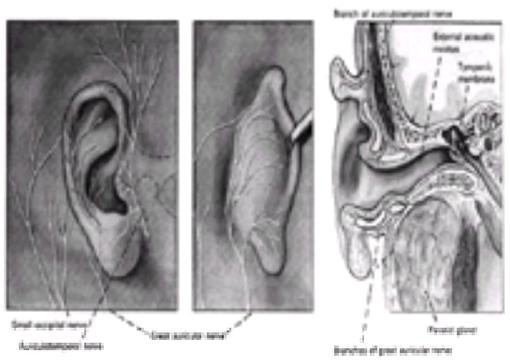

Figure 52-1. Innervation of the ear.

Characteristics of Pain in the Ear (Otalgia)

Pain in the ear can originate locally or can be referred from distant sites. Otalgia in the absence of physical findings can be a manifestation of an upper aerodigestive tract tumor or infectious process, sinus or dental infection, or temporomandibular joint disease. Referred otalgia accounts for up to 50% of all ear pain complaints (6). In such patients, all head and neck areas innervated by the trigeminal, facial, glossopharyngeal, and vagus nerves (all of which provide sensory innervation to the ear) must be carefully examined. The attention of a specialist is essential for full evaluation, and close follow-up and repeated examinations are mandated by unexplained otalgia, particularly when unilateral.

Pain of the auricle is caused primarily by nociceptive stimuli consequent to acute distension of the skin. Tumors and cartilaginous processes tend to be silent until the skin is stretched. Pain in the external auditory canal is related to compression of skin and nerve endings against unyielding circumferential cartilage or bone. The close proximity of the glenoid fossa and temporomandibular joint, just anterior to the external auditory canal, accounts for the pain from either structure to be generalized to this area. The close proximity of major intracranial structures also influences pain in this area. Unilateral or diffuse headaches as well as meningism can all be directly attributable to an otic source.

Infections of the Auricle

Patients tend to present relatively early in the course of auricular infectious processes because of the location of the auricle as an appendage on the face and because of the intensity of the pain. The main infectious processes are perichondritis and chondritis, furuncle, carbuncle, cellulitis, erysipelas, herpes simplex virus, herpes zoster virus oticus, and Ramsay Hunt syndrome.

Furuncles and Carbuncles

Furuncles and carbuncles are infectious processes that present with pain in a circumscribed area around an infected hair shaft. They are usually caused by staphylococcal organisms. These occasionally occur in the lateral external auditory canal as well as at the meatus. Ear pain is typically intense. Examination demonstrates erythema, edema, and possibly abscess formation. Furuncles and carbuncles may be large with considerable erythematous reaction, and the key to differential diagnosis is observing a normal tympanic membrane. If the condition is localized, incision and drainage are all that is necessary. If a considerable erythematous reaction occurs, an antistaphylococcal antibiotic such as dicloxacillin (orally, 250 to 500 mg three times a day for 10 days) should be added (7).

Cellulitis

Cellulitis of the auricle is diagnosed by redness, swelling, and localized pain. Usually, a history of trauma or otitis externa is given. *Streptococcus* and *Staphylococcus* are the usual causative organisms, and the diagnosis of acute mastoiditis can be difficult to rule out unless the eardrum appears to be normal. Antibiotics such as oral penicillin, erythromycin, or clindamycin are used, together with local care, avoiding abrasion, using warm saline solution or Burow's soaks. Intensive periauricular involvement is best treated in hospital with intravenous antibiotics (8).

Erysipelas

Erysipelas is an erythematous reaction that can present in and around the auricle and is caused by group A b-hemolytic streptococci. It is marked by local pain and redness, with a sharply demarcated advancing border. Often, it is associated with systemic symptoms and the patient appears quite ill. Treatment consists primarily of penicillin G given intravenously, which provides rapid relief. Local measures such as those used for cellulitis can alleviate the patient's discomfort.

Perichondritis and Chondritis

Perichondritis and chondritis are infectious processes that involve the cartilage and are usually associated with severe local pain, heat, redness, and fluctuance over the cartilaginous parts of the auricle only, leaving the lobule free of any reaction. The processes can be indolent or acute in nature and usually follow trauma. These infections can cause considerable disfigurement and need to be treated with great care.

Local treatment with compresses can be used; perichondrial collections of blood or pus often require incision and drainage, followed by a carefully applied mastoid dressing with conforming cotton soaked in antibiotic ointment, to reapproximate the skin and subcutaneous tissue back onto the cartilage. Antibiotics effective against gram-negative bacilli should be used, and for severe infections direct cartilaginous irrigations with antibiotic solutions might be necessary.

Herpes Simplex and Herpes Zoster

Herpes simplex virus involvement of the auricle is similar to herpes simplex I infections elsewhere. Typical findings include an initial burning pain and redness, followed by firm, small vesicles. The problem is self-limited but can be highlighted by intense pain and discomfort. Local care is all that is presently used for treatment of the disorder.

Herpes zoster oticus is characterized by groups of tender, painful vesicles with an erythematous base that appear along the course of a dermatome (see Chapter 22). Pain can precede the eruption by several days, and the rash typically spreads and peaks in 10 days. It is usually self-limiting, and local care is all that is indicated (4).

In the elderly patient, postherpetic neuralgia can develop, which can last for months and is difficult to treat. Acyclovir may have a role in suppressing the pain.

Ramsay Hunt Syndrome

Ramsay Hunt syndrome is a related but more serious disorder caused by reactivation of herpes zoster virus within the geniculate ganglion. The syndrome consists of a painful rash (facial and neck), the acoustic symptoms of hearing loss and dysequilibrium, and facial palsy. It is the second most common cause of facial paralysis (9). Treatment is highly controversial. If evidence of motor end-plate denervation is seen on electroneuronography, some physicians treat this lesion by decompression of the facial nerve using a middle fossa approach within 10 days of onset (10). Often patients are given corticosteroids when first seen; high doses of 100 mg or more of prednisone daily for 1 week are used, after which the dose is gradually decreased.

Trauma, Burns, and Other Painful Conditions of the Auricle

Trauma

Contusion of the auricle is characterized by localized pain. Severe blunt trauma to the auricle can cause injury of the cartilage, with shearing of the perichondrium from the cartilage and consequent subperichondrial hematoma that produces severe or excruciating local pain. It is treated by draining any fluid or blood present and by use of a compression dressing to prevent reaccumulation of fluid. A frank hematoma is an indication for administration of an antibiotic such as penicillin or a cephalosporin given orally.

Laceration or avulsion of the auricle, or both, is not uncommon. The excellent blood supply of the auricle, however, greatly enhances reconstruction if it is traumatized or burned. Up to $^{7}/_{8}$ of the auricle can be avulsed and successfully reimplanted using meticulous closure with careful realignment to maintain the contour of the auricle (11). A gentle supporting bandage is helpful for the 7 to 10 days after this type of repair.

Burns

The ear can be burned thermally, chemically, electrically, or by ultraviolet radiation. Moderate to severe pain occurs with first- and second-degree burns, but third-degree burns usually result in anesthesia or hypesthesia. Frequently a pseudomonal, streptococcal, or staphylococcal infection develops as a sequela of a burn. Vigorous cleaning is avoided initially, and a topical antibiotic ointment such as Silvadene is applied. Systemic antibiotics are given to patients with significant burns. Reconstruction of the ear after the most severe burns may be necessary (11).

Chemical burns should be treated with neutralization of the agent that produced the burn. With an intact eardrum the auricle and canal can be washed with dilute sodium hydroxide for an acidic burn, and with 2% acetic acid for an alkaline burn. Electrical burns can be quite deceiving on initial appearance, because tissue injury demarcates later and is proportional to the voltage. It is important to keep the ear clean while demarcation is taking place, and to protect the ear from further trauma. Once demarcation has occurred, the ear is treated as for other burns.

Frostbite

Frostbite, of course, results from exposure to severe cold weather (see Chapter 33). Early in the course of the injury local pallor and numbness develop, but on rewarming, edema, vesicles, and bullae develop and are associated with considerable pain. Treatment consists of thawing the ear quickly with gauze soaked in warm saline solution while avoiding rubbing the ear or subjecting it to any other trauma. Rapid rewarming can be extremely painful. Careful debridement should be used initially until the injury demarcates, after which it is treated as for burns, including a topical antibiotic ointment (11).

Nodular Chondrodermatitis

Another disorder that affects the auricle is nodular chondrodermatitis of the helix, characterized by a small (0.5 to 1.0 cm), smooth, painful nodule, typically with a crest at the superior helical rim. There may be a history of trauma, but often no antecedent injury. Pain is disproportionate to the appearance. When these lesions are seen it is important to rule out carcinoma and actinic keratosis. Intralesional corticosteroids can be used with success, although a simple wedge resection is often used for biopsy (12).

Relapsing Polychondritis

Auricular pain, erythema, and swelling are usually the result of infectious cellulitis; however, relapsing polychondritis is another cause of this symptom complex. It results from an autoimmune process that inflames and destroys cartilage, with the auricle and joint cartilage most often involved. Whites are primarily affected by this disorder, and symptoms are seen most frequently in patients 40 to 60 years old. Renal and cardiovascular involvement may be seen in a small percentage of patients. Treatment is based on nonsteroidal antiinflammatory drugs, corticosteroids, dapsone, and in severe cases, immunosuppressant therapy. Relapses are common (13).

Arteriovenous Malformations

Arteriovenous malformations are sometimes seen in the region of the auricle. These are congenital, spontaneous, or traumatic in origin and are manifested by localized pain with swelling and increased warmth over the area. Treatment consists of surgical excision after embolization, if the lesion is large.

Infections of the External Auditory Canal

External Otitis

External otitis is a common disorder associated with swimming, especially in fresh water, diving, and misuse of cotton swabs. It also has an increased incidence in the postpartum period and in psoriasis and other dermatoses. Typically, an initial itch is present, followed by ear pain that can be severe. The pain may be associated with chewing or opening of the mouth, secondary to the proximity of the temporomandibular joint. Examination reveals the skin of the ear canal to be red, swollen, and draining, and the pain might seem out of proportion to the findings on examination. Often the tympanic membrane cannot be well visualized secondary to the swelling, and the examination is uncomfortable to the patient. Grasping the auricle and moving it posteriorly causes pain. The most common causative organisms are *Pseudomonas* and *Staphylococcus* (14).

Treatment consists of thorough cleaning of the ear canal, which is best performed under an operating microscope. If cellulitis extends lateral to the meatus it should be treated with an antistaphylococcal oral antibiotic. It is sometimes necessary to place a porous wick in the external auditory canal to permit application of corticosteroid-containing antibiotic drops (Cortisporin otic suspension). Wicks should not remain in the external auditory canal for more than 48 hours, at which time the process is usually much improved and the eardrum can be visualized. It is important to follow these patients to the resolution of their symptoms and to rule out necrotizing or malignant external otitis in patients who are diabetics or immunocompromised (15).

Necrotizing External Otitis

Necrotizing external otitis is a life-threatening disorder that cannot be distinguished from diffuse external otitis on the basis of pain alone. It represents a progressive, intractable pseudomonal infection of the temporal bone. Patients with this disorder are often quite sick, can be chronically ill, and frequently are diabetics. Bone destruction and facial paralysis are frequent. Typical findings include granulation tissue in the ear canal, an elevated erythrocyte sedimentation rate, enhancement on ^{67}Ga scanning, and bone destruction on computed tomographic (CT) scan. Treatment should be carried out in a hospital with careful cleaning of the ear and systemic antibiotics effective against *Pseudomonas*, along with aggressive control of diabetes and other comorbid conditions. Surgery is reserved for poor resolution of the process. This problem has a significant mortality (16).

Bullous External Otitis

Bullous external otitis is characterized by sudden severe pain in one or both ears, with a dark red discharge from the ear. Examination shows hemorrhagic bullae on

the wall of the ear canal. This is a self-limiting problem that only lasts for several days and is probably caused by a virus or *Mycoplasma pneumoniae*. Treatment consists of ear canal cleaning and application of drops that contain a combination of a corticosteroid and an antibiotic.

Other Painful Disorders of the External Auditory Canal

Cholesteatoma

Cholesteatoma of the external auditory canal is an unusual problem that often follows surgical trauma or other injury to the bone of the external auditory canal. These patients may present with chronic dull pain in the ear secondary to focal invasion of squamous epithelium into the canal wall. The process continues until eradicated by surgery, which entails removal of all of the involved bone and reconstruction with a mastoidectomy cavity or skin graft (7).

Keratosis Obturans

Keratosis obturans is a disorder of obscure cause. It is characterized by acute severe pain in the ear secondary to large plugs of desquamated keratin. It often occurs bilaterally and is associated with bronchiectasis and sinusitis. Examination of the ear canals shows large plugs of keratin that can be removed as a cast of the lateral surface of the tympanic membrane and the external auditory canal, as well as bony remodeling of the ear canal. Treatment consists of external auditory canal debridement and close follow-up. This chronic disorder requires cleaning of the ear at regular intervals (17). Presently, no curative therapy exists for this condition.

Foreign Bodies

Foreign bodies are a frequent cause of pain in the ear. Foreign bodies are usually inserted by children or by mentally deficient individuals. Insects may fly or crawl into one or both ears. If the insect is alive, infusion of mineral oil or lidocaine solution into the ear canal can be used to float the insect or induce it to exit. If the insect is dead it can often be removed with forceps. Vegetable matter can swell within the ear canal, making removal difficult. A local anesthetic block of the ear canal can be used, but uncooperative patients might have to be given general anesthesia for removal.

Slag Metal Burns

Slag metal burns occur occasionally in people who work with molten metal. The burns are characterized by ear pain and poor healing within the external auditory canal. Tympanic membrane perforations caused by such burns are not intrinsically painful in a high percentage of patients, but they heal poorly and may require tympanoplasty.

Infections of the Tympanic Membrane, Middle Ear, and Mastoid

Bullous Myringitis

Bullous myringitis is a viral or *M. pneumoniae* infection of the tympanic membrane characterized by sudden excruciating ear pain that subsides rapidly after the blebs in the tympanic membrane are ruptured, either spontaneously or surgically. Treatment consists of application of eardrops and surgical rupture of the blebs. The disease is self-limiting even if no treatment is given (18).

Acute Otitis Media

Acute otitis media is an extremely common problem, especially in children. Nearly two-thirds of all children have at least one episode of acute otitis media and nearly one-third have three or more episodes (19). The problem can occur at any age, however, and remains a common problem even in adulthood. Risk factors include the winter season, bottle-feeding, smoke exposure, daycare attendance, cleft lip and palate abnormalities, and preceding upper respiratory infections. Symptoms might be poorly described by children, but they usually pull at the ear and have fever. Those old enough to articulate experience localized pain in the ear, caused by distension of the tympanic membrane. Often, the tympanic membrane perforates, and purulent discharge occurs, with prompt pain relief and consequent resolution of the problem. It should be noted that acute otitis media can progress to mastoiditis in patients who are treated inadequately. The most common organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (19).

Treatment of acute otitis media consists of administration of oral antibiotics (ampicillin, amoxicillin, cefaclor, erythromycin with sulfa, or Augmentin). Gram-negative sepsis must be considered in neonates, and a complete septic workup should be performed. Culture and sensitivity of purulent drainage are indicated in septic patients, in infants younger than 2 months old, and in those with poor resolution despite antibiotics (20,21).

Acute Mastoiditis

Acute mastoiditis is a destructive bacterial infection of the mastoid bone and air cell system, and although it is uncommon today, it remains a potentially serious condition. The classic presentation of acute mastoiditis includes a recent history of acute otitis media and an examination that identifies a displaced auricle and middle ear infection. However, not all patients experience a preceding episode of acute otitis media. Dull postauricular pain and ear drainage are the most common presenting symptoms. *Streptococcus pneumoniae* is the most commonly isolated organism. Initial therapy with parenteral antibiotics is appropriate, but a large percentage of patients need mastoid surgery (22,23).

Bezold Abscess

Bezold abscess is a complication of acute mastoiditis and is characterized by pain, tenderness, and swelling in the upper neck. It consists of lateral breakthrough of pus from the mastoid cortex, either directly or by way of a postauricular lymph node that is deep to the attachment of the sternocleidomastoid muscle to the mastoid bone. Patients are usually symptomatic from acute mastoiditis and can be quite ill. Bezold abscess may be discovered fortuitously when there is poor resolution of an acute mastoiditis that is treated with a simple mastoidectomy. Treatment of Bezold abscess consists of incision and drainage and exploration of the upper neck. The same antibiotics are used as for acute mastoiditis.

Chronic Otitis Media

Chronic otitis media is characterized by a nonhealing tympanic membrane perforation and chronic, recurrent ear drainage. The patient may have dull aching pain that is accentuated by intermittent infection of the middle ear and mastoid. Treatment consists of topical corticosteroid drops containing an antibiotic. Patients should be evaluated by a specialist to consider surgery for chronic otorrhea, cholesteatoma, or closure of the tympanic membrane perforation.

Chronic Mastoiditis

Chronic mastoiditis is associated with cholesteatoma and can be similar in symptoms to chronic otitis media. Sudden increase in local pain suggests complication of a cholesteatoma, such as lateral sinus thrombosis or intracranial abscess. Patients with chronic mastoiditis who develop a sudden increase in pain should therefore be carefully examined for evidence of such complications. The examination should include funduscopy, careful cranial nerve examination, and a CT scan (24,25). Proteus mirabilis, pseudomonal, and staphylococcal organisms are commonly found (26). Mortality secondary to complications of cholesteatoma ranges from 10% to 18% (26).

Otitic Hydrocephalus

Otitic hydrocephalus is a complication of cholesteatoma and chronic mastoiditis. These patients are typically being followed for chronic otitis media and suddenly develop headache, which can be unilateral or diffuse and associated with blurred vision, nausea, and vomiting, as a manifestation of increased intracranial pressure. Characteristically though, no ventricular dilatation is identified on CT imaging, but an associated lateral sinus thrombosis often is present. Treatment is focused on the management of the elevated cerebrospinal fluid pressure so as to prevent atrophy of the optic nerve from persistent papilledema. Serial lumbar punctures or placement of a lumbar drain effectively diminishes cerebrospinal fluid pressures over the several weeks usually required for the condition to run its course.

Mastoidectomy should be performed to manage the chronically draining ear (27,28).

Tumors of the Auricle and External Auditory Canal

Auricle

Tumors of the auricle and periauricular skin are common and notoriously difficult to control. Cutaneous malignancies that commonly occur in these sites are squamous cell and basal cell carcinoma, involving the parts of the auricle that are exposed to sunlight. Tumors of the auricle tend to produce symptoms early and do have a favorable prognosis when small. They are usually treated by a wedge resection and rarely require regional lymph node dissection. Radiation therapy can also be used as an alternative modality for these small auricular lesions. Mohs' surgery is an effective surgical technique for larger and more complex lesions (29).

External Auditory Canal

Tumors of the meatus and external auditory canal are uncommon and generally present with chronic ear drainage, which is often bloody. Examination reveals granulation tissue, polyp, or exposed bone within the external auditory canal. The tumors are usually squamous cell carcinomas. Pain can be persistent and gnawing but variable in intensity. Frequently, the initial presentation is consistent with an external otitis or chronic otitis media, and it is only with poor response to conventional therapy and a high index of suspicion leading to biopsy that the diagnosis is made. Treatment of tumors of the meatus and external auditory canal consists of surgical removal.

PAIN IN THE MIDFACE

Basic Considerations

The midface is composed of a series of air-containing cavities surrounded by bone and soft tissue. The maxillary, ethmoid, frontal, and sphenoid sinuses are all air-containing spaces surrounded by respiratory mucosa and bone. The nose is composed largely of soft tissue that hangs off a small bony skeleton. Sensation in this area is mediated predominantly via branches of the trigeminal nerve. The three major branches of the trigeminal nerve exit the skull through foramina that lie close to the midface structures. Consequently, sensory defects and pain patterns identified by the history and physical examination can localize lesions in this area.

Most disorders in this region cause only local pain, referred pain being rare, although dental and sinus lesions can cause referred otalgia. Most painful disorders of the nose are related to inflammation or distension of soft tissue. Pain in the sinuses is largely the result of compression of the mucosa onto unyielding bony margins.

Trauma

Nasal Trauma

The nose is frequently traumatized because of its prominent position on the face. The thin, paired nasal bony leaflets can be relatively easily displaced by blunt trauma. Bony fractures of the nose are almost invariably associated with epistaxis because of the close opposition of the well-vascularized periosteum and mucosa intranasally. Treatment of bony nasal displacements consists of closed reduction if obvious cosmetic deformity is noted, after swelling has subsided. During an approximately 2-week-long grace period, closed reduction can be performed. After this time open reduction is best.

Trauma to the cartilaginous portions of the nose is extremely common and can cause deflections and reduplication. These injuries can also be seen in neonates, who might have difficulty with nasal breathing. Closed manipulation is generally all that is required in such cases. The sequelae of nasal trauma are septal hematoma and abscess, which can be recognized by an intranasal bulging on either side of the septum that is generally bilateral. Usually, considerable nasal pain is associated with this condition, as is tenderness of the nasal tip on palpation. Treatment consists of an incision and drainage with appropriate intranasal packing.

Trauma to the Midface Skeleton

Trauma to the midface skeleton also frequently occurs, but requires more significant force than that required for nasal fracture. LeFort divided midfacial fractures into types I, II, and III, based on remarkable cadaveric studies he performed in the nineteenth century (30). Type I is a horizontal fracture just superior to the palate; type II is a triangular fracture from the glabella along the infraorbital rim, inferior to the zygoma; and type III includes the zygoma (Fig. 52-2). In practice these types are usually mixed.

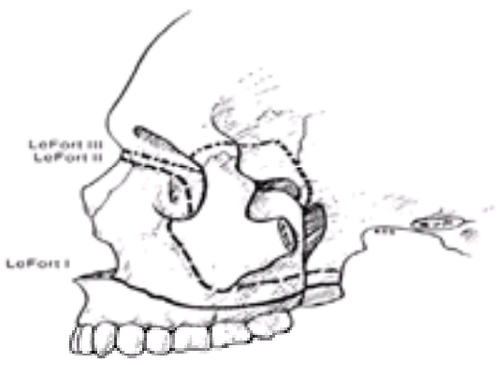

Figure 52-2. Sites of LeFort facial fractures.

Diagnosis is made on the basis of the history and physical examination, which reveals obvious disruption of the midfacial supports on traction. Treatment usually consists of open reduction and internal fixation with facial plating systems (31).

Infections of the Nose

Vestibulitis

Nasal vestibulitis is an infection caused by *Streptococcus* and *Staphylococcus* in the skin at the entrance to the nostril, often associated with folliculitis of the vibrissae. Differential diagnosis should include fissural cysts; these congenital remnants are often dental in origin but can present in the nasal vestibule.

Treatment consists of antibiotics and possible incision and drainage if abscess formation has occurred. Vigilance must be observed, as with any midfacial infection, that the infection does not spread posteriorly along the venous drainage and into the intracranial spaces. Therefore, the patient who does not rapidly respond to treatment should be admitted to the hospital for intravenous antibiotics.

Rhinitis

Rhinitis is an extremely common disorder of varying etiology, including viral, allergic, and nasal spray–induced reactions. It is usually associated with rhinorrhea and nasal stuffiness more than with pain. One variant that is associated with significant pain, however, is caused by the *Klebsiella ozaenae* organism. This type of rhinitis, known as *atrophic rhinitis*, presents with massive crusting of the nose and an extremely foul smell that can be difficult to eradicate. Treatment consists of local debridement and antibiotics.

Rhinoscleroma

Rhinoscleroma is an infectious disorder of the nose and sinuses caused by *Klebsiella rhinoscleromatis*. It is most often seen in people from the Middle East and Southeast Asia and is usually an indolent infectious process that can cause significant atrophy and deformity if left untreated (32). At times it presents with a picture consistent with that of sinusitis, and the associated symptoms and signs cannot be distinguished from those of sinusitis without a high index of suspicion and a biopsy of the granulation tissue. The biopsy shows the characteristic Mikulicz foam cells, with vacuolated cytoplasm. Treatment consists of antibiotics that include tetracycline and erythromycin. The infection sometimes proves difficult to eradicate.

Infections of the Sinuses

Acute Sinusitis

Sinusitis is a common problem that can be caused either by viral, bacterial, or fungal pathogens. It occurs most commonly in the maxillary antrum as a complication of a rhinovirus infection. Epidemiologic studies have indicated that 0.5% of all viral colds are complicated by sinusitis (33,34). Acute sinusitis is usually secondary to an obstruction of the sinus ostia, which normally allows pressure equalization and egress of the mucosal blanket from the sinus into the nose. Acute sinusitis has a bacteriologic spectrum similar to that of acute otitis media, *Streptococcus pneumoniae* and *Haemophilus influenzae* predominating.

Patients usually present early in the course of their disease with pain localized to the region of the affected sinus. An exception is patients with sphenoid sinusitis, who can present with pain at the vertex of the skull. Sinusitis pain is characteristically worse during the day and much better or wholly absent at night. This pain pattern is related to the normal nasal cycle of congestion and decongestion. In children, nasal congestion, cough, rhinorrhea, headache, and facial pain are the predominant symptoms (35).

Diagnosis can be made on physical examination by eliciting tenderness over the thinnest part of the bone of the involved sinus. Radiography (contrast-enhanced CT scan) is reserved for assessment of patients with possible complications of sinusitis.

Treatment consists of topical decongestants and systemic antibiotics. Ampicillin and amoxicillin are first-line drugs. A cephalosporin, erythromycin, and tetracycline can all be used to treat an acute sinusitis. Anaerobic bacteria also play a role in acute sinusitis but are more significant in chronic sinusitis. A poorly responsive sinusitis can therefore be treated with the addition of metronidazole hydrochloride (Flagyl), 250 to 750 mg three times a day orally. It is often advisable to continue antibiotic therapy for 14 to 21 days. In acute sinusitis, surgery is reserved for present or impending complication. This includes sinusitis localized in the sphenoid or frontal sinuses, which does not show definite signs of improving over a 24- to 48-hour period, and an ethmoid sinusitis associated with signs of orbital involvement. Complications of ethmoid sinusitis are more frequent in children but tend to be more serious in adults.

Chronic Sinusitis

Chronic sinusitis occurs secondary to obstruction of the osteomeatal complex. It consists of a symptom complex of dull, aching, gnawing facial pain, with periodic rhinorrhea. Patients often complain of a tired feeling in the ipsilateral eye. Diagnosis is made by history and is confirmed by CT scanning, which shows thickening of the sinus mucosa or opacification.

Because anaerobic bacteria are frequent causative agents, antibiotics for such infections should be used, and b-lactamase coverage should be considered. Current understanding of chronic sinus disease mandates that these infections be treated with prolonged courses of antibiotics. Additionally, a mucolytic agent, a topical nasal corticosteroid spray, and nasal irrigations are considered standard therapy in this setting, and a course of prednisone may augment antibiotic therapy considerably. Sinus surgery is appropriate for continued symptoms or suppurative complications.

Mucormycosis

Rhinocerebrophycomycosis, or mucormycosis, is an uncommon fungal infection that has a rapidly fatal course if treatment is delayed (36). It is characterized by the classic syndrome of diabetic ketoacidosis, unilateral blindness, ophthalmoplegia, and proptosis. The infection should be considered in any patient with sinusitis and diabetic ketoacidosis. Facial pain is typical early in the course of the disease, but it is not characteristic as the infection advances. Examination can show a black turbinate, although the turbinate might appear pale when seen early. These patients are often extremely ill and have signs of cerebrovascular thrombosis with meningocephalitis. Biopsy is usually required for making the diagnosis and shows invasive broad, branching nonseptate hyphae with hemorrhage and tissue infarction (37). Treatment consists of reversal of the acidosis, debridement of involved tissues, which might require an orbital exenteration, and the use of amphotericin B (36).

Complications of Sinus Disease

Mucocele and Mucopyocele

Mucoceles are the most common expanding lesions of the paranasal sinuses and usually arise from the frontal and ethmoidal sinuses (38). The most common symptoms are headache, double vision, and proptosis. The major diagnostic tool is CT scanning, which shows a smoothly marginated cyst and often reveals bony destruction. The usual treatment is surgical exenteration of the involved sinus.

Intracranial Disorders. Sinus infection can progress to intracranial involvement. Persistent headache, particularly one originally localized but that becomes more generalized, together with neurologic changes, mandates the ruling out of intracranial extension. This is best done with a contrast-enhanced CT scan (39).

Osteomyelitis. Frontal sinus osteomyelitis (Pott's disease) is a rare complication of frontal sinusitis. It is characterized by considerable local pain and a swollen erythematous forehead, with *peau d'orange* skin changes. Frequently, the ipsilateral eye is swollen, particularly the upper lid. Treatment consists of antibiotics and surgical drainage. Extensive osteomyelitic involvement of the anterior table of the frontal bone requires removal of this bone, with consequent cosmetic defect unless it is reconstructed. Intracranial involvement is a not infrequent accompaniment, and severe headache, fever, and dizziness, together with poor response to treatment, should prompt a contrast-enhanced CT scan (40).

Other Disorders

Epidemic Parotitis

Epidemic parotitis, or mumps, is a paramyxovirus infection, which is a common cause of pronounced unilateral or bilateral parotid swelling. It is associated with moderate to severe pain and frequently occurs in children and young adults. Occasionally, the submandibular gland is involved. Constitutional symptoms are common, including fever and malaise. Orchitis and oophoritis can also be seen. Uncomplicated mumps resolves within 2 weeks on supportive therapy only. Despite the administration of the mumps vaccine, mumps must still be considered, because the efficiency of the vaccine is between 75% and 90% (41).

Acute Parotitis

Acute suppurative parotitis most frequently occurs in the elderly. It is also known as *surgical parotitis* . *Staphylococcus aureus* is the most common pathogen associated with the condition (42). The clinical entity consists of unilateral pain and swelling in the region of the parotid gland, which is often doughy in consistency and can be enlarged. Pressure on the gland often produces excretion of pus from Stensen's duct. Predisposing factors include dehydration, malnutrition, oral tumors, sialolithiasis, and medications that diminish saliva.

Treatment consists of appropriate antibiotics and rehydration. Occasionally, the process leads to parotid or periparotid abscess, which requires surgical drainage by an experienced surgeon (43).

Sialolithiasis

Sialolithiasis can occur in any salivary gland but is most common in the submandibular gland. It is characterized by pain with meals and can produce swelling of the involved gland secondary to the backup of saliva and distension of the ductal system. Palpation of the involved gland is usually painful. Prolonged blockage can lead to an acute bacterial sialadenitis with constant pain and chronic dysfunction of the involved salivary gland. Ninety percent of submandibular gland stones are radiopaque, but only 10% of parotid gland stones are radiopaque. Once the stone has been identified it is removed with a surgical incision along the duct. Chronic changes might require surgical removal of the gland, which is more frequently necessary for the submandibular than for the parotid gland.

Wegener's Granulomatosis

Wegener's granulomatosis is a systemic vasculitis that often presents in the nose and produces associated manifestations in the sinus, lungs, and kidneys. The inflammatory reaction includes necrosis, granulomas, and vasculitis. A positive antinuclear cytoplasmic antigen finding strongly implicates Wegener's granulomatosis, and the diagnosis is made on biopsy, which shows vasculitis of midsized arterioles (44). Patients with Wegener's granulomatosis can present with nasal granulations, nasal-septal perforation, or pain from sinusitis. Treatment is principally medical, with corticosteroids and cyclophosphamide significantly improving the natural course of the disease (45).

Tumors

Cutaneous Malignancies

Most tumors of the nose and skin of the face are similar to cutaneous malignancies elsewhere in the body. Basal cell carcinoma is the most common, followed by squamous cell carcinoma and melanoma. The pain associated with these lesions is often secondary to associated infection or bone erosion. Cutaneous carcinomas of the midface are renowned for their tendency to burrow and skip, so that simple elliptic incisions of an obvious carcinoma are fraught with subsequent failures. Many tumors in this area can initially be treated by Moh's surgery followed by reconstruction (46,47).

Carcinoma of the Paranasal Sinuses

Squamous cell carcinoma, which is the most common type of sinus malignancy, occurs rather infrequently (48,49 and 50). It is most frequently seen in the maxillary sinus, followed by the ethmoid sinus. Early symptoms are identical to those of benign sinus disease, and a high index of suspicion is required for diagnosis. Approximately 70% of patients present with localized facial pain or swelling, and of these approximately 50% present with nasal obstruction and bloody drainage.

A patient who presents with a history of chronic unilateral bloody rhinorrhea, nasal obstruction, and facial pain should prompt suspicion of a squamous cell carcinoma of the sinus. Plain films often show an opacified sinus with bony destruction, and a CT scan is useful to delineate the size of the lesion, but biopsy is necessary for definitive diagnosis.

Treatment options include surgical excision, radiotherapy, or both. Unfortunately, patients tend to present late in the course of the disease, and surgery is not always feasible in those with large lesions.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma has a high incidence in certain Asian populations (51,52). The most common presenting features are neck mass, retroorbital pain, or pain high and deep in the neck beneath the ear. These tumors may be related to Epstein-Barr virus and can be followed with early antigen and viral capsid antigen titers (53). Radiotherapy has been the traditional mode of treatment, but some information suggests markedly improved survival using concomitant chemotherapy and radiation therapy (54).

PAIN IN THE UPPER AERODIGESTIVE TRACT

In the following discussion, the upper aerodigestive tract is considered to consist of the larynx, pharynx, parapharyngeal space, and deep neck structures. The sensory nerve supply (including nociceptive fibers) of these structures is through the glossopharyngeal and vagus nerves (Fig. 52-3). Consequently, referred pain to the ear, also innervated by these cranial nerves, is a frequent accompaniment of disorders of the laryngeal and pharyngeal regions. Pain from the upper aerodigestive tract is poorly localized by the patient. For example, cricopharyngeal dysphagia can be a manifestation of gastroesophageal junction pathology. Therefore, the differential diagnosis of pain in the upper aerodigestive tract requires consideration of disorders of the esophagus and of the trachea and lungs, as well as glossopharyngeal and vagal neuralgia (see Chapter 47, Chapter 53, Chapter 62, and Chapter 63).

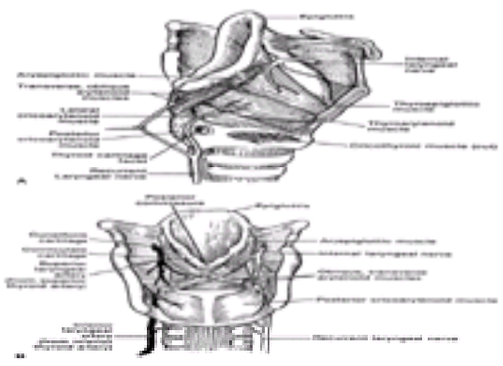

Figure 52-3. **A:** Lateral view of laryngeal muscles and nerves (half of thyroid cartilage and hyoid bone removed). **B:** Posterior view of laryngeal muscles, nerves, and arteries. (Reprinted from Graney DO. Anatomy. In: Cummings CW, Fredrickson JM, Harker LA, et al., eds. *Otolaryngology—head and neck surgery* , 3rd ed. St. Louis: Mosby, 1998, with permission.)

Infections

Pharyngitis

Pharyngitis is an extremely common problem, characterized by sudden onset of sore throat, odynophagia, fever, pharyngeal exudate, and frequently cervical adenopathy. It is most common in childhood but can be seen in those of any age. Causes of pharyngitis include viruses (most commonly adenovirus), *Mycoplasma pneumoniae* , primary or secondary syphilis, tuberculosis (usually with laryngeal involvement), *Candida albicans* (especially in an immunosuppressed patient), b-hemolytic *Streptococcus* , *Gonococcus* , *Meningococcus* , and diphtheria. The latter infection presents with pseudomembranes that bleed with peeling and exudate that extends beyond the tonsils onto the soft palate and uvula (55). Vincent's angina is caused by an anaerobic infection. Symptoms and signs include pseudomembrane with a bleeding base, with a possible necrotic appearance to one tonsil. Agranulocytosis, leukemia, and malignancy are all associated with sore throat and should be ruled out in patients with pharyngitis that does not respond to therapy. Treatment consists of penicillin or erythromycin in allergic patients.

Peritonsillar Abscess

This abscess is a common clinical entity that often follows a tonsillitis episode. The common complaints are fever, painful swallowing, voice change, and ear pain. Common findings include a deviated uvula, a unilaterally medialized tonsil, and fullness of the soft palate on the affected side. The infection is generally polymicrobial

and may involve anaerobes. Incision and drainage and antibiotic therapy are the gold standard treatment.

Acute Epiglottitis

Acute epiglottitis is a rapidly progressive supraglottitis. It is especially common in children 2 to 7 years of age, but it can also be found in infants and adults. The condition begins with a sore throat, fever, and dysphagia, with drooling and exhaustion. Adults have a less fulminating course, but can have inspiratory stridor. History and the characteristic appearance of a child with fever, sitting straight up with head jutted forward, drooling, and gasping for air should cause the physician to be highly suspicious of this disorder. Lateral soft tissue radiography shows an enlarged epiglottis. Because of the danger to the airway, it is a surgical emergency requiring tracheal intubation or tracheotomy. It is most commonly caused by type B *Haemophilus influenzae* , although the Hib conjugate vaccine has dramatically reduced the incidence of Hib disease in the United States (56).

It is best to take the patient to an operating room for tracheal intubation, with tracheotomy reserved if intubation is unsuccessful (57). Examination of the oral pharynx is kept to a minimum before intubation because of the possibility of precipitating a severe laryngeal spasm. Chloramphenicol and ampicillin are given pending culture results. Usually, the edema resolves rapidly and the patient can be extubated in 2 or 3 days (57). This disorder rarely reoccurs.

Acute Laryngotracheobronchitis

Acute laryngotracheobronchitis, or croup, is an acute viral inflammation of the larynx and tracheobronchial tree that typically presents in children younger than 3 years of age in the middle of the night. This condition can follow an upper respiratory infection and tends to have a less fulminant course than supraglottitis. It can begin with a painful croupy cough, hoarseness, and a biphasic or inspiratory stridor with retraction, circumoral pallor, and cyanosis, indicating respiratory fatigue. Cervical soft tissue films are often all that is necessary to make the diagnosis in combination with the history and physical examination. Treatment consists of cold humidification, rest, hydration, oxygen therapy, racemic epinephrine, and antibiotics. Corticosteroids can be used but are often not necessary. Tracheotomy is reserved for patients with severe laryngeal edema.

Tuberculous Laryngitis

Tuberculous laryngitis is almost always secondary to pulmonary tuberculosis and is manifested by painful dysphagia, hoarseness, otalgia, dyspnea, and, later in the course, a cough. The most common site is the posterior larynx in the intraarytenoid fold, followed by the laryngeal surface of the epiglottis. Admission radiographs typically reveal evidence of pulmonary tuberculosis (58). Prognosis is good if treatment is begun early.

Deep Neck Infections

Deep neck infections occur in potential spaces defined by fascial planes (59). The most common causes are oropharyngeal and dental diseases, which allow microorganisms to enter deeper tissues through breaks in the mucosal barrier or by spread from lymphatic or hematogenous routes. Oral anaerobes are the most common bacteriologic offenders, *Streptococcus pyogenes* being the second most common type. Deep neck infections that originate from a cutaneous or parotid source are usually caused by *Staphylococcus* .

Parapharyngeal Space Abscess. The parapharyngeal space is pyramidal in shape, with the base at the skull and the apex at the hyoid bone, and lies just lateral to the peritonsillar space. The pterygoid plexus of veins, which provides major drainage for the midface, runs through the parapharyngeal space. It can be involved secondary to pharyngeal or central facial infections, especially in children. Abscess in the anterior compartment is manifested by trismus, medial displacement of the lateral pharyngeal wall, and retromandibular swelling. Oral intake can be impossible secondary to discomfort. Abscess in the posterior compartment of the parapharyngeal space is characterized by syncope, cranial nerve deficits, and sepsis after involvement of carotid sheath structures.

Retropharyngeal Space Abscess. Retropharyngeal space abscess is most commonly seen in young children because the lymph nodes in this area regress after infancy. The abscess in children is located near the posterior midline and causes pain, nuchal rigidity, dysphagia, and air hunger. Soft tissue films of the neck are helpful in identifying the bulging of the posterior pharyngeal wall. Manipulation of the abscess without airway protection is dangerous because of the possibility of rupture and aspiration of purulent material. Retropharyngeal abscess in adults is usually secondary to tuberculosis, trauma, a foreign body, or cervical spine surgery.

Diagnosis. The diagnosis of deep neck infections is based on physical findings coupled with a typical history of chills, fever, lethargy, and localized pain or tenderness. Brawny induration of the neck can be misleading and an underlying abscess must be ruled out. Neck films using a soft tissue technique are helpful for evaluating airway status and for diagnosing retropharyngeal or epiglottic disorders, as well as for demonstrating gas in the cervical soft tissues. Retropharyngeal thickness seen radiographically must be interpreted cautiously in children.

Treatment. Once identified, a deep neck infection can be treated with intravenous antibiotics and close observation for a short period of time, although it is strongly advised that surgical intervention be carried out whenever an abscess is suspected. Generous incision and drainage, copious irrigation, liberal use of drains, and close follow-up are mandatory to prevent significant morbidity and death (60).

Subacute Thyroiditis

Subacute thyroiditis is an acute self-limiting inflammation of the thyroid gland that often follows upper respiratory infection and is usually secondary to a coxsackievirus infection (61). This condition is characterized by pain in the thyroid region that is increased by swallowing or turning the head and that can radiate to the jaw, ear, and temporomandibular joint. Occasionally, dull pain is the chief complaint. Nervousness, palpitations, fatigue, and a fever can also be associated. Palpation of the thyroid reveals diffuse swelling, acute tenderness, and overlying erythematous skin. Thyroid function test results are normal, but the sedimentation rate is elevated. The treatment consists of analgesics and close follow-up of patients, who can become either hyperthyroid or hypothyroid after the inflammation resolves. Corticosteroids have been used in this condition, but do not shorten the course of the disease (62).

Other Infectious Processes

A number of inflammatory processes do not occur in the upper respiratory tract but, because of their close proximity, produce symptoms that suggest pharyngeal or laryngeal involvement. Patients with pertussis almost universally complain of sore throat in the early stages of the disease. Patients with pneumonias can present with pharyngeal pain.

Stevens-Johnson syndrome is characterized by high fever and vascular and bullous involvement of the oropharynx and skin. These lesions are usually hemorrhagic. Taking anything by mouth is extremely painful. The disorder is seen after patients have been given certain antibiotics, such as sulfa drugs, and it is occasionally fatal. Treatment is supportive and administration of corticosteroids (63).

Tumors

Ninety-five percent of tumors involving the larynx and hypopharynx are squamous cell carcinomas (64). Patients with primary tumors in the glottic larynx manifest hoarseness as an early symptom, but those with tumors in the hypopharynx do not show symptoms until the tumors become advanced. Symptoms depend on the location of the primary tumor, but ear pain in the absence of otic disease is a frequent symptom. Therefore, patients with otalgia in the absence of demonstrable cause should be followed closely to detect any upper aerodigestive tract tumor. Other presenting symptoms include dysphagia, aspiration, and airway compromise.

Tumors of the hypopharynx and supraglottis tend to metastasize to the neck in a high percentage of patients. Carcinomas of the glottis have a much lower rate of regional metastasis. Treatment includes chemotherapy, surgery, and radiation therapy. The choice of treatment depends on the size and location of the primary lesion and regional metastasis. Treatment protocols have changed constantly over the last 20 to 30 years, although organ preservation protocols are presently common.

In patients with persistent but undiagnosable facial pain, parapharyngeal space tumors must be suspected. The most common neoplasm in this area is the benign mixed parotid tumor (65). They usually present as asymptomatic masses. Malignant tumors in this region are usually either lymphosarcomas or malignant schwannomas, which produce constant ipsilateral facial ache or pain and eventually lead to total facial paralysis with flaccidity. The slow onset of the facial paralysis

caused by this condition contrasts with the prompt onset of Bell's palsy. Treatment is usually surgical using a cervical-parotid approach. Carcinomas that produce facial paralysis often have a poor prognosis (66).

Other Painful Disorders

Cricoarytenoid Arthritis

Cricoarytenoid arthritis is manifested by intermittent or constant pain with dysphagia, hoarseness, and dysphonia. It can be caused by rheumatoid arthritis, laryngeal trauma, and other arthritic conditions, but it can also consist of an isolated joint involvement without precise cause (67). Treatment depends on associated systemic manifestations and on the degree of vocal cord movement. Surgical arytenoidectomy or vocal cordotomy might be necessary to enhance the airway if bilateral involvement results in bilateral vocal cord immobility and glottic airway narrowing.

Dysphagia with unilateral otalgia, and possible airway compromise, can also be seen as a consequence of nasogastric intubation, particularly when the tube is placed in the midline as opposed to being placed on either side of the arytenoid cartilages. This can lead to arytenoid arthritis or postcricoid abscess, particularly in diabetics. Treatment consists of early recognition, removal of the nasogastric tube, and parenteral antibiotics.

Stylohyoid Syndrome

The stylohyoid syndrome, also known as Eagle's syndrome, is caused by a dystrophic calcification of the stylohyoid ligament and consists of cervicopharyngeal pain radiating to the ear and the neck pain during mandibular movement, twisting of the neck, or swallowing (68). The pain is stabbing in nature; it originates in the tonsil area and radiates to the ear and sometimes the base of the tongue. Pain is absent with the mouth closed, and no trigger points are present. An elongated styloid or cervical transverse process can also produce symptoms. Not all or even most calcified stylohyoid ligaments, however, cause symptoms. Treatment consists of surgical removal.

Hyoid Syndrome

Hyoid syndrome is characterized by pain in the lateral aspects of the neck and carotid triangle near the tip of the greater cornu of the hyoid bone (69). The pain is usually sudden and severe, especially with head turning or swallowing, and it is often referred to the ipsilateral ear. Between attacks, a chronic dull ache and foreign body sensation can be felt in the throat. Lateral movement of the hyoid causes pain. An elongated lateral extension of the hyoid can be seen on radiography. Treatment consists of surgical excision of the bone.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is a rare cause of throat pain and otalgia that is characterized by radiating pain centered in the region of the tonsil, larynx, and tongue (see Chapter 47). The median age of onset is 64 years. Referred ear pain is the dominant complaint in this disorder. Treatment options include medical therapy such as carbamazepine (Tegretol), percutaneous neurolysis, and open surgical procedures.

Superior Laryngeal Neuralgia

Superior laryngeal neuralgia is similar to trigeminal and glossopharyngeal neuralgias and is characterized by paroxysms of severe, unilateral, lancinating pain radiating from the side of the thyroid cartilage or from the piriform sinus to the angle of the jaw, occasionally to the ear. The trigger zone is usually in the larynx, and attacks are precipitated by swallowing, yawning, sneezing, or by touching the skin over the hyoid bone. Block of the superior laryngeal nerve with local anesthetic produces complete pain relief and can be used as a diagnostic aid. It is also important to rule out laryngeal pathology as well as hyoid and glossopharyngeal neuralgias. Most patients obtain effective pain relief with Tegretol in a dosage of 200 mg daily, gradually increasing to 1,200 mg daily (70).

Carotidynia

Carotidynia is a self-limiting disorder characterized by intense pain in the region of the carotid artery, which is aggravated by palpation (71). Pain is localized to the lateral aspects of the neck, ear, and the angle of the jaw. It can be unilateral or bilateral, usually occurs in female subjects, can last a few days to a week, and is prone to spontaneous remission. Pain may be relieved by inhalation of 100% oxygen. It is important to rule out other pathologies including carcinoma, aneurysm, and inflammatory disorders of the lateral pharynx, salivary glands, and mandible.

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CHAPTER 53

Pain Caused by Cancer of the Head and Neck

Douglas B. Villaret and Ernest A. Weymuller, Jr.

CANCER OF THE HEAD AND NECK

Physicians treating head and neck cancer patients become intimately aware of the many pressing concerns that affect these patients' quality of life and response to treatment. The first hurdle patients face is accepting the diagnosis of cancer, their initial reaction usually being shock and disbelief (1,2). During this time it is important that the oncologist and primary caregiver have empathy and respond to all questions, which frequently are asked multiple times either from difficulty assimilating the information or in the outside hope that a mistake has been made. This is of particular concern for cancers involving the head and neck as the patients not only realize their increased likelihood of death, but also the potential for functional and aesthetic impairment. In addition to the specter of pain, their self-image, socialization, and ability to perform such simple functions as swallowing and breathing may be impaired by the tumor itself as well as the treatment. This chapter focuses on pain as it relates to head and neck cancer. Additional information about cancer pain is contained in Chapter 35 and Chapter 36; palliative care is covered in Chapter 40.

Psychological and Emotional Issues

The response to pain is intimately related to the psychological state of the patient. One study evaluated the needs of newly diagnosed cancer patients (3). The most pressing concern noted was about their health, but they had additional concerns about family, adequate social support, and the financial burden that would be imposed on them. Most had symptoms of fatigue, a worried outlook, and occasional insomnia. Up to 40% of patients complained of pain, with 40% of this group reporting inadequate relief of their pain. Several therapeutic strategies designed to enhance the psychological well-being of patients have been shown to reduce their subjective response to pain (2,3,4 and 5). Ineffective coping strategies of head and neck cancer patients are helplessness and fatalism, which lead to increased difficulty in managing pain and incomplete resolution of many of the patients' concerns (6). Such patients often benefit from talking to a psychiatrist or counselor early in the course of their disease, an option that should be readily available to them.

Head and neck cancer patients are commonly perceived as having a poor overall physical and emotional health profile. This was addressed in a study comparing these patients to age-matched U.S. population norms using the Medical Outcomes Study Short-Form Health Survey (7). All head and neck cancer patients had significantly worse mental health scores on their pretreatment evaluations; both the younger and the more advanced stage patients also had a worse physical health component score. The posttreatment scores showed improvement in both the mental health scale and the bodily pain scale. Unfortunately, these patients do not completely recover their emotional well-being. Among patients who have no evidence of disease 7 to 11 years after intervention, 25% to 40% have clinical depression as defined by *Diagnostic and Statistical Manual*, third edition, criteria (4). In addition, head and neck cancer patients have an increased risk of suicide as compared with other cancer patients (8,9). The chronic usage of alcohol and tobacco in this population, as well as a prevalence of low socioeconomic status, low level of education, and poor social support may in part explain this increased psychological fragility (7,10,11). The treating physician must be aware of these factors and realize the direct effect of the psychological state on the patients' ability to cope with pain. The converse is also true: Inadequately controlled pain has a detrimental effect on the emotional well-being of the patient. Too often the psychosocial aspects of the patients' health are not addressed, ultimately delaying or preventing complete recovery from the disease (6).

Physical Issues

The physical deterioration seen in cancer patients also increases their perception of pain. The pathogenesis of squamous cell carcinoma of the head and neck, the most prevalent histologic diagnosis in this region, is associated with the synergistic effect of alcohol and tobacco abuse in 90% of aerodigestive tract tumors. The excessive use of these carcinogens contributes to a general anorexia (12). Compounding this problem, head and neck cancer patients frequently have bulky tumors that interfere with such homeostatic functions as deglutition and respiration. Subsequent nutritional depletion results in general malaise and depressed immune function, which precipitates intercurrent infections and negatively affects tumor growth control (13). With an increasing tumor burden, an increased production is seen of a lymphokine called tumor necrosis factor, formerly known as cachectin, which contributes directly to wasting (14). Additionally, the cosmetic stigmata of these cancers and their treatment often cause patients to seclude themselves (2,4). In conjunction with the previously mentioned poorer social support system, this may make gaining access to food a problem. This aspect of patient management must be treated aggressively not only to improve pain management, but also to improve the patients' quality of life and chance for survival.

Quality of Life

In dealing with patients who have advanced tumor burdens, it is important to remember that increased survival may not be a worthy goal if the quality of life achieved by potentially radical means suffers dramatically. In an article titled “Treatment of patients with stage IV cancer: do the ends justify the means?” Burns and colleagues report that 42% of the patients believed that “there was virtually no joy in life after treatment” (15). In a separate study, the quality of life in advanced stage oropharyngeal lesions was evaluated (16). A worsening of the overall quality of life score was seen at 6 months posttreatment, followed by a gradual return to baseline over the next 6 months. Chewing, swallowing, and shoulder dysfunction were the categories showing the largest decrease. Pain, as assessed by the patient, improved posttherapy in 67% of those patients undergoing surgery; a smaller percentage showed improvement in the radiotherapy arm. This study included patients in stages II through IV who were disease free at 1 year, a different population than in the study by Burns and colleagues, but it shows the resiliency of cancer patients and their ability to cope with their disease.

Symptom management in terminal head and neck cancer patients can also be difficult. Issues of dyspnea secondary to obstructing lesions are infrequent because of the liberal use of tracheostomies. However, dyspnea caused by chronic lung disease is quite common and usually indicates a need for supplemental oxygen (5). Nutritional deficiencies are common because of the various factors mentioned earlier. Pain control is often inadequate. A study by Talmi and colleagues evaluated both inpatient and home hospice patients with head and neck cancer (5). Close to 20% of patients complained of light to moderate pain, whereas 50% of the home care and 74% of the inpatients complained of severe to incapacitating pain when they were first evaluated by the hospice team. Using the World Health Organization Cancer Pain Relief Program, improvement in the severity of the pain reported was seen in all patients. This underscores the need for aggressive treatment of pain in cancer patients, as discussed in Chapter 36 and Chapter 40.

Global Pain Issues

Tumor-related pain was found to be a significant factor in the lives of 80% of patients with oral cavity and oropharyngeal cancer (17,18). In another study, opioids were required for pain relief in over 60% of patients with advanced head and neck carcinoma (19). The pain experienced by these patients can be classified as nociceptive or nonnociceptive. Nociceptive pain is brought about by direct stimulation of the free nerve endings (A-d and C fibers) and can be subclassified into direct

stimulation, referred pain, and nociceptive nerve pain (20). Nociceptive nerve pain is defined as pain in the distribution of a sensory nerve with evidence of an inflammatory or destructive process occurring along the course of the nerve. Nonnociceptive pain is that generated by abnormally excitable nerve endings, often found in neuromas, and may be significantly influenced by the psychological state of the patient. By definition, an absence of any type of pathologic process is required. This type of pain is often seen in patients after a neck dissection with no evidence of infection or recurrence. In a study involving 25 patients, 84% had nociceptive pain from tumor recurrence, and 16% had similar pain secondary to benign inflammation. Additionally, 24% also suffered from nonnociceptive pain after radical cervical lymphadenopathy (21).

As can be seen by the previous discussion, the perception and tolerance of pain in head and neck cancer patients are influenced by their psychological, emotional, and physical well-being. With the high rate of alcoholism, depression, and poor nutritional status in this population, it is difficult to care for all the needs of these patients. Yet, to adequately meet their pain and symptom requirements, all aspects of their health must be addressed.

Pathology and Symptoms and Signs

To treat pain caused by cancers of the head and neck effectively, it is essential to know the pathophysiology, especially the pattern of spread, and the symptoms and signs produced by cancers in various structures of the head and neck. The following is a brief consideration of this subject. A much more detailed discussion has been presented in Suen and Myers (22) and Thawley and colleagues (23), from which some of the following information is taken.

Oral Cavity

The oral cavity consists of the lips, floor of mouth, anterior two-thirds of the tongue, buccal mucosa, upper and lower alveolar ridges, hard palate, and retromolar trigone.

Lip. Cancer of the lip occurred in an estimated 3,190 patients in 1996 (24). Most (88%) of the tumors are squamous cell carcinomas, most (88% to 98%) occur on the lower lip, and the overall 5-year disease-specific survival is good at 91% (23). In contrast to all other aerodigestive carcinomas, it develops as a result of sun exposure and behaves like other cutaneous carcinomas.

Pattern of Spread. Squamous cell carcinoma starts at the vermilion of the lower lip and invades laterally into the adjacent skin and then the orbicular muscle. Advanced lesions invade the adjacent commissures of the lip and buccal mucosa, the skin and wet mucosa of the lip, the adjacent mandible, and eventually the mental nerve. The *lymphatic spread* is to the submental and submandibular nodes, with occasional spread of upper lip cancers to the parotid nodes. Cervical metastases occur in approximately 8% of patients with less than a 2-cm primary cancer, but occur 6% to 35% of the time in lesions that are larger (23).

Symptoms and Signs. Carcinoma of the lip usually presents as a nonhealing erythematous lesion on the lower lip that crusts. It is often an exophytic lesion that is nontender unless it ulcerates and becomes infected, at which time the pain is moderate to severe (22).

Floor of the Mouth. Most neoplasms of the floor of the mouth are squamous cell carcinomas, usually of moderate grade (25). Adenoid cystic and mucoepidermoid carcinomas account for approximately 5% of malignant tumors in this region.

Pattern of Spread. Approximately 90% of the neoplasms originate 2 cm from the anterior midline floor of the mouth and penetrate quite early beneath the mucosa into the sublingual gland, eventually reaching into the midline genioglossus and geniohyoid muscles. Extension toward the gingiva and periosteum of the mandible occurs early and frequently. Invasion of the mandible is usually a late manifestation. Posterior extension occurs into the muscles of the root of the tongue. *Lymphatic spread* is into the submandibular and subdigastric nodes.

Symptoms and Signs. Most small lesions are asymptomatic and erythematous with rolled edges. As the cancer progresses, it can restrict the mobility of the tongue by direct invasion of muscle or the hypoglossal nerve. Pain or paresthesia is a manifestation of deep infiltration to either the mental or lingual nerves, or direct invasion of the mandible (22).

Oral Tongue. More than 95% of oral tongue lesions are squamous cell carcinomas, usually well differentiated (22). Verrucous carcinomas and minor salivary gland tumors are quite uncommon. The latter also carry a worse prognosis stage for stage than other sites in the oral cavity (26).

Pattern of Spread. Almost all oral tongue squamous cell carcinomas occur on the lateral and undersurface of the tongue and tend to remain in the tongue until quite large. Advanced lesions in the anterior third of the tongue invade the floor of the mouth and root of the tongue, producing ulceration and fixation. Middle third lesions invade the musculature of the tongue and later invade the lateral floor of the mouth, whereas posterior lesions grow into the musculature of the tongue, floor of the mouth, anterior tonsillar pillar, base of the tongue, and glossotonsillar sulcus.

Symptoms and Signs. Initially, the tongue is mildly irritated, and pain occurs only during eating or drinking. As ulceration and infection develop, local pain becomes progressively worse and is frequently referred to the external ear canal. Extensive infiltration of the muscle of the tongue affects speech and deglutition. The mouth of the patient with advanced lesions has a fetid odor. Pain that was initially minimal becomes more severe as ulceration and compression of the lingual and mental nerves produce pain in the tongue and teeth and referred pain to the ear.

Buccal Mucosa. The incidence of squamous cell carcinoma arising out of an area of leukoplakia is highest in the buccal mucosa. Verrucous carcinoma can occur in this area and can be difficult to diagnose. Smokeless tobacco is often the etiologic agent (22).

Pattern of Spread. Almost all squamous cell carcinomas in this region originate along the occlusal plane. Early lesions are usually discrete, elevated tumors that are often exophytic; as they enlarge, however, they penetrate the underlying muscles and eventually penetrate to the skin (25). Peripheral growth occurs into the gingivobuccal gutters and eventually into the gingiva and underlying bone. Posterior growth invades the pterygoid muscles, and superior extension involves the alveolar ridge and palate. *Lymphatic spread* is usually to the submandibular nodes, but occasionally the periparotid or superior deep jugular nodes are involved first.

Symptoms and Signs. Early leukoplakic lesions are asymptomatic and produce the sensation of a lump that is felt with the tongue. Pain is minimal, even when the lesion becomes large, unless it extends posteriorly into the lingual and dental nerves in which case pain becomes moderate to severe and often is referred to the ear. As the tumor spreads posteriorly, it often invades the pterygoid muscles causing trismus and poor oral intake. Parotitis is possible when Stensen's duct becomes involved with the tumor.

Alveolar Ridge, Retromolar Trigone, and Hard Palate. Carcinomas arising from the upper and lower gingiva, including the retromolar trigone, frequently invade the mandible. The most common location is in the posterior third of the mandibular dental arch (22). Almost all of these tumors are squamous cell in origin. Primary squamous cell carcinoma of the hard palate is quite unusual, with most hard palate neoplasms being minor salivary gland tumors. Epidermoid carcinoma can occur within the body of the mandible or maxilla (intraalveolar epidermoid carcinoma), arising from odontogenic epithelium trapped during embryonic development.

Pattern of Spread. Squamous cell carcinomas of the lower gum invade the periosteum and adjacent buccal mucosa and floor of the mouth (25). Low-grade slow-growing lesions tend to produce atrophy of the adjacent bone, whereas moderate- to high- grade lesions invade the bone directly or through recently opened dental sockets. *Lymphatic spread* is to the upper deep jugular nodes (22).

Most carcinomas of the upper gum and hard palate originate in the gingiva and spread secondarily to the soft palate, buccal mucosa, nasal cavity, and maxilla (22). The maxillary antrum is invaded quite late, unless recent extractions have provided an open pathway.

Lesions from the small area of the retromolar trigone spread early to the adjacent buccal mucosa, anterior tonsillar pillar, tongue, and maxilla (22). Posterior spread occurs early into the pterygomandibular space and the medial pterygoid muscle, whereas posterolateral spread occurs into the buccinator muscle and fat pad (25). *Lymphatic spread* is to the upper deep jugular lymph nodes.

Symptoms and Signs The patient usually presents first to the dentist with dental pain, loose teeth or ill-fitting dentures, or a sore that does not heal (25). Mild pain and intermittent bleeding occur when the lesion is traumatized. Invasion into the mandible can involve the inferior alveolar nerve and produce neuralgia, paresthesia, and

anesthesia of the lower lip. Retromolar trigone lesions that involve the lingual and inferior dental nerves cause local pain and pain referred to the external auditory canal and preauricular area. Invasion of the pterygoid muscle produces trismus and severe pain. Erosion through the hard palate eventually produces either oronasal or oroantral fistulas.

Oropharynx

The oropharynx includes four areas: the base of the tongue, tonsillar region (tonsillar fossa and tonsillar pillars), soft palate, and that portion of the pharyngeal wall between the level of the soft palate superiorly and the hyoid bone inferiorly, including the glossoepiglottic and glossopharyngeal folds. Squamous cell carcinomas of the oropharynx tend to be less differentiated and more aggressive than their oral cavity counterparts. They account for 83% to 95% of malignant lesions in this area. Lymphoma accounts for approximately 16% of tonsillar malignancies (an additional 6% being lymphoepitheliomas) and 1% to 2% of malignancies of the base of the tongue (27). The remainder of the lesions are minor salivary gland tumors. Approximately one-half of these are malignant, the two most common being mucoepidermoid and adenoid cystic carcinoma.

Base of Tongue

Pattern of Spread. Vallecular lesions spread along the mucosa to the lingual surface of the epiglottis, laterally along the pharyngoepiglottic fold, and then to the lateral pharyngeal wall and anterior wall of the piriform sinus. Lesions that begin on the lateral base of the tongue can invade the glossotonsillar sulcus and, from there, the tumor escapes into the soft palate or laterally into the neck. Advanced lesions tend to spread toward the larynx or oral tongue.

Symptoms and Signs. Most lesions of the small base of the tongue are asymptomatic and are rarely discovered until they are at least 2 cm. The earliest symptom of a lesion in the base of tongue is often a mild sore throat, with the patient sensing a lump in the back of the tongue or an asymptomatic neck mass. As enlargement occurs, the voice may become muffled or hoarse, with laryngeal involvement, dysphagia becomes more prominent, and referred otalgia via cranial nerves IX or X is common (23). Far advanced lesions affix the tongue and are associated with deep ulceration and necrosis, which produce severe pain and foul breath.

Tonsillar RegionPattern of Spread. Cancer of the anterior tonsillar pillar might consist of erythroplakic lesions early in its course, but can develop into a central ulcer, which eventually infiltrates the palatoglossus muscle. Superior medial spread occurs into the soft palate, the most posterior hard palate, and the maxillary gingiva. Anterolateral spread to the retromolar trigone is frequent, with later spread to the posterior gingival buccal sulcus and buccal mucosa. Invasion of the tongue is frequent. As these lesions advance, they adhere to the mandible and eventually invade the bone.

Lesions of the tonsillar fossa are most commonly found to be indurated and ulcerated with irregular margins. The next most common form is that of a lobulated, exophytic mass within the fossa, and least common is the deeply infiltrating ulcer (22). Invasion into the glossotonsillar sulcus and base of the tongue occurs in 41% to 80% of advanced cases (22). As the lesions advance they penetrate into the parapharyngeal space and gain access to the base of the skull superiorly, with consequent cranial nerve involvement. More advanced lesions invade the mandible, nasopharynx, and base of the tongue.

Lesions from the posterior tonsillar pillar either spread inferiorly along the palatopharyngeus muscle, pharyngoepiglottic fold, and posterior pharyngeal wall. Tonsillar fossa tumors are localized early, but later they spread to the tonsillar pillars and hard palate. Eventually, lateral spread penetrates into the superior constrictor muscle, with subsequent invasion of the pterygoid muscles and base of the skull, and occasionally with compression or invasion of cranial nerves into the parapharyngeal space. Lymphatic spread occurs early to the subdigastric nodes and then along the jugular chain. Cervical adenopathy is sometimes the only manifestation of a microscopic focus of cancer within the tonsil or tongue base.

Symptoms and Signs. The earliest symptom of lesions of the tonsillar region is a sore throat, usually aggravated by food or drink. Odynophagia and dysphagia cause 60% to 80% of the patients with tonsillar lesions to first seek medical attention (22). Ulceration causes local pain that is often referred to the ear. Advanced lesions invade the pterygoid or buccinator muscle or both and produce trismus and severe temporal pain. Invasion of the tongue eventually limits tongue mobility and, when accompanied by ulceration, causes severe pain through the lingual, inferior alveolar, or glossopharyngeal nerves.

Soft Palate

Pattern of Spread. Early mucosal lesions of the soft palate represent leukoplakia or carcinoma *in situ* , which progresses to invasive carcinoma. Often, multiple discrete areas are involved, known as *field-cancerization*. Spread occurs first to the tonsillar pillar and inferiorly to the tongue. Later growth penetrates to the superior constrictor muscles, with subsequent invasion of the medial pterygoid muscle and base of the skull and occasional compression or invasion of the cranial nerves in the parapharyngeal space. Superior growth extends into the nasopharynx.

Symptoms and Signs. The earliest symptom of a lesion of the soft palate is usually a mild sore throat aggravated by food or drink; it is not well localized. Often these tumors are asymptomatic and found by the clinician on routine examination of the oropharynx. An advanced lesion produces dysphagia, can cause voice change, and, if accompanied by destruction, perforation, or fixation of the soft palate, food and liquid are regurgitated into the nasopharynx. Lateral and superior spread to the nasopharynx and parapharyngeal space is associated with trismus or unilateral otitis media, moderate to severe temporal pain or headache, and occasional cranial nerve involvement, initiating along the palatine nerves.

Nasal Vestibule, Nasal Cavity, and Paranasal Sinuses

Tumors of the nasal vestibule, the anterior entrance to the nasal cavity, are considered separately from tumors of the nasal cavity because they are essentially skin cancer and have a different natural history (25). Eighty percent of neoplasms in the nasal vestibule, nasal cavity, and paranasal sinuses are squamous cell carcinoma. Adenocarcinoma of minor salivary gland origin tends to be more aggressive in the sinuses and contributes 6% to 17% of all tumors in this location (28). Malignant lymphoma and midline malignant reticulosis are seen in approximately 5% of patients (29). Other rare lesions include esthesioneuroblastoma (olfactory neuroblastoma), a malignant tumor that originates from the olfactory nerves, and a wide range of soft tissue and bone sarcomas, including chondrosarcoma, osteosarcoma, and Ewing's sarcoma. Delays in the diagnosis of these malignancies are common as the early symptoms mimic rhinosinusitis, the average time between onset of symptoms and definitive cancer diagnosis being 8 months (28).

Nasal Vestibule

Pattern of Spread. These lesions behave in a more indolent manner than their nasal cavity counterparts (30). Local growth is into the skin of the lip, laterally into the lower lateral cartilages of the nose, and medially into the septum. Nasal cavity obstruction is a late finding (29).

Symptoms and Signs. These lesions usually present with few symptoms other than a mass growing in the entrance of the nose, with crusting, scabbing, and occasionally minor bleeding. Pain is usually modest, even with destruction of the cartilage or involvement of the lip. Secondary infection can occur, in which case the nose is painful with manipulation.

Nasal Cavity

Pattern of Spread. The routes of spread are essentially the same for the various histologic lesions except for adenoid cystic tumors, which have a greater propensity for perineural spread (25). Lesions arising from the olfactory region invade the ethmoids, orbit, and anterior cranial fossa and frequently tend to destroy the septum; they can also invade the nasal bone to the skin. Lesions arising in the lateral wall of the nasal cavity invade the medial wall of the maxillary sinus, ethmoids, and orbit. Advanced lesions invade the nasopharynx and spheroid sinus. Some tumors follow the nasal nerves posteriorly and then superiorly toward the pterygopalatine ganglion and the pterygopalatine fossa, or along the maxillary branch of the trigeminal nerve (25).

Symptoms and Signs. Early symptoms of nasal cavity neoplasms are often confused with those of rhinosinusitis, except that the tumors are usually unilateral. Symptoms may include nasal airway obstruction, rhinorrhea, ipsilateral facial pain, and occasional referred otalgia, but even large sinonasal tumors may be surprisingly asymptomatic. The rhinorrhea can be mucoid, purulent, sanguinous, or clear (cerebrospinal fluid) (29). Late findings depend on the location of the tumor: Lesions arising in the olfactory region can cause unilateral or bilateral nasal expansion of the bridge of the nose and a submucosal mass can appear near the inner canthus and eventually ulcerate (25). Extension into the cranial cavity or ethmoid sinus is accompanied by a frontal headache. Invasion of the medial orbit produces

proptosis and diplopia.

Paranasal Sinuses

Most tumors of the paranasal sinuses originate within the maxillary sinus and are usually squamous cell carcinoma.

Pattern of Spread. Ohngren's line divides the maxillary sinus into anteroinferior and posterosuperior compartments. Less ominous lesions, those located anteroinferiorly, tend to invade through the lateral inferior wall or grow through dental sockets or anteriorly into the skin. Lesions of the posterior infrastructure can erode through the posterolateral wall and invade the pterygopalatine and infratemporal fossae. Tumors arising in the upper half (suprastructure) can invade superiorly into the orbit and laterally to the malar region and eventually ulcerate through the skin to produce an antrocutaneous fistula. Far advanced lesions can invade the temporal fossa and zygomatic bone. Suprastructural cancers that develop medially invade the nasal cavity, ethmoids, frontal sinus, lacrimal apparatus, and medial inferior orbit (29).

Tumors of the ethmoid and frontal sinuses are less common and tend to erode into the orbit, nasal cavity, and anterior cranial fossa. The sphenoid sinus is rarely the site of origin of carcinomas. They usually become evident by involving the cranial nerves in the cavernous sinus, including cranial nerves III, IV, and VI, and the ophthalmic and maxillary branches of the trigeminal nerve or the optic nerve. Lateral growth would invade the middle cranial fossa and anterior growth would be into the nasopharynx.

Symptoms and Signs. The symptoms and signs of tumors in the paranasal sinus depend on the structure invaded. Most patients have progressively moderate to severe local pain and neuralgia and cranial nerve palsies, as well as loose dentition or poorly fitting dentures. Visual disturbances such as proptosis, diplopia, and chemosis occur in advanced lesions when tumor breaches the periorbita. Compression or infiltration of the infraorbital nerve in the floor of the orbit can cause neuralgia, paresthesia, and hyperesthesia in the distribution of this nerve. Unilateral nasal obstruction, infection, and bleeding are common complaints with maxillary sinus tumors. Cancers developing in the medial suprastructure of the antrum present with nasal symptoms of discharge or bleeding, infraorbital pain, and displacement of the eye upward and laterally with proptosis, diplopia, and conjunctival edema. Cancer in the lateral suprastructure of the maxillary sinus produces a mass below the lateral canthus associated with pain, deviation of the eye medially and upward, chemosis, diplopia, and proptosis.

Lesions of the ethmoid sinus produce mild to moderate pain referred to the frontal and nasal area early in the course of the disease. Diplopia and proptosis also develop with invasion of the orbit. Neuralgia, paresthesia, and dysesthesia can develop over the distribution of some of the involved sensory nerves. Tumors of the sphenoid sinus frequently cause progressively severe head pain, headache, and cavernous sinus syndrome (cranial nerves III, IV, $V_{1,2}$, and VI).

Nasopharynx

Tumors of the nasopharynx are uncommon in the United States but are common in Southeast Asia, Greenland and Alaska, and parts of equatorial Africa. The nonkeratinizing forms (96%) are associated with elevated titers of Epstein-Barr virus. The various histologies include carcinoma (90%), lymphoma (5%), and miscellaneous (23).

Pattern of Spread. Tumors usually begin in the fossa of Rosenmuller and affect the adjacent eustachian tube orifice early. Inferior extension along the lateral pharyngeal wall and tonsillar pillars occurs in one-third of patients, and into or through the base of the skull (foramen lacerum) in 25% of patients; invasion of the posterior ethmoids, maxillary antrum, and orbit occurs fairly often. Cranial nerve involvement is frequent, most commonly being the maxillary and mandibular branches of the trigeminal nerve (23). Lateral extension into the pterygopalatine and infratemporal fossae may involve the lower four cranial nerves. Tumor can erode through the foramen ovale, foramen lacerum, and foramen spinosum, eventually reaching the cavernous sinus area and gaining access to cranial nerves II to VI. Metastasis to the neck nodes occurs with 80% to 90% of nasopharyngeal carcinoma, with occasional metastasis to the mental and occipital nodes (25).

Symptoms and Signs. The most common symptom of nasopharyngeal carcinoma is that of a painless unilateral metastatic cervical lymph node (22). Usually nasal obstruction, epistaxis, and serous otitis media are also seen. Some patients present with a mild sore throat, whereas many have facial pain in one or more of the three divisions of the trigeminal nerve, usually the mandibular. Pain in the scalp or the mastoid area may be related to involvement of a high jugular lymph node that has become fixed to the skull and spine. Posterior infiltration of the prevertebral muscles causes pain that is aggravated with lifting of the head and extension of the neck. Posterior orbital invasion usually produces proptosis. Trismus and temporal pain occur with invasion of the pterygoid region. Cranial nerve involvement occurs in 20% of patients (31).

Hypopharynx

The hypopharynx includes the pharyngeal walls from the level of the hyoid to the bottom of the cricoid cartilage, the piriform sinus, and the postcricoid pharynx. The larynx is intimately associated with this area, being anterior to the postcricoid space and medial to the piriform sinuses. Ninety-five percent of hypopharyngeal tumors are squamous cell carcinoma and are usually stage III or IV when diagnosed (32). Minor salivary gland tumors occur but are quite rare.

Pattern of Spread. Carcinomas of the posterior pharyngeal wall tend to remain on the posterior wall, grow up or down the wall, and infiltrate submucosally, often for distances over 10 mm. Skip lesions are also frequent in this area (23). As the lesion progresses the tumor bulges into the pharyngeal cavity and a ragged midline ulceration appears (25). The posterior tonsillar pillars can become involved with spread of the upper pillars, eventually reaching the palate. Advanced lesions tend to terminate inferiorly at the level of the arytenoids and can extend superiorly into the oropharynx. Prevertebral muscle invasion is a late finding.

Early tumors of the lateral pharyngeal wall are well-defined exophytic lesions but, as they advance, they tend to penetrate laterally through the constrictor muscle, thus entering the lateral pharyngeal space or the soft tissues of the neck. This may produce a palpable mass in the neck just below the hyoid that might be confused with an enlarged lymph node. The tumor can spread along the muscles of the pharynx that originate from the base of the skull to involve the eustachian tubes, styloid process, pterygomandibular raphe, and hyoid bone. The tumor can also course along cranial nerves IX and X and the sympathetic chain.

Early lesions of the piriform sinus are usually discrete and exophytic, particularly those high on the medial wall (25). Medial wall lesions can grow superficially along the epiglottic fold and arytenoids or invade directly into paraglottic space or posteriorly to the postcricoid region, again mostly by submucosal spread. Lesions arising on the lateral wall invade the posterior thyroid cartilage early, and later penetrate to invade the thyroid gland. They also tend to spread submucosally onto the posterior pharyngeal wall, which eventually becomes eroded and ulcerated. Advanced lesions of the piriform sinus invade all three walls, fix the larynx, involve the posterior pharyngeal wall, invade the thyroid cartilage and thyroid gland, and often escape into the soft tissues of the neck.

Early tumors of the postcricoid pharynx remain localized, particularly those on the posterior wall, and are difficult to diagnose. Lesions from the anterior wall tend to invade the posterior cricoarytenoid muscle and the cricoarytenoid cartilage. Perineural invasion of the recurrent laryngeal nerve is also seen. Advanced tumors eventually encircle the lumen.

Lymphatic spread of pharyngeal wall lesions terminates primarily in the jugular chain and the retropharyngeal node group and secondarily to the spinal accessory chain (23). Lesions of the hypopharynx spread mainly to the jugular chain, with 44% of patients having disease in the retropharyngeal nodes (22). Occult cervical metastases are seen in 50% to 80% of patients with hypopharyngeal cancer and are often bilateral (33). Clinically apparent disease in the neck can be as high as 75% for piriform fossa primaries (22).

Symptoms and Signs. These tumors are often asymptomatic until they reach a large size, accounting for the relatively late stage tumors found at initial diagnosis. Tumors localized to the lateral pharyngeal wall or the piriform sinus produce a unilateral sore throat, which is in contrast to an infectious sore throat that is usually bilateral. The pain is usually moderate but can become severe. Dysphagia, a sensation of a foreign body, referred otalgia, blood-streaked saliva, and voice changes occur later. Lesions of the posterior pharyngeal wall and piriform sinus can produce mild to moderate pain and dysphagia. Lesions of the apex of the piriform sinus or postcricoid area produce edema of the arytenoids and, if the mucous membrane is ulcerated, moderate pain is felt on swallowing. Involvement of the retropharyngeal nodes can produce pain in the neck with stiffness as well as pain radiating to the ipsilateral eye and forehead (23).

Salivary Glands

The parotid glands account for 80% of salivary gland tumors, with the submandibular gland contributing 10% to 20%, and the sublingual and minor salivary glands the remainder (23). Tumors of the major salivary glands account for 4.5% of all head and neck neoplasms (32). Among the major malignant tumors are low- and high-grade mucoepidermoid carcinoma, undifferentiated carcinoma, acinic cell carcinoma, squamous cell carcinoma, adenoid cystic carcinoma, adenocarcinoma, and malignant mixed tumors.

Pattern of Spread. Parotid malignancies infiltrate the remainder of the gland, invade cranial nerve VII, and spread along the nerve sheaths for some distance. They can invade the adjacent skin, adjacent muscles of mastication and facial expression, and the temporal bone and mandible. Extension from the deep lobe via the stylomandibular tunnel allows access to the parapharyngeal space. Malignant tumors of the submandibular gland invade the gland, fix the tumor to the adjacent mandible, and invade the hyoid bone and eventually the tongue, hypoglossal nerve, oral cavity, and oropharynx, with skin invasion occurring in advanced cases. Minor salivary gland tumors arising in the parapharyngeal space (prestyloid compartment) can extend medially to the oropharynx, superiorly to the skull base, posteriorly to the carotid sheath, anteriorly to the maxilla, and laterally to the mandible. High-grade malignancies metastasize 25% to the regional lymphatics, including the intraparotid, preauricular, and jugulodigastric nodes (22).

Symptoms and Signs. A great majority of patients present with a mass that is easily seen and felt in the parotid, associated with mild to moderate pain and pressure. Late findings include facial nerve palsy in 10% to 15% of tumors and dysphagia when the tumor is deep in the lobe. Once the parapharyngeal space is breached, cranial nerves IX through XII can become involved. When the tumor tracks along the auriculotemporal nerve it can extend to the base of the skull and involve the mandibular division of the trigeminal nerve, with consequent neuralgia. Temporal bone invasion causes otalgia and retroorbital pain.

Larynx

Cancer of the larynx affected 1.35% of patients in the total United States cancer population during the years 1985 through 1994 (32). Approximately 12,500 cases are newly diagnosed each year, making it the most common site for head and neck cancers (22). These tumors are found earlier than most other cancers because they cause hoarseness, which accounts for the fact that 61% are diagnosed as carcinoma *in situ* stage I or II (32). The larynx is subdivided into three distinct regions, each with varying natural histories: the supraglottis, glottis, and subglottis. Ninety-four percent of malignant tumors of the larynx arise from the surface epithelium and are therefore squamous cell carcinoma or one of its variants.

Pattern of Spread. Cancers of the supraglottis include those originating on the epiglottis, aryepiglottic folds, false vocal folds, arytenoids, and all but the floor of the ventricle. Most lesions are epiglottic in origin. Lesions of the suprahyoid epiglottis and aryepiglottic folds make up the marginal zone of the supraglottis and can have unhindered access to the abundant lymphatics of the pharynx via the pharyngoepiglottic fold, or can grow as an exophytic mass that does not invade outside its origin (22). Lesions of the infrahyoid epiglottis tend to produce irregular outgrowths of tumor nodules, with simultaneous invasion through the porous epiglottic cartilage into the preepiglottic space (23). Once in this space, the tumor can extend inferiorly to the anterior commissure, superiorly to the vallecula, or anteriorly through the thyroid cartilage or thyrohyoid membrane. False cord carcinomas are usually ulcerative and infiltrative and extend to the infrahyoid epiglottis. Advanced lesions can invade the thyroid, epiglottic, or cricoid cartilage and eventually invade the base of the tongue and pharyngeal wall. As evidenced by dye studies, a supraglottic compartment limits inferior extension to the glottis, but at a late stage tumors involve the anterior commissure and eventually have subglottic extension.

Most cancers of the vocal cords begin in the free margin and upper surface and are easily visible, with two-thirds usually confined to one cord. The four major barriers to spread are the conus elasticus, vocal ligament, anterior commissure, and thyroglottic ligament. As the lesions enlarge they extend to the thyroarytenoid muscle, fixing the cord; then to the vocal process of the arytenoid and laterally to the paraglottic space and thyroid cartilage. Superior extension encompasses the ventricle and false cord and remainder of the supraglottis. Advanced lesions eventually penetrate through the thyroid cartilage or thyrocricoid membrane into the neck and often invade the thyroid gland. Subglottic cancers, which are quite uncommon, usually involve the cricoid cartilage early, although the conus elasticus resists spread into the glottis. Further growth eventually invades the undersurface of the vocal cord, with consequent fixation of the cord, as well as inferior extension into the trachea. Lymphatic spread at the time of diagnosis of supraglottic cancer involves 25% to 75% of patients depending on stage; in 16% of these patients the metastases are bilateral. In glottic cancer the incidence of lymphatic spread at diagnosis is less than 5% for lesions confined locally (T_1), 5% to 10% for T_2 lesions, and 10% to 20% for T_3 and 25% to 40% for T_4 lesions (34,35 and 36).

Symptoms and Signs. Carcinoma arising in the glottis produces hoarseness at an early stage, whereas those arising in the supraglottis or subglottis do this only when the lesion is extensive. Advanced lesions produce pain of varying severity, sore throat, and airway obstruction. Sore throat and dysphagia are the most frequent initial symptoms with cancer of the supraglottic larynx, with odynophagia usually indicating spread to the hypopharynx (22). Mild to moderate pain is the most frequent initial symptom, often described as persistent irritation or sore throat associated with some difficulty in swallowing and the sensation of a lump in the throat. Cancer of the epiglottis does not produce symptoms until it becomes large, at which time it causes pain that is often referred to the ear (by way of the vagus nerve and auricular nerve of Arnold). Late symptoms include weight loss, foul breath, dyspnea, and aspiration.

Thyroid Gland (VIII-1)

Approximately 10,350 cases of thyroid cancer were reported per year in the United States from 1990 through 1994 (32). The 5- year disease-specific survival rate is 89.5% for all stages, with fewer than 1,200 patients dying per year of this disease. Most of the tumors are well differentiated and are either papillary carcinoma (80%) or follicular carcinoma (15%). Medullary carcinoma and poorly differentiated and anaplastic carcinoma form the rest, along with lymphoma (23). The prognosis for patients with papillary or follicular thyroid cancer is generally good, especially for women and those patients younger than 45 years of age.

Pattern of Spread. The spread of thyroid cancers depends on pathology. Low-grade well-differentiated papillary neoplasms tend to have multiple, discontiguous foci within the thyroid gland and to spread to the regional lymph nodes. Follicular neoplasms, on the other hand, tend to be localized within the gland and to spread by the hematogenous route. Medullary carcinoma, associated with multiple endocrine neoplasia syndromes 2a and 2b, most often spreads to the cervical lymph nodes and upper mediastinum. Anaplastic carcinoma is aggressive and spreads into all the local tissues (23).

Symptoms and Signs. Thyroid carcinoma is usually not painful and the initial presenting symptom is a small hard thyroid nodule. Because of the high incidence of thyroid nodules and the fact that only 5% to 20% of solitary thyroid nodules are cancerous, an accurate diagnosis is imperative (23). Factors in the history and physical examination that indicate a high probability of cancer include a history of previous external radiation therapy, relatively recent onset of a firm hard single nodule in the thyroid gland, and the presence of cervical lymphadenopathy. With progression of the disease, hoarseness is an ominous sign indicating recurrent laryngeal nerve involvement. Dysphagia and dyspnea occur, but often are present in large goiters as well. Rapid growth in a previously slow-growing nodule can herald the transformation into an anaplastic cancer.

Eye

The most important cancer of the eye among white adults is ocular melanoma. The annual incidence is 0.7 per 100,000 population in the United States, encompassing 79% of all noncutaneous melanomas (37). The prognosis depends on the size, histologic type, and presence of metastases: Overall disease-specific 15-year survival is 89%; when metastases are present the 5-year survival rate plummets to 10% (38,39). The most common intraocular tumor in children is retinoblastoma, which has a good prognosis unless the tumor escapes into the orbit (22). The most common orbital tumor in children is rhabdomyosarcoma, which accounts for 45% of all sarcomas in the head and neck. Other primary neoplasms of the orbit include adenoid cystic carcinoma and carcinoma ex pleomorphic, both from the lacrimal gland, and various soft tissue sarcomas. Secondary tumors from the skin (squamous cell and basal cell carcinoma) as well as the sinuses and nasopharynx also impinge on the orbit.

Pattern of Spread. The tumors from the lacrimal gland tend to have local and perineural spread along cranial nerves II, III, IV, V_1, and VI. Intraocular melanoma usually begins in the posterior choroid and either spreads laterally between the sclera and retina or pushes the retina anteriorly into the vitreous cavity (37). Other tumors have easy access from the orbit through the thin medial wall, lamina papyracea, to the ethmoid sinus or superiorly into the anterior cranial fossa.

Symptoms and Signs. The clinical symptoms and signs depend on the location and size of the tumor. Small lacrimal gland tumors can produce minimal visual disturbances, whereas large tumors produce pain, severe visual disturbances, and palsy of the cranial nerves within the orbital cavity. Orbital tumors produce proptosis, xerophthalmia, and ophthalmoplegia, with varying degrees of pain. Effective therapy produces a high rate of cure, and death usually occurs only with advanced cases that have been neglected. With small asymptomatic adenomas, appropriate workup and subsequent observation are the treatments of choice, particularly in elderly patients. If the lesion shows progression, particularly rapid growth, or an increase in size beyond 10 mm in diameter and 2 mm in elevation or the

lesion results in visual impairment, proton beam irradiation is the treatment of choice. Small melanomas produce visual changes in acuity, and large melanomas are indications for enucleation. A report from the Collaborative Ocular Melanoma Study Group failed to show a benefit to preenucleation radiation therapy for large orbital melanomas (40).

Cutaneous Cancer in the Head and Neck

The number of nonmelanoma skin cancer cases now numbers greater than 1 million per year in the United States, equal to that of all noncutaneous malignancies (41). Basal cell carcinoma, usually a slow-growing, indolent tumor, accounts for 25% of all human cancers with more than 85% being located on the face, scalp, or neck. They metastasize less than 0.1% of the time (23). Squamous cell carcinoma of the skin, however, makes up only 25% of the nonmelanoma skin cancer, but accounts for 75% of the mortality, with 2% of all patients who get squamous cell carcinoma of the skin dying of their disease.

The early stages of disease are marked by little or no pain, and appropriate surgical therapy cures the patient, but neglected tumors spread and can invade the underlying bone, ulcerate, and become necrotic. Some basal cell carcinomas of the head can erode through the skull and into the brain. These are usually associated with moderate to severe pain, and often have a foul odor (Fig. 53-1).

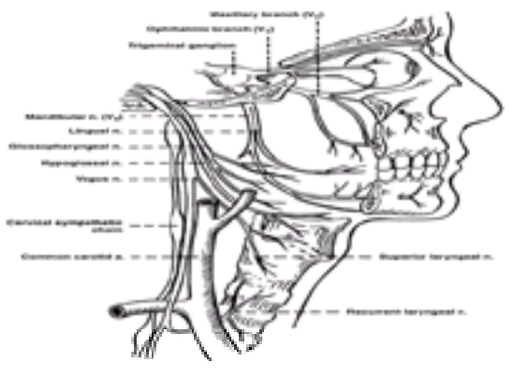

Figure 53-1. The course of the trigeminal, glossopharyngeal, vagal [with superior and recurrent laryngeal nerves (n.) shown], and cervical sympathetic chain is shown, illustrating the pathways of the nerves most commonly implicated in pain transmission from the head and neck. (Superficial cervical sensory nerves not shown.)

Cancer of the Cranium and Brain

Primary Cancer of the Cranial Bones

Severe pain always accompanies primary cancer of the bone, the site of primary Ewing's sarcoma or osteosarcoma. Both types of cancers produce progressively severe pain in the lower jaw. Other tumors originating in the mandible include fibroosseous lesions (fibrous dysplasia, ossifying fibroma, and cementoossifying dysplasia), giant cell tumor, and ameloblastoma, but these do not cause pain unless secondary infection takes place or they have grown to such a size that the nociceptors in the periosteum are affected (37,42). Other primary bone tumors can originate in the calvarium or other cranial bones and produce pain that either is localized or referred as a headache. Occasionally, these produce neuralgia if one of the major divisions of the trigeminal nerve, the intermedius nerve of the facial or glossopharyngeal nerve, or the vagus nerve is compressed.

Primary and Metastatic Brain Tumors

The most common tumors in the cranial cavity are derived from the neuroepithelium, with glioblastoma being the most common, followed by astrocytoma (37,42). Worldwide, the incidence of primary intracranial tumors is estimated to be approximately 7.1 to 8.6 per 100,000 population, with the incidence of glioblastoma alone being in the 3.5 to 5.0 per 100,000 population range (43). Meningiomas, a benign but locally destructive tumor, account for approximately 20% of all intracranial neoplasms in men, but nearly double that for women (44). The 1995 Surveillance, Epidemiology, and End Results (SEER) of the National Cancer Institute (NCI) statistics show a 30% 5-year survival for all brain tumors (24). Glioblastomas are particularly aggressive, with the mean length of survival after diagnosis being 8 to 10 months (37). A bimodal age distribution occurs: Medulloblastoma and ependymomas account for the early peak seen in children (42). Seventy percent of the tumors in children are infratentorial, whereas the opposite is true in adults (37). Consequently, cortical or hemispheric lesions are seen with much greater frequency in the adult population, whereas most pediatric gliomas arise in the cerebellum, brainstem, and midbrain or thalamic region.

In 1978, Posner and Chernik found a 24% incidence of brain metastases in an autopsy study performed on patients dying from cancer (45). Other studies have shown that up to one-half of all intracranial neoplasms are metastases (42). The most common site that metastasizes to the brain is the lung, accounting for 36% to 40% of all such tumors (46,47 and 48). Breast carcinoma is next most frequent with 18% to 29%, followed by tumors from the gastrointestinal tract with 6.7% to 7.1% of the total. Head and neck cancers, reflecting their low percentage of all cancers, make up only 1.9% to 3.1% of all brain metastases. Once these tumors are diagnosed in the intracranial cavity, the median survival ranges from 10 to 14 months, with a 1-year survival rate of 44% to 55% with therapy (46).

Symptoms and Signs. Headache is the most frequent initial presenting symptom in most brain tumors (see Chapter 48). Although fewer than 1% of all headaches for which patients seek medical advice are attributable to tumor, more than 70% of patients with an intracranial neoplasm complain of moderate to severe headaches (46). It is usually mild and episodic early, but with time it increases in frequency, duration, and severity. The headache is usually bilateral and caused by increased intracranial pressure and has a typical temporal pattern: It is often worse in the morning, awakening the patient, and decreases in intensity during the day because of differences in the cerebrospinal fluid draining in the supine versus the upright position and the relative hypercapnia experienced during sleep. Often a regional correlation to the headache is found, especially with anterior or middle cranial fossa lesions causing supraorbital headaches via irritation of the ophthalmic branch of the trigeminal nerve (42). Occipital or posterior fossa lesions can cause occipital and posterior cervical pain and sometimes referred otalgia through irritation of cranial nerves IX and X. Many patients, however, complain of a diffuse headache that varies in location. The headache is aggravated by coughing and straining and is often associated with nausea. The most common sign of increased intracranial pressure from tumor is bilateral papilledema, occurring in greater than 50% of patients with brain tumors (42).

The second most common presenting sign of an intracranial neoplasm is a seizure. Approximately one-fourth of patients with a neuroepithelial tumor have a seizure as their presenting symptom. They are usually nongeneralized seizures, rather than grand mal, and eventually occur in one-third of these patients. Focal neurologic symptoms usually connote a fairly well-developed mass lesion. These include absence or sensory seizures or deficits in vision, hearing, smell, or motor function that occur in relation to specific tumor sites.

The most common presenting symptoms of brain metastases are headache in 55%, motor weakness in 40%, and behavioral changes in 31% (46). Most of the headaches are of the tension type, with some being classified as migraine. Other symptoms of metastases include ataxia and aphasia.

Tumors of the Base of the Skull

Until fairly recently, lesions in certain regions of the skull base were considered inaccessible, and as most are radioresistant, incurable. With new surgical approaches, skull base surgery has been refined, allowing extirpation of lesions without gross deformity. Anatomically, the skull base can be divided into four broad regions: anterior, anterolateral, middle, and posterior (22). The anterior cranial base is usually affected by squamous cell carcinoma, primarily by direct invasion from the paranasal sinuses. Juvenile nasal angiofibroma almost exclusively is found in adolescent boys; esthesioneuroblastoma, mucosal melanoma, lymphoma, and fibrous dysplasia can also be found here. The anterolateral area is most affected by the benign, but locally aggressive, meningiomas and those tumors that extend into the cavernous sinus. The middle cranial base, extending from the orbit to the mastoid, include tumors from the parotid gland, carcinomas from the skin, pinna and ear canal, jugular glomus tumors, jugular neurilemomas, temporal bone metastases, and nasopharyngeal carcinoma. The posterior cranial base harbors acoustic neurilemoma, chordoma, meningioma, and chondrosarcomas. A report on 30 patients with malignant anterior skull base lesions showed a 56% 5-year survival rate

(49).

Pattern of Spread. The skull base neoplasms tend to invade locally through the sinuses, the orbit, along the cranium, and perineurally into the foramina. Nasopharyngeal carcinoma is the exception, with its high rate of metastases to the cervical lymph nodes.

Symptoms and Signs. The manifestations of tumors at the skull base are dependent on their anatomic location. Anteriorly based neoplasms can exhibit nasal obstruction with rhinorrhea, epistaxis, anosmia, and occasionally cerebrospinal fluid rhinorrhea. Often, the tumor causes an obstructive sinusitis with congestion and pain. Orbital involvement produces proptosis, diplopia, epiphora, and eventually decreased visual acuity. Facial pain and swelling also often accompany these lesions. Patients with more posterior lesions often complain of headache, with signs of various cranial nerve dysfunction. One localizing measure is in the pattern of cranial nerve deficits that constitute particular syndromes (Table 53-1).

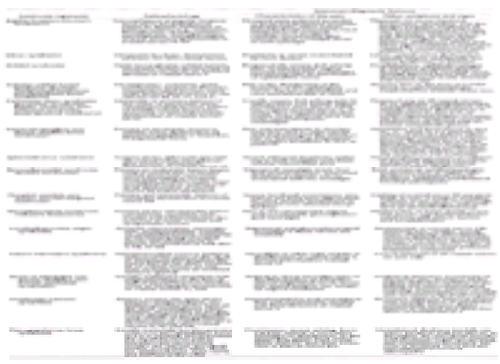

TABLE 53-1. Clinical syndromes caused by tumors involving the skull

MANAGEMENT OF CANCER-RELATED PAIN

Mechanisms of the Pain

The mechanisms by which head and neck cancer can cause pain include direct stimulation of nerve endings in the mucosa and submucosa, ulceration and infection, compression and involvement of sensory nerves, and bone invasion (20). Nonnociceptive pain is seen when nerve fibers exhibit abnormal excitability, as can be seen in the severed nerves after a neck dissection. Pain can also be caused by oncologic therapy.

Stimulation of Nerve Endings

Stimulation and sensitization of nociceptor nerve endings in the mucosa and submucosa are characteristics of the initial phases of cancer growth and can be considered to be mainly responsible for local burning sensation, superficial pain, and referred otalgia in exophytic or erosive lesions.

Ulceration and Infection

Most cancers that arise from the mucous membranes of the mouth and pharynx tend to ulcerate because of both central necrosis and microtrauma. Ulceration does not produce spontaneous pain. Pain is experienced after exposure to a local irritant agent such as alcohol or acid, onset of infection with expression of inflammatory mediators, and resultant inflammation. Movement markedly increases pain caused by ulceration, and its intensity varies from site to site. Exacerbation by functional activity is minimal in static regions such as the cheek, hard palate, nasal and paranasal cavities, and nasopharynx and is severe in dynamic structures such as the tongue, floor of the mouth, soft palate, and faucial arches.

Nerve Compression and Infiltration

An important cause of head and neck cancer pain is infiltration, compression, or both of one or more branches of the trigeminal, glossopharyngeal, or other sensory cranial nerves (see Fig. 53-1). Thus, tonsillar fossa tumors are frequently accompanied by pain that is at first mild and localized to the tonsil; as the tumor grows, however, pain becomes progressively more severe and spreads to the lateral wall of the pharynx and then to the entire area supplied by the glossopharyngeal nerve. In the initial stages the pain is somewhat sharp, but as it spreads it becomes more severe, continuous, persistent, dull, and aching and is accompanied by bouts of lancinating pain, referred otalgia, and generalized headache. Cancers of the maxillary antrum and upper jaw frequently produce pressure on branches of the maxillary nerve and consequent maxillary neuralgia, which is superimposed on the local pain caused by periosteal stretching and consequent stimulation of nociceptive endings.

As indicated in the preceding section, some tumors invade the pterygoid region and the infratemporal fossa and can involve the mandibular nerve or some of its branches to the muscles of mastication to produce neuralgia, trismus, and temporal pain. Tumors of the nasopharynx, oropharynx, or hypopharynx can compress and infiltrate branches of the glossopharyngeal and vagal nerves and produce neuralgia in their distribution, as well as localized pain.

Pain Caused by Bone Involvement

Bony involvement with squamous cell carcinoma of the head and neck usually occurs by direct extension of sinonasal, oral cavity, and oropharyngeal tumors into the adjacent bone of the maxilla, skull base, or mandible. A report by Troell and Terris found only a 5% rate of distant metastases to bone in a review of 97 consecutive patients with head and neck cancer (50). The pathogenesis of bone pain starts with stimulation of A-d mechanoreceptors and C nociceptors that are located mostly in the periosteum, but also in the marrow space along blood vessels and in the tendons (51). The inflammatory cytokines interleukin-1, interleukin-6, and tumor necrosis factor, as well as prostaglandins in the E series, mediate activation of the nociceptors (52). Interestingly, these same humoral factors are responsible for osteoclast activation and subsequent bone destruction. The mechanoreceptors are sensitive to stretching of the periosteum by movement around an eroded area (i.e., the mandible during mastication) or by an expanding (metastatic) lesion contained within an intact periosteal layer (53). Activation of nociceptors may also stimulate localized reflex muscle spasm resulting in increased traction and an increase in pain. This occurs more often in osteolytic bone, which produces more microfractures. For untreated tumors involving the mandible, local growth eventually involves the inferior alveolar nerve and produces numbness, rather than continued pain. This same phenomenon can be seen with involvement of other branches of the trigeminal nerve as well.

Distant metastases from squamous cell carcinoma to the long bones tend to be osteolytic and can produce painful, pathologic fractures. They present a unique management problem in that curative treatment is no longer a realistic goal (see Chapter 37). For solitary lesions, focal radiation can be delivered with significant reduction in pain (54). Hemibody irradiation may be used for multiple metastases, but myelosuppression often occurs. Clodronate, a second-generation bisphosphonate, effectively reduces both the hypercalcemia associated with bony metastases as well as the pain. Given either orally or parenterally, long-term usage does not impair mineralization of bone as etidronate does, and some evidence exists for impairment of growth of existing lesions and formation of new lesions (55). Radionuclides are also used with some efficacy for painful bony metastases. Strontium 89 has a positive effect on pain control in 70% of patients that can last up to 6 months (56). Rhenium 186 complexed to hydroxyethylidene diphosphonate is a newer compound with a shorter half-life (89 hours) than strontium. This compound is taken up in bone that has a high turnover rate and emits beta rays, damaging the adjacent tumor cells while providing some pain relief (57). Both of these compounds cause mild bone marrow suppression. Finally, narcotics and adjunctive analgesics as well as heat therapy, physical therapy, adequate rest (with joints extended rather than flexed), and warm, loose-fitting clothing must also be used for effective pain relief (58).

Pain as a Complication of Oncologic Therapy

Postoperative Pain Syndromes. Surgery followed by radiation for oncologic cure in patients with stage III or IV oropharyngeal cancer has the benefit of providing superior pain relief when compared with primary radiotherapy (16). However, neck dissection, particularly radical neck dissection, frequently causes postoperative

pain because of shoulder dysfunction and neuromas caused by the severing of small and large cervical sensory nerves. Neuromas can be followed by chronic, continuous, aching pain and associated bouts of lancinating pain in the distribution of the nerves.

Mucositis. Oral mucositis from head and neck cancer treatment (radiation, chemotherapy, or both) is usually moderate in severity and self-limiting, but it can be debilitating and dose-limiting, leading to a reduction in the amount of radiation or chemotherapy delivered, thus compromising tumor treatment (59). This topic is discussed in detail in Chapter 38. Patients receiving these treatments, especially chemotherapy, are often myelosuppressed; thus mucositis and ulceration can be portals of entry for endogenous oral bacteria and a significant source for sepsis (60). The oral cavity has been shown to be the source in 25% to 50% of immunocompromised patients with sepsis (61). Mucositis also limits oral intake. For those patients without gastrostomy tubes, an average weight loss of 5 kg has been shown to occur during the course of radiotherapy (62).

Mucositis develops through an initial increase in local cytokines, interleukin-1 and tumor necrosis factor-a being the two most predominant. These are generated by interstitial host lymphocytes reacting to the effect of the radiotherapy or chemotherapy on the proliferating cells in the oral mucosa, with subsequent loss of a significant portion of the dividing epithelial cells (63). Ulceration of the mucosa with potential bacteremia or sepsis occurs next, followed eventually by the healing phase. It is during the ulcerative phase that the lesions are most painful, oral intake is diminished, and the risk for sepsis is the highest (63).

Symptomatic treatment of oral mucositis is designed to reduce pain, prevent dehydration, and help increase oral intake. Oral mouthwashes are effective at decreasing the bacteriologic load and improving hydration, with some improvement in pain (59). One study indicates that saline is as effective as other mouthwashes including chlorhexidine and benzydamine (61). Other local remedies include topical analgesics, often put into Orabase ointment; an antihistamine in a coating agent (Benadryl in Kaopectate); and cytoprotectants such as sucralfate. Severe mucositis may require parenteral narcotics for symptomatic relief. Although these treatments give temporary relief, none hastens the resolution of the mucositis.

Prophylaxis for oral mucositis is an active subject of current clinical trials (60,61,64,65,66,67,68 and 69). Although none of these agents is the present standard of care, some of them show promise. Sucralfate has had mixed results in clinical trials aimed at reducing the severity and duration of oral mucositis. Although this drug acts both by increasing local prostaglandin concentration and as a mechanical barrier, a double-blind, randomized study failed to show any benefit over a placebo (69). Prostaglandin E_2 has been used topically, with two small, nonrandomized studies showing a decrease in the amount of mucositis after either radiotherapy or chemotherapy (70,71). Both granulocyte colony stimulating factor and granulocyte-macrophage colony stimulating factor have been used with some success (72,73). Nemunaitis and colleagues showed a significant reduction in grade 3 and 4 mucositis in patients undergoing intensive chemotherapy for a variety of lymphomas and leukemias (65). The additional advantage of these hematopoietic stimulating factors is that they increase the monocyte and neutrophil cell counts, thereby removing this as a treatment-limiting factor. Antibiotic lozenges containing amphotericin B, polymixin, and tobramycin have shown promise, with two studies yielding objective decrease in mucositis and a third showing a decrease in the amount of pain reported by the patients (62,68,74).

A new agent for the prophylactic treatment of oral mucositis is amifostine, an organic thiophosphate. It is a cytoprotectant that was initially developed by the military to be used as a possible radioprotectant for soldiers exposed to radioactive fallout. Normal cells selectively take up amifostine, which is converted into its active form by alkaline phosphatase (75). At present, this drug has been approved to reduce the nephrotoxicity of cisplatin chemotherapy (76). Buntzel and colleagues designed a randomized study of patients with stage III or IV head and neck cancer who would receive up to 60 Gy of radiation with 70 mg per m^2 of carboplatin with or without 500 mg of amifostine delivered immediately before the chemotherapy on days 1 through 5 and 21 through 25 of treatment (77). No grade 3 or 4 mucositis occurred in the amifostine arm, but 10 of 14 patients had grade 3 and 2 of 14 patients had grade 4 mucositis in the group that did not receive amifostine. Similar, although not as dramatic, efficacy has been seen in other trials (78,79).

A concern has been that amifostine would also decrease the effectiveness of the tumor therapy. In a study of 242 women with advanced ovarian cancer who were undergoing cytoreductive surgery with cyclophosphamide and cisplatin given as adjuvant treatment, not only were neutropenia, nephrotoxicity, and hospital stay all decreased, but a second-look laparotomy showed an increased tumor response rate from 65% to 75% (80). There appears to be promise for this drug at not only reducing mucositis, but also as a cytoprotectant for other organs. The drawbacks are that it has to be given intravenously, and that it often causes hypotension, nausea, and vomiting (81).

Postherpetic Neuralgia. In cancer patients, herpes zoster infection commonly occurs in the area of tumor pathology or in the port of previous radiation therapy (see Chapter 22). The true incidence of postherpetic neuralgia in patients with cancer is unknown, but it is more common in patients in whom the infection develops after the age of 50. A study comparing patients older than 50 years of age to a group younger than 30 noted a difference in the rate of postherpetic neuralgia, 3 months after the acute infection, of 32% (39% versus 7%, respectively) (82). This appears to be related to a functional decrease in the immune system, as evidenced by the high rate seen in individuals infected with human immunodeficiency virus (83). The pathophysiology of the pain is related to damage of the dorsal root ganglia and afferent nerves, decreasing the activation threshold. Atrophy of the affected dorsal horn has been found at autopsy in patients with postherpetic neuralgia (83). Generally, the patient experiences three types of pain: continuous burning pain in the area of sensory loss, painful dysesthesia, and intermittent shocklike lancinating pain. The abnormally discharging dorsal horn cells create an exaggerated response to light touch and temperature changes.

Acute herpes zoster can be alleviated by an anesthetic block of lidocaine with epinephrine in the involved ganglion. This can decrease pain as well as decrease the number of vesicles and hasten resolution (84). Oral antivirals have a beneficial effect on the duration of the zoster and its associated pain, with famciclovir and valacyclovir showing some superiority to acyclovir (83). Oral corticosteroids also lessen the pain of the acute outbreak, although no reduction in the rate of postherpetic neuralgia is noted with its use.

Treatment of postherpetic neuralgia of some months' duration is more difficult. Adrenergic receptor activation, especially with solutions containing epinephrine, causes a worsening of the pain, as opposed to the acute state (85). Attempts at pain control often involve topical anesthetics, narcotics, tricyclic antidepressants, and anticonvulsants. To prevent the occurrence of postherpetic neuralgia, valacyclovir has been shown to be superior to acyclovir in at least one large study, reducing persistent pain at 6 months (19% versus 26%) as well as decreasing the severity of the pain if therapy is instituted within 3 days of appearance of the rash (85).

Methods of Pain Control

Primary Oncologic Therapy

The fundamental method of managing patients with cancer pain is the use of oncologic therapy in the form of radiotherapy, surgery, or chemotherapy, alone or combined, to effect a cure or decrease the size of the tumor. Because the great majority of pain problems arises from a recurrence after previous treatments, it is necessary to consider every treatment not only as an isolated symptomatic measure for palliation, but also as part of a general therapeutic plan in which it must always be remembered that progression of the tumor and severity of the pain are usually related (86).

Surgery. Surgery is the principal modality for many small (T_1 and T_2) cancers of the head and neck. Smaller lesions in anatomic sites where surgical extirpation would disrupt important physiologic functions, such as the base of the tongue and larynx, are more often treated with primary irradiation. Larger (T_3 and T_4) lesions, unless treated under an organ-preserving protocol, are managed with a combination of surgery and radiotherapy. Depending on the site, stage, and nodal status, cure rates between 20% and 95% are achieved (23).

Surgical therapy of *unresectable* cancer for the alleviation of pain, especially nociceptive pain, is a widely accepted practice. Removing a bulky tumor that impinges on cranial nerves (most commonly the lingual, inferior alveolar, or glossopharyngeal nerve) and causes trismus by invasion of the muscles of mastication or infiltrates the cervical sensory nerves brings about a dramatic relief of pain (23). Even though the patient does not derive a survival benefit, the palliation derived from the procedure is worth the effort, as long as morbidity is minimized by preserving as much normal anatomy as possible. Attempts have been made at tumor, and therefore pain, control with the addition of intraoperative radiotherapy. In selected cases in which surgery can reduce tumor volume to a small residual area, a focused dose of electron irradiation is delivered. Because electrons have limited tissue penetrance, adjacent normal structures do not receive excessive doses. Some reports have demonstrated a small improvement in locoregional and pain control (87,88).

Pain is an important component of surgical cancer management. It is an aid to diagnosis both for primary and recurrent tumors. Acute pain in the newly diagnosed patient, especially referred otalgia, has been correlated with more advanced lesions and a worse outcome (89). New-onset pain in a cancer survivor often heralds a recurrence, and if heeded, may result in earlier diagnosis and improved survival. This is especially true for lesions recurring after primary irradiation alone, both at the local site and in the neck. Long-term survival in these patients is approximately 25% (90). Evidence that recurrent cancer does not necessarily equal a grave prognosis comes from a new staging system for maximally treated recurrent oral cavity and oropharyngeal lesions. Yeuh and colleagues could stratify between a high

of 88% and a low of 4.2% 1-year survivability for these cancers after appropriate secondary therapy (91). In treating recurrent cancers with surgery, however, the physician must always keep in mind the potential morbidity of the resection itself versus the prognosis of the patient. The appropriate treatment for the tumor is not always the appropriate treatment for the patient.

Surgical supportive care is an important adjunct in treating patients with advanced cancer. Nutritional support is important to these often-cachectic patients. Nasogastric tubes can be used from days to a few weeks, but the discomfort and potential alar necrosis often necessitates placement of a gastrostomy or jejunostomy tube. Airway distress is one of the most frightening experiences a patient can face. Alert clinicians should intervene whenever possible by placement of a tracheotomy tube before the situation becomes emergent. Bleeding is also fairly common in terminal patients. The most dramatic example of this is the carotid blowout. Patients most at risk for this have been previously irradiated and often have a salivary fistula in the neck. A sentinel bleed is common, and if correctly diagnosed, the blowout can be prevented by urgent ligation of the carotid and regional soft tissue coverage of the ligated vessel.

Radiotherapy. Radiotherapy as the sole therapeutic intervention is appropriate for many sites in the head and neck, especially for stage I or II lesions (see Chapter 37). The most radiosensitive tumors tend to be those that are of high pathologic grade (less differentiated) and located within Waldeyer's ring (the nasopharynx, tonsillar fossa, and base of tongue). Larger lesions can be treated by external beam radiation alone, but are more commonly radiated in conjunction with chemotherapy in an organ-preservation protocol or as an adjuvant to surgical resection. Standard therapy in the United States consists of 70 to 74 Gy to the primary site in daily fractions of 180 to 200 cGy (1). Some centers use hyperfractionation as their standard regimen, with doses of approximately 120 cGy twice a day.

Most painful tumors are improved by radiation, especially in those cases in which the tumor is cured. However, external beam therapy has a side-effect profile that does produce patient discomfort. Oral mucositis is a major source of pain during the treatment and sometimes causes treatment breaks and possibly decreased tumor control secondary to these interruptions. A study by Munro and Potter also showed a significant increase in fatigue and weakness, increasing from pretreatment to at least 4 weeks after the conclusion of therapy (92). Other side effects noted were odynophagia, dysphagia, xerostomia, and altered taste, all peaking during the course of radiation. Potential complications of radiotherapy include osteoradionecrosis, myelitis, cataracts, and encephalopathy. All of these complications are seen less frequently now that three-dimensional conformal planning is available for the lesions nearest to vital structures (1).

External beam radiotherapy is also used in the palliative setting. For those patients who have an unresectable tumor that is causing either pain or obstruction of the aerodigestive tract, radiation can be used to ameliorate the symptoms without undue toxicity if this form of therapy was not used to treat the initial lesion. Radiation is sometimes used even if the patient had received previous radiation, as long as the nearby normal tissues would not exceed the maximal tolerated doses. The specific radiation doses used for recurrent primaries or regional disease is largely empiric, as Hodsen and colleagues found in their exhaustive literature search: “The retrieved literature provides little information on either the frequency, degree or duration of symptomatic relief or the offsetting treatment toxicities that such radical management can produce for these patients, especially those not cured of their disease” (93). Other uses for radiotherapy include palliation of painful distant metastases. One article evaluated bone metastases, and gave a specific recommendation for a single dose of 800 cGy for pain control, as approximately 70% of patients had their symptoms improved (54). The ability to achieve results like this with a single dose is important because the median survival for the patients with bone metastases is 12 to 16 weeks, making short treatment time an important goal to improve the quality of life for these patients in their final days.

Chemotherapy. Chemotherapy has not been shown to be effective in prolonging survival in head and neck cancer in the adjuvant or neoadjuvant setting (see Chapter 37). Response to chemotherapy may be an indicator for response to radiation and is presently used in protocols to preserve the function of the larynx and base of tongue (94). In a previously untreated patient, response rates of 70% to 90% can be seen with neoadjuvant chemotherapy, yet no improvement in survival occurs (95). Some trials, however, have shown moderate improvement in locoregional control and disease-specific survival when the chemotherapy, usually a combination of cisplatin, fluorouracil, and hydroxyurea, is given concomitantly with radiotherapy (96,97 and 98). The Intergroup study 0099 showed a marked improvement in the 3-year overall survival in nasopharyngeal cancer (76% versus 46%) when they compared concomitant cisplatin plus fluorouracil with radiotherapy with radiotherapy alone (99). The combination treatment carries a higher price in the acute side effects, however, with oral mucositis and leukopenia being the major limitations to continuing treatment. Although the standard of care for nasopharyngeal carcinoma has changed, further studies are needed to confirm the results for the other sites in the head and neck.

In the palliative setting, the effect of chemotherapy is much less, with response rates between 15% and 40% in previously treated tumors and a life expectancy of approximately 6 months (unchanged by the addition of chemotherapy) (95,100). Methotrexate has been the standard palliative drug of choice for the past 25 years. In well-tolerated doses of 40 to 60 mg per m^2, the response rate usually is 30%, but again, survival rates are unaffected (95). Side effects are myelosuppression, mucositis, and diarrhea. Other single drugs and combinations have been used, but in these terminal patients, the response rates have not been improved and the side-effect profile is generally worse. For those patients who respond, the benefits can be great. With regression in tumor size, pain is diminished. Physiologic functions such as swallowing and speech can also be transiently improved, yielding a better quality of life in the preterminal setting.

Management of Pain during Oncologic Therapy. The point made in Chapter 35 and Chapter 36, which deserves reemphasis, is that patients undergoing oncologic therapy frequently have moderate to severe pain that persists primarily because an inadequate attempt has been made to control it. Most physicians recognize the importance of alleviating pain, but fears of overdosing or causing addiction persist. These concerns often cause pharmacologic undertreatment, but other avenues are available.

First, patients should be informed about the possible consequences of oncologic therapy without creating new fears and anxieties. This helps patients to mobilize coping skills that allow them to face the consequences of other therapy realistically and calmly. In addition, stress management techniques such as relaxation, hypnosis, and biofeedback enhance patients' ability to facilitate tolerance and adaptive functioning (see Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92 and Chapter 93). These should be supplemented with some type of pharmacologic therapy. Patients with severe pain who are receiving oncologic therapy on an outpatient basis can be prescribed oral morphine either as a liquid every 4 hours or as slow-release morphine, given in doses that produce effective but perhaps not complete relief of pain.

Patients who are being treated in the hospital can be managed by patient-controlled analgesia with opioids or epidural opioids (see Chapter 84 and Chapter 103). If the pain is severe, temporary relief can be achieved by daily blocks of the gasserian ganglia or of one of the major branches of the trigeminal nerve. Another technique that can be used for this purpose alone or in combination with narcotics is transcutaneous electrical nerve stimulation, although this therapy tends to work better for chronic benign pain than for pain secondary to cancer (101). If oncologic therapy is effective in eliminating pain in patients who have been on narcotic therapy for several weeks, it is essential to taper the dose of narcotics over a 1-week period to obviate the abstinence syndrome.

Symptomatic Management of Pain

When oncologic therapy is ineffective in providing relief, the pain must be treated by one or more of the following: (a) systemic analgesics and adjuvant drugs; (b) psychological techniques of analgesia; (c) neurostimulating techniques; (d) regional analgesia with local anesthetics or neurolytic blocks; and (e) neuroablative surgical procedures. Because these techniques and methods are discussed in detail in Chapter 36 and in various sections of Part V, comments here are limited to discussion of issues especially relevant to cancer pain in the head and neck.

It is essential to evaluate the patient and the pain, as discussed in detail in Chapter 35. This requires a thorough history, particularly in regard to the characteristics of the pain at the time of onset, during its course, and at the time the patient is seen, and including previous diagnosis and therapies; a psychological and psychosocial evaluation; careful measurement of the multidimensional aspects of pain; a complete physical examination, especially a careful neurologic study; and appropriate radiologic and laboratory diagnostic tests.

Plain radiography is rarely used to evaluate head and neck tumors because it is often inadequate for assessing these lesions. CT and magnetic resonance imaging are considered to be the most useful diagnostic procedure in evaluating cancer of the head and neck. A CT with contrast is most often used to evaluate cervical nodal disease as well as laryngeal, paranasal sinus tumors and oral cavity tumors that invade bone. Magnetic resonance imaging is used to evaluate tumors in soft tissue such as the parapharyngeal space, base of tongue, and skull base tumors invading dura or brain. Other techniques include radionuclide bone imaging and positron emission scans for metabolically hyperactive lesions. Patients with primary metastatic brain tumors and leptomeningeal metastases require evaluation of the cerebrospinal fluid. Biopsy of the nasopharynx, sphenoid sinuses, or accessible bones might sometimes be necessary to establish the tumor diagnosis. Obviously, these measures should have been carried out before initiation of oncologic therapy, but it is the responsibility of the algologist to review the results carefully. If regional analgesia, either with local anesthetic or with neurolytic agents or a neuroablative procedure, is being considered, it is important to know the prognosis of the patient and the anticipated pattern of metastatic spread.

Selection of the procedure or combination of procedures for the relief of cancer pain in the head and neck requires consideration of the following: (a) the physical, mental, and psychological condition of the patient; (b) the type and stage of the oncologic process and the prognosis; (c) the mechanism, intensity, quality, and location of the pain; (d) the skill and knowledge of the health care personnel and the therapeutic modalities and resources available; and (e) most important, the opinions and feelings of the patient and family after they have been fully informed about the advantages, disadvantages, limitations, and complications associated with the various therapeutic procedures. In all circumstances it is essential to exploit psychological techniques as adjuncts to other therapies (e.g., in the form of relaxation training, hypnosis, or psychological support). Assuming that the patient is agreeable and other resources are available to carry out all the methods, this discussion is divided into two parts: patients in the intermediate stage of the disease who are in good condition, and patients with advanced or terminal cancer who have severe pain.

Pain in Intermediate Stage. Patients with the intermediate stage of the disease, who have not been relieved with oncologic therapy and who have mild to moderate pain, can be managed with systemic medications comprised of aspirin or other nonsteroidal antiinflammatory drugs and adjuvant drugs, as discussed in Chapter 83. This combination is usually effective in relieving mild to moderate pain and can be continued for months to years. Patients with the intermediate stage of disease with severe or excruciating pain, who have not been relieved by oncologic therapy or intensive, high-dose opioids and who are expected to live 6 months or more, are candidates for an ablative neurosurgical or neurolytic procedure to achieve prolonged pain relief.

Pain in the face or head within the distribution of the trigeminal nerve can be managed with trigeminal gangliolysis achieved with the thermocoagulation technique (see Chapter 105 and Chapter 107). This procedure produces analgesia with fewer postoperative sensory deficits and other disturbances than either retrogasserian rhizotomy or alcohol injection. Although a superb procedure for patients with tic douloureux, this operation can be used to relieve cancer pain (102). The results with malignancy are less favorable, probably because of progression of the disease. Thus, Siegfried and Broggi (103) reported on 20 cancer patients, all of whom obtained complete pain relief immediately after the operation, but the relief lasted only a few days in five patients and, at 1 month follow-up, six patients had recurrence of pain, although it was still much less intense. Among the 15 patients who survived to 3 months, 60% remained pain-free, whereas the other 40% had partial or no relief. Among the patients who survived to 12 months, the figures were 70% and 30%, respectively; among those who survived to 18 months the figures were 40% and 60%, respectively. In view of the fact that the gangliolysis can be repeated, it is surprising that this was not done in the patients who had recurrence of pain.

Percutaneous differential radiofrequency rhizotomy of the glossopharyngeal and the vagus nerves can be used for the relief of severe excruciating pain in the throat and larynx. Another neuroablative procedure involves rhizotomy through open operation. As discussed in Chapter 105 and Chapter 108, a retrosigmoid craniectomy allows the use of a supracerebellar approach for better visualization of the cranial nerves.

Patients who have more extensive pain require trigeminal rhizotomy as well as section of the nervus intermedius and perhaps of the glossopharyngeal nerve through a lateral approach combined with a supracerebellar approach to the trigeminal nerve. When the neoplastic disease is more extensive and is producing severe pain involving the sensory fibers of other cranial nerves, a posterior fossa craniectomy is performed to section the roots of cranial nerves VII, IX, and X and, if necessary, the sensory roots of the upper two or three cervical nerves. Side effects can be serious, with a 10% morbidity (meningitis, cerebrospinal fluid leak, severe ataxia, aspiration pneumonia), a 1% chance of a major intracranial bleed, and a 0.6% perioperative mortality (102). Because of this, its use should be limited to patients who are in good physical condition and who can tolerate the stress of general anesthesia and a major surgical intervention.

Severe Pain Caused by Advanced and Terminal Cancer. An attempt should be made to try to control the severe pain of advanced and terminal cancer with a combination of medications including potent narcotics, but, if the pain is severe or extremely severe, the degree of relief is usually less than optimal. In such patients the technique of percutaneous differential radiofrequency rhizotomy of the trigeminal or glossopharyngeal and vagal nerves should be used by a neurosurgeon skilled in these techniques. Another alternative is to use intraventricular morphine delivered by an Ommaya reservoir. Decreased tolerance to morphine occurs when delivered by this route. One study reports that 70% of patients describe their pain relief after receiving intraventricular morphine as very good to excellent, 20% as good, and 10% as poor (101). Another technique is to use deep brain stimulation by implanting electrodes in the periaqueductal and periventricular gray matter for nociceptive pain (104). Other neurosurgical ablative techniques that can be used for severe pain in the head are medullary trigeminal tractotomy, hypothalamotomy, and thalamotomy (Chapter 108 presents detailed results with the use of these techniques in cancer patients).

Unfortunately, these neurosurgical procedures are only performed in major medical centers. If neurosurgery is not an available option, but a skilled anesthesiologist is available, a neurolytic gasserian ganglion block should be considered; such a block is highly effective if the tumor involves structures supplied by the trigeminal nerve (Fig. 53-2, Fig. 53-3 and Fig. 53-4). Even if the pain is located in one of the major trigeminal divisions, it is preferable to carry out gasserian ganglion block at the onset to produce a widespread field of analgesia into which the cancer can spread without producing more pain subsequently. Although this entails the risk of neuroparalytic keratitis and corneal ulcer, effective relief of severe pain for patients with advanced cancer is considered to be worth such risk. Properly done, alcohol block of the gasserian ganglion produces pain relief in more than 80% of patients with advanced cancer pain in the anterior two-thirds of the head (84).

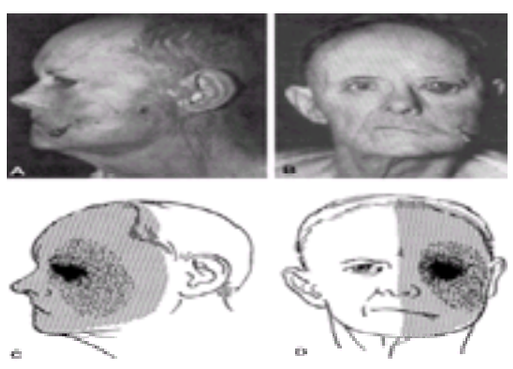

Figure 53-2. **A,B:** A 69-year-old patient with fibrosarcoma of the left orbit with invasion of the maxilla, which produced severe pain in the eye and ipsilateral side of the face, particularly the cheek. The pain became progressively worse and interfered with the patient's comfort despite administration of large doses of morphine. Gasserian block with 1 mL of alcohol produced complete relief of pain and permitted a gradual decrease of morphine until the patient could be made comfortable with codeine and aspirin. **C,D:** Sites of severe pain (*black*) and moderate pain (*stippled*), and the area of analgesia (*cross-hatchin* g) consequent to the neurolytic block.

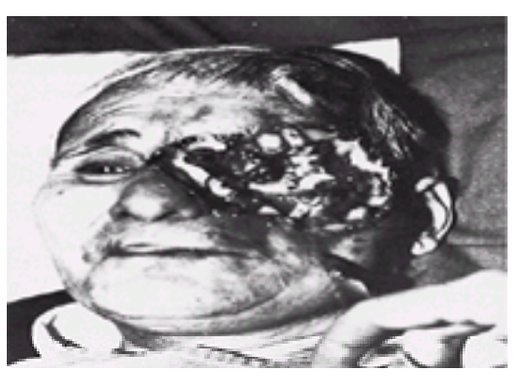

Figure 53-3. Patient with advanced carcinoma of the orbit associated with severe pain that was relieved by gasserian ganglion block with alcohol. (Courtesy of Dr. José Madrid.)

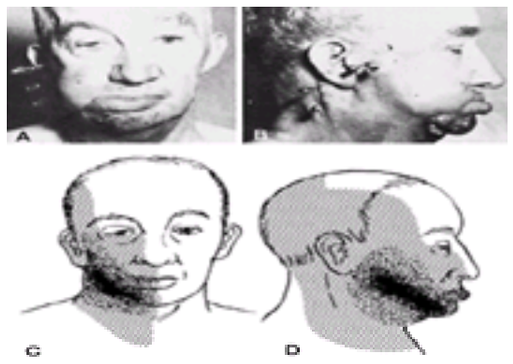

Figure 53-4. **A,B:** Patient with cancer of the tongue with invasion of the cheek, lower jaw, and chin. The severe pain was not relieved by intensive radiation therapy and large doses of narcotic analgesics but was relieved with alcohol block of the right maxillary and mandibular nerves and of the second and third cervical nerves. **C,D:** Sites of severe pain (*black*) and moderate pain (*stippled*), and the area of analgesia (*cross-hatching* in **C**) that persisted until the patient's death 4 months later.

In addition to the severe sharp somatic pain, some tumors of the face and head cause a burning discomfort that requires complementary neurolytic block of the cervical sympathetic chain. However, if the pain involves the structures supplied by the glossopharyngeal and vagus nerves, diagnostic and prognostic blocks of these nerves can be done, but neurolytic blocks should be avoided because they produce prolonged paralysis of the pharyngeal and laryngeal muscles.

Another alternative is neuroadenolysis of the pituitary gland, which involves injection of alcohol into the pituitary gland using a transsphenoid sinus route. This procedure has been alleged to produce effective pain relief in approximately 80% of patients with bone metastases. It produces total body pain relief by a mechanism theorized to include endorphins, as naloxone can block the effect (101). It is not commonly used at this time.

The pharmacologic approach is the mainstay of the management of pain in advanced cancer patients. This includes the analgesic ladder technique, developed and widely advocated by the Cancer Unit of the World Health Organization (see Chapter 36). Properly used, this method produces complete pain relief for moderate pain in almost every patient, and effective (although not complete) relief of severe pain in approximately 70% to 80% of the patients. Head and neck cancers and their treatments can lead to severe pain. It is imperative that all of those who treat such patients are attentive to the complaint of pain and prepared to strive for its relief.

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CHAPTER 54

General Considerations of Pain in the Neck and Upper Limb

John J. Bonica, René Cailliet, and John D. Loeser

Disorders of the neck, shoulder, and upper limb are among the most frequent causes of pain, suffering, and disability. These painful disorders can be caused by infection or degenerative arthritic changes, trauma, or disease of one or more of various parts of the cervical spine, myofascial pain syndromes, neuropathic disorders, and many other causes. Knowledge of the causes, pathophysiology, and symptoms and signs is essential to establish a diagnosis and develop effective therapeutic strategies. The pain management physician should know the functional anatomy and biomechanics of the cervical spine and the anatomy and function of the cervical nerves, cervical plexus, brachial plexus, and their branches for proper interpretation of the patient's history and for performing meaningful general physical, neurologic, and orthopedic examinations.

This first chapter of Section B, like other chapters that introduce the management of pain in various regions of the body, provides a concise discussion of these various considerations. The information is presented in four major parts: basic aspects; description of the segmental and peripheral somatic nerve supplies and the sympathetic nerve supply to the neck and upper limb; summary of the assessment process in evaluating patients and their pain; and a table summarizing pain characteristics and other symptoms and signs in the neck and upper limb to help in making a differential diagnosis. More detailed information has been presented by Bland (1), Cailliet (2), and others (3,4).

BASIC CONSIDERATIONS

This first section discusses the clinically relevant aspects of the anatomy of the cervical spine, including a brief description of the vertebrae, joints, ligaments, and muscles that are attached to the cervical spine; mobility of the spine; and other points essential for understanding the pathophysiology of painful disorders of the neck and upper limb. The second part of this section describes the contents of the vertebral canal, spinal cord, rootlets and formation of the cervical nerves, and, finally, the cervical plexus and brachial plexus, their branches, and the structures they supply.

Anatomy and Biomechanics

Although the embryologic development of the three parts of the vertebral column is quite similar, the anatomy of the cervical spine has characteristics quite different from those of the thoracic and lumbar spines (Fig. 54-1). It allows positions and movements that are adapted to support and move the head and permits the sense organs to function within the head. The extent, direction, and variation of movement of this portion of the spine have the greatest range of any part of the spinal column. The cervical spine, which is both a structural static support of the head and a mobile kinetic mechanism, is an aggregate of seven vertebrae composing a flexible column held together by five intervertebral disks, 12 joints of Luschka, 14 hypophyseal joints, and a system of ligaments and muscles that allow its wide range of motion and mobility (see Fig. 54-1).

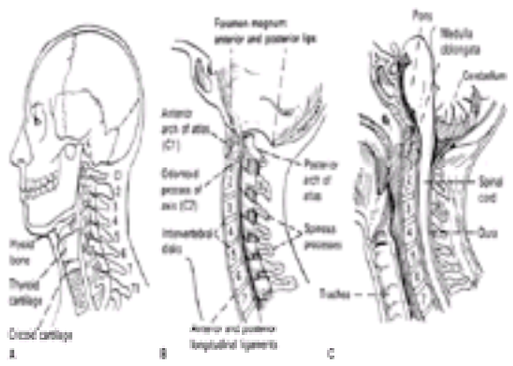

Figure 54-1. Anatomy of the cervical spine. **A:** Lateral view, showing landmarks of the spine, including the hyoid bone, thyroid and cricoid cartilages, and transverse and spinous processes. **B:** View of the skeletal portion of the lower skull and cervical spine. The skull and spinous processes are shown in sagittal section, whereas the vertebral bodies are shown as normal. **C:** Sagittal view of the cervical spine showing the relationship of the brainstem, medulla oblongata, foramen magnum, and spinal canal, containing the spinal cord. Normally, the lower portion of the medulla is outside and below the foramen magnum so that subluxation of the atlas on the axis, and compression of the lower brainstem, can occur by compression from the odontoid process, which moves posteriorly against the neuraxis. (Modified from Bland JH. *Disorders of the cervical spine: diagnosis and medical management*. Philadelphia: Saunders, 1987.)

Cervical Vertebrae

In contrast to the thoracic and lumbar spines, which are basically similar, the cervical spine has two unique units. These upper two segments, the occipitoatlantal unit [occiput of the skull and the atlas (C-1) and the atlantoaxial (C-1 to C-2) unit], form the upper portion, which has special characteristics. The lower five segments are constructed in a similar manner to the other spinal segments.

Upper Functional Units. The atlas (Fig. 54-2A) has no body and is composed of a solid ring of bone with two lateral pillars; the upper and lower surfaces are articulating facets (1,2 and 3). The short anterior arch articulates in a vertical plane with an odontoid process of the axis, whereas the longer posterior arch forms the posterior wall of the spinal canal. The upper facets are ellipsoid and are cupped to articulate with the occipital condyles, whereas the lower facets are round and concave, face laterally and downward, and articulate with the superior facets of the axis. The transverse processes of the atlas are longer than those of other vertebrae, each containing the transverse foramen for the vertebral artery, veins, and sympathetic plexus, and to which are attached powerful muscles that rotate the head.

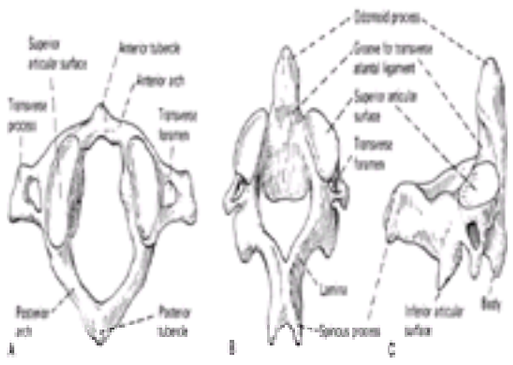

Figure 54-2. Anatomy of the atlas and axis. **A:**Superior view of the atlas. **B:** The axis viewed from a superior and posteroanterior aspect. **C:** Lateral view of the axis.

The axis (Fig. 54-2B and Fig. 54-2C) is composed of a small body from which the peglike odontoid process arises perpendicularly, acting as an eccentric pivot about which the atlas rotates (1,2 and 3). The anterior surface of the process has a facet articulating with the anterior arch of the atlas, and its posterior surface articulates with the transverse ligament (see Fig. 54-2C). The lateral masses have facets above and below, articulating with the atlas above and the C-3 vertebra below. The atlas has thick laminae (posterior arches) and a large bifid palpable spinous process. Its transverse processes are small, with tubercles at their tips, and have transverse foramina for the vertebral artery, veins, and vertebral (sympathetic) plexuses. Neither the atlas nor axis has pedicles or an intervertebral foramen, so the nerve roots of the first and second spinal nerves lie above and posterior to the articulating lateral masses of both vertebrae. This is in contrast to roots of the lower cervical nerves, which lie anterior to the apophyseal joint facets and traverse their respective intervertebral foramina.

Lower Functional Units. All the lower five cervical vertebrae have common characteristics: a body, two pedicles, two laminae, two vertebral arches, and a spinous process (Fig. 54-3). The vertebral arches arise from the posterolateral aspects of the bodies, giving rise to the pedicles, whose upper and lower surfaces are articulating facets of the zygapophyseal joints. The arches face the bodies at an angle of approximately 45 degrees, and the laminae arise from the pedicles and arch backward to meet in the midline, forming the bifid spinous processes that jut down. In front of the facets, the transverse processes arise laterally and project anteriorly and caudally; their upper surfaces are grooved and troughlike and contain the roots of the cervical spinal nerves. Each transverse process of C-3 to C-6 (but not C-7) has a foramen for the vertebral artery, plexus of veins, and vertebral (sympathetic) nerve or plexus. Each transverse process has an anterior and a posterior tubercle that serve as attachments for the scalene muscles. Adjacent bodies are united by the intervertebral disks, anterior and posterior longitudinal ligaments (PLLs), paired posteriorly placed zygapophyseal joints, ligamentum flavum, ligamentum nuchae, intertransverse ligament, and interspinous ligaments. The functional units of this lower portion of the cervical spine, as the lumbar units, consist of an anterior weight-bearing shock-absorbing portion and a posterior guiding-gliding section (5) (Fig. 54-4).

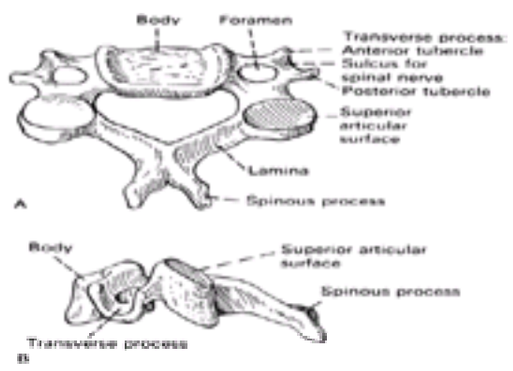

Figure 54-3. Typical cervical vertebra. **A:** View from above. **B:** View from the side. (Modified from Clemente CD, ed. *Gray's anatomy of the human body*. Philadelphia: Lea & Febiger, 1985.)

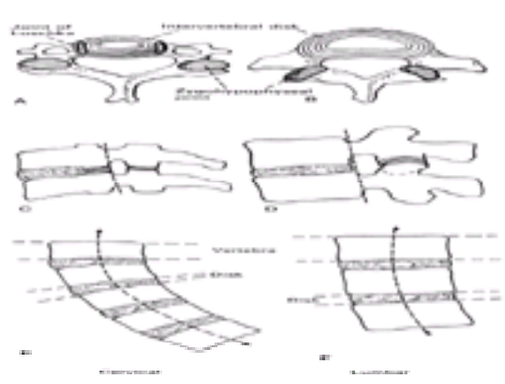

Figure 54-4. Comparative views of the cervical and lumbar functional units. **A:** Cross-section of the five joints of the cervical spine, which include an intervertebral disk, the paired uncovertebral (Luschka) joints, and the paired posterior articulations. **B:** Cross-section of the three joints of the lumbar spine, which include an intervertebral disk and the paired posterior articulations. **C,D:** Lateral views of the same vertebrae shown in **A** and **B**. The dashed lines divide the anterior supporting portion from the posterior gliding portion of each functional unit. **E,F:** Lateral views of the bodies of the vertebrae of the cervical and lumbar spines, depicting particularly the shapes of the intervertebral disks. Note that in the cervical region the anterior portion of the disk is larger (higher) than the posterior portion, whereas in the lumbar region the difference between the anterior and posterior portions is much less. (Modified from Cailliet R. *Neck and arm pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

Anterior Portion. The anterior portion of the lower functional units is comprised of two vertebral bodies separated by the intervertebral disk, which is a self-contained fluid elastic system that absorbs shock, permits transient compression, and allows fluid displacement within its elastic container, thus permitting movement and distortion of the functional unit. The lower and upper plates of the disk are the end-plates of the vertebral bodies composed of articular hyaline cartilage in direct contact with, and adherent to, the underlying resilient bone of the vertebral bodies. These inflexible surfaces form the cephalad and caudad walls of the disk.

The outer wall of the disk, the annulus, is an intertwined fibroelastic mesh that encapsulates the gelatinous matrix of the disk, the nucleus pulposus. The annulus fibers are attached around the entire circumference of both upper and lower end-plates and intertwine in criss-cross oblique directions, thus permitting movement of one vertebra on the other in a *rocker* motion, in a rotary direction, and as a horizontal translatory motion (6) (Fig. 54-5). The nucleus pulposus, contained within the fibrous resilient wall of the annulus and between the floor and ceiling formed by the end-plates of the vertebrae, cannot be compressed, so any external force exerted on the area unit is transmitted undiminished to every unit area of the interior of the annulus. Fluid creates an intradisk pressure that forces the vertebrae apart and keeps the annulus fibers taut. Movement in any direction is permitted by some of the fibers' relaxing while the rest remain taut, thus maintaining intradisk pressure (see Fig. 54-5).

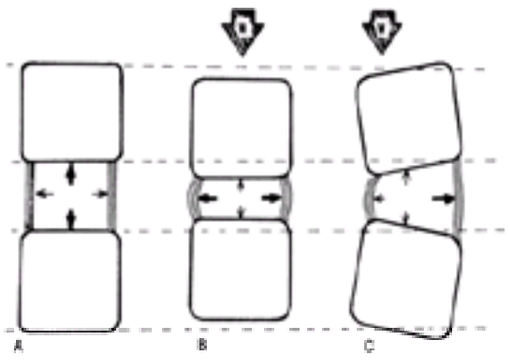

Figure 54-5. Schematic depiction of the hydraulic mechanism of the intervertebral disk. **A:** Normal disk at rest. The internal pressure is exerted in all directions, and the fibers of the annulus are taut. **B:** When the disk is compressed the fluid within the nucleus pulposus cannot compress, so the annulus must bulge. **C:** With flexion of the spine the fluid shifts within the intervertebral disk; the cubic contents remain the same but the fluid shift causes fibers of the anterior annulus to shorten and those of the posterior annulus to elongate. (W, weight.) (From Cailliet R. *Neck and arm pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

The young or undamaged intervertebral disk has predominantly fibroelastic tissue, but aging or injury to the disk causes larger, less elastic fibers to replace the young, highly elastic collagen fibers; consequently, the older disk container is less elastic. The colloidal gel of the nucleus pulposus is a mucopolysaccharide that functions by its physicochemical action: It can imbibe external fluid and maintain its intrinsic water balance. The young disk contains 80% water but dehydrates with age and trauma, causing a decrease in the protein polysaccharide level and thus a decrease in the imbibitory property of the gel. Loss of the intradisk fluid and the decrease in annular elasticity results in a decrease in pressure. The intervertebral disk has a vascular supply that disappears after the second decade of life, and by the third decade the disk is virtually avascular (5), receiving its nutrition by diffusion of lymph and other fluids through the vertebral end- plates and through peripheral vessels of the annulus fibrosis. This is made possible by the alternating compression and relaxation of the elastic container, which acts like a sponge being squeezed and released, thus bringing lymph to the disk and allowing diffusion to occur.

The intervertebral disks make up approximately one-fourth the length of the entire spinal column. They dehydrate (shrink) consequent to weight bearing during the day and rehydrate during rest at night. Disks are relatively thicker in the cervical spine (thickest at C-6 to C-7), the ratio of disk to vertebral body height being 1:3 to 1:2 (1,2). Moreover, in contrast to the symmetric thickness of the annulus in the lumbar region, in the cervical spine the posterior portion is markedly thicker and broader than the remainder of the annulus (see Fig. 54-4), a factor that reinforces the disk at vital sites and protects adjacent nerves, blood vessels, and the spinal cord.

Another difference in the cervical spine is the vertical height of each disk. In the lumbar region the height is only slightly greater anteriorly than posteriorly, so that the upper and lower borders are essentially parallel. In the cervical spine the anterior vertical height of the disk is twice as great as that of the posterior height so that the disk viewed from the side is wedge shaped, a factor that increases the total curvature of the cervical spine (7).

The anterior portion of the cervical functional unit has several other structural differences from the anterior portion of the lumbar unit. Whereas the vertebral end-plates of the lumbar spine are flat and parallel and the nucleus is centrally located in the disk, in the cervical spine the vertebral cartilaginous plates are concave and convex, and the nucleus is located in the anterior portion of the disk (see Fig. 54-4A and Fig. 54-4B). The relationship of the end-plates and their shapes, in addition to the location of the nucleus, permits a rocking movement between the vertebrae in the lumbar region and a forward and backward gliding motion of adjacent vertebrae in the cervical region (6).

Another difference is the presence of the uncovertebral joints, also called the *joints of von Luschka* (3,8). These are not true joints and are absent at birth, appearing at approximately 10 to 20 years of age. They constitute bony projections that articulate on each other and form false joints, or pseudoarthroses. These are important in the function of the cervical spine and in the pathology of neck pain and cervical radiculopathy (1).

Another important difference is the character of the PLL. In the lumbar spine the PLL converges to a point in the caudal area and is incomplete posteriorly in the region of L-3 to S-1, thus inadequately reinforcing the lumbar disk. In the cervical spine the PLL is thick and broad and is complete across the posterior vertebral area; between the vertebrae it is double layered. This powerful reinforcement is a strong deterrent to any disk herniation or bulging, which could cause major peripheral nerve and spinal cord damage.

Posterior Portion. The posterior portion of the lower functional units in the cervical region has a posterior guiding-gliding action. It is composed of two vertebral arches, two transverse processes, a central posterior spinous process, and a paired articulation (2). The transverse processes and posterior spinous processes are bony sites of attachment of the neck muscles that move the spine and support the neck and head and are also sites of attachment for supporting ligaments. The posterior articulation, or *facet*, is comprised of two joints that are lined with synovium and are lubricated by synovial fluid within the joint capsule. They are called apophyseal or zygapophyseal in the sense of being outgrowths, but their articular cartilaginous surfaces classify them as true joints, thus able to undergo degenerative changes referred to as osteoarthritic joint changes. These facets are in opposition and placed in direction and degree of inclination so as to permit and guide the movement of the two adjacent vertebrae. Paired facets are similarly shaped and planed from the C-3 to the C-7 vertebrae, permitting similar movements between these paired joints that are different than those between the occipitoatlantal and atlantoaxial joints.

Ligaments of the Cervical Spine

The ligaments of the cervical spine are sufficiently resilient to control motion, thus aiding the support of the neck muscles, and are lax enough to permit a wide range of motion. Their resiliency is demonstrated by the protection they afford the spinal cord and the spinal nerves against the numerous stresses, strains, and trauma to which the neck is subjected. The head is heavy and eccentrically balanced on a relatively narrow elastic support. In its top-heavy balance it is repeatedly subjected to movement, positional changes, and various degrees of trauma. The ligaments and muscles bear the brunt of these stresses; the ligaments remain the sole support when the muscles are overused, fatigued, or ineffective in their function (Fig. 54-6).

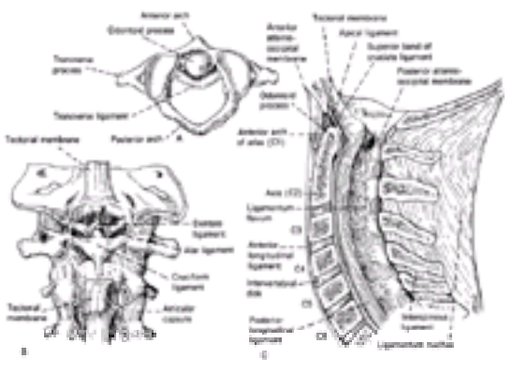

Figure 54-6. **A–C:** Ligaments of various parts of the cervical spine (see text for details). (Modified from Clemente CD, ed. *Gray's anatomy of the human body*. Philadelphia: Lea & Febiger, 1985:343–344; and from Netter FH. *CIBA collection of medical illustrations*. Vol 1. The nervous system. Summit, NJ: CIBA Pharmaceutical Products, 1983.)

Occipitovertebral Ligaments. The ligaments connecting the occiput to the atlas are extremely dense, broad, and strong and protect the entrance of the spinal cord through the foramen magnum into the skull while still permitting some 30 degrees of flexion and extension in a joint having no intervening disks or posterior

articulations (1,2 and 3). The following ligaments are some that connect the occiput with the atlas: (a) the apical ligament of the odontoid process (see Fig. 54-6C), a vestigial remnant attached to the peak of the odontoid process that runs to the anterior lip of the foramen magnum; (b) the alar ligaments (see Fig. 54-6B), which run on either side of the odontoid process to the margin of the foramen magnum, both enclosed in a sleeve or synovial membrane (these tough robust cords check atlantoaxial rotation); (c) the atlantooccipital membrane (see Fig. 54-6C), which extends upward from the anterior longitudinal ligament to connect the anterior margin of the foramen magnum with the anterior arch of the atlas; (d) the tectorial membrane (see Fig. 54-6B and Fig. 54-6C), a fan-shaped continuation of the PLL to the basiocciput whose fibers blend with the dura mater; and (e) the posterior atlantooccipital membrane (see Fig. 54-6C), which arches over the vertebral artery and is much thinner than the ligamenta flava or interspinous ligaments further down the cervical spine and also thinner than the anterior longitudinal ligaments and PLLs.

The stability of the atlantoaxial (C-1 to C-2) joint depends almost entirely on ligamentous structures and, of these, the transverse ligament (see Fig. 54-6A) is most important because it permits the atlas to move around the odontoid process. It is a taut resilient structure that maintains the normal relationship of the atlas on the axis; a tear of this transverse ligament has the same destabilizing effect as a fracture of the odontoid process (9).

Other Cervical Ligaments. In the rest of the cervical spine, from C-2 to C-7, the anterior longitudinal ligament and the PLL reinforce the disk annulus (see Fig. 54-6C). The anterior longitudinal ligament adheres tightly to the front of the vertebral bodies and blends loosely with the annulus as it crosses the disk spaces. The PLL is firmly bound to each disk, but is only loosely bound to the posterior concavity of the vertebral body. The PLL is double layered and reinforces the capsular ligaments; combined, they limit the degree of transverse sliding motion between vertebrae as well as limiting the extent of flexion and extension.

The ligamenta flava are strong elastic ligaments spanning the space between the laminae in pairs attached to the anterior inferior surface of the lamina above and to the posterior superior margin of the lamina below. They stretch laterally to the zygapophyseal joint and, in combination, they reinforce the latter's capsules. The ligamenta flava stretch under tension and retract and relax during undue bulging or folding in the normal state.

The interspinous ligaments (see Fig. 54-6C) are thin membranous structures that connect the adjoining spines. Their attachments extend from the root to the apex of each spinous process and are only slightly developed in the cervical spine. The ligamentum nuchae is a broad, firm, fibrous posterior ligament that attaches to the base of the skull around the foramen magnum and connects the tips of the posterior spinous processes as well as cervical vertebrae. Below C-7 it is replaced by the supraspinous ligaments, which are strong fibrous cords that connect the apices of the spine together from the C-7 vertebra to the sacrum.

Musculature of the Neck

The neck muscles can be divided into two major functional groups: those that flex and extend the head, the so-called capital movers, and those that flex and extend the cervical spine (2) (Fig. 54-7). The capital flexors are mainly the short recti and the longus capitis muscles, whereas the capital extensors are four short muscles extending from the base of the skull to the axis and atlas. These include the posterior rectus capitis minor and major and the obliquus superior and inferior capitis. The longissimus capitis, semispinalis capitis, and splenius capitis are longer muscles that also act as capital extensors when working together bilaterally (2).

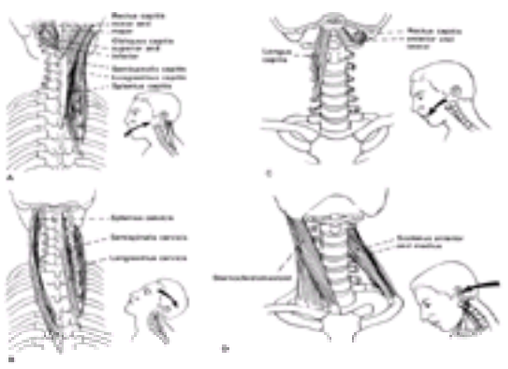

Figure 54-7. Musculature of the head and neck. **A:** The capital extensors attach on the skull and move the head on the neck. **B:** The cervical extensors originate from and attach on the cervical spine and alter the curvature of the spine. **C:** The capital flexors flex the head on the neck. **D:** The cervical flexors attach occlusively on the cervical vertebrae and have no significant functional attachment to the skull. (Modified from Clemente CD, ed. *Gray's anatomy of the human body*. Philadelphia: Lea & Febiger, 1985; and from Cailliet R. *Neck and arm pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

The major flexors of the cervical spine consist of the scalenus anterior, scalenus medius, and scalenus posterior. These attach exclusively to the cervical vertebrae and have no significant functional attachment to the skull. The same applies to the cervical extensors, which include the splenius cervicis, longissimus cervicis, and semispinalis cervicis. The splenius cervicis, splenius capitis, longissimus capitis, and sternocleidomastoid of one side only act as rotators of the head. In addition, continuations of the total erector muscles of the vertebral column also affect movement of the neck. Most of the extensor musculature in the head and neck is at the atlantoaxial region and at the last two (C-6 to C-7 and T-1) articulations. These are the three major sites of stress. The bulk of the flexor musculature centers at the C-4 to C-5 space, implying that most flexion occurs here; it is also the site of maximum lordosis.

Mobility

The cervical spine moves in flexion, extension, lateral flexion, and rotation. The total of movements of the neck is the composite of all segmental movements that move synchronously, but the direction and degree of movement vary at different levels of the segmental spine. The greatest movement in terms of both range and amplitude occurs in the upper portion, between the skull and the C-3 vertebra. The major portion of flexion, extension, lateral movement, and rotation occurs between the skull and the atlas and between the atlas and the axis (2). Below the axis the extent of movement depends on ligamentous elasticity and on the distortion and depression of the intervertebral disk. Because the atlas functions principally with the occiput and the C-7 vertebra functions as a thoracic vertebra, neck movements are basically confined to five vertebrae.

Nodding, a movement of the head up and down in a sagittal plane, occurs between the occiput and atlas. Flexion occurs in a range of 10 degrees and extension in approximately 25 degrees (6,10,11), so that the head can move a total of 35 degrees in flexion and extension without any neck participation. All other movements between the skull and atlas are prevented by the direction of the opposing planes of the articular facets (2). In lateral flexion, and in rotation of the head and neck, the occiput and atlas move as one piece.

The greatest movement of the entire cervical spine occurs between the atlas and axis; between these two vertebrae as much as 90 degrees of rotation is possible from the extreme right to the extreme left (Fig. 54-8). This is one-half of the entire cervical spine rotation (normally 160 degrees) and occurs before any rotation is noted throughout the remainder of the cervical spine. Between the atlas and axis as much as 10 degrees of extension and 5 degrees of flexion are possible. The inferior facet of C-1 is flat and the opposing superior facet of C-2 is convex, so flexion and extension at the level occur as a rocker action of C-1 and C-2.

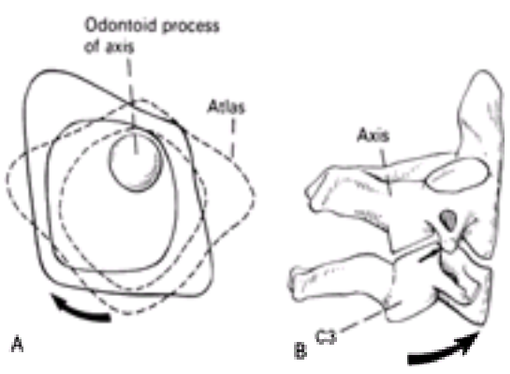

Figure 54-8. **A:** Rotation of the atlas about the odontoid process of the axis (C-1 around C-2). The dashed line shows the normal position of the atlas, whereas the solid line indicates rotation of 45 degrees to the right. **B:** Rotation of C-2 on C-3, which is limited by the mechanical locking of the articular structures. Note that the anterior tip of the upper articular process of C-3 impinges on the lateral margin of the foramen of the vertebral artery. (Modified from Cailliet R. *Neck and arm pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

Rotation of the C-2 vertebra on the C-3 vertebra is mechanically limited by a bony locking mechanism in which the anterior tip of the upper articular process of C-3 impinges on the lateral process of the C-2 vertebra (see Fig. 54-8B). The locking mechanism prevents excessive rotation of the functioning unit and thus protects the vertebral artery and the emerging nerve roots in this specific intervertebral foraminal gutter (2). Movements of flexion and extension and lateral rotation are possible between C-2 and C- 7, flexion and extension occurring as a gliding movement of the upper on the lower vertebra. To permit this movement the disk distorts horizontally and compresses.

In forward flexion the intervertebral foramina become larger, whereas in extension they become smaller (Fig. 54-9). Moreover, in forward flexion the cervical canal lengthens, whereas in extension it shortens (Fig. 54-10). In lateral flexion or rotation the ipsilateral foramina decrease in size and the contralateral foramina enlarge (see Fig. 54-9). In a normal spine the degree of narrowing of the foramina is not enough to compress any tissues contained within the foramina, so that flexion, extension, and rotation of the head leave adequate room. In an abnormal spine, however, in which the vertebrae come closer together or in which movement is excessive, the foramina obviously can become constricted.

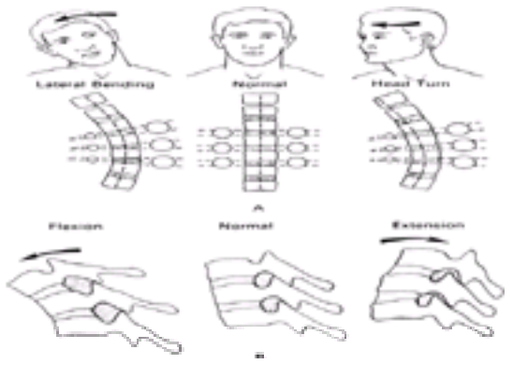

Figure 54-9. Changes in the size of the intervertebral foramina with movement of the neck. **A:** With lateral flexion and rotation of the head the foramina become smaller on the side of the head to which the head flexes laterally or rotates, and they are open on the opposite side. **B:** With forward flexion the intervertebral foramina become larger, whereas with extension they become smaller. (Modified from Cailliet R. *Neck and arm pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

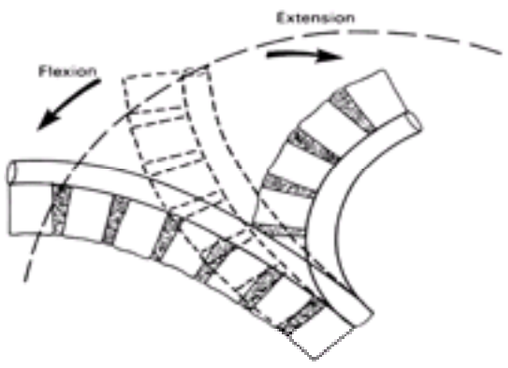

Figure 54-10. Schematic representation of the alteration of the length of the cervical spinal canal with movement from the normal position (*dashed lines*). In flexion the canal is longer and its anterior wall is shorter than its posterior wall, whereas in extension the total length of the canal is shorter, with the anterior wall being longer than the posterior wall. In the normal position both walls of the canal are equal in length. (Modified from Cailliet R. *Neck and arm pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

These various movements affect the position of the structures within the cervical spine. On full forward flexion, in which the spine is concave forward, the anterior portions of the intervertebral disks are compressed and narrowed whereas the dorsal portions are widened and stretched: The anterior longitudinal ligament is slack whereas the PLL is stretched. The nucleus pulposus is dorsally displaced and the paired inferior articular facets of the vertebrae glide forward on the superior facets of the vertebrae below, with a forward slide displacement of the body of the upper vertebra on the body of the lower vertebra. The laminae and spinous processes are open fanwise, the ligamentum flava and interspinous ligaments stretch, and the posterior neck muscles are subjected to tension, with the muscles being the most powerful limiting force for flexion. Extension of the neck reverses these events; the limiting factors are tension on the anterior longitudinal ligament, the approximation and imbrication of the spinous processes, and the locking of the lower border of the lower articular facet and the lamina of T-1.

Vertebral Canal

The vertebral canal is triangular in transverse section. The posterior aspect of the vertebra and the disk constitute the base or anterior wall of the triangle, which is covered by the PLL; the pedicles in their transverse foramina contribute to this aspect (1,2). The other two sides of the triangle laterally and dorsolaterally are the inner aspects of the zygapophyseal joints, the laminae, and the ligamenta flava. The canal is funnel shaped, being widest at the atlas–axis level and narrowing to its smallest sagittal diameter at the posterior inferior edge of the body of C-5 and the lamina of C-6. The sagittal diameter of the vertebral canal in the cervical region varies; at the C-1 to C- 3 level it is approximately 21 mm (range, 16 to 30 mm), whereas at the C-4 to C-6 level it is approximately 18 mm (range, 14 to 23 mm); the transverse diameter at the C-4 to C-6 level is approximately 30 mm.

Spinal Cord

The spinal cord is suspended and cushioned in the subarachnoid space by the spinal fluid (see Fig. 54-1C). The anterior and posterior rootlets traverse the subarachnoid space *en route* to the inner part of the intervertebral foramina, where they join to form the anterior and posterior roots, respectively (see Fig. 54-12). The canal is fairly roomy to the level of C-3, where the cervical enlargement begins and extends to T-2 (1). The sagittal diameter of the cervical cord is approximately 11 mm at C-1, 10 mm at C- 2 to C-6, and 7 to 9 mm below C-6 (1). Its transverse diameters are greater than its sagittal diameters. The circumference at C-6 is approximately 48 mm (1). The cervical cord occupies approximately 40% of the canal, which is greater than at other levels of the spinal cord.

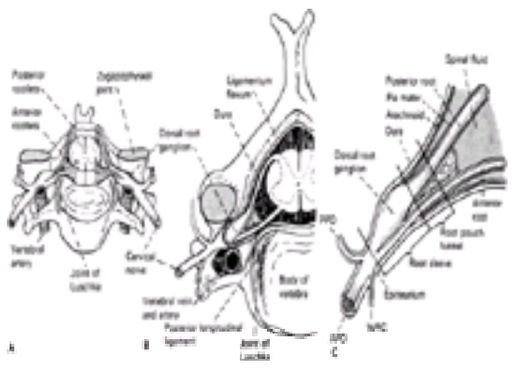

Figure 54-12. Transverse sections of the cervical spine. **A:** The spinal cord, and anterior and posterior rootlets join to form the spinal nerve. Note the relationship of the nerves to the Luschka and zygapophyseal joints and the two vertebral arteries, which pass through the transverse foramina and are located just anterior to the nerve. **B:** Cross-section of a cervical vertebra showing some details of the relationship of the posterior root to the lateral aspect of the ligamentum flavum, which covers the zygapophyseal joint just posterior to it. The anterior root and its dural covering are close to the lateral part of the posterior longitudinal ligaments and to the capsules of the joint of Luschka. The proximal portion of the dorsal root ganglion is in the outer portion of the intervertebral foramen, whereas the remainder is in the gutter of the transverse process. **C:** Detailed anatomy of a nerve root and its meningeal covering. Note the extent of the root pouch and root sleeve. Just distal to the joining of the anterior and posterior roots is the short spinal nerve covered by epineurium (the continuation of the dura), which promptly divides into the anterior primary division (APD) and posterior primary division (PPD) and gives off a white ramus communicantes (WRC). (**A** modified from Bland JH. *Disorders of the cervical spine: diagnosis and medical management*. Philadelphia: Saunders, 1987; **B** and **C** modified from Cailliet R. *Neck and arm pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

With neck flexion the spinal cord and its dura elongate to their full normal lengths; the nerve rootlets and roots provide support within the limits of physiologic tension and occupy an uppermost position in the intervertebral foramina, actually contacting the undersurface of the pedicle. With extension the spinal cord shortens and the dura relaxes to assume a folded or corrugated appearance (*accordion pleats*) that encroaches on the cervical canal. In extension the nerve roots slacken, thus being more vertical to the cord, descending in the foramen and losing contact with the undersurface of the pedicle above (2). In extension the cord is thicker and the posterior inferior margin of the body of the vertebra is thicker than in flexion, but the intradural sagittal diameter is 2 to 3 mm less. Moreover, in extension, the vertebra above approximates the arch of the vertebra below, resulting in protrusion into the cervical canal. These factors cause the cord to have less play in extension than in flexion, a factor with important clinical implications.

The cervical enlargement of the spinal cord is thicker than the lumbar enlargement because it contains all the ascending and descending long tracts for the trunk and upper and lower limbs. The average length of the neuromere (each segment of the spinal cord) is 13 mm at the cervical region. The vertebrae and disks grow faster than the spinal cord during development, resulting in progressively greater discrepancy between the level of the neuromere and the vertebral level. In the lower cervical spine a given spinous process overlies the spinal cord segment located one below it numerically, so that the C-6 spinous process overlies the C-7 spinal cord segment. With increasing age the vertebrae and intravertebral disks lose height, and consequently the spinal cord lengthens relative to the vertebral canal.

Meninges. The meninges of the spinal cord consist of the tough dura mater, a loose-layered arachnoid, and the fine and delicate pia mater (see Fig. 54-12). The arachnoid and dura are separated by a capillary subdural space. As in other levels of the spinal column, the epidural space contains solid and liquid fat, loose areolar tissue, the internal vertebral venous plexus, the endings of the radicular arteries, which break up to contribute to the anterior spinal artery, and the two posterior spinal arteries. All these structures provide the spinal cord with some protection during movement and impact from external forces.

The dura mater is firmly attached to the foramen magnum and to the dorsal surfaces of the C-2 and C-3 vertebral bodies. The dentate ligaments, which are actually thickenings of the pia mater that exist between the anterior and posterior roots, attach the spinal cord laterally to the dural sheath. These dentate ligaments are usually coarse fibrous structures, although in some individuals they are delicate tissue slips whose physical properties may be causative factors in the pathogenesis of cervical myelopathy. These ligaments tense in flexion and become slack in extension, allowing extensive mobility of the cord (1).

Vertebral Arteries

The vertebral arteries deserve consideration here because they are linked with a number of cervical spine syndromes resulting from the unusual tortuous course of the vessels and their close relationship to the cervical nerves and cervical vertebrae (Fig. 54-11). These arteries are the first branches from the subclavian trunk that pass cephalad by coursing through the transverse foramina of C-6 to C-2, where they are directly in front of the cervical nerves and medial to the intertransverse muscles. Accompanying each artery are the vertebral plexus of veins and the vertebral nerve and plexus, which represent postganglionic sympathetic fibers originating in the stellate and intermediate cervical sympathetic ganglia. The course of the artery cephalad to C-2 is summarized in Figure 54-11. The vertebral arteries give off spinal branches that pass through the intervertebral foramina to supply ligaments, dura, and bone. These segmental arteries also communicate with the posterior and anterior spinal arteries, which are also branches of the vertebral arteries (see Fig. 54-11B). The vertebral sympathetic plexus surrounding the vertebral arteries gives off fibers that surround the various branches of the vertebral arteries. It supplies the artery itself as well as the basilar artery and circle of Willis and the branches derived from these vessels. These include the superior cerebellar and posterior cerebellar arteries and other structures within the cranial cavity (see Chapter 46 for details).

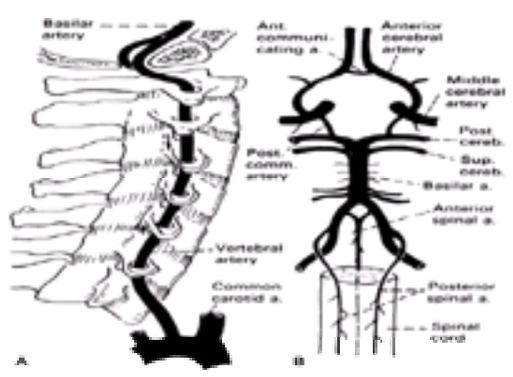

Figure 54-11. **A:** Lateral view of the cervical vertebrae depicting the course of the vertebral artery from C-6 to C-1 through bony ridges of the foramina transversaria. Note the double U-turn the artery makes from C-2 to C-1 in its posterior course around the lateral mass of the atlas. **B:** The two vertebral arteries join to form the basal arteries. Also shown is the circle of Willis. Note the origin of the anterior spinal artery and the two posterior spinal arteries from the two vertebral arteries.

Cervical Nerves

As discussed in Chapter 3 and Chapter 8 and depicted in Figure 8-1, each spinal nerve is composed of an anterior (ventral, predominantly motor) root and a posterior (dorsal, sensory) root. The posterior root, which is composed of the central processes of afferent neurons, breaks into 12 or more rootlets that attach in a linear series to the dorsolateral sulcus of the cord (see Fig. 54-12A). These sensory fibers enter Lissauer's tract and then plunge into the dorsal and ventral horns. The sensory rootlets peripherally converge into two bundles, the fasciculi radiculae, which in turn unite just proximal to the dorsal root ganglion. The anterior root arises from the ventrolateral sulcus of the cord by a smaller number and a less regular series of rootlets. Normally, the posterior root is three times thicker than the anterior root (except for C-1 and C-2) because of the much greater number of axons (see Fig. 54-12B).

Each rootlet is covered by pia mater and, as they come together to coalesce and form the dorsal and ventral roots, the rootlets become enclosed within a

funnel-shaped sac of the pia dura, the *root pouch*, which tapers toward the intervertebral foramen (see Fig. 54-12C). Within the spinal canal each root is separately enclosed in an arachnoid-dural sleeve, with each sleeve being separated by the interradicular septum. The dural root sleeves are attached to the bony margin of the intervertebral foramen, adhering more firmly with age and with the occurrence of pathologic processes such as osteoarthritis (1). As they pass through the short intervertebral foramen the anterior roots are in intimate contact with Luschka's joint and the annulus of the disk, which is covered by the lateral portion of the PLL. The dorsal (sensory) root lies close to the articular process and to the azoapophyseal joint capsule of adjacent vertebrae, factors that are significant in the pathogenesis of neuropathy (see Fig. 54-12B).

The roots normally occupy only one-fifth to one-fourth of the foramen (2). As each root passes distally beyond the foramen, it enters the *gutter* of the sulcus of the transverse process, where the arachnoid and dura blend with the nerve sheath. The arachnoid, and consequently the spinal fluid that envelops the nerve roots, ends at the outer part of the intervertebral foramen. The dura continues more distally, and at the point beyond the joining of the two roots into the formed spinal nerve it blends with the epineurium of the formed nerve. The epineurium continues as the epineural sheath of the brachial plexus and is firmly attached to the bony surface of the cervical spine, thus helping to prevent the nerves from being avulsed from the spinal cord during traction injury (12). The epineural sheath is also firmly attached to the transverse processes of the vertebra and to the fascial prolongation of the PLL, as well as to the fascia of the neck that surrounds the brachial plexus.

In the cervical region the intervertebral foramina open obliquely laterally and slightly anteriorly and inferiorly from 10 to 15 degrees downward. Their shape is like a figure eight and they are largest at the C-2 to C-3 level, becoming progressively smaller down to the C-6 to C-7 level. The average vertical diameter is 10 mm, and the transverse diameter is 5 mm. In addition to the nerve roots, the intervertebral foramina contain the spinal radicular arteries, intervertebral veins and plexuses, and extension of the epidural space, with loose areolar tissue and solid and liquid fat. These provide a protective cushion for the neural elements.

The dorsal root ganglia vary in location, with the upper two located above the vertebral arches and those of the lower cervical segments located partly within and partly distal to the intervertebral foramina in the gutter of the transverse processes, where they are close to the vertebral artery (Fig. 54-13).

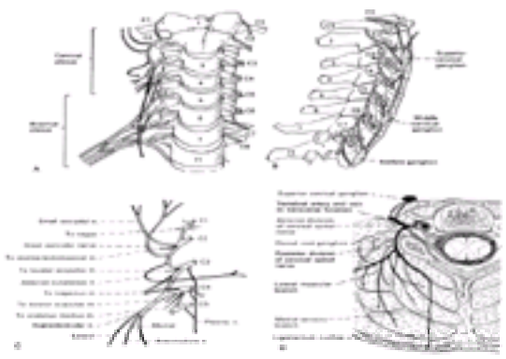

Figure 54-13. Cervical and first thoracic spinal nerves. **A:** Anterior view showing the formation of the cervical and brachial plexuses. **B:** Lateral view showing the course and relation of the cervical nerves and the cervical sympathetic chain. **C:** Origin and composition of the cervical plexus. **D:** Cross-section of the third cervical segment showing the course and distribution of the posterior primary division, with its medial branch passing posteriorly to supply the skin and subcutaneous structures and the lateral branch supplying the muscles. Also shown is a cross-section of the superior cervical ganglion and its connection to the nerve by the white ramus communicantes. Note the vertebral vessels just anterior to the nerve.

The two roots join just beyond the dorsal root ganglion to form the composite spinal nerve. The upper two cervical nerves pass laterally and slightly superiorly, with the first passing between the occiput and C-1 and the second passing between C-1 and C-2. The roots and formed nerves below the C-2 level course within the gutter of the transverse process in a lateral and downward direction and become more oblique with lower levels.

Immediately after emerging from the spinal canal each nerve receives one, two, or more gray rami communicantes from the cervical sympathetic ganglia. The superior cervical sympathetic ganglion contributes fibers to the upper four cervical spinal nerves, the middle and intermediate ganglia to the fifth and sixth nerves, and the inferior ganglion to the seventh and eighth nerves, whereas the first thoracic sends gray rami communicantes over to the eighth cervical and first thoracic nerves. Each cervical spinal nerve gives off a recurrent meningeal branch that returns to supply the coverings of the spinal cord.

At a point approximately 1 cm lateral to the foramen, just posterior to the vertebral artery, each nerve divides into the posterior and anterior primary divisions (Fig. 54-14; see Fig. 54-13). Except for C-1, the anterior divisions are much larger than the posterior divisions. Each cervical spinal nerve, like most spinal nerves, has motor fibers that supply specific muscles (myotomes) and sensory fibers that supply skin (dermatomes) and bones and ligaments (sclerotomes). The structures supplied by each cervical nerve and the first thoracic segments are summarized here (see Table 54-2,Table 54-3, and Table 54-4).

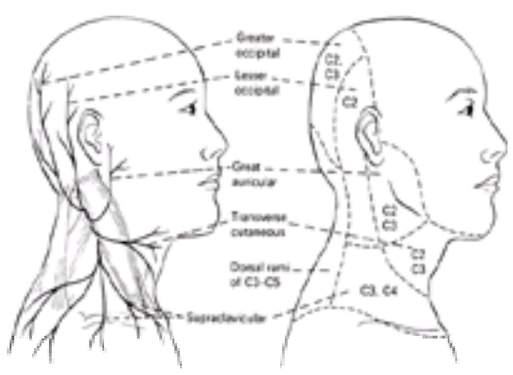

Figure 54-14. Cutaneous nerves derived from the cervical plexus (see text for details).

Muscle	Nerve supply	Muscle	Nerve supply
Capital flexors		Cervical spine extensors	
Rectus capitis anterior	C-1, C-2	Iliocostalis cervicis	C-4 to C-7
Rectus capitis lateralis	C-1, C-2	Longissimus cervicis	C-1 to C-6*
Longus capitis	C-1 to C-4	Semispinalis cervicis	C-1 to C-6*
		Multifidus	C-1 to S-1
Capital extensors			
Rectus capitis posterior major	C-1	Head rotators†	
Rectus capitis posterior minor	C-1	Sternocleidomastoid	Spinal accessory
Obliquus capitis superior	C-1	Splenius cervicis	
Obliquus capitis inferior	C-1	Semispinalis cervicis	
Longus capitis	C-1 to C-4	Longissimus cervicis	
Splenius capitis	C-3 to C-5		
Semispinalis capitis	C-1 to C-5	Other neck muscles	
		Geniohyoid	C-1
Cervical spine flexors		Thyrohyoid	C-1
Scalenus anterior	C-4 to C-7	Sternothyroid	C-1 to C-3
Scalenus medius	C-3 to C-8	Sternohyoid	C-1 to C-3
Scalenus posterior	C-5 to C-8	Omohyoid	C-1 to C-3
Longus colli	C-2 to C-6		
Sternocleidomastoid	Cranial nerve XI; C-2, C-3*		

*When muscles of both sides contract.
†When the muscle of one side contracts.

TABLE 54-2. Nerve supply of muscles of the neck

Segment	Vertebrae	Joints	Ligaments
C-1	Periosteum and body of atlas	Atlantoaxial, medial, atlantoaxial, lateral, atlantoaxial	Alar, cruciform, apical dental, accessory atlantoaxial, articular capsules, medial, anterior atlantooccipital membranes, posterior atlantooccipital membrane
C-2	Periosteum and body of axis	Medial atlantoaxial, lateral atlantoaxial, intervertebral	Anterior longitudinal, atlantoaxial membranes, atlantoaxial, capsules, cruciform, nuchal
C-3	Periosteum and body of C-3 vertebra and dentin	Intervertebral, Luschka, uncovertebral, zygapophyseal	Anterior longitudinal, posterior longitudinal, capsular, nuchal
C-4	Periosteum and body of C-4 vertebra and dentin	Intervertebral, Luschka, uncovertebral, zygapophyseal	Anterior longitudinal, posterior longitudinal, capsular, ligamentum flavum, nuchal
C-5	Periosteum and body of C-5 vertebra and portions of humerus, scapula, and proximal ulna	Acromioclavicular, glenohumeral, Luschka, atlantoaxial, elbow, zygapophyseal, ulnocarpal	Anterior longitudinal, posterior longitudinal, capsular, nuchal, ligamentum flavum
C-6	Periosteum and body of C-6 vertebra and portions of humerus, radius, scapula, and first metacarpal bone	Glenohumeral, intervertebral, Luschka, elbow, zygapophyseal	Anterior longitudinal, posterior longitudinal, capsular, nuchal, ligamentum flavum
C-7	Periosteum and body of C-7 vertebra and portions of humerus, scapula, radius, and ulna	Elbow, Luschka, intervertebral, zygapophyseal	Anterior longitudinal, posterior longitudinal, nuchal, ligamentum flavum
C-8	Periosteum and body of C-8 vertebra and portions of humerus, ulna, carpal bones, and bones of hand and fifth fingers	Intervertebral, Luschka, zygapophyseal, elbow, wrist, hand	Supraspinous, interspinous, anterior longitudinal, posterior longitudinal
T-1	Periosteum and body of T-1 vertebra	Intervertebral, zygapophyseal, costovertebral, elbow, wrist, hand	Anterior longitudinal, posterior longitudinal, supraspinous, interspinous, ligamentum flavum

TABLE 54-3. Sclerotomal distribution pattern of the cervical and first thoracic nerves

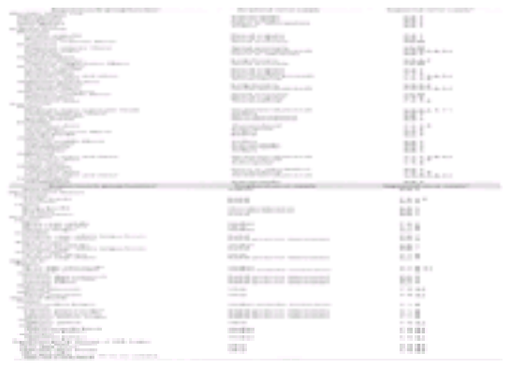

TABLE 54-4. Nerve supply of the muscles of the upper limbs

Posterior Primary Divisions. The posterior primary divisions leave the anterior division and pass posteriorly over the posterior portion of the transverse process around the articular pillar, as shown in Figure 54-13. All posterior primary divisions of the cervical nerves, with the exception of the first cervical nerve, divide into medial sensory and lateral muscular branches. The first cervical nerve, known as the suboccipital nerve, remains as one trunk and is distributed to the muscles of the suboccipital triangle. Sensory fibers of the C-1 nerve supply the periosteum and body of the atlas and occiput, atlantooccipital joint, medial and lateral atlantoaxial joints, and various ligaments around these joints. Occasionally, the C-1 nerve has a cutaneous branch that accompanies the occipital artery to the scalp and communicates with the greater and lesser occipital nerves. The lateral branches of the posterior primary divisions of the other cervical nerves supply the muscles of the posterior part of the neck, whereas the medial branches become superficial to supply the skin (see Fig. 54-13D). The medial branches of the posterior divisions of the second and third cervical nerves form the greater occipital and the third (least) occipital nerves.

Greater Occipital Nerve. The greater occipital nerve, which as noted previously is the medial (sensory) branch of the posterior division of the second cervical nerve, emerges between the posterior arch of the atlas and the lamina of the axis below the oblique inferior muscle, and then ascends obliquely on the latter muscle between it and the semispinalis muscle. It communicates with the third cervical nerve and gains the posterior part of the scalp by piercing the semispinalis and trapezius muscles near their attachment on the occipital bone in a position medial to the easily palpable occipital artery. There it gives off branches that supply the scalp over the vertex and top of the head and gives muscular branches to the semispinalis capitis.

Third (Least) Occipital Nerve. The third (least) occipital nerve arises from the medial sensory branch of the posterior division of the third cervical nerve, ascends in the same manner as the greater occipital nerve, and pierces the splenius capitis and trapezius just medial to the greater occipital nerve. It then ascends in the superficial fascia of the scalp to reach the vertex of the skull.

Anterior Primary Division. The anterior primary division of the cervical nerves passes laterally behind the vertebral artery and between the anterior and posterior intertransversalis muscles lying on the sulcus of the transverse processes of the vertebrae. The anterior rami of the upper four cervical nerves communicate with each other to form the cervical plexus, whereas the lower four cervical nerves and first thoracic nerve unite to form the brachial plexus.

Cervical Plexus

The cervical plexus is formed by the anterior primary divisions of the upper four cervical nerves. After emerging from the sulcus all the anterior trunks (except the first) divide into ascending and descending branches, forming a series of three loops. These loops are situated lateral to the vertebrae and anterior to the levator scapulae and scalenus medius muscles, and are covered by the sternocleidomastoid muscle. From these three loops two sets of branches, the deep and superficial, originate. The cervical plexus communicates with the vagus, hypoglossal, and accessory cranial nerves.

Deep Branches. The deep branches of the cervical plexus remain deep in the neck beneath the sternocleidomastoid muscle. One group of branches proceeds from beneath the muscle in a posterolateral direction toward the posterior triangle and is accordingly named the lateral (external) group. This group gives off muscular branches to the scalenus medius, sternocleidomastoid, trapezius, and levator scapulae muscles and several communicating branches that join the spinal accessory nerve. The other group of branches runs forward and medially toward the anterior triangle and is accordingly named the medial (internal) group. It gives off communicating filaments that join the vagus and the hypoglossal nerves, the descendens hypoglossi, and the superior cervical sympathetic ganglion. This medial group also sends muscular branches to the rectus capitis, lateralis, and anticus, longus capitis and longus colli muscles, and the diaphragm by way of the phrenic nerve. By means of the ansa hypoglossi it also supplies the thyrohyoid, geniohyoid, omohyoid, sternothyroid, and sternohyoid muscles (see Table 54-2).

Superficial (Cutaneous) Branches. The superficial branches of the cervical plexus constitute what is sometimes called the *superficial cervical plexus*. From their point of origin these branches proceed superficially to reach and pierce the deep fascia at approximately the middle of the sternocleidomastoid muscle, where they become subcutaneous. They then curve around the posterior border of the muscle and proceed in one of three general directions to supply the skin and superficial fascia of various parts of the head, neck, and shoulder (see Fig. 54-14).

Lesser Occipital Nerve. The lesser occipital nerve is derived from the anterior primary division of the second cervical nerve or from a loop derived from the second and third cervical nerves. It ascends along the sternocleidomastoid muscle, curving around its posterior border and, near the insertion of the muscle on the cranium, it perforates the deep fascia to continue cephalad along the side of the head, behind the ear, to supply the skin of this part of the scalp. This nerve communicates with the greater occipital and greater auricular nerves to contribute sensory fibers to the posterior part of the scalp. Through its auricular branch it supplies the upper and posterior part of the auricula and communicates with the mastoid branch of the great auricular nerve.

Great Auricular Nerve. The great auricular nerve, larger than the lesser occipital nerve, arises from the second and third cervical nerves, winds around the posterior border of the sternocleidomastoid, and, after perforating the deep fascia, ascends on the surface of that muscle deep to the platysma and divides into an anterior and posterior branch. The anterior (facial) branch is distributed to the skin of the face over the parotid gland and communicates with the facial nerve within the substance of the gland. The posterior (mastoid) branch supplies the skin over the mastoid process in back of the auricula, except its upper part. A filament of the nerve pierces the auricula to reach its lateral surface, where it becomes distributed to the lobule and lower part of the concha. This nerve communicates with the lesser occipital nerve, the auricular branch of the vagus nerve, and the posterior auricular branch of the facial nerve.

Anterior Cutaneous Nerve. The anterior cutaneous nerve arises from the second and third cervical nerves, bends around the posterior border of the sternocleidomastoid at its midportion, and then crosses the surface of the muscle obliquely as it runs horizontally anteriorly. It perforates the deep fascia, passing deep to the external jugular vein, pierces the platysma, and divides into ascending and descending branches. The ascending branches pass cranialward to the

submandibular region, pierce the platysma, and are distributed to the cranial, ventral, and lateral aspects of the neck. The descending branches pierce the platysma and are distributed to the skin of the anterolateral aspects of the neck as far as the sternum.

Supraclavicular Nerve. The supraclavicular nerve arises from the third and fourth cervical nerves (mainly the fourth) and, like the anterior cutaneous nerve, emerges from under the posterior border of the sternocleidomastoid, descends caudad, and divides into three groups of nerves: the medial, intermediate, and lateral supraclavicular nerves. These three groups pass caudad under cover of the investing deep fascia. Near the clavicle they perforate the fascia and platysma to supply the skin and superficial fascia of the clavicular region and the periosteum and bony structure of the clavicle.

The medial (anterior) supraclavicular nerves, also known as the *suprasternal nerves*, cross the external jugular vein, clavicular head of the sternocleidomastoid, and clavicle to supply the skin of the medial infraclavicular region as far as the midline, and laterally as far as the junction of the medial and middle third of the clavicle. They furnish one or two filaments of the sternoclavicular joint.

The intermediate (middle) supraclavicular nerves cross the clavicle and supply the skin over the pectoralis major as far as the second or third rib and communicate with the cutaneous branches of the second and third intercostal nerves.

The lateral (posterior) supraclavicular nerves, also known as the *supraacromial nerves*, pass obliquely across the outer surface of the trapezius and the acromion and supply the skin of the top and dorsal parts of the shoulder. The distribution of the supraclavicular nerves is depicted in Figure 54-14.

Brachial Plexus

The brachial plexus supplies all the motor and almost all the sensory functions of the upper extremity. It is formed by the union of the anterior primary divisions of the fifth, sixth, seventh, and eighth cervical nerves and first thoracic nerve and frequently receives small contributing branches from the anterior primary division of the fourth cervical and second thoracic nerves (Fig. 54-15). After these anterior primary divisions leave the posterior primary divisions outside of their respective intervertebral foramina, they proceed anterolaterally and inferiorly to occupy the interval between the anterior and middle scaleni muscles where they unite to form three trunks, thus initiating the formation of the plexus proper (see Fig. 54-15).

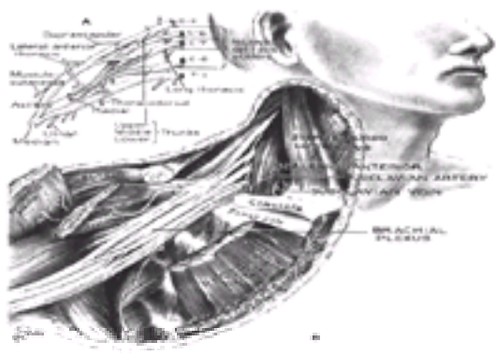

Figure 54-15. Anatomy of the brachial plexus. **A:** Schematic depiction of the brachial plexus. **B:** Relation of the roots of the brachial plexus to the scalene muscles showing the position of the plexus over the first rib and its course into the axilla.

The primary divisions of the fifth and sixth cervical nerves unite to form the upper trunk; the seventh primary division remains alone to become the middle trunk; the eighth cervical and first thoracic nerves unite to form the lower trunk. The three trunks emerge from the interscalenus space at the lower border of these muscles and continue in an anterolateral and inferior direction to converge toward the upper surface of the first rib, where they are closely grouped. At the lateral edge of the rib each trunk divides into anterior and posterior divisions, which pass beneath the midportion of the clavicle to enter the axilla through its apex.

These divisions, by which fibers of the trunk reassemble to gain the ventral and dorsal aspects of the limb, reunite within the axilla to form three cords named the lateral, medial, and posterior because of their relationship to the second part of the axillary artery (Table 54-1). The lateral cord is formed by the union of the anterior divisions of the upper and middle trunks, thus containing fibers derived from the fifth, sixth, and seventh cervical nerves; the medial cord is the continuation of the anterior division of the lower trunk, thus containing fibers derived from the eighth cervical and first thoracic nerves; the posterior cord is formed by the union of all the posterior divisions, thus containing fibers derived from all the nerves making up the plexus.

Structure	Nerve Levels
Branches of cervical nerves	
To phrenic nerve	C-5
To longus colli and scalenii muscles	C-5 to C-7
Branches from roots	
Dorsal scapular nerve	(C-4), C-5
Long thoracic nerve	C-5 to C-7
Branches from trunks (superior trunk)	
Nerve to subclavius	C-5, C-6
Suprascapular nerve	C-5, C-6
Posterior cord (origin chiefly all trunks)	C-5 to C-8, T-1
Branches	
Superior subscapular nerve	C-5, C-6
Inferior subscapular nerve	C-5, C-6
Thoracodorsal nerve	C-6 to C-8
Terminal branches	
Axillary	C-5, C-6
Radial	C-5 to C-8, T-1
Lateral cord (origin superior and middle trunks)	C-5 to C-7
Branches	
Anterior pectoral	C-5 to C-7
Terminal branches	
Musculocutaneous nerve	C-5 to C-7
Median nerve, lateral portion	C-6, C-7
Medial cord (origin inferior trunk)	C-8 to T-1
Branches	
Medial brachial cutaneous nerve	C-8 to T-1
Medial antibrachial cutaneous nerve	C-8 to T-1
Terminal branches	
Ulnar nerve (medial portion)	C-8 to T-1
Median nerve (medial portion)	C-8 to T-1

TABLE 54-1. Organization and branches of the brachial plexus

At the lateral border of the pectoralis minor the three cords break up to give rise to the peripheral nerves of the upper extremity: The lateral cord gives off the lateral head of the median nerve and the musculocutaneous nerve; the medial cord gives off the medial head of the median nerve, the ulnar, the medial antebrachial and brachial cutaneous nerves, and a branch to the intercostobrachial nerve; and the posterior cord terminates as the axillary and radial nerves. These peripheral nerves proceed to the arms, forearms, and hands.

In addition to the terminal branches constituting the peripheral nerves of the upper extremity, the brachial plexus issues other branches and receives communicating fibers. Immediately after their emergence from the intervertebral foramina, the anterior divisions of the cervical and first thoracic nerves receive postganglionic gray rami communicantes from the lower two-thirds of the cervical sympathetic chain and the uppermost thoracic sympathetic chain (described later in this chapter). The anterior divisions of the fifth, sixth, seventh, and eighth cervical nerves also send fibers to the longus colli and to the three scaleni muscles, whereas that of the fifth cervical nerve sends fibers to the phrenic nerve and gives off the dorsal scapular nerve, which supplies the rhomboidei and levator scapulae muscles. In addition, the anterior divisions of the fifth, sixth, and seventh cervical nerves contribute fibers to form the long thoracic nerve, which supplies the serratus anterior muscle (see Table 54-4).

The next set of branches is derived from the upper trunk, which gives off the suprascapular and the subclavius nerves, both of which contain fibers from the fifth and sixth cervical segments. The suprascapular nerve proceeds posteriorly to supply the supraspinatus and infraspinatus muscles and the shoulder joint, whereas the subclavius nerve supplies the subclavius muscle.

Within the axilla, in addition to the terminal branches, the lateral cord gives off the lateral anterior thoracic nerve, the medial cord gives off the medial anterior thoracic nerve, and the posterior cord gives off the upper and lower subscapular and thoracodorsal nerves. The anterior thoracic nerves supply the pectoralis major and minor,

the subscapular nerves supply the subscapular muscle and the teres major, and the thoracodorsal nerve supplies the latissimus dorsi. The following description of some of the major branches of the brachial plexus primarily concerns those that provide sensory innervation to various structures. (The distribution of the most important cutaneous nerves is depicted in Figure 54-19.)

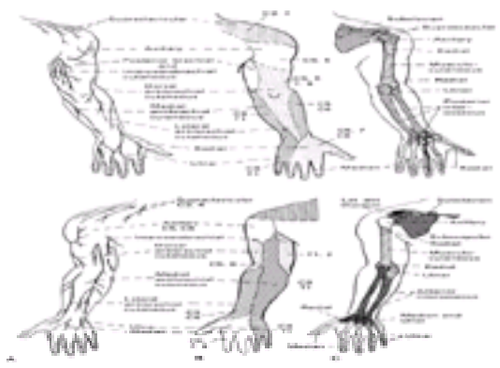

Figure 54-19. Peripheral nerve supply to the upper limb showing the anterior view (*above*) and posterior view (*below*). **A:** Various cutaneous nerves and their territories **(B)**. **C:** Nerve supply to the bones and joints.

Suprascapular Nerve. The suprascapular nerve contains sensory, motor, and sympathetic fibers that supply the supraspinatus and infraspinatus muscles, the shoulder joint, and some of the surrounding structures. Its component fibers are derived from the fourth, fifth, and sixth cervical segments and travel through the anterior primary divisions to reach the upper trunk of the brachial plexus, from which the formed suprascapular nerve emerges. It then proceeds laterally, posteriorly, and inferiorly beneath the posterior belly of the omohyoideus and trapezius muscles, but superficial to the plexus, to reach the superior border of the scapula (see Fig. 54-19). Here it passes through the suprascapular notch beneath the superior transverse scapular ligament and enters the supraspinatus fossa, where it gives off several branches to the supraspinatus muscle and an articular branch to the acromioclavicular and shoulder joints. It then courses around the spinoglenoid notch beneath the inferior transverse scapular ligament to end in the infraspinatus fossa, where it issues branches to the shoulder joint and its periarticular tissues and terminal branches to the infraspinatus muscle. It often gives off a minor cutaneous branch that supplies a small skin area at the apex of the shoulder.

Axillary Nerve. The axillary nerve is the last branch of the posterior cord of the brachial plexus before the latter becomes the radial nerve. It passes over the insertion of the subscapularis muscle dorsal to the axillary artery, crosses the teres minor, and leaves the axilla by passing through the quadrilateral space, where it divides into several branches. The posterior (lower) branch supplies the teres minor and the posterior part of the deltoid. It then pierces the deep fascia at the posterior border of the deltoid as the lateral brachial cutaneous nerves to supply the skin over the distal two-thirds of the posterior aspect of the muscle and over the adjacent head of the triceps brachii. The anterior (upper) branch winds around the surgical neck of the humerus under cover of the deltoid muscle as far as its anterior border to supply this muscle, and sends small cutaneous filaments to the skin covering its distal part. The articular branches of the axillary nerve leave the nerve near its origin and, in the quadrilateral space, supply the anterior and inferior parts of the capsule of the shoulder joint.

Musculocutaneous Nerve. As mentioned previously, the musculocutaneous nerve is derived from the lateral cord, pierces the coracobrachialis muscle, and, lying between the brachialis and the biceps brachii, crosses to the lateral surface of the arm. A short distance above the elbow, it pierces deep fascia lateral to the tendon of the biceps and continues into the forearm as the lateral antebrachial cutaneous nerve. During its course it gives off a branch to the coracobrachialis muscle, provides muscular branches to the biceps and brachialis, supplies an articular filament to the elbow joint, and gives off a branch to the humerus that enters the nutrient foramen with the artery (Fig. 54-16). The lateral antebrachial cutaneous nerve breaks into an anterior branch that supplies the skin over the radial half of the anterior surface and the skin over the thenar eminence. The dorsal (posterior) branch passes distally along the dorsal part of the radial surface of the arm, supplying the skin almost to the wrist and communicating with the dorsal antebrachial cutaneous nerve and superficial branch of the radial nerve.

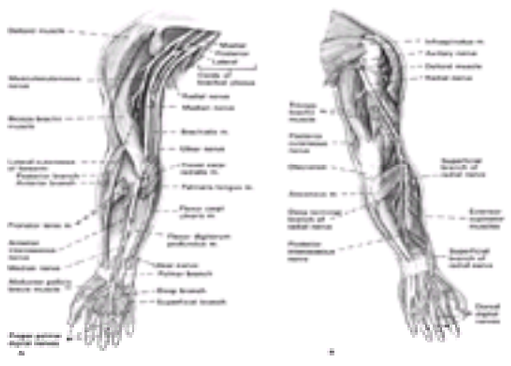

Figure 54-16. Anatomy of the median, ulnar, and radial nerves. Anterior view **(A)** and posterior view **(B)** of the upper limb showing the course of the three nerves and some of the muscles (m.) they supply.

Median Nerve. The median nerve is composed of fibers derived from the sixth, seventh, and eighth cervical nerves and first thoracic nerve and, in some cases, the fifth cervical segments. These fibers traverse the three trunks and their anterior divisions to reach the medial and lateral cords from which the nerve emerges by two heads, the medial head from the medial cord and the lateral head from the lateral cord. These two heads unite at the lower border of the pectoralis minor in the uppermost part of the arm to form the median nerve, which descends down the medial side of the arm in company with the brachial vessels, at first lying lateral to the artery and then medial to it after crossing it obliquely at approximately the middle of the humerus (see Fig. 54-16). At the bend of the elbow it is situated beneath the lacertus fibrosus medial to the artery and the tendon of the biceps and is separated from the elbow joint by the brachialis muscle.

The nerve then proceeds to the forearm, first passing between the two heads of the pronator teres and then between the flexor digitorum sublimis and the flexor digitorum profundus. It courses straight down the forearm, lying between these two muscles to come within 5 cm of the transverse carpal ligament, where it becomes more superficial and is situated between the flexor carpi radialis and the flexor digitorum sublimis posterolateral to the tendon of the palmaris longus. It then passes dorsal to the transverse carpal ligament and into the palm of the hand, where it terminates as muscular branches to the first and second lumbricales, abductor pollicis brevis, opponens pollicis, and superficial head of the flexor pollicis brevis, and as cutaneous branches to the radial two-thirds of the palm and the dorsal aspects of the second, third, and fourth fingers.

At the elbow the median nerve gives off articular branches to the elbow joint and at the forearm it gives off muscular branches to all the pronators and flexor muscles of the forearm, except the flexor carpi ulnaris and the ulnar half of the flexor digitorum profundus, and a palmar cutaneous branch, which pierces the volar carpal ligament, descends across the transverse carpal ligament, and is distributed to a small area of skin on the radial side of the palm. The median nerve supplies filaments to the median artery and its branches (see Segmental and Peripheral Nerve Supplies to the Neck and Upper Limbs, later in this chapter). It also gives articular osseous branches to the wrist and fingers.

Ulnar Nerve. The ulnar nerve supplies the muscles and some of the skin and bones of the ulnar side of the forearm and hand (see Fig. 54-16). The component fibers are derived from the eighth cervical and first thoracic segments and pass through the lower trunk and its anterior division and through the medial cord, from which the nerve arises just medial to the axillary artery. After emerging from the cord at the lower border of the pectoralis minor it descends on the medial side of the arm in front of the triceps muscles, medial to the brachial artery as far as the middle of the arm. Here it pierces the medial intermuscular septum to pass into the posterior compartment of the arm together with the superior ulnar collateral artery. It continues its descent on the medial head of the triceps into a groove between the medial epicondyle and the olecranon, where it is superficially situated and lies immediately beneath the skin and deep fascia; thus, it is easily palpable and accessible to the

anesthetizing needle.

The ulnar nerve then passes between the two heads of the flexor carpi ulnaris to gain the forearm and descend toward the wrist, lying between the flexor digitorum profundus and flexor carpi ulnaris on the medial side of the ulnar artery. During its course in the forearm it gives off branches to the flexor carpi ulnaris and to the ulnar half of the flexor digitorum profundus. At a point approximately 5 cm above the wrist it gives off the palmar cutaneous branch, which ends in the skin of the palm, and a dorsal cutaneous branch, which passes posteriorly to supply the skin of the dorsal surface of the wrist, hand, little finger, and ulnar half of the ring finger. The ulnar nerve then proceeds distally by passing superficial to the transverse carpal ligament, lateral to the pisiform bone, and posteromedial to the ulnar artery, finally reaching the palm, where it ends by dividing into the superficial and deep terminal branches. The superficial branch supplies the skin over the ulnar side of the hand, little finger, and ulnar side of the ring finger, whereas the deep terminal branch supplies the adductor pollicis, interossei, third and fourth lumbricales, deep head of the flexor pollicis brevis, palmaris brevis, and abductor, opponens, and flexor digiti quinti muscles.

The ulnar nerve gives off articular branches to the elbow, wrist and finger joints, vascular filaments that supply the ulnar vessels and their termination, and filaments to bones that supply the medial condyle of the humerus, the medial half of the upper extremity of the ulna, the bones of the little and ring fingers, and contributes to the innervation of the carpal bones.

Radial Nerve. The radial or musculospiral nerve is the largest peripheral nerve derived from the brachial plexus. Its component fibers arise from the fifth, sixth, seventh, and eighth cervical and first thoracic spinal segments, traverse through the three trunks and their posterior divisions, and finally unite within the posterior cord to form the nerve (Fig. 54-17; see Fig. 54-16). Because of its relative size, the radial nerve is often considered as the direct continuation of the posterior cord. From its point of origin at the lower border of the pectoralis minor, the radial nerve descends laterally and inferiorly behind the third part of the axillary artery and the upper part of the brachial artery and in front of the tendons of the latissimus dorsi and teres major. At the lower border of these tendons it turns posteriorly and proceeds distally in a spiral fashion around the humerus within the musculospiral groove between the medial and lateral heads of the triceps muscle. While within the groove it gives off the dorsal antebrachial cutaneous nerve, which supplies the dorsal aspect of the forearm. The radial nerve descends within the groove to a point approximately 10 cm above the external condyle of the humerus, where it pierces the lateral intermuscular septum and enters a cleft between the brachialis and brachioradialis muscles. Within these muscles it continues its descent, first on the anterior aspect of the humerus and then in front of the elbow joint.

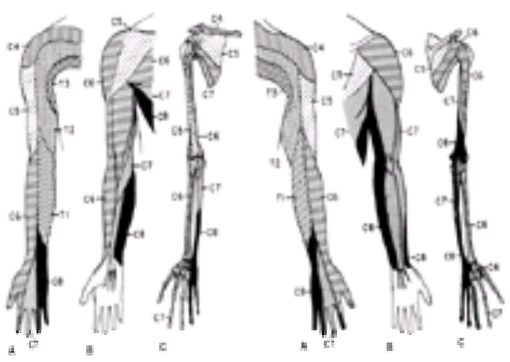

Figure 54-17. Segmental nerve supply to the upper limb showing the anterior view (*left*) and posterior view (*right*). **A:** Dermatomes. **B:** Myotomes. **C:** Sclerotomes.

The nerve then enters the substance of the supinator brevis where it divides into superficial and deep posterior branches, often called the dorsal interosseous nerve. The deep branch passes posteriorly through the substance of the supinator brevis muscle to wind around the lateral side of the radius and become situated between the superficial and deep layers of the extensor muscles on the posterior aspect of the forearm, to which it supplies numerous filaments. It continues its descent and finally reaches the dorsal aspect of the wrist and hand, where it presents a ganglioform enlargement from which filaments are distributed to the ligaments, articulations, and bones of the wrist.

The superficial branch, often considered to be the continuation of the radial nerve and so named, proceeds along the anterior aspect of the forearm beneath the brachioradialis muscle to reach the lateral (radial) side of the radial artery approximately 5 cm distal to the elbow. It continues its descent in this relation to a point approximately 7 cm proximal to the wrist, where it diverges from the artery, passes posteriorly beneath the tendon of the brachioradialis, pierces the deep fascia, and divides into lateral and medial branches. The lateral branch supplies the skin of the radial side and ball of the thumb, whereas the medial branch communicates with a branch of the lateral antebrachial cutaneous nerve and the dorsal branch of the ulnar nerve and supplies the radial two-thirds of the dorsal surface of the hand and thumb and the index, middle, and ring fingers.

In addition to these branches, the radial nerve gives off the posterior brachial cutaneous nerve that arises in the axilla and supplies the back of the arm; muscular branches that supply the triceps, anconeus, brachialis, and brachioradialis muscles; articular branches to the elbow, wrist and finger joints; filaments to bones, including part of the humerus, radius, ulna, and carpal bones; and vascular filaments that supply part of the axillary, brachial, and radial arteries and veins.

SEGMENTAL AND PERIPHERAL NERVE SUPPLIES TO THE NECK AND UPPER LIMBS

This section summarizes the segmental and peripheral nerve supplies to various structures in the neck, shoulders, and upper limbs. In addition, detailed descriptions of the sympathetic nerve supply to the vessels of the upper limbs are presented. Table 54-2 lists the myotomal distribution to the muscles in the neck. Table 54-3 lists the sclerotomal distribution of the first cervical to the first thoracic nerves, and Table 54-4 lists the peripheral and segmental nerve supplies to the muscles of the upper limbs. Figure 54-17 depicts the segmental nerve supply to the upper limb. Figure 54-18 depicts the dermatomal distribution of the upper four cervical nerves, and Figure 54-19 illustrates the peripheral nerve supply to the upper limbs.

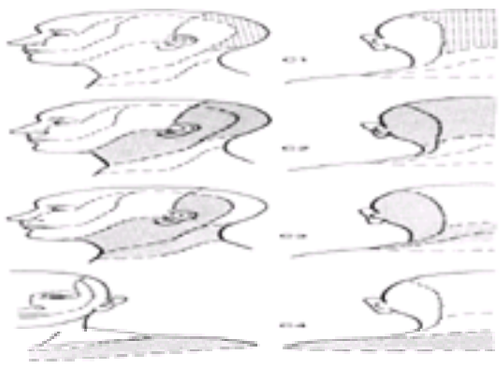

Figure 54-18. Dermatomes of the neck and head derived from the upper four cervical nerves.

Anatomy and Physiology of Sympathetic Nerves

Sympathetic Nerve Supply to Upper Limbs

The sympathetic nerve supply to the upper limbs begins with preganglionic cell bodies located in the anterolateral horn of the spinal cord at the second to eighth thoracic spinal cord segments (Fig. 54-20). In a small percentage of individuals the uppermost preganglionic cell bodies are located in the first thoracic and, in rare cases, the eighth cervical ramus, whereas the lowermost can be in the ninth or tenth, or in rare cases the seventh spinal segment (13,14,15,16 and 17). The axons of

these neurons pass through the anterior roots and white rami communicantes and thus reach the sympathetic trunk. They then ascend within the sympathetic trunk and end and synapse with postganglionic neurons primarily in the second and first and inferior cervical (stellate) ganglia, often in the intermediate and middle cervical ganglia, and in some individuals in the third thoracic ganglion. It has been shown that the second thoracic ganglion contains the greatest number of synaptic connections for the upper limb (18,19 and 20). Afferent fibers from the vessels of the upper limb enter the spinal cord through the first, second, and third thoracic, and even the fourth thoracic dorsal roots (17,18).

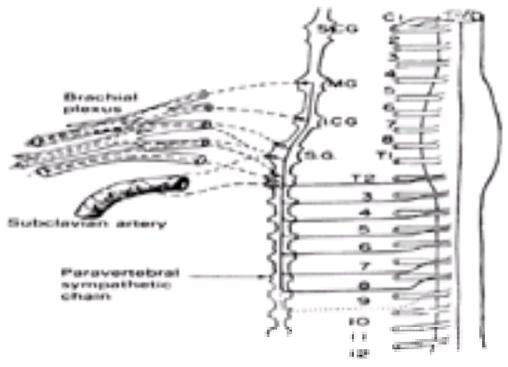

Figure 54-20. Schematic depiction of the origins and courses of preganglionic sympathetic neurons destined to supply the upper limbs. Note that the axons of the preganglionic neurons, which are located in spinal segments T-2 to T-8 (and occasionally T-9), pass through the anterior root as white rami communicantes and from there to the paravertebral sympathetic chain, where they ascend and synapse with postganglionic fibers primarily in the second thoracic, stellate, and intermediate and middle cervical ganglia, and occasionally in the third cervical ganglion (not shown). Some of the postganglionic fibers pass directly to the subclavian artery, but most pass as gray rami communicantes to the roots of the brachial plexus. (From Bonica JJ. *Clinical application of diagnostic and therapeutic nerve block*s. Springfield, IL: Charles C Thomas, 1959.)

Some postganglionic neurons pass directly from the sympathetic trunk as vascular filaments to the subclavian artery and to some of its branches. The principal bulk of postganglionic fibers, however, form the gray rami communicantes that connect the sympathetic trunk to the fifth, sixth, seventh, and eighth cervical nerves and first thoracic spinal nerve, the anterior divisions of which form the brachial plexus. Every one of these nerves receives one or more gray rami communicantes, with the middle and the intermediate cervical ganglia giving one set of gray rami communicantes to the fifth and another to the sixth cervical nerves; the stellate ganglion gives one or two gray rami communicantes to the sixth cervical nerves, two gray rami communicantes to the seventh cervical nerve, and three each to the eighth cervical and first thoracic nerves (Fig. 54-21). According to Sunderland (19), the postganglionic fibers do not travel as distinct bundles in the trunk of the brachial plexus, but are widely dispersed in the components of the plexus, especially where it crosses the first rib.

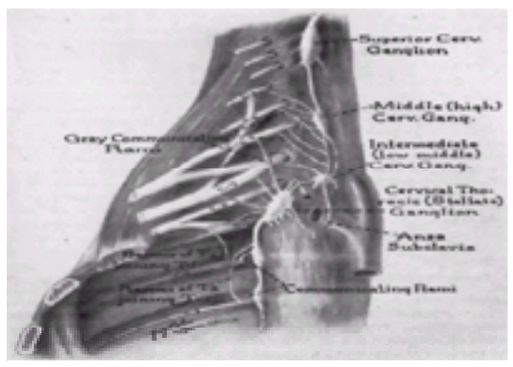

Figure 54-21. Distribution of gray rami communicantes from the cervical and upper thoracic sympathetic ganglia to the roots of the cervical and brachial plexus. Note that postganglionic fibers from T-3 ganglion pass to the third thoracic spinal nerve and from there to the second spinal nerve, and that gray rami communicantes from the second thoracic ganglion pass to the second thoracic spinal nerve and from there to the first thoracic nerve. These nerves constitute a pathway of sympathetic nerves to the brachial plexus that bypass the stellate ganglion and the intermediate and middle cervical ganglia. (From Moore DC. *Stellate ganglion block*. Springfield, IL: Charles C Thomas, 1954.)

In addition, in a significant number of people, an intrathoracic somatic branch arising from the second thoracic spinal nerve joins the first thoracic spinal nerve, which of course takes part in the formation of the brachial plexus. This intrathoracic branch is almost always joined by proximal gray rami communicantes carrying postganglionic fibers that arise in the second thoracic sympathetic ganglion, possibly in lower ganglia, and distal white ramus communicantes (15,20) (see Fig. 54-21). In some individuals a branch also arises from the third thoracic spinal nerve and passes to the second spinal nerve. This second intrathoracic nerve, which also contains preganglionic sympathetic fibers that arise from the third thoracic ganglion, joins the second thoracic spinal nerve proximal to the branch sent by the latter nerve to the first thoracic nerve. Thus, it is apparent that these inconstant preganglionic and postganglionic sympathetic pathways, known as *Kuntz's nerves* (17,20), pass to the lower part of the brachial plexus without passing through the stellate ganglion, a fact of critical importance in attempting complete sympathetic denervation of the upper extremity as previously practiced by Leriche (21). Thus, a pure stellectomy or local anesthetic block limited to the stellate ganglion does not produce complete sympathetic denervation of the upper limbs. In such cases it is also essential to block or resect the second and third thoracic ganglia to denervate the limb completely. Moreover, because all the fibers to the upper limbs pass through the second and occasionally the third thoracic ganglia, they are the key relay stations that can be blocked by small amounts of neurolytic agents or resected surgically to produce sympathetic denervation of the extremity (17,22,23).

Innervation of Blood Vessels, Sweat Glands, and Erector Pilae Muscles. The blood vessels, sweat glands, and erector pilae muscles of the upper extremities receive their innervation by sympathetic fibers that reach them either directly from the sympathetic trunk or indirectly from the peripheral nerves. The subclavian artery, axillary artery, and proximal portion of the brachial artery are supplied by sympathetic postganglionic fibers derived directly from the sympathetic trunk. The lower two-thirds of the brachial artery and all its branches are supplied by sympathetic fibers conveyed peripheralward by the brachial plexus and its constituent nerves, particularly the median, radial, and ulnar nerves. These are distributed to various blood vessels at irregular intervals, with most distal vessels having a greater number of sympathetic fibers than the more proximal ones. These vascular fibers have the same distribution as the nerves that convey them peripheralward, and, in the forearm, their distribution is sharply demarcated into the ulnar, median, and radial zones. The sympathetic supply to the major blood vessels of the upper limbs is depicted in Figure 54-22 and described in detail here. What is said about the arteries applies to the analogous veins.

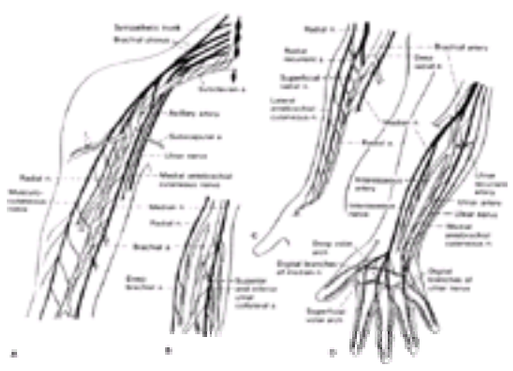

Figure 54-22. **A–D:** Sympathetic nerve supply to the arteries in the upper limbs.

Innervation of the Subclavian Artery and Its Branches. As previously mentioned, the subclavian artery and its branches receive postganglionic fibers directly from the sympathetic trunk, primarily the stellate and middle cervical ganglia. On reaching the artery these fibers form a plexiform network known as the subclavian arterial plexus and subsidiary plexuses, which surround the major branches of the artery. Some of these fibers extend to and surround the axillary artery and the upper third of the brachial artery. These arteries also receive vascular branches from the ansa subclavia and from the paravertebral ganglia, which pass to the seventh and eighth cervical nerves and thence through the lower trunk of the brachial plexus, and a vascular branch from the phrenic nerve. These various contributions form the anterolateral and posterolateral subclavian sympathetic plexuses (nerves) that supply the postscalenic portion of the subclavian artery and contain both sympathetic and sensory fibers.

Vessels of Axilla and Arm

Innervation of the Axillary Artery and Its Branches. The axillary artery is supplied by sympathetic and sensory fibers of a nerve from the posterior cord of the brachial plexus and by extension of the subclavian arterial plexus. The nerve supplied by the brachial plexus travels along the posterior wall of the axillary artery and splits into a twig for the anterior wall of this artery, a second branch for the circumflex scapular artery, and a third branch for the subscapular arteries. The proximal part of the posterior humoral circumflex artery receives a nerve that has a common origin with that of the upper third of the brachial artery. Hovelacque (24) described the axillary artery as being supplied by several nerves: The brachial plexus innervates the upper two-thirds, and the radial circumflex nerve and occasionally the musculocutaneous nerve supply the lower third of this blood vessel (see Fig. 54-22A). In addition, the axillary plexus receives filaments from the pectoral ansa.

Innervation of the Brachial Artery. Various anatomic descriptions indicate that principal vascular nerves containing sympathetic and sensory fibers that supply the brachial artery traverse the medial and lateral cords of the brachial plexus, but accompany the peripheral nerves in a variable manner before they reach the wall of the blood vessels. Pick (17,18), an outstanding authority on the nerve supply to the upper limbs, found that the nerve supply to the brachial artery was meager and distinctly segmental in nature.

The upper third of the brachial artery is innervated by the same nerve from the posterior cord of the brachial plexus (i.e., the radial nerve) that also supplies the posterior humoral circumflex artery, and also by filaments derived from the median and musculocutaneous nerves (see Fig. 54-22A) (18,25). The middle third is innervated by filaments derived from the musculocutaneous and median nerves (24). In some instances it is supplied by a new nerve that has a double root of origin, one from the ulnar and another from the radial nerves (see Fig. 54-22B) (17). The branch from the radial nerve also supplies the profunda brachii artery. The lower third of the brachial artery receives three nervelets from the musculocutaneous nerve and some filaments from the median nerve, which also issues a twig to the superior and inferior ulnar collateral arteries and, in addition, sends other filaments that supply the inferior ulnar collateral artery and the brachial artery in the cubital fossa (see Fig. 54-22B) (17).

Vessels of the Forearm and Hand. The arteries and veins in the forearm and in those of the hand, especially the fingers, receive the richest and most complex sympathetic and sensory nerve supplies (Fig. 54-22C and Fig. 54-22D). In the forearm the major arteries and veins receive fine sympathetic and sensory fibers from the medial, radial, and ulnar nerves and also from the antebrachial cutaneous nerves. These fine fibers take off from the parent nerve trunks at irregular intervals and are embedded in connective tissue. Moreover, these are supplied at much more frequent intervals than those in the proximal vessels. They run nearly parallel to each other from the nerve to the vessels. In the forearm and hand the distribution of these vascular sensory and sympathetic fibers is demarcated into ulnar, medial, and radial zones.

Innervation of the Radial Artery. The sympathetic and sensory nerve supplies to the proximal third of the radial artery consist of one branch from the median nerve and two small filaments from the lateral antebrachial cutaneous nerves (17,18). One of the latter filaments also innervates the radial recurrent artery, which also receives filaments from the deep branch of the radial nerve peripherally. Most investigators (13,15,17,18,24) have found no nerve supply to the middle third of the radial artery, whereas the distal third is innervated by one filament from the superficial branch of the radial nerve and by eight individual twigs from the lateral antebrachial cutaneous nerves. Some (14,15,17,18,24) have described vascular nerves to the radial artery supplied by the musculocutaneous and superficial ramus of the radial nerve and by the main stems of the radial and median nerves (see Fig. 54-22C).

Innervation of the Ulnar Artery. Pick (17,18) described the sympathetic and sensory nerve supply to the ulnar artery as follows. The upper third of the ulnar artery and the ulnar recurrent artery are innervated by filaments from the muscular branch of the median nerve; the middle third of the ulnar artery is supplied by a strong branch of the ulnar nerve; and the distal third of the ulnar artery receives three separate branches from the ulnar nerve and a distinct ramus from the medial antebrachial cutaneous nerve. The volar interosseous artery is supplied by five nervelets from the volar interosseous nerve (see Fig. 54-22D).

Innervation of the Arteries of the Hand. Pick (17,18) also described the innervation of the arteries of the hand. The deep volar arterial arch is supplied by two filaments from the ramus profundus of the ulnar nerve. The superficial volar arterial arch has a rich nerve supply, with nearly a dozen twigs or loops from the common digital branches of the median and ulnar nerves. Each proper digital artery is given 3 to 12 or more individual twigs from its accompanying nerve. This nerve supply to the arteries corresponds to the nerve supply to the skin (see Fig. 54-22D).

Distribution of Nerve Fibers in Vessel Walls. The slender filaments containing sympathetic and sensory fibers enter the adventitia of the vessels to become the intrinsic nerves of the arteries and veins (15). At the outer part of the adventitia of the vessels they form the outer or adventitial plexus. Some of the fibers run longitudinally in the adventitia for short distances with most fibers running distally, but some also run in the opposite (cephalad) direction. * These fibers, which are both myelinated and unmyelinated, form bundles that seem to be arranged with the vasa vasorum so as to afford convenient pathways for the bundles to pass through the adventitial tissue.

From the adventitial plexus, bundles of nerve fibers, chiefly unmyelinated, approach the surface of the media of the artery (and veins) and form a plexus on its surface, the so-called border plexus. From this plexus small bundles and individual small fibers penetrate to the superficial zone of the media to form a plexus, the so-called muscular plexus. The latter is sufficient to account for the innervation of the entire musculature (15). The nerve fibers in the media form dense intricate plexuses that cover the entire coat and extend between muscle fibers, so that they circulate throughout the entire layer.

Degeneration studies indicate that the nerves at the surface and within the media are predominantly sympathetic, whereas those in the adventitia are predominantly afferent (15). The sympathetic fibers that supply the vessels of the skin, subcutaneous tissue, and other somatic structures, except the muscle, make synaptic connections with a-adrenergic receptors, whereas those that supply vessels to skeletal muscles make synaptic connections with b-adrenergic receptors.

The terminations of afferent fibers that supply vessels are either naked or encapsulated. The naked terminations can consist of small terminal branches that end in a treelike fashion or in brushlike endings, primarily in the adventitia. The encapsulated terminations end in pacinian corpuscles or in the end-bulb of Krause (15). Although some have suggested that naked nerve endings of unmyelinated C fibers enter into the intima of the arteries and veins, many investigators dispute this notion (15). It has been suggested that, if they do exist, some of these fibers are chemoreceptors, whereas others are thermal receptors or mechanoreceptors.

Some unmyelinated nerve fibers intimately associated with capillaries have been demonstrated (15). Degeneration studies indicate that these are sympathetic fibers but, because the walls of capillaries contain no contractile tissue comparable with that found in the muscles of arteries and veins, the function of these fibers is not clear.

Physiologic Aspects

The sympathetic fibers contain both vasoconstrictor and vasodilator fibers. The largest arteries, such as the subclavian and axillary arteries and the proximal portion of the brachial artery, have few or no vasomotor fibers, but the arterial trees distal to these have vasomotor fibers, with the distal vessels having more than the proximal ones. When sympathetic hyperactivity occurs, provoked by anxiety, fear, apprehension, or exposure to cold, vasoconstrictor fiber activity predominates. Similarly, loss of blood provokes a change in baroreceptor activity, with consequent stimulation of centers in the hypothalamus and thus of vasoconstrictor fibers. Increase in adrenalin secretion by the adrenal gland causes stimulation of b-adrenergic receptors located in blood vessels that supply muscles of the limbs. This results in a slight increase in systolic blood pressure (a result of the inotropic and chronotropic effects of adrenalin) and a marked decrease in diastolic pressure (because of marked vasodilation of these vessels), with consequent decrease in the mean arterial pressure. Increased secretion of noradrenalin or injection of as little

as 15 µg of adrenalin as an intravenous bolus causes increases in both the systolic and diastolic pressures and consequently in the arterial blood pressure (26).

Block of vasoconstrictor fibers causes dilation of blood vessels to the extremity because tonic impulses that normally are connected to the vessels in a more or less constant stream to maintain the musculature in a state of tonus are removed. The dilation of the arterioles and smaller arteries and veins is not complete, however, because the muscles of these vessels have an intrinsic vasomotor tone. This intrinsic vasomotor tone can be completely eliminated by direct vasomotor paralysis produced by histamine, kinins, local anesthetics applied to the blood vessels, or administration of halothane or other systemic agents that directly paralyze the muscles of these vessels.

The existence of vasodilator fibers in sympathetic nerves has been amply demonstrated in experimental animals and in humans (15). Thus, it has been shown that, when the extremities of normal subjects are naturally cool, vasodilation in response to warming the body becomes evident in the fingers earlier than in the toes and indeed, in some instances, vasodilation can fail to occur in the feet. This delayed response in the toes as compared with the fingers has been attributed not to a difference in time but to a difference in the intensity of the vasomotor relaxation in the upper and in the lower extremities. Warming of the body elicits complete relaxation of the vessels in the upper limbs but only incomplete relaxation of the vessels in the lower limbs. This increase in skin temperature of the hands in response to warming of the body depends on the responsiveness of the arteriovenous anastomoses in the distal parts of the fingers to changes in body temperature. These anastomoses constrict as the body is cooled and dilate as the body temperature increases.

Experiments in humans have also demonstrated that the vasodilation involved in warming the hands is effected through the sympathetic nerves. This is suggested by the fact that warming of the body does not elicit similar responses in hands deprived of the sympathetic innervation. Moreover, studies have shown that this is an active process, and not the result of inhibition of vasoconstrictor impulse activity. Such studies have suggested that vasodilator fibers exist in sympathetic nerves, but this remains controversial. On the other hand, parasympathetic cholinergic vasodilator fibers do exist and innervate the arteries of the external genitalia (penis, clitoris, and labia minora), which markedly dilate during sexual arousal. Parasympathetic vasodilator fibers also supply the pial arteries of the brain.

EVALUATION OF THE PATIENT

Diagnosis of pain limited to the neck or shoulder or to other parts of the upper limb or the entire limb requires a thorough history, physical and neurologic examination, psychosocial evaluation, and, not infrequently, imaging studies and special laboratory tests. Because these aspects of the evaluation are discussed in detail in Chapter 12, only specific relevant points are emphasized here. Usually, the physician already has information available about the age, occupation, race, culture, marital status, and other demographic factors and can proceed to obtain a thorough history.

History

In obtaining the history, it is first essential to evaluate the characteristics of the pain at onset, during the interval since onset, and at the present time, when the pain was first felt, and the nature of the precipitating factor (5). Characteristics of the pain include the type of onset (sudden or gradual), distribution (local or widespread), quality (sharp, dull aching, or burning), intensity (mild, moderate, severe, or excruciating), time-intensity curve (same throughout the day or better or worse in the morning, afternoon, evening, or night), and duration. Were there associated symptoms and signs (numbness, weakness)? What relieved the pain, and what made it worse? The patient should be asked these questions in regard to the course of the pain and currently. What treatment has been received, and what are the results? What has been the effect of the pain on the patient's activities (at work or during leisure time)? How long during the day has the patient been required to rest in bed or to be active?

Localized pain is usually caused by disorders of joints, muscles, and bones; segmental pain is caused by lesions of nerves or nerve roots (intraspinal, vertebral, or paravertebral); and pain with peripheral nerve distribution is caused by lesions of the cervical or the brachial plexus or its branches. A sharp bright quality of the pain indicates a cutaneous or neurologic origin, a burning diffuse pain suggests a vascular origin, and a deep aching pain indicates a muscular, bone, or joint origin. Brief, sharp lancinating pain brought on by coughing or sneezing suggests radiculalgia, which can have many causes; continuous, deep, dull, aching pain aggravated by motion of the neck or extremities is usually of musculoskeletal origin; continuous, diffuse, burning pain associated with hyperalgesia and thermohyperesthesia suggests reflex sympathetic dystrophy of the upper limb; and a diffuse, aching or burning discomfort modified by dependency or elevation suggests peripheral vascular disease. Pain and stiffness on arising suggest a myofascial disorder, pain worsening at night suggests bone involvement, and pain worsening during the latter part of the day after hours of work suggests a musculoskeletal disorder.

Psychosocial Evaluation

History of the pain is followed by a psychosocial evaluation and medical and family histories (27). Detailed information should be obtained about psychological, emotional, and sociologic issues, such as past and current relations with the spouse and family and friends; history regarding the present and former use of tobacco, alcohol, and drugs; and the role of environmental factors and other issues (mentioned in Chapter 12 and discussed in detail in Chapter 16). The past medical history should elicit information about previous injuries, characteristics of the pain associated with the injury, treatment used, and results obtained, as well as other medical disorders the patient has had that might have some relationship to the present problem. Information about the health of the parents and siblings, and whether they have suffered frequent painful disorders and disabilities, should be ascertained.

As emphasized in Chapter 12, the physician has an unequaled opportunity during the taking of the history to develop rapport with the patient and also to study the patient as a whole: the manner, attitude, behavior, and emotional reactions, tone of voice, bearing, facial expression, posture, movements, gait, position of the head, and curvature of the neck. The patient who is slumped in the chair and bobbing the head about while talking, or gesturing with the head and neck, is likely not to have pathology of the cervical spine as a cause of the pain. The examiner should observe the patient as he or she walks in, noting how the head is held and how naturally and rhythmically the head and neck move with body movements. Similarly, the movement of the upper limb as the patient walks, sits, or gesticulates should be observed.

Physical and Special Examinations

A thorough, detailed history should permit the physician to make a presumptive diagnosis that needs to be confirmed or disproved by a thorough physical examination, which should include inspection, palpation, and percussion of various structures that might be involved with lesions producing pain in the neck, shoulders, and upper extremities (28). Palpation and percussion of the neck and movements in various directions indicate if the lesion is in the vertebral or paravertebral region. If these findings are negative, the shoulder should be examined thoroughly. In lesions of the shoulder girdle the pain is aggravated by palpation, percussion, and motion involving joints of the shoulder. The rest of the extremities are then examined thoroughly. In all cases a neurologic examination, including sensory, motor, and reflex tests, should be done (27). Special examinations should include imaging, electrodiagnostic studies, and sympathetic function tests. The rest of this section presents the most important points of the examination for pain in the neck, shoulders, and various parts of the upper limbs. The physical examination of the neck, shoulders, and upper limbs is described in more detail in three subsequent chapters.

Physical Examination

The physical examination should include the following features.

Neck

- Inspection of posture and gait, position of the head, curve of the neck, symmetry, and swelling
- Palpation of the hyoid bone, thyroid cartilage, thyroid gland, first cricoid ring, carotid pulses, lateral and posterior neck, supraclavicular fossa
- Palpation and percussion (to determine effects on pain, tenderness, paresthesia, and so forth) of the spinous processes, transverse processes, scaleni muscles, sternocleidomastoid muscle
- Range of motion (active, passive, against resistance): (a) anterior flexion; (b) lateral flexion (R); (c) lateral flexion (L); (d) extension; (e) rotation (R); (f) rotation (L)
- Effect of head compression test (Spurling's test), head or neck traction

Shoulder and Arm

- Blood pressure
- Position
- Shape
- Atrophy
- Palpation for pain, tenderness, radiation, paresthesia, dysesthesia, trigger points in muscles
- Range of motion at shoulder (active, passive, against resistance): (a) abduction; (b) adduction; (c) internal rotation; (d) external rotation; (e) flexion (at shoulder); (f) extension (at shoulder)
- Effect of each motion on pain and tenderness

Elbow and Forearm

- Inspection of position, shape, atrophy, swelling
- Palpation for pain, tenderness, paresthesia, trigger points
- Range of motion at forearm: (a) flexion; (b) extension; (c) supination; (d) pronation
- Range of motion at wrist: (a) dorsal flexion; (b) palmar flexion; (c) ulnar flexion; (d) radial flexion
- Effect of each motion on pain

Wrist and Hand

- Inspection of skin (color, temperature), pulse, shape, atrophy, swelling
- Palpation for pain, tenderness, paresthesia, trigger points
- Range of motion of fingers: (a) flexion; (b) extension; (c) adduction; (d) abduction; (e) opponens; (f) grip
- Effect of each movement on pain

Neurologic and Special Examinations

All tests involving the limbs should be done bilaterally.

- Sensory tests (determine and record presence of allodynia, hyperalgesia, hyperesthesia, hyperpathia, anesthesia, hypesthesia, hypalgesia): pinprick, pinch, temperature (hot and cold), touch, vibration, pressure
- Reflex tests (determine and record if normal, hyperactive, hypoactive, or absent): normal–biceps, triceps, brachioradialis, wrist jerk, finger jerk; pathologic–invert radial reflex, Hoffmann's reflex, Babinski's sign
- Sympathetic function tests: oscillometry, skin temperature (arm, forearm, hand, fingers), psychogalvanic reflex
- Muscle girth measurements (indicate specific site of measurement in centimeters from elbow for muscles of the limb): neck, arm, elbow, forearm, wrist, hand
- Special tests: head compression (Spurling's), head and neck traction, Adson's test, Allen's test, claviculocostal compression test, Valsalva's maneuver

Laboratory Examinations

A number of laboratory tests for the determination of the etiology of pain can be performed. These elucidate the presence or absence of anatomic and physiologic pathology, but do not determine the presence or absence of pain or its magnitude (see Chapter 14).

Imaging Studies

Radiography of cervical spine: anteroposterior, lateral, and oblique views of right and left sides; lateral views in flexion and extension can reveal recent and old trauma, congenital abnormalities, abnormal movement, neoplasm, infection. Radiography of the extremities can reveal bone and joint changes; they are not effective for soft tissue pathology.

Computed tomography scan of spine and of soft tissues can reveal much greater detail than radiography, particularly of osseous structures.

Magnetic resonance imaging scan is particularly useful in delineating soft tissues such as spinal cord, nerves, and muscles. It is useful in the extremities as well as neck.

Myelography is often combined with computed tomographic scan. It reveals subarachnoid space and any encroachment on dura by disk protrusion, degenerative changes in spine.

Diskography, injection of contrast medium into disk, reveals integrity of the annulus and nucleus and demonstrates presence of effects or damage to either structure; it has limited value because abnormal disks can be found in asymptomatic persons, especially those in the older age group.

Diskometry, injection of saline solution into normal disks, permits only a small amount of fluid to be injected before resistance is met; degenerated disk allows much more fluid to enter and ultimately causes pain and other symptoms; it has limitations because the test is technically difficult, produces discomfort, is clinically difficult to determine which disk to inject, can cause damage to the structure, and does not provide unequivocal information.

Electrodiagnostic Studies

Electromyography is used to determine pathology of formed cervical nerves of brachial plexus, components of the plexus, and dorsal and ventral roots (see Chapter 13 for details and Table 8-3 for nerve supply to various muscles).

Somatosensory-evoked potentials are capable of delineating peripheral nerve as well as spinal cord abnormalities of nerve conduction.

Laboratory Tests

- Routine tests: urinalysis, complete blood count
- Blood studies: calcium, alkaline phosphatase, acid phosphatase, blood glucose, serum uric acid, total cholesterol, triglycerides and high-density proteins, serum glutamic-oxaloacetic transaminase, aldolase, creatinine phosphokinase, creatine to creatinine ratio
- Immunologic studies: rheumatoid factors, complement, antinuclear antibodies, cell measurements, human leukocyte antigen typing, quantitative immunoglobulins (IgG, IgA, IgM), cryoglobulins
- Body fluid analysis: spinal fluid, synovial fluid
- Tissue biopsy if mass lesion identified

DIFFERENTIAL DIAGNOSIS

Table 54-5 lists the most important disorders that produce pain in the neck, shoulders, or upper limbs, or in all these structures, together with a brief description of the characteristics of the pain and the associated symptoms and signs. Acute pain conditions are well described in Weiner's text (28). Table 54-5 is presented to help in making an effective differential diagnosis. Further information on painful conditions in the neck and upper extremity is presented in the next five chapters.

TABLE 54-5. Pain in the neck, shoulder, and upper limb: summary of differential diagnoses

* The segmental distribution of sympathetic fibers by the major nerves to the limbs and their short course in the vessel wall are why periarterial sympathectomy, as originally advocated by Leriche (21), denervates only a segment of the artery and not the entire vessel, which would be the case if the sympathetic fibers passed along the entire length of the vessel.

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CHAPTER 55

Neck Pain

Saadi Ghatan and Robert Goodkin

This chapter provides an overview of the epidemiology, anatomy, clinical evaluation, specific disease states and syndromes, and treatment of acute and chronic neck pain. It is organized to focus primarily on the most relevant and common problems seen in clinical practice, but at the same time provide a comprehensive survey of the etiologies and management of this troublesome complaint and at times perplexing clinical disorder. Neck pain is a nearly ubiquitous clinical problem seen by clinicians ranging from primary care physicians, to medical subspecialists, to surgical subspecialists, and, ultimately, to specialists in pain management. Although a detailed analysis of neck pain is beyond the scope of this chapter, it is written as a starting point for the treating practitioner, no matter what the area of his or her expertise.

EPIDEMIOLOGY

Although neck pain presents a formidable challenge in clinical practice, it has received little attention in the literature in comparison with low back pain. The majority of epidemiologic data on spinal-associated pain focuses on low back pain, and neck pain is included as an adjunct (1). Another challenge in the epidemiology of neck pain is its definition: For the purposes of this discussion, acute neck pain is defined as an episode lasting between 2 weeks and 6 months (2), and chronic neck pain is defined as an episode of greater than 6 months' duration (3). Everyone, to some extent, experiences at least transient neck pain that is self-limited and never comes to clinical attention, and the majority of painful episodes resolve spontaneously (4,5). Little is known about the precise prevalence of neck pain in general, but the most frequently quoted figures list its point prevalence at approximately 10% to 35% (3,6,7,8,9 and 10), with a lifetime prevalence between 35% and 50% (6,7 and 8,11,12). The most recent population-based data on chronic neck pain list a lifetime prevalence at around 13% to 14% (3,9).

One of the most common types of neck pain encountered in clinical practice is posttraumatic, or pain associated with *whiplash*- type movements, describing a hyperextension-hyperflexion neck injury. The subject of the whiplash syndrome and controversy surrounding its nosology are discussed later (see Mechanical Pain), but its common use in clinical practice and the mechanism of occurrence in automobile accidents warrant a discussion of its incidence and prevalence (13). Barnsley and colleagues (14) have calculated the derived annual incidence of symptoms from whiplash at 1.0 to 3.8 per 1,000 population based on numbers of rear- end motor vehicle accidents and the suggestion that 20% of those exposed to rear-end motor vehicle accidents develop neck pain (14,15). They go on to estimate a prevalence between 0.5% and 1.0% of the population having chronic neck pain after whiplash, and 0.2% to 0.4% with severe pain, underscoring its significance as a clinical problem (14). Still, one must approach such data with caution, because other epidemiologic studies have shown a prevalence of whiplash-associated neck pain that equals the population-based estimates of neck pain in the absence of trauma (3,15). Studies generated through insurance databases show conflicting figures, with an incidence of 1 per 1,000 among Australian claimants, with only 0.1 per 1,000 among New Zealanders (16), reflecting complexities of a combination of factors, including motivation, enabling circumstances, perceived benefits, perceived costs, social norms, peer and family pressure, and fear of recurrent pain and disability (14). Litigation also clouds the statistical picture as numerous studies have shown the effect of monetary gain on symptomatic improvement in neck pain (17,18,19 and 20). Treatment outcome with regard to surgery for cervical radiculopathy secondary to soft or hard disk protrusions does not appear to be affected to such a degree by compensation or liability issues (21,22 and 23).

Occupationally related neck pain is also well recognized, and the initial epidemiologic data on neck pain were generated from workplace-based studies. Hult noted that 80% of a population of male industrial and forest workers in a Swedish province reported a history of stiff neck and arm pain, and later studies by the same author showed a 51% prevalence in nearly 1,200 male workers, increasing with age without a difference between patients doing light or heavy work (11,24,25). In another Scandinavian study, Tola and colleagues (26) reported a neck pain prevalence of 81% for machinists, 73% for carpenters, and 57% for those involved in sedentary work. In general, work involving repetitive and forceful movements, as well as awkward postures of the head and neck, particularly when found in combination, is associated with the development of a musculoskeletal neck disorder, with odds ratios ranging from 1.5 to 5.7 (27).

In conclusion, the epidemiology of neck pain is difficult to document accurately given the variability in its observation and reporting and the complexities of pain behavior that influence both. In general terms it can be said that the vast majority of neck pain seen in clinical practice surrounds trauma or an aggravation of a predisposing degenerative spondylotic problem in the cervical spine (3). Still, the practitioner must concern herself or himself with other painful conditions that represent perhaps less than 10% of all pathologic processes affecting the neck. These include inflammatory conditions, infections, tumors, neurovascular conditions, congenital abnormalities, endocrinologic, neurologic, and rare and poorly understood chronic pain conditions.

RELEVANT ANATOMY AND PAIN SOURCES

Understanding neck pain and its myriad sources necessitates a thorough knowledge of the relevant anatomy of the cervical spine; its surrounding ligaments and musculature; the organs, vessels, and nerves contained within its confines; as well as the surrounding structures that may act as a source of referred pain (see Chapter 54). A baseline description of the neck's anatomy provides the framework from which to direct the history, physical examination, and further diagnostic tests that are discussed in the following sections. For the purposes of this discussion, the sources of neck pain and their anatomic correlates are divided into somatic (superficial, as well as deep), radicular, neurogenic, and referred visceral.

Superficial somatic pain rarely presents a diagnostic challenge, because the surface area of the neck is limited, and inspection of the skin and underlying superficial tissues usually provides the source of neck pain (e.g., infection, neoplasia). Herpes zoster (shingles) can occasionally cause a diagnostic challenge before the appearance of vesicles, but a dermatomal distribution of the pain and the ensuing vesicular eruption usually confirms the diagnosis (see Chapter 22).

Historically, sources of deep somatic or spondylogenic pain have been more problematic in their characterization. During the 1990s significant advances were made in the understanding of neck pain through its anatomic bases, particularly in the realm of spondylogenic or deep somatic pain (4,5,28). Most of the work has centered on the most epidemiologically common forms of neck pain, which are mechanical. Although any innervated structure in the neck is a potential source of pain, it comes as no surprise that the key pain generators associated with the most common types of neck pain are found in the cervical spine. Following the epidemiology of neck pain, the spine has been the focus of attention in studies concerning the etiology of neck pain.

The cervical spine is unique in its structural and functional complexity. It is made up of seven vertebrae, two of which have a superspecialized structure (atlas and axis), 14 zygapophyseal (facet) joints, 5 intervertebral disks (excluding C-7 to T-1), and a complex system of ligaments that allow strength and protection while at the same time maximizing flexibility. Disruption, injury, or inflammation involving any of these elements could produce neck pain.

Anatomic studies using cadaveric specimens (4,29,30,31 and 32) and functional studies (33,34,35,36,37 and 38) have provided the foundation for our understanding of neck pain related to the cervical spine. The zygapophyseal or facet joints receive a substantial innervation from the medial branches of the dorsal rami of the cervical nerve roots (30). Dwyer and Aprill, and later Fukui and colleagues, carefully studied pain patterns generated through stimulation of the occipitoatlantal, atlantoaxial, and subaxial facet joints in normal volunteers and patients with neck pain (30,33,36). These studies have laid the foundation for therapeutic maneuvers aimed at treating this now commonly recognized source of neck pain (37).

The atlantooccipital joint represents the articulation between the head and neck and is responsible for approximately 15 degrees of flexion and extension (39). The articulation between the occipital condyles and articular processes of C-1 is a facet joint with a large surface area. Dreyfuss and colleagues and Fukui and colleagues have convincingly demonstrated referred pain to the occipital and upper posterolateral cervical regions via injection of contrast media into and electrical stimulation of this joint (40,36). However, only anecdotal evidence exists to implicate this joint in chronic neck pain and cervicogenic headache (35).

Almost 50% of the head's axial rotation is facilitated by the atlantoaxial junction, with the remaining one-half provided by the subaxial cervical spine (39). The axis articulates with the atlas at three points, with two facet joints laterally and another joint posterior to the odontoid process. Here a synovial bursa separates the dens from the transverse band of the cruciate ligament. Neck pain is the most common presenting symptom in rheumatoid arthritis (RA), which frequently affects these joints. The odontoid process is susceptible to fracture, as well, and although rare, this condition may elude diagnosis and go undetected for some time. The clinician must have a high index of suspicion in the setting of recent and even remote trauma. The pain is centered in the occiput and posterolateral cervical regions; and this has been confirmed with functional studies (36).

Coupled with their involvement in whiplash injury described previously, the zygapophyseal joints also play an important role in radiculopathic neck pain. Neck pain secondary to nerve root irritation is possible in the subaxial cervical spine and is usually accompanied by pain shooting down the arm, known as brachialgia. The dorsal wall of the neural foramen is bordered by the facet joint and capsule; facet joint hypertrophy, a normal consequence of aging, can cause radiculopathy secondary to nerve root impingement (41).

In addition to the 12 other facet joints that exist between C-2 and C-3 and C-7 and T-1, the subaxial cervical spine has another 12 uncovertebral joints that are important clinically in neck pain from a radiculopathic source. Uncinate processes are the bony protrusions on the upper, posterolateral end-plates of the cervical vertebrae C-3 to C-7, that articulate with the neighboring vertebral body in the so-called joint of Luschka, or uncovertebral joint. Bland (4), in a study of 171 cadaveric specimens (42), points to the fact that these are not true synovial joints and are not innervated Therefore, they are not considered susceptible to the same disorders that cause zygapophyseal joint pain, such as systemic synovitis of RA or traumatic inflammation. Nonetheless, their hypertrophy and osteophytic degeneration can lead to progressive neural impingement and pain.

The concept of somatic myofascial or muscular pain has been controversial for over 30 years. Such pain syndromes have been ascribed to myriad pathophysiologic theories. They may be amenable to treatment through identification and therapeutic targeting of trigger points (43). Myofascial pain syndromes are discussed in detail in Chapter 28, Chapter 29, and Chapter 31; the long list of neck extensors, flexors, rotators, and lateral flexors are capable of producing pain caused by prolonged or excessive muscular activity as well as a response to neuropathic processes or primary muscle dysfunction. The pathophysiology of neck muscles is less understood than that of the other structures in the neck (44).

The most common source of radiculopathic neck pain is the degenerated cervical intervertebral disk, but many other etiologies are possible (Table 55-1). The annulus fibrosus of the intervertebral disk is endowed with nociceptive nerve endings (32). Along with its fibers to the facet joints, anterior and posterior longitudinal ligaments, and dura, the sinuvertebral nerve and posterior primary ramus innervate the disk capsule. Disruption of the disk by herniation can irritate these nerve endings, producing neck pain in early protrusion secondary to distortion of the posterior longitudinal ligament, followed by progressive brachialgia caused by nerve root compromise in the foramen (5,45).

Cranial neuralgias
Glossopharyngeal neuralgia
Superior laryngeal neuralgia
Upper cervical (C-2 to C-4) neuropathies
Diseases of the spinal cord and meninges
Intrinsic spinal cord lesions
Extramedullary intradural lesions
Extradural spinal cord lesions
Diseases of spinal nerve roots
Herniated intervertebral disk
Vertebral fracture or dislocation
Arthritis
Herpes zoster
Postherpetic neuralgia
Lesions of formed spinal nerves
Compression by vertebral tumors, arthritis
Compression by paravertebral lesions, abscess, Hodgkin's disease, or other tumors
Inflammation of the nerves
Lesions of the cervical plexus
Acute inflammatory lesions
Compression from tumors in the neck
Compression by aneurysm

TABLE 55-1. Most common causes of cervical neuralgia

It has long been known that simple mechanical compression or traction on a normal nerve root does not induce pain, yet slight manipulation of an inflamed nerve root produces the lancinating, burning pain of radiculopathy (46). The source of nerve root inflammation is not completely defined, but evidence points to an autoimmune phenomenon. The nucleus pulposus is an immunologically privileged site that is exposed after disk rupture, and evidence exists that the autogenous disk material elicits a cell-mediated immune response in the spinal canal. Furthermore, disk material contains inflammatory mediators that have been shown on a molecular biological level (47,48 and 49) to effect nerve root dysfunction electrophysiologically in the absence of mechanical compression (47). Other possible causes of inflammation that deserve mention are ischemia secondary to compressive microvascular occlusion or a mechanical alteration in axonal transport. The effectiveness of antiinflammatory medications in the treatment of neck pain from a radicular source lends further credence to the inflammatory provocation by cervical disk herniation.

Finally, the clinician must be aware of the nature of true radicular pain to distinguish it from a radicularlike pain that can occur in the absence of a true radiculopathy. Pseudoradicular pain can occur in relation to facet joint or disk disease, without nerve root involvement. A dull, aching pain that radiates from the neck into the arm, in contrast to the sharp, lancinating brachialgia or true radicular pain, results from referred pain that appears in mesenchymal structures of the same embryonic sclerotome in the injured tissue of the joint (5). Cervicobrachial neuralgia is discussed in Chapter 56.

Neurogenic pain, described as gnawing, burning, or tingling pain, can result from injury to the central nervous sytem. An unusual example of this is seen in the setting of posttraumatic syringomyelia, wherein a spinal cord injury has led to derangement in flow dynamics of the cerebrospinal fluid. In the area of spinal cord injury, a cystic dilatation of the cord is produced years after the initial trauma. The most common heralding complaint of posttraumatic syringomyelia is pain, localized to the level of the injury and its associated nerve roots. The presumed abnormality in such neurogenic pain is the loss of inhibitory input, allowing an excess of nociceptive information reaching the sensory areas of the cerebral cortex (5).

Pain from viscera that share the same embryologic segmental derivation of the cervical spine can present as neck pain. The submandibular glands, lymph nodes, thyroid, esophagus, heart, lungs, stomach, gallbladder, pancreas, and diaphragm are all capable of eliciting some component of neck pain, although this is rarely the only symptom of disease in these organs. The carotid body is another organ associated with neck pain in carotidynia, or swelling of the carotid bifurcation, although this pain is thought to be analogous to migraine and not visceral referred in nature (4).

HISTORY, PHYSICAL EXAMINATION, AND DIAGNOSTIC STUDIES

Although knowledge of anatomic pain generators is essential in considering the broad differential diagnosis of neck pain, the foundation of accurate diagnosis and treatment of neck pain remains in the history and physical examination. Nowhere are the principles of a detailed and complete history, taking into account the patient's present illness, its relation to concomitant illnesses, social and occupational history, and a thorough physical examination, more important. Neck pain is a common symptom that can arise from a multitude of structures in and outside of the neck and arise from both serious and trivial diseases. The clinician must be able to

distinguish between the two and rely on clinical skills, both to lead to useful diagnostic studies, and ultimately to the correct diagnosis.

The initial considerations in the diagnosis of neck pain are the severity of the problem, whether the neck pain is from a life- threatening source, and whether emergency surgical intervention is necessary to avoid a catastrophic neurologic event. Neck pain accompanied by a rapidly progressive motor or sensory deficit, urinary or fecal incontinence, or progressive gait disturbance should be recognized and promptly evaluated. Compromise of the upper cervical spinal cord segments with loss of phrenic nerve function caused by instability in the setting of trauma, inflammatory spondyloarthropathy, tumor, or infection can lead to respiratory failure and death if untreated. Rarely, neck infection in the form of an abscess leads to a rapidly fatal mediastinitis secondary to dissection of the infection through tissue planes.

Once a life- or spinal cord–threatening illness is ruled out, the characteristics of the patient's neck pain must be understood, including onset, duration, precise localization, radiation, quality (burning, lancinating, dull, shooting, aching), present status, and relation to current and past medical history. Cohen provides a diagnostic framework for the analysis of spinal pain, dividing it into mechanical and nonmechanical sources (50). The former is seen in the vast majority of neck pain cases, in anatomically normal as well as spondylotic spines. Pain is usually poorly localized, exacerbated by movement, and occurs in an essentially well person. Nonmechanical or medical sources such as infection, neoplasm, inflammatory osteoarthritis, and metabolic disease are usually recognized in the patient who is systemically unwell, in whom it is obvious that the clinical condition is not simply localized to the neck. Pain is usually well localized, without diurnal variation or relief from rest.

Issues of age, sex, family, and occupational history help to identify patients in risk groups in which neck pain is more prevalent. Younger patients are more likely to be affected by spasmodic torticollis or trauma, whereas osteoarthritis is predominant in the elderly population. RA is more common in female subjects, whereas ankylosing spondylitis is predominantly a disease of male subjects. Familial predisposition to rheumatic illness is seen in patients harboring the HLA-B27 major histocompatibility complex antigen (ankylosing spondylitis, Reiter's syndrome, and psoriatic arthritis) (see Chapter 27). Finally, the widespread prevalence of occupationally associated neck pain warrants an understanding of any intense, repetitive, sustained, or awkward physical requirements in the patient's job. Jobs that require repetitive flexion, rotation, and extension of the neck, in addition to forceful, repetitive use of the hands, in which sustained neck muscle contraction is necessary, place the patient at a markedly increased risk of developing neck pain, with odds ratios of up to 7.5 times that of workers without these requirements (27).

Finally, Bland points out the pertinence of questioning a patient's use of bifocal glasses, which would place the neck under increased flexion strain, and the patient's pillow use at night. These are simple but often overlooked points that might allow the clinician to understand the source of the patient's pain, and a simple change might solve a great number of cervical spine problems (4).

Physical examination in the setting of neck pain should be divided into (a) inspection; (b) palpation of bony structures; (c) examination of the soft tissues; (d) evaluation of range of motion; followed by (e) special tests in the diagnosis of neck pain. This should supplement rather than replace a thorough general systemic physical examination (see Chapter 12).

Inspection can take place from the moment the patient enters the office or examination room. Observation of the patient's posture in the ambulatory, sitting, and supine positions can be made during the history, with special attention to how the neck is held in relation to the shoulders and upper extremities. Torticollis (wryneck) is usually self-limited and disappears within a few weeks, but long-standing torticollis is associated with facial asymmetry and changes in the sternocleidomastoid muscle. Moreover, Bland cautions the clinician to consider the spine as a single functional unit, rather than divide it into cervical, thoracic, and lumbar segments during the examination, because the neck may be symptomatic because of positional changes arising from a problem in the thoracic or lumbar segments (4). An examination of the neck, with special attention to bony landmarks and skin should follow. The hyoid bone, thyroid cartilage, thyroid gland, and first cricoid ring should be recognized, and skin abnormalities can give important information regarding systemic or localized diseases.

Palpation of bony structures is best done with the patient supine to relax overlying muscles (4). In palpating the anterior neck, the examiner stands at the patient's side and supports the neck from behind with one hand while palpating with the other. The horseshoe- shaped hyoid bone is located at the level of the lower part of C-3 or at the intervertebral disk between C-3 and C-4. The thyroid cartilage is below the hyoid bone at the level of C-4 to C-5 and can be easily palpated, particularly at the prominent Adam's apple. The first cricoid ring is at the level of the C-6 vertebra and is the upper border of the trachea. Approximately 3 cm lateral to the first cricoid ring, the carotid tubercle can be palpated; this is the anterior tubercle of the transverse process of C-6, often called *Chassaignac's tubercle*. The carotid arteries are anterior to the transverse processes and can be palpated easily. They should be examined separately, because the carotid reflex and a syncopal event could be triggered if they are palpated together.

The posterior landmarks of the cervical spine include the inion (external occipital protuberance) in the midline, which marks the center point of the superior nuchal line. This is felt as a transverse ridge extending out on both sides of the inion. The spinous process of C-2 can be palpated, particularly in slender female subjects with the neck held slightly in flexion. The spinous processes of C-3 to C-6 are difficult to palpate, but the spinous process of C-7 (vertebra prominens) is readily palpable low in the neck. Provided the muscles are completely relaxed, the zygapophyseal joints can be palpated as small rounded domes deep in the transverse muscle and approximately 2.5 cm lateral to the spinous process. Each can be identified fairly accurately by remembering that the joint between C-3 and C-4 is at the level of the hyoid bone, the joint between C-4 and C-5 is at the level of the upper edge of the thyroid cartilage, the joint between C-5 and C-6 is at the level of the lower part of the thyroid cartilage, and the joint between C-6 and C-7 is at the level of the cricoid ring. Trauma, infection, malignancy, and osteoarthritis can all produce exquisite tenderness and pain on palpation of these joints. In general, if deep tissue examination is not possible, the examiner must make note as to whether the tenderness is occurring in the midline, often indicating a structural spinal problem, or in the paraspinous soft tissues.

Soft tissue examination is divided into anterior and posterior areas. The anterior neck, bordered laterally by the sternocleidomastoid muscles, superiorly by the mandible, and inferiorly by the suprasternal notch, represents an inverted triangle. The posterior neck includes the remainder of the neck. Again, the soft tissue examination is easier in a relaxed, supine patient.

The thyroid gland, an H-shaped structure, can be palpated in the midline below the thyroid cartilage. Diffuse enlargement, nodules, cysts, tenderness, or pain can be revealed. The sternocleidomastoid muscle is examined by asking the patient to turn the head to the opposite side; this muscle should be examined from origin to insertion. Palpation of the medial border for lymphadenopathy is necessary; if nodes are enlarged and tender, they suggest infection or metastatic disease related to the head and neck.

Examination of the posterior neck is best done with the patient in the sitting position, from the top downward. The occipital arteries are palpable approximately 3 cm lateral to the midline and run near the greater occipital nerves. Palpation that elicits pain or tenderness is seen in the setting of occipital neuralgia. Examination of the origin, insertion, and course of the trapezius muscle, from the C-2 to T-1 spinous processes to the scapular spines, is necessary to evaluate neck pain secondary to muscle trauma. As with the lymph nodes in the anterior neck, another chain of nodes lies along the anterolateral border of the trapezius, and enlargement and tenderness of these suggest infection or metastatic disease.

Range of motion is assessed by having the patient voluntarily flex and extend the neck through all ranges of motion (Fig. 55-1). The normal patient should be able to touch his or her chin to the chest and look to the ceiling without difficulty. Lateral bending should proceed smoothly through 45 degrees, and on rotation the patient should be able to turn the head in line with the shoulder. The authors do not recommend testing passive range of motion, for fear of causing neurologic injury in the setting of spinal instability. The patient protects the neck through tonic contraction of the paravertebral muscles, and overcoming this could have devastating consequences. Strength may be evaluated by testing movements against resistance (Fig. 55-2).

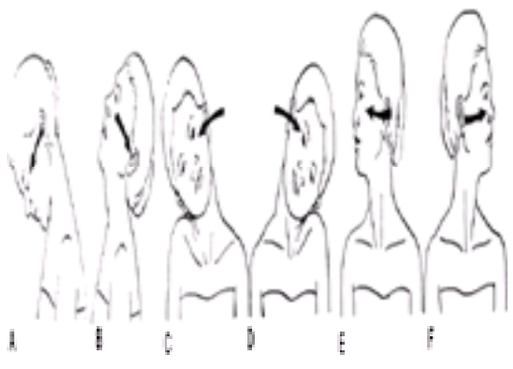

Figure 55-1. Active movement for testing the range of motion of cervical spine and neck muscles. **A:** Full flexion, which should permit touching the chin to the sternum. **B:** In maximum extension the occiput touches the spinous process of T-1. Lateral flexion in the absence of pathology permits the individual to flex 45 degrees to both the right **(C)** and left **(D)** sides. Right **(E)** and left **(F)** rotation. In normal individuals the chin should be in alignment with the shoulder.

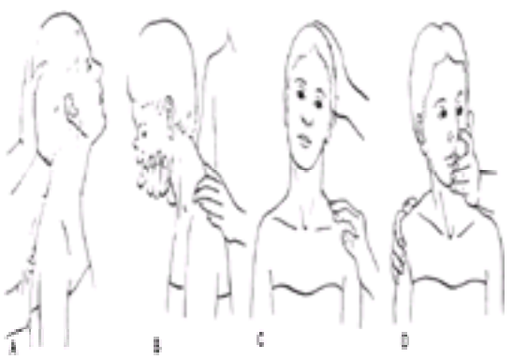

Figure 55-2. Method of testing muscles of the neck against resistance. **A:** Extension. **B:** Flexion. **C:** Technique for testing right lateral flexion against resistance; testing left lateral flexion is carried out by placing the left hand against the patient's head and by holding the shoulder with the right hand. **D:** Technique for testing rotation against resistance. To test right rotation, the examiner's hands are changed accordingly.

The neurologic examination is described in detail in Chapter 12. Muscle strength; sensory modalities including light touch, proprioception, and pinprick; and reflexes should be assessed in detail throughout the upper and lower extremities. Muscle, sensory, and reflex changes should be identified and correlated with the history, bony, and soft tissue portions of the examination to direct further diagnostic evaluation.

Special testing in the neck allows the identification of neurologic and mechanical abnormalities arising in the cervical spine. The distraction test is carried out by having the examiner stand behind the seated patient, lifting the head from the chin and occiput, and removing the weight of the head from the neck. Relief of symptoms during this test might point to foraminal encroachment on a nerve root as the etiology of the patient's neck pain. It also relieves pressure on the zygapophyseal joints. Spurling's maneuver (Fig. 55-3) is essentially a reverse of the distraction test and was classically described to assess nerve root compression or irritation. The head is tilted toward the painful side and pressure is applied to the top of the head. The radicular pain should be reproduced on such a maneuver (51). Valsalva's test is designed to increase intrathecal pressure and exacerbate compression within the cervical canal, either from tumor, infection, disk, or osteophytic change. The patient is asked to bear down as though having a bowel movement, and to describe any painful or sensory changes. Shoulder depression and abduction tests are designed to test nerve root compression and irritation by increasing and decreasing traction on the spinal nerve roots, respectively. Adson's test is used to assess vascular compromise in the arm secondary to subclavian impingement in thoracic outlet syndrome (Fig. 55-4). Here, the radial pulse is palpated and auscultation performed over the subclavian artery. The patient holds a deep breath with the neck extended and the chin turned toward the affected side to assess changes in the intensity of the radial pulse and to listen for a bruit over the subclavian artery (52). Other maneuvers to evaluate neurovascular compression are the costoclavicular (Fig. 55-5) and hyperabduction (52).

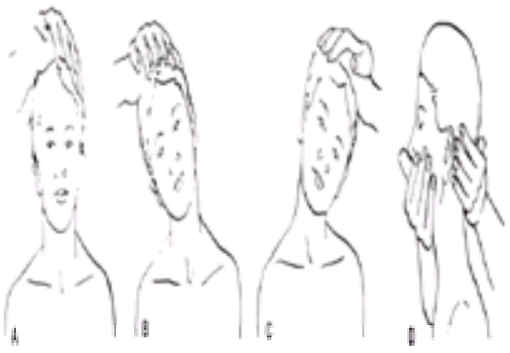

Figure 55-3. Spurling's test for determining the effect of compression of the cervical spine. **A:** The examiner first applies pressure directly downward, with gradual increase and maintenance of constant pressure for 30 to 60 seconds. The same procedure is repeated in right **(B)** and left **(C)** lateral flexion, which tends to close the intervertebral foramina on the side of the flexion even more than normal because of the pressure exerted, thus producing spontaneous pain or paresthesia or aggravation of the pain or paresthesia. **D:** Technique for applying upward traction; the pressure is gradually increased and held for 30 to 60 seconds. This opens the intervertebral foramina and decreases or eliminates pain from foraminal pressure on the cervical nerves.

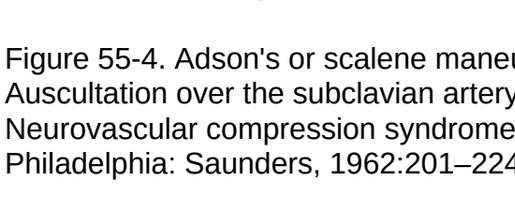

Figure 55-4. Adson's or scalene maneuver. This test is used in both the scalenus anticus syndrome and in patients with a cervical or abnormal thoracic rib. Auscultation over the subclavian artery being tested may reveal a bruit when the artery is partially compressed. (Modified from Allen EV, Barker NW, Hines EA Jr. Neurovascular compression syndromes of the thoracic outlet and shoulder girdle. In: Allen EV, Barker NW, Hines EA Jr, eds. *Peripheral vascular diseases*, 3rd ed. Philadelphia: Saunders, 1962:201–224.)

Figure 55-5. Costoclavicular maneuver. Auscultation over the subclavian artery, above or below the midportion of the clavicle, may reveal a systolic bruit as the artery is being compressed. The radial pulse and the bruit over the subclavian artery disappear when complete compression of the subclavian artery occurs. (Modified from Allen EV, Barker NW, Hines EA Jr. Neurovascular compression syndromes of the thoracic outlet and shoulder girdle. In: Allen EV, Barker NW, Hines EA Jr, eds. *Peripheral vascular diseases*, 3rd ed. Philadelphia: Saunders, 1962:201–224.)

Laboratory Evaluation

Leukocytosis is seen in the setting of infection and even some forms of malignancy, but rarely in mechanical neck pain. The erythrocyte sedimentation rate (ESR) is a more useful laboratory study in differentiating mechanical from nonmechanical and medical neck pain and measures the systemic response to injury. It is a general reflection of inflammation in the body and is usually normal in the setting of mechanical neck pain caused by osteoarthritis or whiplash. Hayes and Stinson (53) reported the normal ranges of ESR according to sex and age: Using the standard Westergren method, the upper limit of normal is 25 mm per hour for women and 15 mm per hour for men younger than 50 years of age, 30 mm per hour for women and 20 mm per hour for men older than 50 years, and can be more than 50 mm per hour over the age of 70 years. The trend in ESR over several weeks is more useful to follow than an absolute value from a single test. However, an ESR over 100 mm per hour usually signifies malignancy or infection. Its shortcoming as a test after surgery is that the ESR can remain elevated for up to 2 weeks (54) in the absence of a postoperative infection. Here, the C-reactive protein may be helpful, because it is an acute-phase reactant that returns to normal shortly after surgery in the absence of infection (54,55).

Blood chemistry tests that are useful in the setting of neck pain include serum calcium and phosphorus. Malignancy is associated with hypercalcemia, whereas calcium levels are normal in the setting of osteoarthritis and most mechanical causes of neck pain. Serum alkaline phosphatase is produced by osteoblasts, and elevations are seen in metastatic spine tumors and Paget's disease of bone.

Radiographic Studies

The clinician's armamentarium of diagnostic radiographic studies is vast and includes plain films, myelography, computed tomography (CT), and magnetic resonance imaging (MRI) (see Chapter 14). A basic description of the indications for each and their strengths and weaknesses in specific diagnoses is presented in this chapter. The clinician must select these studies carefully, balancing the demands of a litigious society with the financial limitations faced in the health care climate, to efficiently and effectively arrive at a diagnosis. Advances in this technology in the 1990s have revolutionized the diagnosis and therapy of neck pain.

Controversy exists surrounding the utility of plain radiography as the initial diagnostic study for neck pain. The lateral, anteroposterior, open mouth odontoid, oblique, and flexion-extension plain films can show the presence of fracture, subluxation, osteophytic changes, ligamentous calcification, and soft tissue swelling or bony destruction in the setting of infectious or neoplastic disease. However, several studies have shown that degenerative changes have a linear relationship with age, and their nearly ubiquitous presence in elderly patients is not significantly different in severity between asymptomatic and symptomatic individuals (56,57). These results are called into question by more recent data by Marchiori and colleagues (58), who found that increasing levels of spinal degeneration are related to increasing chronicity of patient complaints. Although radiography is readily available at a reasonable cost, debate continues over their usefulness in mechanical spinal pain (50).

The most sensitive imaging technique in cases of suspicion of neoplastic or infectious disease is the radionuclide bone scan. Technetium 99m is the radiopharmaceutical used to image osteoblastic activity and provides a general measure of bony inflammatory disease. Its limitation is in its low resolution and lower specificity than other imaging modalities in the cervical spine. Furthermore, a false-positive rate as high as 30% has been found in elderly patients in whom the diagnoses of infection or metastasis are frequently sought (59).

Myelography provides anatomic detail in the relationship between neural and bony structures. A nonionic water-based contrast agent is instilled into the subarachnoid space either through a C-1 to C-2 or lumbar puncture, and radiographs are obtained in the anteroposterior, lateral, and oblique planes. A defect in the dye column points to the area of neural compression; given its invasive nature and common complication of postprocedural headache [seen in up to 68% of postmyelography patients (5)], myelography is usually reserved for preoperative planning or in cases in which MRI scanning is contraindicated (see following discussion).

CT can be used as an adjunct to myelography, or it can be used alone to delineate in detail the bony anatomy of the cervical spine. When combined with myelography after the installation of intrathecal contrast, precise anatomic detail relating bony anatomy to neural elements is obtained. In the setting of trauma, small fractures not evident on plain radiographs can be seen on CT, and degenerative facet enlargement, canal stenosis, and early bony destruction by infection or tumor are readily evident, with spatial relation to the nerve roots and spinal cord.

Although bony detail is the main advantage of CT scanning, its major disadvantage is in the relative lack of soft tissue resolution. This deficiency is overcome in MRI scanning. Here, small differences in tissue density are formed into a computer-generated image with unsurpassed anatomic detail. It is the diagnostic method of choice in the setting of disk herniations, tumors (intramedullary and extramedullary, extradural), infection, intrinsic cord pathology (infarction, atrophy, multiple sclerosis), and osteophytic narrowing of the spinal canal. Recent advances in MRI technology have allowed the detection of nerve roots involved in radiculopathy (60). Patients harboring pacemakers and ferromagnetic aneurysm clips are precluded from undergoing MRI scans, and it is here that myelography may be a useful substitute. However, as with plain radiography, studies have shown that asymptomatic subjects commonly display the same imaging findings on MRI as those who are symptomatic with neck pain (61,62). Thus, although it provides the most sensitive detection of bony and soft tissue abnormalities, MRI scanning's high cost and lack of specificity necessitate caution on the part of the practitioner selecting it as a diagnostic study. As with myelography and CT scanning, it must be sought only in the confirmation of a clinical diagnosis suspected on historical and physical examination findings.

Finally, provocation diskography, although arguably highly sensitive and specific in the lumbar spine, has limited utility in the cervical region. Injection of the lumbar disk with contrast material should reproduce the patient's pain complaint in the setting of lumbar diskogenic pain. This should be relieved on injection with local anesthetic. A false-positive rate up to 40% has been documented in the cervical spine by Bogduk and colleagues in patients undergoing both diskography and zygapophyseal joint blocks, and numerous authors have questioned its validity as a diagnostic test (5,34).

SPECIFIC DISEASES AND DIFFERENTIAL DIAGNOSIS

This section is devoted to introducing specific diseases and syndromes that involve neck pain as their predominant symptom. It is divided into six portions, to cover mechanical pain, pain associated with inflammatory disease, neoplastic pain, pain of infectious etiology, and finally, miscellaneous diagnoses. Each portion should serve as an introductory guide to the most common disease states that affect the neck, as seen in a general clinical practice. Reviews are referenced for each disease state being discussed, to provide an entry point for further investigation by the reader.

Mechanical Pain

Included in this section are the most common pathologic entities that involve the cervical spine and produce neck pain: cervical spondylosis, fractures, subluxations, dislocations, disk herniations, neck strain, whiplash injury, in addition to congenital abnormalities that predispose the patient to neck pain (Klippel-Feil syndrome, os

odontoideum, basilar impression), and finally, rheumatologic disorders (including RA, psoriatic arthritis, and ankylosing spondylitis).

Cervical spondylosis represents a common cause of neck pain and is defined by the development of osteophytic or degenerative change in the disks of the cervical spine, as seen on radiologic studies and cadaveric specimens. It is a nearly ubiquitous disorder of the adult population that increases in severity with age and is probably related to the mobility of the cervical spine (5) and an accumulation of microtrauma. As discussed previously, these changes do not necessarily correlate with findings on plain films or MRI scans (56,57,61,62). The patient is usually older than 40 years of age, and the chief complaints are headache and occasionally neck ache and can be accompanied by radiculopathic or myelopathic symptoms and signs or both. Plain radiography is the diagnostic tool of choice, whereas more detailed images, such as MRI scans, are reserved for those patients with accompanying neurologic deficits, or for those in whom the pain is medically intractable. Treatment usually involves nonsteroidal antiinflammatory drugs (NSAIDs) and physiotherapy, with the use of a neck brace for acute exacerbations. Occasionally, facet joint injections may be helpful (33), but no clinical trials in the setting of spondylosis have been done. Surgery should be considered in those patients with intractable pain or a neurologic deficit.

Acute herniated nucleus pulposus (HNP) or herniated disk of the cervical spine is a more common source of brachialgia than neck pain, but the patient describes pain that seems to begin in the neck and radiates down the arm to the hand. This disorder was first characterized in the early 1940s, but is still incompletely understood (51,63,64). The cervical nerve roots are protected from lateral disk herniation by the laterally placed uncovertebral joints. By the age of 40, Bland maintains that the nucleus pulposus no longer exists because of desiccation and transformation to fibrocartilage (41,42). In fact, he goes so far as to say that “after age 40 years, it is impossible to clinically herniate the nucleus pulposus, as none exists at this point” (41,42). Thus, cervical HNP usually occurs posterolaterally, around the fourth decade of life, and usually gives rise to radiculopathic complaints, affecting the nerve root numbered below the given disk level (e.g., a C-6 to C-7 disk would give rise to a C-7 radiculopathy). The most common cervical HNP occurs at C-6 to C-7, approximately 50% of the time (65), followed by C-5 to C-6 in approximately 30% of cases.

The disk is innervated by the sinuvertebral nerve, which also supplies the periosteum of the surrounding vertebra, dura, and veins (31). Historically, the arm pain exceeds the neck pain and can be exacerbated by tilting the neck and head to the affected side, with axial loading (Spurling's sign) (51). Electromyography is useful in delineating radiculopathy, whereas plain radiography is of little clinical utility. The best radiologic studies in the detection of cervical HNP are CT myelography and conventional MRI. MR neurography may be useful in defining the affected nerve root in multilevel cervical spine disease when the clinical symptoms and findings do not localize the level (66). Most patients with acute HNP respond well to medical management, which includes collar immobilization, NSAIDs, and occasionally traction. In those patients whose pain or radicular complaint is refractory to medical therapy, anterior cervical diskectomy with or without fusion (67), and posterior foraminotomy with or without disk removal are both highly effective (22,68).

Neck strain, neck sprain, and *whiplash* are terms often used interchangeably, but should be considered along a continuum of severity (4). The most common form of neck injury and neck pain, neck strain, refers to nonradiating pain associated with a repetitive mechanical stress or a prolonged malposition of the cervical spine (5). The pathogenesis of the disorder is presumably related to muscular, ligamentous, joint capsular, or disk annular damage (44), and the muscular contraction and tension that are frequent adjuncts to this injury can produce a cycle of pain and spasm that prolongs and exacerbates symptoms produced from relatively insignificant events (5). Neck pain is often accompanied by occipital headache, exacerbated by movement, and eased with immobilization. Physical signs include a decreased range of motion, localized paraspinous muscle tenderness, and occasionally torticollis. Plain radiography may reveal a loss of the normal cervical lordosis caused by tonic muscular contraction and should be obtained to rule out fracture or congenital abnormality in the differential diagnosis. Prognosis for complete resolution of the pain is excellent. Most cases can be successfully treated with immobilization in a soft collar, NSAIDs, and physiotherapy.

Neck sprain can be considered as a traumatic neck injury of severity intermediate between whiplash (see following discussion) and neck strain. Here, minor ligamentous, capsular, or tendinous tears as well as muscular tears, contusions, or both result in symptoms, signs, and radiologic studies similar to those seen in neck strain, and treatment is much the same. Bland emphasizes the need for patient education, because prognosis in this disorder is highly influenced by extraanatomic factors. He associates four factors associated with increased duration of symptoms (greater than 9 months), including strong emotional factors, extensive medical history, prolonged and frequent treatment, and litigation (4).

In some instances the patient sustains a disruption of the supporting spinal ligamentous apparatus, facet joint capsules, and disk secondary to a hyperflexion or hyperextension injury (Fig. 55-6). The patient experiences neck pain without or with neurologic deficit. Imaging studies do not show evidence of a fracture of the vertebra, and there are no jumped facets. In the case of a hyperflexion sprain there is rupture of the posterior ligaments and joint capsules. Plain cervical spine radiography shows evidence of a kyphotic angulation with separation of the spinous processes without jumped facets. Hyperextension sprains may also be diagnosed on plain cervical spine radiography. There is disk space widening anteriorly with tearing of the anterior longitudinal ligament. There may be some retrolisthesis of the cephalad-vertebral body. An associated herniated disk should be ruled out in both conditions. MRI should be obtained to help define the extent of injury and is useful in planning treatment. We favor early operative stabilization, as it has been the authors' experience that prolonged immobilization even in a halo vest may not heal these injuries.

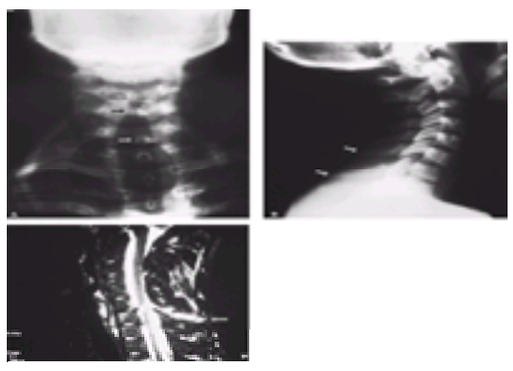

Figure 55-6. Hyperflexion sprain. **A:** Cervical spine radiograph, anteroposterior view, evidences widening between the spinous processes of C-6 and C-7 (*arrows*). **B:** Cervical spine radiograph, lateral view, evidences widening between the spinous processes of C-6 and C-7 (*arrows*), slight anterolisthesis of C-6 on C-7 with kyphotic angulation of C-6 relative to C-7. **C:** Magnetic resonance imaging, sagittal short-time inversion recovery images, evidences high signal of C-6 to C-7 interspinous process ligament (*arrow*) secondary to disruption of the interspinous process ligament and ventral dural indentation at C-6 to C-7 and C-7 to T-1 caused by disk protrusion, epidural hemorrhage, or both. There is increased signal in the spinal cord at the C-6 to C-7 consistent with a spinal cord contusion.

Whiplash injury, introduced in the epidemiology section, most commonly describes a hyperextension injury of the neck, but can also be seen with sudden movement of the cervical spine in hyperflexion and lateral bending (14). It is usually related to a sudden acceleration or deceleration motion that causes bony, ligamentous, muscular, or tendinous injury (Fig. 55-7). Compelling evidence exists for involvement of the zygapophyseal joints in the pathogenesis of whiplash-associated neck pain, from diagnostic studies, surgical intraoperative observations, postmortem examinations, and therapeutic interventions (69). Lord and colleagues (37) found cervical zygapophyseal joint pain in approximately 60% of patients with chronic pain after whiplash injury, using placebo-controlled diagnostic blocks of the joint capsules. Symptoms are often delayed for up to 24 hours after the time of injury and include neck pain, headache, dysphagia, paresthesia, weakness, visual and auditory symptoms, and dizziness, in descending order (70). Neurologic examination is usually normal, but neck range of motion is most commonly limited. Two studies (71,72), however, add to the ongoing controversy surrounding the whiplash injury syndrome. Schrader and colleagues (71) retrospectively studied the natural history of head and neck symptoms 1 to 3 years after rear-end collisions, outside the medicolegal context. They reported that no one had disability or persistent symptoms, and that there was no relation between the severity of the impact and the degree of pain. In attempting to determine whether“‘whiplash injuries' occur in low-speed rear impacts,” Castro and colleagues (72) subjected 19 volunteers to rear-end collisions. They concluded that the“limit of harmlessness” is between a velocity change of 10 to 15 km per hour (6.25 to 9.38 miles per hour) with regard to stresses arising from rear-end impacts.

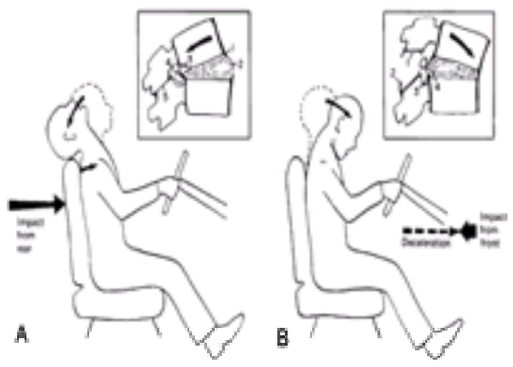

Figure 55-7. Schematic depiction of the mechanism of injury sustained from vehicular accidents. **A:** When the car is at a standstill the impact from the rear causes an acute hyperextension movement of the neck from acceleration. *Insert*: Sites of possible injuries: **1:** Anterior longitudinal tear. **2:** Anterior herniation of intervertebral disk. **3:** Chip fracture of the vertebral body. **4:** Joint encroachment into the intervertebral foramen. **5:** Acute facet impingement. **B:** Hyperflexion is caused by a deceleration injury from a front-end collision, which causes the body to stop suddenly but the head to continue to move forward because of momentum. *Insert*: Possible injuries. **1:** Acute synovitis caused by subluxation of the articular facets. **2:** Capsule tear articulation. **3:** Posterior nuclear herniation. **4:** Posterior longitudinal ligamentous tear. All these can cause injury to the nerve root. The flexion phase of injury can be isolated, can follow as a rebound or an extension injury, or can be followed by a hyperextension phase. (Modified from Cailliet R. *Neck and arm pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

Whiplash injuries have been classified according to their severity in the Quebec Task Force on Whiplash Associated Disorders monograph (70). Briefly, whiplash injury is graded between I and IV according to association of neck pain (grade I) with musculoskeletal (grade II), neurologic (grade III), or bony injury (grade IV), and classified based on duration of symptoms into acute (4 to 21 days), subacute (22 to 180 days), and chronic (greater than 180 days). The Quebec Task Force recommends plain radiography in all patients with grades II, III, and IV whiplash, and CT and MRI scanning are warranted in patients with neurologic or bony injury.

As with neck strain and sprain, most whiplash injuries respond well to medical treatment involving temporary immobilization to allow healing of damaged tissues, coupled with NSAIDs. Prolonged immobilization, which would weaken cervical musculature, is not recommended (70), and as with neck strain and sprain, physiotherapy programs coupled with the practitioner's attention to emotional and psychological factors influencing their pain are critical in the management of whiplash pain.

In some cases of pain refractory to medical therapy, a more invasive interventional approach may be warranted. Lord and colleagues (73) demonstrated the long-lasting efficacy of percutaneous radiofrequency neurotomy in the treatment of chronic cervical zygapophyseal joint pain after whiplash injury. Given the fact that over one-half of all whiplash injuries involve these joints, such treatment may have a significant effect on those patients suffering chronic pain.

Cervical Spine Fractures, Subluxations, and Dislocations

A detailed discussion of cervical spine fractures, subluxations, and dislocations is beyond the scope of this chapter. Trauma is the most common cause, but other causes, such as infection, primary and metastatic cancers, congenital abnormalities, and amyloidosis associated with long-term hemodialysis, are underlying conditions that can cause fractures or olisthesis. The reader is referred to Table 55-2 for a list of the many types of fractures and luxations that occur in the cervical spine.

TABLE 55-2. Traumatic injuries of the cervical spine

Neck pain is the primary complaint offered by the patient without or with neurologic deficit. After trauma in which the patient complains of neck pain, a cervical spine injury must be ruled out with appropriate imaging studies. Patients who have persistent neck pain after imaging studies that have failed to show evidence of a cervical spine injury should have repeat imaging studies and a review of the initial studies to rule out a missed fracture or delayed instability of the cervical spine.

Rheumatologic Disease

Inflammatory joint disease, when it involves the cervical spine, is a common source of neck pain. In the United States, RA is said to occur with an incidence approximating 3% (74), and although the majority of these patients develop joint pain, swelling, and tenderness affecting the joints of the extremities, the most commonly affected component of the axial skeleton is the cervical spine (5). Patients with cervical spine involvement are thought to generally have more severe rheumatoid disease and their prognosis is generally worse (4). Although RA is covered in detail in Chapter 27, its involvement in the cervical spine is discussed here.

Three main types of cervical spine involvement are recognized in RA: atlantoaxial subluxation (usually anterior displacement of C-1 on C-2), cranial settling (vertical migration of the odontoid), and subaxial subluxation (between C-3 and C-7). The presumed autoimmune inflammatory changes that affect the synovial joints and bursae or the appendicular skeleton target the structures lined with synovial membrane in the cervical spine. These include the atlantoaxial, zygapophyseal, and uncovertebral joints, as well as the disks, ligaments, and bursae in the neck. Chronic inflammatory damage of these structures results in laxity and subsequently instability, which threaten the lower brainstem, cervical spinal cord, and nerve roots. Inflammatory pannus behind the odontoid can cause lethal upper cervical cord compression, and vertebral artery compression as well as hydrocephalus and syringomyelia are other well-recognized complications of spinal deformity in RA.

Patients with cervical RA develop neck pain exacerbated by movement, with atlantoaxial disease producing pain in the upper cervical spine, and subaxial involvement producing pain in the lower neck and clavicular areas. Neurologic involvement is seen in more advanced cases of spinal cord or nerve root compromise related to deformity and soft tissue hypertrophy. Plain radiography is useful in showing structural abnormalities, and dynamic studies including flexion-extension, oblique, and open-mouth frontal projections should be obtained. Anterior subluxation at the atlantoaxial joint is the most common form of cervical spine derangement (5), followed by subaxial subluxation, lateral subluxation, cranial settling (vertical subluxation), and posterior subluxation. Therapy for cervical spine–associated RA involves patient education, collar or brace immobilization, particularly in cases of instability, physiotherapy, and medical management with NSAIDs for symptomatic relief, remititive agents such as hydroxychloroquine, d-penicillamine, and methotrexate, and systemic corticosteroids. Although surgery is reserved for patients with intractable pain and threatened or progressive neurologic damage, it can often be overlooked because of the slowly progressive course of cervical RA, the patient's debility caused by systemic RA, the poor correlation of radiologic with physical findings, and the often stoic personality of the RA patient (75). Surgery typically involves traction initially, for realignment, followed by fusion with or without decompression, depending on the extent of neural compromise.

Psoriatic arthritis is a less common form of rheumatologic joint disease, but over one-half of all patients with psoriatic arthritis develop neck pain (76) (see Chapter 27). The majority of these patients present with psoriasis before arthritis, making the diagnosis straightforward. The disease has two types of clinical manifestations in

the cervical spine: (a) disease characterized by erosions and subluxations resembling RA, and (b) disease involving ankylosis and calcification seen in ankylosing spondylitis.

Ankylosing spondylitis is a chronic inflammatory arthritis characterized by enthesopathy, defined as inflammation at the site of ligamentous insertion onto bone, which leads to new bone formation and vertebral fusion. Bony and cartilaginous inflammation causes granulation at these sites followed by ankylosis (joint immobilization) and ossification. Immobilization leads to osteoporosis and risk of fracture.

There is a strong genetic basis for this disease, as 95% of patients have HLA-B27 major histocompatibility complex, a cell surface marker associated with control of the immune response. However, the mechanism by which HLA-B27 antigen results in ankylosing spondylitis is unclear but most likely related to a genetically determined host response to an environmental factor (possibly intestinal flora [77]) in genetically susceptible individuals (5). Involvement of the lumbosacral spine is more common than the cervical spine, and neck pain appears late in the course of the disease. The classic ankylosing spondylitis patient with neck pain is a man in his 30s or 40s with neck stiffness and generalized pain. The posture is stooped because fusion of the cervical spine causes the head to protrude forward, making it difficult to look straight ahead. A resultant focal kyphosis occurs at the cervicothoracic junction (78), which is also the most frequent site of fracture (79) of the brittle, osteoporotic bone. Radiographic evaluation can reveal the characteristic *bamboo spine* in which syndesmophytes (calcification of the disk annulus and anterior and posterior longitudinal ligaments) encase the spine. Laboratory results show an elevated ESR and an absence of rheumatoid factor and antinuclear antibody. Treatment involves patient education, pain control with antiinflammatory medications, physiotherapy, and spinal stabilization and surgical or orthotic correction or both of spinal deformity when necessary.

Tumors

Mechanical neck pain and rheumatologic diseases are much more common sources of neck pain than neoplastic involvement, but overlooking this etiology for severe neck pain can lead to unnecessary morbidity and mortality. Tumors affecting the spine can be divided into metastatic lesions, primary bone tumors, and, less commonly, tumors associated with the nervous system. Neck pain is usually an early symptom of disease, worsening at night and with recumbency, and frequently initiated by a trivial traumatic injury.

Metastases to the cervical spine dramatically outnumber primary bone tumors, and increase in prevalence with age, although the cervical spine is less commonly affected than other areas of the axial skeleton. Each primary tumor has a different propensity to metastasize to the cervical spine, but the most frequently occurring are breast cancer in women and prostate cancer in men, with an incidence as high as 85% (80). Pulmonary, thyroid, renal, and rectal cancers are the second most common, nearing 60% incidence (80). The pathogenesis of vertebral involvement in these forms of cancer is related to the proximity of Batson's venous plexus to the spine and the primary organs involved with the cancer. This valveless venous system is thought to allow embolic cancer cells to metastasize to adjacent regions of the spine when pressure in the vena caval system increases, thereby creating back flow through these paraspinous venous channels.

Patients typically present with neck pain and occasionally torticollis, with tenderness on palpation. When metastasis involves the upper cervical spine (atlantoaxial region), pain predominates, because the cancer usually involves the anterior elements of the spine and neurologic compromise is rare given the wider capacity of the spinal canal at that level. Neural impingement is more likely in the subaxial spine, and pain and tenderness are proportional to destructive instability. A thorough clinical and radiographic examination, including plain films, bone scans, CT, myelography, and MRI scanning may be necessary to define neoplastic involvement. Plain films may be inadequate because 30% to 50% of bone density must be lost before becoming radiologically evident (81). Radionuclide imaging is the diagnostic study of choice, although it is nonspecific for inflammation and also positive in one-third of older patients who are at highest risk for metastasis but also have a high incidence of osteoarthritis (59,82). CT scanning is usually reserved for those patients in whom a positive bone scan is not confirmed by plain radiographic abnormalities, or in patients requiring preoperative planning. Myelography should be reserved for patients with neurologic compromise. MRI, although less accessible and more expensive, is the most sensitive and specific of the diagnostic studies in its ability to define the extent of the lesion, associated spinal involvement, bony infiltration in cases in which bone scans are nondiagnostic, and distinguish osteoporotic fracture from metastatic pathologic fracture. Indeed, in an age of ever-increasing diagnostic accuracy, the most common error in misdiagnosis of metastatic disease is inadequate diagnostic workup (4,43). Medical (hormonal), radiation, and surgical therapies are mostly palliative and are used to prevent catastrophic neurologic damage and to control pain.

Primary bone tumors must not be overlooked, particularly in the patient less than 50 years of age in whom metastatic disease is less likely. Malignant processes in this category include multiple myeloma, chondrosarcoma, chordoma, and lymphoma. Multiple myeloma is the most common primary bone malignancy in adults and represents a tumor of plasma cells, which reside in the bone marrow of the vertebral bodies. Bone pain and pathologic fractures are seen, accompanied by increases in serum calcium. Pain is the most common presenting complaint, although the cervical spine is the least commonly affected portion of the spine. In addition to hypercalcemia, multiple myeloma patients have elevations of Bence-Jones protein (excess immunoglobulin light chain) in the urine. Radiographic investigations are the same for metastatic disease with the exception of bone scans, which have no utility in multiple myeloma because of an absence of osteoblastic activity. Treatment involves chemotherapy with melphalan and prednisone, and bisphosphonates to control hypercalcemia by inhibition of osteoclastic activity. Pain management routinely uses NSAIDs and opiates.

Benign tumors, such as osteoblastoma, aneurysmal bone cyst, giant cell tumors, and osteoid osteoma are rare bony tumors and an even rarer cause of neck pain. Pain is usually insidious in onset and develops over months to years. The degree of neurologic involvement varies with the site of vertebral involvement, and most patients have a benign course. Although diagnostic studies such as CT and MRI are useful in diagnosis, tissue diagnosis and surgical extirpation remain the mainstays of diagnosis and treatment.

Infection

The rarity of tumor-associated neck pain is mirrored in neck pain of infectious etiology: Although it is an uncommon source of neck pain, its misdiagnosis can lead to catastrophic consequences, and the clinician must maintain a high index of suspicion to establish early diagnosis and initiate effective treatment. Vertebral osteomyelitis, diskitis, extradural abscess, and meningitis make up the vast majority of infectious diseases affecting the cervical spine.

Pyogenic osteomyelitis of the cervical spine is uncommon, affecting 1 in 250,000 in the general population, with an increased incidence among intravenous drug users and immunocompromised patients (83). Hematogenous spread via Batson's paravertebral venous plexus or nutrient arteries to the vertebral body are the common routes of infection; contiguous spread from soft tissue, lung, dental, and endocarditic infections is also seen. Local pain at the site of infection is the most common presenting complaint, usually insidious in onset and nonmechanical in nature. Local tenderness and decreased range of motion are found on examination. Neurologic deficits may be seen when the osteomyelitis is accompanied by a spinal epidural abscess (84). The ESR and blood cultures are the two most useful laboratory tests to obtain. The ESR, although nonspecific, can be used to monitor response to treatment, and blood cultures may be abnormal in up to 50% of patients with acute osteomyelitis, thereby negating the need for bone biopsy (5). As with metastatic disease, the bone scan remains the screening radiographic test of choice in the setting of infection, as it can demonstrate infection within the first few days, whereas plain radiography demonstrates changes approximately 1 month after the onset of infection (4,85). MRI carries the greatest sensitivity and specificity of the radiologic tests and can be used to assess adjacent soft tissue and disk space involvement, as well as neurovascular compromise.

As with tumors, histologic diagnosis is most important in predicting course and directing treatment. CT-guided biopsy of the spine is the usual diagnostic method when blood cultures fail to show an infective agent, but this is not always effective (Ghatan, Goodkin, and colleagues, *unpublished results*), and open biopsy may be necessary. Certainly, when bony destruction leads to spinal deformity or neurologic compromise is present necessitating surgical involvement, antibiotics should be withheld until definitive cultures have been taken. The organism most commonly seen in pyogenic osteomyelitis remains *Staphylococcus aureus*, although gram-negative organisms such as *Escherichia coli* and other Enterobacteriaceae are seen in osteomyelitis associated with urinary tract infections, and *Pseudomonas* predominates in intravenous drug use–associated disease (86). Treatment involves broad-spectrum antibiotics that include gram-positive, gram-negative, and anaerobic organisms initially, that are later tailored to culture results. Orthotic immobilization, NSAIDs, and opioid analgesics are the most effective means of pain management. Surgical decompression and stabilization are necessary in patients who have neurologic compromise and advanced bony destruction with deformity.

Infective diskitis can occasionally accompany vertebral osteomyelitis, but on its own it is a rare cause of spinal infection. Insidious and often long-standing neck pain is the common presenting complaint, and in the absence of osteomyelitis, the diagnosis must be considered in the patient who has had recent iatrogenic exposure, either through disk surgery or diagnostic diskography.

Spinal epidural abscess must be quickly recognized and effectively treated given its rapid and morbid course, whether it accompanies or is separate from vertebral osteomyelitis. Patients at risk are the immunocompromised, diabetics, alcoholics, and intravenous drug users. *S. aureus* is the most common infective organism. The

patient typically presents with neck pain that can rapidly progress to radicular symptoms and quadriplegia if untreated (87). The mechanism for neurologic damage is either mass effect from the abscess or thrombotic ischemia within subarachnoid vessels. Treatment involves surgical evacuation and appropriate antibiotic management.

Acute neck pain accompanied by generalized stiffness (meningismus), fever, and mental status changes are pathognomonic for meningitis. Viral or aseptic meningitis rarely has a defined etiology, but is occasionally caused by an enterovirus, and most commonly has a self-limited course. The more common bacterial meningitis is caused by *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenza* in more than 80% of normal adult cases (88), whereas tuberculous, fungal, cryptococcal, and protozoan (toxoplasma) meningitides are seen in the immunocompromised patient. Prognosis is dependent on the general health and immune status of the patient, the infective organism, and the speed with which antimicrobial therapy is initiated.

Extracranial internal carotid artery dissection usually presents with headache and facial pain, neck pain, or both and is a recognized cause of stroke, especially in young persons (89). Unilateral, severe persistent neck pain of sudden onset may be the only symptom of extracranial internal carotid artery dissection (89,90). Patients may also present with a painful Horner's syndrome, pulsatile tinnitus, amaurosis fugax, and cerebral infarction without pain. There may be a history of minor trauma occurring a few hours to days preceding the onset of symptoms. Useful diagnostic studies include carotid duplex, transcranial Doppler, MRI, magnetic resonance angiography, CT angiography, and cerebral angiography. Treatment involves anticoagulation, starting with heparin.

Spontaneous cervical epidural hematoma presents with acute neck pain that may be accompanied by intrascapular pain or radiation of pain to the shoulders or upper extremities. Within hours the patient manifests neurologic symptoms, signs, or both. The patient may give a history of minor antecedent trauma or manipulation (91). One patient gave a history of a“bearlike hug” after which the patient developed acute excruciating neck pain. The patient was seen an emergency room and sent home with analgesic medication, only to return the following day with progressive neurologic deficit (personal case). MRI of the cervical spine and in some instances a CT of the cervical spine are diagnostic in most cases. Urgent neurosurgical intervention is usually performed (92,93), although in some cases patients have been treated without surgical intervention with resolution of the epidural hematoma and improvement in their neurologic deficits (94,95 and 96).

Postoperative Neck Pain

Postoperative neck pain is expected and usually subsides within a few days to a week. Prolong neck pain should alert the physician to possible complications. When seen after spinal surgery, it may be indicative of infection, spinal instability, postlaminectomy kyphosis, bone graft fusion failure or pseudoarthrosis, or may be just failure to relieve the patient's preoperative neck pain. In the latter situation the surgeon should consider whether the surgery accomplished its goal or whether further surgery may be warranted to further decompress the spinal canal or foramen or to remove, for example, a retained or missed extruded disk fragment.

Neck positioning and tracheal tube irritation during surgery can cause postoperative neck pain. Singer (97) reported on neck complaints after tonsillectomy or adenoidectomy. The differential diagnosis includes muscle spasm, cervical adenitis, retropharyngeal abscess, parapharyngeal abscess, peritonsillar abscess, cervical osteomyelitis, bacterial meningitis, and atlantoaxial subluxation. In the latter condition torticollis is present and may be present in cases of muscle spasm, retropharyngeal abscess, parapharyngeal abscess, or peritonsillar abscess. Evaluation includes physical examination, cervical radiographs, CT, MRI, or both CT and MRI, and, in some circumstances, radioisotope-imaging studies. Obviously, treatment is dependent on the diagnosis. Subarachnoid hemorrhage secondary to a ruptured cerebral artery aneurysm has been reported to present as postoperative neck pain (98).

“An unusual cause of ‘pain in the neck’” after flexible sigmoidoscopy and neodymium:yttrium-aluminum-garnet laser treatment for a sessile tubulovillous adenoma of the rectum was reported by Manjunath and Trash (99). A 76-year-old woman developed pain in her throat and neck after this procedure. She had diffuse swelling of her neck with crepitus. Radiographic studies evidence retropneumoperitoneum, pneumomediastinum, and surgical emphysema. The patient had sustained a perforation of the rectum at the time of the procedure.

Hosono and colleagues (100), in a retrospective study of surgery for cervical spondylotic myelopathy, reported a concerning incidence of postoperative neck and shoulder pain, and shoulder muscle spasms, 26% and 29%, and 42%, respectively, in patients who had undergone laminoplasty. The nuchal pain developed an average of 5.5 months postoperatively and decreased in the majority of patients within 1.0 to 1.5 years, although in four patients the pain persisted for more than 2 years. Shoulder pain developed an average of 1.5 years postoperatively and usually resolved within 1 year, although it persisted for more than 2 years in four patients. The most common postoperative axial symptom was shoulder muscle spasm. It presented an average of 6.4 months postoperatively and persisted for more than 1 year in 25 patients and more than 2 years in 10 of 30 patients who complained of postoperative muscle spasms.

Dysesthetic neck pain with syncope after surgery for neck tumors is a relatively recently reported syndrome (101). The patients complained of a burning or throbbing pain in the neck developing at varying times postoperatively up to 4 years later. This syndrome is distinguished from glossopharyngeal neuralgia without or with syncope. Spinal cord stimulation was reported to be successful in the treatment of two of the four patients.

Miscellaneous Diagnoses

This section covers several rare diagnoses of neck pain that deserve mention because of their difficulty in diagnosis as a source of chronic and refractory pain. Some studies have shed new light on their etiology and pathogenesis, making them more recognizable and perhaps more treatable.

The neck-tongue syndrome is characterized by pain in the neck and altered sensation in the ipsilateral half of the tongue, which is exacerbated by neck movements. Bogduk (29) has shown that the anatomic basis for the syndrome involves compression of the C-2 nerve root by subluxation of the lateral atlantoaxial joint. The afferent (proprioceptive) fibers of the lingual nerve travel via the hypoglossal nerve to the second cervical nerve root, and are compressed, resulting in a *proprioceptive* numbness, similar to that seen in Bell's palsy. Treatment involves a local nerve block at C-2, spinal manipulation, and orthotic immobilization. Atlantoaxial fusion has been effective in the treatment of medically refractory symptoms (102).

Eagle's syndrome, or neck pain related to an elongated styloid process, is characterized by recurrent throat pain, foreign body sensation, dysphagia, or facial pain, with occasional radiation to the ipsilateral ear (103). The clinical condition is exacerbated by palpation of the styloid process in the tonsillar fossa, and the etiology for the disorder is thought to be related to stretching of the fifth, seventh, ninth, and tenth cranial nerves in the peritonsillar tissue during fibrosis and scarring after tonsillectomy (104). Surgical treatment involving reduction of the elongated styloid process has been reported to be effective (105).

A variant of the syndrome is thought to be related to carotidynia, a painful nonspecific inflammatory disorder affecting the carotid artery or body. Symptoms include unilateral neck pain, and occasionally bilateral, radiating to the face, jaw ear, or scalp. There is tenderness over the cervical carotid artery, usually at the region of the carotid bifurcation. The pain may subside in a few hours or last days or even weeks. The pain may be acute and self-limiting. This acute form has been attributed to viral infections of the carotid sheath or other carotid lesions, such as carotid body tumors, arteritis, atheroma, occlusion, fibromuscular dysplasia, and aneurysms (90). Extracranial internal carotid artery dissection should be considered in the differential diagnosis (see previous discussion). A recurrent chronic syndrome is also described, and current opinion suggests that it is a migraine equivalent (4,90,103), triggered on examination by gentle palpation of the carotid body, and worsened by head and neck movement. It responds well to antimigraine medications (103). This condition must be differentiated from extracranial internal carotid artery dissection (see following discussion).

The hyoid bone syndrome is considered to be an insertional tendonitis or enthesopathy and is defined by pain and tenderness at the site of the greater cornu of the hyoid bone. Symptoms include discomfort, aching, or both on one or both sides of the neck at the level of the hyoid bone. Other complaints may be hoarseness or dysphagia on initiating swallowing. The syndrome is reported to have been first described in 1954. Medical management includes use of NSAIDs, injection of a local anesthetic, and corticosteroids. Surgical intervention with excision of the greater cornu of the hyoid bone has been reported to relieve the pain in 90% of patients operated who failed medical management (106).

The Barré-Liéou syndrome (posterior cervical sympathetic syndrome) involves a group of cranial symptoms including headache, vertigo, tinnitus, and ocular complaints that arise after whiplash injury (107). Variable and seemingly unrelated secondary symptoms such as restlessness, irritability, and lack of concentration develop. The syndrome is thought to arise because of injury to the cervical sympathetic chain, with resultant chronic neurovascular changes. Indeed, the wide-range subjective complaints in the absence of signs make the diagnosis extremely difficult, and the patients are often confused with malingerers (see Role of Psychosocial Factors in Neck Pain, later in this chapter). Radiographic characteristics, however, show cervical osteoarthritis; when the vertebral artery is compressed by osteophytes in the foramen transversarium, neck movement can exacerbate the symptoms, supporting a neurovascular etiology for the disorder (4). Cervical

sympathetic blocks are effective in the treatment of the disorder, and correction of mechanical compressive deformity has shown good results (107).

Calcific retropharyngeal tendonitis is an infrequently mentioned cause of neck pain. There is increasing anterior neck and throat pain aggravated by head and neck movement, and dysphagia. On examination there is neck tenderness and limited range of motion. Occasional mild fever, leukocytosis, and elevation of the ESR are present (108,109). It is diagnosed by findings of amorphous calcification anterior to C-1 to C-2 and asymmetric soft tissue swelling evidenced on CT, and diffuse swelling of the longus colli muscles causing a high signal in the prevertebral region on T2-weighted MRI (108,110). The symptoms usually subside in 1 to 2 weeks. Treatment is supportive. Retropharyngeal abscess and osteomyelitis and infectious spondylitis are among other conditions included in the differential diagnosis (43).

Other reported syndromes included in the differential diagnosis of cervical pain, albeit rare, are the thyroid cartilage syndrome and mastoid process syndrome in which there is“impressive tenderness” over the thyroid cartilage or mastoid process. The pain was improved with oral or topical NSAIDs (111). Neck pain as a presenting symptom of malignant hypertension was reported by Stockwell and George (112). They suggested that the neck pain is caused by cerebellar tonsillar herniation caused by increased intracranial pressure.

Role of Psychosocial Factors in Neck Pain

Up to this point, the epidemiologic, anatomic, and clinical discussions have focused mostly on objective symptoms, signs, diagnostic studies, and treatment protocols. To overlook the psychology of neck pain would ignore a vital aspect of the diagnosis and management of the disease. According to Bland, more than 30% of patients who consult their primary care physicians have significant psychological problems (4). Considering the ubiquitous nature of neck pain and its often-debilitating course, psychological factors are likely to play a prominent role in the presentation of these patients. Discrepancy between the level of pain and the person's general well-being, no identifiable organic cause for neck pain, vague complaints, exaggerated symptoms, gait or posture abnormalities, a defensive and aggressive attitude, nonanatomic neurologic deficits, the existence of litigation and compensation issues, and resistance to rehabilitation and therapy are some of the factors that should alert the physician to the possible role of psychological factors (4,5,113,114). Psychological assessment strategies and treatment concepts are discussed elsewhere in this text (see Chapter 16 and Chapter 24, Chapter 25 and Chapter 26).

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CHAPTER 56

Cervicobrachial Neuralgia

John D. Loeser

Cervicobrachial neuralgia, often referred to as *brachial neuralgia*, is a broad descriptive term used to denote pain in the distribution of the lower four cervical and first thoracic nerves. It is caused by pathologic processes involving the spinal cord, nerve roots that make up the brachial plexus, the plexus itself, or its major branches (1,2 and 3). Neurologic evaluation supplemented by electrodiagnostic and imaging studies is the basis of differential diagnosis.

GENERAL CONSIDERATIONS

Etiology

In most instances brachial neuralgia is a symptom secondary to disease involving the roots, trunks, cords, or peripheral branches of the brachial plexus. The most common causative factor, particularly as the population ages, is cervical spondylosis; other common diagnoses include herniated nucleus pulposus, brachial plexopathy, trauma to the neck and shoulder with root stretching or avulsion, variants of the thoracic outlet syndrome, and peripheral neuropathies resulting from compression or trauma. Most neck and shoulder pains are musculoskeletal in origin, as discussed in Chapter 57, Chapter 58 and Chapter 59.

Brachial neuralgias can be categorized on the basis of the site of pathology: lesions of the spinal cord and dura; lesions of the spinal nerve roots; lesions of the formed spinal nerves; lesions of the brachial plexus; and lesions of one or more of the peripheral nerves derived from the plexus (e.g., median neuralgia).

Epidemiology

The precise incidence of cervicobrachial neuralgia is not known because of the lack of population-based studies. Several investigators have studied this problem and obtained reasonable data. Lawrence (4), in a study of approximately 2,100 men and 1,850 women in England, found that 9% of the men and 12% of the women had cervicobrachial pain. An apparent correlation with radiologic changes in the cervical spine and increasing prevalence with advancing age was found. History or findings of radicular or spinal cord disease were noted in less than 3% of the subjects.

Hult (5), in a study of Swedish forest and industrial workers, again found an age-related prevalence of cervicobrachial pain, which appeared to correlate with roentgenologic signs of cervical spondylosis. Almost 80% of those in the study group had a history of cervicobrachial pain. In another study, Hult (6) determined the frequency of symptoms among men in different professions who could be segregated into two major groups, those doing light work and those doing heavy work. The 471 men in the light work group were employed in retail trade, light industry, or a sedentary occupation, whereas the 660 men in the heavy work group included stevedores and those employed in construction, heavy industry, and the food industry. The findings are shown in Figure 56-1. The incidence of neuralgia among light workers plateaued to around 10% to 12% in those between the ages of 25 and 44 years, but increased to approximately 40% in those aged 45 to 49, after which it remained above 30%. The incidence of cervicobrachial neuralgia for heavy workers aged 25 to 29 was approximately the same as for light workers, but rose steadily with age. Between the ages of 30 and 44, the incidence for heavy workers was approximately 20%, after which it climbed steadily to an incidence of approximately 40% in those aged 55 to 59.

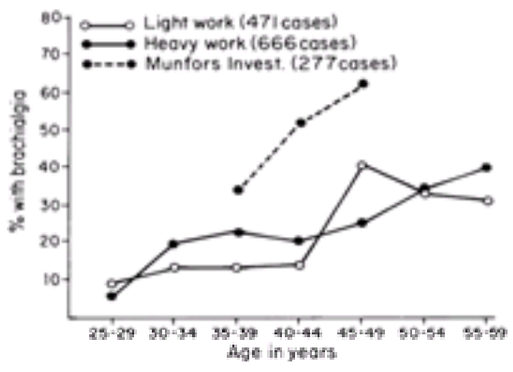

Figure 56-1. Incidence of brachialgia in three groups of subjects doing different types of work, showing the differences among the three groups and according to age groups. [Modified from Hult L. Cervical, dorsal and lumbar spinal syndromes. *Acta Orthop Scand* 1954; 17(Suppl):1–102.]

From these and the results of similar studies, it can be deduced that cervicobrachial pain is relatively common, is frequently associated with degenerative radiographic changes, and is usually a self-limiting symptom. Recurrent episodes of pain are common and increase in incidence with advancing age. Occupational stressors can lead to cervicobrachial pain (7). It is also well recognized that imaging studies may correlate better with age than with symptoms or signs (8).

Symptoms and Signs

The chief complaint of cervicobrachial neuropathy is usually pain, which is distributed according to the site of the lesion. Spinal cord or dorsal root lesions usually present with a radicular pain pattern that follows a dermatomal distribution. Lesions of the brachial plexus present with pain both in the root of the neck and in a peripheral nerve pattern. Lesions of the peripheral nerves distal to the plexus usually present with pain in the distribution of the affected peripheral nerve. The pain can be described as mild to severe, constant or intermittent, and lancinating or burning. A local dull, deep pain can also be present at the site of the lesion. Movements that stretch the involved nerves usually accentuate the pain.

It is common to have sensory disturbances accompany the pain of cervicobrachial neuralgia. All forms of sensory aberrations can be seen, including anesthesia, hypesthesia, paresthesia, hyperesthesia, hyperalgesia, and dysesthesia. If the offending lesion is primarily intrinsic to the spinal cord, pain and temperature sensation can be lost over several segments of the body, with preservation of light touch (girdle sensory loss).

Motor abnormalities are also common. Upper extremity myotatic reflexes can be depressed or absent. Muscle strength and bulk can be reduced. If the ventral roots or their axons are significantly compromised, fasciculations can be observed. Abnormalities in sympathetic nerve function are sometimes encountered and can include the loss of sweating and piloerection and a cool extremity, Horner's syndrome, and a diffuse forequarter deep pain. The dominance of the pain, sensory changes, and motor findings vary as a function of the site of the lesion and its causes.

Local tenderness is commonly noted at the lesion site. When the pathology involves the osseous structures of the neck, movements of the head and neck often exacerbate the pain. Lesions in the mixed nerves or brachial plexus result in pain to palpation in the supraclavicular region. Peripheral nerve lesions are often painful at the site of the lesion. If the lesion has been present for more than a month, and if axons have been damaged, a neuroma sign is often noted at the site of the lesion. Percussion at this area produces paresthesiae in the distribution of the involved nerve. If the lesion has been present long enough for regeneration to occur in the involved nerve, Tinel's sign can be elicited: Percussion of the nerve distal to the site of injury results in paresthesiae perceived in the distribution of the involved nerve. Tinel's sign indicates that some regeneration of the axons has occurred.

Diagnosis

The diagnosis of the cause of cervicobrachial neuralgia is based primarily on history; careful physical examination is also essential. Modern neurodiagnostic studies can be of great value in establishing a final diagnosis, but must be based on the history and physical findings if they are to be used efficiently. The general strategies for obtaining a history and performing a physical examination, as described in Chapter 12, should be used.

After a careful history has been obtained, the examiner should focus on the location and radiation of the pain. The neck should be inspected for loss of normal contours, atrophy of muscles, or other deformities. Localization in the neck without radiation into the arm usually implies musculoskeletal dysfunction. Radiation to the shoulder or distal arm is most often seen with root or plexus lesions; localized pain in the arm suggests a peripheral neuropathy.

The effects of motion of the neck and all the major joints should be ascertained next. Limitation of motion and pain locally suggests disease of the tendons, ligaments, joint capsule, or the joint itself (see Chapter 27, Chapter 28, Chapter 29, Chapter 30 and Chapter 31 and Chapter 55). Palpation of the painful region often increases the patient's pain. Relief of pain following infiltration of local anesthetics into the painful area confirms the presence of a localized musculoskeletal process. Myofascial pain syndromes of the neck and upper dorsal region are common (see Chapter 28, Chapter 29 and Chapter 30).

A thorough examination of the neck requires considerable skill. First, the patient should be asked to flex, extend, rotate, and laterally flex the head voluntarily as far as possible. Next, the effect of gentle traction on the head and of compression of the head should be noted. If significant reductions in the range of movement are seen, and if compression aggravates the pain while traction alleviates it, it is likely that cervical spondylosis or a herniated cervical disk is a causative factor. In such a patient, coughing, sneezing, and straining commonly cause an increase in pain. Other intraspinal lesions, although less common, can also be present.

The examination must include an assessment of the adequacy of the thoracic outlet, because congenital or acquired lesions can cause pain and neurovascular dysfunction by compressing the subclavian artery and lower brachial plexus. The radial pulse should be palpated with the arm dependent and with the arm externally rotated and extended while the neck is rotated toward and away from the arm. Obliteration of the pulse is common, even in a patient without any symptoms, and cannot be taken as indicative of a surgically treatable cause of the pain.

The course of the major nerves from the plexus distally should be palpated, looking both for local tenderness and for a possible neuroma sign or Tinel's sign. The skin should be inspected and palpated to ascertain temperature and sweating changes. Subtle autonomic changes can be present, indicating an occult neuropathologic process. The neurologic examination should be carried out with particular attention to the brachial plexus segments (Table 56-1). Knowledge of the cervical dermatomes is essential (9) (see Fig. 54-19). Spinal cord function should also be assessed by testing the lower extremities. The presence of Lhermitte's sign (electrical shocks radiating into the arms and legs when the neck is flexed) usually indicates an intradural spinal cord lesion. It is not pathognomonic for multiple sclerosis or any other disease state.

Ancillary diagnostic studies can include thermography; this does not indicate the presence of pain but does indicate an alteration in skin temperature, which suggests either vascular or neurologic dysfunction. Electromyography, nerve conduction velocities, and somatosensory-evoked potentials can be exquisitely localizing and can confirm the findings on physical examination (see Chapter 13).

Roentgenologic examination always starts with plain radiographs of the suspect area. Following these, tomography, computed tomographic (CT) scanning, or magnetic resonance imaging (MRI) can be ordered. If an intraspinal or radicular lesion is suspected, myelography is usually indicated (see Chapter 14).

Disk	Nerve root compressed	Finding
C4 to C5	C5	Pain radiates from midline neck to shoulder, often to medial scapula, anterior chest, and lateral aspect of upper arm; weakness in deltoids, supraspinatus, biceps, and brachioradialis; hyporeflexia at biceps and brachioradialis; numbness over deltoid and upper lateral arm
C5 to C6	C6	Pain radiates from midline of neck to shoulder, lateral upper arm, and radial forearm, sometimes to medial scapula and anterior chest; weakness in biceps and extensor carpi radialis; hyporeflexia at biceps; numbness over radial forearm, thumb, and first finger
C6 to C7	C7	Pain radiates from midline neck to shoulder, lateral upper arm, occasionally into index finger, and sometimes into anterior shoulder and medial scapula; weakness in triceps; numbness in index and middle fingers, often into palm
C7 to T1	C8	Pain radiates from midline neck to medial aspect of arm and ulnar side of forearm, and sometimes into medial scapula or anterior shoulder; weakness of triceps, wrist, and finger extensors except for flexor and extensor carpi ulnaris, all intrinsic hand muscles; hyporeflexia at triceps; numbness over fourth and fifth fingers and ulnar aspects of hand, forearm

TABLE 56-1. Findings with cervical nerve root compression

When the examination and diagnostic study results have failed to reveal a cause for cervicobrachial neuralgia, it is essential to remember that visceral pain can be referred to the neck and upper extremities. Lesions of the heart, mediastinum, lungs, diaphragm, and abdominal viscera can lead to pain in this region.

Local anesthesia can be used to establish a diagnosis when the findings are not clear-cut. Blocks of the spinal nerves, plexus, or peripheral nerves can help to localize the site of the causative lesion (see Chapter 102). Infiltration or dry needling of myofascial trigger points can often lead to dramatic relief and to the prompt establishment of a diagnosis in an otherwise puzzling patient.

LESIONS OF THE SPINAL CORD

Intrinsic Spinal Cord Lesions (IX-3)

Neoplasms or cysts of the cervical spinal cord can produce pain in the neck and arm. Significant neurologic deficits are almost always found in association with the pain. Vague and poorly localized pains over the trunk and arms can be seen, but the most common type of pain occurs in a segmental distribution at the level of the mass lesion, probably caused by stretching or compression of the intradural dorsal rootlets. This type of pain is usually aggravated by movements of the neck. Intrinsic lesions often lead to the loss of pain and temperature sensation in a girdle region a few segments below the level of the lesion, in this case usually over the upper thorax. This is because the decussating fibers of the spinothalamic tract are compromised (see Chapter 4). Neoplasms of the spinal cord, syringomyelia, herniated nucleus pulposus, or posttraumatic cysts are the common pathologic findings with lesions of this area. Infections are rare.

Neurodiagnostic studies are required to establish the diagnosis. Initial treatment is usually surgical, sometimes followed by radiation, chemotherapy, or both.

Extramedullary Intradural Lesions

Lesions within the dura but extrinsic to the spinal cord itself are not common, but they do occur and produce characteristic signs and symptoms. The two most common causes of this type of pathology are neurofibroma or meningioma; other tumors or congenital lesions occur rarely (10). The neurofibroma usually grows from a ventral root but can start on a dorsal root. The lesion typically presents with radicular pain and segmental motor and sensory changes. As its size increases, spinal cord dysfunction can occur, manifested by upper motor neuron findings in the lower extremities. A dumbbell neurofibroma can have a palpable mass in the neck and an intradural component, causing cord and nerve root compression.

Meningiomas usually originate dorsal or ventral to the spinal cord and do not have early radicular pain or signs; spinal cord dysfunction is usually the presenting complaint. Nonetheless, local neck pain can occur and, rarely, radicular pain and loss of function. Diagnosis is established by imaging studies. Treatment is exclusively surgical; these benign lesions should, whenever possible, be totally excised. Neurofibromas can grow both intradurally and in the spinal nerve, constricted by the bony foramen. Such a dumbbell tumor often requires a two-stage operation for excision.

Meningeal Carcinomatosis

Leptomeningeal metastases from solid tumors elsewhere in the nervous system or even in another organ can produce severe radicular pain (11,12) (See Chapter 35, Chapter 36 and Chapter 37). Patients with meningeal carcinomatosis have no significant mass lesions at the site of their painful neuropathy; the pain and nerve root dysfunction are caused by direct invasion of the nerve roots rather than by extrinsic compression. The pain-producing lesions can be too small to be seen by neuroimaging studies such as myelography, CT scanning, or MRI, although they may be visible on enhanced studies.

Carcinoma of the breast or lung, malignant melanoma, lymphoma, and leukemia are the most common primary tumors. Both children and adults can be afflicted with meningeal carcinomatosis, and radicular pain can be the first sign of this complication of the underlying disease. In children, leukemia is a frequent cause (13). Headache and pain along the entire spinal axis are also common. Many patients have sensory and motor deficits in multiple nerve roots, because meningeal carcinomatosis is usually a diffuse disease process.

The diagnosis is confirmed by identifying malignant cells in the cerebrospinal fluid by lumbar puncture. Radiotherapy or chemotherapy, depending on the primary lesion, is the appropriate treatment. The pain produced by this disease is relieved by narcotics to a varying degree. It has some of the characteristics of a deafferentation pain and is not exclusively nociceptive. Thus, anticonvulsants can sometimes be helpful (14).

Extradural Spinal Lesions

Extradural spinal lesions are more frequent than both types of intradural lesions. The most common diagnosis is herniated nucleus pulposus or cervical spondylosis (see Cervical Spondylosis, later in this chapter). Other causes of cervicobrachial pain that originates in the extradural space include metastatic tumor and abscess. Unusual lesions such as aberrant arteries can also compress nerve roots (15). Neoplasms that metastasize by way of the bloodstream frequently grow in the epidural space; carcinoma of the lung, especially apical (Pancoast's tumor), and breast, prostate, and thyroid tumors are the most likely primary lesions. The patient can have an epidural metastasis as the first sign of neoplasia, or the tumor might have long been recognized and treated before epidural metastasis.

The patient usually complains of severe pain in the region of the lesion and develops both radicular and spinal cord dysfunction. Diagnosis is established by myelography, CT scanning, or MRI. Chemotherapy, radiation therapy, and decompressive laminectomy can all be used. Treatment depends both on the biological properties of the tumor and on the patient's overall condition. If bone destruction is severe, a fusion may be indicated both to protect spinal cord function and to restore stability so that pain is reduced.

Epidural Abscess (IX-5)

An epidural abscess is usually painful; it is a surgical emergency and must be promptly treated by laminectomy and decompression as well as by appropriate antibiotics (16). The infection is usually blood borne from another region of the body, but cases with no known antecedent infection have been reported. The patient presents with severe pain in the midline overlying the region of the abscess, with tenderness to palpation of the involved area. Radicular pain can be present, especially on movement of the involved region. The patient usually has a fever and appears quite ill.

Tabes Dorsalis (IX-9)

Tabes dorsalis (tabetic neurosyphilis), characterized by demyelinization of the posterior column, dorsal roots, and dorsal root ganglion, can produce lancinating pain in a radicular pattern involving the cervical, thoracic, lumbar, or sacral roots (17). The usual patient is middle-aged, because it takes 10 to 20 years for this form of syphilis to develop its painful signature. The disease is much less common since the development of effective treatment for the destruction of the spirochete that causes the infection.

Symptoms and Signs

The patient describes shooting, stabbing, or lightning pains, much like those seen in tic douloureux in the face. The pains can shift from one region of the body to another; individual pains last only moments, but repeated episodes of pain can last for hours or days.

Sensory aberrations are uniformly present, including both hypersensitivity and hypesthesia. Paresthesia and dysesthesia of the distal extremities are common. Both the posterior columns of the spinal cord and the dorsal roots are involved in this syndrome; thus, long tract signs such as decreased vibration and position sense are often noted. Charcot joints and trophic skin changes caused by lack of protective sensation can be seen. Alterations in bowel and bladder function are common.

Treatment

Although the myelopathy or radiculopathy has no effective treatment, the lightning pains can often be ameliorated by anticonvulsants such as carbamazepine or phenytoin (14) (see Chapter 23). When medications do not control the pain, cordotomy is usually effective (18). This disease became rare in developed countries but has recrudesced as part of the acquired immunodeficiency syndrome epidemic (19). Scant data about the newer treatment options, either medical or surgical, are available (20).

LESIONS OF THE NERVE ROOTS (RADICULOPATHY)

Cervical Spondylosis

Etiology and Pathophysiology

The most common cause of pain in the cervicobrachial area is cervical spondylosis (cervical osteoarthritis) (1). The exact mechanism of the pain is not completely understood because innervated structures such as the ligaments, facet joints, and periosteum can produce radiating pain when they are mechanically distorted (21). Nevertheless, mechanical pressure on a dorsal root or dorsal root ganglion can lead to radicular pain. The details of this degenerative bone disease are discussed in Chapter 27 and Chapter 55. Compression of dorsal roots and ganglia can be the result of bony spurs and loss of foraminal height (Fig. 56-2). It is also possible that a subtle neuropathic process is responsible for myofascial and radicular pains (22,23). Degenerative processes in the cervical spine are related to age and to trauma but symptoms are not directly correlated with the magnitude of imaged changes (24).

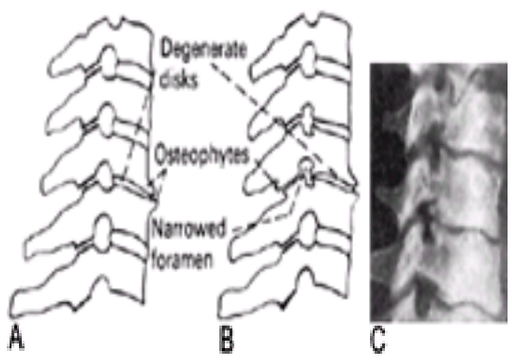

Figure 56-2. Osteoarthritis of the cervical spine, showing development of cervical spondylosis. **A:** Initially simple degeneration causes narrowing of the intervertebral disk, with formation of osteophytes anteriorly. **B:** Later the posterior or facet joints are affected, the articular cartilage is worn away, and marginal osteophytes encroach on the intervertebral foramen. **C:** Oblique view of the cervical roentgenogram shows severe encroachment of osteophyte, most pronounced at C-6 and C-7. Note the normal foramen below. (Modified from Adams JC. *Outline of orthopaedics,* 10th ed. London: Churchill Livingstone, 1956.)

Symptoms and Signs

Patients with cervical spondylosis can present either with spinal cord or nerve root dysfunction or both. The radicular signs are often multifocal (25). Pain can also be referred to the base of the skull or into the lower neck, chest, and shoulders.

Treatment

The initial treatment is aimed at alleviating the mechanical cause, reducing the inflammatory changes that occur in the nerve root secondary to repeated trauma (1), and providing symptomatic relief. Some patients respond well to a cervical collar and nonopioid analgesics; others might respond to cervical halter traction, muscle relaxants, analgesics, and antiinflammatory agents. Patients who do not achieve adequate pain relief with medications and physical therapies require surgical decompression of the bone spurs that impinge on the nerve roots and, sometimes, on the spinal cord (26). Myelopathy is an indication for urgent surgical treatment; radiculopathy can be managed conservatively with less risk of a major, sudden, irreversible increase in neurologic defect.

Herniated Nucleus Pulposus (IX-1)

Symptoms and Signs

Herniated nucleus pulposus in the cervical region is much less common than in the lumbar area (4,5 and 6). The typical patient has a history of intermittent neck pain with the sudden onset of severe radicular pain (radiculalgia), which usually follows trauma. Radicular pain is aggravated by coughing, sneezing, movement of the neck, especially extension, and Spurling's test, and is reduced by head traction (see Chapter 55). Significant radicular sensory and motor loss is often present; if the herniated fragment of the disk is large, spinal cord compression can also occur.

Most herniated disk fragments occur at the C-4 to C-5, C-5 to C-6, and C-6 to C-7 levels (Fig. 56-3). The pain pattern usually identifies the compromised nerve root; in some patients the pain is not localized and does not pinpoint the involved level. Some patients report diffuse pain in the suboccipital or lower cervical and upper chest regions, which can simulate the pain of myocardial infarction (see Chapter 61). Motor loss and the pattern of sensory changes can also help to localize the lesion (3). The cervical roots exit the spinal canal above the vertebral body of the same segment (the C-6 root is compromised by a C-5 to C-6 disk fragment). Typical radicular patterns in the cervical area are described in Table 56-1.

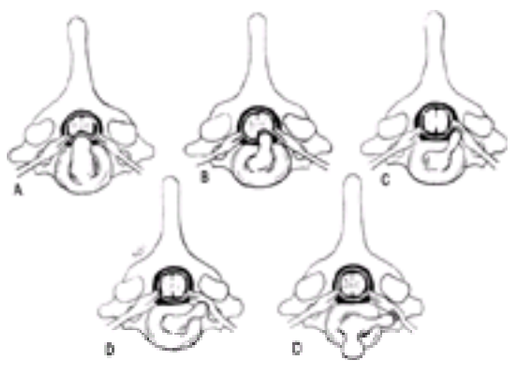

Figure 56-3. Various types of protrusions (herniations) of cervical intervertebral disks. **A:** Dorsomedial, which can produce bilateral cord compression (Stookey group I). **B:** Paramedian, which can produce unilateral cord compression (Stookey group II). **C:** Dorsolateral, which can compress the nerve roots intraspinally against the lateral part of the vertebral lamina (Stookey group III). **D:** Intraforaminal, which can compress the radicular nerve against the articular processes. **E:** Lateral and ventral protrusions. The lateral type can compress the vertebral artery and vertebral nerve.

Diagnosis and Treatment

Myelography and CT scanning reveal a discrete epidural defect; electromyography reveals a radicular pattern of denervation (see Chapter 13). If prompt symptomatic relief does not occur with cervical immobilization, traction, muscle relaxants, and analgesics, surgical removal of the herniated fragment is usually the optimal treatment. The surgical procedure can be performed either with an anterior interbody approach or with a posterior laminotomy and foraminotomy.

Fractures of the Cervical Spine (IX-4)

Spinal roots can be injured at the time of a cervical fracture or dislocation. Usually the acute neck pain is caused by the osseous and ligamentous injury; if a root has been compressed by the injury the patient also has radicular pain. Diagnosis is established by anterior posterior and lateral cervical spine roentgenography, CT, and MRI scanning.

Acute management obviously requires immobilization and realignment of the cervical spine, which can alleviate the root compression. When it does not, surgery for

decompression of the involved root must be considered, both to alleviate the pain and to maximize the opportunity for return of function.

In the chronic phase, a patient who develops radicular pain associated with neck movements should be thought to have an unstable neck until proven otherwise. Careful imaging studies to delineate abnormal motion are essential. Stabilization or surgical decompression of the compromised root, or both, usually relieve(s) the radicular pain and can restore lost nerve root function.

Brachial Plexus Avulsion (IX-11)

Avulsion of the brachial plexus is a misnomer: It is usually the dorsal and ventral roots that are torn from their entry zones into the spinal cord. Of course, a component of stretch of the roots or of the plexus with such an injury can be present. The entire syndrome is discussed here, recognizing that portions of the pain picture can result from pathology that exists in addition to the avulsion of the roots, such as a spinal cord or brachial plexus injury.

Etiology

In the adult the most common mechanism of avulsion of the roots is lateral flexion of the neck and downward thrust of the shoulder, putting maximal pressure on the upper roots of the plexus (C-5 to C-7). Motorcycle accidents are the common cause, and young men are most often injured. The resulting palsy can be partial or complete; some or all of the roots can be avulsed, some just stretched, and others not involved at all. Other mechanisms for injury occur in infants and children who rarely, if ever, develop a pain syndrome, no matter how profound the injury (27).

Symptoms and Signs

The pain can begin at the time of injury or can develop days to months later (28). It is usually described as burning or aching and is so intense as to disrupt totally the patient's life. The pain is perceived in the entire upper extremity but is usually maximal in the hand. It can be triggered by cutaneous stimulation over the chest or neck and is often aggravated by cold, anxiety, or stress. Often, tenderness is felt over the traumatized plexus; a neuroma sign can develop if the root is intact but the plexus is disrupted.

Diagnosis

The severity and extent of a brachial plexus avulsion injury should first be ascertained. Electrodiagnostic studies are essential. Myelography or MRI is important, because the root avulsions can actually be seen in many patients (29,30). Obviously, an avulsed root has no opportunity for regeneration. Careful documentation of the motor and sensory changes establishes a baseline that can be used to plot return of function. The presence of Horner's syndrome, paralysis of the serratus anterior, levator scapulae, rhomboids, or diaphragm all indicate root damage and probable avulsion. All these indicate injury central to the trunks of the brachial plexus. The likelihood of developing a severe pain syndrome is increased when many roots are avulsed.

Treatment

Local neck pain at the time of injury can be transient and can be a result of the trauma itself. In this phase the usual methods of treating musculoskeletal pain are effective. When the pain is referred into the anesthetic arm, brachial plexus avulsion pain can be diagnosed. This is not a pain caused by nociception; rather, it is a deafferentation pain. Management strategies must be based on the nature of the injury, the interval since injury, and the severity of the pain. Because the limb is often totally paralyzed and useless, the patient and uninformed physicians might advocate early amputation. Although this would eliminate an extremity that actually does impede the patient's activities, it never alleviates the pain.

Ablative and hazardous procedures should not be offered until the likelihood of regeneration has been considered; if significant regeneration can occur, the pain syndrome can abate without intervention. Hence, the interval since injury needs to be considered in assessing motor and sensory function to determine if any regeneration has been noted in the appropriate time frame. If regeneration is occurring, it is necessary to wait until the nerve has had the opportunity to regrow its connections before embarking on ablative surgical procedures to treat the pain.

Opiate analgesics are not often effective in the management of brachial plexus avulsion pain. If oral opiates fail, spinal opiates can be tried. Few studies support the effectiveness of any other medication, but most clinicians who have had experience with this syndrome recognize patients who seem to respond to anticonvulsant or antidepressant medications (14,31). Phenytoin, 300 mg per day; gabapentin (Neurontin), up to 1,200 mg four times a day; carbamazepine, 200 mg four times a day; and doxepin, 150 mg at bedtime, are often prescribed; dosages often require adjustment, and other medications can also be useful. Nerve blocks do not appear to have either a diagnostic or a therapeutic role.

When it is reasonably certain that regeneration is not going to occur, a surgical procedure can be contemplated. As stated previously, amputation does nothing to relieve the pain. Surgical repair of the brachial plexus can reduce pain as well as restore functions (32). When repair is not feasible, evidence suggests that dorsal root entry zone (DREZ) lesions are the most likely surgical procedures to stop this type of pain (33) (see Chapter 106). Cordotomy, myelotomy, and ablative brain lesions do not seem efficacious. Some patients have achieved relief with thalamic stimulation (34) (see Chapter 101). Spinal cord stimulation has been reported to be efficacious, but this has not been my experience (35).

The outcome from any treatment is difficult to assess, because many patients with brachial plexus avulsion pain gradually lose their complaints over a few years (28). Whether this reflects neural changes at the injury site or simply patients' recognition that no treatment works, and thus they stop complaining and searching for a cure, is unclear at this time.

The problem of brachial plexus injury was eloquently reviewed by Wynn-Parry (28), who commented on the importance of an accurate diagnosis: If the roots are not avulsed, repair of the plexus may be warranted. He found that comprehensive medical and rehabilitative care optimized pain relief. Some patients did respond to transcutaneous stimulation, but only if some innervation of the arm was intact. Our experience is similar to that of Wynn-Parry's: In the early stages of avulsion and stretch pain, patients require education and training in the use of relaxation, tensing, distraction, and physical therapy. Patients must know that spontaneous improvement over several years is common. Anticonvulsant and antidepressant medications can be helpful, whereas sedative-hypnotics are not. Transcutaneous electrical stimulation helps some patients, but there must be sensation in the region stimulated to achieve pain relief (see Chapter 98). Early return to normal social activities and gainful employment is also an essential component of a treatment program.

Postherpetic Neuralgia (IX-8)

Herpes zoster can affect the cervical dermatomes; postherpetic neuralgia of these segments can cause severe radicular pain. This syndrome is discussed in detail in Chapter 22; nothing is unique about its occurrence in the cervicobrachial area. The causative lesion does involve the dorsal roots, but the dorsal horn of the spinal cord and the peripheral nerve are also involved with the inflammatory and degenerative changes. This is a difficult pain syndrome to treat. It does not usually respond to opiate analgesics. DREZ lesions can be effective (see Chapter 106).

Diabetic Pseudotabes

Diabetes mellitus is associated with a plethora of myelopathies and neuropathies, many of which are difficult to diagnose conclusively (see Chapter 19 and Chapter 23). One form, known as *diabetic pseudotabes*, resembles tabes dorsalis with both radicular and dorsal column dysfunction and a radicular lancinating pain (20). This syndrome is distinguished from tabes by the negative serologic test results for syphilis and by the positive test results for abnormalities of sugar metabolism. Effective management of the diabetes seems to reduce the likelihood of this complication. Anticonvulsants are sometimes effective in the control of the lancinating pain.

LESIONS OF THE BRACHIAL PLEXUS

In all disorders of the brachial plexus pain can be increased by neck motion, use of the shoulder, or deep inspiration. Palpation or percussion of the supraclavicular fossa can lead both to the report of local pain and, often, to pain referred down the arm. Electrodiagnostic studies (see Chapter 13) are helpful in localizing the lesion. Reports on the frequency of the various lesions that can cause brachial plexus dysfunction and pain have been related to the patient referral system and to the

special interests of a particular author. Table 56-2 presents an approximation of the relative incidence of lesions of the brachial plexus.

Cause	Example(s)	Incidence (% of cases)
Trauma	Penetrating injuries (e.g., gunshot, knife); closed injuries—obstetric (newborn), mechanical distortion	70
Compression	Exogenous (knapsack paralysis); congenital abnormality; developmental abnormality	10
Vascular	Local disease of major vessels; generalized vasculopathy (lupus erythematosus, arteritis); secondary to radiation therapy	5
Infectious	Viral, bacterial (local sepsis, abscess, or cellulitis)	1
Neoplastic	Primary tumors of brachial plexus; secondary involvement of plexus by tumors of surrounding tissues (Pancoast's tumor)	10
Miscellaneous causes	Electric shock; parainfectious; following serum therapy; unknown	2

TABLE 56-2. Causes of brachial plexus lesions

Thoracic Outlet Syndromes (IX-13)

Numerous anatomic variations can be found at the cervicothoracic junction, some of which can compress either the vascular or neural structures, or both, that traverse the neck to enter the arm. The four major thoracic outlet syndromes are the scalenus anticus syndrome (Fig. 56-4), costoclavicular syndrome (Fig. 56-5), cervical syndrome (see Fig. 56-4), and hyperabduction syndrome (Fig. 56-6).

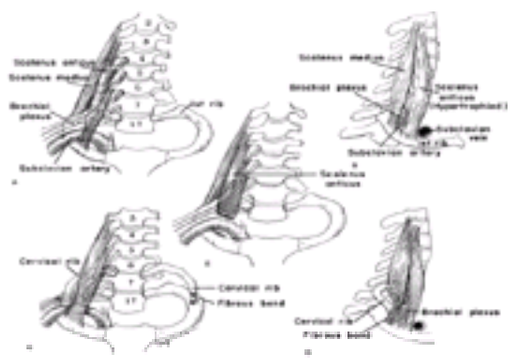

Figure 56-4. Mechanisms of the scalenus anticus syndrome with and without cervical rib. **A:** Normal anatomic relationship of the brachial plexus, subclavian artery, and scalenus anticus and medius muscles. **B:** Hypertrophied scalenus anticus muscle compressing the nerves and artery. **C,D:** Compression caused by cervical rib. **E:** Relief of compression by scalenotomy.

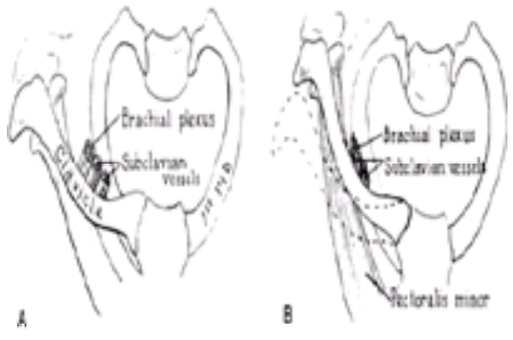

Figure 56-5. Mechanism of the costoclavicular syndrome. **A:** Normal relationship of the brachial plexus and the subclavian artery to the clavicle and first rib. **B:** Nerves and vessels are compressed with abnormal downward and backward bracing of the shoulders.

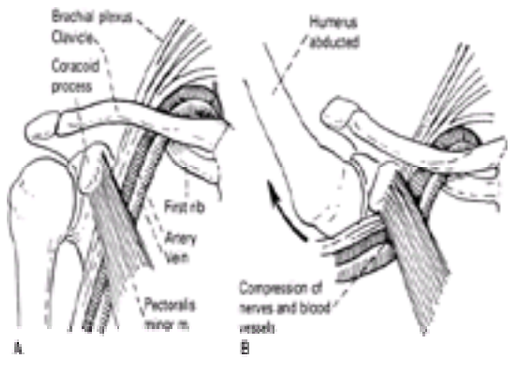

Figure 56-6. Mechanism of the hyperabduction or subcoracoid-pectoralis minor syndrome. **A:** Patient's right arm is represented as being dependent at the side of the body: The subclavian artery and vein and brachial plexus are not compressed in this position. **B:** With the arm laterally abducted to an elevated position, the brachial plexus and vessels are compressed by tension of the pectoralis minor muscle and to a lesser extent by the coracoid process.

Etiology

Thoracic outlet syndrome has been ascribed to such lesions as cervical rib, abnormal first thoracic rib, hypertrophy of the scalenus anticus, scalenus medius abnormal insertion, bands in Sibson's fascia, costoclavicular abnormalities, hyperabduction of the arm, and others. Most of these are known to occur without any symptoms in some people. Hence, their specificity should be questioned. Some of the structural abnormalities can impinge on various portions of the brachial plexus and produce neurologic deficits that are not typical of the lower trunk. Careful examination and diagnostic testing indicate the likelihood of such an atypical case. Some well-described variants of thoracic outlet syndrome have been seen, however, with consistent relationships between the patient's complaints and findings and an anatomic variation.

A well-characterized example is the cervical rib that impinges on the lower trunk and leads to atrophy and weakness in the hand and forearm, pain in the ulnar aspect of the forearm, and paresthesiae in the ulnar arm and forearm. Surgical treatment of this congenital anomaly usually relieves symptoms (36). Some are related to abnormal positioning of otherwise normal structures, whereas others can be caused by abnormal ribs or cartilage or abnormal muscle attachments and insertions (see

Fig. 56-5 and Fig. 56-6). Sunderland (37) has described the anatomic variations and how they might lead to compression of the relevant structures. Unfortunately, many authors have made unsubstantiated claims for various surgical procedures that are purported to relieve nonspecific complaints of shoulder, neck, arm, and hand pain. Others have questioned the actual existence of many of the alleged syndromes. Currently, physicians seem to find fewer patients with variants of the thoracic outlet syndromes than did physicians of earlier generations (38,39).

Symptoms and Signs

The usual syndrome involves the subclavian vessels and the lower trunk of the brachial plexus (C-8 and T-1). Varying degrees of vascular or neurologic compromise or both can be found, possibly with local supraclavicular pain. The pain and sensory changes are usually aggravated by any activity that puts tension on the plexus, including carrying heavy objects, working with the arms over the head, or performing repetitive movements of the arm. Pain is often in a radicular pattern, suggesting involvement of the C-8 and T-1 roots. Some patients report a deep ache within the arm without much localization. Cold weather often exacerbates the symptoms. The complaint of pain can precede by months or years the development of any other neurologic symptoms or signs.

Motor deficits are most common in the intrinsic muscles of the hand. Vasomotor changes are seen and are not necessarily associated with signs of vascular insufficiency, leading many to believe that the sympathetic fibers that accompany the subclavian artery are the cause of this phenomenon.

Diagnosis

Inspection and palpation often reveal a fullness of the supraclavicular fossa. The neural structures can be tender to palpation. Obliteration of the radial pulse with arm extension or abduction or traction can be present (Adson's or Allen's test), but this is often seen in asymptomatic people and does not reliably lead to any diagnosis or treatment success. Roentgenography of the neck can reveal a cervical rib or abnormality of the first thoracic rib. CT or MRI scanning is helpful in delineating soft tissue abnormalities (40). The differential diagnosis must include cervical spondylosis with radicular compression, myofascial pain syndrome, tumor of the brachial plexus, and almost any other cause of chronic pain in the neck.

Treatment

Conservative management is called for in patients thought to have a thoracic outlet syndrome. If frank vascular or major neurologic impairment is present, surgical decompression is a reasonable consideration (Fig. 56-7), but only a small proportion of patients fall into this category. The specific surgical procedure must be tailored to the findings at the time of surgery. The goal must be to provide adequate room for both the vascular and neural structures. A high cervical nerve root lesion, usually at C-4 to C-5, can cause spasm of the scalenus anticus, which can compress the lower trunk of the plexus. Such a patient has both a C-5 radiculopathy and signs of C-8 and T-1 dysfunction. Treating the cervical spondylosis or disk at C-4 to C-5 might obviate the need for scalenotomy.

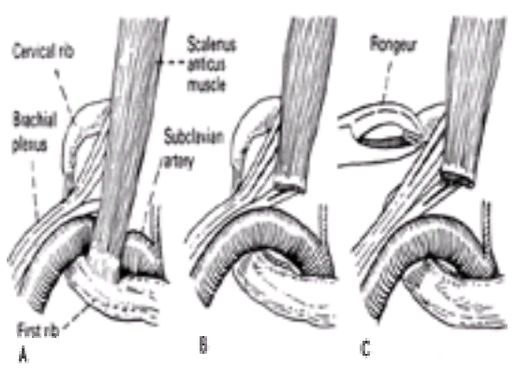

Figure 56-7. **A:** Pressure is exerted on the subclavian artery and the brachial plexus by the anterior scalenus muscle and by a tendinous band extending from the tip of a cervical rib to the first thoracic rib. **B:** Pressure on the subclavian artery is relieved by section of the anterior scalenus muscle but the tendinous band extending from the rib still compresses the brachial plexus. **C:** Pressure on the brachial plexus is relieved by removal of the tendinous band and the tip of the cervical rib.

Those on the staff of pain clinics see too many patients with severe neurologic deficits following surgical procedures for thoracic outlet syndrome. Many of these unfortunate sufferers did not have either vascular or nerve compression but were operated on for vague pains. Major vascular and nerve injuries occur too frequently to warrant exploratory surgery in this area (41).

Neoplasms (X-1)

Intrinsic Tumors

Tumors of the brachial plexus can present with pain and neurologic dysfunction. These are almost always benign schwannomas or neurofibromas, which can occur in isolation or can be part of a systemic disorder, such as multiple neurofibromatosis.

Symptoms and Signs. The involved plexus is usually tender to palpation and the mass can sometimes be felt or seen through the skin. Local and referred pain in the distribution of the involved segments is usually present. Sensory and motor loss are generally progressive. CT or MRI scanning is helpful in establishing a diagnosis; electrodiagnostic studies help to localize the lesion within the plexus.

Treatment. Treatment involves excision of the involved segments and repair of the plexus with cable grafts. This is often difficult if the neoplasm is in the middle of the plexus; only an expert in the management of peripheral nerve lesions should attempt this type of surgery. Malignant degeneration of these lesions can also occur, in which case surgery is then only palliative. Narcotic analgesics are often helpful in managing the pain of an intrinsic neoplasm, but some patients also have pain caused by deafferentation. Anticonvulsants or tricyclic antidepressants can be helpful for such patients.

Pancoast's Tumor (IX-12)

A tumor of the apex of the lung often involves the brachial plexus and is commonly called *Pancoast's tumor* (42). Pain is a common problem with such a lesion, and many patients are treated for diseases of the shoulder and neck for months or years before the true nature of the pathologic process becomes apparent (see Chapter 64 for more detailed discussion of Pancoast's tumor). These tumors are rare, accounting for only 5% of lung cancers (43). The initial pain syndrome usually involves the lower cervical roots or trunks.

Symptoms and Signs. Most patients with Pancoast's tumor have pain as their initial complaint (42). Although it was originally described as part of this syndrome by Pancoast, more recent studies indicate that Horner's syndrome is found in a minority of patients. CT scanning or MRI through the suspected region reveals a mass lesion that might be missed on plain roentgenography.

Treatment. The most common source of the neoplasm is the lung; the tumor is often radioresistant and might not respond to chemotherapy. When narcotics do not control the patient's pain adequately, a surgical or neurolytic procedure must be considered. Dorsal rhizotomy can be undertaken if the arm is already functionless secondary to tumor invasion of the plexus, but high cervical cordotomy is probably a wiser choice. Intracranial procedures have also been used, with varying results (44). Intrathecal or epidural narcotics can control this pain effectively in some patients.

Some patients develop severe pain following radiation therapy and chemotherapy, as well as surgery, for Pancoast's tumor. It is often impossible to determine the cause of the pain in such a patient. Nerve injury is often a major part of this patient's pain syndrome; the response to treatments designed to eliminate the pain of tissue damage is often poor. For example, such a patient, when treated by deep brain stimulation, may require an electrode both in the periaqueductal gray and in the

lateral thalamus to obtain complete pain relief (see Chapter 101).

Brachial Plexitis (X-2)

Brachial plexitis is an acute disorder that almost always begins with unilateral diffuse pain in the shoulder area and is soon followed by weakness, which is usually more pronounced in the proximal muscles than in the arm or hand. Sensory changes are usually less pronounced than the motor deficit, but varying amounts of paresthesia, dysesthesia, and hypesthesia have been noted. The pain usually subsides after the acute phase, and return of function generally occurs. Electrodiagnostic studies can help to establish this diagnosis (45).

The pathogenesis is not clear, but most believe that this is a viral illness or an autoimmune phenomenon (46). A rare, familial, recurrent brachial plexus neuropathy has also been described (47). Inflammatory lesions in the brachial plexus can also be caused by local hemorrhage or bacterial infection. The patient who develops profound paresis of the shoulder muscles can develop chronic shoulder pain because of the weight of the arm distracting the humeral head from the glenoid fossa. An arm sling alleviates this problem until return of function occurs.

Postradiation Plexopathy (X-4)

Lesions of the brachial plexus can follow radiation therapy for cancer (2,46,48). The differential diagnosis among tumor recurrence, scarring around the plexus secondary to surgery, and radiation-induced plexopathy is not easy. It is unusual for radiation plexopathy to develop less than 1 year after the termination of radiation therapy, unless high doses of radiation have been administered. The shortest latency seen is approximately 6 months, but latency periods of several years have also been reported. If the patient develops a brachial plexus lesion in less than 6 months or in more than 3 years following radiation therapy, however, tumor recurrence is more likely than radiation plexopathy. Chemotherapy, given in addition to radiation therapy increases the risk of plexitis (49). It is common that upper roots and trunks are initially involved in radiation plexopathy.

Symptoms and Signs. Alterations in sensation are the usual presenting symptoms in radiation-induced plexopathy. Chronic pain in the shoulder and arm is also found early in the course. Alterations in deep tendon reflexes appear at the same time as paresthesiae and definite hypesthesia. Motor deficits are the last to appear and usually follow the pain and sensory changes by several months. In some patients, pain and reflex changes can be the only findings.

Almost all patients with radiation plexopathy have skin changes caused by radiation and also might have changes in the deeper structures. Horner's syndrome is not found in radiation plexopathy; if present, the more likely diagnosis is tumor recurrence. The earlier that plexopathy follows the end of radiation therapy, the more likely is the disease to progress to complete loss of brachial plexus function. Lymphedema caused by radiation usually occurs within the first year after treatment; if it develops several years later, it is more likely that tumor is to be found. Palpation of the supraclavicular region does not discriminate between tumor recurrence and radiation-induced fibrosis unless a large mass of tumor has developed.

Diagnosis. When a patient develops brachial plexopathy after carcinoma, surgery, and radiation therapy, it is important to establish an accurate diagnosis. Roentgenography and CT or MRI scanning can be helpful (50). Often, needle biopsy or open exploration of the brachial plexus must be done. If tumor can be positively identified, a further course of radiation therapy can be warranted and might provide pain relief.

Treatment. Radiation-induced plexopathy is exceedingly difficult to treat. Physiotherapy can help to maintain range of motion and tissue health. The efficacy of neurolysis is debatable, although some favorable reports about pain relief have been published (48,51). Symptomatic therapy with narcotics helps some patients. Ablative neurosurgical procedures such as cordotomy or DREZ lesions are sometimes effective (52). Good results have also been reported with deep brain stimulation in the lateral thalamus (34).

Contusion or Stretching

Etiology and Pathophysiology. Much of the discussion of brachial plexus avulsion injuries is relevant to stretching or contusion of the plexus. Of course with avulsion, no potential for regeneration exists, but with stretch or contusion, regeneration is a possibility if the nerves have not been damaged so badly that fibrosis prevents regeneration. The mechanisms of stretching injury are the same as those of avulsion; clinically, it is often hard to discriminate between the two, and most injuries represent a combination of avulsed and stretched roots. Contusion is usually a result of blunt trauma to the lateral neck. The severity of the injury to the plexus is difficult to determine on initial examination. The brachial plexus can be injured during cardiac procedures, either by excessive retraction after a median sternotomy or by trauma to the lower cord during jugular venous catheterization (53).

Symptoms and Signs. Both contusion and stretching are associated with acute pain; the difficult management problem is, however, the development of chronic pain. Usually, the chronic pain is proportional to the severity of the injury and the pain diminishes as restoration of sensory function occurs. Exploration of the brachial plexus can be warranted in the acute phase for determining the extent of the injury and, if appropriate, when microsurgical repair of the disrupted plexus is contemplated. A successful repair not only maximizes the return of function but also reduces the likelihood of the development of a chronic pain syndrome.

Treatment. The development of chronic pain after contusion or stretching of a nerve or plexus mandates careful management. Obviously, an ablative procedure of any type is not warranted while the potential for nerve regeneration remains. Clinical examination and electrodiagnostic studies can indicate the degree and rate of return of function and can help in management decisions. When the pain has a component of electric shock–like jabs it is often helpful to prescribe an anticonvulsant for some patients, such as phenytoin or carbamazepine, whereas other patients have found tricyclic antidepressants to be helpful (see Chapter 85 and Chapter 86). Narcotics are not often useful because this is a form of deafferentation pain.

When the residuals of the injury appear to be fixed, a surgical approach should be considered. Exploration and repair of the plexus can help to restore nerve function, but often are not effective for the pain itself. If major functional deficits are present so that the arm is useless, DREZ (see Chapter 106) seems to be effective. Dorsal rhizotomies are not reliably useful, nor is cordotomy. No surgical or medical treatment has a consistently high chance of success.

Penetrating Trauma

Penetrating injuries of the brachial plexus can lead to severe pain. Complex regional pain syndrome type II can be an outcome (see Chapter 20), or other neuropathic pain syndromes can develop. Primary repair of the plexus, when carried out properly, is the best means of preventing a chronic pain syndrome. If a causalgic pain syndrome develops, prompt sympathetic blockade is indicated. If the plexus has been repaired, ablative lesions should not be undertaken until time for regeneration has elapsed. The likelihood of the development of a chronic pain syndrome following penetrating trauma decreases as nerve regeneration and return of function occur.

LESIONS OF THE PERIPHERAL NERVES

Acute Trauma

Symptoms and Signs

Any nerves of the shoulder girdle and arm can be injured by blunt or penetrating acute trauma. The injury is itself painful and neuropraxia occurs immediately; the development either of permanent neurologic deficits or of a chronic pain state depends on the severity of the injury. Obviously, penetrating injuries need to be explored acutely, and the nerve examined and the ends tagged for future repair, if possible. It is usually best to delay nerve suture until the extent of damage is demarcated in approximately 3 weeks after injury. When a major injury to a nerve has occurred, chronic pain can be a result of neuroma formation or entrapment in scar at the injury site; alternatively, it could be caused by central changes secondary to deafferentation. The pain is usually at the region of injury, but can also be referred distally in the sensory distribution of the nerve.

Treatment

Neurolysis or neurorrhaphy often alleviates the pain and restores neurologic function (54,55). Every attempt should be made to repair the nerve, because this greatly

reduces the likelihood of the formation of a painful neuroma (54). Minor nerves that are trapped in a scar can sometimes be rendered less painful by local injection of corticosteroids and local anesthetics. Medications are not helpful. Searching for small nerves in scarred tissue is rarely a successful surgical procedure in spite of the fact that local anesthesia can arrest the pain. Entrapment of a nerve in scar can lead to local pain and tenderness that may be alleviated by scar excision and pedicle or free flaps (56).

Entrapment Syndromes

Symptoms and Signs

Chronic trauma to the nerves in the arm occurs in various entrapment syndromes; at least one has been described for every nerve in the upper extremity (57) (Fig. 56-8 and Fig. 56-9). Entrapment syndromes usually present with local pain at the site of compression. The pain can radiate both proximally and distally. Depending on the nerve involved, sensory, motor, or sympathetic changes can occur in the distal territory of the nerve. Pain can also occur in the sensory field of the nerve. The various entrapment syndromes for the cervicobrachial region are contained in Table 56-3. The possibility of entrapment at more than one site must be kept in mind (58).

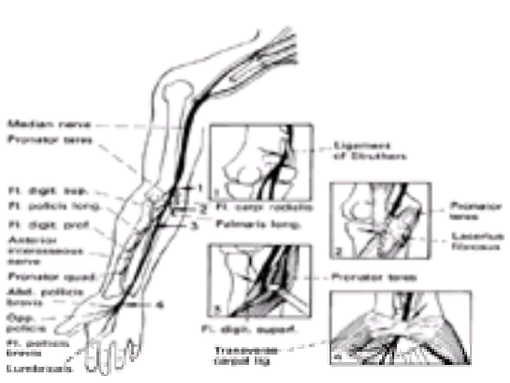

Figure 56-8. Entrapment syndromes involving the median nerve. **1:** Entrapment of the nerve above the elbow as it passes behind the supracondylar process and through the opening created by the ligament of Struthers. **2:** Entrapment by the lacertus fibrosus (bicipital aponeurosis) through its passage between or under the pronator teres. **3:** Entrapment of the anterior interosseous branch of the median nerve deep to the pronator teres and in relation with the flexor digitorum superficialis, flexor digitorum profundus, and flexor pollicis longus. Hypertrophy of any of these can entrap the anterior interosseous nerve. **4:** Carpal tunnel syndrome. Each of these syndromes produces local pain, radiating pain, or both, sensory changes, and weakness or loss of function of the muscles supplied by the nerve distal to the entrapment. See Chapter 59 for more details. (Developed by Bonica JJ, Domenowske M, from information in Dawson DM, Hallett M, Millender LH. *Entrapment neuropathy*. Boston: Little, Brown, 1983.)

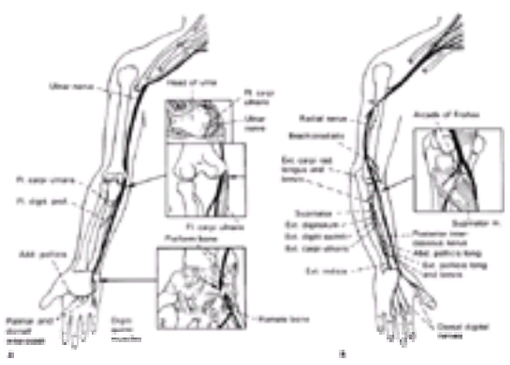

Figure 56-9. **A:** Entrapment syndromes of the ulnar nerve. **1:** Entrapment in the cubital fossa at the elbow either as a result of injury (fracture, subluxation) or through hypertrophy of the flexor carpi ulnaris. **2:** Entrapment of the ulnar nerve in Guyon's canal at the wrist. **B:** Entrapment syndromes of the radial nerve. This can occur high near the axilla to produce *Saturday night palsy* or can involve the posterior interosseous nerve after it enters the supinator muscle under the arcade of Frohse, where it can be compressed by hypertrophied muscle or tumors, ganglia, or synovitis. See Chapter 59 for more details. (Developed by Bonica JJ, Domenowske M, from information in Dawson DM, Hallett M, Millender LH. *Entrapment neuropathy*. Boston: Little, Brown and Company, 1983.)

TABLE 56-3. Upper extremity entrapment syndromes

Treatment

The management of entrapment syndromes involves attempting to decompress the nerve at its point of constriction. Sometimes this can be accomplished by physical means, such as a sling or wrist splint. Some patients have reported relief from perineural injection of corticosteroid solutions. Nerve blocks can help to localize the lesion, but they are rarely therapeutic. Often, however, surgical decompression is the most effective means of relieving the symptoms and of preventing further damage to the nerve.

Neoplasms

Tumors of the peripheral nerves in the upper extremity can present with pain, both locally and referred into the sensory distribution of the nerve (59). Varying amounts of motor and sensory loss can be found; the findings are usually gradually progressive. These are most often slowly growing benign lesions. Treatment entails surgical excision of the mass with repair of the nerve as required. Benign tumors can also arise adjacent to a nerve and can lead to a compression neuropathy.

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CHAPTER 57

Musculoskeletal Upper Limb Pains

Barry Goldstein

Musculoskeletal disorders of the upper limb constitute the most frequent cause of pain and disability involving this region of the body. These disorders represent a continuum from a rotator cuff tear, which has both relatively clear diagnostic criteria and pathophysiology, to peritendinitis of the forearm, which is defined primarily by the specific location of pain and has a pathophysiology that is less well defined. From a clinical and epidemiologic perspective, some of these upper limb disorders present challenges similar to those of low back pain.

This chapter contains two sections. First, the anatomy, physiology, and biomechanics of the upper limb are described. This section is presented in a regional manner with a particular focus on musculoskeletal and nervous structures. Regions of the limb are organized into joints (e.g., sternoclavicular, glenohumeral, elbow, wrist) or limb segments (arm, forearm, and hand). There is a particular emphasis on function and clinically relevant topics. Second, there is a section on the clinical application of this material. General principles are provided rather than a comprehensive regional approach to upper limb problems. A detailed discussion of shoulder, arm, and elbow pain follows in Chapter 58 and forearm, wrist, and hand pain in Chapter 59.

ANATOMY

Shoulder

Pectoral Girdle

All vertebrates have limbs that are connected to the axial skeleton by way of a limb girdle. The human pelvic and pectoral girdles are designed in a way that reflects the overall function of the respective limb. In contrast with the lower limb, with its weight- bearing and locomotive functions, the pectoral girdle is built for mobility and does not have a bony junction with the vertebral column at all. Rather, the girdle articulates with the thoracic cage at the sternoclavicular joint, thereby permitting a wide range of motion for placement of the hand.

The pectoral girdle consists of two bones (scapula and clavicle), two synovial joints (sternoclavicular and acromioclavicular), and two movement interfaces (scapulothoracic and humeroacromial). The humeroacromial interface is discussed with the glenohumeral joint.

Clavicle. The S-shaped clavicle is a long bone, superficial and horizontal throughout most of its course. The medial two- thirds is rounded and convex forward to clear the neurovascular bundle of the upper limb at the apex of the axilla. Its sternal end is expanded and fits into the notch on the manubrium at the sternoclavicular joint. The lateral one-third is flat and its sternal end is expanded as it curves back to meet the scapula at the acromioclavicular joint (Fig. 57-1).

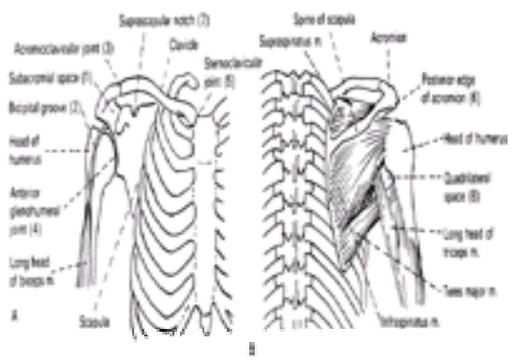

Figure 57-1. Anterior **(A)** and posterior **(B)** views of the shoulder identifying the various bones and joints and also the sites of pathologic processes that produce pain and tenderness. (1) Subacromial space, which can be involved with calcific tendinitis, rotator cuff tendinitis and impingement syndrome, and rotator cuff tear; (2) bicipital groove, which can be involved in bicipital tendinitis and biceps tendon subluxation and tear; (3) acromioclavicular joint, which can be involved with degenerative and infectious processes; (4) anterior glenohumeral joint, which can be the site of glenohumeral arthritis, osteonecrosis, glenoid labial tears, and adhesive capsulitis; (5) sternoclavicular joint, which can be the site of pain caused by infection, degenerative changes, or trauma; (6) posterior edge of the acromion, which can contribute to rotator cuff tendinitis, calcific tendinitis, and rotator cuff tear; (7) suprascapular notch, which can be the site of suprascapular nerve entrapment; and (8) quadrilateral space, which can be the site of axillary nerve entrapment.

Scapula. The scapula, or shoulder blade, is a remarkably thin, triangular bone that is attached to the thorax via muscular attachments and to the clavicle by way of the acromioclavicular joint (see Fig. 57-1). It possesses three borders and three angles. The three borders are the superior, medial (vertebral), and lateral (axillary). The three angles are the superior, inferior, and lateral. The scapula has costal (anterior) and posterior surfaces with its anterior surface in contact with the thoracic cage. From the upper part of the posterior surface, the spine of the scapula projects laterally, terminating in the acromion, which forms the lateralmost tip of the shoulder.

The lateral angle of the scapula is thick and strong, with an expanded large, shallow glenoid fossa, facing slightly forward and upward, ready to receive the head of the humerus. Just medial to the glenoid fossa is the coracoid process as it projects upward from the neck of the scapula. The coracoid process serves as an attachment site for several important ligaments and muscles.

Sternoclavicular Joint. The only bony articulation between the upper limb and axial skeleton occurs between the clavicle and the manubrium at the sternoclavicular joint. The entire pectoral girdle moves about the clavicle braced on the thorax at this saddle- shaped joint. The medial end of the clavicle is concave and fits over the convexity of the much larger sternocostal surface (Fig. 57-2). An articular disk between the sternum and clavicle divides the joint into two spaces and provides a greater congruence of surfaces than the bony articulation alone.

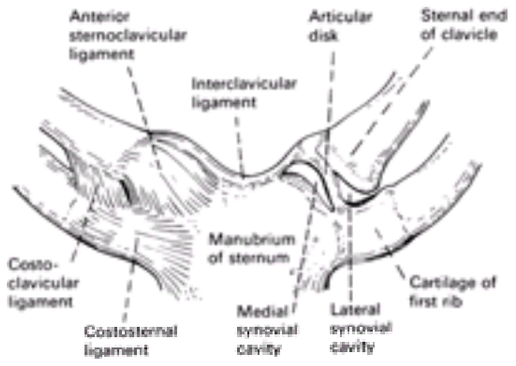

Figure 57-2. Anatomy of the sternoclavicular joints viewed from the front. (Adapted from Clement CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:366–367.)

Stability of the joint is provided by a strong, lax capsule and is enhanced by ligaments superiorly (interclavicular ligament) and posteriorly (posterior sternoclavicular ligament). The major stabilizing factor of the sternoclavicular joint is the strong costoclavicular ligament, attached from the first rib to the undersurface of the clavicle (see Fig. 57-2). This ligament limits elevation and rotation of the clavicle. It also serves as the fulcrum of movements at the sternoclavicular joint. The joint is weakest anteriorly where dislocation tends to occur (although dislocation is rare) and an effusion (e.g., infection) tends to point.

Acromioclavicular Joint. The overriding lateral end of the clavicle meets the medial border of the acromion at the acromioclavicular joint, a small, flat joint of the plane variety. The *step-off* between the two bones is often appreciated on physical examination. The joint capsule is lax and not very strong. It is strengthened superiorly by the acromioclavicular ligament, a quadrilateral band of parallel fibers extending between the acromial end of the clavicle and the adjoining part of the acromion. The major stabilizing structure at this joint is the unyielding coracoclavicular ligament (Fig. 57-3). The conoid portion of this ligament is fan- shaped, with its apex lying inferiorly, and lies in the frontal plane. It is attached from the *elbow* of the coracoid process to the apex of the posterior arc of the distal clavicle and serves as a vertical axis for scapular rotation. The trapezoid portion inserts into the medial border of the upper surface of the coracoid process and runs superiorly and laterally. It has a more horizontal course and attaches from the upper aspect of the coracoid to the clavicle. The trapezoid ligament serves as a hinge for scapular motion about a horizontal axis. A fall on the point of the shoulder may cause partial or complete disruption of the coracoclavicular ligament, resulting in separation of the acromioclavicular joint.

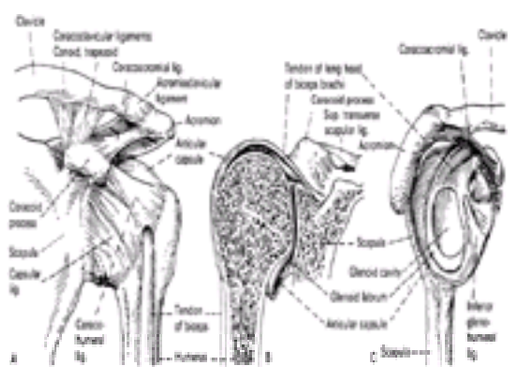

Figure 57-3. Anatomy of the shoulder joint. **A:** Anterior view of ligaments of the left shoulder. **B:** Coronal section through the head of the left humerus and shoulder joint, anterior half viewed from behind. **C:** Interior of the right shoulder viewed from its lateral aspect. (Adapted from Clement CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:368–372.)

Scapulothoracic Interface. Scapulothoracic movements are of a gliding nature and occur at an interface between the ventral surface of the scapula and the rib cage. The contacting surfaces involve the subscapularis and bare areas of the scapula with the serratus anterior overlying the second through the seventh ribs. Although the scapula is without bony or ligamentous connections with the thorax, numerous muscles hold the scapula in close opposition to the chest wall (e.g., serratus anterior, trapezius, rhomboids). Normally, the scapula is set obliquely on the thorax at an angle of 30 degrees, open anterolaterally, and moves along a curved thoracic surface during protraction and retraction (Fig. 57-4).

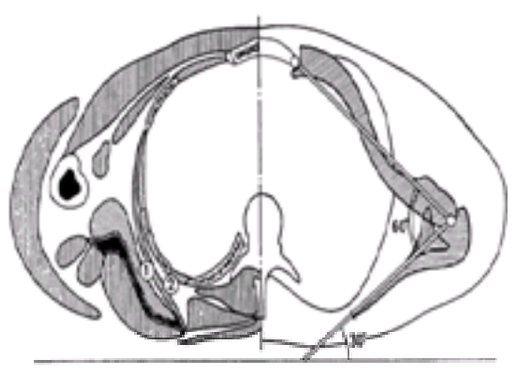

Figure 57-4. In the left half of this horizontal section through the thorax, the space between the scapula and serratus anterior is seen at (1). The space between the thoracic wall and serratus anterior is seen at (2). The right half of the section shows that the scapula runs obliquely, forming an angle of 30 degrees with the frontal plane. The clavicle also runs obliquely, forming an angle of 60 degrees with the scapula. (Reprinted from Kapandji IA. *The physiology of the joints*, 5th ed. Vol 1: Upper limb. Edinburgh, UK: Churchill Livingstone, 1982:39, with permission.)

Movements. Movements of the pectoral girdle include elevation-depression, protraction-retraction, and upward-downward rotation (Fig. 57-5 and Table 57-1). The fulcrum of movements is through the costoclavicular ligament. As the lateral end of the clavicle moves, the medial end moves in the opposite direction. During elevation, for example, the scapula and lateral extremity of the clavicle are raised, while the medial aspect of the clavicle slides inferiorly. During depression, the scapula and lateral aspect of the clavicle are depressed and the medial part of the clavicle is raised. Crutch walking is a good example of an activity in which active depression of the pectoral girdle occurs. Protraction, a movement that occurs during pushing activities, involves forward movement of the scapula and lateral clavicle and is accompanied by retraction of the medial clavicle.

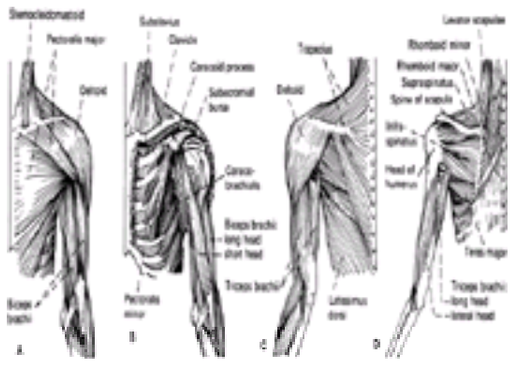

Figure 57-5. The muscles of the shoulder girdle and arm. Anterior views showing the superficial muscles **(A)** and deep muscles **(B)**. Posterior views showing the superficial muscles **(C)** and deep muscles **(D)**.

Elevation	Trapezius (upper fibers)
	Rhomboids
	Levator scapulae
Depression	Latissimus dorsi
	Pectoralis major (costal fibers)
	Trapezius (lower fibers)
Protraction	Serratus anterior
	Pectoralis minor
	Pectoralis major
Retraction	Trapezius
	Rhomboids
Upward rotation	Trapezius
	Serratus anterior
Downward rotation	Rhomboids

TABLE 57-1. Prime movers of the pectoral girdle

Rotation of the pectoral girdle occurs with movements of the shoulder above the horizontal plane. Both the clavicle and scapula rotate. Upward rotation of the scapula (the glenoid cavity moves superiorly) is required for full abduction and forward flexion of the shoulder (Fig. 57-6). The prime movers are the trapezius (upper and lower fibers) and serratus anterior. Axial rotation of the clavicle follows this movement passively once the capsule and ligaments of the acromioclavicular joint are put on tension. Downward rotation of the pectoral girdle is usually passive and assisted by gravity.

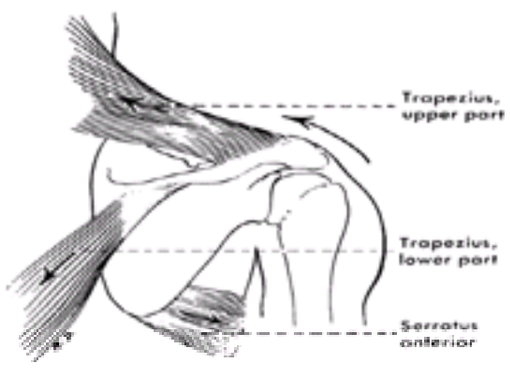

Figure 57-6. The muscles that rotate the scapula upward during abduction of the arm. Note that the upper part of the trapezius, which is attached to the outer part of the scapular spine, pulls upward, and that the lower part of the serratus anterior, attached to the lower part of the scapula, pulls the inferior angle laterally, while the lower portion of the trapezius, attached to the medial part of the scapular spine, pulls downward. (From Rosse C, Gaddum- Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:235, with permission.)

Glenohumeral Joint

The glenohumeral joint is a synovial joint of the ball-and-socket type, linking the free limb through the ball (head of the humerus) to the socket of the pectoral girdle (glenoid cavity of the scapula). The head of the humerus is approximately one-third of a sphere, and it is much larger than the socket on the scapula by approximately four times. In anatomic position, the head faces superiorly, medially, and posteriorly with the lesser tuberosity in front and the greater tuberosity pointing laterally (Fig. 57-7). The rotator cuff muscles attach to the tuberosities.

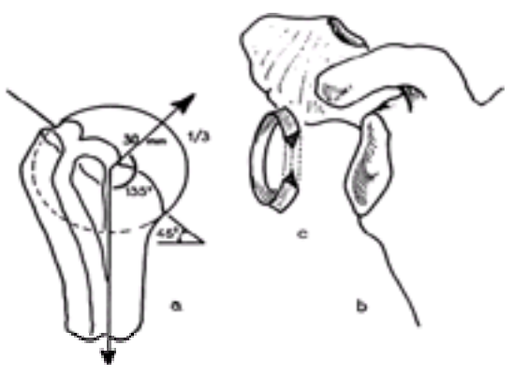

Figure 57-7. **A:** Head of humerus. **B:** Glenoid cavity of scapula. **C:** Glenoid labrum. The articular surfaces of the glenohumeral joint are typical of a ball- and-socket joint, which has three axes and three degrees of freedom. The head of the humerus faces superiorly, medially, and posteriorly. It corresponds to a third of a sphere 3 cm in radius. Its axis forms with the axis of the shaft an angle of 135 degrees and with the frontal plane an angle of 30 degrees. It is separated from the rest of the superior epiphysis of the humerus by the anatomic neck, which makes an angle of 45 degrees with the horizontal plane. The glenoid cavity of the scapula lies at the superolateral angle of the scapula and points laterally, anteriorly, and slightly superiorly. The glenoid cavity is much smaller than the head of the humerus but is deepened by a ring of fibrocartilage, the glenoid labrum. This is attached to the margin of the glenoid cavity and deepens it appreciably so as to make the articular surfaces more congruent. (From Kapandji IA. *The physiology of the joints*, 5th ed. Vol 1: Upper limb. Edinburgh, UK: Churchill Livingstone, 1982:23, with permission.)

The margin of the shallow, pear-shaped glenoid cavity is slightly raised and attaches to a ring of fibrocartilage, the glenoid labrum (see Fig. 57-7). The labrum deepens the socket significantly and is an important factor in the overall stability of the joint. Two small tubercles above and below the cavity (supraglenoid and

infraglenoid) serve as attachments for the long head of the biceps and triceps, respectively.

The capsule of the joint is thick and strong but lax, especially inferiorly, to allow great range of movement (see Fig. 57-3). It is attached to the humerus around the articular margins of the head except inferiorly, where its attachment is to the surgical neck, thus enclosing a portion of the epiphyseal line. The capsule then encompasses the joint completely and is attached to the scapula just beyond the glenoid labrum. With the arm hanging loosely at the side, there is a loose recess inferiorly, sometimes called the axillary fold, to allow space for the head of the humerus during full abduction (see Fig. 57-3). Conditions in which there are contractures or fibrosis of the capsule result in restriction of glenohumeral motion.

Thickenings of the anterior capsule are specified (superior, middle, and inferior glenohumeral ligaments) and strengthen the anterior and inferior capsule. The coracohumeral ligament attaches from the coracoid process to both of the tuberosities (anterior band to the lesser and posterior band to the greater tuberosity). These bands are quite strong and limit extension and flexion, respectively. The capsule and ligaments are a significant stabilizing factor at the end ranges of motion. Deficiencies in these ligaments are important in the development of instability.

The coracoacromial ligament extends from the undersurface of the acromion to the coracoid process (see Fig. 57-3). Along with the acromion and the coracoid process, it acts as a large articulating surface for the head of the humerus. The subacromial and subdeltoid bursae lie between the rotator cuff tendons and the arch. This structure has been implicated in shoulder impingement.

The synovial membrane lines the capsule and is in continuity (through the foramen of Weitbrecht in the anterior aspect of the capsule) with the subscapularis bursa. Synovium also invests the long head of the biceps as it courses beneath the transverse ligament, the latter being a thickened part of the capsule that bridges the gap from the greater to lesser tuberosity (e.g., over the upper end of the bicipital groove). The synovial cavity does not normally communicate with the subacromial bursa.

Humeroacromial Interface. The humeroacromial or subdeltoid interface is between the coracoacromial arch and the head of the humerus. The significance of this interface in the healthy shoulder is uncertain and its physiologic role during normal shoulder motion is still debated. There has been speculation that abduction of the internally rotated shoulder may result in mechanical impingement between the humeral head and overhanging arch.

The humerus is in contact with the coracoacromial arch when there is upward displacement of the humeral head (e.g., rotator cuff weakness, tears, or both) (Fig. 57-8). Compression of the supraspinatus tendon and bursa results in progressive injury of the rotator cuff. Furthermore, in the setting of large rotator cuff tears, the coracoacromial arch provides superior stability to the humeral head. Acromioplasty may result in superior instability during abduction activities.

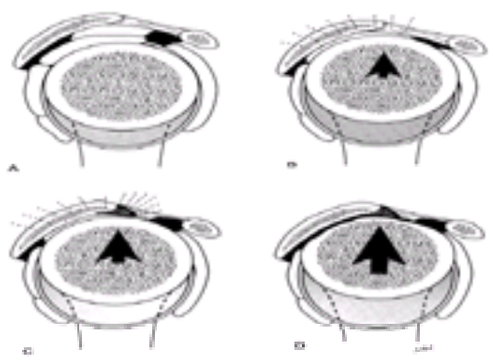

Figure 57-8. With progressive cuff fiber failure, the head moves upward against the coracoacromial arch. **A:** Normal relationships of the cuff and the coracoacromial arch. **B:** Upward displacement of the head, squeezing the cuff against the acromion and the coracoacromial ligament. **C:** Greater contact and abrasion, giving rise to a traction spur in the coracoacromial ligament. **D:** Still greater upward displacement, resulting in abrasion of the humeral articular cartilage and cuff tear arthropathy. (From Matsen FA. *Practical evaluation and management of the shoulder*. Philadelphia: Saunders, 1994:123, with permission.)

Mobility versus Stability. Full range of shoulder movement includes motion of both the glenohumeral joint and the pectoral girdle. At the glenohumeral joint, the ball and socket configuration allows relatively free movements of flexion -extension, abduction-adduction, and medial-lateral rotation. The prime movers are listed in Table 57-2 (Fig. 57-9).

Flexion	Pectoralis major (clavicular head)
	Deltoid (anterior fibers)
Extension	Latissimus dorsi
	Deltoid (posterior fibers)
Internal rotation	Pectoralis major
	Latissimus dorsi
	Teres major
	Subscapularis
External rotation	Infraspinatus
	Teres minor
	Deltoid (posterior fibers)
Abduction	Deltoid
	Supraspinatus
Adduction	Pectoralis major
	Latissimus dorsi
	Teres major
	Subscapularis

TABLE 57-2. Prime movers of the glenohumeral joint

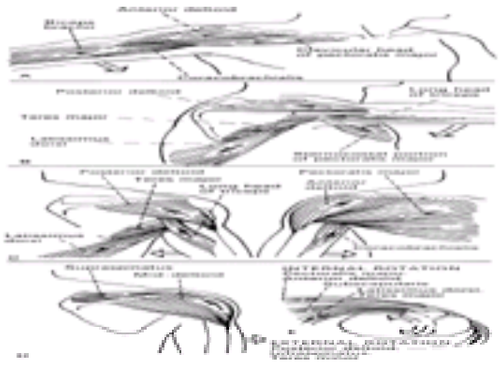

Figure 57-9. Muscles that move the shoulder and arm: flexors **(A)**, extensors **(B)**, adductors **(C)**, abductors **(D)**, and rotators **(E)**. (Adapted from Hollinshead WH. *Anatomy for surgeons*, 3rd ed. Vol 3: The back and limbs. New York: Harper & Row, 1982:325–330.)

Raising the arm above the head into flexion or abduction is brought about by a combined action at the glenohumeral joint and of the pectoral girdle. Abduction without any girdle movement is limited to approximately 90 degrees. This is because there is no further articular surface on the humeral head. Further abduction is made possible by way of external rotation of the humerus, thus providing further articulating surface.

There is also further abduction provided by upward rotation of the pectoral girdle. Of every 15 degrees of abduction of the arm, 10 degrees occurs at the glenohumeral joint and 5 degrees from upward rotation of the girdle. This 2:1 ratio of humerus to scapula exists throughout the entire range in a smooth, rhythmic pattern. The abduction or elevation of the arm overhead (180 degrees) requires 60 degrees of scapular rotation to alter the angle of the glenoid fossa on which the humerus articulates (Fig. 57-10).

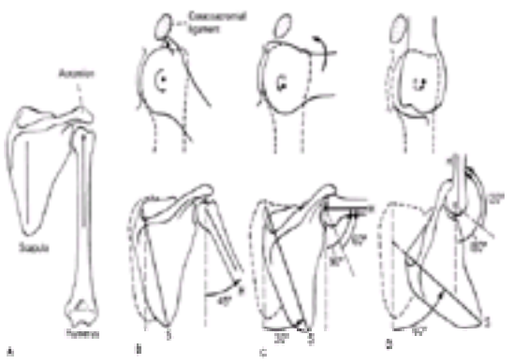

Figure 57-10. Biomechanics of the glenohumeral movements of arm abduction. **A:** Normal position of the head and shaft of the humerus (H). The circle in the head of the humerus indicates the center of rotation. **B:** Humerus abducted 45 degrees and the scapula (S) beginning upward rotation. The upper panel shows that the incongruity of the articulating surface of the head of the humerus, and the surface of the glenoid cavity causes the greater tuberosity of the humerus to impinge on the coracoacromial ligament. The upper panel in **C** shows that to allow the greater tuberosity to pass under the coracoacromial hood during arm abduction, the humeral head is depressed (depicted by downward movement of the center of rotation) and the humeral head rotated (*thin arrow*). The abduction movement of the arm is accomplished in a smooth coordinated movement during which for each 15 degrees of arm abduction, 10 degrees of motion occurs at the glenohumeral joint and 5 degrees occurs because of scapular rotation on the thorax. Thus, as noted in **C**, abduction of the arm to 90 degrees is accomplished by 60 degrees' rotation of the humerus and 30 degrees' rotation of the scapula. Full abduction of the arm, as shown in **D**, is accomplished by 120 degrees of rotation at the glenohumeral joint and 60 degrees rotation of the scapula. (Modified from Cailliet R. *Shoulder pain*, 2nd ed. Philadelphia: FA Davis, 1981.)

As compared with the hip, the shoulder is seen as a remarkably mobile but inherently unstable structure. Although this is undoubtedly true, stability of the shoulder is often underrated. Many individuals with a spinal cord injury live for several decades (some World War II veterans are now in their 80s and have been living with a spinal cord injury for more than 50 years), using their upper extremities for support, reaching, and wheelchair mobility without stability problems.

End-range stability is quite different than midrange stability. Three factors are important in end-range stability: bony, ligamentous, and muscular. Although not the major factor, bony factors at the shoulder are significant; the size and shape of the glenoid fossa is especially important. Furthermore, the integrity of the glenoid labrum is essential in enhancing bony surface congruity. Ligamentous factors, including the articular capsule, are critically important for end-range stability (see Fig. 57-3). These dense connective tissues act as check reins at the limits of motion. Muscles that connect to the humerus also limit motion and provide end-range stability.

Different mechanisms provide midrange stability, principally coaptation of the articular surfaces and glenohumeral balance. Coaptation of the articular surfaces keeps the head of the humerus pressed against the glenoid cavity. The rotator cuff muscles are important in this role and act as dynamic ligaments, shortening and compressing the glenohumeral joint regardless of the position of the shoulder (Fig. 57-11).

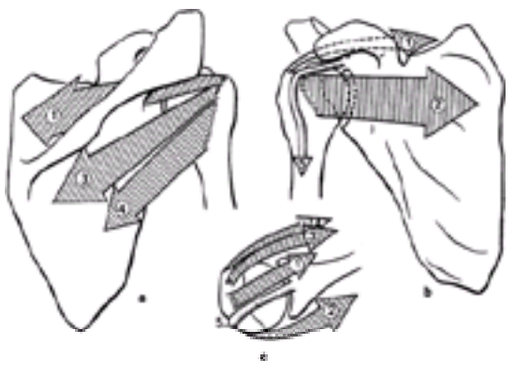

Figure 57-11. Scapula as seen from behind **(A)**, front **(B)**, and above **(C)**. Short, periarticular muscles run transversely across the joint, providing dynamic stability to the joint in all positions by pressing the humeral head against the glenoid cavity. Five muscles are illustrated in these figures as follows: supraspinatus (1), subscapularis (2), infraspinatus (3), teres minor (4), and the long head of the biceps (5). (Reprinted with permission from Kapandji IA. *The physiology of the joints*, 5th ed. Vol 1: Upper limb. Edinburgh, UK: Churchill Livingstone, 1982:35.)

Glenohumeral balance is the process in which the glenohumeral joint is positioned in space for maximal stability. This primarily involves positioning the scapula so the net humeral joint reaction force is aligned with the center of the glenoid cavity (Fig. 57-12). Both of these processes are dynamic and can be fortified by strengthening the rotator cuff muscles in the first case and scapular muscles in the second. A rotator cuff tear illustrates the importance of this mechanism. The rotator cuff muscles consist of the supraspinatus, infraspinatus, teres minor, and subscapularis. Tendons of the first three muscles insert onto the greater tuberosity, whereas the subscapularis tendon inserts on the lesser tuberosity (see Fig. 57-5). The tendons are broad and insert into the capsule of the glenohumeral joint, thus providing a strong conjoined tendon-capsule. Although the rotator cuff muscles are not as strong as many of the shoulder muscles (e.g., deltoid, pectoralis major, latissimus dorsi), their insertion into a continuous cuff around the humeral head permits stabilization of the glenohumeral joint in almost any position. Tears of the rotator cuff result in weakness of the shoulder because the shoulder joint cannot be stabilized for other stronger prime movers.

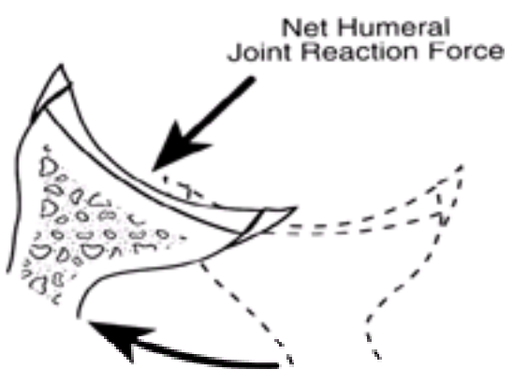

Figure 57-12. Glenohumeral balance is a stabilizing mechanism in which the glenoid is positioned so that the net humeral joint reaction force passes through the glenoid fossa. (From Matsen FA. *Practical evaluation and management of the shoulder.* Philadelphia: Saunders, 1994:62, with permission.)

Arm and Elbow

Arm

The arm consists of flexor and extensor compartments. The flexor compartment consists of the neurovascular bundle from the axilla and three muscles that are innervated by the musculocutaneous nerve (branch of the lateral cord; major segments are C-5 and C-6).

Flexor Compartment. As in the thigh, part of the flexor compartment is occupied by adductor musculature. The coracobrachialis, a muscle that is functionally and clinically unimportant, is the last vestige of adductors in the upper limb. The other powerful adductor muscles have migrated to the thorax, thereby providing great strength yet allowing substantial freedom of movement at the shoulder. Biceps brachii and brachialis are powerful flexors of the elbow (Fig. 57-13). In addition, the biceps is the major supinator of the forearm.

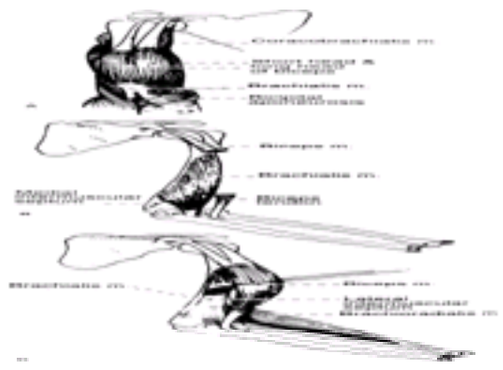

Figure 57-13. Flexor muscles of the elbow from **(A)** an anterior view; **(B)** with the bulk of the biceps resected; and **(C)** with the bulk of the brachialis resected. (From Rosse C, Gaddum-Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:252, with permission.)

The biceps is a common source of pain. The long head of this muscle arises as a rounded tendon from the supraglenoid tubercle and passes through the shoulder joint capsule. It invaginates into the synovium until a sleeve of synovial membrane surrounds it. Thus, the tendon is intracapsular yet remains extrasynovial. On leaving the joint, the biceps tendon exits the capsule at the level of the transverse ligament between the humeral tuberosities and descends in the intertubercular groove. The short head of the biceps arises from the coracoid process. Each tendon expands into fleshy bellies that lie side by side in the arm and then converge into a flattened tendon that crosses the elbow joint to its insertion into the posterior lip of the bicipital tuberosity of the radius. There is a small bursa (bicipitoradial) between the distal tendon and its insertion.

Extensor Compartment. The extensor compartment of the arm consists of the triceps muscle, a strong extensor of the elbow and weak extensor of the shoulder. This muscle arises by three heads, one from the infraglenoid tubercle of the scapula and two from the humerus. The triceps inserts into the upper surface of the olecranon, the tendon of insertion separated from the olecranon by the subtendinous bursa. Innervation of the triceps is the radial nerve (branch of posterior cord; C-7 and C-8 are the major cord segments).

There is also a bursa between the olecranon and the overlying skin, termed the *olecranon bursa*. It allows the skin to glide freely over the olecranon process. Bursal inflammation around the elbow principally affects this bursa.

Neurovascular Bundle. There is a major neurovascular bundle that passes from the neck into the upper limb in a similar manner as the bundle that passes from the pelvis into the lower limb. The subclavian artery becomes the axillary artery as it passes the first rib and then changes name to the brachial artery at the lower border of the teres major. Rich anastomoses surround the scapula and the proximal humerus, making the upper extremity relatively unaffected by trauma and peripheral vascular disease as compared with the lower. The profunda brachii branch provides the extensor compartment with arterial blood; the brachial artery supplies the flexor compartment. Infrequently, there is a small fibrous band in the distal arm, attached from an anomalous supratrochlear spur to the medial epicondyle (ligament of Struthers), under which the brachial artery and median nerve may pass. Compression of the artery, nerve, or both might result.

Several major nerves enter the arm. Their origins are discussed in Nerve Supply of the Upper Extremity, later in this chapter. The radial nerve is the continuation of the posterior cord of the brachial plexus. As it leaves the axilla, the nerve enters the posterior compartment of the arm and lies on the proximal fibers of the medial head of the triceps in the radial groove. After innervating the triceps, it continues down through the arm and emerges through the lateral intermuscular septum in the distal arm. Here it lies between the brachialis and brachioradialis; its superficial branch is sensory and continues down the forearm as the superficial radial nerve. Its deep branch pierces supinator and becomes the posterior interosseous nerve.

The musculocutaneous nerve enters the arm by piercing the coracobrachialis and then supplies all three muscles of the flexor compartment. It emerges at the distal lateral arm and continues as the lateral antebrachial cutaneous nerve. A large branch from the medial cord and lateral cords of the brachial plexus join together to form the median nerve. It passes through the arm providing no branches until the elbow and forearm and is described in the following section. Similarly, the ulnar nerve does not innervate any structures in the arm. In the middle of the arm, the ulnar nerve pierces the medial intermuscular septum and descends in front of the medial head of the triceps. A thin aponeurotic band, the arcade of Struthers, extends from the medial head of the triceps to the medial intermuscular septum. The ulnar nerve passes under the arcade of Struthers and is occasionally entrapped at this site. In the distal arm, the ulnar nerve enters the cubital tunnel from the posterior compartment. Two cutaneous nerves traverse the arm. The medial cutaneous nerve of the arm (also known as *medial brachial cutaneous*) is subcutaneous and supplies the skin of the medial arm. The medial cutaneous nerve of the forearm (also known as medial antebrachial cutaneous) crosses the elbow anteriorly and enters the forearm to supply sensory innervation to the medial forearm as far distal as the wrist.

In crossing the elbow, each of the three major nerves of the forearm passes through two heads of a muscle as follows: median nerve through pronator teres, ulnar nerve through flexor carpi ulnaris, and radial nerve through supinator.

These sites are potential entrapment points of the nerve and are discussed in Localized Nerve Lesions, later in this chapter.

Elbow

The elbow is the joint of the upper limb that constitutes the mechanical link between the arm and forearm. As the shoulder positions the limb in space, the elbow allows the forearm to place the hand at any distance from the body. The elbow joint is of the hinge variety, between the humerus above with radius and ulna below, allowing 160-degree flexion-extension of the forearm. The articulating surfaces provide great stability to the joint. The distal end of the humerus has two articular surfaces, the pulley-shaped trochlea and the spherical capitulum (Fig. 57-14). The proximal ends of the two forearm bones have surfaces corresponding in shape to those of the humerus. Medially, the trochlear notch of the ulna articulates with the trochlea. It consists of a curved surface and ridge between two projections, the coronoid process anteriorly and the olecranon posteriorly. Laterally, the proximal end of the radius is shaped like a cup with a concavity that fits into the capitulum. Above the articular surfaces there are two humeral concavities. The anterior coronoid fossa receives the coronoid process of the ulna in full flexion and the posterior olecranon fossa receives the olecranon during extension (Fig. 57-15).

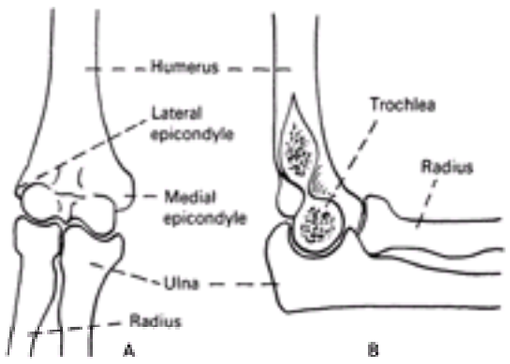

Figure 57-14. **A,B:** The bones of the elbow joint. (Modified from Matsen FA III. Biomechanics of the elbow. In: Frankel VH, Nordin M, eds. *Basic biomechanics of the skeletal system*. Philadelphia: Lea & Febiger, 1980:243–253.)

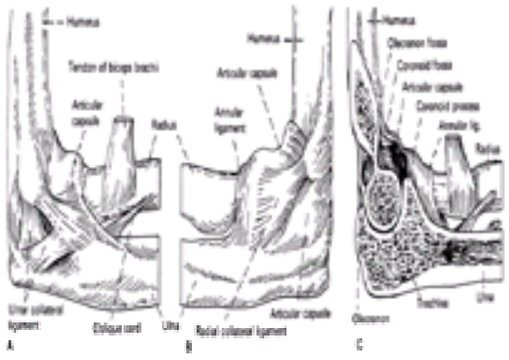

Figure 57-15. **A,B,C:** The ligaments of the elbow joints. (Modified from Clement CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:375–382.)

The capsule of the joint is relatively thin, enclosing both the elbow joint and the superior radioulnar joints. Attachments of the capsule surround the anterior and posterior fossae, but do not enclose the humeral epicondyles. Strong collateral ligaments act as stays located on the medial and lateral side of the joint and are named correspondingly, the medial (ulnar) and lateral (radial) collateral ligaments (see Fig. 57-15).

Synovium lines the capsule and is attached to the articular margins of all three bones. The membrane is reflected over the inner surface of the capsule and covers the fat pads within the anterior and olecranon fossae. Synovium also lines the gap between the proximal ulna and radius.

Movements

The range of active flexion is approximately 145 degrees, limited by apposition of the soft tissues. Extension is limited first by soft tissues (anterior capsule and flexor muscles) followed by the impact of the olecranon process on the olecranon fossa. The prime movers for flexion are brachialis, biceps brachii, and brachioradialis, although biceps is used when power is required. Accessory flexors include those muscles that arise from the medial epicondyle. The flexor muscles are at their optimal length and power when the elbow is at 90 degrees. The prime mover for extension is the triceps. Because the only prime mover is a biarticular muscle (unlike the flexors), the efficiency of the triceps depends in part on the position of the shoulder. Flexion of the shoulder lengthens the long head of the triceps and enhances its power. Weak accessory muscles arise from the lateral epicondyle (anconeus and supinator and the muscles that arise from the lateral epicondyle) but are thought to be functionally insignificant.

Nerve Supply

The musculocutaneous, median, ulnar, and radial nerves innervate the joint.

Forearm and Wrist

Forearm

The forearm consists of 20 muscles, found within a flexor and extensor compartment, which act across several joints (e.g., elbow, superior radioulnar, inferior radioulnar, wrist, and small joints of the hand). As with the arm, the major neurovascular bundles are found within the flexor compartment.

Flexor Compartment. There are eight muscles in the anterior compartment of the forearm. An easy memory scheme to remember the muscles is 2-2-2-2:

- Two muscles flex the wrist (flexor carpi radialis and ulnaris).
- Two muscles flex the fingers (flexor digitorum superficialis and profundus).
- Two muscles pronate the forearm (pronator teres and quadratus).
- Two muscles are *long* (flexor pollicis *longus* and palmaris *longus*).
- Most of these muscles are innervated by the median nerve except the ulnar nerve innervates flexor carpi ulnaris and the ulnar half of the flexor digitorum profundus (muscle bellies to the ring and little fingers).

The flexor compartment has a superficial, intermediate, and deep layer. In the superficial group, all of the muscles attach to the medial epicondyle and arise from a common flexor tendon. The muscles include pronator teres, flexor carpi radialis, palmaris longus, and flexor carpi ulnaris (Fig. 57-16). Irritation of the common flexor tendon (also known as medial epicondylitis) results from repetitive wrist flexion or pronation activities related to sports, occupation, and performing arts.

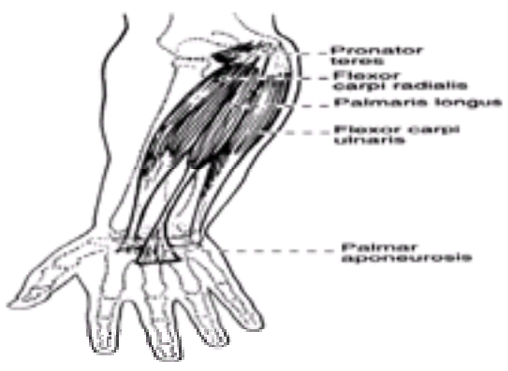

Figure 57-16. The superficial forearm muscles of the flexor compartment consist of pronator teres (cut in this figure), flexor carpi radialis (FCR), palmaris longus, and flexor carpi ulnaris (FCU). With the heel of the hand placed over the opposite medial epicondyle, palm lying on the forearm, the fingers point down along the four superficial and one intermediate muscles: thumb for pronator teres, index for FCR, middle finger tucked beneath the other fingers as the flexor digitorum superficialis, ring finger for palmaris longus, and little finger for FCU. (From Rosse C, Gaddum- Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia:

Lippincott–Raven, 1997:260–261, with permission.)

The intermediate layer consists of the flexor digitorum superficialis (Fig. 57-17). Its origin is from the common flexor origin, proximal ulna (coronoid process), and proximal radius. There is a fibrous arch that stretches from the ulna to the radius. The median nerve passes behind this fibrous arch and is sometimes entrapped. In the distal third of the forearm, the muscle gives rise to four tendons; two are superficial (middle and ring fingers) and two are deep. A synovial sleeve, termed the *common synovial tendon sheath*, invests all of the long finger flexors (both flexor digitorum superficialis and profundus) as they pass beneath the flexor retinaculum in the carpal tunnel (Fig. 57-18). The tendons then emerge from the common sheath into the palm of the hand and each tendon enters an individual digital synovial sheath. The individual superficialis tendons finally split into two halves and insert onto the middle phalanx (Fig. 57-19).

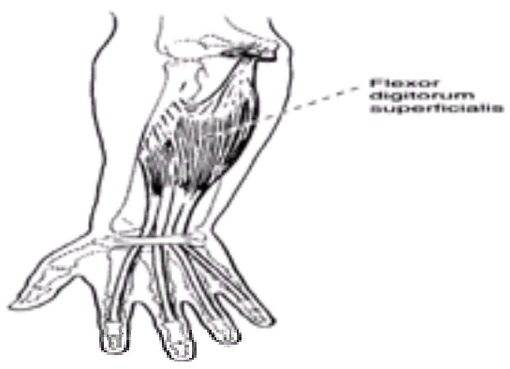

Figure 57-17. The flexor digitorum superficialis arises from the common flexor origin and deeper structures as well (proximal ulna and radius). The muscle gives rise to four tendons that insert onto the middle phalanges. (From Rosse C, Gaddum-Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:260–261, with permission.)

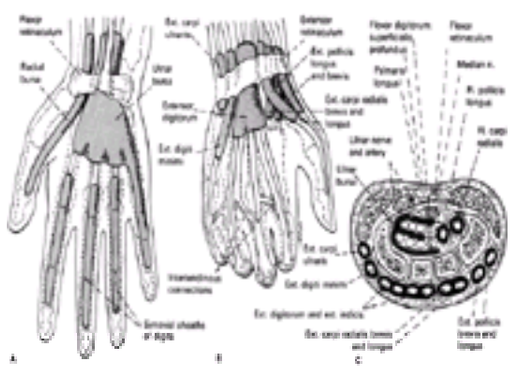

Figure 57-18. **A:** Palmar view of the wrist and hand showing the synovial sheaths of the flexor tendons in the carpal tunnel of the hand. Note the proximal extent of the radial and ulnar bursae in relation to the flexor retinaculum. **B:** Extensor retinaculum with the tendons and their synovial sheaths on the dorsum of the wrist. **C:** Transverse section of the wrist across the carpal tunnel, showing the relationship of the median nerve deep to the flexor retinaculum and superficial to the synovial membranes of the flexors to the wrist and hand. All eight flexor tendons of the fingers share a common sheath (ulnar bursa) **(A,C)**, as do the four tendons of the extensor digitorum on the back of the wrist **(B,C)**. (Adapted from Rosse C, Clawson DK, eds. *The musculoskeletal system in health and disease*. New York: Harper & Row, 1980.)

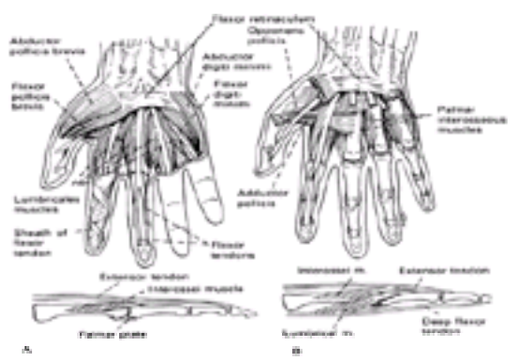

Figure 57-19. **A:** Palmar view of the intrinsic (thenar and hypothenar) muscles of the hand: superficial muscles. The palmar aponeurosis has been removed, and the synovial sheaths of the tendons of extrinsic plexus are not shown. **B:** The deeper intrinsic muscles with the tendons of the extrinsic plexus cut and removed. The lower panels show side view of finger to show the attachments of the interossei **(A,B)** and lumbrical **(B)**. (Modified from Rosse C. The hand. In: Rosse C, Clawson DK, eds. *The musculoskeletal system in health and disease*. New York: Harper & Row, 1980:227–251.)

The deep layer contains three muscles, flexor digitorum profundus, flexor pollicis longus, and pronator quadratus (Fig. 57-20). Flexor digitorum profundus arises from the proximal ulna and interosseous membrane. The muscle gives rise to four tendons, which lie side by side beneath the superficialis tendons. Each tendon passes into the digital synovial sheath immediately beneath its superficialis counterpart. The profundus tendon goes through the split in the superficialis tendon and continues to its insertion on the distal phalanx (see Fig. 57-19). Flexor pollicis longus arises from the radius. The muscle gives rise to a tendon that passes through the carpal tunnel and inserts on the distal phalanx of the thumb. A separate synovial sheath invests the tendon throughout the course from the distal forearm to its insertion (see Fig. 57-18).

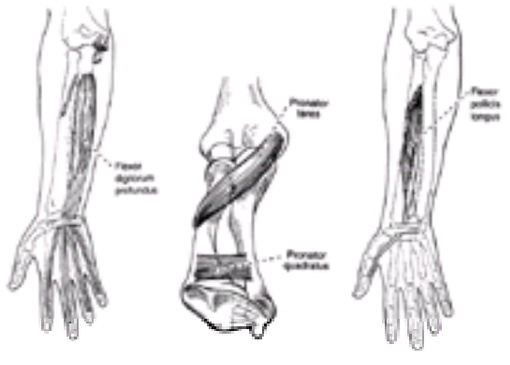

Figure 57-20. The deep layer of the flexor compartment consists of flexor digitorum profundus, flexor pollicis longus, and pronator quadratus. All of these muscles are

innervated by the anterior interosseous nerve. (From Rosse C, Gaddum-Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:260–261, with permission.)

Extensor Compartment. There are 12 muscles in the posterior compartment of the forearm. These muscles are best remembered by the scheme 3-3-3-3:

- Three muscles extend the wrist (extensor carpi ulnaris, radialis brevis, and radialis longus).
- Three muscles extend the fingers (extensor digitorum communis, indicis, and digiti minimi).
- Three muscles act on the thumb (abductor pollicis longus, extensor pollicis brevis and longus).
- Three muscles cross the elbow and spell B-A-S (brachioradialis, anconeus, and supinator).

The radial nerve innervates all 12 of the muscles in the extensor compartment. The extensor compartment has a superficial and a deep layer. In the superficial group, the muscles arise from the supracondylar ridge (brachioradialis and extensor carpi radialis longus) and the lateral epicondyle (common extensor tendon) of the humerus (Fig. 57-21). The muscles attaching to the common extensor origin include extensor carpi radialis brevis, extensor digitorum, extensor digiti minimi, and extensor carpi ulnaris. Irritation of the common extensor tendon (also known as lateral epicondylitis) results from repetitive wrist and finger extension.

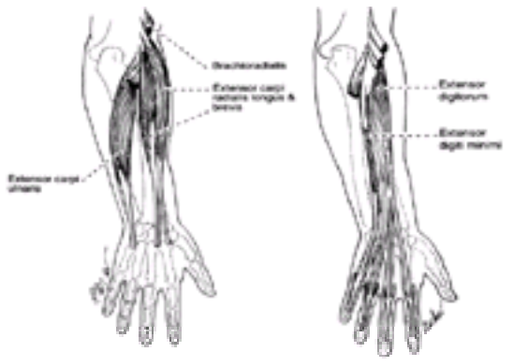

Figure 57-21. The superficial group of extensor muscles of the forearm consist of muscles that arise from the supracondylar ridge (brachioradialis and extensor carpi radialis longus) and the common extensor origin (extensor carpi radialis brevis, extensor digitorum, extensor digiti minimi, and extensor carpi ulnaris). (From Rosse C, Gaddum-Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:260–261, with permission.)

Tendons crossing the dorsal wrist are enclosed for part of their course in tenosynovial sheaths (see Fig. 57-18). The extensor tendons pass through six fibroosseous, tenosynovial tunnels beneath the extensor retinaculum. The abductor pollicis longus and extensor pollicis brevis are usually in a single sheath and involved in DeQuervain's stenosing tenosynovitis.

Neurovascular Considerations. Two nerves share in the supply of the flexor compartment: median and ulnar. The median nerve passes through the two heads of pronator teres (also known as pronator passage), supplies all of the superficial and intermediate muscles (except flexor carpi ulnaris), and then passes down the forearm between the long finger flexors. Just distal to the pronator passage, the anterior interosseous nerve branches and enters the deep compartment of the flexor compartment. It innervates all of the deep muscles except the ulnar half of flexor digitorum profundus. Sensory fibers innervate the inferior radioulnar and wrist joints. The ulnar nerve enters the forearm by passing into a space, sometimes called the cubital tunnel, bordered by the olecranon and medial epicondyle and a fibrous sheath between them. It then passes through the two heads of flexor carpi ulnaris and down the forearm between that muscle and the underlying flexor digitorum profundus. It innervates both muscles, although only the ring and little fingers of the latter. Sensory fibers innervate the inferior radioulnar and wrist joints. Unlike the median nerve, the ulnar nerve does not enter the carpal tunnel; it crosses superficial to the flexor retinaculum with the ulnar artery.

While still in the arm, the radial nerve innervates the brachioradialis and extensor carpi radialis longus because both muscles arise from the supracondylar ridge on the humerus. The radial nerve then divides into superficial radial and posterior interosseous nerve in the distal arm. The latter passes through the two heads of supinator and supplies all of the remaining forearm extensors. The superficial radial nerve is entirely sensory at this point and supplies a small area of skin on the dorsum of the hand.

Radioulnar Joints. The radius and ulna are joined by an interosseous membrane and by two synovial joints (superior and inferior radioulnar joint). Supination and pronation, also known as rotation of the forearm, occur between these two bones. Supination-pronation is one of the most important movements in the upper limb because it is essential for the control of hand orientation during work, grasping an object, and activities of daily living (e.g., toileting, grooming, and feeding). In supination-pronation, the radius is the moving bone around a relatively stationary ulna.

Superior Radioulnar Joint. The superior radioulnar joint is of the pivot variety and has one degree of freedom (i.e., rotation between the radius and ulna). The head of the radius and its cylindrical rim are covered by articular cartilage and join with three structures: the capitulum of the humerus, the radial notch of the ulna, and the annular ligament (Fig. 57-22). The superior radioulnar joint communicates with the elbow joint and is included in the same articular capsule. Inferiorly, the quadrate ligament stretches between the neck of the radius and the inferior border of the radial notch on the ulna. Its fibers reinforce the inferior aspect of the elbow joint capsule. The major stabilizing factor of the superior radioulnar joint is the annular ligament, attached to the anterior and posterior margins of the radial notch of the ulna. It surrounds the head of the radius and binds it to the radial notch and also serves as an articular surface in contact with the head of the radius as it rotates during supination and pronation (Fig. 57-23).

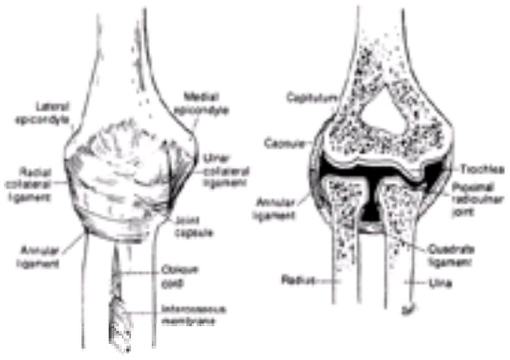

Figure 57-22. The elbow joint: On the left, the joint capsule is shown with its associated ligaments. The coronal section of the joint on the right shows the relation of the proximal radioulnar joint to the elbow. Articular cartilage is shown as an *even white line;* synovial membrane as a *ruffled white line;* synovial fluid is *black.* (From Rosse C, Gaddum-Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:297, with permission.)

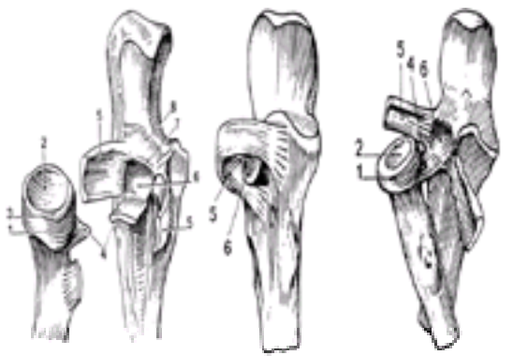

Figure 57-23. The superior radioulnar joint has 1 degree of freedom, rotation between the head of the radius and the radial notch of the ulna. The annular ligament (5) consists of a strong fibrous band attached by its ends to the anterior and posterior margins of the radial notch of the ulna. It surrounds the head of the radius and binds it to the radial notch. The quadrate ligament (4) consists of a fibrous band attached to the inferior border of the radial notch and to the neck of the radius. It reinforces the inferior aspect of the capsule and prevents distraction of the radial head away from the radial notch. Other anatomic features of interest include the following labeled structures: the head of the radius covered by articular cartilage (1); the cupped head of the radius articulating with the capitulum (2); and the radial notch of the ulna (6). (From Kapandji IA. *The physiology of the joints*, 5th ed. Vol 1: Upper limb. Edinburgh, UK: Churchill Livingstone, 1982:107, with permission.)

NERVE SUPPLY. The musculocutaneous, median, ulnar, and radial nerves innervate the joint.

Inferior Radioulnar Joint. The inferior radioulnar joint is also of the pivot variety and lies between the distal ends of the radius and ulna. Three-fourths of the cylindrical portion of the ulnar head articulates with the concave ulnar notch of the radius (Fig. 57-24). An articular disk lies in a horizontal plane at the distal edge of the joint and binds together the distal edge of the radius and the lateral aspect of the ulnar styloid process while allowing rotational displacement of the radius about the stationary ulna (see Fig. 57-24). The disk also separates the inferior radioulnar joint from the wrist joint, although the two joints are enclosed within the same capsule. Its proximal surface is in contact with the distal surface of the ulnar head. Its distal surface faces the carpal bones and is compressed during full adduction of the wrist. The synovial membrane lines the articular disk and the distal ends of the ulna and radius; between the bones, there is a redundant pouch of synovium called the sacciform recess (see Fig. 57-24).

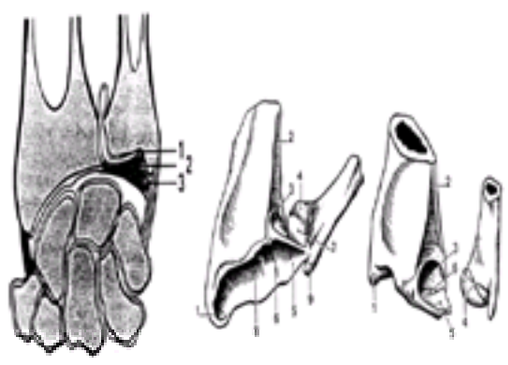

Figure 57-24. Figure at left: The articular disk separates the radio-ulnar joint from the radio-carpal joint. Figures at right and middle: The ulnar notch of the radius (3) faces medially and is concave. It articulates with the cylindrical portion of the ulnar head (4). At its distal edge is inserted the articular disk (5), which lies in a horizontal plane. It fills the gap between the ulnar head, the triquetrum, and acts as an elastic cushion, which is compressed during adduction of the wrist. The articular disk also separates the radioulnar joint from the radiocarpal joint. Other anatomic features of interest in the middle and right figures include the following labeled structures: radial styloid process (1), distal surface of the ulnar head (7), and carpal surface of the radius (8). (From Kapandji IA. *The physiology of the joints*, 5th ed. Vol 1: Upper limb. Edinburgh, UK: Churchill Livingstone, 1982:111, with permission.)

NERVE SUPPLY. The anterior and posterior interosseous nerves innervate the joint.

Wrist

The wrist is the distal joint of the upper limb and allows the hand to assume an optimal position to grasp an object. It is an ellipsoid joint between the distal surface of the radius and the proximal row of carpal bones that allows flexion-extension and adduction-abduction (Fig. 57-25). For most activities, the major articulation is between the radius proximally and the scaphoid and lunate distally. During full adduction of the wrist, the articular disk covering the head of the ulna and the ulnar styloid process articulate with the triquetral and pisiform bones. With flexion and extension some movement also occurs at the midcarpal joint (see Carpal Bones and Intercarpal Joints, later in this chapter).

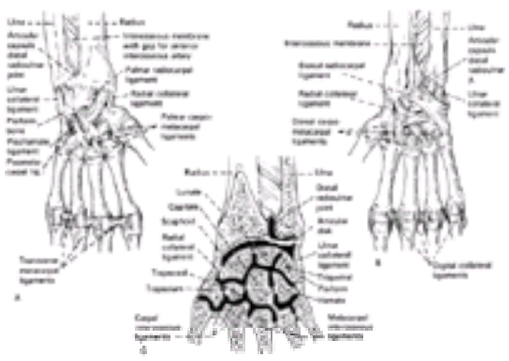

Figure 57-25. The bones and ligaments of the lower part of the forearm and the wrist: palmar view **(A)**, dorsal view **(B)**, and vertical section **(C)** to show the joints and ligaments (see text for details). (Adapted from Clement CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:382–383.)

Several ligaments strengthen the capsule of the wrist joint. Strong palmar and dorsal ligaments attach from radius and ulna to corresponding carpal bones (e.g., scaphoid, lunate, and triquetrum) (see Fig. 57-25). The palmar ligaments are particularly important during extension, counteracting the tendency for the carpal bones to be displaced proximally and anteriorly. Synovium lines the joint capsule but does not communicate with the inferior radioulnar joint.

Movements. The range of flexion is 80 degrees and does not quite reach a right angle. The prime movers for flexion include flexor carpi ulnaris, flexor carpi radialis, and palmaris longus. Extension range is slightly less at approximately 75 degrees because of tighter palmar than dorsal ligaments, and performed by extensor carpi ulnaris and extensors carpi radialis longus and brevis. When the wrist is fully flexed or extended, little movement into adduction or abduction is possible. In the neutral position, the range of adduction (45 degrees) is approximately three times that of abduction (15 degrees). The two ulnaris muscles adduct the wrist (flexor and extensor carpi ulnaris), whereas the abductors include the radialis muscles (flexor and extensor carpi radialis longus and brevis), abductor pollicis longus, and

extensor pollicis longus and brevis. True rotation does not occur at the wrist, but circumduction can occur as a combination of the movements described previously.

The position of maximal efficiency and strength for prehension is at 40- to 45-degree wrist extension and slight wrist ulnar deviation (15 degrees). This is the position in which the finger flexors are at their optimal length for a powerful grip. It is also important to observe that the wrist does not move in a direct anatomic plane. Many activities of daily living (e.g., eating) and work-related activities (e.g., hammering) illustrate that movement occurs along an oblique plane from extension combined with radial abduction to flexion combined with ulnar adduction.

Nerve Supply. The ulnar, anterior, and posterior interosseous nerves innervate the joint.

Hand

The human hand is remarkable in that powerful prehension is combined with finely controlled accuracy and sensitive tactile abilities. Free mobility of the thumb and a wide range of opposition, the ability to bring the thumb into contact with each finger, provide the hand with versatile abilities in positioning, grasping, and exploring.

Overall Organization. The skin of the dorsum and palm is quite different. On the dorsum the skin is loose and freely mobile, thus allowing free movement during prehension. In contrast, fibrous bands anchor and stabilize the skin of the palm with the underlying palmar aponeurosis. The soft tissues of the palm are organized into the same four layers as the foot. Beneath the palmar aponeurosis lie the short muscles of the thumb (thenar) and little finger (hypothenar). The next layer consists of the long flexors of the fingers (flexor digitorum superficialis and profundus) and the lumbricals. More deeply is the adductor muscle of the thumb, which comprises the third layer. Finally, the interosseous muscles lie between the metacarpal bones on the palmar and dorsal surfaces. Two neurovascular bundles lie on either side of the long flexor tendons.

Fibrous sheaths attach to the fingers and form fibroosseous tunnels along the concave palmar surfaces of the phalanges (Fig. 57-26). Synovial sheaths then surround the long flexor tendons and glide within the fibrous sheaths. The middle fingers each have a synovial sheath that is discontinuous with the common synovial tendon sheath (see description in Forearm and Wrist). The little finger has a synovial sheath that is continuous with the common synovial sheath (see Fig. 57-18). Finally, the thumb has a separate synovial sheath that does not connect with the common synovial sheath but is continuous through the carpal tunnel.

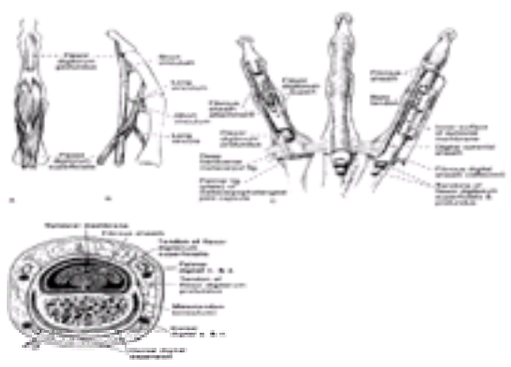

Figure 57-26. The arrangement of **(A,B)** the flexor tendons and **(C)** digital synovial sheaths and fibrous digital sheaths in the fingers. **D:** A transverse section across the proximal phalanx of a finger to show the arrangement of flexor tendons and their synovial sheaths within the fibrous flexor sheaths. (From Rosse C, Gaddum-Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:278–279, with permission.)

The dorsum of the hand has little in the way of soft tissue layers. Skin and fascia slide freely over extensor tendons and bone. Digital nerves and vessels run in the subcutaneous fat. Beneath the deep fascia, the long extensor tendons terminate in the extensor hood known as the dorsal digital expansion.

When the long extensor tendons (extensor communis, indicis, and digiti minimi) reach the metacarpal heads, they are joined by the tendons of the interossei and lumbricals, thus forming the dorsal digital expansion on the dorsum of each finger (Fig. 57-27). The expansion divides over the dorsum of the proximal phalanx into a central slip and two lateral bands. The central slip is inserted principally into the base of the middle phalanx. The two lateral bands pass on either side of the proximal interphalangeal joint, fuse with each other beyond it, and insert into the base of the distal phalanx. Changes in the position of these parts of the extensor hood from trauma or disease produce common finger deformities (e.g., swan neck deformity and boutonnière deformity).

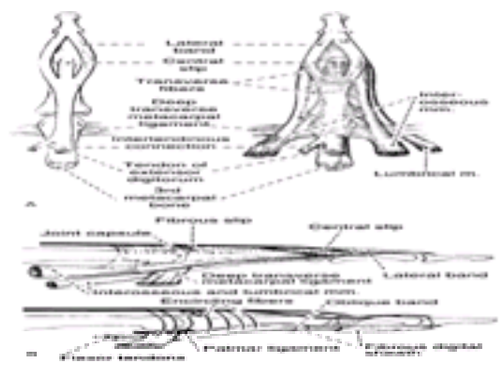

Figure 57-27. **A:** Components of the dorsal digital expansion seen from the dorsal aspect. **B:** The dorsal digital expansion seen from the side and some of its components illustrated schematically. (From Rosse C, Gaddum-Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:295, with permission.)

Many small bones and joints provide the anatomic foundation of the hand. Carpal, metacarpal, and phalangeal bones join at the intercarpal, carpometacarpal, metacarpophalangeal, and interphalangeal joints.

Carpal Bones and Intercarpal Joints. Eight wrist bones are arranged in two horizontal rows of four and assemble a semicircle, the convexity of which is proximal and articulates with the forearm bones at the wrist (Fig. 57-28). The carpal bones form a gutter that is concave on the palmar side to accommodate the flexor tendons (see Fig. 57-18). The gutter is transformed into the carpal tunnel by the flexor retinaculum (also known as volar carpal ligament), attached to carpal bones that make up the anterior borders of the gutter (e.g., scaphoid and trapezium laterally, pisiform and hamate medially) (Fig. 57-29). The ulnar tunnel (Guyon's canal) transmits the ulnar nerve at the wrist. It is bounded on the sides by the hook of the hamate and the pisiform bone. The floor and roof of the tunnel are the transverse carpal ligaments and volar carpal ligaments, respectively.

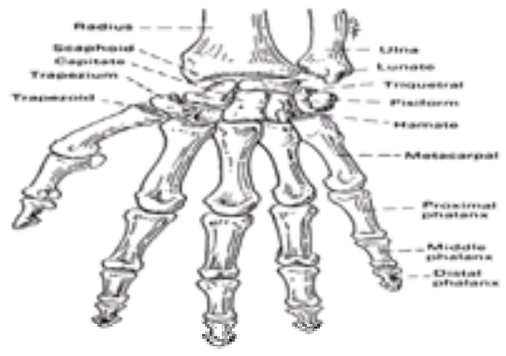

Figure 57-28. The bones of the lower forearm, wrist, and hand.

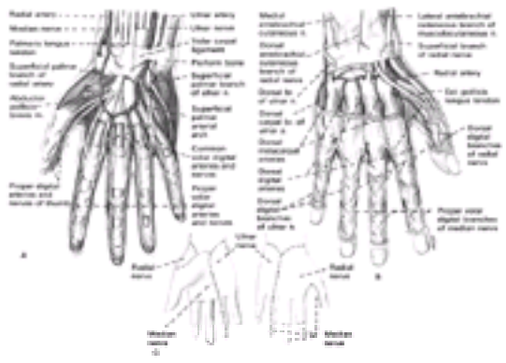

Figure 57-29. The nerves and arteries of the hand. **A:** Palmar view. **B:** Dorsal view. **C:** The cutaneous nerve supply of hand. Developed from numerous sources.

Functionally, the carpal bones and metacarpals consist of three vertical columns (Fig. 57-30). The lateral column of the thumb is made up of the scaphoid, trapezium, and first metacarpal. The intermediate column is important as the axis of the hand and is composed of the lunate, capitate, and third metacarpal. The medial column is the least important functionally and consists of the triquetrum, hamate, and medial two metacarpals (fourth and fifth).

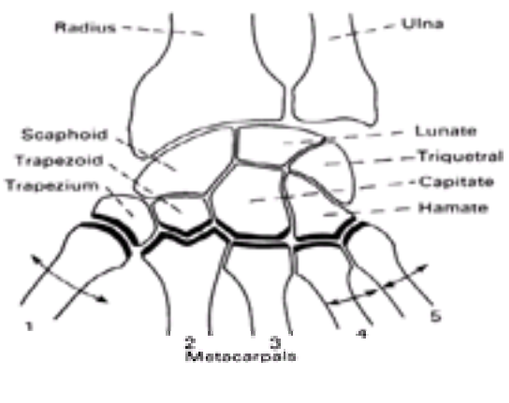

Figure 57-30. Articulations of the carpus with the radius and ulna and the metacarpals. Note that five metacarpal bones articulate with four carpal bones. The articulations of the second and third metacarpals are such that they immobilize this segment, whereas the articulations of the first, fourth, and fifth metacarpals permit mobility about the fixed central segments. (Adapted from Cailliet R. *Hand pain and impairment*, 3rd ed. Philadelphia: FA Davis, 1982:14.)

The carpal bones form synovial joints with one another. Palmar and dorsal capsular ligaments strengthen the intercarpal capsules (see Fig. 57-25). Joints between the proximal row of carpal bones communicate with the midcarpal joint, a large synovial joint between the proximal and distal row of bones that allows flexion-extension at the wrist. Distally, there is a large synovial cavity between the distal carpal bones, the carpometacarpal joints, and the intercarpal joints.

Nerve Supply. The ulnar, median, anterior, and posterior interosseous nerves innervate these joints.

Carpometacarpal Joints. Four carpal bones articulate with five metacarpal bones (see Fig. 57-30). The metacarpals have expanded bases by which they articulate with the carpal bones and each other. Carpometacarpal joints are of the plane variety and some movements of flexion-extension occur. The second and third metacarpal heads articulate with the trapezoid and capitate; as a unit they comprise a central, immobile segment. They are relatively fixed so that, as the hand is cupped, the first carpometacarpal moves on the radial side and the ulnar carpometacarpal joints (ring and little fingers) move on the ulnar side of this segment. The joint between the hamate and fifth metacarpal is particularly mobile and aids in this cupping motion. There is a single large capsule and joint space that communicates with all of the carpometacarpal joints (except for the first), intermetacarpal joints, and intercarpal joints of the distal row.

The first carpometacarpal joint is different from the rest and fundamental to the function of the thumb (Fig. 57-31). The thumb metacarpal is shorter and thicker; its base articulates with the saddle-shaped trapezoid. The shaft is set at nearly 90 degrees with the palm so that its flexor surface faces across the palm. The capsule of the joint is lax but strong; it does not communicate with the carpometacarpal joint. Several strong ligaments attach from the trapezoid to the base of the first metacarpal (e.g., anteromedial ligament and posteromedial ligament). Movements at this joint include flexion-extension (although most of this occurs at the metacarpophalangeal and interphalangeal joints), abduction-adduction, and opposition.

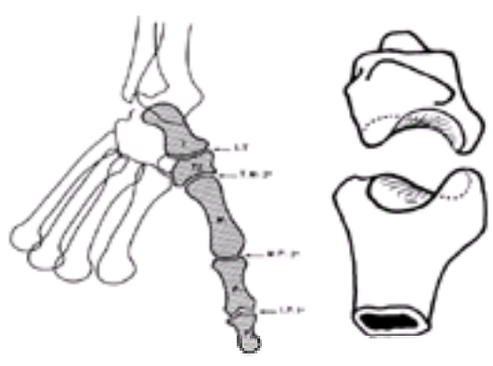

Figure 57-31. The carpometacarpal joint of the thumb is between the trapezoid and thumb metacarpal. It is a saddle joint with two saddle-shaped surfaces concave in one direction and convex in the other. (From Kapandji IA. *The physiology of the joints*, 5th ed. Vol 1: Upper limb. Edinburgh, UK: Churchill Livingstone, 1982:209, with permission.)

Nerve Supply. The ulnar, median, anterior, and posterior interosseous nerves innervate these joints.

Metacarpophalangeal Joints. The heads of the metacarpals are large and rounded with an articular surface that extends further on the palmar than extensor surface (Fig. 57-32). The bases of the proximal phalanges have a much smaller biconcave articular surface, thus forming an ellipsoid joint. The joint capsule is loose with recesses found anteriorly and posteriorly to permit freedom of movement. Indeed, free passive range of movement, including rotation, may be elicited in the relaxed hand. Only flexion-extension and abduction-adduction are possible actively. The joint capsule is thickened anteriorly by a stiff fibrocartilaginous pad called the palmar ligament or palmar plate (Fig. 57-33). These plates allow maximal contact between the bony surfaces and are flexible enough that flexion is not limited. Three types of ligaments attach to the palmar plate: collateral ligaments, deep transverse metacarpal, and the fibrous digital sheaths. Collateral ligaments are found on either side of the joint and are attached posterior to the center of curvature of the joint. Therefore, the ligaments are slack in extension and taut in flexion. Clinically, metacarpophalangeal joints must never be immobilized in extension in view of the risk of development of contractures of the collateral ligaments.

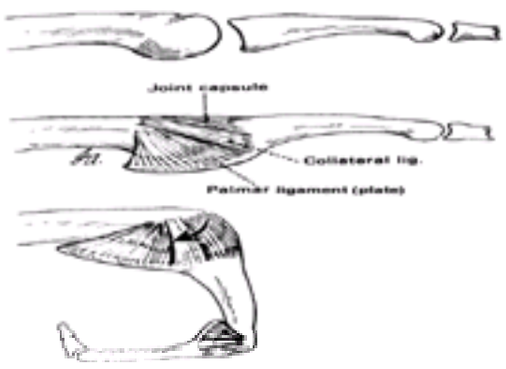

Figure 57-32. The metacarpophalangeal and interphalangeal joints: The attachment of the deep transverse metacarpal ligament to the palmar plate of the metacarpophalangeal joint is not shown. (From Rosse C, Gaddum-Rosse P. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:304, with permission.)

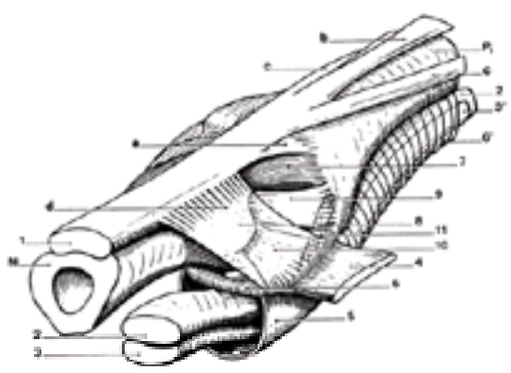

Figure 57-33. The ligaments of the metacarpophalangeal (MP) joints are viewed in this view from behind and above a joint. The insertion of the extensor digitorum communis is dorsal to the capsule of the MP joint and divides into a medial slip (b) and lateral slips (c). The joint capsule is thickened anteriorly by the palmar ligament (4). Collateral ligaments attach to the lateral tubercles (8) and also reinforce the capsule. Other anatomic features of interest include the following labeled structures: extensor digitorum communis tendon (1), flexor digitorum profundus tendon (2), flexor digitorum superficialis tendon (3), metacarpal pulley (5), and fibrocartilaginous plate (6). (From Kapandji IA. *The physiology of the joints*, 5th ed. Vol 1: Upper limb. Edinburgh, UK: Churchill Livingstone, 1982:181, with permission.)

The palmar plates are held together by way of the deep transverse metacarpal ligament of the palm so that its fibers span the entire width of the hand. It prevents separation of the metacarpal heads and contributes to the formation of the fibrous tunnels for the interossei.

Dense collagenous tissue forms a rigid tunnel for the flexor tendons of each finger. These fibrous digital sheaths attach to either side of the phalanges (palmar surface) and to the deep transverse metacarpal ligament.

Movements. Flexion has a range of approximately 90 degrees, whereas active extension is only approximately 30 degrees. Adduction and abduction are more limited to 20 to 30 degrees. Flexors of the metacarpophalangeal joints include flexor digitorum superficialis and profundus, the lumbricals, and the interossei. The major extensors are extensor digitorum communis, extensor indicis, and extensor digiti minimi. Abduction and adduction are performed by the interossei; the palmar interossei adduct (PAD) while the dorsal interossei (DAB) abduct the metacarpophalangeals.

The first metacarpophalangeal joint permits up to 70 degrees' palmar flexion and 25 degrees' extension. Flexor pollicis brevis and longus flex the first metacarpophalangeal. Extensor pollicis brevis and longus extend the joint.

NERVE SUPPLY. The deep branch of the ulnar nerve and the digital branches from the ulnar and median nerves innervate these joints.

Interphalangeal Joints. These are hinge joints with only flexion and extension movements (see Fig. 57-32). The head of each proximal and middle phalanx is pulley shaped with a central groove. The base of the immediately distal phalanx has a reciprocal surface with a crest that fits into the central groove. The capsule and ligaments are similar in structure to the metacarpophalangeal joints except there is no similar structure to the deep transverse metacarpal ligament.

Movements. The range of flexion at the proximal interphalangeal joints is slightly greater than 90 degrees. At the distal interphalangeal joints, maximum flexion is less than 90 degrees. At both the proximal interphalangeal and distal interphalangeal joints, range increases from the second to the fifth finger. Prime movers for flexion at the interphalangeal joints are both flexor digitorum superficialis and profundus at the proximal interphalangeal and only the latter at the distal interphalangeal. There is little, if any, active extension beyond the neutral position. The prime extensors of the proximal interphalangeal and distal interphalangeal joints are the lumbricals and interossei.

The interphalangeal joint of the thumb allows 90 degrees' palmar flexion and up to 35 degrees' extension. The flexor pollicis longus flexes the interphalangeal joint of the thumb and the extensor pollicis longus extends the joint.

NERVE SUPPLY. The digital branches from the ulnar and median nerves innervate these joints.

Nerve Supply of the Upper Extremity

Sympathetic Supply of the Upper Limb

A postganglionic (gray ramus) sympathetic nerve joins each root of the brachial plexus after exit from the intervertebral foramina and these sympathetic fibers hitchhike through the plexus and its nerves. Thus, each dermatome of the upper limb is supplied via the cutaneous nerves by sympathetic fibers to innervate blood vessels, sweat glands, and arrector pili muscles. The postganglionic nerve arises from cell bodies in the appropriate sympathetic ganglion from the lower cervical and

first thoracic sympathetic chain (see Chapter 8).

The preganglionic fibers for the upper limb originate within the spinal cord (preganglionic fibers arise from the thoracolumbar outflow) from the upper segments (T-2 to T-6). The cell bodies are located in the lateral horn and the axons exit via the ventral roots. They ascend in the sympathetic chain to synapse in the ganglion mentioned previously.

Brachial Plexus. In all vertebrates, each limb is organized into compartments. Limb plexuses supply the skin and muscles of these compartments. In the plexus, spinal nerves interchange fibers so that the major nerve branches distal to the plexus receive contributions from two or more segmental spinal nerves. The evolution of plexuses was an important adaptive structural and functional advancement, allowing further complex neuromusculoskeletal behavior and protection from injury.

All of the vertebrates, including humans, have a similar organization of limb plexuses. From fish to reptiles to humans, each limb plexus has the following features in common: (a) several spinal nerves (connected to spinal cord enlargements) contribute nerve fibers to the plexus, intermingle, and regroup; (b) each spinal nerve divides into a dorsal ramus and ventral ramus, however, only the ventral ramus contributes nerve fibers to the limb plexus; (c) each plexus divides into anterior divisions to supply flexor muscles and the overlying surface of the limb and posterior divisions to supply extensor muscles and the surface; and (d) each plexus is an organized meshwork of sensory, motor, and sympathetic fibers that innervates most of the extremity.

The brachial plexus, approximately 15 cm long and comprised of approximately 150,000 axons in the adult, is an extremely durable and load-tolerant structure. The roughly diamond-shaped plexus is strong and lax, features that make the plexus resistant to mechanical stresses within the normal physiologic ranges of motion. Additional strength is provided proximally, where the spinal nerves are bound down to the transverse processes with dense connective tissues. However, the connective tissue binding down the upper spinal nerves (C- 5, 6, 7) is denser than that of C-8 and Th-1, thereby protecting the upper roots from avulsion injuries. The plexus is further reinforced by the connective tissues of the nerves themselves (epineurium, perineurium, endoneurium), which makes them further resistant to tensile forces. All of these protective features are particularly important in mammals with mobile shoulders capable of full abduction (swimming, burrowing, climbing, and flying mammals) such as moles, birds, primates, and humans. For in these animals, the plexus is fixed at one end to a mobile neck and affixed at the other to an upper extremity built for free movement. The plexus is at additional risk of injury because it runs in close proximity to the shoulder joint, a remarkably mobile structure composed of bones that are sometimes dislocated and fractured.

General Survey of Upper Limb Innervation. The brachial plexus supplies most of the sensory, motor, and sympathetic innervation to the upper extremity including the pectoral girdle musculature and joints. There are exceptions to this rule. For example, branches of the cervical plexus supply part of the levator scapulae, and the spinal accessory nerve innervates the trapezius and sternocleidomastoid by way of a circuitous course that does not involve the brachial plexus. Sensory exceptions include skin overlying the pectoral girdle musculature (segmentally innervated by branches of the intercostal nerves) and the proximal, medial arm (innervated by the intercostobrachial nerve from Th-2).

Formation of the Brachial Plexus. Five spinal nerves, C-5, 6, 7, 8, and Th-1 emerge from their respective intervertebral foramina and course downward along the gutter-shaped transverse processes of the lower cervical vertebrae, immediately dividing into a small dorsal ramus and large ventral ramus. The brachial plexus is formed by the ventral rami of these five nerves after they have given segmental branches to the scalene muscles and a branch from C-5 to the phrenic nerve. More often than not, a slender branch from C-4 contributes fibers to the plexus (1). Also, there is often a small branch from Th-2, but this might be primarily composed of sympathetic fibers.

Distal to the roots the orderly junction and separation of nerve fibers can be identified (Fig. 57-34). (a) The formation of three trunks: Of the five major roots of the plexus, the upper two unite to form the upper trunk, the lower two unite to form the lower trunk, and the middle root continues as the middle trunk. Therefore, C-5 and 6 intermix in the upper trunk, the middle trunk carries only C-7 fibers, and the lower trunk is composed of C-8 and Th-1 fibers. (b) The separation into six divisions: The three trunks each divide into an anterior and posterior division behind the clavicle. (c) The formation of three cords: Just distal to the divisions, at the outer border of the first rib, all three posterior divisions unite to form the posterior cord whereas the anterior divisions form the lateral and medial cords. The anterior division from the lower trunk continues as the medial cord whereas those from the upper and middle trunks unite to form the lateral cord. Therefore, the posterior cord is composed of C-5, 6, 7, 8, and Th-1 fibers; the medial cord contains C-8 and Th-1; and the lateral cord has fibers from C-5, 6, and 7. The medial cord, ulnar nerve, or both frequently receive a communicating branch from the middle trunk and carry C-7 fibers.

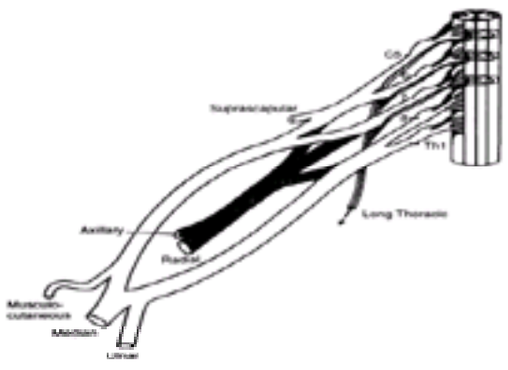

Figure 57-34. Diagram demonstrating the formation of the brachial plexus and the origin of major nerve branches. (From Goldstein B. Applied anatomy and electrodiagnosis of brachial plexopathies. *Phys Med Rehabil Clin North Am* 1994;5:479, with permission.)

Position of the Plexus and Surrounding Anatomy. After the spinal nerves travel a short distance they proceed downward and anterolaterally in the interval between the anterior and middle scalene muscles, where they unite to form the three trunks. At this point, the brachial plexus is beneath the floor of the posterior triangle, enclosed within the prevertebral fascia and at risk during operations in this area. The fascia envelops the brachial plexus in a *sleeve* or sheath, enclosing the neurovascular bundle as it courses down the neck and into the axilla. Therefore, there is a fascial-enclosed neurovascular compartment that extends from the cervical transverse processes, across the posterior triangle, beneath the clavicle, and well into the axilla. Extremely violent injuries often tear this fascia in conjunction with the scalene muscles and avulse the tubercles of the transverse processes from which the muscles and fascia attach.

The three trunks emerge from between the scalenes and converge toward the upper surface of the first rib, where they are arranged in a fairly vertical manner (i.e., upper, middle, and lower). The lower trunk is in contact with the first rib, a relationship that has been discussed in great detail in the thoracic outlet and postmedial sternotomy plexopathy literature. As the trunks cross the first rib they are in close proximity with the subclavian artery, anterior scalene muscle, and subclavian vein. Because of the slope of the first rib, the order is not only front to back but also rising upward; the vein being so low as to be hidden entirely by the clavicle. This permits a brachial plexus block (supraclavicular block) above and behind the vessels.

Each trunk then divides into anterior and posterior divisions, which pass inferior to the concavity of the medial two-thirds of the clavicle and accompany the axillary artery. Finally, the divisions reunite to form the cords within the axilla, named by their relationship with the second part of the axillary artery.

The brachial plexus can be palpated in the posterior triangle of the neck, in the angle between the clavicle and sternocleidomastoid. To map out the surface anatomy, the brachial plexus in the neck lies below a line from the posterior margin of the sternocleidomastoid at the level of the cricoid cartilage to the midpoint of the clavicle.

Branches of Spinal Nerves Before the Plexus Is Formed. The branches from the most proximal part of the spinal nerves are extremely important to the electromyographer. Although somewhat artificial and arbitrary, the early branches can be separated into four subdivisions. (a) Primary rami: Each spinal nerve divides into a dorsal and ventral ramus. The dorsal ramus innervates the dorsal dermatomes and myotomes—therefore, the skin, subcutaneous fat, deep fascia, and longitudinal extensor musculature of the spine. (b) Sympathetics: Each spinal nerve from Th-1 to L-2 (or L-3) has a branch that consists of myelinated, preganglionic fibers (white ramus communicantes) destined for the sympathetic chain. It is important to recall that there is great divergence in the sympathetic system. Therefore, from a relatively small area of preganglionic cells in the spinal cord (Th-1 to L-2) the axons diverge, stimulate the postganglionic cells within the sympathetic chain, and thereby innervate all of the glands and body wall. Because the Th-1 preganglionic fibers innervate the head and neck, avulsion of the Th-1 spinal nerve results in

the sympathetic-deficient clinical syndrome of Horner. (c) Segmental branches: Segmental nerves from the ventral rami innervate the scalene muscles (anterior, middle, and posterior), prevertebral muscles (longus capitis and longus colli), and sensation to the deep fascia of the neck (prevertebral fascia). (d) Contribution to the phrenic nerve: The communication with the phrenic nerve from C-5 arises from the proximal ventral ramus.

Branches from the Brachial Plexus. When the basic formation of the brachial plexus has been learned, it is a simple matter to put in the branches of the plexus if one remembers the odd number rule: 3-1-3-5-5. The rule states that three nerves branch from the roots, one from the upper trunk, and the remaining nerves branch from the cords (three from the lateral cord, five from the medial cord, and five from the posterior cord). Clinically, it is helpful to focus on those supraclavicular branches off the proximal aspects of the plexus (roots and trunks) and the infraclavicular branches from the cords.

SUPRACLAVICULAR BRANCHES (THREE NERVES BRANCH FROM THE ROOTS). The nerves from the roots together with the branches of spinal nerves before the plexus are of paramount importance because they all arise from the proximal aspect of the spinal nerves. Involvement of these nerves is evidence of nerve root avulsion in most cases.

The three branches from the roots arise from C-5 to C-7 in a successive manner: dorsal scapular nerve from C-5; nerve to subclavius from C-5, 6; and long thoracic nerve from C-5, 6, and 7 (Table 57-3). The branches from the roots might also be remembered as the *nerve to*'s—therefore, nerve to rhomboids, nerve to subclavius, and nerve to serratus anterior. The *dorsal scapular nerve* (C-5) is unusual in that a single segment innervates the target muscles, the rhomboids and part of levator scapulae. This is helpful in attempting to distinguish a proximal injury that only involves C-5 from one that involves caudal segments as well. The *nerve to subclavius* (C-5, 6) branches from the roots or might also arise from the superior trunk. The distinction is trivial and the nerve unimportant to the clinician except to help remember the odd number rule and its occasional contribution to the phrenic nerve. The *long thoracic nerve* (C-5, 6, 7) travels on the outer surface of the serratus anterior and supplies it in a segmental fashion (upper slips of the serratus anterior are innervated by C-5, middle muscle fibers by C-6, and the lowest by C-7).

TABLE 57-3. Supraclavicular branches

SUPRACLAVICULAR BRANCHES (ONE NERVE FROM THE UPPER TRUNK). The only nerve that branches from the trunks is the suprascapular nerve (C-5, 6) which innervates the supraspinatus and infraspinatus muscles (see Table 57-1). To differentiate a suprascapular mononeuropathy from an upper trunk injury, other C-5, 6 innervated muscles might be examined (deltoid and biceps).

INFRACLAVICULAR NERVES (3-5-5 FROM THE CORDS). The cords continue distally to form the principal nerves of the limb. Each cord terminates into two principal nerves as follows: lateral cord (lateral head of the median and musculocutaneous); medial cord (medial head of the median and ulnar); posterior cord (axillary and radial). The remaining branches are listed in Table 57-4.

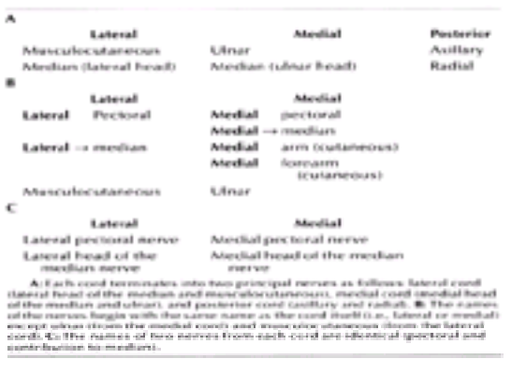

TABLE 57-4. Infraclavicular branches

Memorizing the brachial plexus is often a frustrating task, and one that is soon forgotten. There are many mnemonics and memory aids, as well as descriptions of the infraclavicular nerves. There is no need to repeat them here. However, it is appropriate to review some general facts and principles of the infraclavicular nerves.

The junction of the three posterior divisions from each trunk forms the posterior cord. Its five branches innervate the extensor muscles of the shoulder, elbow, wrist, and fingers. The radial nerve supplies all of the posterior muscles of the arm and forearm. The axillary nerve innervates the deltoid muscle (and teres minor). The remaining nerves supply the muscles of the posterior axillary fold (subscapularis, teres major, and latissimus dorsi). As a group, these latter muscles extend, medially rotate, and adduct the shoulder.

The lateral and medial cords innervate the flexor muscles of the upper extremity and are best remembered together. It is particularly easy to remember the names if two details are kept in mind. First, the names of the nerves from both of these cords begin with the same name as the cord itself (i.e., lateral or medial) except ulnar from the medial cord and musculocutaneous from the lateral cord (see Table 57-2). Second, the names of two nerves from *each* cord are identical (pectoral and head of the median). Finally, the cutaneous branches from the medial cord, annoying details when first studying the plexus, are extremely important in differentiating lower proximal plexus lesions (medial cord, lower trunk, and lower roots) from distal lesions (ulnar nerve). They are the medial cutaneous nerves of the arm and forearm.

The major nerves to the upper limb are discussed in greater detail within each anatomic section (e.g., arm, forearm, and hand). Common focal nerve lesions and palsies are then discussed in the clinical section on nerve compression syndromes.

APPLIED ANATOMY AND CLINICAL REFERENCES

There are many different classification schemes of painful upper limb musculoskeletal and neurologic disorders. Most of those that produce pain in the shoulder, arm, and elbow are in Chapter 58; those that afflict the forearm, wrist, and hand are discussed in Chapter 59. Cervicobrachial neuralgia is reviewed in Chapter 57. Causalgia is discussed in Chapter 20, myofascial pain syndromes in Chapter 29, and fibromyalgia in Chapter 30.

The following section is organized into three areas: joint and bone pain, overuse injuries and soft tissue pain, and nerve pain. Common painful conditions are presented to highlight anatomic principles and practical problems in the upper limb.

Joint and Bone Pain

Upper extremity joint and bone pain are frequent presenting complaints in many patients. Details about the mode of onset, number and localization of affected joints, and distribution of joint involvement assist in the diagnosis of arthropathies.

Acute Onset

The acute onset of joint pain is characteristic of infectious arthritis, although several other arthropathies may have an acute presentation. Examples of an acute onset also include crystal-related arthropathies, rheumatic fever, and palindromic rheumatism. Rheumatoid arthritis (RA) and psoriatic arthritis sometimes present with a sudden onset, although an insidious presentation is more common. Infectious arthritis is discussed as a typical example of an acute monoarthritis.

Infectious Arthritis. The annual incidence of bacterial arthritis is approximately 10 to 20 per 100,000. The higher incidence is related to a warm, humid climate and poorer socioeconomic conditions.

Several bacterial and nonbacterial agents have been found as the cause of infectious arthritis although *Neisseria gonorrhoeae* and *Staphylococcus aureus* are the most common causes. Most cases of infectious arthritis are the result of hematogenous spread; posttraumatic infection, direct inoculation, and spread from adjacent osteomyelitis also occur. Postoperative cases (e.g., postoperative diskitis) and infected prostheses are major causes as well, although antibiotic prophylaxis has resulted in a dramatic decrease in infection rate. In the immunosuppressed individual nongonococcal and nonbacterial arthritis occur more commonly. The incidence of tuberculosis continues to increase and may be the source of upper extremity infectious arthritis.

Bacterial arthritis usually presents with a single hot swollen joint, although a child may present with a high fever and other systemic signs. When the upper extremities are involved, acute bacterial and nonpyogenic arthritides most commonly affect the wrist joint. The sternoclavicular, elbow, and small joints of the hand are also sometimes involved. Pain is often present at rest and exacerbated by movement. The joint capsule is typically distended and warm and held in the neutral position to give maximum compliance and avoid higher intrasynovial pressure. The diagnosis requires analysis of joint fluid. Joint fluid should be completely drained as some agents (e.g., *S. aureus*, gram-negative bacilli) result in rapid cartilage and bone destruction. For example, a delay in treatment beyond 2 to 3 days may result in significant joint destruction in septic arthritis of the elbow. Treatment consists of early and aggressive drainage of the joint and administration of appropriate antibiotics.

Acute Osteomyelitis in the Upper Extremity. Acute osteomyelitis usually affects children or young adults and is often difficult to differentiate from an acute monoarthritis. Typically, the infection begins in the metaphysis of the radius or humerus, although the carpal bones and metacarpals are sometimes involved. In the young child, the cartilaginous growth plate is still vascular, and it is common for the infection to spread into the epiphysis. Involvement of the joint cavity is common in this younger age group. The older child and young adult have an avascular growth plate and spread to the joint is less common.

Chronic Joint and Bone Pain

Chronic pain, stiffness, and loss of function occur in a variety of rheumatologic diseases. Three common rheumatologic disorders are reviewed here: RA, osteoarthritis (OA), and gout.

Rheumatoid Arthritis. RA is a chronic, systemic, inflammatory disease that affects approximately 2.5 million people in the United States. Both genetic and environmental factors are involved in this autoimmune disease. A genetic influence is suggested by a fourfold increase in concordance in monozygotic compared with dizygotic twins. The mean age at onset is 35 to 55 years, and there is an insidious onset in 70%. More women than men develop RA by a ratio of 3:1.

Local symptoms and signs involve joint pain with three or more joint areas involved, morning stiffness, rheumatoid nodules, and warm, swollen joints. Constitutional symptoms include fatigue, anorexia, weight loss, depression, generalized weakness, malaise, lymphadenopathy, and low-grade fever. Morning stiffness usually lasts longer than 1 hour, along with extraarticular symptoms such as achiness. Pain occurs at rest and with movement, often disturbing sleep.

Early in the course of the disease, several changes in joint structure occur. Joint effusion, tenderness, and inflammation of the synovium occur, producing a soft tissue swelling that is easily detected during evaluation of the patient. Additionally, decalcification localized in or adjacent to the involved joints often occurs.

RA affects most of the joints in the upper limbs, and the associated disability is great. For example, 9 of 10 people with RA have significantly reduced function after 10 years, particularly related to impaired hand function. Fewer than 50% are able to continue to work after living with RA for 15 years (2).

In the upper limbs, RA has the greatest affinity for the small joints of the hands and usually starts in the metacarpophalangeal and proximal interphalangeal joints. These joints are typically symmetrically involved, boggy, swollen, and warm early in the disease. The surrounding skin is erythematous. Volar subluxation and ulnar drift of the metacarpophalangeals are characteristic deformities.

The wrists (radiocarpal joints) and distal radioulnar joints are usually involved in RA. The synovium is boggy and palpable on the dorsal surface of the wrist. Early changes also include loss of range of motion, particularly with wrist extension. Synovitis commonly affects the weakest support of the wrist on the ulnar side. Finally, clicking of the distal radioulnar joint may be present at the early stages of RA.

Tenosynovitis of the tendon sheaths is found in approximately two-thirds of rheumatoid hands. Pain, swelling, nodules, and eventual rupture of both long flexor and extensor tendons are commonly found in RA. A trigger finger is a frequent feature of flexor tenosynovitis.

Later manifestations of RA are well described. Pain and deformity result from intraarticular and extraarticular tissue injury. The boutonnière deformity develops as a result of thinning and destruction of the extensor mechanism at the proximal interphalangeal joint (see Fig. 59-23). The lateral bands move progressively in a volar direction, eventually generating a flexion movement at the proximal interphalangeal joint rather than one of extension. The digit then assumes a flexed posture at the proximal interphalangeal joint and extended position at the distal interphalangeal joint. The swan neck deformity develops as a result of joint destruction to the palmar ligament at the proximal interphalangeal joint (see Fig. 59-24). The palmar ligament normally limits extension; therefore, after its destruction, hyperextension occurs (typically at the proximal interphalangeal joint). This allows the lateral bands to bowstring on the dorsal aspect of the middle phalanx, resulting in a decreased extension movement at the distal interphalangeal joint. Flexor digitorum profundus then pulls the distal interphalangeal joint into a flexed position.

Rheumatoid nodules often develop in the upper extremities as later manifestations of RA. These nodules are subcutaneous and occur on extensor surfaces about the olecranon process and proximal bony prominence of the ulna and over the extensor surfaces of the metacarpophalangeal and proximal interphalangeal joints.

Radiographic changes of RA also include joint space narrowing. Bony erosion occurs in the joint itself and osteopenia, or diminished bone density, can be present in the periarticular region.

Osteoarthritis. OA is an age-related disorder that is the most common type of joint disorder in the world (3). The majority of people over 65 years of age have some form of OA, and approximately 16 million people have OA in the United States. Age, systemic factors (e.g., obesity), exposure, and genetic factors are all thought to play a role in the disease. OA is a disease confined to the joints and is characterized by destruction of the articular cartilage and subchondral bone. It is classified as primary and secondary. Secondary OA occurs in response to previous injury, prolonged heavy use, or damage by prior infection or inflammatory arthritis; primary OA has no known causes. Research indicates that the familial tendency of primary OA may be linked to a defect in a procollagen gene.

The patient with OA typically has slowly developing joint pain, inactivity stiffness, and enlargement of joints. Reduced joint function and severe disability often result from OA. Pain is usually described as use-related; however, rest pain and night pain occur in many individuals. Bone and muscular pain are also frequently reported.

Joint involvement is usually asymmetric, and in the upper extremities, the distal interphalangeal, proximal interphalangeal, and thumb base are most frequently involved. Early disease usually consists of aching in the affected joints. Inflammation occurs intermittently, and involved joints may present with warmth and tenderness. The hallmarks of hand involvement in OA are Heberden's (distal interphalangeal) and Bouchard's (proximal interphalangeal) nodes. These nodes are firm

swellings that are often tender and erythematous. Loss of motion and frank instability may develop. Trapeziometacarpal joint involvement occurs in approximately one-half of individuals with OA and commonly leads to loss of hand function. As the joint deformity develops, the base of the thumb enlarges giving a swollen or *squared* appearance. It is sometimes confused with wrist involvement because it may present with poorly localized pain at the base of the thumb and wrist joint. The patient often complains of pain during grasping types of activities (e.g., opening a jar) and pinch activities.

OA of the acromioclavicular joint is common. Pain, tenderness, and crepitus are well localized to the joint. Pain is worse with movements of the shoulder above 90 degrees because most movement of the AC joint occurs during full abduction and flexion activities. OA at this joint is frequently associated with inferior osteophytes and rotator cuff tears.

Radiographic changes in OA include joint space narrowing from the eroded cartilage, subchondral sclerosis and cysts, and osteophyte formation. There is relatively poor correlation between radiographic grading and reporting of pain.

Crystal-Related Arthropathies. The deposition in and around joints of crystals often leads to inflammation, deformity, loss of function, and pain. Monosodium urate monohydrate (gout), calcium pyrophosphate dihydrate (pseudogout), and basic calcium phosphates are the more common causes of crystal-related arthropathies. Acute and chronic forms of the disease may occur. The differential diagnosis of the rapid presentation of a hot, swollen joint is that of an acute monoarthropathy. In the chronic setting, the differential diagnosis includes RA, OA, and other destructive arthropathies. The diagnosis is established by analysis of joint fluid and radiography. Crystal identification under polarized light differentiates monosodium urate monohydrate (strong negative birefringence) from calcium pyrophosphate dihydrate (weak positive birefringence). Radiographic changes in gout usually demonstrate erosive changes in affected joints, yet calcification is usually absent. In pseudogout, radiography demonstrates chondrocalcinosis and degenerative joint changes.

Gout most commonly affects middle-aged men. Although the joints of the lower extremity are more commonly involved, the small joints of the hands or wrist might be involved in acute gouty arthritis. Virtually any joint may be involved in chronic gout. Tophi are characteristic firm nodular or fusiform swellings and histologically demonstrate a foreign body granuloma surrounding a core of monosodium urate monohydrate. Tophi develop over joints, in the subcutaneous tissue on the extensor surface of the forearm, on synovial sheaths and bursae, and in subchondral bone. Tophi are often confused with rheumatoid nodules.

Pseudogout is predominantly a disease of the elderly. Acute synovitis (usually termed *pseudogout*) and chronic arthritis (usually termed *chronic pyrophosphate arthropathy*) occur. As with gout, any joint may be involved, but the more commonly affected upper extremity joints include the wrist, glenohumeral, and elbow. Affected joints usually reveal signs of OA and varying degrees of synovitis.

Repetitive Motion Disorders of the Upper Extremity and Soft Tissue Pain

Repetitive motion disorders of the upper extremity are common. The United States Department of Labor Statistics showed that more than 60% of new occupational illnesses in 1992 were associated with repetitive motion and there has been an increase since then. The overall national rate increased from 5 cases per 10,000 workers in 1982 to 44 per 10,000 in 1992. A great proportion of these cases is upper extremity repetitive-related disorders such as rotator cuff dysfunction and peritendinitis about the wrist. Repetitive motion disorders are also common in avocational activities. It is estimated that approximately one-fourth of all sports participants develop overuse injuries, and many of these involve the soft tissues of the upper limbs (4).

These disorders have a diversity of terminologies (e.g., overuse injury, repetitive stress syndrome, activity-related musculoskeletal disorder) and have complex multifactorial etiologies. Further, they can involve many tissues such as muscle, nerve, ligament, and tendon. Although many of these terms imply that the pathophysiology is well understood, overuse injuries probably represent several different pathologic entities (e.g., in tendon tendinitis, tendinosis, peritendinitis) associated with distinct etiologies (repetition, cumulative trauma, sustained static loading). A useful operational definition is that an overuse injury is one in which there is a summation of biomechanical loads applied beyond the tolerance of the biological tissues.

The fundamental questions that arise in repetitive motion disorders are what is the relationship between biomechanical loads and tissue response, and why do some loads induce adaptive responses while others lead to pathologic changes? The tendons and ligaments of the upper extremity provide many different examples of both adaptive and pathologic changes. For example, where tendons change directions, traverse narrow tunnels, pass through a pulley, or are impinged by surrounding structures, the anatomy and composition of the tendon change from that of a regularly arranged dense connective tissue to that of fibrocartilage. This has been demonstrated in the region of the tendon that experiences compressive and frictional forces rather than the usual pure longitudinal forces. In other words, when a tendon experiences significant compression and friction, it undergoes adaptive changes from a primary fibrous tissue to one that is more fibrocartilaginous in nature. Although initially adaptive, fibrocartilage is less vascular and less capable of responding to repetitive microinjury compared with a typical tendon. Eventually, pathologic changes develop and chronic overuse injuries are the result. There are numerous clinical examples of this problem in both the lower and upper extremity (e.g., Achilles tendinitis in runners and dancers, supraspinatus tears in pitchers). Indeed, tendon injury within a zone of relatively hypovascular fibrocartilage is probably one of the most important unifying concepts of chronic, overuse injuries.

Other tissues experience injury after repetitive mechanical loading in addition to tendons and ligaments. Nerve compression syndromes are common and reviewed in a separate section below. Injuries to cartilage, bone, muscle, and skin are also known. Several common problems are discussed below.

Shoulder

Rotator Cuff Tendinopathy. Rotator cuff tendinopathy is the result of prolonged or repetitive use of the upper extremity, particularly in an abducted position. There is considerably less pathologic study of the early stages of rotator cuff disease by comparison with more accessible tendons (e.g., forearm flexors). Yet, there are similar findings in that the designation *rotator cuff tendinitis* might be a misnomer; *tendinosis* is perhaps a more suitable term. Pathologic findings range from degenerative necrosis without a cellular infiltrate to degenerative lesions with abundant neovascularization (5,6).

Rotator cuff tears are age-related and activity-related conditions, and eventually there is tearing of the cuff in middle age or older. In most cases, they are thought to start as small focal failures of the supraspinatus tendon and progress to larger tears. A relatively minor injury might or might not be noted. Rotator cuff tears occur in younger people as a result of trauma or repetitive forceful overhead activities (e.g., a major league pitcher).

Rotator cuff tears are either partial (incomplete) or full thickness (complete). Pain, weakness, and functional problems are typical after a rotator cuff tear. Pain is often progressive and may radiate down the lateral aspect of the arm or into the base of the neck. Weakness and functional deficits primarily relate to abduction activities. It is important to note that as progressive tearing occurs and weakness develops, there is worsening upward displacement of the humeral head (see Fig. 57-8). This results in further compression of the rotator cuff and the subacromial bursa.

Subacromial Bursitis. Inflammation of the subacromial bursa may present as acute or chronic shoulder pain. Pain is typically located in the lateral shoulder and worse with movement. The bursa may be compressed by a narrowed humeroacromial space (e.g., traction spur on the undersurface of the acromion and upward displacement of the humeral head in the case of rotator cuff weakness). In chronic cases the bursa may become thickened and fibrotic. Radiographic studies may be entirely normal, although a calcium deposit in the subdeltoid or subacromial bursa may be seen. It is sometimes difficult to distinguish between subacromial bursitis, acromioclavicular arthritis, bicipital tendinitis, and rotator cuff tendinopathy. Many of these disorders may coexist.

Bicipital Tendinitis. The course and angulation of the long head of the biceps make it susceptible to degenerative changes and tears. Pain is typically anterior in location, worse with use, and radiates down the anterior arm. Rupture of the transverse humeral ligament sometimes occurs with complaints of a catching or clicking sensation as the long head subluxes in and out of the bicipital groove. Examination is directed at reproducing the pain, subluxation, or both of the long head. Provocative tests include resisted flexion and supination of the forearm. After a tear, there is obvious asymmetry between the symptomatic and asymptomatic sides since the torn biceps bulges distally in the arm.

Elbow

Epicondylitis. Medial and lateral epicondylitis is a common cause of elbow and forearm pain. Epidemiologic studies have estimated that up to 3% of the population develop lateral epicondylitis (7). Age, systemic factors, and repetitive overuse have been implicated in the cause of epicondylitis. Commonly, the cause is related to the musculotendinous origin at the epicondyle. Nerve entrapments, infection, and periostitis occur less frequently.

Pathologic studies have not supported an inflammatory-mediated process. Rather, histopathologic examinations have demonstrated disorganized granulation tissue and necrotic areas. Epicondylosis and tendinosis have been proposed as more appropriate terminology by some authors (8). These studies have also questioned the local and systemic use of antiinflammatory medications as a treatment strategy in these conditions.

Medial and lateral epicondylitis typically present with an insidious onset. Pain is localized over the respective epicondyle with sporadic radiation into the forearm. Use of the forearm extensors (with lateral epicondylitis) and flexors (with medial epicondylitis) aggravates the pain. Resisted wrist extension typically reproduces the pain in lateral epicondylitis. Resisted wrist flexion and pronation reproduce symptoms in medial epicondylitis. Palpable tenderness over the respective epicondyle and common musculotendinous origin are also characteristic.

Investigative studies are used to rule out other conditions on the differential diagnosis such as nerve entrapment (electrodiagnostic studies) and arthritis (radiography).

Olecranon Bursitis. Olecranon bursitis is the result of overuse, trauma, inflammation, or infection. It is a common problem (approximately 3 in 1,000 outpatient visits), particularly in those who have recurrent elbow trauma at work or play. The affected elbow usually reveals a posterior elbow swelling that is warm, erythematous, and mildly tender. Systemic symptoms are unusual. Individuals with rheumatic disease (e.g., RA or gout) often have an acute aseptic inflammatory olecranon bursitis. Since the bursa is subcutaneous, direct inoculation from work-related activities is common. Septic olecranon bursitis is usually caused by *S. aureus*, group A b-hemolytic streptococcus, and *S. epidermidis*. Percutaneous aspiration of the bursa should be performed whenever inflammation or infection is suspected.

Wrist and Hand

Tenosynovitis and Peritendinitis. There have been many descriptive studies and case series of tenosynovitis and peritendinitis about the wrist. Most of the studies are related to work (9,10). Numerous studies have demonstrated that repetitiveness of work movements and the use of high forces were risk factors for the development of forearm tenosynovitis and peritendinitis. Local ache, pain during movement, weakness in gripping, and tenderness have been observed after repetitive activities such as assembly line and meat cutter's work. Both acute and chronic stages of the condition have been identified. The diagnosis of wrist tenosynovitis and peritendinitis is based on clinical findings since there are no diagnostic tests to establish the actuality of the diagnosis.

DeQuervain's Disease. DeQuervain's stenosing tenosynovitis is the prototype of a tendon entrapment syndrome. This disorder involves the synovial sheaths of the abductor pollicis longus and extensor pollicis brevis (see Fig. 57-18). Risk factors are related to vocational and avocational activities. Repetitive pinch activities while moving the wrist in radial and ulnar directions result in pain along the involved tendons. DeQuervain's tenosynovitis was also thought to be an inflammatory disorder. However, histopathology has demonstrated peritendinous fibrosis without inflammation and fibrocartilaginous metaplasia of tendon sheath tissue. Once again, the terminology is misleading, and DeQuervain's disease should probably be thought of as a degenerative disorder. Most patients report pain on the radial aspect of the wrist and at the thumb base during pinch grip and grasping activities. The tendon sheaths of abductor pollicis longus and extensor pollicis brevis are often tender and swollen. Crepitus may be palpable.

Trigger Finger or Thumb. Trigger or snapping finger is the most common repetitive motion disorder of the hand (11). Tenosynovitis of the long flexor tendons results in fibrosis and constriction of the fibrous sheath; a tendon nodule often develops at the same site. The nodule is able to slide through the tendon sheath when the finger is flexed but hangs up on the end of the sheath. The finger gets stuck in a flexed position. With increased force, the tendon snaps back into extension. Pain is local around the stenotic area and over the nodule. Individuals with trigger finger often have rheumatologic problems (e.g., RA) or diabetes mellitus.

Localized Nerve Lesions

Localized nerve lesions are a common source of pain in the upper extremity. There are several possible mechanisms that result in focal injury to a nerve, yet compression and trauma are the most common causes. Many compression lesions involve nerves that are otherwise normal. However, there are predisposing conditions that make nerves more susceptible to injury (e.g., diabetes mellitus, alcoholism, and Guillain-Barré syndrome).

The diagnosis of a focal nerve lesion depends on elucidating weakness and atrophy of the muscles supplied by the nerve distal to the lesion. Sensory findings, which usually appear earlier, provide less reliable localizing signs than motor deficits because sensory dermatomes overlap considerably. Electrodiagnostic tests can delineate the exact distribution of denervated muscles and localize a focal nerve lesion. MR neurography can also be useful.

Median Nerve

In the arm, compression of the median nerve is rare. Entrapments by the bicipital aponeurosis, by extreme flexion of the elbow, and by the ligament of Struthers have all been reported. Compression of the nerve beneath the ligament of Struthers occurs at a point proximal to the pronator teres (12).

In the cubital fossa, the median nerve passes between the two heads of the pronator teres muscle and under the origin of the flexor digitorum superficialis. The nerve can be entrapped by either structure. The pronator teres syndrome has been reported as a repetitive strain injury in athletes and in such workers as carpenters, mechanics, and writers.

The anterior interosseous nerve is entrapped or damaged in the forearm, resulting in the syndrome of Kiloh and Nevin (also known as anterior interosseous syndrome) (13). This may be the result of direct trauma, forearm fractures, phlebotomy from the cubital vein, or fibrous bands related to the flexor digitorum superficialis. Three muscles are weak as a result of injury to the anterior interosseous syndrome: flexor pollicis longus, the radial half of flexor digitorum profundus, and pronator quadratus. The pinch maneuver (ask the patient to make the *OK* sign) results in flattening of the distal aspect of the thumb and second digit; a triangle is formed rather than a circle. Symptoms include forearm pain and weakness of pinch, grip, or both.

Entrapment of the median nerve in the carpal tunnel is the most common entrapment neuropathy. Carpal tunnel syndrome is most common in persons working in jobs that require use of hand-held vibrating tools, repetitive wrist motion, forced hand movements, or all three, as performed by assembly workers, packers, bricklayers, and musicians.

The increase of pressure inside the carpal tunnel compresses the median nerve beneath the unyielding flexor retinaculum. Pain and paresthesias on the palmar-radial aspect of the hand characterize the syndrome in addition to symptoms that are often worse at night, exacerbated by repetitive, forceful use of the hand, or both. Patients often describe relief by shaking their wrist (flick sign). Careful neurologic examination and electrodiagnostic testing are important in establishing the diagnosis. In severe cases, weakness and atrophy of thenar muscles are present. Electrodiagnostic studies are used to confirm the diagnosis.

Ulnar Nerve

Ulnar nerve compression at the elbow is the second most common entrapment neuropathy. Elbow pain may extend to the forearm and is accentuated by repeated trauma (e.g., heavy labor), leaning on the nerve (e.g., individuals with paraplegia who frequently lean on the elbow or medial forearm), or repeated elbow flexion (e.g., painting, hammering). Hypertrophy of the flexor carpi ulnaris occurs in overhand athletes and may compress the nerve in the cubital tunnel.

Sensory symptoms and signs typically involve the medial hand (distribution of the ulnar nerve). Sensory loss of the medial forearm is not consistent with an ulnar nerve lesion at the elbow since this area is innervated by a separate nerve, the medial antebrachial cutaneous (medial cord; C-8 dermatome). Weakness may occur in any of the ulnar innervated muscles (flexor carpi ulnaris, fourth and fifth bellies of flexor digitorum profundus, hypothenar muscles, adductor pollicis, and the interossei), although it is much more common that the hand muscles are involved.

Ulnar nerve compression at the wrist occurs in the canal of Guyon. Repeated trauma at work or play such as stapling or bicycling is the usual cause. Extrinsic pressure from a synovial cyst, calcium deposits, and handcuffs has also been reported. The clinical features of this entrapment are variable, since the ulnar nerve separates into several end-branches within Guyon's canal. Both sensory (little finger and medial half of the ring finger) and weakness (hypothenar muscles, interossei, and adductor pollicis) effects are well described. Diagnostically, it is helpful to remember that the cutaneous branches to the proximal aspect of the medial hand (both palmar and dorsal nerves) separate from the ulnar nerve in the forearm, but the branches to the fingers come off the ulnar nerve distally in the canal.

Therefore, compression in Guyon's canal spares the ulnar aspect of the hand but not the fingers.

Radial Nerve

Radial nerve compression occasionally occurs in the proximal arm or region of the spiral groove. Although this usually is the result of fracture, compression by crutches or leaning against a hard object (*Saturday night palsy*) have also been described. Radial nerve palsy from axillary compression (*crutch palsy*) results in triceps weakness as well as all of the muscles in the extensor compartment of the forearm. Compression in the spiral groove spares the triceps. Clinically, the patient complains of arm and forearm pain with characteristic wristdrop (weakness of wrist and finger extensors).

The most common radial nerve compression palsies occur about the elbow. Pain at the lateral aspect of the elbow, sometimes with radiation to the dorsal forearm, is a common manifestation of radial nerve compression in this area. Exacerbation of pain during or after heavy work is typical, and a deep, aching sensation in the forearm extensors is often described. Radial nerve compression at the elbow is frequently confused with lateral epicondylitis since both often present with lateral elbow pain. Several structures might compress the nerve including the margin of extensor carpi radialis and the fibrous arch of supinator (arcade of Frohse). The posterior interosseous nerve syndrome is compression of the deep branch of the radial nerve at the arcade of Frohse. In this syndrome, brachioradialis and the radial wrist extensors are spared. Therefore, weakness of the wrist is not as pronounced as more proximal radial nerve lesions, and there is characteristic radial deviation of the wrist during extension. Entrapment of the posterior interosseous nerve is thought to result from forceful repetitive supination-pronation of the forearm or abrupt extension of the elbow (e.g., hammering, Frisbee throwing, and backhand tennis stroke). Direct pressure such as that produced by Canadian (forearm) crutches might also result in similar nerve palsy.

Brachial Plexopathies

Clinical Presentation. A lesion of the brachial plexus results in motor, sensory, sympathetic, or all three kinds of disturbances. Tragically, in many cases, there is a high proportion of intractable pain. Because of the changing arrangement of the brachial plexus as it is followed distally, injuries of it may result in many diverse paralyses, anesthesias, and paresthesias, depending on the exact level at which it is injured and the extent of injury to the various elements at that level. Sympathetic fibers might also be involved, resulting in decreased sweating with postganglionic lesions. If a Th-1 root avulsion occurs, preganglionic sympathetics might be interrupted and a Horner's syndrome may result. Finally, findings typical of a lower motor neuron process might occur—therefore, decreased tone, atrophy, and hyporeflexia.

Classification. The various classifications of brachial plexopathies are confusing. Anatomic, surgical, etiologic, pathophysiologic, and mechanistic classifications have all been used and are not repeated here. However, it is helpful to consider a few general organizational differentials since the implications for electrodiagnostic evaluation, treatment, and prognosis are considerable. These include the following: (a) mechanism of injury (traction, compression, vascular, ischemic); (b) type of injury (neurapraxia, axonotmesis, neurotmesis, root avulsion); (c) open versus closed injuries; and (d) preganglionic versus postganglionic lesions.

Etiology. The causes and incidence of brachial plexopathies may vary greatly, particularly when comparing wartime periods with those during civilian life. Undoubtedly, trauma accounts for a large proportion of brachial plexopathies during both periods. *Closed injuries* are much more common in civilian life, with vehicular injuries, industrial accidents, and sports-related trauma accounting for most of them in adults. Violent torsion of the upper extremity, either upward or downward, may damage the plexus. Injuries to the brachial plexus of the infant may occur during birth, as a result of the strain placed on the plexus by wide separation of the head and shoulder during a difficult delivery. The mechanism of traumatic injuries— therefore, the force, rate of deformation, and direction of injury—ultimately determine the extent and location of the injury. *Open injuries* are common during both wars and civilian life. Gunshot wounds and knife injuries to the neck or axilla, shrapnel, and blast injuries can all result in brachial plexus lesions. *Iatrogenic injuries* occur during surgery (particularly procedures in the posterior triangle of the neck and in the shoulder, and when the thorax is opened), regional anesthetic blocks, and by other procedures with needles and cannulas.

At other times the causes are not as obvious. Cervical ribs, fascial bands, tumors, and scar might all directly compress the brachial plexus. Aneurysms and thrombosed veins (i.e., subclavian) may press directly on the trunks of the plexus. Years after radiation therapy a slowly progressive brachial plexopathy might appear. Brachial plexopathies might follow a vaccination. And idiopathic brachial plexus lesions, of several anatomic varieties and scores of names (brachial plexus neuropathy, multiple neuritis of the shoulder girdle, neuralgic amyotrophy of Parsonage and Turner, localized nontraumatic neuropathy in military personnel, paralytic brachial neuritis, cryptogenic brachial plexus neuropathy) occur, yet the cause remains obscure.

Differential Diagnosis. Particularly with nontraumatic brachial plexopathies, a fairly broad differential must be considered when there is a presentation of pain, numbness, weakness of the upper extremity, or all three. The differential should include musculoskeletal problems including disorders of the shoulder and cervical spine, spinal cord injury, anterior horn cell disorders, syringomyelia, intraspinal neoplasms, myopathies, peripheral neuropathies, and psychogenic paralyses. Coexistent musculoskeletal and central nervous system injuries (e.g., spinal cord injury, traumatic brain injury) are common after violent trauma and present a challenging diagnostic evaluation. Up to 80% of severe traumatic brachial plexopathy cases sustained multiple trauma to the head and skeletal system.

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CHAPTER 58

Shoulder, Arm, and Elbow Pain

Michael J. Moskal and Frederick A. Matsen III

Pain is a most common shoulder and elbow symptom. The causes of shoulder and elbow pain are many and varied, including injury, degeneration, inflammation, vascular disease, tumor, and referral from a distant site. Shoulder pain is exceeded in clinical frequency only by backache, neck pain, and headache (1). The reason for this high frequency is that the shoulder girdle is a complex articulation; its stability and smooth function depend on the integrated function of numerous ligaments, tendons, muscles, and five distinct articulations. The frequency of pain in the elbow region is less than shoulder pain. Nevertheless, painful conditions involving the elbow also significantly impair the function of the upper limb and deserve serious consideration.

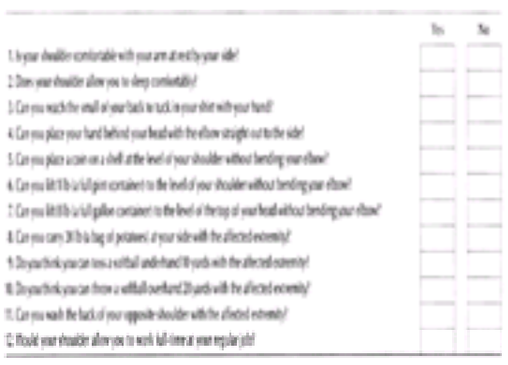
SHOULDER AND UPPER ARM PAIN

The shoulder girdle consists of three cartilage-to-cartilage articulations—acromioclavicular (AC), sternoclavicular, and glenohumeral joints—as well as two atypical articulations—scapulothoracic interface and humeroscapular motion interface (HSMI). A painful shoulder may involve one or more of these structures. Motion, stability, strength, and smoothness characterize a well-functioning shoulder. Many etiologies of pain are mechanical and can be attributed to shoulder stiffness, instability, weakness, or roughness.

Patient Self-Assessment

We find that patient self-assessments of health status and shoulder function help characterize the patient's condition from his or her own perspective. We obtain these assessments at the time of initial presentation as part of the baseline before treatment, or the “ingo.” These patient self-assessment questionnaires are filled out periodically after treatment has been instituted to define the “outcome” of treatment. For these purposes, we use a general health assessment, the short form 36 (SF-36), and a shoulder-specific questionnaire, the simple shoulder test (SST) (2).

The SST is an inventory of 12 common shoulder activities that provides a basic characterization of the shoulder's function. The 12 yes or no questions were derived from the common complaints of patients presenting to the University of Washington Shoulder and Elbow Service for evaluation (Table 58-1). The SST has been shown to be (a) reproducible on test-retest (2,3), (b) practical in a busy practice setting (2,3), (c) sensitive to a wide variety of shoulder disorders (2,3 and 4), and (d) able to quantitate the change in shoulder function resulting from treatment and to permit the identification of treatment failures (5).



	Yes	No
1. Is your shoulder comfortable with your arm at rest by your side?		
2. Does your shoulder allow you to sleep comfortably?		
3. Can you reach the small of your back to tuck in your shirt with your hand?		
4. Can you place your hand behind your head with the elbow straight out to the side?		
5. Can you place a can on a shelf at the level of your shoulder without bending your elbow?		
6. Can you lift 1 lb (a full pint container) to the level of your shoulder without bending your elbow?		
7. Can you lift 10 lb (a full gallon container) to the level of the top of your head without bending your elbow?		
8. Can you carry 20 lb (a bag of potatoes) at your side with the affected extremity?		
9. Do you think you can toss a softball underhand 30 yards with the affected extremity?		
10. Do you think you can throw a softball overhand 20 yards with the affected extremity?		
11. Can you wash the back of your opposite shoulder with the affected extremity?		
12. Would your shoulder allow you to work full-time at your regular job?		

TABLE 58-1. The simple shoulder test (SST)

The SF-36 is a general health status questionnaire that has been widely used to demonstrate the health status of control populations and populations with well-defined medical and psychological conditions, including the effectiveness of orthopedic management (6,7,8,9,10,11,12,13,14,15 and 16). The form documents health status from the standpoint of the patient; it is practical and easy to complete, and it has been shown to be sensitive to musculoskeletal disease and to orthopedic treatment. The importance of factors such as the SF-36 scales of emotional role function, mental health, and social function is well demonstrated in the work of Summers et al., who found that the objective severity of the disease showed little relationship to patients' reports of pain (17). Psychological variables were much more closely correlated with measures of pain and functional impairment (18).

We use the information gained from the SST and SF-36 self-assessment questionnaires to monitor the effectiveness of our treatment. The efficacy of the treatment is the difference between the ingo scores (at presentation) and the outcome scores (after treatment). We find that monitoring treatment efficacy using self-assessment tools is often more meaningful than using traditional medical metrics, such as range-of-motion and strength testing. Interestingly, Bostrom et al. (19) found that standardized assessments of shoulder function were more reliable and reproducible than conventional range-of-motion measurements.

Evaluation of the Patient

In that our primary interest is the mechanical treatment of painful and dysfunctional shoulders, we seek a mechanical cause of the patient's problem. We attempt to define the problem in terms of the shoulder's four mechanical properties: motion, stability, strength, and smoothness (2). If a patient's problem can be understood in mechanical terms, mechanical treatment may be effective. Shoulder pain that is not mechanical in origin usually requires a nonmechanical solution. Symptoms from mechanical problems typically relate to certain activities or positions. They are reproducible and usually well localized. By contrast, nonmechanical problems are typically not related to shoulder activity or position and may be more difficult for the patient to localize. Nonmechanical pain is diffuse and may involve the entire extremity. Nonmechanical problems may be accompanied by heat, swelling, redness, and tenderness and are often most manifest at night. Shoulder pain may also have a neurologic pattern, with radiation from neck to locations distal to the deltoid tubercle, or be aggravated by certain neck positions rather than shoulder positions.

History

It is important to obtain a complete history of any painful condition from onset up to the time of presentation. Details about the characteristics of the pain, including

precipitating factors, location, intensity, quality, duration, and aggravating and relieving factors, should be obtained. The presenting complaint and associated symptoms can give valuable clues to the correct diagnosis. For example, a patient with cervical spondylosis may present with shoulder pain and weakness in addition to paresthesias in a radicular distribution. A large, full-thickness rotator cuff tear may produce shoulder pain and weakness without sensory changes. The pain of acute calcific tendinitis characteristically comes on suddenly and is of such severity that the shoulder often cannot be used. The pain of degenerative joint disease is often insidious in onset and unrelated to any particular inciting process, although it may be exacerbated by injury. Pain from subacromial roughness produces symptoms when the shoulder is used in midrange positions, such as drinking from a glass, but diminishes when rested. Pain unassociated with shoulder use should always make the physician consider the possibilities of infection, tumor, or referred pain.

The location of shoulder pain provides useful information. Cervical radiculopathy often produces pain in the upper part of the shoulder and at the base of the neck. AC joint disorders (e.g., inflammation or degenerative changes) often produce pain and other symptoms just anterior to that particular articulation. Pain over the lateral deltoid is frequently of rotator cuff origin, whereas pain over the posterior glenoid humeral area often is related to conditions of the glenohumeral joint articular surface. The activities and motions that produce shoulder pain provide additional information of diagnostic significance. For example, anterior glenohumeral subluxation usually produces pain when the shoulder is abducted, extended, and externally rotated such as in an overhead throwing motion. Subacromial roughness usually produces pain when the arm is used in intermediate positions of elevation. A frozen shoulder is painful and globally restricted in all motion planes. Extension and rotation of the neck commonly exacerbate shoulder pain from cervical spondylosis. The complete history should also note other medical conditions of possible relevance to the shoulder pain. Examples might include rheumatoid arthritis, epilepsy (may result in a shoulder dislocation), diabetes (often associated with a frozen shoulder), infection, and neoplasia. Previous evaluations, treatments, medication, physical therapy, and surgery should be noted. Patients having numerous steroid injections to treat “bursitis” not infrequently turn out to have rotator cuff tears. The relationship of the shoulder pain to a patient's occupation is critical to understanding the impact of the problem on the patient's life and may also suggest the possibility of secondary gain considerations. The patient's use of pain medication is important for gaining a complete understanding of the patient's problem. Finally, attention should be paid to the patient's age, habitus, occupation, body type, posture, and emotional and cognitive functions as well as physical state.

Physical Examination

A reproducible examination consisting of inspection, palpation, range of motion, and motor testing has proved useful in the examination of patients with shoulder pain. The examiner begins by viewing the anterior aspect of both shoulders simultaneously. One should look for generalized or focal swelling, atrophy, and skin changes, including scars. Postural abnormalities such as forward-rolled or drooped shoulders should be noted. Muscular atrophy is suggestive of chronic rotator cuff tears or denervation. Scapular winging may result from nerve dysfunction or glenohumeral abnormalities.

Determining the range of motion of the cervical spine should be part of the examination of all patients with shoulder pain (Fig. 58-1A). It is particularly important to note if neck extension and rotation to the painful side exacerbate the shoulder pain. These motions narrow the intervertebral foramina on the side to which the head is turned, accentuating cervical radiculopathy. Examination of the cervical spine should be accompanied by neurologic screening of the upper extremities, with the physician looking for hypesthesia, weakness, or reflex loss (see Chapter 55 for a detailed description of the examination of the cervical spine).

Figure 58-1. First four maneuvers in palpation of painful shoulder. **A:** Palpation of the cervical spine. **B:** Palpation of the biceps tendon. **C:** Location of the supraspinatus tendon. **D:** Palpation of the coracoid process.

Figure 58-1B shows the maneuver to locate and palpate the biceps tendon. This tendon is identified as the point on the proximal humerus that lies straight anterior when the arm is internally rotated 10 degrees. Tenderness at this point may suggest bicipital tendinitis; however, many normal individuals have tenderness here. Once the biceps tendon has been located, the supraspinatus tendon insertion is palpated at the greater tuberosity just lateral to the biceps tendon (Fig. 58-1C). This is the area of the rotator cuff most commonly affected by subacromial roughness and rotator cuff disease. The normal coracoid process is frequently tender if vigorously palpated; it is rarely the site of shoulder pathology (Fig. 58-1D). The next two steps are palpation of the AC and sternoclavicular joints. The AC joint is a relatively common site for inflammatory, degenerative, and traumatic disorders, whereas the sternoclavicular joint is much less commonly affected. These joints can be palpated easily just beneath the skin (Fig. 58-2). Crepitus at various sites is felt with passive or active range of motion. Subacromial roughness at the HSMI produces a sound and a feel somewhat like wadding up newspaper. The examiner places his or her hand over the superior aspect of the shoulder, stabilizing the scapula, while the abducted arm is passively internally and externally rotated (Fig. 58-3A). Glenohumeral crepitus results when there is loss of the articular cartilage over the glenohumeral joint, producing a harder grating sound like sandpaper on wood. The joint is best palpated posteriorly just beneath the angle of the acromion as the adducted arm is internally and externally rotated (Fig. 58-3B). Scapulothoracic crepitus can usually be palpated over the superior medial border of the scapula when the patient elevates or protracts the shoulder (Fig. 58-3C). The sound is similar to the noise produced when two sets of knuckles are rubbed against each other.

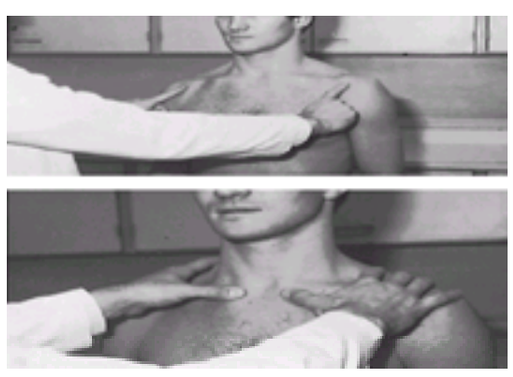


Figure 58-2. **A:** Palpation of both acromioclavicular joints. **B:** Palpation of both sternoclavicular joints.

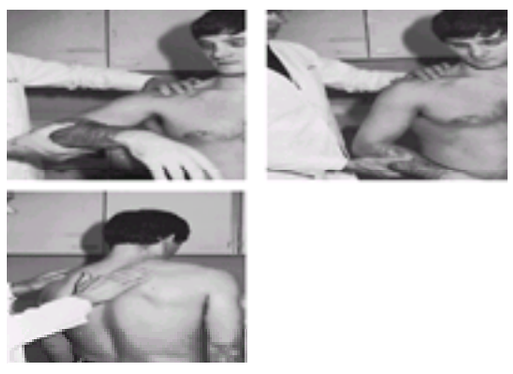


Figure 58-3. Palpation of various regions for crepitus. **A:** Subacromial region. **B:** Glenohumeral region. **C:** Scapulothoracic region.

A patient's maximal range of motion can be characterized using six basic parameters: (a) Forward elevation is measured as the maximal angle of humeral elevation in relation to the thorax as viewed from the side (Fig. 58-4A). External rotation is measured (b) at the side and (c) with the arm at 90 degrees of abduction (Fig. 58-4B). Internal rotation is measured (d) with the arm at 90 degrees of abduction as well as (e) the highest segment of posterior midline anatomy that can be reached by the thumb (trochanteric, gluteal, sacral, lumbar, or thoracic segment) (Fig. 58-4C). (f) Maximal cross-body adduction is the distance between the antecubital fossa and the contralateral anterolateral corner of the acromion (Fig. 58-4D). In addition to documenting the maximal range of motion, the quality of movement (ease, smoothness, and associated pain) and the rhythm during movement should be recorded.

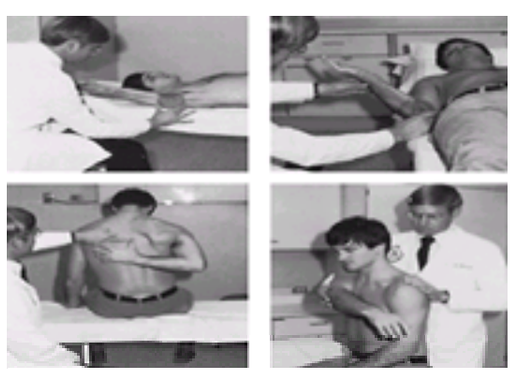


Figure 58-4. Evaluation of the passive range of motion of various parts of the upper limb. Measurement of the angle of range in forward elevation **(A)**, external rotation **(B)**, internal rotation **(C)**, and cross-body adduction **(D)**

The shoulder exam should include testing the strength of the rotator cuff and deltoid muscles. The supraspinatus can be evaluated by having the patient resist a downward force while his or her arm is elevated in the anterior scapular plane and internally rotated (thumb pointed to the floor). The infraspinatus is tested by assessing the power of external rotation at the side or with the arm abducted to 90 degrees. The subscapularis should be tested while the arm is internally rotated and the hand presses away from the posterior thorax while the examiner resists “lift off.” As the examination progresses, other muscle groups such as the scapular stabilizers (rhomboids, trapezius, serratus anterior) and power movers (deltoids, pectorals) of the shoulder may be included in the evaluation.

Radiographic and Other Studies

Imaging studies of the shoulder are costly and should be used with discretion. We obtain a standard series of shoulder radiographs on most new patients to exclude arthritis, calcification, dislocation, tumor, and old trauma (2,20,21,22 and 23). Other studies, such as ultrasound, magnetic resonance imaging (MRI), bone scans, cervical spine films, and electromyography/nerve conduction velocity, are reserved for conditions in which they are likely to alter the patient's management.

Specific Shoulder Conditions

Shoulder Stiffness

Shoulder stiffness can result from abnormalities of the joint surface, such as fracture or arthritis. These are considered later under the section on roughness. In this section we consider stiffness attributable to problems with humeroscapular soft tissues: frozen shoulder and posttraumatic or postsurgical stiff shoulder. The term *frozen shoulder* (or adhesive capsulitis) refers to an idiopathic limitation of humeroscapular motion due to contracture and loss of compliance of the glenohumeral joint capsule. By contrast, in a *posttraumatic* or *postsurgical stiff shoulder*, adhesions, scarring, and capsular contracture result from previous injuries or surgery to the soft tissues around the glenohumeral joint and the HSMI. A stiff shoulder may accompany or even mask other conditions, including cervical radiculopathy, rotator cuff disease, or neoplasm.

Evaluation. It is important to document the circumstances surrounding the onset of stiffness, the duration of the condition, and any tendency toward worsening or improvement. Possible risk factors, such as a period of immobilization, metabolic diseases (diabetes or hypothyroidism), or referred pain from the neck, chest, or abdomen, should be sought out. In posttraumatic stiff shoulders, the relationship of motion loss to previous surgery or injury becomes evident from the history. The age of patients with frozen shoulder is typically between 43 and 63 years. The history often reveals that patients have difficulty sleeping comfortably on the affected side, throwing overhand, washing the back of the opposite shoulder, and tucking in their shirts.

Physical examination may reveal loss of range of flexion, external rotation, internal rotation, cross-body adduction, or a combination of these. Pain often occurs at the limits of the range of motion, but the shoulder is often comfortable in the easily allowed range. Muscular function is typically unaffected in the allowed ranges of motion.

We typically obtain two radiographic views of a stiff shoulder: (a) an anteroposterior (AP) radiograph in the plane of the scapula, with the humerus in 35 degrees of external rotation, and (b) an axillary radiograph to evaluate the glenohumeral joint articular surface fracture or dislocation.

Diagnosis. Functionally significant restriction of shoulder motion and the absence of major previous shoulder injury or surgery support the diagnosis of frozen shoulder. Glenohumeral motion is typically limited in all directions. Radiographs may show osteopenia but not other pathologic abnormalities. The diagnosis of a posttraumatic or postsurgical stiff shoulder is based on functionally limited motion after trauma or surgery; the loss is often not symmetrical. Radiographic studies are important to rule out conditions associated with loss of articular cartilage or other problems limiting shoulder range and motion, such as an overlooked posterior dislocation of the shoulder. It is important to remember that a stiff shoulder may be associated with underlying conditions, such as cervical radiculopathy, metastatic tumor, shoulder tendinitis, and other disorders.

Treatment. Frozen shoulder is treated by gentle, frequent, patient-conducted stretching exercises and a general aerobic fitness program. These exercises are performed at least five times a day. Forceful passive stretching should be avoided because of the risk of fracture or damage to the articular surface, labrum, capsule, or rotator cuff. Pain should be controlled with nonnarcotic oral medications and assurance. Occasionally, pain may significantly inhibit patients' ability to perform their exercises. These patients may benefit from a steroid injection into the glenohumeral joint (24,25). Most, but not all, cases of idiopathic frozen shoulder improve substantially with nonoperative treatment (26,27). In the situation in which a well-motivated patient continues to have major functional limitations after 4 to 6 months of an exercise program, a more aggressive approach may be considered. For a classic frozen shoulder, a gentle examination performed under anesthesia (28) may be considered. Manipulation is not used in the posttraumatic or postsurgical stiff shoulder because of the risk of fracture or of cuff tearing. For refractory shoulder stiffness, an open surgical release (29,30), arthroscopic release (31,32), or a combination of the two may be considered. After manipulation or surgical release, an early motion program is implemented, ideally with continuous passive motion.

Summary. The evaluation and management of shoulder stiffness requires localizing the site of involvement and quantifying the severity of each limited motion. Equally important is identifying possible concomitant musculoskeletal and systemic disorders. Most cases of stiff shoulder respond to a patient-conducted home exercise and fitness program.

Shoulder Instability

For the upper extremity to carry out its many and varied functions, the shoulder must provide a stable link between the humerus and thorax. This requires that the

humeral head be held centered within the glenoid. The shoulder does not have the intrinsic stability provided by the deep socket of the hip. In contrast to other joints with shallow sockets (knee, elbow, or ankle), the shoulder is not stabilized by isometric ligaments. The primary mechanism for maintaining head centering is concavity compression (2). Instability may arise from a traumatic episode or from the decompensation of the mechanisms normally providing midrange stability.

The glenohumeral joint has static and dynamic stabilizers. Static stabilizers include the glenoid articular surface, the glenoid labrum, the capsule, and its ligaments. Dynamic stabilizers include the rotator cuff and deltoid and also the periscapular musculature. The rotator cuff and deltoid provide compression of the humeral head into the glenoid socket and control of the net joint reaction force. The periscapular muscles control the scapula, which orients the glenoid to support the humeral head. In the midrange of motion when the static restraints are lax, compression of the head into the glenoid concavity is the primary mechanism of shoulder stability. At the extremes of motion the capsule and ligaments tighten sharply to check motion and stabilize the joint.

The patient's answer to three questions may help the physician to synthesize a problem with instability:

1. “Did your problem start with a major injury, and if so, what was the position of your arm?”
2. “In what positions does your shoulder go out?”
3. “Can you make your shoulder go out for me?”

From these questions, one can infer the type of instability. Traumatic instability is anteceded by a significant forceful injury. The position of the arm at the time of injury will result in a typical direction of instability. A patient with problems of instability in the midrange of motion with significant antecedent injury may have multidirectional instability.

Traumatic Glenohumeral Instability. Traumatic instability arises from an injury of sufficient magnitude to tear the glenohumeral capsule, ligaments, and/or rotator cuff or fracture the humerus or glenoid. Avulsion of the anterior glenohumeral ligament mechanism deprives the joint of stability in positions in which they are major stabilizers—that is, maximal external rotation and extension of the arm. Midrange stability may also be compromised if the glenoid is damaged, reducing its surface area. The exact location and type of traumatic injury depend on the age of the patient and the magnitude, rate, and direction of force. Avulsions of the glenoid labrum or glenoid rim tend to occur in young people. For patients older than 35 years of age, traumatic instability tends to be associated with greater tuberosity fractures and rotator cuff tears. Although the humeral head may disassociate from the glenoid in any direction, the most common direction is anterior. In traumatic instability, intrinsic stabilizing mechanisms are altered: diminished angles of balance stability, loss of concavity compression, loss of adhesion-cohesion, loss of the glenohumeral suction cup, loss of finite joint volume, and loss of capsuloligamentous restraint (2,3,33).

Evaluation. In evaluating traumatic instability, the most important element is the definition of the original injury. Common injury mechanisms are a fall while skiing, an arm tackle in football, or a block in volleyball. Traumatic instability may occur without a complete dislocation. Shoulder instability may manifest as apprehension when the arm is placed near the position of injury. Characteristically, the shoulder is comfortable when troublesome positions are avoided. Patients who have recurrent dislocation are anxious and apprehensive that the shoulder may “go out” when it is placed in certain positions. There may be a history of increasing ease of dislocation or dislocation during sleep. The most consistent functional impairments tend to be the inability to throw overhand, to put the hand behind the head, and to lift 8 pounds to head level.

The goal of the physical examination is largely to confirm the impression obtained from the history: instability with a certain combination of arm position and force application. The most common direction of instability is anteroinferior. Stability in this position is challenged by externally rotating and extending the arm elevated in the coronal plane (Fig. 58-5A). Apprehension, the fear of uncontrollable glenohumeral translations, typically occurs if stability is compromised. Pain in this position is not specific for instability; such pain may also relate to stiffness or abutment of the glenoid against the posterior cuff insertion on the humeral head. The load and shift test (Fig. 58-5B) determines the integrity of the anterior glenoid labrum. The examiner compresses the humeral head into the glenoid fossa and attempts to translate the head anteriorly. If the labrum is intact, the humeral head will not translate anteriorly, and one can conclude that the labrum is not contributing to instability. In all patients, especially those older than 35, the strength of external rotation and internal rotation must be examined to evaluate the rotator cuff. Finally, a careful neurologic examination is in order to determine whether any nerve lesions are associated with the instability (34). Radiographs frequently help to confirm the diagnosis. The instability series of radiographs consists of an AP view in the plane of the scapula, with the humerus in 35 degrees of external rotation, an apical oblique view (35), and an axillary view. Findings may include an impaction fracture of the posterolateral humeral head (Hill-Sach's lesion) from contact with the anteroinferior corner of the glenoid, a periosteal reaction to the ligamentous avulsion at the glenoid lip (Bankart lesion), or occasionally a fracture of the glenoid rim (36). In the patient with suspected rotator cuff pathology (age older than 35 years and weakness), imaging, such as by expert ultrasound or MRI, is of value because (a) the best results are obtained with prompt repair of traumatic cuff tears, and (b) the approach for rotator cuff surgery is quite different from that for repair of an anteroinferior capsular lesion.

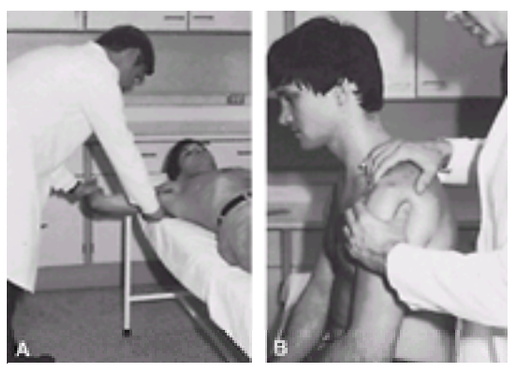


Figure 58-5. Maneuvers to evaluate stability of the glenohumeral joint. **A:** Apprehension test. **B:** Load and shift test.

Diagnosis. The diagnosis of traumatic instability is based on (a) a mechanism of injury sufficient to tear the glenohumeral ligaments, such as a major external rotation torque applied when the arm is elevated near the coronal plane, and (b) functionally significant recurrent episodes of apprehension or instability (2,36,37). In the evaluation of recurrent anterior instability, apprehension or instability should be present when the arm is externally rotated and abducted to 90 degrees. The diagnosis is supported when previous radiographs document a dislocation or current radiographs show the characteristic posterolateral humeral head fracture and/or a glenoid lip fracture or calcification.

Treatment. For some patients, appropriate management consists solely of education about the nature of the lesion and identification of the positions and activities that need to be avoided. Strengthening the shoulder musculature may help prevent the shoulder from being forced into positions of instability. We consider surgical treatment for informed patients who are unwilling to accept the functional limitations imposed by recurrent instability. The goal of surgical treatment of traumatic anterior glenohumeral instability is the safe, secure, and anatomic reattachment of the detached glenohumeral ligaments to the lip of the glenoid from which they were avulsed. No attempt is made to modify the normal laxity of the anterior capsule. The anatomic reattachment should reestablish not only the capsuloligamentous check rein but also the fossa-deepening effect of the glenoid labrum (38). A secure repair allows early controlled mobilization and protected activities of daily living, thereby minimizing the possibility of unwanted stiffness. Surgical treatment of traumatic anterior involuntary instability has a success rate of 95% to 98% (37,39,40,41,42,43 and 44).

Atraumatic Glenohumeral Instability. Atraumatic instability arises without major trauma, occurs in the midrange of motion, and is typically symptomatic in more than one direction. A shoulder that has been stable may become unstable after a minor injury or a period of disuse. Certain shoulders may be more susceptible to atraumatic instability. A flat or small glenoid fossa, a thin excessively compliant or redundant glenohumeral capsule, weak rotator cuff muscles, or poor neuromuscular control may, individually or in combination, contribute to instability of the glenohumeral joint.

Evaluation. Atraumatic instability presents most commonly in persons younger than 30 years of age. A relatively minor event such as an awkward lift or a sneeze may be all that is needed to launch a predisposed, but compensated, shoulder toward instability. The patient may notice that the shoulder is loose or that it slips out. The instability may be sufficiently subtle that the patient is aware only that the shoulder does something unnatural in certain positions. The patient may volunteer that the

shoulder can be popped out or that at times the shoulder feels as if it needs to be popped out. The positions of the shoulder, frequency of symptoms, and any associated atypical symptoms such as numbness or tingling should be documented. These patients typically have difficulty sleeping, lifting overhead, or throwing. Physical examination begins with the patient demonstrating the positions in which the shoulder feels unstable or different. The patient may demonstrate a spontaneous jerk test by bringing the elevated arm horizontally across the chest, causing the humeral head to subluxate posteriorly, and by returning the elevated humerus to the coronal plane, the joint reduces with a clunk. Patients may demonstrate that the joint subluxates inferiorly when they attempt to lift an object or tie their shoes. Finally, when they lie on the shoulder or elevate it in a posterior humerothoracic plane, they may produce anterior subluxation. As the patient is maneuvering his or her shoulder in space, faulty patterns of scapulohumeral mechanics such as the lateral scapular droop during lifting or retracting the scapula during anterior humeral elevation may become apparent.

The extent of laxity on manual testing is documented for all directions of translation; however, the magnitude of translation for shoulders with atraumatic instability may be the same as that of normal shoulders or those with traumatic instability (2,45). Therefore, we pay particular attention to the patient's response during laxity testing, seeking recognition of the provocative direction(s) of translation. We always make a point of examining the contralateral shoulder. Usually, but not always, the opposite shoulder yields similar translational distances as compared with the symptomatic shoulder. This provides a foundation to discuss with the patient and family the rationale for a rehabilitation program to regain dynamic control. Strength testing of the rotator cuff and deltoid and periscapular muscles is used to gauge muscle power and to infer its contribution, or the lack of it, to stability. Radiographic examination includes an AP view, with the humerus in 35 degrees of external rotation, an apical oblique view, and an axillary view. These views may show that the humeral head center is translated away from the glenoid center or a dysplastic glenoid. In most cases, however, the x-rays are normal.

Diagnosis. The diagnosis is predicated on demonstrating the patient's inability to keep the humeral head centered in the glenoid fossa, especially in the midrange of motion, along with the absence of an injury that could tear glenohumeral ligaments. The physical examination should reproduce symptomatic glenohumeral translations. Radiographs show an absence of any traumatic lesion.

Treatment. The hallmark of treatment is patient education and neuromuscular rehabilitation. Patients should avoid positions or activities of instability and specifically avoid voluntary subluxations, even if they feel that their shoulder “needs” to be popped out of joint. An exercise program is instituted that consists of rotator cuff strengthening (internal and external rotation), humeroscapular balance retraining, and muscular endurance (2,46). Good or excellent results can be expected in more than 80% of patients treated with rehabilitation (47).

In those patients who remain disabled, operative intervention may be considered. The patient must understand that capsulorrhaphy is not always curative and that the potential for recurrence is significant. He or she must also understand that surgery typically tightens the capsule, which may limit motion and may cause discomfort. Even after surgery, good strength and kinematics techniques remain the primary stabilizers of the joint.

Summary. Patients with atraumatic instability are usually young, perhaps with a family predisposition to “loose joints” and do not have a history of major trauma. The instability is most prevalent in the midrange positions commonly used in activities of daily living; the contralateral shoulder may be “loose.” Rehabilitation is the treatment of choice.

Patients with traumatic instability usually have a readily defined traumatic event; however, a complete dislocation of the glenohumeral joint is not necessary. The shoulder is unstable near the extreme of joint motion, and instability or apprehension can be reproduced by placing the arm in a position similar to injury. For the well-informed patient who does not wish to accept the positional instability, surgery usually corrects the definable defect in the capsulolabral complex.

Shoulder Weakness

Rotator Cuff Tears. The four muscles of the rotator cuff are uniquely adapted to contribute to muscle balance and make a major contribution to shoulder strength. Their insertion into a continuous cuff around the humeral head permits these muscles to provide an infinite variety of moments to oppose unwanted components of the stronger deltoid and pectoralis muscles. When the function of the cuff muscles is compromised, the shoulder loses both balance and strength due to the loss.

Full-thickness cuff lesions are unusual in those younger than age 40 because the young healthy rotator cuff is highly resistant to disruption or degeneration. When cuff lesions occur in the younger age group, they may be only partial thickness, or they may include the avulsion of bone from the tuberosity. Like the rest of the body's connective tissues, rotator cuff tendon fibers become weaker with disuse and age; as a result, less force is required to disrupt them. The symptoms from an acute cuff tear may resolve, leaving the shoulder asymptomatic, except for an increment in weakness. Thus, we not infrequently encounter patients with large cuff defects and minimal or no symptoms. If these shoulders remain stable, with the humeral head centered in the glenoid, they can demonstrate excellent function. Bilateral degenerative cuff defects are common. In one of our studies we found that 55% of patients presenting with a symptomatic cuff tear on one side also had a tear on the opposite side (48).

Cuff failure may progress as major episodes of tendon tearing or as creeping tears involving relatively few fibers at a time. Degenerative lesions of the cuff typically start at the deep surface of the anterior insertion of the supraspinatus near the long head of the biceps. It is difficult for these lesions to heal because of the compromised vascularity and large applied loads that the healing tissue must endure. When a tendon fiber fails, the attached muscle fibers contract and increase the gap needed to be closed; synovial fluid enzymes remove the fibrin clot necessary for healing of the cuff tear. In the absence of repair, the degenerative process tends to continue through the substance of the supraspinatus tendon to produce a full-thickness defect in the anterior supraspinatus tendon. A full- thickness defect tends to concentrate loads at its margin, facilitating additional fiber failure with smaller loads than those that produced the initial defect.

As the rotator cuff fibers fail, the humeral head is subjected to the unbalanced upward pull of the deltoid. As a result, the thinned cuff allows the humeral head to move superiorly toward the coracoacromial arch. The cuff is abraded with motion against the arch. The progression from partial-thickness tear toward massive cuff tears can take place as a subtle, subclinical degenerative process. It can also progress as a series of episodes interpreted as “tendinitis,” “bursitis,” or “impingement syndrome,” as sequential injuries produce acute extensions of the defect. It is important to note that cuff defects arising with minimal or no injury suggest that the cuff tissue is of poor quality and thus is more likely to fail again after surgical repair. By contrast, acute tears resulting from major injuries are more likely to involve robust tissue that is amenable to a durable repair.

The disuse of torn tendon leads to scarring and atrophy of tendon and muscle. Loss of cuff material from the degenerative process limits what is available for repair. Local injections of steroids may further compromise the healing potential of failed cuff fibers. As a result of these factors, the effectiveness of repair is limited by the quantity and quality of the tissue available at the time of surgery.

Evaluation. A tentative diagnosis of rotator cuff tear can be made by history and physical examination (49,50 and 51). A typical scenario for degenerative cuff fiber failure is an older individual who has an insidious onset of weakness of flexion and external rotation, perhaps punctuated by episodes of “bursitis” or “tendinitis.” Failure of weakened tendon tissue may not produce much in the way of pain, bleeding, or swelling. If the patient has pain, it is typically referred to the deltoid insertion. The shoulder may have been treated with steroid injections, with some relief of discomfort but without improvement in strength. More acute incremental losses of strength from tear propagation may follow lifting or falls. Patients with full-thickness rotator cuff tears are older than 30 and typically older than 40 years old. Patients with cuff tears typically have problems with such activities as sleeping on the affected side, placing the hand behind the head, lifting 8 pounds, and throwing overhand.

A greater injury is required to tear the cuff of individuals at the younger end of the age distribution. Younger patients with cuff tears commonly give a history of a sudden eccentric loading, such as trying to support a falling load or trying to cushion a fall with the arm; often, they complain of “tearing” and may hear a snapping sound as the tendon gives way. Traumatic glenohumeral dislocations in individuals older than the age of 40 years have a strong association with rotator cuff tears. These traumatic cuff tears may also involve the subscapularis, producing weakness in internal rotation.

Shoulder weakness may also result from neurologic lesions. Long thoracic nerve palsy causes posterior winging of the scapula on attempts to elevate the arm. Radiculopathy of the sixth cervical nerve results in pain on top of the shoulder with radiation down the arm below the deltoid tubercle, weakness of the cuff and biceps, diminished biceps reflex, and sensory changes on the lateral forearm. Suprascapular neuropathy from brachial neuritis typically has an acute onset of pain lasting several weeks, followed by weakness of external rotation and flexion.

On physical examination, atrophy of the spinatus muscles can be seen by casting a shadow from a light over the head of the patient. Rotator cuff defects may be palpable just posterior to the bicipital groove and just medial to the greater tuberosity. Crepitus upon rotation of the arm elevated to shoulder height may result from

the abrasion of torn tendon margins against the coracoacromial arch (a positive “abrasion sign”).

Many patients with substantial complete cuff tears retain the ability to elevate their shoulders, although this movement is often weak. Passive motion is typically greater than active. Isometric tests that challenge the strength of different components of the cuff demonstrate weakness, pain, or both, a positive “tendon sign.” The supraspinatus is challenged by isometric flexion of the internally rotated arm, which has been elevated 90 degrees in the plane of the scapula. The infraspinatus is challenged by isometric external rotation with the arm in neutral rotation at the side. The subscapularis is challenged by isometric internal rotation, pushing the hand away from the waist in the posterior midline.

Partial tears tend to demonstrate a minimal loss of strength with relatively more pain and stiffness. Passive forward elevation, internal rotation up the back and in abduction, and cross-body adduction are limited due to selective tightness of the posterior capsule. The shoulders will often be painful with elevation, due to stretching of the capsule as well as forced translation of the humeral head toward the acromion, compressing the rotator cuff. Large tears may involve both the infraspinatus and supraspinatus and compromise external rotation strength. Massive tears compromise the subscapularis and weaken internal rotation in addition to external rotation at the side and in abduction.

Standard radiographs may be helpful in evaluating shoulder weakness. We obtain an AP view, an axillary lateral view, and a 30-degree caudal AP view. On the AP view, chronic cuff disease may be accompanied by sclerosis of the undersurface of the acromion or cysts in the greater tuberosity and tuberosity avulsion fractures in younger patients with acute tears. Traction spurs in the coracoacromial ligament, from forced contact with the cuff and the humeral head, are best seen on the 30-degree caudal-tilted AP. In large cuff tears, the head of the humerus may be subluxated upward toward or against the undersurface of the acromion, narrowing the AC interval (Fig. 58-6). In cuff tear arthropathy, the humeral head may have lost the prominence of the tuberosities (become “femoralized”), and the coracoid, acromion, and glenoid may have formed a deep socket (become “acetabularized”). Incomplete-thickness rotator cuff lesions usually have normal radiographs.

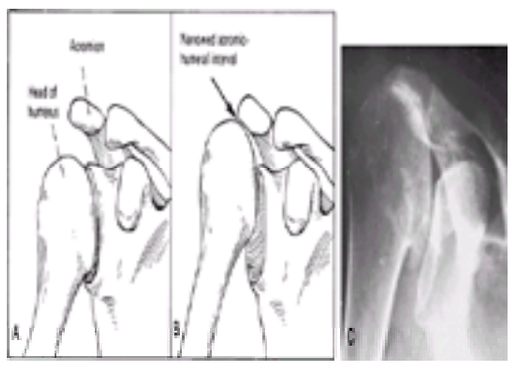


Figure 58-6. **A:** Diagram of the normal relationship of the acromion and head of the humerus, the so-called acromiohumeral interval. **B,C:** Diagram and radiograph of narrowed acromiohumeral interval, probably due to rotator cuff tear.

A number of different studies are available for imaging the rotator cuff. MRI can reveal information about the tendon and muscle. Dynamic ultrasonography (52) can reveal the thickness of the various components of the cuff and the extent of cuff defects. Each of these tests adds expense to the evaluation of the patient. Resources can be conserved by not ordering imaging tests unless it will change the management of the patient. Patients younger than age 40 years without a major injury are unlikely to have significant cuff defects; thus, cuff imaging is usually not helpful. At the other extreme, patients with weak external rotation and atrophy of the supra- and infraspinatus muscles whose plain radiographs show the head of the humerus in contact with the acromion do not need cuff imaging to establish the diagnosis of a rotator cuff defect. The management of patients with nonspecific shoulder symptoms and an unremarkable physical examination is unlikely to be changed by the results of any cuff-imaging test. The primary indication for cuff imaging is to establish the diagnosis in situations in which it would affect treatment, such as a 47-year-old patient with weakness of flexion and external rotation after a major fall on the outstretched arm and who has normal radiographs.

Diagnosis. Patients with incomplete-thickness rotator cuff lesions are typically 30 to 52 years of age at presentation, whereas patients with complete-thickness rotator cuff tear usually present between 48 to 75 years of age. Onset in younger patients is related to injury that unexpectedly applies a major eccentric load to an elevated humerus during work or sport, whereas in older patients, the onset may be insidious and apparently atraumatic. Patients with cuff tears typically complain of significant weakness, especially on elevation of the arm in anterior planes, and functional problems such as difficulty sleeping, difficulty lifting 8 pounds to shoulder level, and difficulty throwing.

On physical examination, patients with incomplete-thickness rotator cuff lesion usually have positive tendon signs, with pain as a significant component. An abrasion sign (crepitus on passive rotation of arm in elevated position) is often present if the tear involves the superior surface of tendon. Those patients with complete-thickness rotator cuff tear have positive tendon sign, with less pain. Atrophy of the supraspinatus and possibly infraspinatus is seen and often there is an abrasion sign.

Patients with cuff tears often have normal radiographs. With chronic full-thickness tears, radiographs may show superior displacement of the humeral head in relation to the acromion and a traction spur formation in the coracoacromial ligament. There may be cystic changes in the greater tuberosity and sclerosis of the undersurface of the acromion.

Treatment. Treatment of shoulder weakness caused by cuff failure is determined by the functional needs of the patient and the state of the cuff tendon. Substantial information concerning the reparability of a rotator cuff defect can be determined from the history. Acute tears in younger, healthy individuals without prior shoulder disease are likely to be repairable. Long-standing tears associated with major weakness in older patients probably offer tissue of insufficient quality and quantity to be repairable. The prognosis for a durable repair is further compromised if the history reveals prior treatment with local or systemic steroids, smoking, or difficulties in healing from previous injuries or surgeries. Critical determinants of the success of operative treatment are the quality of the residual tendon and muscle and the amount of cuff tendon tissue that has been lost. The expected strength of the cuff diminishes with age, disuse, and the duration of the cuff defect. With chronic tears, there is time to explore nonoperative management, including a general shoulder strengthening and stretching program. This nonoperative program may be the treatment of choice for patients who are not candidates for surgery or for those in whom achieving a durable repair seems unlikely. The goals of a nonoperative program are to optimize the strength and coordination of the muscles about the shoulder that remain intact. The rehabilitation program initially emphasizes stretching: supine forward elevation, cross-body adduction, internal rotation up the back, and external rotation. As the range of motion increases and pain decreases, strengthening exercises are added. It is important to avoid aggravating positions and activities.

Operative repair is considered when the shoulder demonstrates weakness from a cuff defect, and there appears to be a substantial chance of achieving a durable functional repair—that is, the quality and quantity of tendon are sufficient for repair. A prompt surgical repair of the rotator cuff is considered for physiologically young patients with acute tears and tears associated with instability. Repair should be carried out before tissue loss, retraction, and atrophy occur. If inspection of the cuff at surgery reveals good-quality tissue in sufficient quantity, the contractures are released, and the tendon is secured to the anatomic insertion site on the humerus under normal tension with the arm at the side. The repair is accomplished as a tongue in groove, with the cuff tendon drawn into a trough near the tuberosity, providing a smooth upper surface to glide beneath the acromion. Cuff repair is a shoulder-tightening operation; thus, it is not a treatment for the shoulder with functional limitation caused by tightness, even if a cuff defect is present. If the shoulder demonstrates stiffness, especially of the posterior capsule, a shoulder mobilization program is instituted before consideration of surgery.

Rotator cuff surgery (cuff repair or debridement) is considered for chronic or “atraumatic” tears with persistently substantial symptoms in spite of a nonoperative treatment trial. If there is major tissue loss and the residual tendon is of poor quality, a robust repair cannot be performed. Under these circumstances, the coracoacromial arch is preserved to provide the shoulder with its last vestige of superior stability. We smooth the torn cuff edges and excise the hypertrophic bursa and scar tissue in the subacromial area to allow unimpeded passage of the humeral head and residual cuff beneath. It is also helpful to smooth the uncovered tuberosities if they are prominent or irregular.

After rotator cuff surgery, the patient is returned to the recovery room with the affected arm in continuous passive motion. Immediate postoperative motion, facilitated if

the surgery is performed under a brachial plexus block, is valuable because there is a tendency for scarring between the undersurface of the acromion and the upper aspect of the rotator cuff or proximal humerus. The patient is expected to perform passive exercises in flexion and external rotation. Before discharge, the patient should be able to attain 140 degrees of passive flexion and 40 degrees of passive external rotation. A progress chart mounted on the patient's wall helps to document progress toward these discharge goals. The specific rehabilitation program depends on whether the cuff was repaired or debrided. Patients are usually pleased with the results of cuff surgery. However, it may be difficult to determine what aspect of the treatment program is responsible for the improvement. Many patients with deficient cuffs are surprisingly comfortable and functional and therefore never undergo surgery. It is also known that the tissue encountered at surgery is not infrequently insufficient to allow a durable repair, yet the patient is improved after debridement surgery.

We studied the integrity of the rotator cuff repair and patient satisfaction. The integrity of the rotator cuff at follow-up, not the size of the tear at the time of repair, was the major determinant of the function after surgical repair. Five years after surgery, the chances of the repair of a large tear remaining intact were not as good as those for a small tear. Older patients tended to have larger tears and a higher incidence of recurrent defects. Patients were generally satisfied with the results of surgery, even when expert sonography showed that the cuff was no longer intact at follow-up. Shoulders with intact repairs at follow-up had the greatest range of active flexion as compared with those with large recurrent defects, and the patients also had demonstrated the best function in activities of daily living. For patients without an intact cuff, the degree of functional loss was related to the size of the recurrent defect.

Surgical complications may worsen the function of a cuff-deficient shoulder. A serious complication is compromise of the deltoid muscle, the most important motor for shoulder elevation. Nerve injury or failure to achieve a strong reattachment of the anterior fibers to the acromion may compromise deltoid function. Scarring in the HSMI between the acromion and deltoid and the cuff and humerus can restrict humeroscapular motion, negating any benefit achieved from restoring cuff integrity. This complication results from immobilization of the cuff against the acromion and deltoid after surgery and the formation of adhesions or spot welds that inhibit motion. Loss of superior stability can result when the coracoacromial arch is sacrificed without reestablishing stability with a durable cuff repair. In this situation, deltoid contraction pulls the head of the humerus anterosuperiorly, rather than elevating it (Fig. 58-7A and Fig. 58-7B). The deltoid becomes stretched so that the humeral head seems to be just below the skin (Fig. 58-7C).

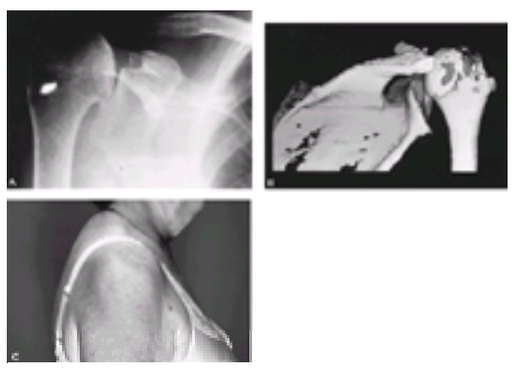


Figure 58-7. **A:** The humeral head is anterosuperiorly displaced upon the glenoid after surgical resection of the anterior acromion and coracoacromial ligament. **B:** A three-dimensional computed tomography reconstruction viewing the glenohumeral joint from a posterior aspect. **C:** The humeral head is anterior and superior and prominent below the skin.

Although cuff repair may increase the strength of the shoulder, our preference is to avoid having the patient return to heavy lifting, pushing, pulling, or overhead work after a major cuff repair. Thus, we attempt to initiate vocational rehabilitation as soon as the diagnosis is made, indicating that in spite of optimal treatment, there is a substantial risk of retearing if the cuff is subjected to major loads. It is important to remind both the patient and the employer that a cuff tear usually occurs through abnormal cuff tendon. Repairing the tear does not restore the quality of the tendon tissue; thus, the cuff remains vulnerable to sudden or large loads.

Summary. Rotator cuff tears increase in prevalence with increasing age and are common causes of shoulder weakness. With the exception of young patients with significant trauma, most rotator cuff tears occur in degenerated tissue, which makes the cuff susceptible to small, eccentrically applied loads. Many patients with torn rotator cuffs are surprisingly comfortable and functional and therefore never undergo treatment. For other patients, the mainstay of treatment may be education, stretching, and strengthening.

Rotator cuff repair is strongly considered in active patients who develop sudden weakness after an injury. Selected patients with chronic tears who are functionally disabled after a trial of nonoperative treatment may be candidates for rotator cuff surgery. The tissue encountered at surgery maybe insufficient to allow a durable repair.

Calcific Tendinitis

Acute calcific tendinitis is a common cause of shoulder pain and is often self-limited. The calcium deposits most frequently occur in the supraspinatus tendon (53). The etiology and pathophysiology of acute calcific tendinitis are not well understood. Some have attributed the calcium deposition to local microtrauma, whereas others have attributed it to local hypoxia (54,55). The pathogenesis of calcific tendinitis seems to be a degenerative process with secondary calcification within the tendon fibers (7,56,57). Cailliet (56) proposed that small particles, consisting primarily of calcium salt, are formed during degeneration of the tendon. The hyperemia associated with an acute episode causes coalescence of the calcium with formation of a liquid calcium mass, but as the vascularity subsides, this calcified mass returns to a dry state that can be seen radiographically. Uhthoff et al. (55) suggested that the primary stimulus is hypoxia, which results in transformation of a portion of the tendon into fibrocartilage. According to this view, calcification occurs in extracellular matrix vesicles located in the areas that have undergone fibrocartilaginous transformation and not associated with inflammation or scarring.

Evaluation. Calcific tendinitis often presents with the sudden onset of well-localized pain without a history of trauma (58). Calcific tendinitis typically occurs in patients approximately 40 years of age (59). The pain can be severe enough to limit shoulder motion and interfere with sleep. The rotator cuff is locally tender and strength testing reveals pain and mild weakness. Bursal hypertrophy and subacromial roughness are not uncommon. Radiographs show calcium deposits in the supraspinatus or one of the other tendons of the shoulder (Fig. 58-8). Usually a calcific deposit is seen on underpenetrated radiographs of the shoulder, particularly if the radiograph is taken so that the deposit is not superimposed on the humerus itself. Consequently, oblique angles are sometimes required to demonstrate the calcific deposit in profile.

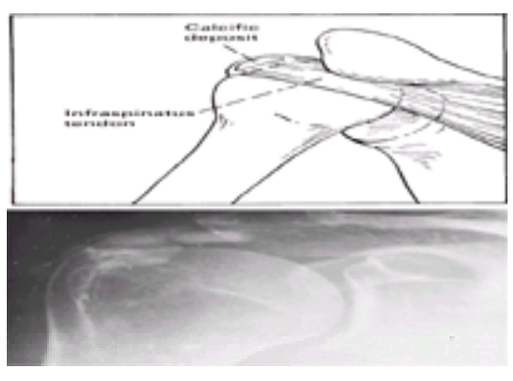


Figure 58-8. Diagram **(A)** and radiograph **(B)** of the infraspinatus tendon with a calcific deposit.

Diagnosis. Diagnosis of acute calcific tendinitis is based on its characteristic history, localized pain, and rotator cuff tenderness. Radiographs show calcification commonly in the supraspinatus tendon. It is important to differentiate this condition from chronic calcium deposition in the shoulder, which is frequently asymptomatic (53).

Treatment. Antiinflammatory medication, rest, and a single subacromial injection of local anesthetic and steroid are usually helpful. In the early phases of the condition, the calcium may be aspirated with a large-bore needle. Active assist and passive range-of-motion exercises help maintain shoulder motion. Functionally significant persistent symptoms can be treated by surgical removal of the calcium deposits followed by rotator cuff rehabilitation.

Summary. Acute calcific tendinitis is often self-limited; however, simple excision is typically curative for patients with prolonged symptoms and functional impairment.

Shoulder Roughness

There are five areas of the shoulder in which smoothness is required for optimum function. Two are atypical articulations known as the scapulothoracic interface and the nonarticular HSMI. The three cartilage-to-cartilage articulations are the AC, sternoclavicular, and glenohumeral joints. These articulations may be affected by trauma, autoimmune diseases, neuromuscular disorders, and aging. Roughness produces problems during active use of the shoulder. The positions and circumstances that elicit a problem should be carefully defined.

Subacromial Roughness. Subacromial roughness or abrasion involves the HSMI. The HSMI is a partially bursa-lined interface that lies between a deep group of structures (proximal humerus, rotator cuff, and biceps tendon sheath) and a superficial group of structures (deltoid, acromion, coracoacromial ligament, coracoid process, and tendons attaching to the coracoid). Excursions of up to 4 cm take place at this nonarticular interface (2). This motion interface includes what is often referred to as the subacromial “space.” However, empty spaces do not exist in the intact shoulder, and the area beneath the acromion and coracoacromial ligament is occupied by bursa and cuff in contact with each other. Normal humeroscapular motion requires smoothness at this interface just as much as it depends on smoothness at the glenohumeral articulation.

Subacromial roughness rarely results from the superficial aspect of the motion interface (the undersurface of the coracoacromial arch) as a consequence of developmental variances in the shape of the acromion or coracoid, or from secondary traction spurs in the coracoacromial ligament. More commonly, roughness of the deep aspect of the interface results from complete or partial- thickness cuff tears involving the upper surface of the tendon, bursal hypertrophy, sutures or lumpy tendon attachments after cuff repair, prominent tendon calcifications, or abnormal prominence of the tuberosities.

Alterations in the normal postural relationships of the humerus and scapula can result from capsular imbalance or cuff deficiency. Tightness of the posterior capsule can produce superior obligate translation of the humeral head on the glenoid on elevation of the humerus in anterior scapular planes, forcing abrasive contact between the cuff and the undersurface of the coracoacromial arch. Cuff deficiency may also allow superior translation of the humerus in relation to the scapula, creating localized abrasion of the proximal humerus beneath the unyielding acromion. Repeated forced contact of the cuff or proximal humerus with the undersurface of the anterior acromion can produce a traction spur extending out into the coracoacromial ligament. However, this intraligamentous spur does not compromise the smooth passage of the humerus and cuff beneath the arch. Continued subacromial abrasion may grind up the remaining interposed rotator cuff tissue. When the cuff is gone, this abrasive contact erodes the humeral articular cartilage, leading to cuff tear arthropathy.

Evaluation. The most common complaint of patients with subacromial roughness is limited function with the arm in intermediate positions of elevation. Patients may complain of grinding, catching, or snapping in addition to weakness. It is important to have the patient describe the onset of the problem, mechanism of injury, and nature and progression of functional difficulties as well as the specific maneuvers that reproduce the symptoms. The patient should be asked about the response of the shoulder to previous treatment, including exercise, injections, physical therapy, and surgery.

On physical examination, the examiner can distinguish the site of roughness by selectively restricting motion to one joint at a time. Roughness in the subacromial area of the HSMI is usually manifested on rotation of the arm near 90 degrees of humeroscapular elevation while stabilizing the clavicle, acromion, and scapular spine on the chest wall. Crepitus upon this maneuver, which reproduces the patient's complaint, constitutes a positive subacromial “abrasion sign.” The tenor of the crepitus is usually a higher-pitched sound, like the sound produced by wadding up a piece of paper. Strength testing of the rotator cuff tendons may elicit pain, weakness, or both. Stiffness, especially of the posterior capsule, is frequently present and is manifested as limited cross-body adduction and internal rotation.

Radiographic examination includes an AP view in the plane of the scapula, a 30-degree caudal-tilted AP view, an outlet view, and an axillary view. Primary or secondary changes of the undersurface of the coracoacromial arch, such as sclerosis or traction spurs of the coracoacromial ligament, may be seen.

Diagnosis. The diagnosis of subacromial roughness is characterized by limited function with the arm in intermediate positions of elevation. With the scapula stabilized, rotating the humerus in midrange elevation produces subacromial crepitus that reproduces the function-limiting symptoms, a positive abrasion sign. The coexistence of rotator cuff disease manifested as tendon signs and/or radiographic changes such as subacromial sclerosis or a traction spur of the coracoacromial ligament further supports the diagnosis of subacromial roughness.

Treatment. Unless the diagnostic evaluation dictates otherwise, the patient is reassured that crepitus and occasional catching do not necessitate surgical intervention. Crepitus on moving the humerus with respect to the deltoid and coracoacromial arch is very common and may be of little functional significance. For patients with functionally significant roughness of the nonarticular HSMI, the aim of nonoperative management is to restore normal kinematics: minimize stiffness, optimize shoulder mechanics, and increase strength and endurance. The first goal is flexibility, eliminating adhesions or posterior capsular tightness that may cause obligate anterosuperior humeral translation and subacromial abrasion. As flexibility is improved, attention is then directed at optimizing the normal stabilizing effect of the rotator cuff musculature by strengthening exercises, emphasizing internal and external rotation strength and endurance. Finally, the periscapular muscles are strengthened to improve posture and shoulder rhythm.

If a persistent and thorough rehabilitation effort fails to restore functional humeroscapular smoothness, consideration may be given to a surgical approach to the problem. Surgical smoothing is likely to be of functional benefit only if the patient's functional problem can be clearly localized to the subacromial region. Some patients demonstrate compromised smoothness of various aspects of the HSMI after injury or surgery—for example, roughness at the site of surgical reattachment of the subscapularis as it passes beneath the coracoid muscles on rotation. However, most functionally significant problems are in the subacromial zone and associated with some type of rotator cuff disorder. Subacromial surgery may not be beneficial for poorly defined pain or cuff strain; subacromial surgery may actually compound shoulder stiffness by creating additional sites for adhesion formation. We have found that surgical treatment of subacromial roughness is most likely to be successful in a well-motivated patient older than age 40 whose problem has been refractory to a good home program effort and whose symptoms are reproduced by the abrasion sign. The patient needs to understand what the procedure may or may not accomplish. The procedure is not expected to restore the shoulder to heavy work or to high-level athletics, but it should improve the shoulder's ability to perform activities of daily living, light work, and recreation. Workers injured on the job tend not to return to heavy, over-the-head labor (60,61). Maximal improvement after this procedure may take 6 to 12 months and will require home exercises identical to those before surgery. At time of surgery, other abnormalities may be encountered that need attention, such as a defect in the rotator cuff, bony abnormalities, or calcium deposits.

In the surgical management of subacromial roughness, it is essential to preserve the deltoid and the coracoacromial ligament to maintain the “roof” of the shoulder. The bursa on the deep surface of the deltoid muscle is entered. Thickened bursa is resected to help smooth the space and to allow inspection of the subjacent rotator cuff. The undersurface of the acromion is assessed and then bony and/or soft tissues are smoothed if indicated. An evaluation of the integrity of the cuff is made at this time. If a cuff defect is present, its reparability is assessed. When substantial roughness of the nonarticular HSMI exists in the presence of an irreparable cuff defect, emphasis is placed on smoothing the contacting surfaces rather than “decompression.” Rough edges of the acromion, hypertrophic bursal tissue, prominent tuberosities, and irregular edges of cuff tissue are removed to leave the smoothest possible HSMI. Smoothness of the motion between the anterior aspect of the subscapularis and the deep surface of the muscles originating from the coracoid process must be verified as well. If tightness is present, the approach may need to be modified to allow appropriate releases.

After surgery, the shoulder is placed in immediate passive motion. We hypothesize that immediate postoperative passive motion induces the undifferentiated cells in the surgical site to generate a smooth new motion interface, rather than irregular and adherent surfaces. We use immediate postoperative continuous passive motion until the patient can carry out his or her mobilization program without assistance. Again, the specifics of the postoperative rehabilitation program are tailored to the

patient and the nature of the operative procedure.

At present, “failed acromioplasty” is a very common condition among patients referred to our shoulder service. Postacromioplasty problems often include (a) no improvement, (b) increased pain, (c) loss of anterior deltoid strength, (d) increased stiffness, and (e) anterior-superior instability. These failed open or arthroscopic acromioplasties were usually performed for a preoperative diagnosis listed as “impingement syndrome.” However, a careful history often suggests other diagnoses, such as a stiff shoulder, cuff strain, partial-thickness cuff tears, and nonspecific shoulder pain. Poor results from subacromial surgery result when an excessive amount of acromion was removed, the acromion was transected, an irregular undersurface of the acromion resulted, or deltoid reattachment failed.

Summary. Roughness of the HSMI is frequently subacromial in location. Crepitus and occasional catching do not mandate surgical intervention unless they are associated with major refractory symptoms.

Glenohumeral Roughness. The humeral head and the glenoid normally articulate through smooth, congruent, and well-lubricated joint surfaces. Glenohumeral arthritis results when these joint surfaces are damaged by congenital, metabolic, traumatic, degenerative, vascular, septic, or inflammatory factors. The causes and pathophysiology of these conditions are identical to those of similar disorders affecting other joints. It is significant, however, that destruction of the glenohumeral joint surface can proceed from any of these causes in the absence of involvement of other joints (62). Especially in older populations, the prevalence of these conditions approaches 20% (63,64 and 65). In degenerative joint disease, the glenoid cartilage and subchondral bone are typically worn posteriorly, sometimes leaving intact articular cartilage anteriorly. The cartilage of the humeral head is eroded in a pattern of central baldness, often surrounded by a rim of remaining cartilage and osteophytes. In inflammatory arthritis, the cartilage is usually destroyed evenly across the humeral and glenoid joint surfaces. Cuff tear arthropathy occurs when a chronic large rotator cuff defect subjects the uncovered humeral articular cartilage to abrasion by the undersurface of the coracoacromial arch. The erosion of the humeral articular cartilage begins superiorly rather than centrally. Neurotrophic arthropathy arises in association with syringomyelia, diabetes, or other causes of joint denervation. The joint and subchondral bone are destroyed because of the loss of the trophic and protective effects of its nerve supply. In capsulorrhaphy arthropathy, prior surgery for glenohumeral instability leads to joint surface destruction. In this situation excessive anterior or posterior capsular tightening forces the head of the humerus out of its normal concentric relationship with the glenoid fossa. The eccentric glenohumeral contact increases contact pressures and joint surface wear. Most commonly, an overtightened anterior capsule produces obligate posterior translation, posterior glenoid wear, and central wear of the humeral articular cartilage.

Evaluation. The patient with significant glenohumeral arthritis usually presents with pain and loss of function that are refractory to rest, antiinflammatory medications, and exercises. The history should include a description of the onset of the problem, the mechanism of any injuries, and the nature and progression of functional difficulties. Systemic or polyarticular manifestations of sepsis, degenerative joint disease, or rheumatoid arthritis may provide helpful clues. A past history of steroid medication, fracture, or working at depths may suggest the diagnosis of avascular necrosis. Past injury or surgery suggests the possibility of secondary arthritis or capsulorrhaphy arthropathy. Often, the patient can describe motions that are problematic or specific maneuvers that are required to “unlock” to get past a certain sticking point. Occasionally, patients describe a sensation of apparent instability or unwanted shifting of the shoulder. Interestingly, the degree of functional compromise of the shoulder at the time of presentation for evaluation is comparable for the different diagnoses (2,66). Apparently, it is the level of functional impairment, irrespective of the diagnosis, that brings the patient in for evaluation. Matsen et al. reported the self-assessment of 103 patients with primary glenohumeral degenerative joint disease (2,67). More than half of the SF-36 pain and physical role function scores were more than one standard deviation below those of age- and sex-matched controls. These patients consistently reported the inability to perform standard shoulder functions, such as sleeping comfortably, lifting 8 pounds to shoulder height, washing the back of the opposite shoulder, throwing overhand, and tucking in a shirt behind. Self- assessment of shoulder function and health status was used to compare patients with those with rheumatoid arthritis and degenerative joint disease of the shoulder (17). Not all patients with glenohumeral roughness are the same; some patients are severely compromised due to the systemic nature of their disease, whereas others may have their problem well localized to the shoulder and be otherwise healthy. The self-assessed overall health status of individuals with glenohumeral arthritis is most compromised in the domains of physical role function and overall comfort. For patients with primary and secondary degenerative joint disease, other SF-36 parameters such as vitality and overall health were relatively close to population-based age- and gender-matched controls. The health status of patients with rheumatoid arthritis, capsulorrhaphy arthropathy, and avascular necrosis was poorer than controls of the same age and sex.

Physical examination often reveals mild or moderate muscle wasting about the shoulder due to disuse or muscle fiber failure. Isometric strength is documented in flexion, extension, abduction, and rotation. Individuals being considered for prosthetic arthroplasty should have good deltoid and rotator cuff strength. Limited range of motion commonly accompanies arthritis, which is related to adhesions and contractures of the glenohumeral capsule, rotator cuff muscles, and the HSMI. The limitation of glenohumeral motion is most easily identified if one of the examiner's hands is used to stabilize the scapula while the flexion/extension and internal/external rotations of the humerus relative to the scapula are documented with the other. Crepitus at the glenohumeral joint is often best palpated posteriorly just inferior to the angle of the acromion as the humerus is rotated at the patient's side.

In the evaluation of glenohumeral arthritis, standardized radiographic views are necessary to understand the disease process and its severity. Standard views include an AP view in the plane of the scapula and a true axillary view. These views indicate the thickness of the cartilage space between the humerus and glenoid, the relative positions of the humeral head and glenoid, the presence of osteophytes, the degree of osteopenia, and the extent of bony deformity and erosion (Fig. 58-9). Superior displacement of the humeral head relative to the scapula suggests major rotator cuff deficiency. If a humeral arthroplasty is being considered, a templating AP view of the humerus in 35 degrees of external rotation relative to the x-ray beam with a magnification marker and the arm in 45 degrees of abduction is obtained. This view places the humeral neck in maximal profile, allowing comparison of the proximal humeral anatomy with that of various humeral prostheses and places the middle of the humeral articular surface in the middle of the glenoid fossa. Thinning of the central aspect of the humeral articular cartilage typical of degenerative joint disease (the “Friar Tuck” pattern) is revealed, whereas radiographs with the arm in other positions may suggest the presence of a thicker layer of cartilage at the periphery of the head. Articular cartilage loss can be substantially underestimated even with appropriately taken radiographs.

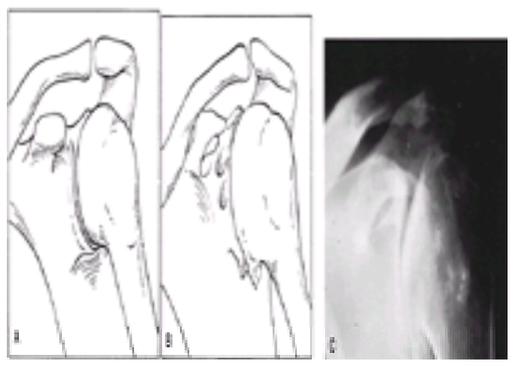


Figure 58-9. **A:** Diagram of normal glenohumeral joint in anteroposterior view. **B,C:** Diagram and radiograph of joint showing degenerative changes (sclerosis, osteophytes, cysts, and diminished joint space) associated with osteoarthritis.

Computed tomography (CT) scans are obtained if there is question about the amount or quality of bone available for reconstruction. Most often these questions can be answered from plain radiographs alone. Imaging of the rotator cuff by MRI or ultrasound is carried out only if it will affect management of the patient. Usually the status of the rotator cuff can be understood from evaluation of the history, the physical examination, and the plain radiographs.

Diagnosis. The diagnosis of glenohumeral roughness is based on the documentation of impaired motion resulting from disruption of the joint surface smoothness. Patients complain of limited function, and on physical examination, crepitus and limited glenohumeral motion are common. On radiographic examination, joint space narrowing, periarticular sclerosis, and varying degrees of osteophytes can be seen.

Treatment. In the early stages of glenohumeral roughness, the mechanics of the shoulder can be optimized by patient-conducted gentle range-of-motion and strengthening exercises, nonsteroidal antiinflammatory medications, and specific treatment for rheumatologic and septic involvement. It is important that vigorous torques and forces not be applied in an attempt to regain motion because of the concern for causing obligate translation and accelerated wear. Surgery is considered for well-informed, well-motivated, cooperative, healthy patients with functionally significant glenohumeral roughness that is not responsive to the home exercise program. Patients who are well informed and motivated before shoulder reconstruction are more likely to obtain an optimal result. The realistic goals of glenohumeral arthroplasty for a given shoulder should be discussed with the patient. Prosthetic arthroplasty is not recommended for patients who intend to return to occupational or

recreational activities that apply sudden impact or heavy loads to the joint. Such individuals should be counseled to delay the procedure, to consider an alternative reconstructive operation, or to alter their lifestyle to accommodate more appropriately a prosthetic arthroplasty.

Two approaches to glenohumeral roughness do not involve a prosthesis; they represent opposite extremes of surgical intervention. Glenohumeral arthrodesis is usually reserved for attempts at salvaging septic arthritis or complex deficiencies of the joint surface associated with permanent loss of the rotator cuff and deltoid. A nonprosthetic arthroplasty is considered for the uncommon young shoulder demonstrating early glenohumeral joint surface roughness and significant stiffness. The anterior capsule is typically tight and glenohumeral osteophytes are present. There is substantial remaining articular cartilage, with the shoulder in the “centered position” on both the AP radiograph in the plane of the scapula and the axillary view, and there is no posterior subluxation of the humeral head on the glenoid in the axillary view. In this circumstance, a capsular release and thorough osteophyte resection may help restore smoothness and motion.

Shoulder prosthetic arthroplasty is considered for patients who understand the risks and limitations of this procedure and who have sufficient bone stock, stability, and muscle control. Contraindications to arthroplasty include an active or recent shoulder infection and major loss of deltoid function. The chances of a good result are diminished by several factors. A history of smoking or narcotic use, unrealistic patient expectations, and poor patient motivation can compromise the postoperative course. Deltoid weakness, rotator cuff tears, tuberosity nonunion or malunion, and poor quality of tissues increase the technical difficulties during surgery and potentially compromise the final result. Finally, special preoperative and postoperative considerations need to be taken into account for patients who have had previous shoulder surgery, previous shoulder trauma, neurotrophic arthropathy, and a history of remote infection. The characteristic pathologies of the disease processes help guide the surgical approach.

Capsular release, subscapularis lengthening, and freeing of the nonarticular HSMI are usually incorporated in every shoulder arthroplasty. The technical demands of these procedures are high because of the critical interplay between the pathoanatomy, the amount of bone resected, the soft tissue balancing, the size and positioning of the components, and the quality of the bone and soft tissues. In glenohumeral arthroplasty, the humeral head is replaced by a metal alloy, such as cobalt chrome, and the glenoid is resurfaced by ultrahigh-molecular-weight polyethylene.

Prosthetic humeral arthroplasty without a glenoid component is considered in four circumstances: (a) if the humeral joint surface is rough, but the cartilaginous surface of the glenoid is intact; (b) if there is insufficient bone to support a glenoid component (e.g., after severe medial erosion of the glenoid in rheumatoid arthritis); (c) if there is fixed upward displacement of the humeral head in relation to the glenoid in association with massive cuff deficiency; and (d) if extraordinary demands will be placed on the shoulder that would increase the risk of glenoid component complications (e.g., motion disorders or paralysis of the lower extremities). Prosthetic humeral hemiarthroplasty offers the opportunity to restore the normal smooth convexity of the proximal humeral articular surface with an essentially normal glenoid surface. The need for humeral head replacement most commonly arises in atraumatic avascular necrosis or in fractures involving the humeral head. When performing a hemiarthroplasty, the goal is to restore the humeral articular surface to its normal location and configuration. Because the glenoid is not replaced, the size, radius, and orientation of the prosthetic humeral joint surface must duplicate those of the original biological humeral head. Often the details of the patient's normal humeral anatomy can be best obtained from radiographs of the opposite shoulder.

In degenerative joint disease, the glenoid face is typically flattened and often eroded posteriorly from chronic posterior subluxation. The glenoid may be distorted by peripheral osteophytes, masking the location of the anatomic fossa. The humeral head may be flattened in a corresponding manner and effectively enlarged by the proliferation of “goat's beard” osteophytes from the anterior, inferior, and posterior articular rims. Intraarticular loose bodies may lie hidden in the subcoracoid or axillary recesses. Anterior capsular and subscapularis contractures are common in degenerative joint disease.

In the rheumatoid shoulder, the soft tissues and the osteopenic bone are often fragile and susceptible to disruption or fracture at and after surgery. Usually, the glenoid face has been concentrically eroded medially, occasionally to an extent that precludes placement of a glenoid component. The humeral head and glenoid are often small, with a corresponding reduction in joint volume. The rotator cuff may be torn or attenuated. In juvenile rheumatoid arthritis, the diminutive osseous morphology may require smaller or even custom- made components.

Shoulders affected by capsulorrhaphy arthropathy and posttraumatic arthritis present additional challenges. Previous surgery or trauma can cause significant scarring about neurovascular structures and alter their anatomic positions. Soft tissue contractures, bone deficiencies, and implants from previous surgery complicate surgical exposure and increase potential for glenohumeral instability after the arthroplasty. Malunions or nonunions of the humeral shaft, surgical neck, tuberosities, or glenoid substantially increase the difficulty of the bony reconstruction.

Because the primary goals of arthroplasty surgery are to provide motion and smoothness, immediate postoperative passive motion is important. The immediate postoperative program is essentially the same as that used after the release of a frozen shoulder. We use a simple motor-driven adjustable cam and pulley system that puts the shoulder through a 90-degree arc of flexion and a 45-degree arc of rotation for much of the first 48 postoperative hours. The patient is taught to use the opposite arm for assisted elevation and external rotation. A motivation chart is maintained on the wall of the patient's hospital room, displaying progress toward the discharge goals of 140 degrees of elevation and 40 degrees of rotation. Grip and external rotation isometrics are started immediately. Unless a rotator cuff repair has been performed, the patient is encouraged to use the shoulder as comfort permits for active elevation and activities of daily living. If rotator cuff repairs or osteotomies have been performed, active motion and isometric cuff strengthening are delayed until healing has occurred.

Summary. The management of glenohumeral roughness provides an opportunity to combine all available knowledge about the shoulder in formulating the best treatment plan for the patient. Ultimately, surgery offers the opportunity to optimize capsular laxity and muscle mechanics, as well as joint surface smoothness, size, shape, and orientation (68,69,70 and 71).

Acromioclavicular Joint Roughness. The AC joint is a diarthrodial joint composed of the distal clavicle, medial acromial facet, and interposed fibrocartilaginous disk. Stability of the AC joint is enhanced by the capsular ligaments as well as the coracoclavicular ligaments. Fractures, compression injuries, dislocations and/or instability, and osteolysis of the distal clavicle can precipitate articular surface roughness and subsequent pain. Articular cartilage degeneration (joint surface roughness), subchondral cysts, and metaplastic bone formation (spurs) are common findings. Spurs are found more commonly on the superior surface than the inferior surface. Radiographically, AC osteoarthritis is seen much more often than osteoarthritis of the glenohumeral joint (72).

Evaluation. Patients with AC arthritis may complain of pain in the anterolateral aspect of the shoulder. They may or may not give a history of trauma (73). Osteolysis (bone resorption) of the distal clavicle most commonly occurs without antecedent trauma (74,75). Weightlifters or patients engaged in repetitive weightlifting seem to be at an increased risk to develop osteolysis of the distal clavicle (76). The pain tends to be increased by overhead, across-the-chest arm movement or lying on the affected shoulder. The signs and symptoms share common features with rotator cuff disease and glenohumeral arthritis. On physical examination, passive cross-body adduction and/or forward elevation, especially greater than 90 degrees, produce pain in the area of the AC joint. Pain posteriorly or laterally is more suggestive of glenohumeral pathology. Shoulder motion typically is not appreciably decreased, but the local pain is exacerbated at the extremes of movement. An unduly prominent lateral end of the clavicle suggests AC joint separation. This prominence is due to the scapula sagging inferiorly rather than an upwardly displaced clavicle. The clavicle can be displaced posteriorly into the trapezius muscle or tent the skin in severe separations. Palpation (see Fig. 58-2A) can reveal an irregular bony thickening of the joint margins due to the osteophytes of arthritis; in contrast to septic arthritis, there is no soft tissue thickening and no increase of local skin temperature. Swelling at the AC joint may not be from primary AC joint pathology but rather from cyst formation due to a massive chronic rotator cuff tear (77,78).

Radiographic examination of the AC joint alone includes an AP view, a 15-degree cephalad-tilted AP view, and occasionally a coned-down view of the joint. A cephalad-tilted view places the AC joint on profile without the spine of the scapula obscuring the view. An AP of the shoulder can overpenetrate the AC area and thereby diminish radiographic details. Coning down the view of the joint enhances bony detail by allowing for appropriate penetration. An axillary view can be very helpful; although obscured by the humerus, the position of the joint and presence of an os acromiale can be determined. For example, an AC joint separation in which the clavicle is posteriorly displaced into the trapezius is best visualized on the axillary view. The use of weights to enhance subtle instability has been shown to be ineffective (79) and, acutely, can be painful.

Diagnosis. The diagnosis of AC roughness is based on an insidious onset of pain, which may or may not have been preceded by an injury. The pain should be relatively directed to the AC joint area. AC instability and separation are preceded by an injury, typically a direct blow to the shoulder. Joint space narrowing, bony hypertrophy, and subchondral cysts and sclerosis are common radiographic findings (Fig. 58-10). In osteolysis, osteopenia and cyst formation are more characteristic.

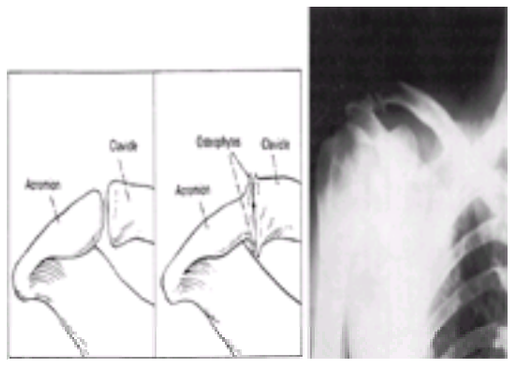


Figure 58-10. **A:** Diagram of a normal acromioclavicular joint. **B,C:** Diagram and radiograph showing degenerative changes associated with subluxation and osteoarthritis of the joint.

Treatment. If the patient has mild to moderate pain, nonsteroidal antiinflammatory drugs as well as avoiding overhead use of the arm can minimize symptoms. Acute mild AC subluxation can be managed by rest and a sling for a few days. Early shoulder motion diminishes the propensity for adhesion formation and decreased motion. Surgical intervention for AC joint arthritis should be considered only if severe pain and disability persist and can be localized specifically to the AC joint. Care must be taken to avoid excessive clavicular resection, heterotopic bone, and instability or weakening of the deltoid origin. Severe cases of AC separation such as posterior displacement of the clavicle into the trapezius muscle or skin tenting should be managed surgically by excision of the lateral end of the clavicle and stabilization of the clavicle, which may include reconstruction of the coracoclavicular (conoid and trapezoid) ligaments (80).

Summary. Roughness of the AC joint is often well tolerated with activity modification and antiinflammatory medications; failing nonoperative treatment, surgical resection of the distal end of the clavicle may result in symptomatic improvement. Mild instability of the AC joint is often well tolerated; acute operative intervention should be reserved for severe symptomatic separations.

Sternoclavicular Joint

Pain due to arthritis, instability, and trauma in the region of the sternoclavicular joint is uncommon. Like the AC joint, the sternoclavicular joint is a diarthrodial joint composed of the medial end of the clavicle, an interposed fibrous disk, and the sternum. The costoclavicular, interclavicular, and capsular ligaments provide stability.

Evaluation. The sternoclavicular joint is one of the least commonly dislocated joints in the body. Tremendous forces, direct or indirect, are usually required to produce a traumatic dislocation. Arm movement increases pain in a patient with an acute fracture or dislocation. Often there is prominence or retraction about the sternoclavicular joint in anterior or posterior dislocations, respectively. However, soft tissue swelling may accompany a posterior dislocation, giving the appearance of an anterior dislocation. In recurrent dislocation or subluxation, the clavicle can be felt to click out of joint when the shoulders are braced back and to go back into position when the shoulders are arched forward (72). Posterior dislocations can be accompanied by circulatory or respiratory compromise. Arthritis of the sternoclavicular joint is often associated with hypertrophy of the medial end of the clavicle without soft tissue swelling or erythema. Often the patient complains of crepitus, pain, or both associated with arm movement. Sternoclavicular joint tenderness is commonly present in arthritic conditions as well as acute dislocations.

Plain radiographs are useful to delineate gross anatomic alignment of the joint. A 40-degree cephalic-tilted AP view of both sternoclavicular joints will show an anterior displaced clavicle to be superior to a horizontal line at the level of the joint, whereas a posteriorly displaced clavicle will appear inferior. Computerized tomography is the best modality to evaluate the bony architecture of the sternoclavicular joint in acute and chronic disorders.

Diagnosis. The appearance of the sternoclavicular joint on plain x-rays can be difficult to interpret due to overlying structures. A CT scan will confirm the position of the clavicle relative to the sternum. Like other arthritic conditions, pain associated with sternoclavicular arthritis begins insidiously and is increased by arm movement.

Treatment. Anterior dislocations can be reduced but typically redislocate. Although prominent, a chronic anterior dislocation is often well tolerated (81). Acute posterior dislocations can be reduced by closed techniques and are usually stable after reduction. Should operative reduction be necessary, a thoracic surgeon should be available. The patient should be carefully evaluated, as concomitant vascular or pulmonary injuries are not uncommon. Antiinflammatory medications and rest usually reduce the pain of arthritis. For those patients with pain and functional limitations, surgical resection of the medial head of the clavicle with preservation of the costoclavicular ligament may be helpful (82).

Summary. Sternoclavicular disorders are uncommon. Most disorders are well tolerated. Posterior dislocations can be usually reduced closed. Concomitant injuries can be significant, and a thorough evaluation is required. Most commonly, arthritis responds favorably to nonoperative modalities.

Scapulothoracic Motion Interface

The scapulothoracic motion interface is the site of movement between the scapula and the chest wall. The deep aspect of this interface consists of the ribs and their covering musculature. The superficial aspect of the interface consists of the scapular border along with the serratus muscles. No muscle covers the anteriorly inclined superior medial corner of the scapula. This corner is a potential site of bony contact between the scapula and the thoracic wall, especially if the normal postural relationship between the scapula and the rib cage is altered. If injury or disuse allows the scapula to ride low on the chest, for example, the superior medial corner of the scapula may “washboard” over the ribs, producing a snapping scapula. Thinning of the interposed subscapularis and serratus muscles may yield a similar effect. Malunions of scapular or rib fractures can also present major irregularities at the scapulothoracic motion interface. Hypertrophy of the subscapular bursa or osteochondromata of the anterior surface of the scapula can also disrupt smooth gliding of the scapula on the chest wall.

Evaluation. Patients often complain of a popping or clicking in their shoulder with scapular movement. Scapular maltracking can accompany rotator cuff disorders as well as glenohumeral instability (83). Nerve palsies such as of the long thoracic or spinal accessory nerve can produce weakness and subsequent dysfunction. The examiner can help distinguish scapulothoracic roughness from glenohumeral problems or from problems at the humerothoracic motion interface by selectively restricting the motion at first one site and then the other. Shrugging, protracting, and retracting the scapula while the examiner disallows glenohumeral motion permits independent assessment of the smoothness of the scapulothoracic motion interface. Palpation of the site for roughness may localize the problem to the superior medial border of the spine of the scapula. Alternatively, rotating and elevating the arm while the examiner stabilizes the clavicle, acromion, and scapular spine on the chest wall allows independent evaluation of the glenohumeral joint and the HSMI.

Radiographic examination should include an AP and lateral views in the plane of the scapula; CT can help localize the sites of specific structural abnormalities but is of minimal value in evaluating a snapping scapula resulting from abnormal posture.

Diagnosis. Rarely, roughness in the scapulothoracic motion interface is caused by an anatomic abnormality such as a malunited fracture or an osteochondroma on the anterior undersurface of the scapula. These unusual causes can often be diagnosed on a lateral radiograph of the scapula. Scapulothoracic crepitus, or “snapping scapula,” is most commonly caused by altered scapulothoracic posture and mechanics.

Treatment. The primary treatment of this condition is reassurance; restoration of normal posture; and strengthening of the serratus anterior, subscapularis, trapezius, and rhomboids. It is essential that the patient avoid voluntary or habitual scapulothoracic snapping. More aggressive treatment is considered only in the rare patient who has functionally significant, involuntary, nonvocationally related scapulothoracic snapping that has failed to respond to a prolonged, nonoperative management program. Refractory cases of snapping scapula may respond to local injection, to bursal resection, or to resection of the superior medial angle of the scapula. Because these procedures do not treat the primary problem of altered scapulothoracic posture, failure to improve shoulder function is not infrequent unless postoperative rehabilitation reestablishes normal muscle positioning. Complications of surgery can be related to failure to reattach securely the muscles inserting on the superior medial angle of the scapula, to injury to the nerve to the lower trapezius, to leaving residual prominent edges of the scapula, and to scarring in the scapulothoracic motion interface.

Summary. Snapping scapula is usually secondary to abnormal scapular posture and tracking; structural abnormalities are uncommon. Scapular winging and maltracking can be associated with primary glenohumeral pathology or muscular weakness. Periscapular muscular strengthening exercises are helpful to improve postural relationships between the chest wall and scapula.

Neuropathy

Peripheral nerve entrapment about the shoulder is unusual. Suprascapular nerve compression, quadrilateral space syndrome, thoracic outlet compression, and acute brachial neuritis all can result in diffuse shoulder pain, weakness, or both.

Evaluation. Nerve lesions about the shoulder often cause vague shoulder pain, weakness, or both. Isolated infraspinatus involvement is suggestive of compression of the suprascapular nerve at the spinoglenoid notch, whereas involvement of both the supraspinatus and infraspinatus is characteristic of suprascapular notch compression. In long-standing cases, atrophy of the supraspinatus or infraspinatus fossae, or both, are present, and electrodiagnostic tests will show increased latency. External rotation at the side and abduction are often weak. Occasionally, space-occupying lesions such as ganglia arise from the glenohumeral joint and compress local nerves as in a spinoglenoid notch cyst compressing the nerve to the infraspinatus. Axillary nerve compression by fibrous bands in the quadrilateral space is uncommon. Malunited clavicle fractures can limit the space between the clavicle and first rib and compress the brachial plexus. Acute onset of pain without antecedent trauma followed by a reduction in pain with a variable persistence of weakness is suggestive of acute brachial neuritis (84).

Radiographic examination of the shoulder is typically negative. If a history of trauma exists, oblique views of the scapula may be helpful in delineating the bony morphology after fractures. For ganglia, MRI may be helpful to identify the ganglia as well as associated labral pathology. Magnetic resonance neurography may also delineate the site of nerve pathology for major nerves and the brachial plexus.

Diagnosis. A high index of clinical suspicion is needed. Often symptoms are vague and can be mistaken as primary rotator cuff, AC, or glenohumeral pathology. In severe cases, electrophysiological studies may be positive. Radiographic and angiographic studies can be supportive if structural abnormalities exist.

Treatment. In the absence of structural abnormalities, thoracic outlet syndrome (85) and suprascapular neuropathy (86) respond favorably to nonoperative therapy such as postural exercises, antiinflammatory medications, and physical therapy. In acute brachial neuritis, expectant management with or without pharmacologic therapy is appropriate. Pain typically resolves, whereas mild weakness can persist. Surgical decompression should be reserved for those patients with persistent significant pain and functional limitations that can be conclusively attributed to nerve compression.

Summary. Peripheral nerve lesions about the shoulder occur infrequently, signs and symptoms are vague, and ancillary studies are frequently nondiagnostic. Surgical decompression may be indicated when the lesion is defined and significant symptoms persist.

ELBOW AND LOWER ARM PAIN

The elbow consists of three distinct articulations. The ulnohumeral joint allows flexion and extension; the proximal radioulnar and radiocapitellar joints allow axial rotation. Pain in the elbow is caused by diseases and injuries similar to those affecting the shoulder. Like the shoulder, motion, stability, strength, and smoothness characterize a well-functioning elbow. A normal elbow enables the hand to be placed in various positions around the body. The etiologies of pain will be divided into stiffness, instability, weakness, and roughness; entities such as olecranon bursitis and neuropathy will be part of an additional category. Frequent extraarticular causes of pain in the elbow region are lateral (tennis elbow) and medial (golfer's elbow) epicondylitis, ulnar neuropathy, and olecranon bursitis. Intraarticular disorders such as arthritis, loose bodies, and osteochondritis dissecans occur less often. Elbow stiffness may be due to lesions that are intraarticular, extraarticular, or a combination of both etiologies.

Patient Self-Assessment

Patient self-assessments of health status and elbow function are useful tools to help characterize patients with elbow pain. They provide practical, standardized, and meaningful characteristics of the status of the patient at the time of presentation. According to Turchin et al., patient self-completed functional questionnaires can be valid and reliable assessment tools for the elbow and do not suffer from observer-based bias (87). We believe that the complete evaluation of patients with elbow problems requires both disease-specific and overall health status measurements. We use the information gained from the simple elbow test (SET) (Table 58-2) and SF-36 self-assessment questionnaires to monitor the effectiveness of our treatment. The SET is a binary (yes or no) patient self-completed inventory of activities that can be performed. Effectiveness is the change from ingo scores (at presentation) to outcome scores (after treatment). The results of treatment, both operative and nonoperative, are dependent on the physician, the procedure, and rehabilitation. Again, it is important to remember that the objective severity of the disease showed little relationship to patients' reports of pain, whereas psychological variables were much more closely correlated with measures of pain and functional impairment (18).

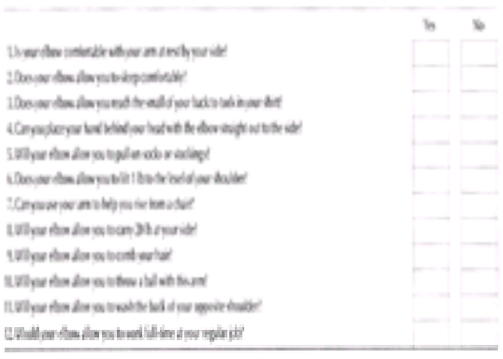


TABLE 58-2. The simple elbow test (SET)

Anatomic-based patient assessments have been used extensively to monitor the results of orthopedic treatment. Observer-based aggregate scoring systems seem to reliably assess the anatomic aspects of elbow impairment (87). However, Bostrom et al. found that standardized assessments of function are more reliable and reproducible than conventional range-of-motion measurements. Functional inventories provide useful information that is meaningful to both the treating physician and the patient.

Evaluation of the Patient

The diagnosis of elbow pain can be a challenging task and should be undertaken within the context of the patient's overall status. In the patient with elbow pain, we attempt to define the problem in terms of the elbow's four mechanical properties: motion, stability, strength, and smoothness. If a patient's problem can be understood in mechanical terms, effective treatment plans can be formulated. All elbow pain is not mechanical in origin and may be best managed by a multidisciplinary approach. Identifying the best management approach for each individual patient is the primary challenge a physician faces. Mechanical elbow problems are typically related to certain activities or positions and are reproducible. Although the patient recognizes them as mechanical in nature, the localization of pain may be due to secondarily affected structures as in ulnar nerve neuritis secondary to chronic valgus instability of the elbow. Nonmechanical problems are typically not related to activity or position and are more diffuse in nature. We will limit our discussion of mechanical etiologies of elbow pain.

History

Like the shoulder, elbow disorders do not exist in isolation, but rather in the context of the overall health of an individual. It is essential to obtain a complete history of

any painful condition at the onset, during the interval time between onset and presentation, and at the time of the physician interview. Details about various characteristics of the pain, including precipitating factors, location, intensity, quality, duration, and aggravating or relieving factors, should be obtained. Mechanical elbow pain can be fairly well localized to the joint. Pain radiating to the mid-arm, forearm, and hand may be due to nerve entrapment.

Physical Examination

During the physical examination, both arms must be uncovered so that the painful part of the affected limb can be compared with the opposite limb. As in the shoulder, an examination should include inspection, palpation, and determination of the active and passive range of motion. During inspection, special note should be made of the bony contours and alignment, muscle mass, and the presence of scars or other signs of injuries. Articular effusions are best appreciated in the lateral triangle created by the olecranon, lateral epicondyle, and radial head. Bursal effusions are seen posteriorly over the olecranon tip. Palpation should be systematic and include the flexor and extensor muscle tendinous insertions; radial capitellar joint; posterior ulnohumeral joint; collateral ligaments; and the areas of the posterior interosseous nerve (radial tunnel), ulnar nerve (cubital tunnel), and median nerve at the pronator teres muscle. Muscle power and stability testing may be painful and should be undertaken last.

Normal flexion and extension of the ulnohumeral joint have a range of approximately 0 to 140 degrees. Supination and pronation should be tested with the elbow flexed at a right angle and the arm adducted to the side to eliminate rotation of the shoulder. The normal range is approximately 80 degrees of supination (palm up) and 80 degrees of pronation (palm down). If the range of rotation is restricted, the possible causes may be in the forearm and wrist as well as in the elbow. Motion accompanied by crepitus can be due to articular incongruity such as in arthritis, loose bodies, or intraarticular adhesions. Flexion, extension, supination, and pronation power should be evaluated and compared with that of the same muscles on the opposite side. Wrist extension and flexion strength as well as any associated symptoms should be elicited. The integrity of the lateral and medial ligaments of the elbow, stability of ulnar nerve at the cubital tunnel, and the competence radiocapitellar joint should be documented. The neurologic examination consists of cervical spine range of motion, assessment of symptom exacerbation due to neck position, a functional evaluation of the cervical nerve roots, and sensory and reflex testing as indicated in each unique case.

Radiographic Examination

Radiographs may provide additional evidence to ascertain the diagnosis. The minimal examination includes AP views of the distal humerus and proximal forearm and lateral views in maximal flexion and extension. The AP view should be perpendicular to the elbow in complete extension. Elbows that do not extend fully should have separate perpendicular AP views of the distal humerus and proximal forearm. Accessory radiographs such as radiocapitellar, cubital tunnel, oblique, and stress views can be added as the clinical situation dictates. MRI, CT scans, and bone scans are occasionally needed in the workup of disorders such as osteochondritis dissecans, loose bodies, or fractures.

Elbow Stiffness

A flexion contracture, loss of elbow extension, may be caused by fractures, dislocations, arthritis, burns, head injury, and increased spasticity as, for example, from cerebral palsy (88,89,90,91,92 and 93), and the resulting loss of motion may cause significant morbidity. The specific components of posttraumatic elbow contracture vary according to the mechanism of injury (94,95 and 96). A useful way to classify elbow contractures is to identify the structures involved as to what severity. Contractures may be divided into intrinsic (intraarticular changes—fracture, loose bodies, synovitis) and extrinsic (capsular contracture and scarring, collateral ligaments, flexor-extensor musculature, heterotopic bone and skin) etiologies and combined intrinsic and extrinsic causes.

Evaluation

The nature of the initial injury, duration of time, previous treatment (operative and nonoperative), and associated injuries should be assessed. The duration of stiffness or the initial injury may have rendered the articular cartilage incompetent and limit functional return. Previous surgical procedures and extraarticular posttraumatic deformities may have altered the neurovascular anatomy around the elbow joint. The sequelae of a head injury should be stable and the patient should be able to cooperate with the requisite intensive rehabilitative effort if surgical treatment is considered. Active and passive pronation, supination, flexion, and extension should be recorded. Associated crepitus, catching, or popping is suggestive of intrinsic pathology. Muscle strength should be tested and any associated spasticity is noted. Finally, the patient should have realistic goals and realize that gains as well as pain relief may not be complete.

Radiographs of the elbow are essential. Elbows that do not extend fully should have separate perpendicular AP views of the distal humerus and proximal forearm taken. Lateral views of the elbow in maximum flexion and extension help to assess the role of bony abutment in stiffness. Occasionally, CT scans can better assess the bone contours and fracture healing that may influence treatment.

Treatment

Most activities of daily living are performed in an arc of motion of the elbow from 30 to 130 degrees of flexion (97), and therefore treatment is usually indicated for patients who have functional limitations due to contractures of greater than 30 degrees or flexion of less than 130 degrees, as well as those patients whose occupation or functional demands require more than the available range of motion. Those patients with a lesser degree of contracture who have pain, popping, or locking of the elbow suggesting some intraarticular derangement may also be candidates for management of their contracture.

For contractures of short duration and little evidence of intraarticular damage, conservative therapy for elbow flexion contractures may include early range-of-motion exercises and an aggressive active and passive physical therapy program coupled with dynamic or static splinting (98,99).

Surgical treatment is indicated for well-informed and motivated patients refractory to conservative treatment and patients in whom an increase in range of motion as well as decrease in roughness is beneficial. Many patients have combined intrinsic and extrinsic etiologies of elbow stiffness. Our surgical approach is sequential; the anterior soft tissues and bone are addressed first followed by the posterior structures. Intraarticular adhesions, osteophytes, the anterior radial capitellar joint, and the anterior capsule are addressed sequentially. As dictated by the resultant range of motion, attention is then directed to the posterior compartment. The triceps can be elevated and released off the humerus, adhesions and olecranon tip osteophytes are removed, and the olecranon fossa is dábrided and widened as necessary. Range-of-motion exercises are started immediately after surgery. Neural function, especially the ulnar nerve, is monitored postoperatively. Neural excursions may not be able to compensate for the postoperative increase in elbow joint motion.

Summary

Elbow stiffness can cause significant functional impairment and pain. In carefully selected patients, significant improvement in function and pain relief can be achieved by surgical debridement, soft tissue release, and aggressive postoperative range-of-motion rehabilitation.

Elbow Instability

The elbow joint is highly constrained due to its osseous configuration. The articular surfaces are closely approximated, and the radiocapitellar and ulnohumeral articulations provide bony buttresses against varus and valgus stresses. The medial collateral and lateral collateral ligamentous complexes provide additional restraint to valgus and varus stresses, respectively.

Valgus Instability

The anterior oblique bundle of the medial collateral ligament of the elbow is the primary stabilizer to valgus stress (100,101 and 102). The diagnosis of valgus instability is often difficult, requiring a combination of a careful history and physical examination.

Evaluation. Major trauma to the medial collateral ligament such as simple dislocations rarely result in symptomatic instability (103). Medial collateral ligament compromise may be disabling in the context of lateral collateral ligament or bony insufficiency. Nerve injuries, especially the ulnar nerve, are not uncommon after elbow dislocations. Stretch injuries or entrapment of a nerve may be a source of continuing pain and altered function. Minor degrees of valgus instability may be symptomatic in competitive overhead athletes such as tennis or baseball players. The patient often gives a history of repetitive overhead activities such as throwing.

An overhead athlete often complains of medial pain, increased ease of fatigue, pain, or a combination of these symptoms associated with an acute injury. Pitchers may complain of pain during acceleration as well as ulnar nerve symptoms (104). Valgus stress testing is performed by applying a valgus load to the elbow brought through an entire arc of motion. One hand applies the stress while the other hand palpates the medial side as the elbow is brought through an entire arc of motion. Pain, tenderness, or both; crepitation at the medial ulnohumeral, radiocapitellar, posterior olecranon-medial humerus; or laxity are suggestive of valgus instability. In most cases, the examination results are rather subtle, characterized by a mild increase in laxity with an ambiguous end point. Valgus stress testing can be performed with the patient sitting and the arm braced next to the body; alternatively, the patient can be placed prone on an examining table, the arm is stabilized against the table, and valgus stress is applied.

Radiographs for instability include an AP, lateral, and, if indicated, AP stress views. In chronic cases, bony hypertrophy of the medial aspect of the posterolateral humeral column with concomitant changes of the lateral olecranon and radiocapitellar chondromalacia is a common finding. Stress AP views show medial joint space widening with concomitant lateral widening between the olecranon and the distal humerus due to ligamentous incompetence. An avulsion fracture or cortical hypertrophy of the medial epicondyle are common findings as well.

Diagnosis. Medial collateral instability is characterized by a history of major trauma, such as an elbow dislocation or repetitive overhead throwing with increasing functional disability. A demonstration of instability by physical examination or imaging studies is important. Arthroscopy may play a role in the evaluation of valgus instability (105). Opening of the medial ulnohumeral joint to valgus stress as little as 1 to 2 mm indicates disruption of the anterior bundle of the medial collateral ligament.

Treatment. Patients with severe instability despite congruous articular reduction, the failure to achieve a congruous reduction after an elbow dislocation, or elbow dislocations associated with unreconstructable radial head fractures also should be stabilized surgically. Most patients with minimal instability respond to rest, antiinflammatory medications, and physical therapy stressing flexor- pronator strengthening. If symptoms persist and the patient desires to return to highly competitive sport or the elbow is grossly unstable after major trauma, a ligamentous repair or reconstruction can be offered to the patient. After surgery, the patient needs to resume a flexor-pronator and generalized muscular strengthening program.

Posterolateral Rotatory Instability

Lateral collateral ligament insufficiency is being recognized more commonly. According to O'Driscoll et al., rupture of the ulnar part of the radial (lateral) collateral ligament is the primary lesion in posterolateral rotatory instability of the elbow (106). The radial head and ulna abnormally subluxate posteriorly and laterally on the humerus. Patients may complain of lateral elbow symptoms, and these may have been previously misdiagnosed as lateral epicondylitis.

Evaluation. Incompetence of the lateral collateral ligament complex commonly occurs after a posterior elbow dislocation. Patients with lateral instability often give a history of elbow trauma or previous surgery on the lateral side of the elbow. For example, the patient may not be aware of the significance of a fall. An elbow “sprain” with persistent symptoms may have been either a dislocation with spontaneous reduction or a significant subluxation. Often, symptoms arise with axial loading such as rising from a chair with arm assist. Patients may complain of popping, catching, or grinding. Occasionally, patients will notice that the elbow slips out of place or locks in when the forearm is extended.

The relationship of the radial head and the humerus is the focus in provocative testing of the lateral elbow. The posterolateral rotatory instability test (pivot shift) (106) is a useful provocative maneuver. In this examination an axial and valgus load is applied to the elbow, with the forearm supinated. Palpation of the radiocapitellar joint may reveal that the radial head subluxates posterolaterally on the humerus. With greater degrees of instability, the subluxation of the radial head and ulna causes a prominence over the radial head. A dimple may appear with reduction of the ulna and radius at approximately 40 degrees of flexion.

Radiographic examination includes an AP view, a lateral view, and occasionally a lateral stress view. Stress views may demonstrate a radial head that is slightly inferior to the capitellum. CT or MRI scans with or without intraarticular contrast are occasionally helpful.

Treatment. As with medial instability, a course of nonoperative treatment, including rest, medication, behavioral modification, and functional strengthening, is instituted. However, nonoperative therapy is typically less successful for posterolateral instability than for valgus instability. Operative stabilization involves capsular plication, ligamentous repair, or reconstruction with a tendon graft.

Summary. Elbow instability is often subtle in its presentation and physical examination. A high index of suspicion, a thorough history, and a careful examination often confirm the diagnosis. Isolated valgus instability requiring operative intervention is uncommon except in athletes with high-demand overhead activity.

Elbow Weakness

Epicondylitis

Epicondylitis is one of the more common painful afflictions of the elbow. The etiology is thought to be a series of small tears in the origin of the extensors at the lateral epicondyle or the flexor-pronator mass at the medial epicondyle. Laterally, the extensor carpi radialis brevis and, medially, the pronator teres and flexor carpi radialis are most commonly affected. Although often referred to as an “- itis,” evidence of substantial local inflammation is usually lacking. Histologically, the pathologic tissue consists of a vascular fibroblastic proliferation that characteristically lacks inflammatory cells (65). Intraarticular changes such as synovitis or synovial thickening are occasional findings.

Evaluation

Medial epicondylitis is often called “golfer's elbow,” whereas lateral epicondylitis is referred to as “tennis elbow.” However, most patients with epicondylitis are neither golfers nor tennis players. Pain that interferes with activities of daily living is the most common presenting complaint. Morning stiffness and a generalized ache are not uncommon. The patient often localizes the pain to the medial epicondyle, distal to the medial aspect of the antecubital fossa, or just distal to the lateral epicondyle. The patient with lateral epicondylitis may complain that the pain is accentuated by grasping or lifting. Difficulty turning the key to start a car or to pick up objects with the palm up (wrist flexion) is commonly associated with medial epicondylitis.

On physical examination, palpation reveals tenderness localized just at the insertion of the forearm wrist flexors into the medial epicondyle or the wrist extensors into the lateral epicondyle (extensor carpi radialis brevis). Stretching or contracting the involved musculotendinous units against resistance should reproduce the patient's symptoms.

Posterior interosseous nerve compression may occur in approximately 5% of patients who seem to have lateral epicondylitis (107) and can be the cause of failed surgical treatment for refractory lateral epicondylitis (108). The posterior interosseous nerve can be palpated approximately 5 cm distal to the lateral epicondyle between the extensor digitorum longus and the brachioradialis (the radial tunnel). A history of burning pain and tenderness in the radial tunnel is suggestive but nonspecific. Likewise, the ulnar nerve should be evaluated as part of a medial epicondylitis workup. Ulnar nerve tenderness and paresthesias on the dorsum of the hand and ulnar two fingers with elbow hyperflexion are suggestive of an ulnar nerve neuritis. Posterolateral rotatory and valgus instabilities of the elbow, although completely different entities, can have symptoms similar to epicondylitis.

Although we often recommend an AP and lateral x-rays of the elbow, radiographic studies typically do not demonstrate abnormalities. Occasionally, calcifications of the soft tissues or bony changes of the epicondyle are encountered.

Diagnosis. The diagnosis of elbow epicondylitis is made by history of heavy elbow use and a characteristic physical examination. Tenderness just distal to the prominence of the epicondyles near the tendinous insertions, as well as pain with resisted wrist extension or flexion, is typical. Radiographs, bone scans, and electrodiagnostic tests are usually negative.

Treatment. Treatment of epicondylitis should include activity modification, rest, and antiinflammatory medication. Occasionally, enforced rest with a dorsiflexion wrist splint or a counter-force brace is helpful. Sometimes local steroid injections into the area of maximal pain are useful. After the acute symptoms have subsided, the extensor carpi radialis brevis is stretched by elbow extension, forearm pronation, and wrist flexion. In a similar fashion, the flexor-pronator mass can be stretched by elbow extension, forearm supination, and wrist extension. Postexercise cryotherapy is useful to diminish pain. When stretching is no longer painful, a progressive

strengthening program should be instituted to prevent recurrent episodes. These exercises must not be done to the extent that they produce pain; rather, the patient should strive for multiple repetitions of the exercise against light resistance to build endurance and strength.

For patients with continued functionally significant symptoms, a release of the extensor carpi radialis brevis from the lateral epicondyle (9,109,110 and 111), or the flexor-pronator mass from the medial epicondyle, may diminish symptoms.

Summary. Epicondylitis is a noninflammatory degeneration of the tendinous insertions at the medial or lateral epicondyles of the elbow. Most cases respond well to nonoperative therapy: a stretching and strengthening program. Refractory cases can be managed by dábriding the area of degenerative tendons and resuming postoperative stretching and progressive resistance exercises as part of functional rehabilitative program.

Distal Biceps Tendon

Rupture of the distal end of the biceps brachii tendon occurs infrequently compared with its proximal counterpart. According to Gilcrest and Albi, 97% of biceps tendon ruptures occur proximally, whereas only 3% occur distally (112).

Evaluation

The tendon typically avulses from the radial tuberosity (113), frequently tears the lacertus fibrosis, and thereby eliminates muscle function (114). Patients usually describe that they were attempting to lift a heavy object before rupture. Ecchymosis of the forearm, elbow, and arm is typical. Distal ruptures are associated with substantial loss of elbow flexion and supination strength and can cause major functional deficits. The distal biceps tendon avulses and migrates proximally; it can be palpated proximal to the antecubital fossa. Occasionally patients may present late after their initial injury. These patients complain of pain and weakness but do not have the signs of an acute injury. Radiographs should include an AP and a lateral of the elbow and are typically normal.

Diagnosis

Patients who sustain distal biceps tendon ruptures are typically middle-aged males involved with heavy lifting. They have loss of flexion and especially supination strength. The biceps tendon is often palpable proximally in the antecubital fossa.

Treatment

To avoid weakness and the associated functional disability, we recommend acute anatomic repair. Morrey et al. (113) compared results of immediate anatomic reattachment, delayed reattachment, attachment to the brachialis tendon, and nonoperative treatment of distal biceps ruptures. Immediate reattachment restored normal strength in flexion and supination at 1 year in comparison with conservative treatment, which resulted in a 40% loss of supination strength and 30% loss of flexion strength. Late reconstruction by inserting the tendon into the brachialis resulted in improved, but not to normal, supination and flexion power (115). Anatomic repair of the distal biceps tendon can performed by a two-incision technique similar to that described by Boyd and Anderson (116) or a one-incision technique through a modified Henry approach (117).

Patients who present with chronic distal biceps rupture require careful and thoughtful management. Anatomic repair is difficult, if not impossible, after chronic rupture due to prolonged musculotendinous unit contracture, tendon degeneration, and scarring around the radial tuberosity. There have been isolated case reports describing surgical management of chronic distal biceps rupture using fascia lata graft (118) or free semitendinosus graft (119) to bridge the gap between retracted tendon and the radial tuberosity. Since 1990, one of us (FAM) has offered reconstruction with an autogenous semitendinosus graft and has good results.

Summary

Early anatomic repair of acute distal biceps ruptures is the ideal treatment to restore strength and function. Late reinsertion can yield good results; however, these are usually inferior to acute repairs. A semitendinosus autograft can be considered for patients who have a chronic tear of the distal biceps tendon that has retracted so that it can no longer reach the radial tuberosity.

Elbow Arthritis

The most common types of arthritis affecting the elbow are osteoarthritic, posttraumatic, and rheumatoid. Classic findings in the osteoarthritic elbow include osteophytes from the coronoid and olecranon (120), loose bodies, and bony hypertrophy of the distal humerus (121).

Athletes who throw in their sport are particularly prone to lesions in the posterior compartment degenerative osseous changes due to valgus loads placed on the elbow (122). Posteromedial olecranon osteophytes corresponding with hypertrophy of the humerus (123), radiocapitellar chondromalacia, and loose bodies are common (124). Pain may result from repeated impaction during the late acceleration and follow-through phases of throwing (125).

The elbow is the second most common site of osteochondritis dissecans (72,126). This disorder is characterized by necrosis of part of the articular cartilage and of the underlying bone, with eventual separation of the fragments to form intraarticular loose bodies (Fig. 58-11). The precise cause of this condition is unknown (72,126), although injury may play a prominent role. The capitellum seems to be primarily affected, perhaps due to impairment of blood flow to the affected segments of bone and cartilage by thrombosis of the end artery (72) or due to the inherent mechanical properties of the capitellar articular surface. Increased strain on the capitellum during high valgus loads as in pitching may predispose the capitellum to injury. Topographically, significant differences exist in the mechanical properties and thickness of capitellar and radial head articular cartilage (127). The size of the necrotic segments of the articular surface as well as secondary radial head changes vary. A line of demarcation forms between the avascular segment and the surrounding normal bone and cartilage; after an interval of months, the avascular segment separates as a loose body.

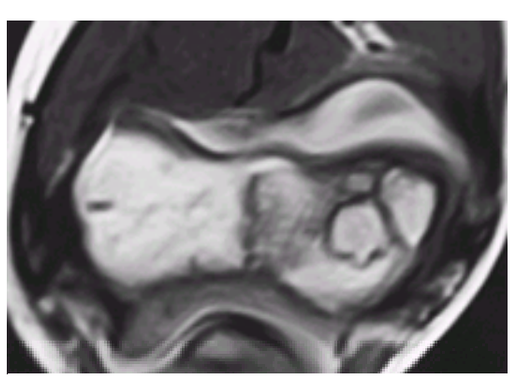


Figure 58-11. A magnetic resonance imaging scan of the distal humerus. Osteochondral fragments are readily seen in the capitellum.

Evaluation

Characteristics of a patient with osteoarthritis of the elbow are fairly consistent. Patients tend to be older males, except throwing athletes, who tend to present at younger ages. They have mechanical symptoms due to bony changes, including locking, grinding, and catching. Flexion contractures associated with posterior mechanical abutment are common. The patient complains of pain, which is aggravated by use of the elbow. The range of motion of the elbow is frequently limited, with extension greater than flexion. Palpation of the elbow elicits tenderness and effusions are occasionally present. Strength is typically diminished. Patients with inflammatory arthritis have a more variable presentation. Pain and mechanical symptoms are similar, although significant articular effusions are more common in

inflammatory arthridities, such as rheumatoid arthritis.

Radiographs may reveal loss of radiographic joint space, osteophytes, distal humeral hypertrophy, and loose bodies; posttraumatic deformities; and osteopenia and bony erosions in inflammatory arthritis. Conventional radiography, however, typically underestimates the number of loose bodies found at surgery (128,129,130,131 and 132); a patient with mechanical symptoms may have symptomatic loose bodies without radiographic evidence. Occasionally, CT scans and MRI may help in the evaluation of disorders such as early osteochondritis dissecans or significant posttraumatic deformities.

Diagnosis

An arthritic elbow is usually stiff, crepitant, and painful on joint motion. Loose bodies typically manifest as popping or catching with motion. Inflammatory elbow arthritis is usually accompanied by an elbow effusion, which is most often apparent in the area of the radiocapitellar joint. Aspiration of an elbow effusion is usually indicated to confirm inflammatory or septic etiologies. Radiographs may or may not be confirmatory.

Treatment

Gentle physical therapy and antiinflammatory medications along with activity modification may satisfactorily control the symptoms of elbow arthritis. Patients with osteochondritis dissecans without fragmentation may benefit from splinting until symptoms resolve.

Surgical debridement with osteophyte excision, loose body removal, and capsular release is an effective means of treatment in selected patients with mild arthritis. However, arthritic conditions tend not to improve by loose body removal alone (130,131,132,133,134 and 135). Loose bodies are commonly found in both anterior and posterior compartments in elbows with osteoarthritis and osteochondritis dissecans (136,137 and 138). Isolated loose body removal is effective in cases of osteochondritis in which the fragments of bone and cartilage are separated (72).

The goal of surgical debridement and smoothing is to improve elbow mechanics. Occasionally, isolated roughness of the radiocapitellar joint may exist, associated with pain on pronation and supination without substantial problems on elbow flexion or extension (139,140 and 141). Simple radial head resection in a stable elbow may provide dramatic relief.

In some cases of severe arthritic conditions, such as rheumatoid arthritis, an elbow arthroplasty usually produces excellent results (142,143). However, the patient must not place high demands on the elbow. Joint replacement for posttraumatic or osteoarthritis is not as successful as in rheumatoid arthritis. These patients tend to place higher stresses across the elbow, and the nature of the arthritic disorder tends to result in bony hypertrophy and diminished range of motion.

Summary

In carefully selected patients, surgical debridement and smoothing relieve pain, with some increase in motion. However, degenerative changes and subsequent symptoms may progress despite debridement. Total elbow arthroplasty reliably diminishes pain and improves function in low-demand patients, especially those with rheumatoid arthritis.

Olecranon Bursitis

The olecranon bursa normally allows for the smooth gliding of the skin over the prominence of the olecranon. Trauma, infection, and autoimmune disorders can produce a persistent bursal effusion.

Evaluation. Most disorders of the olecranon bursa are not painful, although septic olecranon bursitis may produce substantial discomfort. The primary symptom is a swollen area over the point of the elbow (Fig. 58-12). Patients may not like the appearance or have difficulty placing their elbow on a hard surface. Palpation over the olecranon bursa usually elicits tenderness. Infectious bursitis can be associated with erythema. Radiographic evaluation may demonstrate spurs on the olecranon.

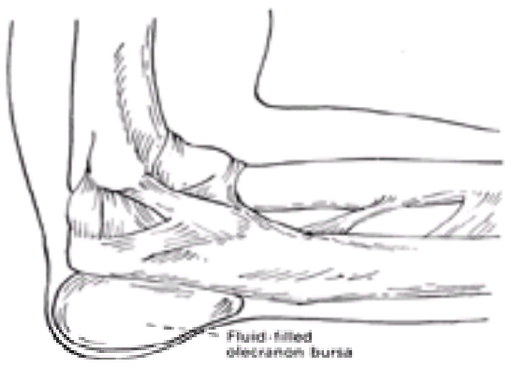


Figure 58-12. Diagram of bursa distended with fluid in olecranon bursitis.

Diagnosis. A swollen olecranon bursa is easily distinguished from an elbow effusion by its subcutaneous location. Whenever infection is suspected, aspiration of the bursa followed by Gram's stain and culture is indicated (144,145).

Treatment. Traumatic olecranon bursitis often subsides with rest of the arm, an elbow pad, and antiinflammatory medications. Occasionally, refractory cases require surgical excision. Septic olecranon bursitis may require incision and drainage if not responsive to systemic antibiotics.

Summary. Olecranon bursitis is usually self-limited and responds well to nonoperative treatment. If an infectious etiology is suspected, an aspiration is usually indicated; however, repeated aspirations are not recommended. Surgical excision, although usually successful, carries an increased risk for postoperative skin complications.

Neuropathy

The major nerves to the hand pass by the elbow, and each is associated with a specific entrapment syndrome. The median nerve can be trapped under the pronator teres muscle (146,147) or its anterior interosseous branches distal to the elbow (107,148); the radial nerve can be trapped in the radial tunnel (149); and the ulnar nerve, in the cubital tunnel (150,151). Inflammatory or idiopathic mononeuropathies such as posterior interosseous nerve palsy may occur without structural compression.

Evaluation

Pain in the proximal forearm and hand may be due to nerve entrapment. The distribution of pain often follows the anatomic distribution of the nerve but the pain is occasionally vague. For instance, posterior interosseous neuropathy produces vague proximal forearm pain yet this nerve does not provide cutaneous sensory innervation. Characteristic motor and sensory losses may occur and are perhaps most common for ulnar entrapment at the elbow. The anatomic location of the major nerves should be palpated in sequential fashion: the radial (posterior interosseous) nerve approximately 5 cm distal to the lateral epicondyle in the radial tunnel, the median nerve in the proximal forearm as it passes between the two heads of the pronator teres, and the ulnar nerve as it passes posterior to the medial epicondyle and into the flexor-pronator mass. Provocative maneuvers such as elbow hyperflexion (ulnar nerve), resisted pronation (median nerve), and resisted long finger extension (radial nerve) are helpful but not diagnostic. Strength and sensory testing should be part of the routine evaluation.

Radiographs are typically nondiagnostic except in the unusual cases of osseous deformity. Nerve conduction velocities and electromyography can demonstrate neural changes and may help guide treatment. Magnetic resonance neurography may be useful.

Diagnosis

Clinical history and physical examination supported by ancillary studies are often diagnostic of neuropathy. Exacerbation of the symptoms by compression, muscle contraction, or joint position that accentuates the entrapment is characteristic.

Treatment

Exercises, injections, antiinflammatory medications, and splinting can be effective for nerve entrapment syndromes. Activity modification is helpful but may not be realistic. If symptoms are substantial or progressive, surgical decompression may be required (107,146,147,149,150,151 and 152). The results of surgical decompression are usually good, provided a specific and accurate diagnosis has been made.

Summary

Neuritis may occur as an isolated phenomenon or as common sequelae of an elbow disorder such as chronic valgus instability. Failure to recognize neural pathology as primary or secondary elbow pathology can compromise the result of treatment.

CONCLUSIONS

Disorders of the shoulder and elbow can affect eight separate articulations. Each can be compromised by stiffness, weakness, instability, and roughness. Often, these basic characteristics do not exist in isolation but rather in combination. Identification of a mechanical problem may suggest a rational orthopedic treatment.

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CHAPTER 59

Painful Conditions of the Forearm, Wrist, and Hand

Edward E. Almquist

The wrist and hand are the working unit of the upper extremity and are considered to constitute 90% of its function (1). The forearm, elbow, arm, and shoulder are primarily units for placing the functional device of the upper extremity, the hand, in an appropriate position. This predominant role of the wrist and hand and their complex anatomic functions make this region of the body susceptible to accidental injuries and inflammation caused by wear and tear, most of which usually produce pain. Moreover, because the hand and arm occupy a significant part of one's body image, they are considered an outward extension of one's personality. Injury, disfigurement, and pain cause important psychological disturbances in many patients. For example, a painful neuroma of the finger may cause embarrassment because of the inability to shake hands and greet people properly. This may, in effect, produce a more timid personality than would be normal for a particular patient. Therefore, it is important to recognize and treat not only the pathologic disorder but also its associated psychological reactions.

This chapter includes discussion of the most important painful conditions of the forearm, wrist, and hand. The material is presented in five major sections: basic considerations, which include epidemiology and evaluation of the patient; painful disorders of the forearm; painful disorders of the wrist; painful disorders of the hand; and neuropathic disorders of the wrist and hand. More detailed information can be found in various books on these subjecyts (2,3,4,5 and 6).

BASIC CONSIDERATIONS

Epidemiology

Injuries to the hand and wrist are the most common type of upper extremity trauma. In an epidemiologic study of industrial injuries in the state of Washington, upper extremity injuries, mostly of the hand and wrist, constituted the majority of industrial claims for musculoskeletal disorders (7). In addition to obvious trauma, including fractures and lacerations, there are even more frequent nonspecific painful conditions, such as tendinitis, ligamentous sprains, muscle strains, and compressed or irritated nerves. Arthritis is also enormously common in the upper extremity. Arthritic conditions of the distal joints of the fingers probably are the most common arthritic conditions in the body, followed closely by that of the basilar joint of the thumb. Rheumatoid arthritis can be a devastating incapacity to the upper extremity, with one-third of those affected being severely disabled or totally dependent (8,9 and 10).

In addition to injuries and arthritis, an estimated 5 million American workers had symptoms of synovitis, bursitis, or tenosynovitis of the upper extremity in 1980. These caused 37 million days of restricted activity, 5 million days of bed disability, and 2.2 million days of work lost. Approximately 40% of these cases involved the wrist and hand (11).

Evaluation of the Patient

The diagnosis of disorders of the forearm, wrist, and hand is made through a comprehensive history and a detailed and specific physical examination, frequently aided by roentgenography and other special tests. It is important to remember that pain in the forearm, wrist, and hand is often referred from disorders of the cervical spine, occasionally from shoulder disorders, and not infrequently from around the elbow.

History

The detailed history should alert the examiner to the diagnosis in approximately 70% of cases. It is imperative, however, that the examiner ask the appropriate questions, listen carefully to the responses, and determine what these responses mean to the patient. If the patient has pain, its location, intensity, quality, and temporal characteristics should be established. The examiner should ask the patient to point with one finger to the most painful area and show where the pain radiates. The patient should be asked what aggravates the pain, what relieves it, and how the pain is affected by cold, heat, rest, and activity. The patient should be asked if there is swelling present and under what circumstances, if there is crepitus or snapping, and if so, what makes these signs occur.

If a specific injury was involved in producing the disorder, the examiner must determine the forces involved in the accident or injury as accurately as possible from the patient's description. He or she should ask the patient to reconstruct in pantomime the sequence of events: which way the hand or arm was twisted, how it moved, what struck the hand, what type of force was involved. Was the wrist or hand in dorsiflexion or volar flexion? Was there a rotary force involved in producing the injury? As an example, when a 1.5-horsepower drill turning in wood strikes a nail and suddenly stops, it produces a sudden rotary force to the wrist of the drill operator. Such details of the injury should be determined by careful questioning of the patient (12).

Physical Examination

The key to the physical examination is a careful knowledge of the underlying anatomy. The forearm, wrist, and hand lend themselves well to anatomic examination. Most of their components are palpable and identifiable through surface evaluation, and they can be compared with the opposite side to reveal any visual or palpable differences.

Examination of the Forearm. Both forearms should be uncovered to above the elbow, with all jewelry removed, and the two sides compared. They should be observed for any deformity, engorgement, inflammation, change in color, or swelling, as well as skin damage, bruising, and masses (13). Rotation should be evaluated by placing both elbows firmly against the patient's trunk and having the patient turn the hands actively, palms up and palms down. Supination and pronation should be 70 to 90 degrees from the neutral plane, or that position of the forearm with the thumb pointed upward. The majority of people have a range of approximately 80 degrees. This can be checked with a goniometer by placing it across the flexion crease of the wrist in its maximum rotation and aligning the other end of the goniometer with the humerus. Tender areas in the forearm should be elicited initially by having the patient point to the tender area, which then should be carefully evaluated by the examiner. Next, the various extensor muscles should be palpated, the sulci between the muscles noted, and any masses or acute tenderness recorded. The flexor muscles are somewhat less distinct, but the general area can be identified. Masses should be described as to position and size, as well as tenderness and consistency. The examiner should ascertain whether tapping the mass elicits a tingling sensation farther distal (positive Tinel's sign).

Examination of the Wrist. Inspecting the wrist, the examiner should note swelling and where it is localized, venous engorgement, texture and quality of the skin, and visible masses. Range of motion of the wrist can be evaluated in dorsiflexion, volar flexion, ulnar deviation, and radial deviation, as outlined in Figure 59-1. As there is variation in motion among individuals, usually the motion of the wrist is compared with that of the opposite side. Gripping strength of the hand and wrist is next evaluated, preferably before specific tender areas are elicited and perhaps aggravated. Use the dynometer three separate times, alternating between the painful and the nonpainful side and checking for consistency of readings. The dynometer may also be set at varying squeeze-grip settings between wide and narrow. At the very wide and the very narrow settings, the grip should have less strength than at the intermediate, assuming a good range of motion of the fingers. The nondominant arm is usually 10% to 15% weaker. Inconsistent efforts, tremulousness, and cog wheeling are suggestive of anxiety, depression, inattention, or other reactions to the injury. Weakness inconsistent with the appearance of muscle bulk suggests conscious motivational problems.

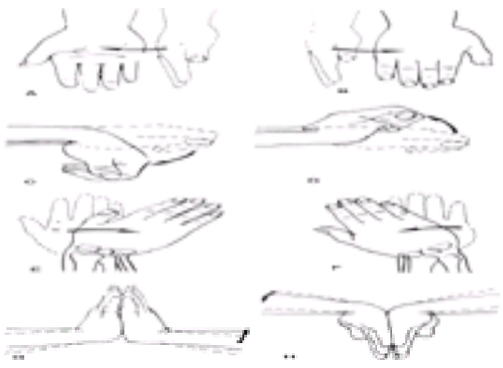

Figure 59-1. Movement of the wrist and hand. **A:** Supination. **B:** Pronation. **C:** Palmar flexion. **D:** Extension (dorsal flexion). **E:** Abduction (radial deviation). **F:** Adduction (ulnar deviation). To test the strength of the muscles responsible for these movements, the patient is asked to make each movement against resistance offered by the physician. **G,H:** Sample methods of measuring wrist flexion and extension. (Modified from Burton RE, ed. *The hand: examination and diagnosis*, 2nd ed. New York: Churchill Livingstone, 1983:8–9.)

The dorsiflexion of the wrist is measured by a goniometer along the flexor aspect of the wrist and then paralleling the third metacarpal. It should average 70 degrees. Volar flexion is likewise measured by placing the goniometer along the dorsum of the wrist and along the third metacarpal, and it averages 80 degrees. Ulnar deviation is measured by placing the goniometer along the midaxis of the forearm and then noting the angle of deviation of the third metacarpal, which is 30 to 40 degrees. Radial deviation using the same landmarks is 20 degrees (see Fig. 59-1).

The key to most unobvious diagnoses of the wrist is palpation. The most important aspect of that evaluation is knowing the underlying anatomy. That can be evaluated by examining one's own wrist and determining each anatomic point, starting at the skeletal prominence on the radial aspect of the wrist (Fig. 59-2). The most prominent radial structure is the styloid. One centimeter proximally, the sharp ridges dividing the first dorsal compartment of the adductor pollicis longus and the extensor pollicis brevis muscles may be felt running approximately 30 degrees obliquely from proximal and lateral to palmar and distal. Another centimeter dorsal to the radial styloid lies a prominent bony structure, Lister's tubercle, around which the extensor pollicis longus tendon angulates to approach the thumb. The flat area ulnar to Lister's tubercle is the fourth interosseous compartment, occupied by the common extensor and indicis proprius tendons. Just ulnar to the fourth canal is the head of the ulna, a smooth, rounded bone that can be felt moving independently of the radius. It is important to palpate that structure in pronation and supination and to check its stability in palmar and dorsal translocation and compare it with the opposite side.

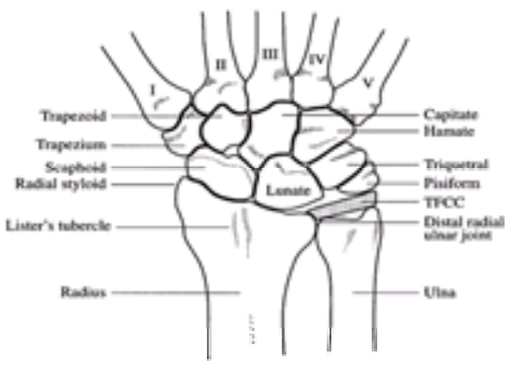

Figure 59-2. Bony anatomy of the wrist. (TFCC, triangular fibrocartilage complex.)

On the volar side of the wrist, the radial artery can be palpated just to the flexor side of the radial styloid, and it often can be visualized pulsating in thin individuals. The ulnar artery is deep to the head of the ulna and is difficult to palpate, as it lies beneath the flexor carpi ulnaris tendon.

The flexor carpi radialis, palmaris longus, and the flexor carpi ulnar tendon can be seen tensing the volar wrist skin. It is important to remember that approximately 15% of people do not have a palmaris tendon. The individual carpal bones and their attached ligaments can also be evaluated. The scaphoid lies in the anatomic snuffbox between the first and second dorsal compartments. These landmarks are readily visualized as one extends the thumb on the radial deviated wrist. A depression in the skin denotes the snuffbox, and deep to that lies the body of the scaphoid bone. The distal scaphoid can be evaluated by feeling the volar bony prominence just proximal to the base of the thumb. This rounded, firm mass, 1 cm in diameter, is the tuberosity scaphoid. By grasping between the bony firmness beneath the extensor tendon to the thumb, just distal to the radius, and the scaphoid tuberosity, the examiner can define the two poles of the scaphoid. Its stability can be tested by applying pressure to the tuberosity and noting the stability of the dorsal portion of the scaphoid. Also, Watson's test can be performed by pressing on the tuberosity of the scaphoid and moving the wrist from ulnar to radial deviation, noting a click or pain, which would indicate instability of the scaphoid, or scapholunate separation.

The scapholunate interval may be palpated between the scaphoid and the lunate with the wrist in ulnar deviation. The lunate is covered by the fourth dorsal compartment, comprising the common extensor and indicis proprius tendons. It is less clearly palpable than the scaphoid, but its dorsal surface can be evaluated, and it is important to observe whether any tenderness or mass is present. To the ulnar side of the lunate lies the triquetrum. The stability of that bony structure distal to the ulnar head can be readily evaluated. Its stability relative to the ulnar head and to the lunate should be noted. Also, tender areas in the triquetrum, or just on the proximal surface of it in the area of the triangular fibrocartilage complex (TFCC), should be noted. This is a common area for synovitis and ligamentous tears (see Fig. 59-2).

The stability of the midcarpal joint, that series of joints between the scaphoid, lunate, and triquetrum and the trapezium, capitate, and hamate, is next evaluated. Firmly grasp the wrist over the lunate and scaphoid and then dorsally and volarly translocate the remaining carpus. This often elicits a click and may be startling to the patient. In loose-jointed individuals this is not unusual and can be compared with the opposite side. The stability of this joint and any tenderness across it should be ascertained. Tenderness over the scaphotrapeziotrapezoid joint can be defined from either the more proximal scaphoradial or the more distal trapezial-first metacarpal joints, and this is not an uncommon site of specific pain and tenderness associated with arthritis. In radial and ulnar deviation of the wrist, the triquetral hamate joint glides obliquely, proximally dorsally, and distally volarly and can be evaluated for tenderness and stability.

The distal carpal joints where the carpi meet the metacarpals are next evaluated. In the thumb area, this is a very mobile joint. It is discerned by grasping the thumb and, with the opposite hand, the scaphoid and trapezium and rotating the thumb as well as translocating it in radial-ulnar and dorsal-volar positions. Stability, pain, and crepitus are easily ascertained. The second carpometacarpal joint should be stable and can be evaluated by running a finger along the dorsum of the second metacarpal and noting as a small sulcus appears at its proximal portion as it articulates with the capitate. The same procedure can be performed for the third metacarpal joint. The fourth and fifth metacarpal joints are mobile to 30 to 40 degrees and can be evaluated by grasping the third and fourth metacarpals and translocating that onto the hamate.

The pisiform, which is a sesamoid bone in the carpus, not a true component of the structural wrist segment, can be palpated just proximal to the proximal portion of the hypothenar eminence. With the wrist in a slightly flexed, ulnar-deviated position, this bony prominence can be palpated and then moved with pressure by the examiner's thumb. Tenderness and crepitus, if present, should be noted. One centimeter distal to that and slightly toward the midline is a barely palpable firmness, the hook of the hamate. This is the radial aspect of Guyon's canal.

Examination of the Hand. The hand lends itself readily to evaluation of its anatomic components (14). There is little soft tissue covering it, and its functional components are readily visualized and palpated. Inspection should include comparing with the opposite hand. The color of the hand, swelling, sweating, the presence or absence of calluses compared with the opposite hand, and in particular, the texture of the hand are invaluable observations. The patient may say that the hand is useless or too painful to allow any activity at all, yet if vigorous calluses are present, the validity of that statement may be questioned. The examiner should also note masses, swelling, or deformity across joints, the general nutrition of the skin, whether necrosis is present, clubbing of the fingernails, and tumorous changes in the skin.

Range of motion of the hand is evaluated by noting the full extension of the fingers and the thumb and the flexion of the fingers relative to the opposite side. The fingers should be able to touch the distal crease in the palm. Range of motion should be noted both actively, as the patient's ability to bend or extend, and passively, as the examiner's ability to bend or extend, each finger. That may be noted as the inability to touch the distal palmar crease by X cm or the lack of full extension by X cm. Also, the metacarpophalangeal (MCP), the proximal interphalangeal (PIP), and the distal interphalangeal (DIP) joints should be evaluated for range of motion individually. Range of motion of the MCP joints averages 0 to 90 degrees, with 0 being full extension. Occasionally, the index finger has a range 10 to 15 degrees less than 90 degrees. PIP joints should go from complete extension (0 degrees) to 110 degrees of flexion and DIP joints from 0 to 60 degrees of motion. Increased extension of the PIP joints beyond 0 degrees is called hyperextension. Some patients may have considerable hyperextendability or may even show a deformity called *swan neck*, in which the PIP joints hyperextend and the distal joints flex. This may be normal in loose-jointed people or abnormal following ligamentous tears or erosion of the ligaments from rheumatoid arthritis and so forth.

The MCP joints also abduct and adduct away from the third metacarpal as the fingers are spread apart and closed. The index finger should abduct approximately 20 degrees and the little finger approximately 30 degrees from the plane of the third finger. Thumb motion is checked for in full extension and full flexion. The thumb should be able to touch the fifth metacarpal head. The thumb should also be checked, in adduction, for how close it comes to the second metacarpal; in abduction, how far it moves away from the plane of the second metacarpal; and in opposition, how it rotates out and across the palm (Fig. 59-3 and Fig. 59-4).

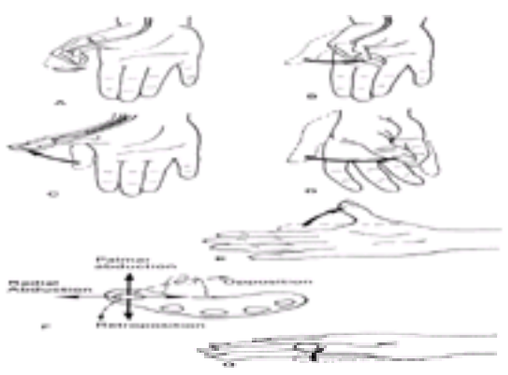

Figure 59-3. Movements of the thumb. When the thumb is in a neutral position, its palmar surface is oriented medially and its dorsal surface is directed laterally. **A:** Flexion of the distal phalanx is effected by the flexor pollicis longus. **B:** Flexion at the carpometacarpal joint is effected by the flexor pollicis brevis and opponens pollicis. **C:** Radial abduction is produced by the abductor pollicis longus and brevis. Not shown is adduction, achieved by the adductor pollicis. **D:** Opposition of the thumb to the fingers is achieved by the combined action of the flexor pollicis brevis, opponens pollicis, and the abductors. In this manner the metacarpal bone is rotated to a position in which the palmar surface of the thumb faces the palmar surface of the little finger. **E:** Palmar abduction is achieved by the abductor pollicis longus. **F:** Definition of thumb movements. **G:** Extension is effected by the extensor pollicis brevis and longus and the abductor pollicis longus. (Modified from Burton RE, ed. *The hand: examination and diagnosis*, 2nd ed. New York: Churchill Livingstone, 1983:9–26.)

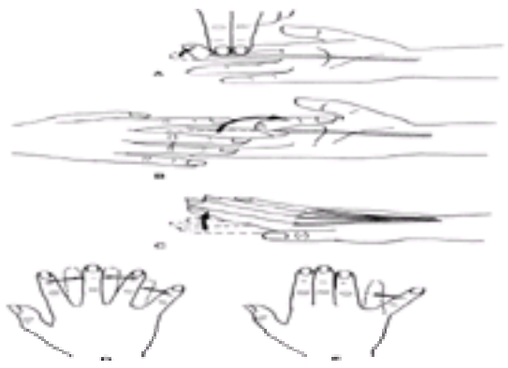

Figure 59-4. Movements of the second through fifth fingers. **A:** Action of the flexor digitorum profundus is tested by having the patient bend the tip of each finger while the examiner stabilizes in extension the proximal interphalangeal joint. As each muscle is examined, the muscle is tested against resistance. **B:** Function of the flexor digitorum superficialis for each finger is individually tested by having the patient bend the finger at the middle joint while the examiner stabilizes in extension the other fingers, so as to eliminate the action of the flexor digitorum profundus. The procedure is repeated for each finger to test passive and active motion against resistance. **C:** Function of the extensor digitorum communis is tested by having the patient place the hand flat on the table in a neutral position and then having the patient raise the fingers above the table as far as possible. **D:** Testing the function of the interosseous muscles. The dorsal interossei abduct the fingers from an imaginary line longitudinal through the axis of the middle finger. In addition to the dorsal interossei, the abductor pollicis longus and brevis abduct the thumb and the abductor digiti minimi abducts the little finger. The palmar interossei adduct the second, fourth, and fifth fingers toward the middle finger, whereas adduction of the thumb is achieved by the adductor pollicis. **E:** Testing the function of the abductor digiti minimi. (Modified from Burton RE, ed. *The hand: examination and diagnosis*, 2nd ed. New York: Churchill Livingstone, 1983:9–26.)

The various tendons and muscles that move and give strength to the fingers and thumb should next be evaluated. Each finger has two flexor tendons, except that 45% of individuals have only one flexor tendon in the little finger. Each finger has a series of extensor tendons (common extensors that extend the MCP and PIP joints) and a complex arrangement of the small muscles of the hand that extend the PIP and DIP joints. [These are well described in detailed anatomy texts such as Netter's *Atlas of Human Anatomy* (15).]

The examiner should check the function of the distal joint, where the profundus tendon inserts. Grasp the finger just proximal to the distal joint, ask the patient to flex the finger, and check for strength. The profundus tendons generally originate in one muscle mass, so individual distal joint motion is difficult. Specific function of the sublimus or superficialis tendon can be evaluated by grasping the fingers not to be examined, holding them in extension, and asking the patient to flex the examined finger. For example, to examine superficialis muscle function of the middle finger, extend the index, ring, and little fingers and then have the patient flex the middle finger; only the sublimus tendon will be able to move that finger. It may be of interest to check the little finger with that test to see if there is a sublimus tendon to the little finger. Frequently, that is congenitally absent. The thumb has one long flexor tendon, which can be evaluated by grasping the base of the thumb and having the patient flex the distal joint. It is important to check not only mobility, but also the strength of each tendon muscle unit that activates finger-thumb mobility.

The strength of the intrinsic muscles of the hand also can be evaluated. The first dorsal interosseus muscle radially deviates the index finger. Its strength and bulk can be readily palpated in the sulcus between the thumb and the index finger. Strength of abduction and adduction of the fingers quantitate ulnar nerve muscle function. Strength of the thumb in opposition and adduction evaluates the three thenar muscles. Two of them are usually supplied by the median nerve, and one, the deep, short flexor to the thumb, is generally innervated by the ulnar nerve. The strength and bulk of the muscle should be evaluated by having the patient oppose and abduct the thumb against the examiner's resistant finger and comparing it with the opposite side. Atrophy or weakness of that muscle may indicate median nerve dysfunction.

Evaluation of Circulation. The hand is usually liberally supplied with circulation by a series of vascular arcades running between the radial and ulnar arteries, and the hand can readily survive with only one major artery intact. Allen's test can verify both radial and ulnar artery patency. Have the patient elevate the hand above the head and make a firm grasp. The examiner should then firmly press over the ulnar and radial arteries on the volar side of the head of the ulna at the wrist level and at the volar side of the radial styloid. This should occur as the patient is holding the hand over the head and grasping. The hand may then be brought down and opened, and the examiner should note the paleness of the fingers and the palm. Release pressure on the radial styloid and note the usual flush of color coming into the fingers from the radial side. Absence of that flush indicates nonpatency of the radial artery. Repeat the test, releasing the ulnar artery from beneath the ulnar head and noting the flush of blood. The ulnar artery is located in Guyon's canal on the radial side of the hypothenar eminence, and tenderness or a thrill in that area may indicate vascular stenosis or an aneurysm, especially if Allen's test shows no blood flowing through the ulnar artery.

A digital Allen's test also can be performed by elevating the hand and compressing both sides of the finger on the flexor lateral margins while compressing the finger itself with the examiner's grasp. Then, the pressure on one side of the finger can be released and digital artery patency monitored by the flush of returning blood. The test is then repeated on the other side of the finger. A more accurate evaluation can be done using Doppler studies or, in critical situations, arteriography. Sudomotor stability of the hand may also be checked by immersing the hand in cold water and noting color and vascular changes.

Evaluation of Nerve Function. The three major nerves to the hand should be evaluated individually. The median nerve enters the forearm at the flexormedial aspect at the elbow. It goes deep to the flexor tendons in the midforearm and passes beneath and slightly to the radial side of the palmaris longus tendon, which is in the midline of the wrist. The palmaris longus tendon becomes prominent when the wrist is minimally flexed against resistance. This tendon is absent in approximately 15% of individuals. The median nerve supplies sensation to the thumb, index, and middle fingers and the radial half of the ring finger normally, although not infrequently this innervation pattern can shift one finger radially. Median nerve motor function supplies the thenar muscles and the index- and middle-finger lumbrical muscles. Therefore, checking thenar muscle function is an important aspect of strength testing for the median nerve, and strength should be compared with that of the opposite side. The median nerve in the forearm supplies the long flexors to the thumb, index, middle, and ring fingers. It also supplies the radial wrist flexor.

Sensory testing should include stroking the finger and asking the patient whether it feels the same as other fingers or the same finger on the opposite side. Sensibility also can be checked by stroking the finger with a soft object, such as cotton. It can best be quantitated by evaluating how well the patient can distinguish two points from one (Weber's discrimination test). To perform this test, place two paper clip ends lightly on the tip of the finger, just blanching the skin. Begin with the two ends widely separated, and if there is abnormal sensation start in a normal sensory area. Once the patient learns the test, progressively diminish the distance between the two points. Test each finger and thumb so that the patient cannot see what is happening. Two-point discrimination varies from 3 to 5 mm on the fingers and the flexor surface of the thumb. However, blind Braille readers can learn to discriminate points less than 2 mm apart. Other parts of the hand are much less acutely discriminating. On the back of the hand two-point discrimination is roughly 10 mm and on the palmar aspect of the hand 8 to 10 mm. Only the tongue has two-point discriminatory sensation as acutely sensitive as that of the fingertips.

Vibratory sensation should be tested under certain circumstances, and different frequencies are used in threshold testing. A tuning fork is placed lightly on the finger, and the patient's sensation thresholds are evaluated for different frequencies. A Semmes- Weinstein Fine-Hair Testing System can be used, particularly in research applications. This test is often performed by hand therapists and requires specific training to perform properly. Sensitivity to hot and cold may be important in specific proximal neurologic disorders.

The radial nerve supplies sensation to the back of the hand overlying the middle and index fingers and the dorsum of the thumb. Sensation in that area can be tested by light touch. The radial nerve innervates the long extensor muscle to all the fingers, thumb, and wrist. The distal portion of this nerve can be palpated, particularly on thin individuals; over the radial styloid, three or four nerve branches can be rolled under a gently moving finger just dorsal to the radial styloid. The muscle function of the radial nerve is tested by noting strength in the extensor tendons of the wrist and the extensor tendons of the fingers and comparing with the opposite side.

The ulnar nerve has both a major sensory and a motor component. It passes into the forearm dorsal to the medial epicondyle at the elbow, runs beneath the flexor carpi ulnaris muscle, and enters the hand through Guyon's canal, a small confined space just on the ulnar side of and superficial to the carpal canal. It cannot be readily palpated in any of these areas distal to the medial epicondyle area at the elbow. Function of this nerve is tested by examining the sensation of the little finger and the ulnar half of the ring finger. Occasionally, the ulnar nerve also goes to the ulnar half of the middle finger. Muscle strength is best tested by evaluating the first dorsal interosseous muscle: Have the patient radially deviate the index finger against resistance and note that strength, comparing it with the opposite side, and note

the bulk of the first dorsal interosseous muscle. The ulnar nerve also supplies function to the long flexor (profundus) to the little finger.

Abducting and adducting the fingers test the intrinsic muscles of the hand, which are ulnar innervated. Atrophy of the intrinsic muscles or atrophy between the metacarpal muscles is pathognomonic of ulnar nerve dysfunction at some level. Froment's sign is positive when ulnar nerve motor dysfunction is present. Froment's sign is tested by placing a piece of paper between the patient's index finger and the thumb and checking the position of the thumb as the examiner tries to pull the paper away from the patient. Normally, the distal joint of the thumb remains in extension, but if ulnar nerve dysfunction is present, the tip of the thumb flexes significantly to increase pressure and attempt to keep the paper from moving.

In checking sensation or lack of sensation, it is important to evaluate sudomotor activity. This is particularly important in children who often cannot cooperate fully in testing, particularly for pinprick sensation. If the patient says he or she has no feeling in the fingers yet is sweating vigorously over the finger, either there is a proximal neurologic lesion or there is false information. Lack of sweating in young children is often important in evaluating their nerve function because they may have difficulty cooperating with testing. Ninhydrin testing can be used to evaluate lack of sweating objectively. Ninhydrin stains the proteins in the sweat glands. After the hand is sprayed with ninhydrin and blotted on paper, absence of a fingerprint denotes lack of nerve function. Also, lack of wrinkling when the fingers are placed in water would indicate lack of pseudomotor activity and hence nerve function.

Radiography and Laboratory Tests

Radiography. Radiographs are almost always required for diagnosis and treatment of injuries and many other conditions of the forearm, hand, and wrist. Extraosseous calcification can substantiate a diagnosis of tendinitis, and fractures or suspected fractures, of course, require the use of radiography. Often spot, oblique, and additional views are necessary to establish the presence of a fracture. Stress fractures of the forearm, although not common, can be the source of pain, and radiographs reveal them. Some fractures are not evident on initial radiographs (e.g., fracture of the scaphoid often shows up only in later radiographs). Colles' fractures and radial fractures, particularly epiphyseal fractures in children in which only the epiphyseal plate is involved, may not show up until callus appears. Standard posteroanterior and lateral radiographs may need to be supplemented by other views.

The six-view series of radiographs for wrist instability includes the standard (posteroanterior) view of the wrist and the anteroposterior or supinated view of the wrist, with the hand in maximum ulnar and radial deviation, and also with the hand contracted into a fist. These views often show scapholunate separation that may not be visualized in static views. Cineroentgenography can show dynamic instability and is easily obtained.

Other Imaging Techniques. Magnetic resonance imaging (MRI) and computed tomography show good details of the forearm and confirm the diagnosis of ischemic necrosis of the lunate in Kienböck's disease before it is seen by radiography. These techniques also show soft tissue tumors in the forearm, wrist, and hand, as well as a deep ganglion. Newer MRI technology also has isolated the ligaments of the wrist and in particular the TFCC, the soft tissue articulating structure at the distal end of the ulna. General use of this technology is somewhat limited by expense.

Arthrography is useful for evaluating ligamentous continuity in the wrist. It can show disruptions, but must be read with some discretion in that very small tears in the ligaments between joints may be visible where they are not clinically significant. Arthrography is used almost exclusively at the wrist joint. The three component joints of the wrist are usually evaluated: the distal radioulnar joint, proximal carpal joint, and midcarpal joint. If dye is placed in the proximal carpal joint, it should not flow into the distal radioulnar joint. If it does so, it is an absolute sign for disruption of the TFCC. Dye flowing between the lunate and triquetrum would indicate disruption of the lunotriquetral ligaments. They may be subtle or partially disrupted and still show leakage. It may be necessary to define these leaking joints by placing the dye in the midcarpal joint and seeing if it flows retrograde into the proximal carpal joint.

Ultrasound has advanced to the point at which it can ascertain abnormal structures in the wrist, in particular the presence of occult ganglions. It is less expensive than MRI but requires skilled examiners.

Arthroscopy is another diagnostic tool for wrist evaluation. It involves surgical penetration of the wrist with at least a local anesthetic and considerable technical skill and imaging equipment. In complex cases and uncertain diagnoses this tool may be necessary. TFCC tears and ligament disruptions in localized areas of arthritis are readily evaluated in all three joints using this technique.

Laboratory Tests. Laboratory tests are not routine for evaluating the painful hand and wrist but can be useful in special circumstances. Lupus erythematosus, rheumatoid arthritis, gout, and septic arthritis, to name a few, are diagnoses whose confirmation is substantiated by laboratory tests. The reader is referred to Chapter 27 for further discussion of arthritides and diagnostic testing.

PAINFUL DISORDERS OF THE FOREARM

Table 59-1 lists the most important painful conditions of the forearm, wrist, and hand that are considered in this chapter. Once the diagnosis of a specific condition is made, the most effective therapeutic strategy can be developed and carried out.

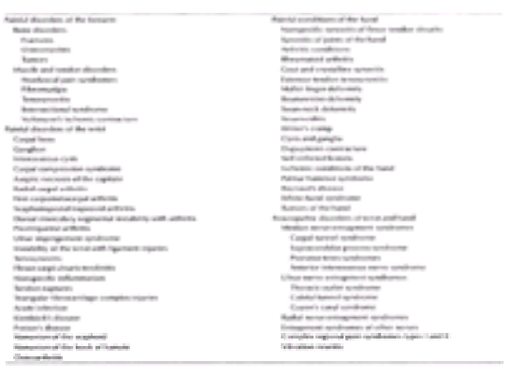

TABLE 59-1. Painful conditions of the forearm, wrist, and hand

Bone Disorders

Fracture and Dislocation

Among all age groups, fractures of the radius and the ulna are the third most frequent type involving the upper extremity, exceeded only by fractures of the phalanges of the hand and of the carpal bones (10,16). Because of the critical role the radius and ulna play in the function of the upper limb, fractures of these bones are also the third most frequent cause of restricted activity days and bed disability days, and the fourth most common cause of days lost from work (10).

Etiology. Fractures of the forearm are of three types: proximal, shaft, and distal. Proximal fractures are in or associated with the elbow and are discussed in Chapter 58. Midforearm or shaft fractures usually involve both bones of the forearm. They can be subtle, markedly deformed, or even open. Because of the multiple and complex rotatory forces of the muscles acting on the various segments of the forearm bones, open stabilization of shaft forearm fractures is almost always necessary in adults to maintain stability. Children have a thick periosteum that frequently adequately stabilizes forearm fractures to obviate the need for open stabilization. A direct blow to the ulna or radius may cause a one-bone forearm fracture. These are often stable, requiring only immobilization. Occasionally, a stress fracture is seen in these bones and may need bone scanning to define.

The third type of forearm fracture is distal, near the wrist joint, and represents 15% of fractures in adults. Usually these are caused by a wrist extension injury. On occasion, they may be subtle and difficult to recognize. Tenderness directly over the area associated with deformity or bruising should arouse a high degree of

suspicion. Radiographs are usually diagnostic. In children's fractures, a type 1 epiphyseal injury occurs only across the epiphyseal plate and may not be evident by radiography until new bone is forming. Torus fractures in children are a crinkling of the dorsum cortex of the radius, an effect of the deforming force on the softer, more resilient bone in children. The clinical deformity is minimal. Lateral radiographs are diagnostic. Cast immobilization only is the treatment.

Distal radial fractures are classified, like all fractures, as stable or unstable, open or closed, intraarticular or extraarticular. Stable fractures are those that, when reduced, remain in position. Most distal radial fractures are stable and extraarticular. If there is more than a little angulation at the fracture site, reduction is necessary; more than 10 degrees of dorsal angulation of the radial articular surface is not well tolerated by the adult patient.

Intraarticular radial fractures need to be well reduced. Articular fractures with displacement of greater than 1 mm almost universally lead to later arthritic changes in that joint. It is important to do what is necessary to reduce and stabilize these fractures. Sometimes closed reduction is sufficient, or external fixation traction or surgical stabilization with pins or plates may be necessary. There is often considerable crushing and shortening of the radius with distal fracture. Reduction of the shortening and stabilization to prevent resettling may be necessary. If a radial fracture heals with much deformity or misalignment, poor function results. This is of particular concern in the younger patient.

Most distal radial fractures involve the ulna, and usually only a small fragment is fractured from the styloid process. If, however, no ulnar fragment is present, it usually means the TFCC (a ligamentous-like structure on the ulnar side of the wrist) has been torn. This is treated by immobilization of the radial fracture. In significant wrist fractures sustained in hyperextension injuries, the proximal radial head at the elbow should be evaluated and probably radiography performed because radial head fractures are not uncommonly associated with this type of injury.

Osteomyelitis

Acute osteomyelitis is rather uncommon in the forearm bones, but when it develops, infection may be blood-borne (hematogenous) or may be introduced from without, usually as a result of a compound fracture. The hematogenous type occurs mainly in children and usually affects the radius more often than the ulna, and the lower metaphysis rather than the upper one (16,17). Because the upper metaphysis of both the radius and ulna is partly or wholly within the capsule of the elbow, infection of the metaphysis can spread directly to the joint to cause pyogenic arthritis. In contrast, at the wrist the metaphysis of the radius is wholly outside the capsule, and consequently direct spread of infection to the joint is unlikely.

Symptoms and Signs. The clinical features of osteomyelitis include a rapid onset of pain over the affected bone and general malaise. Physical examination reveals systemic illness with pyrexia and exquisite tenderness, which is clearly circumscribed over the affected bone. The overlying skin is warmer than normal, and often the soft tissues are indurated, but later a fluctuant abscess may be present.

Diagnosis. The diagnosis of acute osteomyelitis is made through the history, physical examination, radioisotope scanning with technetium 99m, and laboratory studies including white cell count, erythrocyte sedimentation rate, and blood cultures, which may be positive in the incipient stage but are not invariably so (16).

Treatment. Treatment includes bed rest, systemic antibiotic therapy for at least 6 weeks, and, if necessary, surgical incision to release pus to reduce the risk of ischemic bone necrosis. Chronic osteomyelitis of the radius and ulna usually follows an acute untreated infection. In addition to bed rest and antibacterial drugs given for nonsuppurative flares of infection, surgical intervention to effect a thorough drainage and sequestrectomy for persistent purulent discharge may be necessary. More detailed discussion of osteomyelitis is found in Chapter 95.

Tumors of the Forearm

Various types of benign tumors can develop in the bones of the forearms; these include osteoma, chondroma, osteochondroma, and giant cell tumor (18). Chondroma of the ulna or the radius may retard growth in the affected bone, whereas growth of the other bone proceeds normally. This may cause marked curvature of the affected bone and a severe deformity from uneven growth. This usually requires surgical correction by osteotomy.

Giant cell tumor frequently develops in the lower end of the radius, which is one of the favorite sites of this tumor in the upper limb. The lower end of the ulna is also susceptible. Treatment involves surgical excision. If the lower end of the ulna is the part affected, the bone should be excised up to a point well proximal to the tumor, whereas if the tumor is in the lower end of the radius, radical excision and replacement by a suitable bone graft are recommended (18).

Fibromatosis is a tumorlike condition, primarily of childhood and adolescence, which seems to follow trauma. Scarlike tissue becomes invasive and may enlarge, producing a firm mass; it may encompass the nerves with compression-type syndromes; or it may erode into the radius or ulna, producing not only pain but also fractures. Lytic lesions of the bone in the midforearm in adolescents are suspicious for this condition.

Neurofibroma is another tumor condition that affects the forearm, with large, tender masses associated with hyperpigmentation of the skin. The patient usually has other areas of involvement. MRI evaluation can define the mass.

Blood vessel tumors, hemangiomatosis and arterial venous malformations, are tender, sometimes painful conditions of the forearm associated with vascular changes. These tumors are more distal, often presenting with swelling and venous engorgement. They can be localized and possibly excised, but not infrequently are widespread and invasive.

Neurilemmoma is a benign tumor of the Schwann cell in a large or small nerve, ultimately affecting the nerve function. This may be quite significant when the tumor is in a major nerve. Most commonly, however, these tumors are in small nerves and can be diagnosed by the presence of Tinel's sign over the mass.

Benign lipomas are perhaps the most common tumors in the forearm and often are associated with multiple lipomas in the body, showing hereditary prevalence. They are usually quite superficial, but may be bothersome or become tender with persistent manipulation by the patient.

Malignant tumors, either primary or metastatic, rarely involve the radius and the ulna. When osteosarcoma does occur in the forearm, the lower end of the radius is the usual site. Malignant bone tumors invariably produce moderate to severe pain, which may be localized or felt through the entire forearm, hand, and even the arm. Therapy for the tumor and for pain control is discussed in detail in Chapter 35 and Chapter 95.

Disorders of the Muscles and Tendons

Myofascial Pain Syndromes and Fibromyalgia

These syndromes are defined by pain and tenderness developing in muscles and soft tissue areas, often associated with activity, in circumstances in which there is no other specific pathologic entity identified (see Chapter 30 for detailed discussion of this topic). There is a tender muscle not associated with nerve compression, with a tear in the tendon such as in tennis elbow, or frictional tenosynovitis. This type of condition has been an enigma to clinicians. It seems to respond favorably to local anesthetic injections, often with cortisone, when the condition is quite localized to *trigger points*. It is often associated with people who use their arms vigorously and has been a common complaint in the workforce. There is little objective evidence of its pathogenesis. The more generalized condition of fibromyalgia is being developed as a rheumatologic entity in the literature, and forearm problems are among the related complaints. It is important to rule out specific disorders that may mimic this condition. Appropriate treatment includes pain relief, job and activity changes, injections, antidepressant medication, and antiinflammatory medication. These are often coupled with physical therapy modalities. Diagnosis of these conditions is discussed in Chapter 29 and Chapter 30.

Tenosynovitis

Acute and chronic frictional tenosynovitis, also called *tendinitis*, is a common clinical condition, particularly in young adults whose occupations demand repetitive movements of the wrist and hand. The condition is attributed to friction between the tendons and the surrounding tendon sheath resulting from overuse of the hand. The tendons affected are those of the deep muscles of the back of the forearm, especially the extensors of the thumb and the radial extensors of the wrist. The pathophysiology consists of a mild inflammatory reaction of the tendon and paratendon with local swelling and edema. This condition is discussed in some detail in

the sections on the wrist and hand.

Intersectional Syndrome

Intersectional syndrome is tenosynovitis that affects the forearm where the adductor pollicis longus and pollicis brevis extensor tendons cross the radial wrist extensor tendons. It is diagnosed by a tender, often swollen area 8 to 10 cm proximal to the wrist joint along the radius. Crepitus is often heard or palpated when moving the thumb and wrist. This condition seems to be caused by unusual or strenuous use of the thumb. The treatment is rest by splinting the wrist and thumb, antiinflammatory medication, and local corticosteroid injection. Rarely, in chronic cases, surgical debridement of the inflamed bursa is necessary.

Volkmann's Ischemic Contracture

Volkmann's ischemic contracture is characterized by fixed contracture of the flexor muscles in the forearm and deformity of the wrist and fingers.

Etiology and Pathophysiology. The ischemia of the muscle can be brought about by injury to, or obstruction of, the brachial artery near the elbow or by tense edema of soft tissue of the forearm constrained within an unyielding fascial compartment (19). Any major fracture in the elbow region or upper forearm may lead to arterial occlusion. Especially important is a supracondylar fracture of the humerus with displacement causing severance or contusion of the brachial artery by the sharp lower end of the main shaft fragment. The rapidity and severity of the ischemia depend on the rapidity and degree of injury. Sudden, severe occlusion of the brachial artery may cause severe ischemia and gangrene of the fingers and hands. More often, the collateral circulation provides sufficient perfusion to the hand for it to remain viable, but not enough to nourish adequately the flexor muscles of the forearm or the main peripheral nerve trunks. Severe tense edema in the anterior fascial compartment of the forearm also can produce ischemia, a consequence of severe injury in the region. The ischemia causes necrosis of muscle fibers of the forearm flexor group, especially the flexor digitorum profundus and flexor pollicis longus, with subsequent fibrosis and shortening. In some cases the cause of the vascular obstruction is an overly tight plaster cast or bandage of the forearm or arm.

Symptoms and Signs. Soon after the injury, the patient experiences severe ischemic pain in the forearm, which may radiate to the hand. On examination in the incipient stage, the fingers are white or blue and cold, the radial pulse is absent, and active finger movements are weak and painful. Passive extension of the fingers is especially painful and restricted. At this stage, evidence of severe nerve impairment (e.g., anesthesia of the fingers and paralysis of the small muscles of the hand) sometimes is present but not always.

In the established stage of Volkmann's ischemic contracture, which develops gradually within a few weeks or a month of the injury, a striking flexion contracture of the wrist and fingers from shortening of the fibrotic forearm flexor muscles is present. Sensory and motor paralysis of the hand may persist as complicating factors, but they are not an essential feature of Volkmann's contracture (16, 20).

Diagnosis. Diagnosis is based on the history and physical examination. In the incipient stage, absence of the radial pulse associated with severe pain on forced extension of the fingers should suggest a diagnosis of Volkmann's contracture. The presence of anesthesia and paralysis of the hand confirms this diagnosis. In the established phase the diagnosis is confirmed by the history and the clinical findings.

Treatment. If the incipient stage of Volkmann's contracture is diagnosed soon after the injury based on the presenting clinical symptoms and signs, the condition should be handled as an emergency because the effects of occlusion become irreversible after approximately 6 hours (16, 19, 20). All splints, plaster, and bandages that might be obstructing the circulation should be promptly removed. In the case of fracture, gross displacement of the fragments is corrected by gentle manipulation, and a well-padded plaster splint is applied. These measures may be performed under regional analgesia achieved by blocking the brachial plexus in the axilla. This procedure not only promptly relieves the pain but also effects sympathetic interruption and consequent increase of the collateral circulation. If these measures fail to bring about a return of adequate perfusion within 60 to 90 minutes, the anterior fascia of the forearm should be exposed surgically and split longitudinally to permit exploration of the brachial artery; if severe damage is noted, it should be repaired. Continuous brachial plexus block analgesia is maintained in the postoperative period to control pain and produce vasodilation of the collateral vessels (see Chapter 102 for details of technique).

In the established stage of Volkmann's contracture, restoration to normal is impossible. In mild to moderate cases, acceptable function may be restored by intensive exercise under the close supervision of a hand therapist. In more severe cases, the muscle shortening may be counteracted by lengthening of the forearm muscles or by detachment and distal displacement of the flexor muscle origin (16).

Myofascial Pain Syndromes and Fibromyalgia

These have already been mentioned in reference to the forearm in this chapter. They are discussed in detail in Chapter 29 and Chapter 30. They are just as much of a mystery in the wrist as they are elsewhere in the body.

PAINFUL DISORDERS OF THE WRIST

Although sprains and tendinitis of the wrist are common diagnoses, they convey little specific pathologic meaning. They tend, in fact, to be *wastebasket* diagnoses. More specific diagnoses of disorders of the wrist are now possible because of our increased understanding of the biomechanical processes involved and the inflammation they produce. In addition, the modern diagnostic procedures mentioned in the introductory part of this chapter and discussed in Chapter 14 have enhanced our ability to make specific pathologic diagnoses.

Most nonacute wrist pain results from the effects of inflammation. Inflammation is either endogenous, such as that associated with collagen disease or infection, or secondary, resulting from mechanical injury such as nonunion of bones, loose bodies, and torn cartilage. Specific diagnosis of such conditions is possible and should be pursued. For example, generally the specific ligament injured and the specific area of the carpus affected by the loose body or the specific cartilaginous deficit can be identified. In other words, general diagnoses should be supplanted by specific ones, such as scapholunate ligament tear, torn triangular fibrocartilage, and chondromalacia of the lunate. Specific anatomic and pathologic entities causing wrist pain are discussed in the following sections.

Carpal Boss

Carpal boss is characterized by a specific tender area over the junction of the second, third, or both second and third carpometacarpal joint, often associated with osteophyte formation and sometimes associated with a ganglion (21). This condition is illustrated in Figure 59-5.

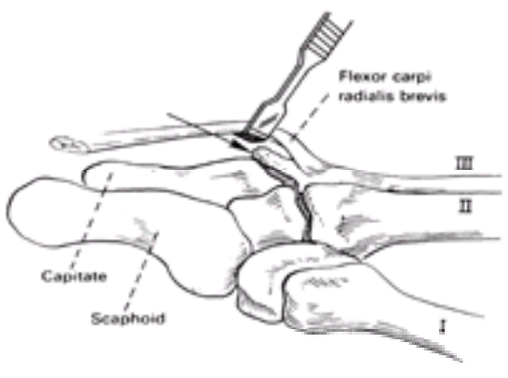

Figure 59-5. Carpal boss syndrome, which is caused by a painful dorsal exostosis (*arrow*) on the adjacent surface of the second and third carpometacarpal joints. Lateral radiograph may show a bony prominence or even an ossicle.

Etiology

The cause of a carpal boss is unclear. It may be associated with a chronic sprain. Excessive mobility of the second and perhaps the third metacarpal and the rocking movement of that joint, which was designed for little movement, could produce excessive wear (21).

Symptoms and Signs

A carpal boss is very tender directly over the joint. The pain is moderately sharp, locally radiating, aching, and often follows strenuous activity. For instance, if the hand is used extensively for gardening during the day, the pain may become quite severe that evening. The pain is not specifically localized to the joint but involves a generalized ache in the wrist and hand. The tender area on the wrist just at the second or third carpometacarpal joint, however, is specific.

Diagnosis

Lateral radiographs or tomograms may show an osteophyte or loose body. Triphasic bone scan shows increased technetium 99m pickup in the area of the second or third carpometacarpal joints (Fig. 59-6).

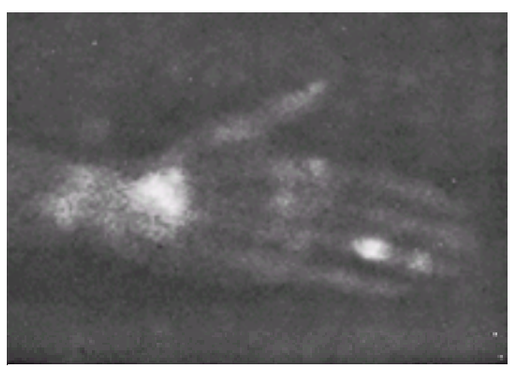

Figure 59-6. Technetium 99m triphasic scan of a hand shows a positive uptake in the second and third phase over the area of the carpal boss reflecting intense inflammatory reaction in this area.

Treatment

The majority of cases of carpal boss are mild and can be treated with splinting for rest, oral antiinflammatory medications, and injections directly into the joint of a long-acting corticosteroid such as triamcinolone, together with a local anesthetic agent. When such conservative treatment is not adequate, surgical treatment may be indicated. Many patients benefit from debridement of the joint by removal of the osteophytes and loose bodies. Fusion of the joint is sometimes required to afford relief. Surgical debridement alone without fusion is successful in approximately 90% of patients (22).

Ganglion

A ganglion is a fluid-filled mass located about tendons or joints (Fig. 59-7). It may be small or quite large. The fluid contains a high concentration of hyaluronic acid. The wrist is the most common area for ganglia, but they can occur in other parts of the body, most notably the fingers and the feet. Some have suggested that friction, related to excessive motion or a subtle injury, causes a ganglion (22). Another theory is that ganglia are outpocketings or herniations of synovial fluid, producing a pseudoepithelium and cyst (22).

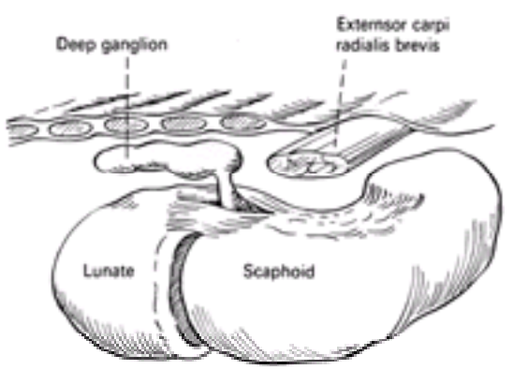

Figure 59-7. Deep ganglion, which usually presents as a painful tender area on the dorsum of the wrist usually just over the proximal scaphoid and lunate and deep to the extensor tendons. Ganglia are usually so deep and small that frequently it is difficult to palpate them.

Symptoms and Signs

Deep ganglia may or may not be painful. If not painful, they are usually ignored. Some patients complain of localized pain and marked tenderness, particularly in the area of the scapholunate joint where either no mass or a faintly palpable firmness is noted. Some large masses may not be tender at all. Others appear small but are painful in the period of expansion of the ganglion. Small intracapsular cysts may be very tender with localized general mechanical soreness that radiates from the wrist and a deep, aching pain usually related to activity.

Diagnosis

The typical ganglion presents as a large, soft mass on the dorsum of the wrist or, less commonly, on the volar aspect and radial side of the wrist. All are easily diagnosed. They are often painful, seemingly because they stretch the adjacent radial artery. Deep, small ganglia may not be palpable in the dorsum of the wrist. These can be a very slight mass but are associated with a tender area, usually localized between the junction of the scaphoid and lunate. Technetium 99m scans are usually minimally active. MRI or ultrasound can delineate these occult ganglia.

Treatment

Treatment of ganglia depends on the number of symptoms. Often, with a small mass that is not painful, simple aspiration just to establish a diagnosis, followed by observation, is sufficient. Repeated aspirations or aspirations with cortisone injection have been reported to be no more effective than observation, because ganglia often disappear spontaneously.

If a painful, tender mass persists, surgical removal may be necessary. Excision should be done under adequate operative conditions so that the cyst can be identified. The joint is usually entered and the cyst removed completely. Removal of a large ganglion sometimes requires grafting a small portion of the retinaculum over the

extensor tendons to close the joint (22).

Dorsal cysts almost always come from the area at the junction of the scaphoid, lunate, and capitate. Some patients, particularly women, have multiple areas of cysts in the dorsal capsule of the wrist. These tend to recur; if noted at the time of the initial surgery, a large excision with a graft may be necessary (22).

Interosseous Cysts

Cysts in the lunate or scaphoid or other carpal bones are often clinically undetectable and are noted only by radiography (Fig. 59-8). They appear as small lytic areas and are noted particularly on tomography.

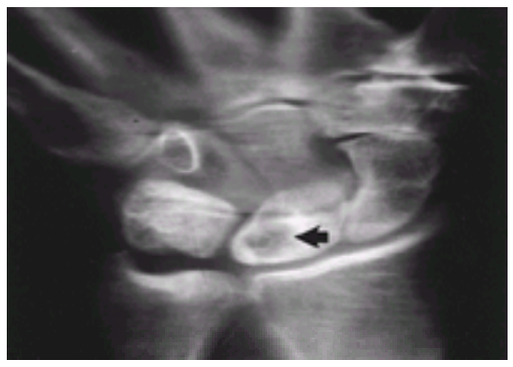

Figure 59-8. Radiograph showing a carpal cyst (*arrow*). Most painful carpal cysts are in the scaphoid or lunate.

Etiology

The cause of carpal cysts is unclear. They seem to represent ganglia that are intruding into the bone. Some seem to be related to old injuries, and some may be caused by small fractures in the chondral plate with impulsion of synovial fluid. Once the cyst has begun to develop, a trap-door phenomenon can occur in which a small amount of fluid is pushed into the area and the cartilage acts as a hinge, not allowing the fluid to extrude and causing positive pressure, which expands the cyst within the bone.

Symptoms and Signs

Many of these cysts are minimally painful. Others, although small, produce a dull, aching, joint-type pain that is aggravated by activity, but often present as a constant ache with or without excessive use. The pain is deep in the wrist and is not well localized.

Diagnosis

Diagnostic blocks with a local anesthetic injected into the wrist do not relieve much or all of the pain. Triphasic bone scans are markedly positive. Tomography is particularly helpful in outlining the cyst and may even show its proximity to the joint surface. Some cysts are secondary to obvious arthritic changes within the wrist; loss of joint space and eburnation of the adjacent subchondral plate are typical osteoarthritic or rheumatoid arthritic changes.

Treatment

Treatment depends on the severity of the symptoms. Some asymptomatic cysts found only on radiographs need not be treated. Painful cysts, particularly those large enough to cause a small fracture and resulting in pain with activity, should be treated by curettage of the cyst, approaching it from a nonarticular area. The cyst should be packed with cancellous bone graft. Healing of the graft usually produces complete relief of symptoms.

Carpal Compression Syndrome

Carpal compression syndrome is the aftermath of acute or chronic extension injury to the wrist in which the scaphoid (at times the lunate) sustains cartilage damage, impinging beneath the lip of the radius (Fig. 59-9). It is often associated with carpal instability. The chief symptoms of carpal compression syndrome are localized tenderness in the dorsal margin of the proximal carpal row and pain, particularly on extension of the wrist and on direct compression over the scaphoid or lunate. Lateral tomograms may reveal small osteophyte formations, or even loose bodies, on the dorsal scaphoid or lunate. Triphasic bone scans are distinctly positive. The most effective treatment of this condition is limitation of activity and antiinflammation medication. Rarely, excision of osteophytes or drilling of the sclerotic bone margin is necessary, although this gives only partial relief.

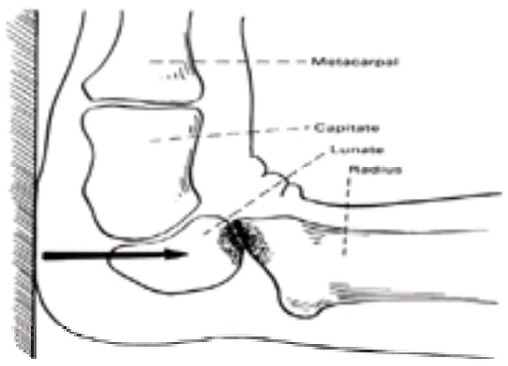

Figure 59-9. Carpal compression syndrome, which usually results from a hyperextension wrist injury. As a result, the adjacent surfaces of the dorsal radius and lunate or scaphoid are compressed enough to cause cartilage damage and loss (*arrow*). Eventually, osteophytes may even develop.

Aseptic Necrosis of the Capitate

Aseptic necrosis of the capitate is relatively uncommon, but not rare (Fig. 59-10). It is usually seen in men who do strenuous work. The exact pathologic process is unclear, but a stress fracture across the proximal neck of the capitate is the most likely explanation.

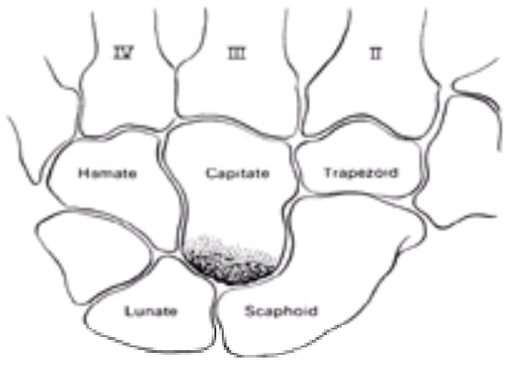

Figure 59-10. Aseptic necrosis of the capitate bone of the wrist.

Symptoms and Signs

Patients with this condition complain of progressive dorsal pain and tenderness. The tenderness is in the midcarpal area, particularly with compression, dorsiflexion, or marked volar flexion.

Diagnosis

In the early phases of aseptic necrosis of the capitate, often for a year or so, radiographs appear normal. Lateral tomograms may reveal early erosion of the head of the capitate. Triphasic bone scans are markedly positive in this localized area. Degenerative changes and capitate sclerosis subsequently become more apparent.

Treatment

Limitation of activity, splinting, and antiinflammatory drugs help in early cases. The only effective treatment, however, is surgical fusion of the capitate to the lunate and scaphoid (23).

Localized Arthritic Areas of the Wrist

Radial Carpal Arthritis

Radial carpal arthritis is characterized by pain and tenderness on the radial side of the wrist joint and is aggravated by activity. Often there is swelling, weakness of grip, and limited range of motion of the wrist joint. The scaphoid can be palpated and is tender. (The reader is referred to the earlier section, Physical Examination.) Translocating and compressing the joint are painful, and often there is crepitus. Radiographs should establish the diagnosis, showing sclerosis of the scaphoid and adjacent radius, narrowing the joint space, as well as some cyst formation. Occasionally, when arthritic change is early or quite localized, very little radiographic evidence is noted; bone scan is helpful in that situation. Frequently, this type of arthritic change is associated with a previous ligamentous injury that allows the scaphoid to move excessively and to disengage itself from the contiguous surface of the radius. This motion causes wear of the cartilage and ultimately arthritis. Six-view radiographs should be taken in all cases of scaphoradial arthritic change to determine if a scapholunate change has preceded this condition.

Treatment consists of localized care. If the condition is severe enough, a localized wrist fusion is effective in eliminating pain while maintaining adequate motion across the midcarpal joints. Before performing this procedure, it is important to determine whether there is any arthritic change between the capitate and the lunate in the midcarpal joint of the wrist. In scapholunate separation, the initial arthritic changes develop between the scaphoid and the radius; secondarily, the midcarpal joint from the capitate to the lunate is involved. If this capitate-lunate joint is involved, either a wrist fusion or the scapholunate advanced collapse wrist procedure [as described by Watson et al. (24)] should be performed, rather than a limited wrist fusion of the scaphoid, lunate, and radius.

Trapezial-Metacarpal Arthritis (First Carpal-Metacarpal Arthritis)

This common, painful condition of the wrist is a result of a sliding motion between the first metacarpal and the trapezium. Ligamentous laxity contributes to this problem. It is more common, therefore, in loose-jointed people and is particularly more common in women than in men. It is believed that 50% of women at age 50 years have some degree of arthritic change in this joint, although most are not symptomatic. The usual complaint is pain when grasping a heavy object, and the pain is described as being in the wrist rather than the thumb. Deformity at the base of the thumb and localized tenderness may be present. There may also be a positive grind test, in which the examiner holds the wrist firmly and rotates and compresses the thumb metacarpal against the carpus. Radiographs usually clearly show a narrowing of space between the first metacarpal and the trapezium. Subluxation of that joint and often loose bodies and osseous cysts are present.

Treatment consists of rest with splinting and limiting activity, antiinflammatory medications, intraarticular corticosteroids, and, if the condition is severe enough, surgical replacement. This is commonly done by removing the trapezium and part of the trapezoid and placing an interposition tendon sutured as a ligament in this space. Such a procedure is very effective in relieving pain and increasing stability and strength.

Scaphotrapezial Trapezoid Arthritis

The scaphotrapezial trapezoid joint is 1 cm proximal to the metacarpaltrapezial joint. The difference is often not appreciated clinically, but in scaphotrapezial trapezoid arthritis, careful examination reveals tenderness proximal to the trapezium. The symptoms are essentially the same as those of the basilar thumb joint arthritic condition. Radiographs show a narrowing of the scaphotrapezial trapezoid joint and, frequently, cystic formation in the tuberosity of the scaphoid. Usually, there is an element of first carpometacarpal arthritic change associated with this joint arthritis, but not always. The treatment is wrist splinting, limiting activity, antiinflammatory medications, or surgery. Intraarticular injections are only occasionally indicated. The scaphotrapezial trapezoid joint communicates with the entire wrist-carpal articulation, and multiple cortisone injections within an otherwise normal joint are usually not indicated. Surgical treatment involves either fusing the joint or pantrapezial arthroplasty. Fusion limits wrist motion significantly, while arthroplasty works well and is the surgical procedure of choice. This is the same procedure that is performed for carpal-metacarpal arthritis.

Dorsal Intercalary Segmental Instability with Arthritis

This condition is not rare and is diagnosed in the presence of arthritic changes with narrowing of the joint and cyst formation across the midcarpal area of the wrist. The patient complains of pain and soreness on wrist motion, particularly when loading and with activity, and tenderness in that midcarpal joint. Occasionally, crepitus is present. Lateral radiographs show a dorsal-facing lunate to the capitate; the capitate is almost subluxed dorsally out of the concave surface of the lunate. Dorsal intercalary segmental instability can be congenital or the result of trauma. Because it is frequently bilateral, it is probably more often congenital, but the abnormal mechanics of this wrist articulation allow early wearing of the joint. The joints involved are the scaphotrapezial trapezoid, capitolunate, and triquetral-hamate. If rest, splinting, and antiinflammatory medications do not provide sufficient symptomatic relief, midcarpal fusion is advocated and allows relief while preserving functional motion in the proximal carpal joint.

Pisotriquetral Arthritis

Pisotriquetral arthritis is an unusual, but not rare, painful condition of the wrist, which is not readily apparent on radiographs (Fig. 59-11). The cause is repeated compression injuries involving pressure of the pisiform against the articular surface of the triquetrum. Workers whose jobs entail pounding on the hypothenar eminence (e.g., body and fender repair workers) have a higher incidence of this condition than do others.

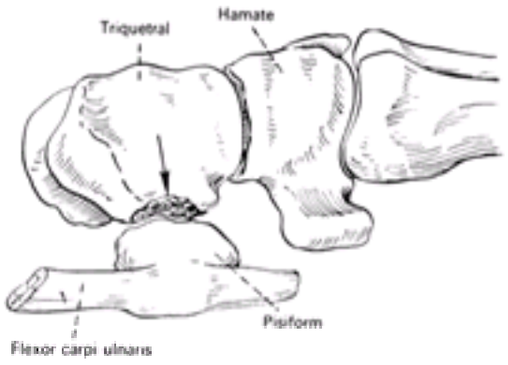

Figure 59-11. Medial view of the wrist depicting pisotriquetral arthritis.

Symptoms and Signs. The patient often complains of diffuse pain, usually on the ulnar side but rarely in the specific anatomic area of the problem. The pain is deep, activity related, and radiates out toward the fingers and the wrist. Pisotriquetral arthritis can be readily diagnosed clinically if the physician is appropriately suspicious. Careful examination, including grinding of the pisiform across the hamate, and carefully positioned radiographs help to establish the diagnosis. Blocking the joint with local anesthetic can relieve the discomfort and confirm the diagnosis. Specific tenderness along the proximal margin of the hypothenar eminence and crepitus characterize this condition.

Treatment. In milder cases, splinting, antiinflammatory medications, and limitation of activity afford adequate treatment for this condition. If this conservative treatment is ineffective, excision of the pisiform with preservation of the enveloping tendon generally affords excellent relief (24). The pisiform is not necessary for mechanical stability of the wrist. Care should be taken, however, to preserve the flexor carpi ulnaris tendon.

Ulnar Impingement Syndrome

In ulnar impingement syndrome, an elongated ulna pushes against the adjacent carpus, namely the triquetrum, producing cartilage damage or bone erosion. This syndrome is related to unusual length of the ulna, which results either from a congenital ulnar-plus variance (present in up to 10% of the population) or from an old fracture of the radius, which results in shortening of the radius and subsequent relative elongation of the ulna.

The patient with ulnar impingement syndrome has pain and tenderness along the ulnar column of the wrist around the distal ulna. Tenderness is most marked over the triquetrum.

Diagnosis

Ulnar-positive variance (Fig. 59-12) is noted on radiographs, often with erosions of the triquetrum. Triphasic scans are positive. Attritional rupture of the triangular fibrocartilage is often present and can be noted on arthrography or arthroscopy. Ulnar deviation accentuates the pain, which is relieved by a diagnostic block with local anesthetic.

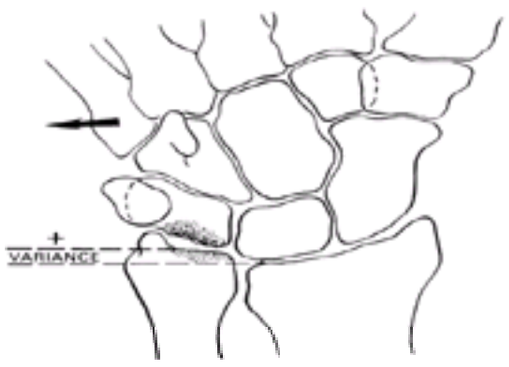

Figure 59-12. Ulnar impingement syndrome. Note variance in ulna length, which is the underlying cause of this syndrome. Ulnar deviation (*arrow*) increases symptoms.

Treatment

Treatment of ulnar impingement syndrome involves either limitation of activity, particularly that involving ulnar deviation, or surgical relief. If there is no arthritis or significant erosion of the triangular fibrocartilage, surgical shortening of the ulna generally produces excellent relief of symptoms. This can be done using a compression plate somewhat proximal to the joint on the shaft of the ulna.

Instability of the Wrist with Ligament Injuries

Instability patterns of the wrist are defined as conditions in which the normal separation or alignment between the carpal bones is exceeded. This can occur only if the ligaments separating the carpal joints have been ruptured or stretched. These instability patterns have been recognized for a long time, but the clinical significance and the magnitude of the problems created by such conditions have been only more recently appreciated. Although there are many ligaments in carpal articulations, we discuss only three of the most common injuries: scapholunate separation, ulnar column instability, and midcarpal instability.

Diagnosis

Scapholunate separation. is a separation between the lunate and the scaphoid bones beyond the normal limits, defined as 3 mm (Fig. 59-13). When the tear is complete, the separation is readily diagnosed with appropriate radiographs. In some cases, however, the tear is incomplete or the scaphoid remains relatively stable unless stressed (25,26). It is, therefore, important to obtain a true lateral wrist radiograph, with metacarpal and radius parallel, and to measure the angle between the long axis of the scaphoid and the radius. If this angle is greater than 70 degrees, it is abnormal.

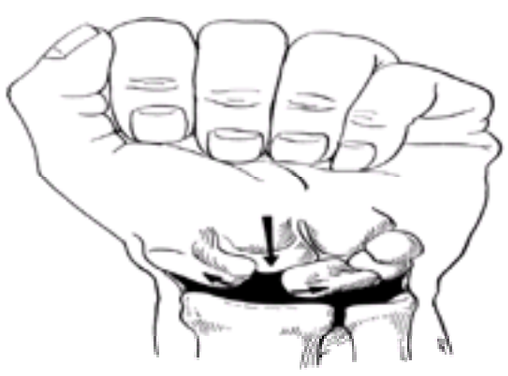

Figure 59-13. Diagrammatic anteroposterior view of scapholunate separation (*arrows*).

Scapholunate separation is most readily seen when the hand is radiographed in the palms-up position. The wrist should be radially deviated and then ulnarly deviated; then the patient makes a tight fist, compressing the bones together. Such anteroposterior radiographs may reveal scapholunate separation even when the standard series of posteroanterior radiographs is normal. The normal maximum separation between the lunate and scaphoid bones is 3 mm; any separation greater than this almost always is abnormal. Cineroentgenograms may also show instability of the scaphoid, even when static radiographs are normal. Clinical tenderness and ballottement of the proximal pole of the scaphoid between the finger and thumb of a discerning examiner can also diagnose this condition.

Ulnar-column instability. involves excessive motion between the triquetrum, hamate, and ulna. This general diagnosis refers to several specific disorders including torn meniscus, torn triquetral-ulnar ligaments, and torn triquetral-hamate ligaments (27,28 and 29).

Patients with this condition generally present with rather severe pain and tenderness on the ulnar side of the wrist. The patient may complain of a *clunking* sensation. Palpation, particularly over the triquetrum, gives an often dramatic sense of looseness. The carpus tends to supinate away from the plane of the distal ulna and radius (Fig. 59-14). Arthrograms can demonstrate triangular fibrocartilage disruption and separation between the lunate and triquetrum. Triphasic bone scan is usually markedly positive (Fig. 59-15), although it may be negative when the patient has only chronic triangular fibrocartilage tears. Small erosive lesions often are noted in the triquetrum adjacent to an old triquetral-lunate joint disruption. These may become apparent only on tomograms.

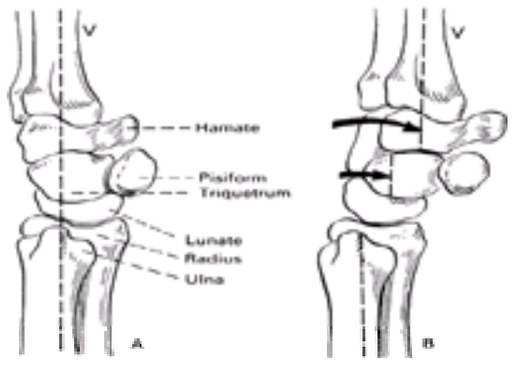

Figure 59-14. **A:** A normal, well-aligned ulnar column, as indicated by the dashed line. **B:** Ulnar column instability, which is characterized by excessive movement (*arrows*) between the distal ulna, triquetrum, and hamate. This condition, which causes pain on mobility, can be caused by trauma or attritional rupture of the constraining ligaments. Palpating the resistance to movement between each of these bones defines the instability. Because there are great individual variations in ulnar-wrist column motion, comparison with the contralateral limb is helpful in making the diagnosis. Mobility and bilateral comparisons are helpful.

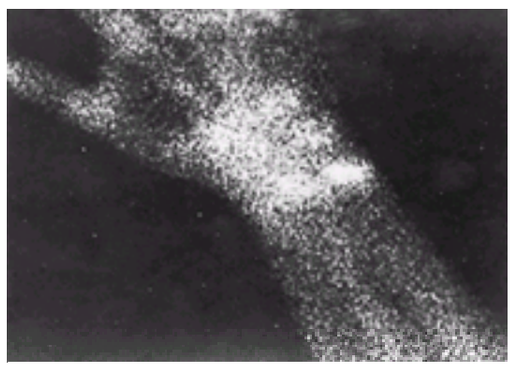

Figure 59-15. Positive technetium 99m scan reflecting a synovitis and cartilage erosion in a chronically lax ulnar column.

Midcarpal joint instabilities, in which there is volar or dorsal rotation of the lunate, produce tender areas of pain in that joint (30). Opinions vary as to the amount of variation between the longitudinal axis of the capitate and the longitudinal axis of the lunate that is accepted as normal. Some authors state that a 10-degree variance is abnormal, but most agree that the variance must be 30 to 40 degrees to be considered abnormal (Fig. 59-16).

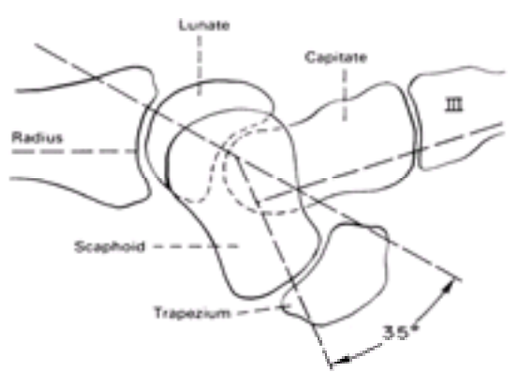

Figure 59-16. Volar intercalary segmental instability, a condition characterized by lax or ruptured ligaments, which allow the midcarpal joint (the joint between the capitate and the scaphoid and lunate) to tilt palmarward to a degree that is almost dislocating. The axis of the radius, lunate, and capitate should be nearly parallel in lateral radiographs. Note the concave surface of the lunate facing palmarward instead of straight ahead.

Stress radiographs, in which the distal segments of the carpus are forced volarly and dorsally, can demonstrate the variance in comparison with the opposite side. In some stress lateral radiographs, the capitate seems to dislocate from the lunate. The normal parameters of this have not been determined, but the injured side should always be compared with the uninjured side. Some patients have a congenital laxity.

Treatment

Treatment for carpal instability is difficult and not clearly defined. For scapholunate separation and for midcarpal instabilities, either extensive ligament repairs (grafting, drilling holes through the capitate, scaphoid, lunate, and radius, and attachment of ligaments), or limited fusions are generally performed. In triangular fibrocartilage tears, excision of the cartilage, such as is done in the knee, can lead to increased instability. Shortening of the ulna sometimes affords relief, particularly if arthritic changes have not yet developed in the adjacent triquetrum and lunate. Direct repair of peripheral TFCC tears seems to be the treatment of choice (31,32).

Tenosynovitis

Etiology. Tenosynovitis of the wrist is a noninfectious, activity-related inflammation along the parietal and visceral tenosynovium. It is particularly common in the wrist and finger area, where a great deal of movement of tendons occurs in a relatively enclosed space; the resulting friction can activate an inflammatory response. Everyone probably has a threshold for activity-related inflammation, but the specific threshold varies among individuals. In some people, a relatively minimal amount of activity triggers this response. Other factors, such as cold temperature, excessive or unusual hormone level (inflammatory responses are more common in pregnancy), and repetitive activity, seem to contribute to the onset of tenosynovitis of the wrist (33).

Diagnosis

DeQuervain's tenosynovitis, the most specific tendon inflammation in the wrist, involves the tendons of the abductor pollicis longus and extensor pollicis brevis within a relatively tight first extensor compartment (Fig. 59-17). It is usually readily diagnosed and has well-known specific symptoms, namely pain with activity of the wrist and thumb. The pain is deep and aching, and sometimes has a burning quality. It is at times associated with a nerve irritation or tingling sensation over the dorsum of the thumb. Tenderness is specific over the first dorsal osseous canal at the radial styloid. Finkelstein's test, full flexion of the thumb along with ulnar deviation of the wrist, causes pain. Injection of a local anesthetic into the first extensor compartment relieves the discomfort and establishes the diagnosis (34).

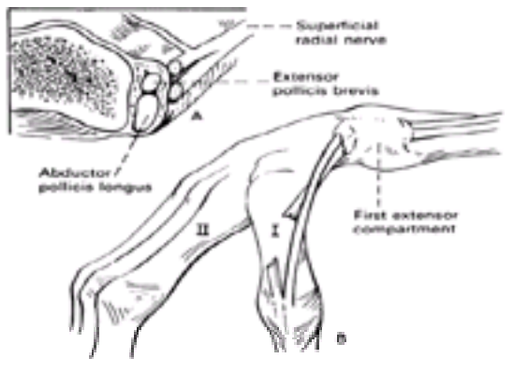

Figure 59-17. DeQuervain's tenosynovitis. **A:** Cross-section of the wrist showing the tendons of the abductor pollicis longus and extensor pollicis brevis encased in an edematous, swollen first extensor compartment. **B:** Superolateral view showing the swollen mass, which can often be palpated at the radial styloid.

Flexor carpi radialis tendinitis, which is more obscure diagnostically, is characterized by volar pain radiating to the hand (Fig. 59-18). The pain is deep, nonspecific, and activity related. Tenderness is augmented by flexing the wrist, particularly against resistance. Sharp pain and tenderness are localized in the flexor carpi radialis sheath. Because this tendon sheath runs deep beneath the thenar eminence to the second metacarpal base, the tenderness is located especially in the thenar area. Relief of pain by blocking the tendon sheath with a local anesthetic establishes the diagnosis (35).

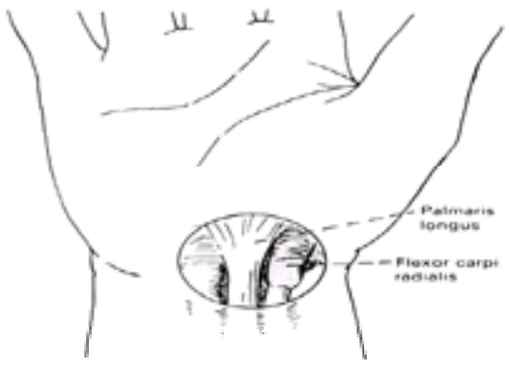

Figure 59-18. Tendinitis of the flexor carpi radialis tendon.

Inflammation of the sixth interosseous canal is occasionally seen, with and without locking. Specific tenderness, snapping, and relief from tendon sheath blocking establish the diagnosis.

In *extensor carpi ulnaris tendinitis*, the tendon may become irritated, the capsule thickened, and a stenosing type of tenosynovitis develops. This can be associated with snapping as the swollen, irritated, or roughened tendon moves out from under the confines of the tendon sheath over the distal ulna. The snap is noted when the examiner radially deviates the wrist joint. There is localized tenderness and often swelling in the ulnar styloid area. Subluxation of this tendon can produce similar symptoms. In supinating and pronating the wrist a snap is felt, and the tendon can be palpated as it slips out of the bony groove on the ulna.

Treatment

Initial treatment of tendinitis in the wrist is similar to that in other areas (i.e., splinting, rest, and antiinflammatory medication) and results in improvement in most patients. The next level of treatment, for more recalcitrant cases, is injection of a long-acting corticosteroid in the tendon sheaths. If these measures are not successful, surgical decompression generally gives quite good relief. When symptoms are significant enough, a subluxing tendon can be reconstructed surgically.

Nonspecific Inflammation

Several inflammatory arthritides, not associated with specific collagen diseases, cause wrist pain. Acute calcific tendinitis of the wrist usually is characterized by severe or excruciating pain that is well localized to the wrist and often is associated with swelling and erythema; later, the pain radiates to the elbow and fingers. Radiographs may show subtle calcific deposits (Fig. 59-19). Aspiration of the deposits often yields liquefied calcium crystals.

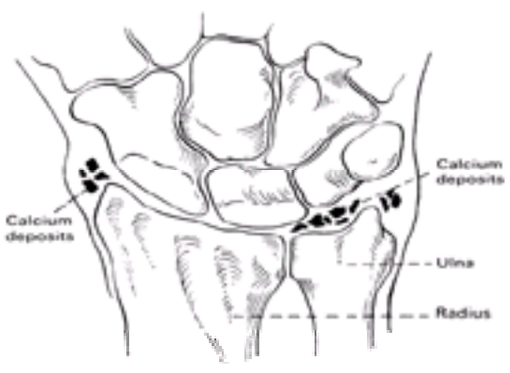

Figure 59-19. Calcific tendinitis of the wrist joint, a condition characterized by an acute inflammatory and swollen wrist joint. The traumatic-looking calcification seen

on radiographs helps to differentiate this from aseptic arthritis.

Gout and pseudogout also cause painful wrist with swelling and tenderness. Elevated uric acid levels differentiate the diagnosis of gout. In pseudogout, there may be radiograph-positive deposits in the triangular fibrocartilage. Aspiration samples demonstrate needlelike calcium pyrophosphate crystals with 11 degrees of positive birefringence. Radiographs of the knee may show calcification in the meniscus, which is a pathognomonic sign for pseudogout. Collagen disease can also begin in the wrists. If symptoms indicate, appropriate tests should be ordered to establish these diagnoses (see Chapter 27).

Treatment depends on the specific diagnostic entity. Acute calcific tendinitis responds rather dramatically to rest and antiinflammatory medications. Gout and pseudogout respond to colchicine and to antiinflammatory medications. Surgery is not indicated in any of these conditions.

Tendon Ruptures

Nontraumatic tendon ruptures, those not associated with laceration or acute trauma, can develop across the wrist. They are most common on the radial side of the wrist in the long extensor to the thumb. Such a rupture is described as a sudden mild soreness in the wrist, often with swelling and tenderness, and the patient notes a subtle change of function in the thumb. There is a drop of the distal joint of the thumb, which can be partial and is not readily recognized by the patient. The extensor carpi ulnaris is another tendon that occasionally ruptures spontaneously. The same symptoms can occur on the ulnar side of the wrist, with swelling and soreness, and examination reveals a lack of strength on ulnar deviating and extending the wrist.

Rupture of the flexor tendons is somewhat less common, and the flexor carpi radialis is perhaps the most common of those tendons that rupture. This condition is usually associated with tenderness and swelling. The lack of flexion function is very subtle. Rupture of the finger flexors also occurs, both the superficialis and profundus tendons. Pain and soreness are noted, and occasionally carpal tunnel syndrome develops. This usually occurs in patients with rheumatoid arthritis but may occur in otherwise normal individuals. All the tendon ruptures may be associated with roughness of the adjacent bony structures and an erosive proclivity to the adjacent tendon.

Treatment of tendon ruptures depends on the tendon involved. The thumb extensor should almost always be repaired, but because rupture can occur over a wide area (i.e., several centimeters of disrupted tendon), simple repair is seldom possible. It usually requires a tendon graft or transfer of an adjacent tendon to that area. In the thumb, that would be the indicus proprius tendon. The flexor carpi radialis tendon need not be repaired, as loss of its function is insignificant. The sublimus tendons likewise need not be repaired, but profundus tendon ruptures are generally considerably disabling and require repair.

Triangular Fibrocartilage Complex Injuries

The TFCC is a bonelike structure occupying a space between the triquetrum and the distal ulnar. It is attached to the radius and to the collateral ligaments between the ulna and the triquetrum. It is a stabilizing as well as articulating surface. It is subject to injury, particularly rotational injury, and traumatic tears. In older patients, tears occur from attritional changes, generally in the central portion of the TFCC and often associated with an elongated ulna that would produce more pressure across that structure. The traumatic tears result in avulsion of either the radial or the peripheral ulnar attachments to the TFCC.

Frequently, a clicking associated with pain is present when rotating or extending the wrist. There is tenderness distal to the ulnar styloid in the sulcus between it and the triquetrum. There is often laxity in the carpus in relation to the ulna and radius. Radiographs are usually negative, although if a large portion of the ulnar styloid is avulsed with the injury, that will be apparent, and painful nonunions can develop in the area. Chronic injury to the TFCC can lead to arthritic changes on the proximal surface of the triquetrum and lunate. Small erosive areas are noted on radiographs, and bone scans are positive. Diagnosis of tears of the TFCC, particularly radial or central tears, is done by arthrography or arthroscopy.

Traumatic tears are often relatively self-limiting, and a conservative clinical trial of splinting is warranted. On occasion, persistent significant problems develop and repair of the radial or peripheral tear is warranted. Central tears, if symptomatic, can be debrided. When arthritic changes are present between the lunate and triquetrum, shortening of the ulna to decompress the area gives moderate relief.

Acute Infection

Symptoms and Signs

Acute infection of the wrist produces a severe, deep, unrelenting pain radiating as far as the elbow and shoulder. The hand and wrist are barely movable. There is usually swelling, but erythema may not be widespread in the early stages. The infection is usually within the tendon sheath or within the wrist joint itself. *Staphylococcus* and *Streptococcus* are the most frequent causative organisms in adults. In children, particularly those younger than 4 years of age, infection with *Haemophilus influenzae* is common. In very young children, gram-negative organisms are often seen. The infection is usually blood borne (36).

Diagnosis

Differentiating between osteomyelitis adjacent to a joint and a septic arthritis often is difficult. Early diagnosis is critical for successful treatment. Appropriate radiographs, technetium 99m bone scans, and aspiration of the joint are important diagnostic tools, but the most significant factor in establishing a diagnosis is a high degree of suspicion on the part of the physician.

Treatment

Treatment depends on the stage at which diagnosis is made. Early diagnosis allows nonsurgical treatment, including appropriate and heavy doses of antibiotics; occasionally, aspiration of the joint by needle, splinting, and immobilization are required. Surgical decompression may be necessary if pus has accumulated under pressure; this is mostly likely to occur when treatment is begun later than 4 days after symptoms commence. If treatment is delayed more than 7 days after commencement of symptoms, permanent joint damage is highly likely (37). Treatment of osteomyelitis adjacent to a joint also may require removal of a sequestrated portion of the bone.

Kienböck's Disease

Kienböck's disease is an aseptic necrosis of the lunate, generally thought to be the result of loss of blood supply from a stress fracture. The initial incident often is obscure (38,39).

Symptoms and Signs

Often the first specific finding is a painful, mildly swollen wrist, with tenderness localized in the dorsal midcarpal area. Initial radiographs may not show abnormality, but within 2 to 3 months a fracture, sclerosis, or both of the lunate becomes apparent. This can progress to fragmentation of the lunate and secondary arthritic changes (Fig. 59-20).

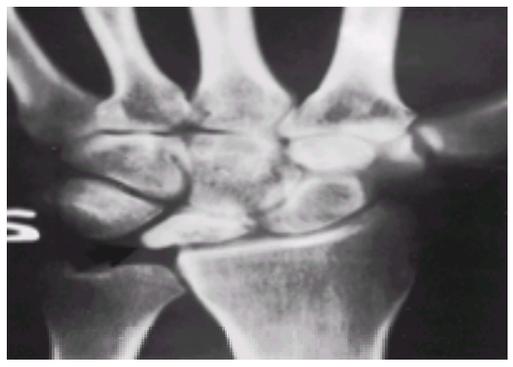

Figure 59-20. Radiograph of wrist joint affected by Kienböck's disease. Note the fragmentation and collapse of the lunate, characteristic of late stages of this disease.

Treatment

Treatment depends on the stage of the disease. Decompression of the lunate in the early phases by shortening the radius or the capitate, or by lengthening the ulna, is common and has had good results. If fragmentation of the lunate has occurred, decompression would not seem reasonable; limited fusions or tendon arthroplasty replacement have proven effective in this late stage (40).

Preiser's Disease: Aseptic Necrosis of Scaphoid from Nonunion

Aseptic necrosis of the scaphoid not associated with a fracture is called *Preiser's disease*, an idiopathic loss of circulation. The proximal pole scaphoid becomes sclerotic and often begins to disintegrate, producing considerable wrist pain, swelling, and disability. It is imperative to take multiple radiographic views to determine whether any preexisting nonunion of the scaphoid is present. MRI clearly shows the aseptic process. Treatment of early cases is by complete rest. If there is marked disintegration of the scaphoid, aggressive surgical reconstruction is necessary, with either limited fusions or a combination of fusion and arthroplasty. Osteocartilaginous bone grafting can be performed in some patients with spectacular results. In nonunion of the scaphoid, bone grafting and internal fixation should be performed if arthritis has not developed. If arthritis is present in the scaphoradial joint, the treatment is the same as for an arthritic joint.

Nonunion of the Scaphoid

The initial cause of nonunion of the scaphoid, a remarkably common condition, is traumatic injury, often a sports injury, from dorsiflexion of the wrist. The injury may have seemed relatively minor to the patient, and its details only vaguely remembered (41).

Symptoms and Signs

Symptoms of nonunion of the scaphoid may not become apparent for years when inflammatory changes develop around the excessively mobile fragments of the scaphoid. By the time symptoms appear, arthritic changes may already have occurred in the adjacent scaphoid surface. Tenderness is maximized on the radial side of the wrist in the anatomic snuffbox, just distal to the radial styloid. There may be limitation of motion. Radiographs establish the diagnosis.

Treatment

In established nonunions, prolonged casting does not produce a union. Bone grafting of the fracture fragments, with or without internal fixation, is necessary to afford healing of the nonunion, but to relieve the symptoms this must be done before arthritic changes develop. Grafting should also halt the progression of arthritic processes between the scaphoid and the radius, the usual sequelae to nonunion. Resection of the radial styloid also affords some relief. When arthritis has already developed, limited fusion is recommended (42).

Nonunion of the Hook of the Hamate

The hook of the hamate is a small, bony, horn-shaped structure protruding from the body of the hamate toward the flexor side, deep within the hypothenar space. It forms the ulnar margin to the carpal canal. Injuries such as those caused by vigorous swinging of a baseball bat or by striking the earth while hitting a golf club can avulse the hook of the hamate. This produces tenderness localized 1 cm distal to the flexion crease of the wrist and in the proximal hypothenar area. Such a fracture or nonunion is seldom seen on normal radiographic evaluation. A skyline view showing the hook of the hamate tangentially, taken on a hyperextended wrist, is the method of choice. Treatment is by excising the hook of the hamate. It requires careful dissection as the deep branch of the ulnar nerve is just at its distal ulnar border.

Osteoarthritis

The wrist is a relatively common site of early osteoarthritic changes. It often is difficult to identify a specific cause, but old or repetitive trauma or congenitally lax ligaments allowing excessive mobility are the likely culprits (43). It can occur in relatively young people and some hereditary predisposition seems likely.

Symptoms and Signs

Symptoms of osteoarthritis of the wrist include a mechanical type of deep, aching pain, aggravated by activity. The pain is often accentuated by cold weather and approaching storms. Indeed, many patients can forecast changes in the weather by the amount of discomfort in the wrist joint. Swelling following activity is common (43).

Diagnosis

Appropriate radiographs of the wrist, localized tenderness in the affected area, and a diagnostic joint block with local anesthetic generally can establish the diagnosis of osteoarthritis of the wrist. Under specific conditions, triphasic bone scans show an area of fibrillating articular cartilage and adjacent inflammation. Arthroscopy may be necessary when radiographs do not show the early changes.

Treatment

Treatment usually begins with rest, antiinflammatory medications, and corticosteroid injections in the affected joint. Joint arthroplasty or limited fusion may ultimately be required. Arthroplasty of the scaphotrapezial and trapeziometacarpal joints has given very satisfactory results.

PAINFUL CONDITIONS OF THE HAND

Painful conditions of the hand are less common than those of the wrist. Most pain associated with the hand reflects a specific injury such as laceration, fracture, previous amputation, or torn ligament. These specific entities are discussed in Chapter 31. This section deals with less obvious and more chronic conditions involving the hand. A specific diagnosis should be pursued and usually dictates the treatment.

Nonspecific Synovitis of Flexor Tendon Sheaths

Perhaps the single most common chronically painful condition in the hand is synovitis of the flexor tendon sheath.

Etiology

This condition is usually the result of nonspecific inflammatory processes, perhaps associated with unusual or strenuous activities. It can also be caused by rheumatoid arthritis or other collagen diseases. Acute infectious tenosynovitis may occur following a puncture wound.

Symptoms and Signs

Pain along the flexor aspect of the finger, markedly aggravated by activity, is characteristic of flexor tenosynovitis. Chronic synovitis of the tendon sheath may be associated with triggering, a phenomenon in which the finger or fingers go into a flexed position and either cannot be straightened or straighten with a *snap*. The snap is felt at the distal joint, but the pain and tenderness are at the MCP joint level on the flexor surface. Acute infectious tenosynovitis produces more marked pain, redness, and swelling (Fig. 59-21).

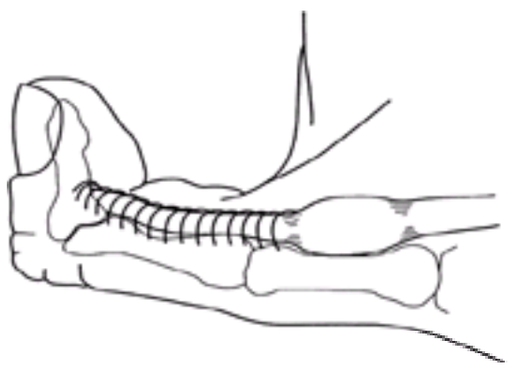

Figure 59-21. Trigger thumb. Note the bulge in the flexor tendon that locks the interphalangeal joint of the thumb (or distal interphalangeal joint of the finger) in flexion. It often can be released with a snap that feels like a joint problem.

Diagnosis

It is critical to differentiate between infectious and nonspecific tenosynovitis. Acute infectious tenosynovitis is a fulminating inflammatory process in the flexor tendon sheath causing marked pain and diffuse swelling of the finger. The finger is mildly bent. Tenderness extends from the distal flexor sheath of the finger to the palmar crease. Nonspecific tenosynovitis can develop quite acutely, often following excessive activity. The pain is acute and triggering may be present (44).

Treatment

Acute bacterial tenosynovitis, which is a closed-space infection, needs immediate drainage. Pus under pressure in the closed space impedes the mesentericlike blood supply to the flexor tendon, resulting in ischemic necrosis of the flexor tendons.

Chronic nonspecific tenosynovitis is often effectively treated with rest and corticosteroids injected directly into the tendon sheath. Most triggering phenomena can be successfully treated this way. The needle is introduced directly into the tendon sheath at the MCP joint level. The placement is tested by wiggling the finger and noting the motion at the tip of the needle. The needle is then withdrawn slightly until the space is identified. A maximum of one or two injections of long-acting corticosteroid should be given. With recalcitrant triggering or extensive and prolonged tenosynovitis, synovectomy or pulley release is necessary and very effective.

Synovitis of the Joints of the Hand

Etiology

Inflammatory response in a joint, which can be an early manifestation of osteoarthritic changes, has a variety of causes. It may be caused by excessive activity and stress, which trigger inflammatory responses in the lining of the joint. Injuries such as jamming or compressing the joint surface can cause an inflammatory response with hemorrhaging into the joint, which may last for weeks.

Chronic instability of a torn ligament produces a mechanical abnormality, which promotes synovitis and pain. A common example of this is *gamekeeper's thumb*, in which the ulnar collateral ligament of the MCP joint of the thumb has been ruptured. The term for this condition originated in Britain, where the hunter's assistant would wring the necks of wounded fowl or small game, incurring chronic sprain of the thumb and ultimately a lax ligament. Today this injury is frequently seen as a result of industrial and athletic injuries, especially ski injuries. The instability results in swelling, pain, and, ultimately, degenerative changes. The MCP joints and PIP joints of the other digits are also susceptible to this problem, but only rarely the distal joints.

Symptoms and Signs

The pain and swelling are localized over the joint. Stressing the joint in almost any position or direction causes pain, a deep, diffuse, aching discomfort, with considerable radiation to adjacent areas. For instance, synovitis in the index finger MCP joint can produce pain as far distally as the tip of the index finger and as far proximally as the wrist joint. Activity certainly aggravates these symptoms.

Diagnosis

Tenderness at the joint level and abnormal findings on stress testing are noted on examination. Stress radiographs show excessive mobility. Arthrograms may show rupture of the joint. Triphasic bone scans are positive, but seldom necessary, because the diagnosis is usually readily apparent by examination and history. Injection of 0.5 mL of 1.0% lidocaine into the joint relieves the discomfort and is a useful diagnostic tool.

Treatment

Treatment of synovitis depends on its cause. If it is activity related, rest, antiinflammatory medication, or both are often sufficient. With more severe or chronic cases, intraarticular injections of a long-acting corticosteroid such as triamcinolone produce good relief for several months. If the inflammation is secondary to instability, surgical reconstruction of the ligaments may be necessary. If arthritic changes have developed in the joint, ligament reconstruction is not sufficient to relieve the symptoms, and fusion or arthroplasty is necessary (45).

Arthritic Conditions

Osteoarthritic conditions not associated with specific instability patterns are common in the hand. They are most frequent in the distal joint, less common in the PIP joints, and least common in the MCP joints. The tendency to develop arthritic changes seems to occur in families and is much more common in women than in men. Repeated heavy injuries, old injuries or fractures, chronic instability, and hereditary predilection are the causes.

Symptoms and Signs

The symptoms are those typical for joint pain: deep, aching discomfort aggravated by activity and relieved by rest. Diagnostic blocks with a local anesthetic help to establish the specific diagnosis. Often, several joints are involved. Radiographs usually can establish a diagnosis; these show sclerosis of the margins, small cystic

formation of the bone, loss of joint space, and often osteophytes. Small ganglion cysts may come from the joint spaces, particularly the distal joints of the fingers. The nails may be deformed by the pressure of the cyst on the germinal plate of the nail.

Treatment

Treatment is usually symptomatic, including rest and pain control with nonsteroidal antiinflammatory drugs. Injection of corticosteroids and, occasionally, limited fusion or joint arthroplasty sometimes are necessary.

Rheumatoid Arthritis

Rheumatoid arthritis is a generalized disease and is discussed in Chapter 27. Frequently, it develops initially as a pain in the hand associated with persistence, swelling of the MCP or PIP joints, and occasionally persistent inflammation along either the extensor or flexor tendons. In the early stages of the disease radiographs may be negative. In patients with persistent swelling, soreness, and pain across the joints or the flexor or extensor tendons and no apparent specific cause, a laboratory evaluation for rheumatoid arthritis and other collagen diseases is in order (46). Such evaluations are discussed in Chapter 27.

Gout and Crystalline Synovitis

Inflammatory changes in the joints may result from crystalline inflammation, as in gout or pseudogout. Tophaceous development across the joints, visible as subdermal white deposits, is pathognomonic for gout, but subtle, painful rheumatoid or osteoarthritic changes may occur in the early stages. There are no distinguishing characteristics of this type of inflammatory change. It presents with swelling, soreness, redness, and tenderness at the joint levels. Chemical evaluation of serum uric acid should define gout. Crystalline synovitis of pseudogout is more difficult to establish. Interarticular aspiration and evaluation of the crystalline structure establishes the diagnosis. Sarcoidosis is another, relatively rare, condition causing painful hand. The pain is deep, periarticular, and associated with lytic phalangeal lesions observed by radiography.

Extensor Tendon Tenosynovitis

Extensor tendons of the hand have fewer inflammatory problems in general than their counterparts on the flexor side. Inflammatory changes do occur, particularly on the back of the hand, from chronic overuse or repetitive activity. The extensor retinaculum over the metacarpals, particularly the third and fourth metacarpals, can rupture, allowing the tendons to subluxate into the groove between the metacarpal heads. This produces friction synovitis, which sometimes results in the inability to completely straighten the finger.

Diagnosis of extensor tendon synovitis is established by careful examination, noting whether the tendon subluxates, and palpation of the tender or swollen extensor tendons. Diagnostic block injected into the tendon sheath helps establish the diagnosis.

Treatment of extensor tendon synovitis depends on its specific cause. If the cause is repetitive activity and use, oral antiinflammatory medications and rest usually suffice. Occasionally, tendon sheath injections with corticosteroids are necessary. Repeated injections should not be given because of the danger of rupture of the extensor tendons. If the retinaculum of the extensor tendon of the MCP joint is subluxating, surgical reconstruction is indicated. At times, this may require grafting of the extensor tendon retinaculum over the joint.

Mallet Finger Deformity

Mallet finger deformity is another type of irritation of the extensor tendon (Fig. 59-22). It develops when the distal portion of the extensor tendon is avulsed from the bone. A piece of the distal phalanx may be avulsed as well, but not necessarily. This is often a relatively minor injury that can be caused by actions such as pulling on socks, for example, if the finger gets caught. Initially it may not be painful, but soreness and swelling develop across the distal joint on the extensor surface, and the finger has an extensor lag. If untreated, the joint tends to become more flexed and often increasingly painful. Simple continuous splinting of the DIP joint in the straight position for 8 weeks is a very effective treatment in almost all cases.

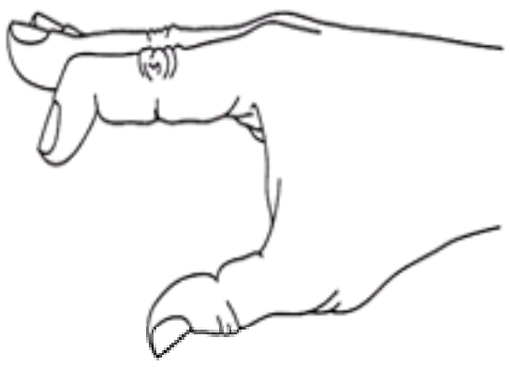

Figure 59-22. Mallet finger deformity. Avulsion or laceration of the extensor tendon insertion at the distal joint causes this deformity.

Boutonnière Deformity

Boutonnière deformity is a similar avulsion of the central slip of the extensor tendon over the PIP joint, often following a blunt injury to the back of the finger (Fig. 59-23). It need not be an extensive injury. Presumably, the tendon is devascularized and stretches over time. The joint develops a flex position, cannot be actively extended, and may become moderately painful as well as awkward. Immediate splinting of the PIP joint, continued for 8 weeks, is likewise an effective treatment, although if delayed it probably is not beneficial. In severe cases, surgical reconstruction, though difficult, can be achieved.

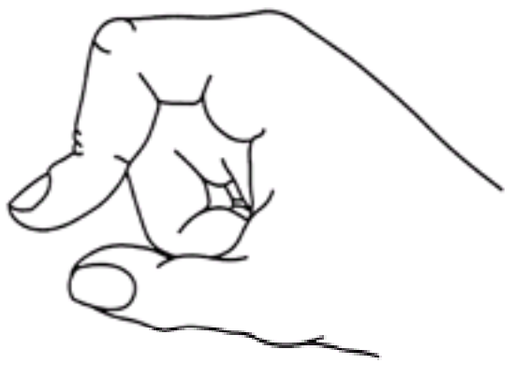

Figure 59-23. Boutonnière deformity. Loss of integrity of the central slip insertion of the extensor tendon at the proximal interphalangeal joint results in this deformity.

Swan-Neck Deformity

The swan-neck deformity occurs when the volar plate on the flexor aspect of the PIP joint ruptures or is stretched, and the PIP joint goes into hyperextended position (Fig. 59-24). This occurs congenitally in some people with lax joints, but if it is traumatic or extensive, the PIP joints can become locked in extension, an awkward and moderately painful condition. This is not uncommon in rheumatoid arthritis, nor is boutonnière deformity. Occasionally, it is seen with intrinsic tightness, when the interosseous muscles in the hand develop contractures. The PIP joint subsequently hyperextends and cannot flex, particularly when the MCP joint is in extension. When the MCP joint is in flexion, the muscles are relaxed and the PIP joint can relax. Swan-neck deformity can be treated by reconstructing the volar ligaments of the PIP joint, usually using a slip of the superficial tendon. If intrinsic tightness is present, releasing the intrinsic tendons is beneficial.

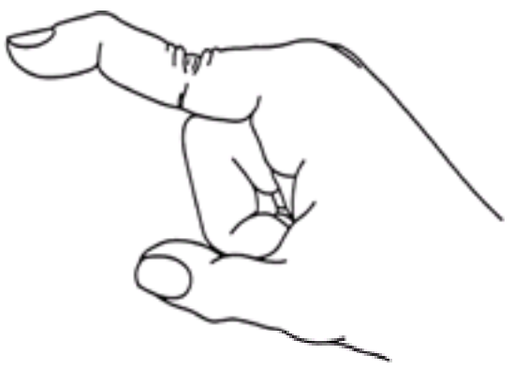

Figure 59-24. Swan-neck deformity. Loss of stability of the volar plate ligament at the proximal interphalangeal joint coupled with over-pull of the extensor tendon causes this deformity.

Sesamoiditis

Sesamoiditis is an unusual and painful condition occurring over the flexor aspect of the thumb. It probably is related to repetitive use of the thumb and pressure on the small sesamoid bones in the flexor aspect of the MCP joint of the thumb. It is most common on the radial side of the thumb, where the condyle of the metacarpal is less congruous with the surface of the sesamoid. There is tenderness directly over the sesamoids, aggravated by direct pressure in that area. The pain is relatively localized and usually activity related. Radiographs are rarely diagnostic of sesamoiditis except in advanced cases. Tomograms are helpful to outline bony change, and a triphasic bone scan demonstrates positive uptake in the area of the joint.

Treatment of sesamoiditis consists of rest, antiinflammatory medications, or both. An injection of a local anesthetic is usually helpful. In severe cases, surgical excision of the afflicted sesamoid is required.

Writer's Cramp

Etiology

Writer's cramp, a fairly common debilitating and painful condition of the hand, is brought on by repetitive activity, such as prolonged writing. The exact causes are obscure but include ulnar nerve compression syndrome and chronic increased compartmental pressure within the dorsal compartments of the hand, most frequently the first dorsal interosseous. Abnormalities of calcium metabolism should also be considered. Most cases are considered idiopathic (47).

Symptoms and Signs

During an episode of writer's cramp, the hand is forced into an intrinsic-plus position, with the MCP joints flexed and the PIP joints extended; often the thumb is adducted into the palm. A deep, aching pain radiates into the fingers and up the arm.

Diagnosis

Musicians and pianists, in addition to writers, often complain of this problem. It can be differentiated from a true nerve compression problem by the lack of associated numbness and negative electromyographic results. Specific testing for ulnar nerve irritation should be done. Compartmental pressure testing may show high levels of activity-related extracellular fluid pressure.

Treatment

Although decompression of compartments of the hand has been reported to give good results in some patients, treatment is often difficult and unsatisfactory. Some patients are helped by changing their writing style or reducing repetitive activities of the hand. Muscle relaxants, such as diazepam, have helped, as has biofeedback. If a more general condition is present, with specific or prolonged muscle spasticity, a diagnostic brain scan for tumor should be done. We have encountered four cases of writer's cramp in which the brain scan has revealed an unsuspected tumor.

Cysts and Ganglia

Cysts and ganglia along the flexor tendon sheaths are fairly common. Characterized by a tender mass on the flexor aspect, just distal to the MCP joint, they are often noted after periods of increased hand activity. They may be painful, especially when the patient grasps hard objects with the hand. They usually respond to simple cortisone injection, but occasionally it is necessary to excise them.

Cysts on the dorsal surface of the hand generally arise from joints and are usually not painful. They may be associated with arthritis, in which case it is the arthritis that causes the pain, not the cyst. Removal of the cyst itself, therefore, seldom relieves the discomfort.

Dupuytren's Contracture

Dupuytren's contracture is a relatively common condition, particularly in people of northern European extraction. Men are more commonly affected than women (48). This disease is characterized by an increasingly flexed position of the palmar surface of the hand and fingers. A firm mass can be palpated, and dimpling of the skin is often observed. The ring and little finger are most commonly affected, but all fingers can be involved. Dupuytren's contracture is sometimes associated with tender nodules in the dorsal aspect of the PIP joints (*knuckle pads*). Occasionally, there are tender nodules in the palm, more commonly in women than in men. The only effective treatment for Dupuytren's contracture is excision of the palmar fascia that has hypertrophied and caused the fingers to contract. No other treatment modalities have proven successful. Excision is indicated, however, only when significant contracture of the fingers has developed.

Self-Inflicted Lesions

Self-inflicted lesions peculiar to the hand and wrist are sometimes encountered. Pain in the hand and wrist, particularly on the nondominant side, associated with ecchymotic lesions, chronic swelling, or unexplained ulcerations or open wounds may be the result of self-mutilation. The lesions can be severe and present in a patient who otherwise seems mentally healthy. The diagnosis often is difficult to confirm and may require seeing the patient many times. If the lesions heal after extended protective casting, self-infliction should be suspected.

Ischemia

Ischemic conditions of the hand are usually associated with a systemic propensity. They often present with extremely painful, tender fingers, with some color changes, either whiteness or in more severe cases with dark areas of ischemia on the fingertips. Careful diagnostic evaluation is necessary. If the condition is unilateral and localized, arterial thrombosis should be suspected and appropriate diagnostic procedures undertaken. The reader is referred to the diagnostic section in the initial part of this chapter.

Palmar hammer syndrome occurs when the patient has used the butt of the hand as a hammer, and aneurysm or occlusion of the ulnar artery in Guyon's canal develops. Localized ischemia, primarily to the ulnar side of the hand, is the result, with a positive Allen's test for lack of ulnar blood flow. If the ulnar nerve is irritated enough, the patient may present with tingling in the little and ring fingers. Localized resection and vascular grafting are extremely effective. The evaluation for general ischemic conditions of the hand associated with collagen diseases is discussed in Chapter 27.

Raynaud's disease and *white-hand syndrome* are intermittent vascular conditions of the hand. Raynaud's disease is associated with swelling and redness, followed by whitish and then bluish color, often with the stimulus of cold or emotional tension. The fingers become very painful, numb, and tingling. The cold pressor test, immersing the hand in cold water and observing sudomotor activity, often establishes the diagnosis. Usually, the patient's complaints are specific enough to raise a high degree of suspicion.

White-hand syndrome is associated with outdoor workers who are exposed to persistent cold and who use vibratory tools such as chain saws. Symptoms are whiteness of the fingers with an aching pain, usually relieved by warming the hands. This condition may become chronic. Vibratory neuritis may be a component of this syndrome, which otherwise presents as arterial insufficiency.

Treatment of these problems is difficult and varied; vasodilating medications and avoidance of cold are foremost in the treatment plan. Occasionally, an interdigital neurolysis is warranted to excise the digital sympathetic nerve branches to the artery and, rarely, sympathetic ganglion resection at the cervical level. Sympathetic block often gives dramatic temporary relief.

Tumors of the Hand

A few benign tumors characteristically produce pain in the hand and wrist and therefore are considered in this chapter (49,50 and 51).

Pathophysiology

Osteoid osteoma is a small vascular tumor of bone characterized by sclerotic or reactive bone formation, which may be quite small, often with a tiny lucent area in the center of the sclerosis. Tomography often can help establish the diagnosis. The pain is deep and unrelenting and seems to respond well to aspirin.

Glomus tumor is a small benign vascular tumor, frequently located beneath the nail. It is characterized by marked pain and exquisite tenderness to pressure on the nail just in the affected area.

Enchondroma is a benign tumor of cartilage. Generally, it is not tender until a fracture occurs. Often just a small stress fracture produces enough osseous mobility to cause discomfort.

Giant cell tumor of the tendon sheath may present as a painful swelling from a joint or tendon. It is usually seen in the second and third decades of life. This tumor should be differentiated from a giant cell tumor of bone, a low-grade malignant growth within bone that is usually not painful.

Inclusion cysts are small benign cystic lesions thought to result from a puncture wound that carries squamous epithelium within the body. The epithelium then grows and expands in a closed space. When a low-grade infection ensues, pain results.

Hemangiomas of small capillaries and cavernous hemangiomas may be slow growing and moderately painful. They are characterized by bluish discoloration. Arteriography is diagnostic but not usually necessary.

Malignant tumors are rare in the hand. A dark lesion, particularly on the palmar aspect of the skin, with irregular borders and changing color is suspicious of melanoma. A dark lesion underneath the fingernail is highly suspicious of this condition and almost always should be biopsied. Those conditions usually are not painful. Squamous cell carcinoma of the skin presents as an irregular, sometimes ulcerating, raised dermal lesion, erythematous in color. Biopsy establishes the diagnosis, and wide excision, often with grafting, is usually curative. Metastatic tumors produce lytic areas in the bones of the hand. These are rare but may be painful and may produce pathologic fractures. If primary lesions are not apparent, diagnostic biopsies should establish the primary site. Primary malignant bone lesions of the hand also are very rare and may present as painful masses or areas where lytic lesions are apparent by radiograph. Biopsies define the lesion, and treatment varies with the type of lesion diagnosed.

Treatment

Surgical treatment of benign tumors of the hand is dictated by the tumor itself. Usually excision is indicated. For osteoid osteoma, *en bloc* excision of the mass is necessary, and often a small bone graft is required afterward. Glomus tumor needs surgical excision beneath the nail. The nail must be removed and the tumor localized; it is usually a small, firm mass within the sterile matrix of the nail. An enchondroma is treated by excision, including, of course, biopsy specimen, thorough curettage, and bone grafting. Giant cell tumors of tendon sheath, inclusion cysts, and hemangiomas should be excised.

NEUROPATHIC DISORDERS OF THE WRIST AND HAND

In this section we discuss pain in the hand or wrist associated with neuropathic conditions (i.e., abnormalities of the nerve itself). Although a stretch injury can result in neuropathy (e.g., following hyperextension injury to the wrist with ligamentous strain), this is relatively uncommon. Generalized disease processes such as diabetes, vitamin deficiency, and metabolic toxicity can result in neuropathy (see Chapter 19). Diabetic neuropathy, in particular, can cause numbness and some dysesthesia, but this is not consistently encountered. Other such neuropathies are not difficult to diagnose and seldom cause much pain within the hand and wrist.

Neuropathy in the hand and wrist can be the result of virus infection. Herpes zoster, the classic example, occurs in dermatomal patterns, and the characteristic rash establishes the diagnosis. Treatment of this condition is discussed in Chapter 22. Painful neuropathies of the wrist and hand having a mechanical cause, which are the most common, are discussed in detail in this section (see Table 56-3 and Figure 56-4, Figure 56-5, Figure 56-6, Figure 56-7 and Figure 56-8 for more information).

Median Nerve Entrapment Syndromes

Carpal Tunnel Syndrome

The vast majority of painful neuropathies of the hand and wrist result from nerve compression, most frequently compression of the median nerve in the carpal tunnel (Fig. 59-25A). Brain described this syndrome in 1948, and it has been well documented in the medical literature since then (52,53).

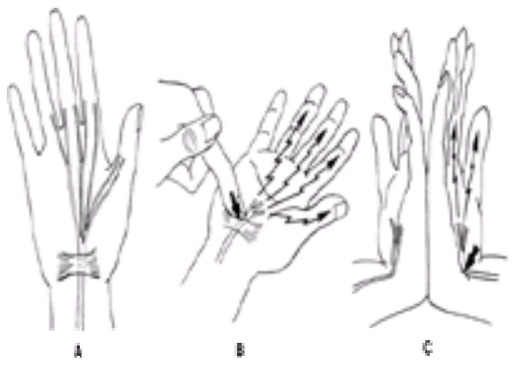

Figure 59-25. **A:** Normal distribution of the median nerve. **B:** Elicitation of Tinel's sign in a patient with carpal tunnel syndrome by percussing the wrist over the carpal tunnel. **C:** Modified Phalen's sign, which is elicited by holding both wrists in extreme flexion, is a painful numbness in the thumb and the second, third, and fourth fingers.

Symptoms and Signs. Carpal tunnel syndrome is characterized by a numbness and pain, usually in the distribution of the median nerve, but not limited to it. The pain varies from sharp and severe, with itching and burning associated with numbness, to hyperesthesia. It is characteristically present at night, causing the patient to wake from sleep. Flexing and extending the wrist seem to aggravate the pain, which frequently is first noted following unusual or prolonged repetitive activity. Carpal tunnel syndrome is a major concern of industry because of the resultant loss of time at work. It is associated with pregnancy, patients who undergo kidney dialysis, diabetic neuropathy, hypothyroidism, and acromegaly (54).

The cause can be unusual activity, collagen disease (rheumatoid arthritis, lupus erythematosus, and so forth), a ganglion within the carpal canal, or occasionally a tumor (soft tissue or calcified). A mechanical problem in the wrist joint also can produce the symptoms of carpal tunnel syndrome. The wrist joint occupies the dorsal surface of the tunnel; swelling there, because of nonunion of the navicular with secondary arthritis, scapholunate separation, or even lunate dislocation, may present itself as a carpal tunnel syndrome. For this reason, radiographs should be obtained when carpal tunnel syndrome is suspected.

Amyloid disease and calcinosis can cause deposits within the lining around the synovium, and acromegaly can cause narrowing of the bony aspects of the canal. These entities can produce carpal tunnel syndrome. Most patients with the syndrome, however, have no other specific etiologic disorders, and the neuropathy usually is the result of swelling of the synovium around the flexor tendons.

Diagnosis. A positive Phalen's sign, which is indicative of carpal tunnel syndrome, refers to numbness or increasing numbness, primarily in the median nerve distribution, when the wrist is held in a flexed position (Fig. 59-25C). Tinel's sign, produced by tapping over the median nerve at the wrist, with resultant shocklike sensation, is also a common finding (Fig. 59-25B). Tests of sensation, including two-point discrimination, light touch, and vibratory touch, frequently produce positive findings. In more severe cases, the patient has muscle weakness and atrophy of the thenar musculature. Electromyographic and nerve-conduction studies showing reduced conduction velocity across the carpal tunnel (greater than 4 milliseconds between the flexion crease of the wrist and the thenar musculature) should lead one to suspect carpal tunnel syndrome (see Chapter 13). Fibrillation, positive waves, and diminished amplitude in recruitment isolated to the thenar muscles also suggest this condition.

Differential diagnosis is important when symptoms suggest carpal tunnel syndrome. The compressive neuropathy in this syndrome is not due to a problem in the nerve itself but is a result of swelling around the nerve and the resultant interference of the nerve's blood supply. This is usually caused by thickening or inflammation along the flexor tendon's synovium within the canal. The cause of the synovitis should be determined, if possible.

Treatment. Treatment of carpal tunnel syndrome depends on the cause of the neuropathy (55). Most patients get better with conservative treatment, which includes splinting of the wrist in neutral position for rest, oral antiinflammatory medication, and corticosteroid injection into the ulnar bursa of the flexor aspect of the wrist (Fig. 59-26). The injection should *not* be made into the carpal tunnel itself, because this risks injecting the corticosteroid directly into the median nerve, which is not desirable. Favorable response to vitamin B_6 therapy has also been reported, but controlled studies and personal experience do not confirm positive responses from these types of treatments.

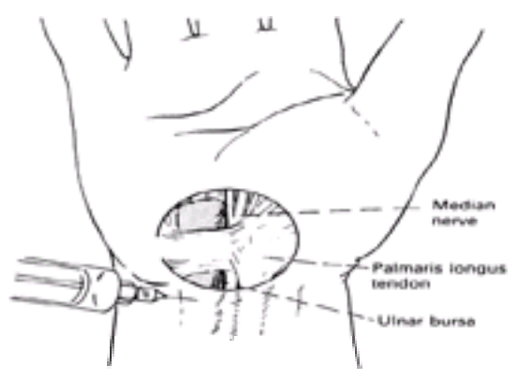

Figure 59-26. Injection of the ulnar bursa for the treatment of carpal tunnel syndrome.

If these treatments fail and the symptoms warrant, surgical decompression of the carpal canal, with or without localized flexor tendon synovectomy, is indicated. This treatment has produced favorable results in a large percentage of patients. Recurrences do happen, but probably in fewer than 10% of patients. Both open and endoscopic carpal tunnel releases have been successful.

Other Median Nerve Entrapment Syndromes

Several other neuropathies of the median nerve cause symptoms that mimic carpal tunnel syndrome.

Supracondylar Process Syndrome. Approximately 2.5% of the population has an aberrant spur of bone on the anteromedial surface of the humerus approximately 5 cm above the median epicondyle. This structure, called the *supracondylar process*, is often connected to the medial epicondyle by a fibrous band called the *ligament of Struthers*. Usually, the median nerve and often the brachial artery pass behind the process and then anteriorly between the fibrous band and the bone. Moreover, the upper fibers of the pronator teres arise from the process and the band. Consequently, the median nerve can be compressed by the ligament or by the fibers of the pronator teres (see Fig. 56-8). Persons who have this entrapment syndrome experience pain above the elbow and local tenderness in the region of the ligament. Radiographs of the elbow show the bony process above the median condyle of the humerus, and a positive Tinel's sign is present (see Fig. 59-25B).

Pronator Teres Syndromes. As the median nerve crosses the elbow, it first passes posterior to (beneath) the lacertus fibrosis (a thick fascial band extending from the biceps tendon to the ulnar forearm fascia), then between the superficial and deep heads of the pronator teres, and then beneath the flexor digitorum superficialis arch (54). Consequently, the nerve sometimes is compressed beneath the lacertus fibrosis or by the hypertrophied pronator teres or a fibrous band within the pronator teres. The nerve also can be compressed by a tight fibrous arch of the flexor digitorum superficialis.

The pronator syndrome produces mild to moderate aching pain in the proximal forearm, which may radiate to the wrist and hand and is associated with tingling and numbness, symptoms similar to those of carpal tunnel syndrome. The pain is usually aggravated by heavy use of the forearm and arm and repetitive elbow motions; as the pain intensifies, it may radiate proximal to the elbow even to the shoulder. These syndromes are associated with a positive Tinel's sign at the cubital crease,

weakness in the flexor muscles of the forearm, and a numbing sensation when the pronator muscle is stretched against resistance to produce compression of the nerve at that level.

Anterior Interosseous Nerve Syndrome. Anterior interosseous syndrome, another neuropathy of the median nerve, usually involves only the anterior interosseous branch as it leaves the median nerve just distal to the elbow. The syndrome is characterized by loss of strength of the flexor to the thumb and the flexor profundus to the index finger, not associated with numbness (56). It often commences with a deep aching pain in the forearm following unusual activities. Patients characteristically do not recognize their limited thumb or index finger strength for some period of time.

Treatment. Median nerve neuropathies at the elbow are initially treated conservatively with antiinflammatory medication and rest, which provide adequate relief in many patients. If symptoms persist and electromyographic changes are significant, decompression is warranted. The median nerve should be released well above the elbow down through the pronator and beyond the insertion of the two heads of the flexor digitorum superficialis.

Ulnar Nerve Entrapment Syndromes

Pain in the hand and wrist may result from a compressive neuropathy of the ulnar nerve, of which there are three general types.

Thoracic Outlet Syndrome

Neuropathy of the ulnar nerve due to compression by the lower trunk of the brachial plexus as it passes over the first rib, scalenus anticus, or medius muscles is commonly referred to as *thoracic outlet syndrome*. It produces an aching pain along the ulnar nerve distribution in the forearm and hand, and often some numbness in the little and ring fingers. Activities that stretch the scalenus muscle, such as Adson's maneuver, result in loss of pulse, vascular changes, or both in the hand. These changes suggest this syndrome.

Cubital Tunnel Syndrome

Cubital tunnel syndrome (compression of the ulnar nerve at the elbow) can manifest itself by pain in the hand and pain and numbness in the little and ring fingers. Generally, ulnar nerve neuropathy involves only the little finger and the ulnar half of the ring finger, but in a significant number of people it involves the entire ring finger and part of the middle finger. Neuropathy of the ulnar nerve from this level produces numbness on the dorsum of the hand, which differentiates it from ulnar neuropathy at the wrist level (Guyon's canal syndrome).

Cubital tunnel syndrome sometimes is associated with cubitus valgus position from an old injury or fracture at the elbow. It also can result from chronic subluxation of the ulnar nerve at the elbow. In some patients, it is associated with osteoarthritis of the elbow joint in which swelling compresses or irritates the nerve. Frequently, however, cubital tunnel syndrome is not associated with any particular predisposing condition (53).

Guyon's Canal Syndrome

Guyon's canal is the anatomic structure through which the ulnar nerve and ulnar artery pass from the flexor compartment of the forearm to the hand. It is the site of a compressive neuropathy of the ulnar nerve much like median nerve neuropathy in the carpal tunnel. This compression produces pain and numbness in the ulnar nerve distribution (usually the little and ring fingers) with loss of strength in the ulnar-innervated intrinsic muscles. It does not, however, result in numbness on the dorsum of the ulnar side of the hand. The deep branch of the ulnar nerve may be the only structure involved (particularly when the compression is associated with a ganglion), and therefore there is no numbness, just intrinsic muscle wasting. Muscle wasting and strength are best tested by spreading the fingers against resistance and radially deviating the index finger while palpating the first dorsal interosseous muscle.

Differential Diagnosis

The three types of ulnar neuropathies can be differentiated by an electromyographic study and a careful clinical evaluation (54). MR neurography (see Chapter 14) may also delineate the site of a lesion. As mentioned earlier, Adson's maneuver gives characteristic findings in thoracic outlet syndrome. Guyon's canal syndrome produces numbness of the fingers and intrinsic muscle atrophy but not numbness of the dorsum of the hand; this last symptom is characteristic of cubital tunnel syndrome.

Treatment

Treatment of ulnar neuropathies obviously depends on the area of involvement. In thoracic outlet syndrome, shoulder-elevating exercises, rest of the arm, and antiinflammatory medication are often sufficient. In severe cases with muscle loss and persistent numbness, resection of the first rib or release of the scalenus muscles is indicated, although this operation is often unsuccessful and can lead to major complications.

Initial treatment of mild cubital tunnel syndrome for the ulnar nerve involves padding the elbow and keeping the elbow relatively straight for a period of time. Often the condition improves, particularly in cases in which the ulnar nerve is subluxating. If symptoms persist and electromyographic changes are significant, surgical release is warranted. The author has become more surgically aggressive with experience, believing that continuing too long with conservative treatment can result in intraneural scarring and produce less satisfactory results than early surgical treatment. In extremely mild cases of cubital tunnel syndrome, simple release of the nerve as it goes around the epicondyle and through the decussations of the origin of the flexor carpi ulnaris muscle may be sufficient, although a fairly high rate of recurrence has been noted with this treatment. If significant neuropathy is present, submuscular transfer of the nerve is an option. In this procedure, the ulnar nerve is placed near the median nerve and the muscles are sutured relatively loosely back to the epicondyle, leaving plenty of room for the nerves. Fairly early motion is recommended after this procedure. The results, in the author's estimation, have been very good.

In Guyon's canal syndrome, surgical release is warranted in any documented case that is at all persistent. Occasionally, inflammation or blockage of the ulnar artery at the wrist accompanies this condition and may require resection of a thrombosis or a small aneurysm. The incision should be the same as that for carpal tunnel syndrome, and the neurologically sensitive hypothenar area should be avoided.

Radial Nerve Entrapment Syndromes

Etiology and Pathophysiology

Compression of the radial nerve proximally at the level of the axilla produces symptoms and signs of *Saturday night palsy*, characterized by paralysis of the wrist extensor and digital extensor muscles and sensory deficit over the dorsum of the hand, sometimes with little or no pain.

Just below the elbow, the radial nerve divides into a superficial sensory branch and a deep motor branch called the posterior interosseous nerve, which supplies the extensor muscles of the wrist and hand. The posterior interosseous nerve enters the supinator muscle under the arcade of Frohse and at this point can be compressed by tumors, ganglia, or synovitis. Spontaneous compression also can occur at the point of passage through this arcade (54). The patient develops weakness or total paralysis of the extensors of the wrist and fingers. Half of patients also have pain in the elbow and proximal forearm, which lasts a few days. Tenderness is often found over the nerve within the extensor muscle mass immediately distal to the radial head. Electromyographic changes are diagnostic.

Pain in the hand and wrist caused by radial nerve neuropathy is relatively uncommon and relatively mild, except following trauma to the radial styloid. Three to five branches of the radial nerve course over the radial styloid, a bony prominence on the radial side of the wrist. These branches frequently can be compressed at that level because there is relatively little soft tissue padding to protect them. Radial nerve neuropathy can be caused by direct blunt trauma, such as a striking force, by swelling from a ganglion or inflamed tendon, and even by a tight wristband. Most cases, however, are associated with surgical or accidental lacerations. Surgery for DeQuervain's disease or for removal of a ganglion frequently produces some temporary neuropathy due to retraction or severance.

Symptoms and Signs

Radial nerve neuropathy is characterized by a burning pain in the dorsum of the thumb, index, and middle fingers, with dysesthesia, numbness, or both. It seems to produce an extraordinary amount of pain and disability, considering that the radial nerve is relatively small and relatively unimportant to sensation. Because this nerve does not govern sensation in the flexor surface of the hand, its function is not as critical as that of the median or ulnar nerve.

Treatment

Treatment of radial nerve neuropathy depends on the cause. Rest usually suffices to reduce the compression forces resulting from watches, casts, or blunt trauma. Occasionally, surgical removal of the cause of the compression (e.g., a ganglion) is necessary. When the radial nerve has been lacerated, treatment is more complicated. Repair of the nerve is sometimes warranted, even if it requires nerve grafting, to lessen its sensitivity and the possibility of neuroma formation. A procedure involving resection of the nerve and burial of the neuroma has been performed in serial sections up to the level of the elbow, but it is frequently unrewarding (54).

Entrapment Syndromes of Other Nerves

Lateral Cutaneous Nerve

The distal branches of the lateral cutaneous nerve to the forearm can innervate the base of the thumb. This is the distal branch of the musculocutaneous nerve, not the radial. Occasionally, neuropathy of the cutaneous branch of the musculocutaneous nerve results from impingement at the elbow. This produces a burning pain in the distal forearm, wrist, and the palmar portion of the proximal thumb. The cause is entrapment of the nerve as it exits from a deep space at the level of the cubital fossa. Treatment with rest and antiinflammatory medications usually is satisfactory, but occasionally the treatment of choice is surgical decompression.

Palmar Cutaneous Nerve

Injury to the palmar cutaneous branch of the median nerve can produce a burning, dysesthetic pain in the flexor aspect of the thumb in the thenar area. The discomfort may be excruciating. The median nerve itself is not involved. A positive Tinel's sign is present at 4 to 6 cm proximal to the flexion crease of the wrist. This neuropathy is usually associated with a sharp injury, including surgical scar. Resection or burial of the neuroma or release of the nerve is the preferred treatment.

Digital Nerve

Occasionally, a digital neuropathy develops because of a mass irritating the nerve. An osteophyte at the PIP or DIP joint, a ganglion, and other tumors are typical examples. The result is diminished sensation in the distribution of the nerve. Sharp pain when the nerve is tapped over the site of compression (Tinel's sign) is diagnostic. *Bowler's thumb* causes a similar problem. It is a neuroma on the digital nerve of the thumb that develops because of chronic impingement between the metacarpals and a poorly fitting bowling ball grip.

Complex Regional Pain Syndrome Type I

Another cause of pain in the wrist and hand is a group of disorders known now as *complex regional pain syndrome*, formerly called *reflex sympathetic dystrophy*. It is mentioned in this section only for the sake of completeness and is described in detail in Chapter 20. The shoulder-hand syndrome, a similar type of symptom complex, is described in Chapter 58.

A relatively uncommon cause of hand and wrist pain, complex regional pain syndrome produces diffuse burning and aching pain and often is associated with vascular changes of the distal part of the limb. There is also a diffuse tenderness and mild to moderate swelling, shininess of the skin, and temperature lability (57,58). Reflex sympathetic dystrophy can be caused by minimal trauma to soft tissue or damage to a nerve in the hand and wrist. It sometimes follows iatrogenic complications or disease of viscera or the central nervous system. Unfortunately, because complex regional pain syndrome is often misdiagnosed and appropriate therapy is not carried out, progression of the disease is common.

Vibration Neuritis

In vibration neuritis, a chronic vibratory force on the hands produces pathologic changes in the small nerves of the fingers. Tools such as chain saws, vibrating sanders, and ultrasonic instruments can be the offending agents. Symptoms include pain and tingling in the fingers, sensitivity to cold, and vascular instability. Symptoms can mimic carpal tunnel syndrome. Electromyographic and nerve studies for carpal tunnel syndrome should be normal. Very detailed testing for sensitivity and specifically testing for vibratory thresholds at varying frequencies are diagnostic. Treatment is withdrawal from irritating mechanisms.

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CHAPTER 60

General Considerations of Pain in the Chest

John J. Bonica and Daniel O. Graney

The chest is among the most common sites of pain and suffering encountered in clinical practice. Chest pain can be caused by disease of the thoracic viscera or by disorders of muscles, bones, and other pain-sensitive structures of the chest wall. It can also be projected from disease of the spinal cord or spinal nerves or referred from structures outside of the chest, or it can be a combination of two or more of these conditions. It is important for the clinician to have a thorough knowledge of the functional anatomy and physiology of the thorax and related structures to interpret the history properly and to carry out a meaningful general physical, neurologic, and orthopedic examination, prerequisites for making an accurate diagnosis and developing and implementing the most effective therapeutic strategy.

This chapter, like other chapters that introduce the management of pain in various regions of the body, provides a concise discussion of these various considerations. The material is presented in three major sections: (a) Basic Considerations, including anatomy of the thorax and the muscles attached to it, a brief description of the thoracic spinal cord and thoracic spinal nerves, and a general description of the sympathetic and parasympathetic nerve supplies to the chest; (b) Innervation of the Thoracic Viscera; and (c) History and Examination. Additionally, a table is provided containing a summary of the characteristics of pain and other symptoms and signs in the chest that should help the clinician to make a differential diagnosis. Detailed information on pathophysiology as related to pain in the chest is given in subsequent chapters. Further discussions are found in relevant textbooks and reviews of anatomy and neuroanatomy (1,2,3,4,5,6,7,8 and 9).

BASIC CONSIDERATIONS

In this first section, we discuss the clinically relevant aspects of the anatomy of the thoracic spine, chest, and abdominal wall, including a brief description of vertebrae, joints, ligaments, and muscles attached to these structures. (The muscles of the posterior chest are discussed with those of the lumbosacral spine in Chapter 75.) This is followed by a brief description of the thoracic spinal cord, spinal nerves, and the structures they supply in the chest and abdominal wall; these are presented here because the course of thoracic spinal nerves and the structures they supply (the chest and abdominal wall) are similar.

Anatomy of the Thorax

Skeletal Structures

Figure 60-1 depicts the skeletal parts of the thorax or chest, which form an osseocartilaginous cage that protects the principal organs of respiration and circulation (1). The thoracic cage extends inferiorly over the upper part of the abdomen and covers a portion of certain abdominal viscera. Its conical shape is a result of the fact that its superior or cervical inlet is of a lesser diameter than its inferior abdominal part. In transverse section the thorax appears to be kidney shaped because of projection of the vertebral bodies into the cavity. The thoracic cage is formed by the ribs, with their costal cartilages attached anteriorly to the sternum (see Fig. 60-1A) and posteriorly to the thoracic vertebrae of the spinal column (see Fig. 60-1B).

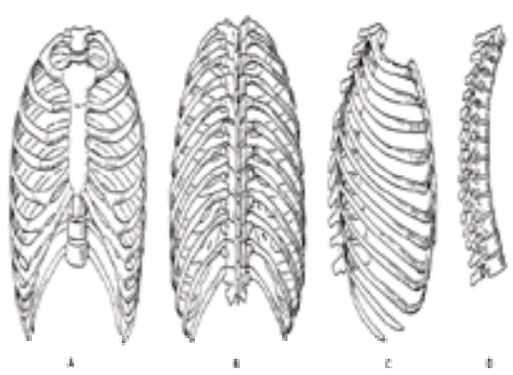

Figure 60-1. Anatomy of the thoracic cage. **A:** Anterior view. Note that all 12 of the ribs articulate with their respective thoracic vertebrae, but only the first seven attach directly to the sternum; the eighth, ninth, and tenth ribs attach to the cartilages of the seventh rib on each side, while the eleventh and twelfth pairs have no anterior articulation. **B:** Posterior view. Each rib articulates with its respective thoracic vertebra and, as the ribs encircle the trunk, they proceed in an inferolateral direction. **C:** Lateral view from the right side. Initially the ribs course in an anterolateral direction from the vertebral column and then proceed inferomedially to reach the costal cartilages and the sternum. **D:**View of the right side of the thoracic part of the vertebral column. (Modified from Clemente CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:148–150.)

The thorax is bounded posteriorly by the twelve thoracic vertebrae and the posterior parts of the 12 ribs, anteriorly by the sternum and the costal cartilages, and laterally by the ribs. These are separated from each other by the 11 intercostal spaces, within which are located the intercostal muscles and membranes, nerves, and vessels. The superior opening of the thorax, formed by the T-1 vertebra, the cranial margin of the sternum, and the first rib on each side, is broader from side to side than anteroposteriorly. The plane of the aperture slopes inferiorly from the spinal column down to the sternum, and its upper part lies 3 to 5 cm below the upper border of the body of the T-1 vertebra. The inferior opening, or thoracic outlet, is formed posteriorly by the 12 thoracic vertebrae, laterally by the eleventh and twelfth ribs, and ventrally by the cartilages of the seventh to tenth ribs, which slope on each side to form the infrasternal angle of the xiphoid process.

The thorax of female subjects differs from that of male subjects in the following respects: Its capacity is less; the sternum is shorter; the cranial margin of the sternum is on a level with the inferior part of the body of the T-3 vertebra, whereas in the male subject it is on a level with the inferior part of the body of the T-2 vertebra; and the upper ribs are more movable, permitting a greater expansion of the superior part of the thorax (1).

Thoracic Spine. The thoracic spine, composed of the 12 thoracic vertebrae, is concave anteriorly and articulates with the ribs, thus forming the supporting structure of the rib cage. Figure 60-2 depicts the anatomy and articulating surfaces of a typical thoracic vertebra, as well as its articulation with the head, neck, and proximal portion of the rib.

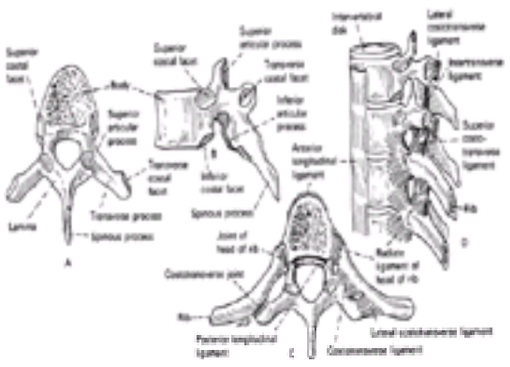

Figure 60-2. Anatomy and articulations of the thoracic vertebrae. **A:** Superior view. **B:** Lateral view. The articular facets and the posteroinferior direction of the spinous processes are shown. **C:** Superior view. The synovial cavities of the joint of the head of the rib and the costotransverse joint are on the left, and the various ligaments are on the right. **D:** Lateral view of four thoracic vertebrae depicting the ligaments of the costovertebral joints.

The thoracic vertebrae are intermediate in size between the cervical and lumbar vertebrae, providing a gradual transition from the small cervical vertebrae superiorly to the large lumbar vertebrae inferiorly. The body of a thoracic vertebra is larger posteriorly than anteriorly. The thoracic vertebrae are distinguished by the presence of costal facets on the side of the body for articulation of the heads of the ribs and by other articular facets in the transverse processes of the upper 10 thoracic vertebrae for articulation with the tubercles of the ribs. The T-1 vertebra has an entire articular facet for the head of the first rib and a demifacet for the cranial half of the head of the second rib on each side of the vertebral body. The T-2 to T-8 vertebrae have similar demifacets, the T-9 vertebra has only one demifacet above, and the T-10, T-11, and T-12 vertebrae have one entire facet.

The pedicles of the thoracic vertebrae are directed dorsally and slightly superiorly from the transverse process; the inferior vertebral notches are large and extend more superiorly than in any other region of the vertebral column, thus making the intervertebral foramina ample for the exit of the nerves. The laminae are broad, thick, and imbricated, with the one superiorly overlapping the next inferiorly like tiles on a roof. The spinous processes are long, triangular in coronal section, and directed obliquely inferiorly, and end in a tuberculated extremity. The spinous processes of the T-5 to the T-8 vertebrae are oblique and overlap to a greater degree than those of the upper and lower thoracic vertebrae.

Ribs. The ribs are flattened narrowed elastic arches of bone that form a large part of the thoracic skeleton. The first 7 of the 12 ribs are called *true* or *vertebrosternal* ribs; they connect dorsally with the vertebral column and ventrally with the sternum by means of costal cartilages. The remaining five pairs are *false* ribs and consist of two types; the eighth to tenth ribs have their cartilages attached to the cartilage of the rib above (vertebrochondral), while the eleventh and twelfth ribs are free at their anterior extremities and are therefore referred to as *floating* or *vertebral* ribs, because they do not attach to the sternum. Figure 60-3 depicts the anatomy of the typical central rib of the left side viewed from below and from the side, and shows the peculiar anatomy of the second and first ribs.

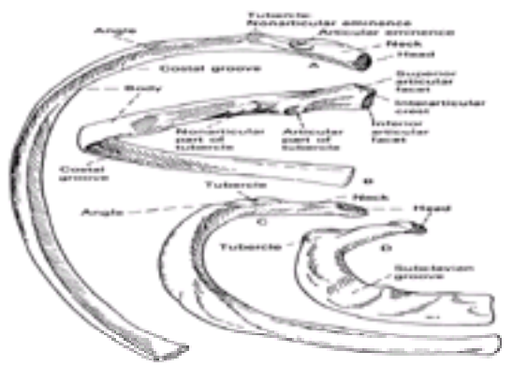

Figure 60-3. Anatomy of the ribs. **A:** Inferior aspect of a typical central rib from the left side. The principal parts of the bone include the head, neck, tubercle (which possesses an articular eminence and a nonarticular eminence), and curved body of shaft. The costal groove contains the intercostal vessels and nerves. **B:** Typical central rib from the left side, viewed from behind. The vertebral extremity at the end of the head of the rib contains a large inferior facet for the numerically corresponding vertebra and a smaller facet for the adjacent vertebra above; the interarticular crest attaches to the intervertebral disk between the two facets. **C:** Right second rib, viewed from above. **D:** Right first rib, viewed from above; the subclavian groove below the head of the large tubercle is occupied by the subclavian artery and brachial plexus and the more anterior groove by the subclavian vein. (Modified from Clemente CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:154–155.)

The *costal cartilages* are bars of hyaline cartilages that go along the ribs anteriorly and render the chest wall more elastic to accommodate, for example, the movements of respiration. The first seven pairs are connected to the sternum, the next three pairs articulate with the lower border of the cartilage of the preceding rib, and the last two pairs have pointed anterior extremities that end in the musculature of the abdominal wall.

Sternum. The sternum is an elongated flat bone that forms the middle portion of the anterior wall of the thorax and is composed of the manubrium, body, and xiphoid process. The upper portion of the manubrium articulates with the clavicle and the first and second ribs. The body articulates with the cartilage of the second to the seventh ribs, while the xiphoid process is a thin elongated structure that is cartilaginous in children but is more or less ossified proximally in adults (Fig. 60-4; see Fig. 60-1A).

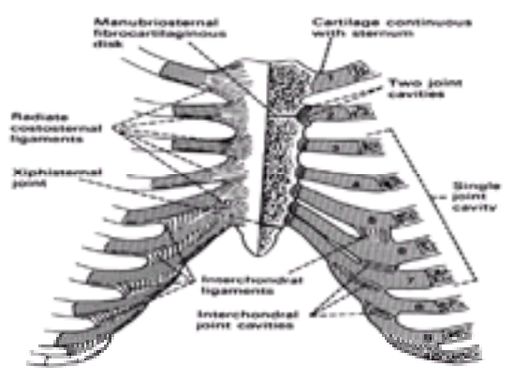

Figure 60-4. Anterior view of the sternum and costal cartilages showing the sternocostal and interchondral articulations. On the left side of the sternum the synovial cavities are exposed by coronal section of the sternum and cartilages. (Modified from Clemente CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:356.)

Joints and Ligaments

Joints and Ligaments of the Vertebral Column. The joints and ligaments of the thoracic portion of the vertebral column are similar to those discussed in Chapter 54 in relation to the cervical spine (1). These include the intervertebral disks and the anterior and posterior longitudinal ligaments (see Fig. 60-2C and Fig 60-2D). The intervertebral disks of the thoracic spine are nearly of uniform thickness, and the anterior concavity of this part of the column is almost entirely a result of the shape of the vertebral bodies; as mentioned previously, these are larger posteriorly than anteriorly. The intervertebral disks adhere to thin layers of hyaline cartilage that cover the superior and inferior surfaces of the vertebral bodies. Each disk is composed of an outer lamina of fibrous tissue called the *annulus fibrosis* and an inner core of a soft gelatinous and highly elastic substance called the *nucleus pulposus*.

The anterior longitudinal ligament, which extends from the occipital bone to the sacrum, is narrower but thicker in its passage over the anterior surface of the vertebral bodies than over the intervertebral disk. It consists of dense longitudinal fibers that adhere closely to the intervertebral disks and the prominent margins of the vertebrae but are not attached firmly to the middle parts of the body, where it is thick and fills the concavities of the anterior surfaces, thus giving the anterior aspect of the vertebral column a more even contour. This anterior aspect is composed of several layers of fibers that vary in length but are closely interlaced with each other. The most superficial fibers are the longest and extend across four or five vertebrae; a second subjacent set extends between two or three vertebrae; and a third set, the shortest and deepest, reaches from one vertebra to the next.

The posterior longitudinal ligament extends from the axis to the sacrum and passes over the dorsal surface of the bodies of the vertebrae and the intervertebral disks. Superiorly, it is continuous with the tectorial membrane. Inferiorly, it is narrow and thick over the center of the bodies, from which it is separated by the basivertebral veins, and broadens over the intervertebral disks. It is composed of longitudinal fibers that are denser and more compact than those of the anterior ligaments.

Joints between the Vertebral Arches. Joints between the articular processes of the thoracic (and other) vertebrae are plain or gliding joints enveloped by capsules lined by synovial membrane (see Fig. 60-2B and Fig. 60-2C). The articular capsules are thin and loose and are attached to the margins of the articular processes of adjacent vertebrae. The ligamenta flava connect the laminae of adjacent vertebrae. Each ligamentum flavum consists of yellow elastic tissue attached to the anterior and inferior surfaces of the lamina above and to the posterior surface of the lamina below. The fibers of the ligamenta flava are almost perpendicular to the laminae to which they are attached. They are thin in the cervical region, thicker in the thoracic region, and thickest in the lumbar region. Their marked elasticity permits separation of the laminae during flexion of the vertebral column and also helps to preserve the upright posture (Fig. 60-5).

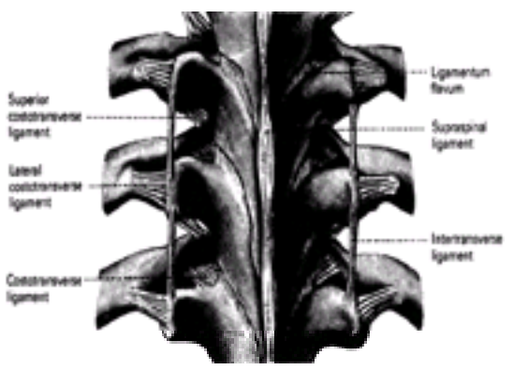

Figure 60-5. Posterior aspect of part of the thoracic spinal column showing the supraspinal, intertransverse, and costotransverse ligaments and the ligamentum flavum. (From SOBOTTA. *Atlas der anatomie des menschen*, 20th ed. Munich: Urban & Schwarzenberg, 1993.)

The interspinous ligaments are thin and membranous and interconnect adjoining spinous processes, extending from the root to the apex of each process. The supraspinous ligament is a strong fibrous cord that connects together the apices of the spinous processes from the C-7 vertebra to the sacrum (see Fig. 60-5). Fibrocartilage develops into ligament at its point of attachment to the tips of the spinous process and, in older persons, this can extend into the interspinous portions of the ligament. The intertransverse ligaments are interposed between the transverse processes, which in the thoracic region are rounded cords that are intimately connected with the deeper muscles of the back.

Movement. Normally, the movements permitted in the vertebral column include flexion, extension, lateral flexion, circumduction, and rotation. In the thoracic region, however, notably in its upper part, all movements are limited to minimize interference with respiration (1). The almost complete absence of the upward inclination of the superior articular surfaces prohibits any marked flexion, whereas extension is checked by the contact of the inferior articular margins with the laminae and by the contact of the spinous processes with one another. The mechanism of the inferior end of the cervical spine limits extension and also serves to limit flexion of the thoracic region when the neck is extended. Rotation is free in the thoracic region; the position of the articular processes allows rotation around a vertical axis that passes through the bodies of the midthoracic vertebrae but is anterior to the vertebral bodies of the upper and lower thoracic vertebrae. The direction of the articular facets would allow free lateral flexion, but this movement is considerably limited by the resistance of the ribs and sternum.

Costovertebral Joints. The articulation of the ribs with the vertebral column can be divided into two sets, one connecting the heads of the ribs with the bodies of the vertebrae and the other uniting the necks and tubercles of the ribs with the transverse processes (1).

Articulation of the Heads of the Ribs. A series of plane or gliding joints is formed by the articulation of the heads of the typical ribs with the facets on the contiguous margin of the bodies of the thoracic vertebrae and with the intervertebral disks between them (see Fig. 60-2C and Fig. 60-2D). Although the heads of the second to ninth ribs each articulate by means of two facets, the articulation is considered to be a single joint because only one articular capsule is present, even with two synovial sacs. Figure 60-2C depicts two parts of this joint, the articular capsule and the radiate ligament. The radiate ligament connects the anterior part of the head of each rib with the sides of the bodies of two adjacent vertebrae and the intervertebral disks between them. The intraarticular ligament, situated in the interior of the joint, consists of a short flat band of fibers attached by one extremity to the crest separating the two articular facets on the head of the rib and by the other to the intervertebral disk. It divides the joint into two cavities, each of which is lined by a synovial membrane.

Costotransverse Joints. The articular surface on the tubercle of the upper ten ribs forms a plane or gliding joint with the articular facet on the adjacent transverse process of the corresponding vertebra (see Fig. 60-2C and Fig. 60-2D). This articulation is missing in the eleventh and twelfth ribs. These joints include an articular capsule, which is a thin fibrous membrane attached to the circumference of the articular surface.

The superior costotransverse ligament is attached to the sharp crest of the superior border of the neck of the rib and passes obliquely upward and laterally to the lower border of the neck of the transverse process immediately above. It is composed of two layers; the anterior layer blends laterally with the internal intercostal membrane and is crossed by the intercostal nerves and vessels, while the posterior layer blends laterally with the external intercostal muscle. Its medial border is thickened and free and bounds an aperture that transmits the posterior division of the spinal nerves and posterior branches of the intercostal vessels.

The costotransverse ligament, sometimes called the ligament of the neck of the rib, consists of short strong fibers that connect the rough surfaces on the back of the neck of the rib with the anterior surface of the adjacent transverse process.

The lateral costotransverse ligament is a short, thick, and strong fasciculus. It passes obliquely from the apex of the transverse process of the vertebra to the rough and nonarticular portion of the tubercle of the corresponding rib.

Movement at the Costotransverse Joints. The heads of the ribs are so closely connected to the bodies of the vertebrae by the radiate and intraarticular ligaments that only slight gliding movements of the articular surfaces on one another can take place (1). Similarly, the strong ligaments binding the necks and tubercles of the ribs to the transverse process limit the movements of the costotransverse joints to a slight gliding motion. The joints at the head of the ribs and the costotransverse joints move simultaneously in the same direction, with the total effect being that the neck of the rib moves as if on a single joint. The chief movement of the necks of the upper six ribs is one of rotation around their own long axes, with only slight upward and downward movements. Thus, backward rotation of the neck of the rib results in lowering of the anterior end of the rib, whereas forward rotation of the neck of the rib causes elevation of the anterior end. The necks of the seventh to the tenth ribs can move either upward, backward, and medially, or downward, forward, and laterally, thereby altering the shape of the rib cage with only a slight rotation

accompanying these movements (1).

Articulation with the Sternum

Sternocostal Joints. The medial ends of the costal cartilages fit into the slight concavities along the lateral border of the sternum to form the sternocostal joints, which have an articular capsule and are strengthened by the radiate sternocostal ligaments, the intraarticular sternocostal ligaments, and the costal xiphoid ligaments (see Fig. 60-4). These joints are supplied by the anterior perforating branches of the intercostal nerves. Sternocostal joints permit only a slight gliding movement.

Interchondral and Costochondral Joints. The contiguous borders between the sixth and seventh, seventh and eighth, eighth and ninth, and sometimes even those of the ninth and tenth costal cartilages, articulate with each other by small smooth oblong facets. Each joint is enclosed in a thin articular capsule lined by synovial membrane and strengthened laterally and medially by the fibrous interchondral ligaments (see Fig. 60-4).

The lateral end of each costal cartilage is received into a slight depression of the sternal end of the rib. The cartilage and bone are bound together by the periosteum of the bone, which becomes continuous with the perichondrium of the cartilage.

Articulation of the Sternum

Manubriosternal and Xiphisternal Joints. The interior surface of the manubrium is united with the superior surface of the body of the sternum by a fibrocartilaginous disk, which is shaped to conform to the hyaline cartilage-covered bony surfaces. The lateral margins of this synthesis are contiguous with the second sternocostal joints. At this joint site, the manubrium and sternal body usually present a slight anteriorly projecting ridge called the *sternal angle*, which is palpable beneath the skin and serves as an important surface landmark for clinicians. The articulation between the xiphoid process and the inferior border of the sternal body is cartilaginous but, by 30 years of age, this joint has usually become ossified. The joint is secured laterally by radiating fibers of the sternocostal ligaments. Generally, the seventh costal cartilage articulates with the sternum at the lateral margin of the xiphisternal junction (see Fig. 60-4).

Muscles of the Thorax

The muscles considered in this section are primarily those attached to the ribs and concerned with movements, especially in relation to respiration. In addition, brief mention is made of the deep muscles of the back attached to the thoracic spine and ribs. The anterior muscles of the chest, including the pectoralis major, pectoralis minor, subclavius, and serratus anterior, were considered in the preceding section in connection with the shoulder.

Muscles of Respiration. The most important muscles that influence movement of the ribs and are concerned with respiration are listed in Table 8-2, which also presents their primary action and nerve supply. Only a brief description of these muscles is given here, particularly of the intercostal muscles, to provide a background for discussion of the position of the intercostal nerves. Before doing so, however, it is necessary to mention the fascia that covers the thoracic cage proper, composed of ribs and the intercostal muscles. The cage is covered internally and externally by thin layers of deep fascia. The outer layer essentially covers the external intercostal muscles, whereas the inner layer, consisting of loose areolar tissue called the *endothoracic fascia*, lines the internal aspect of the thoracic cage. It covers the inner surface of the intercostal muscles and intervening ribs, along with the subcostal and transversus thoracis muscles and the diaphragm. It lies between the parietal pleura and the thoracic cage, which in the absence of adhesions can therefore be easily separated. Posteriorly, the endothoracic fascia continues over the bodies of the vertebrae and intervertebral disks. In this mediastinal region, certain structures such as the azygos and hemiazygos veins, the thoracic duct, the sympathetic chain, and the splanchnic nerves are partially or completely surrounded by the fascia. Superiorly, the endothoracic fascia extends over the apices of the lung where, somewhat thickened, it forms the suprapleural membrane, or Sibson's fascia. Inferiorly, it becomes thin over the superior surface of the diaphragm but is continuous with the internal investing fascia of the abdominal cavity, dorsal to the diaphragm at the lumbosacral arches and through the aortic hiatus (1).

Intercostal Muscles. The intercostal muscles are composed of three thin layers of muscular and tendinous fibers that occupy each of the intercostal spaces. The external intercostal muscles, 11 on each side, extend from the tubercles of the ribs posteriorly to the cartilages of the ribs anteriorly, where they each end as a thin fibrous sheet, the external intercostal membrane, which continues forward to the sternum (1). Each external intercostal muscle arises from the lower border of the rib above and is inserted into the upper border of the rib below. In the lowest two spaces, the muscles extend to the ends of the cartilages, while in the uppermost two or three spaces they do not quite reach the ends of the ribs. These muscles are thicker than the internal intercostals; the fibers are directed obliquely inferolaterally on the posterior part of the thorax and inferolaterally and somewhat ventrally on the anterior aspect of the thorax (Fig. 60-6).

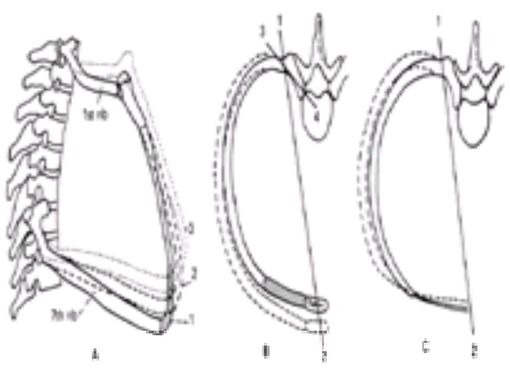

Figure 60-6. **A:** Superior view of the intercostal space showing the various intercostal muscles and a thoracic spinal nerve dividing into posterior and anterior primary divisions, the latter becoming the intercostal nerve. **B:** Anterior view of the chest showing the relation of the intercostal nerves and their branches and the relation of the intercostal nerves to the sympathetic chain. **C:** Cut section of two adjacent ribs and the intercostal muscles showing the intercostal vessels and nerves. Note the direction of the fibers of the muscles. See text for details. (Modified from Clemente CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:11.)

The internal intercostal muscles, also 11 on each side, begin anteriorly at the sternum in the interspaces between the cartilage of two ribs and at the anterior extremities of the cartilages of the false ribs, and extend posteriorly as far as the angles of the ribs, where they continue to the vertebral column by thin aponeuroses, the internal intercostal membranes. Each muscle arises from the ridge on the inner surface of the rib above as well as from the corresponding costal cartilage, and inserts into the upper border of the rib below. These fibers are directed obliquely but pass in a direction perpendicular to that of the external intercostal muscles.

The innermost (intimi) intercostal muscles are frequently considered to be the deepest parts of the internal intercostal muscles. They are located deep to the intercostal nerves and vessels interposed between these structures and the parietal pleura (see Fig. 60-6). They extend between the costal groove of the rib above to the inner lip of the upper margin of the rib below. The fibers generally course in the same direction as those of the internal intercostal muscles. The intimi intercostal muscles are not well developed and might be absent in the upper four or five interspaces.

The subcostal muscles consist of oblique muscular and aponeurotic fasciculi located on the inner surface of the posterior part of the chest. Usually they are well developed only in the lower part of the thorax (1). Each arises from the inner surface of one rib posteriorly near its angle and is inserted into the inner surface of the second or third rib below. Their fibers run in the same direction as those of the intimi intercostal muscles and, similarly, separate the intercostal nerves and vessels from the pleura (1) (see Fig. 60-6).

The sternocostalis, or transversus thoracis muscles, are a thin plane of muscular and tendinous fibers situated on the inner surface of the anterior chest wall. They are situated deep to the intercostal nerves and vessels and deep to the internal thoracic artery. They arise on each side from the inferior third of the inner surfaces of the body of the sternum, xiphoid process, and second to sixth costal cartilages. The fibers fan out from the back of the body of the sternum and xiphoid process to the costal cartilages of the second to sixth ribs; the upper fibers are ascending, while the lower fibers are horizontal and in continuity with the transversus abdominis muscle.

Levatores Costarum. The levatores costarum, 12 on each side, are located in the posterior surface of the thoracic cage. They consist of tendinous fleshy bundles that arise from the ends of the transverse process of the C-7 and T-1 to T-11 vertebrae. The muscles pass obliquely inferolaterally like the fibers of the external intercostals in this posterior region. Each is inserted into the outer surface of the rib immediately below the vertebra from which it takes origin, between the tubercle and the angle. They elevate the ribs and bend the vertebral column laterally, rotating it slightly toward the opposite side. The intercostal nerves also supply these muscles.

Action. All the intercostal muscles and levatores costarum are supplied by the intercostal nerves, which constitute the anterior division of the thoracic spinal nerves (see following discussion). The external intercostal muscles raise the ribs during inspiration but can also be active during expiration (1,2 and 3). The action of the internal intercostal muscles varies; the anterior portion of the upper four or five intercostal muscles that interconnect the costal cartilages elevates the ribs during inspiration, whereas the more lateral and posterior of these muscles depress the ribs during expiration. The intimi intercostal muscles also depress the ribs, while the transversus thoracis muscles draw the ribs downward (2,3). The levatores costarum elevate the ribs and then the vertebral column laterally and rotate it slightly to the opposite side.

Diaphragm. The diaphragm is a dome-shaped musculofibrous septum that separates the thoracic cavity from the abdominal cavity. Its convex upper surface forms the floor of the thorax, while its concave inferior surface forms the roof of the abdomen. Its peripheral part consists of three groups of muscular fibers that originate from the circumference of the thoracic outlet and converge to be inserted into a central tendon. The sternal part of the muscular fibers arises from two fleshy slips from the dorsum of the xiphoid process; the costal part arises from the inner surface of the cartilages and from adjacent portions of the last six ribs on each side, interdigitating with the transversus abdominis muscle, and the lumbar part arises from two aponeurotic arches on each side (the medial and lateral arcuate ligaments) and from the lumbar vertebrae by two pillars, or crura. The most central portion of the diaphragm is innervated by the phrenic nerves, which arise from the two cervical plexuses (C-3 to C-5), while its peripheral muscular fibers are supplied by the sixth to the eleventh or twelfth intercostal nerves.

Biomechanics of the Thorax

Through the action of the various muscles mentioned previously, and of others, the thoracic cage either increases or decreases in size. Each rib possesses its own range of movements but, in combination, the ribs allow respiratory excursions of the thorax. Each rib can be regarded as a lever, the fulcrum of which is situated immediately lateral to the costotransverse joint so that the neck of the rib is depressed when the shaft of the rib is elevated, and vice versa (1). Because the arms of the lever are of different lengths, a slight movement at the vertebral end of the rib is greatly magnified at the anterior extremity.

The anterior ends of the rib lie at a more inferior plane than the posterior ends; thus, when the shaft of the rib is elevated, the anterior extremity is also thrust forward. Because the middle of the shaft of the rib lies at a plane inferior to one passing through the two extremities of the rib, the shaft is elevated at the same time as it is thrust forward from the median plane of the thorax (Fig. 60-7A). Moreover, each rib forms the segment of a curve that is greater than that of the rib immediately above it, and therefore the elevation of the rib also increases the transverse diameter of the thorax.

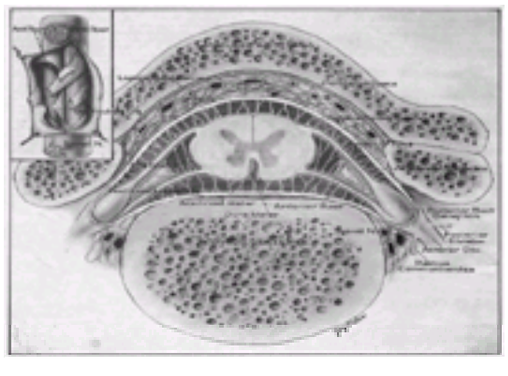

Figure 60-7. Schematic depiction of the biomechanics of the thorax during respiration. **A:** Lateral view of the first and seventh ribs showing the movements of the sternum and ribs in ordinary expiration (1), quiet inspiration (2), and deep inspiration (3). **B:** Axes of movement (1 to 2 and 3 to 4) of the vertebrosternal rib. **C:** Axis of the movement (1 to 2) of the vertebrochondral rib. See text for more details. *Dotted lines,* position of rib during inspiration. (Modified from Clemente CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:365.)

The first pair of ribs moves with the manubrium as a single piece, with the anterior portion being elevated by rotary movements of the necks of the ribs near the vertebral extremities. During normal quiet respiration the movement is virtually nonexistent. Movement of the second pair of ribs is also slight in normal respiration because their anterior extremities are fixed to the manubrium and are therefore prevented from moving upward. Elevation of the third to the sixth ribs raises the thrust of their anterior extremities forward, with the greater part of the movement being affected by rotation of the rib neck (Fig. 60-7B).

The vertebrochondral ribs (eighth to tenth), along with the seventh rib, have movements that assist in enlarging the thorax for respiratory purposes but that also increase the upper abdominal space for viscera displaced by the action of the diaphragm (Fig. 60-7C). The costal cartilages of the sixth to tenth ribs articulate with one another so that each pushes up the costal cartilage above, with the final thrust being directed to pushing the lower end of the body of the sternum forward and upward. Slight rotation of the rib neck permits only a limited elevation of the anterior extremity. Elevation of the rib shaft is accompanied by an outward and backward movement that results in a considerable increase in the transverse diameter and a decrease in the median anteroposterior diameter of the lower chest and upper abdomen.

Even more important than the action of the ribs, and of the muscles that control their movements, is the action of the diaphragm. Acting from their attachment on the ribs and lumbar vertebrae, the muscle fibers of the diaphragm draw the central tendon downward and forward during inspiration. This tends both to increase the volume and decrease the pressure within the thoracic cavity and to decrease the volume and increase the pressure within the abdominal cavity.

All these structures take part in the respiratory cycle of inspiration and expiration, which is the result of the increase and decrease in the capacity of the thoracic cavity. Inspiration, the increase in the volume of the cavity, results from the muscular action of the descent of the diaphragm, which increases the vertical dimension of the thorax, and from the action of the muscles in the ribs, sternum, and vertebral column, which increases the transverse and anteroposterior dimensions of the thorax. Expiration, associated with a decrease in the volume of the thoracic cavity, is primarily a passive process because of the elastic recoil of the thoracic wall and of the tissues of the lungs and bronchi. Thoracic volume can also decrease, however, as a result of the action of the abdominal muscles, which force the diaphragm upward by increasing the abdominal pressure, and by the action of certain muscles of the ribs and vertebral column, which actively contract the thoracic wall.

Neurologic Considerations

The canal of the thoracic portion of the spinal column in the adult contains more than two-thirds of the spinal cord. Although variations occur in most individuals, this portion of the canal contains the second thoracic to first sacral segments inclusively. As discussed in Chapter 54, the spinal cord only partially fills the spinal canal, its diameter being approximately half the diameter of the latter. Figure 60-8 shows the relationship of the spinal cord to the vertebral canal and depicts the thoracic spine, meninges, and attachment of spinal nerves to the spinal cord. Because this was discussed in previous chapters, the remainder of this section describes the anatomy of the thoracic spinal nerves and the phrenic nerves because they supply motor fibers to the diaphragm and sensory fibers of the pericardium and other structures in the chest and abdomen.

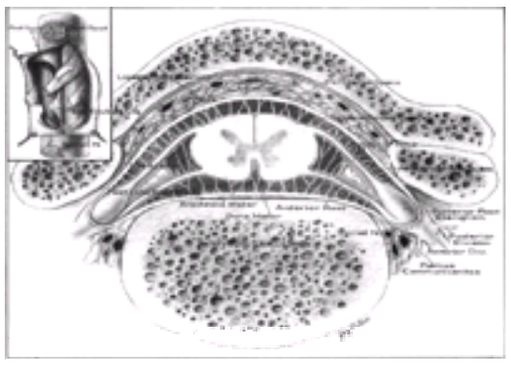

Figure 60-8. Cross-section of the thoracic spine showing detailed anatomy of the spinal cord and its meninges and the subarachnoid and epidural spaces. The section was taken between dentate ligaments (not shown). Inset: Attachment and coverings of the roots of spinal nerves.

Thoracic Spinal Nerves

The thoracic nerves consist of 12 pairs of somatic spinal nerves derived from homologous spinal cord segments located between the seventh cervical and ninth thoracic vertebrae (see Fig. 8-2). Generally, they retain their segmental relationship throughout their distribution by coursing below the corresponding rib to supply segments of muscles, skin, and other somatic structures of the thorax and abdomen. They also supply the parietal pleura and peritoneum.

Soon after they are formed within the spinal canal by the union of the anterior and posterior roots, the thoracic spinal nerves emerge below the corresponding vertebrae through the intervertebral foramen, and each divides into a posterior primary division and an anterior primary division (see Fig. 60-6). Just before dividing, each of these nerves gives off a recurrent branch that returns through the foramen to supply the corresponding vertebra and its ligaments and a segment of the meninges covering the cord. Also before dividing, the formed thoracic spinal nerves are connected to the thoracic sympathetic chain by white rami communicantes, which contain myelinated preganglionic fibers and visceral afferents, and by gray rami communicantes, which contain unmyelinated postganglionic fibers.

The smaller posterior primary divisions diverge from their anterior counterparts and run posteriorly to supply the muscles and skin of the back through medial and lateral branches. In the upper six thoracic (and all cervical) segments the medial branches supply chiefly the skin and subcutaneous tissue, with the lateral branches almost entirely supplying muscles; in the lower thoracic (and lumbar and sacral) segments the reverse is true. The posterior division of each thoracic spinal nerve, often involved in painful conditions of the vertebrae and muscles, migrates within muscles inferiorly for a progressively greater distance before emerging from the muscle to supply the skin and subcutaneous tissue over the spinous process and the paravertebral region (see Chapter 8 and Fig. 8-9). Thus, the cutaneous branch of the posterior division of the T-6 nerve supplies the skin of the T-9 to T-10 dermatomes (posteriorly), the T-10 nerve supplies the skin of the L-2 to L-3 region, and the T-12 nerve supplies that of the L-5 to S-1 region (see Table 8-1).

Each of the larger anterior primary divisions, after leaving the posterior primary division, proceeds laterally below the corresponding rib to become distributed to the parietes of the thorax and abdomen. The first 11 are situated between adjacent ribs and are therefore named the *intercostal nerves*, while the twelfth nerve is called the *subcostal nerve*. The intercostal nerves are distributed chiefly to the parietes of the thorax and abdomen. They differ from other spinal nerves in that each pursues an independent course and, except for the first intercostal nerve, does not enter into the formation of plexuses.

The anterior primary division of the first thoracic nerve, after leaving the posterior primary division, divides into a larger superior branch and a smaller inferior branch. The superior branch runs in a superior and lateral direction across the neck of the first rib, leaves the thoracic cavity, and enters the interval between the anterior and middle scaleni muscles, where it joins the anterior primary division of the eighth cervical nerve to form the lower trunk of the brachial plexus. The inferior branch, which can be considered as the true first intercostal nerve, runs within the first intercostal space in the same fashion as other typical thoracic intercostal nerves. Usually, it does not give off a lateral cutaneous branch, but sends a small branch to the intercostobrachial nerve.

Thoracic Intercostal Nerves. The anterior primary divisions of the second through sixth thoracic nerves are often called the *thoracic intercostal nerves*, because they supply the parietes of the chest. All these have a similar course and distribution and are therefore discussed as a group. After emerging through the intervertebral foramina they proceed laterally, each becoming situated for a short distance midway between the neck of the rib above and the neck of the rib below, lying between the pleura and the internal (posterior) intercostal membrane. Approximately 3 cm lateral to the foramina they pierce the intercostal membrane and run obliquely across the interspace toward the angle of the rib above to enter the costal groove, where they come to lie below the intercostal vein and artery and between the innermost (intimi) intercostal muscles and the internal intercostal muscles (see Fig. 60-6).

They continue their distal course between the two muscles as far as the junction between the ribs and costal cartilages, where they enter the interval between pleura and muscle. Proceeding within this interval they pass anteriorly to the internal thoracic artery and the transverse thoracic muscle to within 1 to 2 cm of the lateral border of the sternum, where they pierce the internal intercostal muscle, the anterior intercostal membrane, and the pectoralis major to become the anterior cutaneous branches. Each of these branches supplies a segment of skin over the anterior chest and breast and sends filaments that overlap 2 cm beyond the midline to supply the skin of the opposite side. The anterior branch of the first intercostal is often absent, and that of the second frequently communicates with the medial supraclavicular nerves of the cervical plexus. The latter nerves supply the skin over the first, second, and often the third thoracic segments.

Collateral and Lateral Cutaneous Branches. At or near the neck of the rib, each intercostal nerve gives off a collateral branch and a lateral cutaneous branch (Fig. 60-9; see Fig. 60-6). The collateral branch runs along the lower border of the intercostal space and ends anteriorly as a separate cutaneous nerve or by rejoining the main nerve to supply the skin and other structures in the anterior chest.

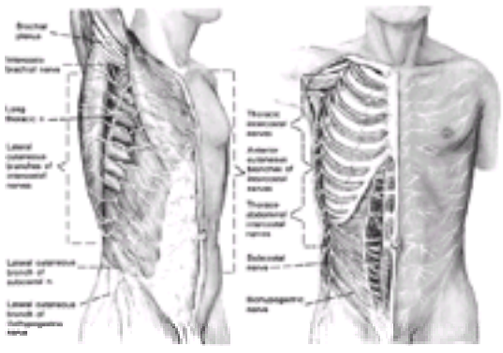

Figure 60-9. Distribution of the intercostal nerves. **A:** Anterolateral view of the lateral cutaneous branches of the intercostal nerves emerging from the muscles and deep fascia and dividing into anterior and posterior subdivisions. Note especially the distribution of the lateral cutaneous branch of the twelfth thoracic nerve, which supplies the anterior part of the gluteal region. The anterior cutaneous branches are also shown. **B:** Anterior view of the chest with the muscles removed on the right side to depict the location and distribution of the intercostal nerves. The anterior parts of the intercostal nerves enter the rectus abdominis muscle to provide motor branches to the muscle and then pass anteriorly through the muscle and its fascia to supply the cutaneous structures of the middle part of the abdominal wall.

The lateral cutaneous branch accompanies the main intercostal nerve as far as the midaxillary line before piercing the internal intercostal muscle and then runs obliquely through that muscle, the external intercostal muscle, and the serratus anterior muscle to reach the subcutaneous tissue, where it divides into anterior and posterior subdivisions. The anterior subdivisions run anteromedially to supply the skin of the lateral and anterior parts of the chest and breast; those of the fifth and sixth nerves also supply the superior digitations of the obliquus externus abdominis (see Fig. 60-9). The posterior subdivisions supply the skin over the posterolateral

and posterior parts of the chest that overlie the latissimus dorsi muscle and the scapular region.

The lateral cutaneous branch of the second intercostal nerve, the intercostobrachial nerve, does not divide; it crosses the axilla to reach the medial side of the arm, where it pierces the deep fascia, communicates with branches of the medial and posterior brachial cutaneous nerves, and then proceeds to supply the skin of the upper half of the medial and posterior parts of the arm. The anterior subdivision of the lateral cutaneous branch of the third intercostal nerve often gives off a large filament that joins the intercostobrachial nerve to supply the axilla and upper medial aspect of the arm. Injury or sacrifice of the intercostobrachial nerve during axillary surgery results in hypesthesia of the skin on the medial surface of the arm.

Muscular Branch. The upper thoracic nerves give off numerous muscular branches to the intercostals, the subcostals, the levatores costarum, the serratus posterior superior, and the transversus thoracis muscles. At the anterior part of the thorax some of these muscular branches cross the costal cartilages from one intercostal space to another (1).

Thoracoabdominal Intercostal Nerves

The anterior primary divisions of the seventh to eleventh nerves, often called the *thoracoabdominal intercostal nerves*, have the same course as those already described as far as the anterior end of the intercostal space. Here they run anteromedially to pass behind (posterior to) the costal cartilages and to enter the interval between the transversus abdominis and internal oblique muscles. They run medially within this interval as far as the semilunar line, where they perforate the posterior sheath of the rectus abdominis muscle near its lateral margin. They then follow a medial course within the muscle, to which they give numerous filaments, and then abruptly turn anteriorly, piercing the anterior sheath of the rectus abdominis muscle to become the anterior cutaneous branches.

The anterior cutaneous branch of the sixth intercostal nerve supplies the skin over the xiphoid process, those of the eighth and ninth supply the skin between the xiphoid process and umbilicus, that of the tenth supplies the skin around the umbilicus, and that of the eleventh supplies the skin just below the umbilicus.

The lateral cutaneous branches of these lower intercostals have similar subdivisions and distribution as the upper intercostals except that the anterior subdivisions supply the skin of the abdominal wall as far as the lateral margin of the rectus abdominis (linea semilunaris), while the posterior subdivisions supply the skin over the posterior part of the back as far as 4 to 5 cm from the midline (see Fig. 60-9).

Muscular Branches. The thoracoabdominal intercostals give off muscular branches that supply the corresponding intercostals, the transversus abdominis, the external and internal oblique and rectus abdominis muscles, and the peripheral part of the diaphragm. The latter three also supply the serratus posterior inferior muscles.

Twelfth Thoracic Nerve. The anterior primary division of the twelfth thoracic nerve, the subcostal nerve, is much larger than the others. After emerging from its intervertebral foramen it gives off a branch that joins the first lumbar nerve and then passes laterally under the lateral lumbocostal arch in front of the quadratus lumborum to reach the transversus abdominis muscle, which it perforates to enter the interval between this and the internal oblique muscle. After this, its course and distribution are the same as those of the other lower intercostals, except that after perforating the muscles its lateral cutaneous branch does not divide but descends over the iliac crest to supply the skin of the anterior portion of the gluteal region as far as the greater trochanter. Its anterior cutaneous branch supplies a segment of skin 3 to 4 cm above the pubis.

Phrenic Nerves

The phrenic nerves, generally considered to be the motor nerves of the diaphragm, also contain many sensory and sympathetic fibers. Each nerve is formed by a large root from the anterior primary division of the C-4 nerve, but is also augmented by fibers from the anterior division of the C-3 and C-5 nerves (Fig. 60-10). Each phrenic nerve receives gray rami communicantes from the superior and middle cervical sympathetic ganglia, and often from the vertebral ganglion and ansa subclavia. The three roots unite at the superolateral border of the anterior scalenus muscle. The nerve then passes downward on the anterior surface of that muscle, gradually crossing from its lateral to its medial side. It descends under cover of the sternocleidomastoid muscle and is crossed by the anterior belly of the omohyoid muscle and by the transverse cervical and suprascapular vessels. The nerve continues with the scalenus anterior between the subclavian vein and artery, and as it enters the thorax it crosses the origin of the internal thoracic artery and is joined by the pericardiophrenic branch of this artery. It then passes downward over the cupula of the pleura, and anterior to the root of the lung, and along the lateral aspect of the pericardium between it and the mediastinal pleura until it reaches the diaphragm, where it divides into its terminal branches.

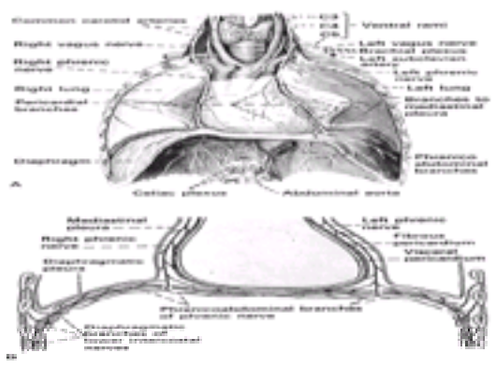

Figure 60-10. Anatomy of the phrenic nerves. **A:** Anterior view of the chest with the lungs reflected to show the origin, course, and distribution of both phrenic nerves. **B:** Schematic depiction of the distribution of the motor and sensory fibers of the phrenic nerves. The sensory fibers contribute to the sensory innervation of the pericardium, the central portion of the superior and inferior surface of the diaphragm, and send branches to the inferior phrenic plexus (a subsidiary of the celiac plexus), through which the sensory nerves of the phrenic nerves supply a number of upper abdominal viscera. (Modified from Netter FH. *The CIBA collection of medical illustrations*. Nervous system. Part I, Anatomy and physiology. West Caldwell, NJ: CIBA Pharmaceutical, 1983:114.)

The right phrenic nerve is situated more deeply, is shorter, and runs more vertically downward than the left nerve. In the upper part of the thorax it is lateral to the right brachiocephalic vein and the superior vena cava. The left phrenic nerve is longer than the right because of the inclination of the heart toward the left and because of the more inferior position of the diaphragm on this side (see Fig. 60-10). At the thoracic inlet the left nerve passes anterior to the subclavian artery behind the termination of the thoracic duct and proceeds downward between the left subclavian and left common carotid arteries. As it crosses the left side of the arch of the aorta it is lateral to the vagus nerve. It continues downward anterior to the root of the left lung and between the mediastinal pleura and fibrous pericardium covering the left surface of the heart to reach the diaphragm.

While passing through the thorax, both phrenic nerves supply nerve filaments to the fibrous pericardium, to the costal and mediastinal pleura over the apex of the lung, to the mediastinal pleura along its length, and to the central region of the diaphragmatic pleura. As previously mentioned, the sensory nerves to the margin of the diaphragm and to the corresponding areas of the overlying pleura and peritoneum are provided by lower intercostal nerves. The left phrenic nerve often sends a twig to the left pulmonary plexus and the right nerve supplies filaments to the inferior vena cava, with both nerves communicating with the greater splanchnic nerves.

The right phrenic nerve pierces the central tendon of the diaphragm through or near the orifice of the inferior vena cava, while the left nerve penetrates the diaphragm close to the anterior edge of its central tendon just lateral to the cardiac apex. Each nerve divides into three diverging phrenicoabdominal branches below the diaphragm. These supply the diaphragm from its inferior surface and also supply sensory fibers to most of the peritoneum covering the diaphragm except for marginal areas, which receive their nerve supply from the lower intercostal nerves. Sensory fibers also supply the coronary and falciform ligaments of the liver. On the right side a branch near the inferior vena cava communicates with the inferior phrenic plexus, a subsidiary of the celiac plexus, which accompanies the inferior phrenic arteries. A small phrenic ganglion is usually found at the point at which the filaments from the phrenic nerve join the phrenic plexus. Filaments from the inferior phrenic plexuses pass through the gastroesophageal junction, the cardiac end of the stomach, the porta hepatis, and the adrenal (suprarenal) plexuses.

Thoracic Sympathetic Nerves

The thoracic portion of the sympathetic trunk consists of a series of paravertebral ganglia situated on each side of the thoracic vertebral column. Although it is usually stated that one ganglion is found on each side of each vertebra, with 12 ganglia in each of the two trunks, this occurs only rarely. In most cases, the first ganglion fuses with the inferior cervical ganglion to form the stellate ganglion. According to Hovelacque (4), the second thoracic can also take part occasionally in the formation of the stellate ganglion. In addition, fusion of two lower thoracic ganglia or of the twelfth thoracic and first lumbar ganglia can occur, so that the number is reduced further. In most instances, therefore, ten, and not infrequently 11, ganglia, can be found in each of the thoracic sympathetic trunks (Fig. 60-11).

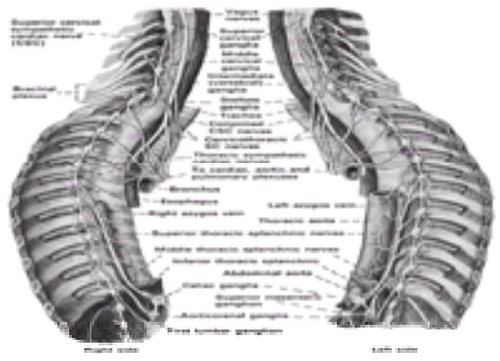

Figure 60-11. The cervical, thoracic, and upper lumbar sympathetic trunks and their branches. Note their relation to the vertebrae and ribs at various levels. (SC, sympathetic cardiac.)

These ganglia vary greatly in size and shape. In most cases they are triangular or quadrangular and are 8 mm long and 3 mm wide. The first and second ganglia are the largest and the twelfth is next in size, whereas in the midportion of the trunk the ganglia can be so small as to be almost indistinguishable from the interganglionic cord.

As they emerge from the intervertebral foramina the spinal nerves pass posterior to the interganglionic cord. The pleura is immediately in front of and in close relation to the ganglia, separated from them by the thin endothoracic fascia.

Hovelacque (4) described the branches of the thoracic ganglia as internal and external, although currently they are termed *medial* and *lateral* branches. The lateral (external) branches consist of one, two, sometimes three, and rarely four gray rami communicantes and one white ramus communicans, which pass to the adjacent spinal nerves. There is usually one white ramus connecting the anterior primary rami of spinal nerves T-1 through L-1 (L-2) to the respective sympathetic ganglion. None of the other sympathetic ganglia has white rami. Although the emphasis of this chapter is the thoracic viscera, it should be noted that preganglionic fibers of T-1 are the sole sympathetic fibers of the head and face. Interruption of these fibers results in Horner's syndrome. This topic is well reviewed by Bannister and Matthias (9). The medial (internal) are vascular and visceral branches, with those of the upper four or five ganglia supplying the thoracic viscera and the thoracic aorta and its branches and those derived from the lower six or seven ganglia contributing to the formation of the splanchnic nerves. The thoracic visceral branches reach the viscera either directly or by first passing through the pulmonary, esophageal, and cardiac plexuses. The cardiac and pulmonary plexuses are described in the next section.

Splanchnic Nerves. The splanchnic nerves arise from the medial border of the lower seven ganglia and pass to the celiac plexus to effect a connection between this structure and the sympathetic trunk (5,6). Usually three groups of these nerves are found on each side: the greater splanchnic nerves, the lesser splanchnic nerves, and the least splanchnic nerves. DeSousa-Pereira (7) found a fourth splanchnic nerve in 4% of cases, and he called it the *accessory splanchnic nerve*.

Greater Splanchnic Nerve. The greater splanchnic nerve is formed by roots that arise from the midportion of the thoracic sympathetic chain. According to Hovelacque (4), it is usually formed by three roots, less frequently four, sometimes only two, and rarely five or six. This description of its formation, subsequently corroborated by the work of DeSousa-Pereira (7), who carefully dissected and studied the splanchnic nerves in 100 cadavers, is different from the usual textbook description, which states that it is most frequently formed by five or six roots. The roots are usually given off by the seventh, eighth, and ninth ganglia, each ganglion giving off only one filament. Sometimes, however, the uppermost root takes origin from the sixth or fifth ganglion, rarely the fourth or third, while the lowest root originates from the tenth ganglion. In most cases the roots are given off by adjacent ganglia but in some cases are given off from a superior group and an inferior group, with two or three ganglia in between that do not contribute any fibers. These roots run inferiorly, anteriorly, and medially on the anterolateral aspect of the vertebral column and come together at the level of the ninth or tenth vertebra to form the greater splanchnic nerve. Near the origin of the formed nerve an enlargement called the *splanchnic ganglion* is usually found (70% of cases).

The greater splanchnic nerve is of considerable size, firm, and white. In its downward course it passes over the anterolateral aspect of the vertebrae, being separated at intervals from the vertebrae by the intercostal vessels and throughout its extent by the azygos vein on the right and by the hemiazygos vein and aorta on the left (see Fig. 60-11). It is in close relation with the pleura, behind and medial to it. It passes through the diaphragm within the space that separates the internal from the external crura and enters the abdominal cavity. Its course within this cavity is short, never more than 2 cm (4), and is in an anteromedial and inferior direction. The nerve usually breaks up into its terminal branches, which spread out like a fan and terminate in one or more ipsilateral celiac ganglia (see Fig. 65-6 and Fig. 104-31).

During its course the greater splanchnic nerve gives off fine collateral filaments that join the intercostal vessels, the azygos veins, and the aortic plexus and others going to the diaphragm and the spinal cord. In addition, some filaments join the lesser splanchnic nerve.

Lesser Splanchnic Nerve. The lesser splanchnic nerve is usually formed by two roots, sometimes by one or three, which arise from the lower portion of the thoracic chain. The roots are given off by the tenth and eleventh ganglia, and rarely by the twelfth ganglion (4). Soon after their origin these roots converge into one trunk, which descends inferiorly, anteriorly, and medially on the anterolateral aspect of the vertebral column. It lies between the sympathetic chain, which is posterolateral to it, and the greater splanchnic nerve, which is anteromedial to it. It leaves the thoracic cavity and enters the abdominal cavity by passing through the diaphragm lateral to and accompanied by the greater splanchnic nerve to terminate in the celiac or aorticorenal ganglion.

Least Splanchnic Nerve. The least splanchnic nerve is usually formed by one root that arises from the twelfth thoracic ganglion. This nerve is a fine cord that passes anteriorly, medially, and slightly inferiorly below the lesser splanchnic nerve. It perforates the diaphragm along with the other two splanchnic nerves to enter the abdominal cavity, where it proceeds toward and ends in the aorticorenal ganglion.

Accessory Splanchnic Nerve. The accessory splanchnic nerve, when present, arises from the twelfth thoracic ganglion, has the same course as (but is independent of) the least splanchnic nerve, and ends in the aorticorenal ganglion.

INNERVATION OF THE THORACIC VISCERA

This section presents a detailed description of the anatomy of the nerves to the heart, aorta, lungs, and other visceral structures in the chest. More detailed reviews of these various aspects have been presented by Hovelacque (4), Kuntz (5), Mitchell (6), Miller (8), White and colleagues (9,10,11 and 12), Mizeres (13), and Hirsch and Borghard-Erdle (14).

Innervation of the Heart

The nerve supply of the heart is complex and, like other visceral organs, is composed of efferent and afferent sympathetic and parasympathetic efferent fibers (Fig. 60-12). Most of the nerves arise well above the cardiac level because the heart develops initially in the neck region and later migrates to the thorax (4). Efferent and afferent fibers are involved in important reflexes and are influenced in their activities by centrifugal and centripetal impulses from many parts of the body. This is not

surprising, considering the prime importance of the heart and major vessels in the body's physiologic economy, represented at every level in the nervous system (Chapter 8 reviews the central and peripheral portions of the autonomic nervous system). Here, only those aspects relevant to the innervation of the heart are considered.

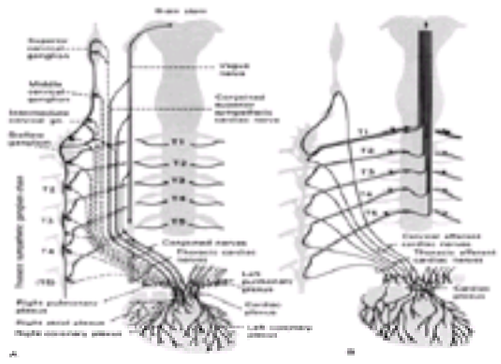

Figure 60-12. Nerve supply of the heart. **A:** On the left is shown the sympathetic preganglionic fibers (*solid lines*), which have their cell bodies in the intermediolateral column of the T-1 to T-5 segments. These preganglionic axons synapse with cell bodies of postganglionic fibers (*dashed lines*), some of which join vagal fibers to form conjoint nerves. **B:** Sympathetic afferents. These transmit nociceptive information and have their cell bodies in the dorsal root ganglion. The proximal axons synapse with dorsal horn neurons whereas the distal axons pass through the white rami communicantes and thence through the sympathetic chain and the various cardiac sympathetic nerves that contribute to the cardiac plexus and its various subsidiary plexuses that supply the heart. No interruption or synapse of these fibers is found anywhere along their course. See text for details.

Sympathetic Nerves

The sympathetic nerves to the heart contain both efferent preganglionic and postganglionic fibers and afferent fibers. The sympathetic preganglionic cardiac fibers are the axons of cells located in the intermediolateral column of the spinal cord at the level of the T-1 to the T-4 or T-5 spinal segments (in an undetermined percentage of individuals, a cranial or caudal shift of one or even two segments might be present) (6). The representation is inverted, with the fibers destined for the ventricles arising above those destined for the atria (6). As emphasized in the following section, these cells are influenced both by impulses coming from the heart and by impulses descending from the sympathetic centers in the hypothalamus, which in turn is influenced by higher centers of the brain as well as by impulses ascending from the neuraxis. These preganglionic myelinated axons leave the spinal cord via the ventral roots of the upper four or five thoracic spinal nerves and pass through the white rami communicantes to reach the paravertebral sympathetic chain. Some of these axons synapse with ganglionic cells in the ganglia that they enter, while most ascend in the trunk to end in the inferior, intermediate, middle, or superior cervical sympathetic ganglion.

The postganglionic axons have thin myelin sheaths, so thin that they appear to be unmyelinated when ordinary staining methods are used. The axons destined for the heart, aorta, and other large vessels pass through the superior, middle, and inferior cervical sympathetic cardiac nerves and the thoracic cardiac nerves. Like the parasympathetic nerves the sympathetic cardiac nerves vary in number, site of origin, size, and distribution. The following discussion is in accordance with the views of Hovelacque (4), Mitchell (6), and Mizeres (13) (Fig. 60-13).

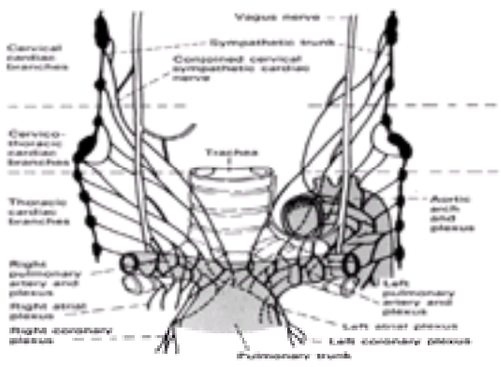

Figure 60-13. The cardiac plexus and its subsidiary plexuses. See text for details. (Modified from Mizeres NJ. The cardiac plexus of man. *Am J Anat* 1963;112:141–151.)

Superior Cervical Sympathetic Cardiac Nerve. The superior cervical sympathetic cardiac nerve originates by one, two, or occasionally three rootlets from the lower and medial parts of the superior cervical sympathetic ganglion or can arise from any part of the upper cervical sympathetic chain, from its upper pole down through the level of the lower border of the C-6 vertebra (5). The rootlets often unite and soon thereafter often join with a corresponding cervical vagal branch to form a conjoined nerve that descends behind the common carotid sheath and its contents near the main sympathetic trunk and laterally through the trachea and esophagus. *En route*, it communicates through slender filaments with the pharyngeal, laryngeal, carotid, and thyroid plexuses and with other cervical cardiac nerves. It then proceeds behind the ipsilateral subclavian artery at the root of the neck to reach the cardiac plexuses.

On the right side the nerve passes posterolateral to the innominate artery and aortic arch to end in the cardiac plexus. On the left side the nerve is in contact with the left side of the left common carotid artery and passes between this and the left subclavian artery or around the root of the latter vessel before curving downward across the left side of the aortic arch to the cardiac plexus. This nerve is often connected with the middle, or inferior, group of cardiac branches of the left vagus nerve somewhere between the root of the neck and the aortic arch, and always communicates with the middle and inferior cervical sympathetic cardiac nerves or with vagal branches. As described in the following sections, as these partially commingled nerves descend across the ipsilateral side of the aortic arch they give off three to six filaments, which form the preaortic plexus.

Middle Cervical Sympathetic Cardiac Nerve. The middle cervical sympathetic cardiac nerve originates by rootlets from the middle cervical ganglion or from the adjacent part of the sympathetic trunk and also receives rootlets contributed by the intermediate cervical (vertebral) sympathetic ganglion. Mitchell (6) stated that this is the largest of the sympathetic cardiac nerves. On the right side the nerve enters the thorax behind the subclavian and innominate arteries and reaches the cardiac plexus by passing between the tracheal bifurcation and aortic arch. On the left side it runs between the left common carotid and subclavian arteries or around the root of the latter and crosses the left side of the aortic arch to reach the cardiac plexus. Mitchell (6) and Mizeres (13) agree that often this nerve cannot be distinguished as a complete and separate entity at the level of the aortic arch because of its intercommunication with other sympathetic and vagal cardiac branches. On both sides the nerve communicates with the thyroid, tracheal, esophageal, and aortic nerves and with filaments from the left recurrent laryngeal nerve. The nerve furnishes one or two filaments to the preaortic plexus.

Inferior Cervical Sympathetic Cardiac Nerves. The inferior cervical sympathetic cardiac nerves consist of a variable number of filaments arising from the stellate ganglion, the intermediate cervical (vertebral) sympathetic ganglion, and the ansa subclavia. When the inferior cervical and first thoracic ganglia are not fused into the stellate ganglion, the inferior cervical cardiac nerves arise from separate filaments from each ganglion. Their course is similar to that of the middle cervical sympathetic cardiac nerve. Mizeres (13) pointed out that, because these branches often arise from the sympathetic trunk at the level of the C-7 and C-8 and T- 1 vertebrae (which include the stellate ganglion, ansa subclavia, and vertebral or intermediate ganglion), they should be called the *cervicothoracic cardiac sympathetic nerves*. These nerves often fuse with the vagal branches to become conjoined nerves that pass inferiorly by coursing between the aorta and the bronchi to contribute to the cardiac and both pulmonary plexuses and to the plexus of the aortic arch, with some proceeding directly to the coronary plexuses. An inconstant communication

exists between these nerves and the phrenic nerves.

Thoracic Cardiac Sympathetic Nerves. The cervical sympathetic cardiac nerves were recognized nearly 400 years ago by Fallopius (c. 1600 ad) and by many others thereafter. It was not until 1927, however, that the thoracic sympathetic cardiac nerves were identified. Their clinical importance was emphasized independently and simultaneously by Braeucker (15) and by Ionesco and Enachesco (16), although Mitchell (6) pointed out that they were noted in a calf by Weber (1815) and in humans by Swan (1830). Obviously, these small anatomic structures are important clinically because they provide direct connection between the sympathetic trunk and the cardiac plexus. Usually three, four, or five rather slender branches on each side originate from the T-2 to the T-4 or T-5 (rarely the T-6) sympathetic ganglia, or from the interganglionic portion of the sympathetic trunk.

These nervelets pass anteriorly and medially; some enter the cardiac plexus directly or unite with neighboring filaments destined for the trachea, esophagus, aorta, or pulmonary structures, and then separate again as they approach the heart to contribute to the cardiac plexus. Mizeres (13) found that nervelets on the right side fuse immediately with at least one of the cervicothoracic cardiac sympathetic nerves and with one of the thoracic cardiac vagal nerves, and contribute directly to the right pulmonary and atrial plexuses. In contrast, on the left side, they do not fuse but proceed individually and send filaments into the plexus on the arch of the aorta, directly into the thoracic vagal trunk, and also to the left pulmonary and atrial plexuses.

Cardiac Branches of the Vagus Nerves

The vagus nerves that supply the heart and thoracic aorta have both preganglionic parasympathetic fibers and afferent fibers. The parasympathetic preganglionic fibers are contained in the vagus and in the cranial part of the accessory nerve that joins the vagus. The cell bodies of these preganglionic parasympathetic fibers are located in the dorsal motor nucleus of the vagus, which is an elongated structure that extends inferiorly to the upper cervical part of the spinal cord. These preganglionic axons course through each vagus nerve and through the cardiac vagal nerves on both sides to end in the terminal extrinsic ganglia in the cardiac plexus or in the small intrinsic cardiac ganglia in the subepicardial tissue of the heart and the myocardium. The finely myelinated preganglionic parasympathetic axons synapse with the cell bodies of the thinly myelinated or unmyelinated postganglionic fibers; these are short and, in contrast to the sympathetic postganglionic fibers, have a rather circumscribed distribution.

The vagal cardiac branches arise both in the neck and thorax and vary in size, number, and distribution. Nevertheless, it is generally agreed that these vagal cardiac nerves can be divided into three groups: the superior [referred to by Mizeres (13) as the cervical vagal cardiac nerves]; the middle or cervicothoracic vagal cardiac nerves; and the lower or thoracic vagal cardiac nerves.

Superior (Cervical) Vagal Cardiac Nerves. The superior vagal cardiac nerves originate from any part of the cervical part of the vagus as far inferiorly as the lower border of the C-6 vertebra (13). In some instances, two or three filaments arise just below the superior laryngeal nerve, whereas in others the vagus gives off only a single branch. In any case, they soon coalesce to form a single nerve; as mentioned previously, this invariably joins the superior cervical sympathetic cardiac nerve to form a conjoint nerve. The rootlets of the nerve itself often communicate with the pharyngeal and superior laryngeal nerves and occasionally with the carotid nerve. Mizeres (13) found that the right branch usually courses posteriorly to the aorta and enters the right pulmonary plexus, while the left branch descends anteriorly to the carotid sheath and arch of the aorta, contributing to its plexus and to the coronary plexuses. Occasionally both course anteriorly to the aortic arch.

Middle (Cervicothoracic) Vagal Cardiac Nerves. These nerves can consist of one, two, or three rootlets arising from the vagus in the lower half or third of the neck. They almost always communicate with the cervical sympathetic cardiac nerves and not infrequently course as conjoined nerves before reaching their destination. If these nerves remain separate they pass directly to the cardiac plexus, lying posterolaterally to the innominate artery and aortic arch on the right side and laterally to the left common carotid aortic arch on the left side. Mizeres (13) found that the right cervicothoracic vagal cardiac nerve usually arises from filaments from the right recurrent laryngeal nerve and from the vagal trunk at the level of the C-7 and T-1 vertebrae. Near their origin the filaments usually join the right cervical and cervicothoracic sympathetic cardiac nerves and course inferiorly as conjoined nerves posterolaterally to the innominate artery and aortic arch before reaching their destination, which is usually the right pulmonary plexus, a subsidiary of the cardiac plexus. The one or two left cervicothoracic vagal cardiac branches arise from the left vagal trunk at the level of the C-7 and T-1 vertebrae and usually course laterally to the left common carotid and subclavian arteries and then pass anteriorly to the arch of the aorta, contributing to the plexus on the arch and to the left atrial plexus.

Inferior (Thoracic) Vagal Cardiac Nerves. The two to four right thoracic vagal cardiac nerves arise from the thoracic vagal trunk between the level of the lower border of the T-1 vertebra and the pulmonary hilus. They soon join the cervicothoracic or thoracic cardiac sympathetic nerves before coursing anteriorly to the right bronchus, where some filaments join the right pulmonary plexus and others proceed to the right atrial plexus. The left thoracic vagal cardiac branches arise from the left vagus at approximately the level of the origin of the left subclavian artery and run across the left side of the aortic arch to the cardiac plexus. Mizeres (13) found that in many instances one root arises from the left recurrent laryngeal nerve and another from the left vagal trunk just below it. Of the group of filaments that arise from the left recurrent laryngeal nerve, one group courses posteriorly to the arch of the aorta and joins the left atrial plexus directly while the other group courses anteriorly to join the left pulmonary plexus and proceeds in the fold of the left superior vena cava posteriorly to reach the left atrial plexus.

Afferent (Sensory) Fibers

The sensory fibers that supply the heart and great vessels pass centrally through the vagus nerves and the sympathetic nerves. Those associated with the vagus nerves have their cell bodies in the ganglion nodosum with the distal axons passing through the vagus and the cardiac vagal nerves to terminate in the heart, while the proximal axons enter the medulla to end in the nucleus of the tractus solitarius. The afferent fibers associated with the vagus that supply the heart carry impulses concerned with the subconscious reflex mechanisms that regulate cardiac action and blood pressure. Although some have suggested that some afferent fibers in the vagus convey all nociceptive impulses from the heart, clinical evidence does not support this notion (10,11 and 12,17,18). It has been shown that interruption of sympathetic afferents that pass into spinal cord segments T-1 to T-5 produce virtually complete relief of cardiac pain in the chest, arms, and neck, thus indicating they are the primary pathways for cardiac pain (10,11 and 12,17,18). Interruption of these sympathetic afferents may not relieve pain in the lower jaw, however, and does not eliminate the dyspnea and the feeling of constriction or tightness of the throat. It is possible that these sensations, which are the earliest and most frequent symptoms of myocardial ischemia in many patients, are transmitted by vagal afferents. Moreover, studies indicate that stimulation of the cardiac vagal afferents can activate cells in the brain stem; in turn, these cells produce descending modulating impulses that inhibit high-threshold and wide dynamic range cells of spinothalamic and other ascending systems at T-1 to T-5 levels known to be involved in transmission of nociceptive *pain* information to the brain (19,20 and 21). It has been suggested that this might be one of the mechanisms for the absence of pain in patients with silent myocardial infarction (19,22) (see Chapter 61 for details).

The afferent fibers associated with the sympathetics, now commonly known as *sympathetic afferents* (23), are tonically active and not only mediate nociceptive impulses, but also mediate impulses involved in segmental and suprasegmental reflexes. These fibers are mainly excitatory in nature with positive-feedback characteristics and thus contribute to the neural regulation of circulatory functions (23). These sympathetic afferent fibers pass centrally through all the cardiac sympathetic nerves except those that arise from the superior cervical ganglia (see Fig. 60-12B). The cell bodies of these sympathetic afferents are located in the posterior root ganglia of the upper four or five thoracic spinal nerves. Their central branches course to the spinal cord dorsal horn while their long peripheral branches pass distally through the upper four or five thoracic white rami communicantes and through the upper four or five thoracic ganglia and the inferior, intermediate, and middle cervical sympathetic ganglia to reach the heart through the thoracic, cervicothoracic, and middle cervical sympathetic cardiac nerves. These peripheral branches travel uninterrupted in the ganglia or plexuses and terminate as typical sensory nerve endings in the pericardium, walls of the heart, and adventitial plexuses of the coronary arteries and the aorta. Many of these sensory fibers are of the A-d and C categories, characteristic of nociceptive pathways (see Chapter 61).

Cardiac Plexus

All vagal and sympathetic cardiac nerves and associated afferent fibers converge on the cardiac plexus, which is contained in the thoracic cavity (Fig. 60-14; see Fig. 60-13). Although it has generally been stated that the plexus lies between the concavity of the aortic arch and the tracheal bifurcation (1,26), Mizeres (13), in his careful dissection of 36 cadavers of different ages, found that the cardiac plexus lies on the anterior and posterior walls of the pulmonary trunk at its bifurcation (see Fig. 60-13). Moreover, he, like Mitchell (6), believed that although the cardiac plexus is described as consisting of superficial and deep parts, this separation is an artifact created by dissection. The plexus, in its position on the adventitial wall of the pulmonary trunk, consists of the following subsidiary plexuses: the right and left pulmonary plexuses; the right and left coronary plexuses; the right and left atrial plexuses; and a plexus on the arch of the aorta. The pulmonary plexuses and the plexus on the arch of the aorta are discussed later in this chapter.

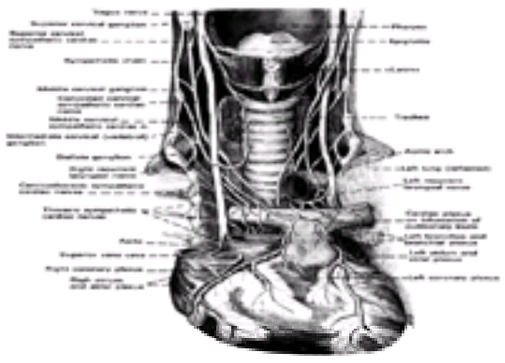

Figure 60-14. Anterior view of the chest depicting the anatomy of the nerves that contribute to the cardiac plexus and its subsidiary plexuses, including the coronary plexuses that follow the coronary vessels.

Coronary and Atrial Plexuses. The coronary plexuses are formed mainly by extensions of the right pulmonary plexus, with some contribution from the left pulmonary plexus and from the plexus on the arch of the aorta. The coronary plexuses can also receive direct contributions from the cervical and thoracic cardiac branches, and usually send filaments into the anterior surfaces of the walls of both ventricles. Each coronary plexus follows its analogous artery and its branches, giving off subsidiary plexuses throughout the heart (see Fig. 60-13 and Fig. 60-14).

The right atrial plexus is usually formed as an extension of the right pulmonary plexus, passing between the superior vena cava and aorta to end in the right atrium. The left atrial plexus is an extension of the left pulmonary plexus, coursing directly into the left posterior atrial wall and sending filaments into both posterior walls of the two ventricles. The plexus on the arch of the aorta sends filaments that course to the wall of the pulmonary arterial trunk, ending in both the left and right coronary plexuses. All these plexuses are interconnected.

Although sympathetic and vagal efferent and afferent fibers intermingle and lose their identities within the cardiac plexus, a tendency toward subdivision into right and left halves exists, from which fibers are distributed to the heart along the two coronary arteries by the left and right coronary plexuses (5,6). The right atrial and right coronary plexuses distribute mainly to the right atrium and ventricle, while the left plexuses are distributed to the corresponding parts of the heart on the left side.

The coronary nerves give off branches that ramify in the subepicardial tissues that overlie all the cavities of the heart. Whereas the larger branches of the nerves lie alongside the main coronary arteries, many of the smaller nerves run independently of vessels over the surface of the heart.

Several small extrinsic cardiac ganglia, in which a proportion of the vagal preganglionic fibers synapse with short postganglionic fibers, are present in the cardiac plexus. The largest is usually called the *ganglion of Wrisberg*, and is seldom more than 2 or 3 mm in diameter (6). Mizeres (13) found that this ganglion is not constant. The small intrinsic cardiac ganglia are located in the subepicardial tissue of the heart and, less commonly, in the myocardium.

Distribution of Nerves in the Heart. The heart is richly supplied with motor and sensory nerves containing myelinated and unmyelinated fibers derived from both sympathetic and vagus (parasympathetic) nerves. Hirsch and Borghard-Erdle (14) suggested that for purposes of orientation, the innervation of the heart can be categorized according to the distribution of the nerves to the several anatomic structures: the coronary arteries, the myocardial muscle tissue, the conducting system, and the supporting stroma, including the valves and their leaflets.

Innervation of the Coronary Arteries. Coronary arteries and their branches have abundant motor and sensory nerves contributed by both sympathetic and parasympathetic nerves (5,6,24). Indeed, it has been authoritatively stated that the coronary arteries in the heart have the richest nerve supply of all the arteries in the body (25). The following summary is based on the findings of Hirsch and Borghard-Erdle (14) in their studies of the human heart (except as otherwise noted). The adventitial fibrous tissue of the arteries has many large and small rounded nerve trunks containing myelinated and unmyelinated nerve fibers. These nerves accompany the arteries toward the endocardium and, at the arteriolar level, are diminutive round or flat structures. The thicker nerve trunks, which have vagal fibers, supply the adventitial and periadventitial fibrous tissue, while the thinner sympathetic nerves innervate the smooth muscle cells of the media of the coronary arteries to the level at which the contractile tissues disappear.

The coronary arterioles and precapillary blood vessels are supplied only by vagal fibers. At the precapillary level the vagal fibers have flat segments, but beyond this level they continue into or send terminal branches into the nearby myocardium, where they end either in a bulbous tip or in a brushlike terminus amidst the myocardial syncytium. These nerves have fine and slightly coarser fibrils that are in close continuity with the myocardial cells.

Innervation of the Myocardium. In addition to contributions by the coronary nerves, some large and small nerve trunks enter the myocardium directly and not in association with branches of the coronary arteries. These nerves divide dichotomously at considerable intervals in the heart muscle and some rather large ones reach the endocardium to divide further, being distributed in muscle tissue near the endocardial lining. After they have penetrated into the myocardium these nerves have scanty perineurium, and the fine nerve fibrils in them appear to extend directly into the contiguous myocardial cells. Motor end-plates resembling those of cell muscle have not been found in studies of the human heart (14).

The existence of sensory nerve endings in the heart was first suggested by Berkley (26) in 1894, and subsequently by others, who demonstrated that these sensory nerves are associated with both the vagus and sympathetic nerves to the heart (19). Early work by Wollard (25) and later by Nonidez (27), based on nerve degeneration following bilateral stellectomy, suggested that the largest proportion of cardiac sensory nerve endings are of vagal origin. Studies entailing the resection of the thoracic ganglia, however, showed that a significant proportion are associated with sympathetic nerves and are made up of myelinated and nonmyelinated afferents (28,29).

In the heart the sensory fibers terminate as complex unencapsulated endings that are usually distinguished as either diffuse or compact (19,27,29,30). The sensory nerve terminals exist in the subendocardial tissue as well as in the depth of the myocardium and around the coronary vessels. These sympathetic afferents innervate the same regions and layers of the heart as the vagal fibers. Moreover, the sympathetic afferents and endings frequently lie side by side with afferent fibers and endings of the vagus nerves (30).

Innervation of the Conducting System. Much evidence has shown that the sinoatrial node of Keith and Flack, the atrioventricular node of Tawara, and the atrioventricular bundle of His are abundantly supplied with nerve fibers and terminal networks around their constituent cells (5,6,14). Clusters of nerve cells are closely associated with these nerve bundles and plexuses, and belong to the intrinsic cardiac ganglia (5,6,14).

Innervation of Stroma Tissues. The fibrous tissues about the coronary arteries and their branches, down to the precapillary level, have a rich nerve supply that is mainly vagal. Nerve trunks extend throughout the myocardium, divide dichotomously, and split into compound terminal plexuses (14). The presence of myelinated fibers in nerves of supporting noncontractile tissues suggests that they are sensory fibers. Fibers in these nerves and their branches innervate the supporting stroma as well as form the endocardial plexus that extends into the leaflets of the valves.

Pericardium

The innervation of the pericardium varies according to its two major layers. The serous pericardium, which is composed of a single layer of mesothelial cells that covers the atria and the ventricles and extends beyond along the great vessel for 2 or 3 cm, is supplied by nerves derived from the cardiac, coronary, and epicardial plexuses containing sympathetic, parasympathetic, and afferent fibers. The serous layer that lines the inner surface of the fibrous pericardium, often called the *parietal pericardium*, together with the fibrous pericardium is supplied by sensory fibers derived from the phrenic nerves and the anterior parts of the thoracic intercostal nerves, and also receives sympathetic and vagal fibers through the cardiac plexus (6). Nociceptive information is transmitted by the sensory fibers principally in the phrenic nerves, by a few fibers from the intercostal nerves, and perhaps by sympathetic afferents.

Innervation of the Thoracic Aorta

The ascending aorta and arch of the aorta are supplied by both sympathetic and parasympathetic vagal fibers, many of which are afferent in nature and are distributed mainly in the adventitial plexus of the ascending aorta (4,5 and 6). Some vagal twigs enter the vessel directly, and others reach it through the cardiac plexus. The sympathetic fibers for the ascending aorta and the aortic arch arise from the stellate and upper thoracic ganglia and are often incorporated in the thoracic cardiac nerves, although occasionally separate filaments can be traced directly to the aorta (6). Aortic fibers in the thoracic cardiac sympathetic nerves pass to the cardiac and preaortic plexuses without interruption and reach the adjacent parts of the aorta in fine short branches (Fig. 60-15). The various aortic vagal and sympathetic filaments break up to form terminal plexuses in the walls of the aorta. The adventitial plexus is especially well marked around the ascending aorta, which is a special pressoreceptor area.

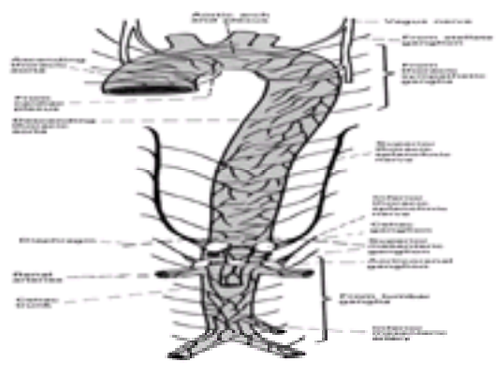

Figure 60-15. Innervation of the thoracic aorta. See text for details.

The small aortic arch body is a chemoreceptor structure similar to the carotid body and is usually located in the angle between the aortic arch and the ligamentum arteriosum and occasionally found at other points in the adventitia of the aortic arch. Additional small masses with similar morphologic characteristics sometimes exist in or adjacent to the adventitia of the ascending aorta or of the innominate artery.

Extensions from the aortic arch plexus continue along and supply the intrathoracic parts of the innominate, left common carotid, and left subclavian arteries.

The descending thoracic aorta is innervated by a variable number of direct filaments from the T-4 and T-5 sympathetic ganglia and from the greater splanchnic nerves or their rootlets of origin. Mitchell (6) pointed out that, in approximately 10% of individuals, on the right side and less often on the left side, a delicate paraaortic nerve is found lying along the posterolateral aspect of this part of the aorta and helps to supply it. This nerve interconnects the lowest thoracic cardiac nerve and the lower aortic and esophageal branches, and rarely extends above the level of the T-4 or T-5 vertebra.

Afferent fibers associated with both the vagus and sympathetic nerves supply the ascending aorta and arch of the aorta. White (12), White and associates (11,18), Bonica (17), and others (31) suggested that the afferents that transmit nociceptive impulses from the ascending aorta and aortic arch, as well as from the descending aorta, pass through the neuraxis via sympathetic pathways. They produced symptomatic relief of the severe pain of aortic aneurysm by injecting the upper thoracic sympathetic ganglia with a local anesthetic. Bonica (17) followed the diagnostic and prognostic injections with block of the sympathetic chain by alcohol. Injection of the ganglia on the right side is indicated for pain caused by aneurysm of the ascending aorta, but, if the arch or descending aorta is involved, the ganglia must be blocked on the left side or bilaterally to provide relief (17,18,31) (see Chapter 102).

Reichert (personal communication, 1952) relieved severe pain from an aneurysm involving the lower part of the thoracic aorta by injecting the T-2 to T-6 ganglia with a local anesthetic. In one of White's patients, severe pain produced by a large aortic arch aneurysm that expanded upward into the thoracic inlet was referred to wide areas supplied by the cervical and intercostal nerves, suggesting it might be caused by pressure on neighboring structures, yet it was completely relieved by alcohol injection of the upper thoracic sympathetic ganglia (18).

The branches of the descending thoracic aorta, the most important of which are the bronchial, pericardial, mediastinal, esophageal, phrenic, posterior intercostal, and subcostal, all receive prolongations from a periarterial nerve plexus around the thoracic aorta. The bronchial arteries receive reinforcing filaments within the lungs. The esophageal arterial plexus is supplemented by twigs from the esophageal plexus, and branches of the phrenic nerves have been noted close to the pericardial and phrenic arteries, helping to innervate them. The posterior intercostal and subcostal arterial plexuses are also joined by small bundles of fibers from the adjacent intercostal and subcostal nerves, which contain a relatively high complement of sympathetic fibers, and from the thoracic splanchnic nerves at the points where the vessels pass behind them (5,6).

Innervation of the Lungs

The lungs, including the trachea and bronchi, are innervated by both sympathetic and parasympathetic nerves, which contain efferent and afferent fibers. The nerves to the lungs reach the pulmonary vessels and lung tissue through the pulmonary plexuses. These are apart from filaments supplying the extrapulmonary parts of the bronchial arteries, which as noted previously are extensions from the parent periaortic plexus surrounding the descending thoracic aorta.

Pulmonary Plexuses

The pulmonary plexuses are composed of larger vagal and smaller sympathetic contributions. The sympathetic pulmonary nerves are the axons of postganglionic sympathetic fibers that have already synapsed in sympathetic ganglia with preganglionic fibers. The cell bodies of the latter are located in the intermediolateral column of the spinal cord at the level of the T-2 to T-6 or T-7 segments. The synapse with postganglionic fibers takes place in the T-2 to T-6 or T-7 thoracic ganglia and occasionally in the stellate ganglion. The postganglionic fibers pass anteriorly and inferiorly and often merge with the thoracic cardiac, aortic, and esophageal branches and separate from them as they approach their destination. The sympathetic nerves, which also contain afferent nerves, run primarily to the posterior pulmonary plexus but also travel to the anterior pulmonary plexus (Fig. 60-16A). They unite with the corresponding branches of the vagus and are distributed along with them to the vessels, bronchi, and glands in the lungs.

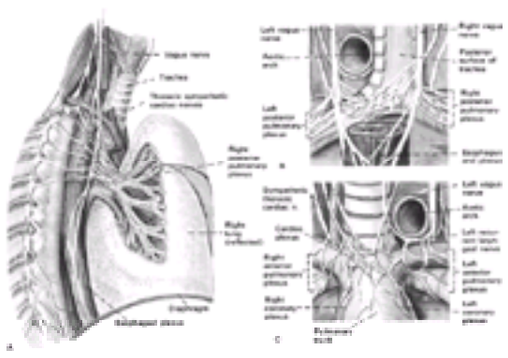

Figure 60-16. Anatomy of the pulmonary plexuses and their distribution. **A:** Right parasagittal view showing origin, course, and termination of the nerves that contribute to the right pulmonary plexus. **B:** Posterior view. **C:** Anterior view of the trachea and two primary bronchi to show relation of the pulmonary plexus to these structures.

The vagal pulmonary nerves contain both preganglionic and afferent fibers, the former originating in dorsal vagal nuclei and the latter having their cell bodies in the inferior vagal (nodose) ganglia. Just above the root of the lung each vagus nerve divides into smaller anterior and larger posterior parts, which embrace the lung root (Fig. 60-16B and Fig. 60-16C). Most of the pulmonary branches of the vagus derive from the larger part of the nerve lying behind the root of the lung but three or four branches are also given off before the main nerve splits, and smaller twigs are supplied by the smaller part of the nerve that passes anterior to the lung (4,5 and 6). The various branches form smaller anterior and larger posterior pulmonary plexuses. The nerves do *not* subdivide and reunite frequently, as shown in most illustrations, but rather they spring from the parent nerves almost perpendicularly and run straight outward anterior and posterior to the roots of each lung (6). They do divide as they enter the lung, however, and become dispersed around the vascular and bronchial structures. The posterior pulmonary branches are much more conspicuous than the anterior branches and receive direct or indirect contributions from the upper thoracic sympathetic ganglia.

The pulmonary plexuses always communicate with the cardiac, aortic, and esophageal plexuses, and the left anterior pulmonary plexus is often interconnected by delicate strands with the left phrenic nerve. The pulmonary plexuses proceed distally and, immediately after entering the lungs, the nerve filaments become partly segregated into groups that accompany the main bronchi and vessels and bronchial arteries. No plexus formation is noted around these structures, with the nerve bundles merely winding around them and giving off branches at irregular intervals. A plexus formation is well in evidence, though, by the level of the third-order bronchi and their accompanying vessels (6). Segregation between the perivascular and peribronchial nerves and plexuses is not at all complete; they are frequently interconnected by small bundles of fibers. Coburn (32) has described preganglionic vagal fibers synapsing in ganglia along the tracheobronchial tree.

The supply to the various vessels within the lungs varies in richness: the small bronchial arteries have the best supply; the pulmonary arteries are less richly innervated; and the pulmonary veins have a poor supply limited to their extrapulmonary parts and large intrapulmonary branches (6). The larger bundles of pulmonary arterial nerve fibers are located on the side of the vessels facing the bronchi and can be traced to the extremities of these vessels, with some extending beyond them to the visceral pleura (6). The filaments passing through the bronchial arteries come from the adjacent extrachondral parts of the bronchial nerve plexus. Although some investigators have described rich nerve plexuses around the walls of the capillaries in the lung parenchyma (33), others could not confirm these findings (34).

Both myelinated and unmyelinated fibers have been found in the pulmonary nerves and plexuses. Some of these fibers have sensory receptors in the pulmonary blood vessels and are involved in reflex control of the pulmonary circulation, which apparently has vasoconstrictor and vasodilator fibers supplied by the sympathetic and parasympathetic efferent nerves, respectively.

The lung also has two types of receptors that probably have nociceptive function: the type J receptors with C afferents, and the *lung irritant receptors* with afferents in the A-d range all running in the vagus nerves (35). The type J receptors are located in the interstitial space close to the capillaries, whereas the lung irritant receptors are found in the epithelial lining of the lung and its airways. These are activated by various stimuli that produce mechanical distortion within the lung, such as pulmonary congestion, microembolism, atelectasis, pneumothorax, and chemical irritants. It is likely that this pain, caused by mechanical or chemical damage of the lung, is mediated by these A-d and C fibers (35).

Larynx, Trachea, and Main Bronchi

Larynx. The nerves to the larynx are derived from the vagus nerve by way of the internal and external branches of the superior laryngeal nerve and by the recurrent laryngeal nerves. The internal laryngeal branch, which is sensory, enters the larynx by piercing the posterior part of the thyrohyoid membrane above the superior laryngeal vessels and divides into three branches. One is distributed to both surfaces of the epiglottis, a second to the aryepiglottic fold, and a third, the largest, supplies the mucous membrane over the back of the larynx and communicates with the recurrent laryngeal nerve. The external laryngeal branch supplies the cricothyroid muscle. The recurrent nerve passes superiorly beneath the inferior border of the inferior pharyngeal constrictor muscle immediately dorsal to the cricothyroid joint. It supplies all the muscles of the larynx except the cricothyroid. The sensory branches of the laryngeal nerves form subepithelial plexuses from which fibers end between cells that cover the mucous membrane. Fibers from the sympathetic nerves supply the blood vessels and glands of the larynx.

Trachea and Main Bronchi. The trachea and main bronchi are supplied by filaments from the vagus and the recurrent laryngeal nerves and by fibers from the sympathetic trunk. These filaments are distributed to the trachealis muscles and between the epithelial cells. As mentioned in Chapter 8, the sympathetic postganglionic nerve fibers produce relaxation of the trachealis muscles and increase the size of the trachea and bronchi, whereas the parasympathetic nerves have a bronchoconstrictor effect. Morton and colleagues (36) demonstrated that the sensory nerves that transmit nociceptive impulses are afferents of the vagus nerves and their branches. They carried out experiments in human volunteers in which electric stimulation of the tracheobronchial tree through a bronchoscope produced pain that was referred to the anterior chest or lower part of the neck (Fig. 60-17). They noted that points of the areas of reference were ipsilateral to the site of stimulation. Moreover, they demonstrated in patients with carcinoma that section of the vagus below the recurrent laryngeal nerve but above the pulmonary plexus abolished the pain on the side of vagotomy (37). In a few cases, following section of the one vagus nerve, pain of tracheobronchial origin was referred to the contralateral side, probably because of interconnection between nerves of each side.

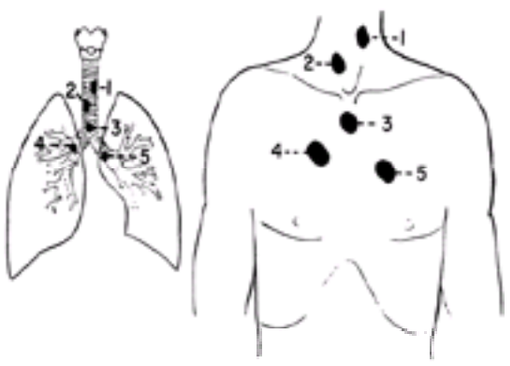

Figure 60-17. Pain referred to the anterior chest stimulation of the mucous membrane of the tracheobronchial tree. The areas of pain are ipsilateral to the sites of stimulation. (Modified from Morton DR, Klassen KP, Curtis CM. Clinical physiology of human bronchi. I. Pain of tracheobronchial origin. *Surgery* 1950;28:669–704.)

Similar findings were reported by Teodori and Galletti (38). They noted that electrical stimulation of the normal mucosa produces little pain, but stimulation in patients with inflammation of the mucosa of the tracheobronchial tree produced pain in the anterior chest wall, even when the stimulus was applied to the posterior wall of the trachea and bronchi. When the stimulation was applied to the carina or at the beginning of the primary bronchi, painful sensation was localized in the parasternal region occupying the area between the first and the fifth intercostal spaces, whereas when the stimulation was applied more distally the pain extended as far as the sixth intercostal space. They also noted a decrease in electrical skin resistance limited to the T-2 to T-5 segments. In subjects with inflammation of the tracheobronchial mucosa, the stimulation was followed hours later by cutaneous hyperalgesia.

Pleura

The visceral pleura is supplied by sympathetic fibers that have a vasomotor function. It has afferent fibers, but these have no nociceptive function because the visceral pleura is insensitive to noxious stimuli and pain does not arise from disorders of the visceral pleura (39,40). The visceral pleura also receives parasympathetic fibers through the pulmonary plexuses (35,36).

The parietal pleura is supplied by the intercostal nerves on its lateral aspects, by the T-1 spinal nerve on its apex, and by the phrenic nerves on the diaphragmatic surface (Fig. 60-18). In addition, the parietal pleura receives parasympathetic and sympathetic nerves through the pulmonary plexuses, and these nerves accompany the ramification of the bronchial arteries.

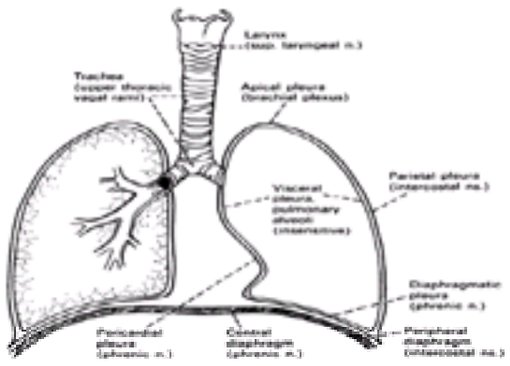

Figure 60-18. Schematic of the sensory nerve supply to the tracheobronchial tree, parietal pleura, upper surface of the diaphragm, and the diaphragmatic pleura. (Modified from White JC. Sensory innervation of the viscera: studies on visceral afferent neurons in man based on neurosurgical procedures for the relief of intractable pain. In: Wolff HG, Gasser HS, Hinsey JC, eds. *Pain*. Baltimore: Williams & Wilkins, 1943:373–390.)

HISTORY AND EXAMINATION

A general consideration of the approach to diagnosing the specific cause(s) of pain in the chest is presented here. It is intended as a supplement to Chapter 12, which contains a detailed discussion of the evaluation of patients with pain. Comments made here are relevant to pain in the chest. Chapter 61, Chapter 62 and Chapter 63 provide a more detailed discussion of diagnostic procedures for patients with pain of cardiac and aortic origin, pain of pulmonary origin, and pain of esophageal origin. This section and Table 60-1 are intended to help determine diagnostic possibilities, followed by a more detailed assessment of the probable cause(s) of pain in the chest.

TABLE 60-1. General physical examination for chest pain [a]

In many instances, the diagnosis of chest pain becomes relatively simple after the patient relates the story of the pain. Occasionally, the cause is difficult to determine because so many lesions can cause similar pain. This is not surprising when one considers that the afferent nerves of the heart, aorta, esophagus, lungs, and upper chest wall have a common pathway in the spinal cord, and that visceral pain has somewhat similar qualities regardless of the organ affected (17,41). The clinical application of this knowledge indicates that neither the location, quality, or area of reference of chest pain arising from these organs can denote the origin or nature of the underlying disorder with certainty. This information can only be obtained from a thorough history of the pain, particularly of the factors or circumstances that reproduce, aggravate, or relieve the pain, and from the history and character of the associated signs and symptoms. Diagnostic tests can also help confirm clinical impressions.

Of course, the approach to the diagnosis of chest pain varies according to the circumstances in which patients are seen. Patients who present in acute distress require a vigorous investigation performed with dispatch, slanted initially either to establish or exclude life-threatening disease of the cardiorespiratory systems, such as myocardial infarction, large pulmonary embolism, and dissecting aneurysm of the aorta (41). The approach in such acute situations should be brisk; common sense dictates that in some circumstances (e.g., patients are in a state of collapse) immediate supportive treatment, such as clearing of the airway, adequate oxygenation, and maintenance of cardiac action and blood pressure, takes precedence over the formulation of an exact diagnosis.

With most patients who are seen in the physician's office or who present themselves at the emergency room, time can be taken to obtain an abbreviated history and physical examination and to perform a few tests, such as electrocardiography and chest radiography, before transferring patients to an intensive care unit. Patients with obvious acute myocardial infarction should be sent to a coronary care unit without delay, accompanied by someone who can perform cardiopulmonary resuscitation.

By contrast, with patients who come to the physician for consultation after having experienced chest pain that has dissipated, or who are in between episodes of recent pain, it is not necessary to hurry. The physician should take the time to carry out a detailed history and comprehensive physical examination supplemented by appropriate radiographic, electrocardiographic, and other laboratory tests and therapeutic trials. In such cases diagnosis can be made at the first visit or thereafter, when additional tests and trials have been done.

In assessing patients with chest pain, the following characteristics of the pain should be elicited through a detailed and meticulous history: speed of onset of the pain, site, radiation, quality, and intensity of the pain, temporal characteristics (i.e., is the pain continuous or episodic and, if intermittent, what is the duration of each episode or attack? What time of day is it worse and when is it better? What is the time-intensity curve and what is its relationship to meals and position of the body?). Patients should be specifically asked to indicate the precise effect on pain of physical exertion, mental stress, breathing, coughing, straining, swallowing, defecation, urination, motion of the trunk, and motion of the neck (forward flexion, lateral flexion, extension, rotation). What effect does motion of the upper extremities, such as swinging of the arms or lifting, have on the pain? How does walking influence the pain?

Perhaps the most important information to elicit is determination of those activities or factors that aggravate the pain, relieve the pain, and have no influence on the pain (17,41). Thus, a history of sharp aggravation by breathing, coughing, or other respiratory movements usually indicates disorders of the pleura, pericardium, mediastinum, or chest wall. Similarly, the pain that regularly appears with rapid walking and vanishes in a few minutes on standing suggests a diagnosis of angina pectoris, although orthopedic disorders can also cause such chest pain.

Also important is obtaining a history of any *associated phenomena* such as the following: palpitation, dyspnea, coughing, expectoration, or hemoptysis, suggestive of lung disease; nausea, vomiting, distension, or abdominal tenderness, suggestive of gastrointestinal disease; and dysphagia or odynophagia (pain on swallowing), suggestive of esophageal disorders. Following elucidation of the characteristics of the pain, the past medical and family histories, and demographic data, a physical examination is carried out. Table 60-1 suggests the most important parts of such an examination.

The following points can help the clinician to determine the probable cause of pain and to make a tentative diagnosis. Bonica (17) and Levene and associates (41) have suggested that it is most practical to consider chest pain in several categories: (a) central chest pain caused by disease of viscera within the chest; (b) lateral pleuritic, musculoskeletal, or neurologic chest pain; (c) chest pain referred from disorders of structures outside the chest; and (d) chest pain primarily of psychological origin.

Visceral (Central) Chest Pain

Structures producing central chest pain include the esophagus, the myocardium, the trachea and bronchi, the pericardium, the pulmonary arteries, and the aorta, in approximately that order of frequency (41). The following points in the history help to determine the causative factor.

History

Speed of Onset. The sudden and severe onset of pain suggests dissecting aneurysm, ruptured esophagus, or pulmonary embolism. A less abrupt onset occurs with acute myocardial infarction, reflux esophagitis, and pneumothorax.

Location and Radiation. Retrosternal chest pain with radiation to the jaw and arms suggests myocardial ischemia. Radiation of the pain to the back should suggest esophagitis, esophageal spasm or rupture, pancreatitis, or dissecting aortic aneurysm.

Duration. Stable angina pectoris is characterized by short-lived pain, while the pain of unstable angina or myocardial infarction lasts longer, frequently much longer. Pain coming from other organs also lasts for minutes to hours.

Aggravating Factors. Pain brought on by general body exertion, emotional stress, or anger is considered to be caused by myocardial ischemia until proven otherwise. Exertion is a nonspecific stimulus, however, that can produce effects other than those on the cardiovascular system. For example, pain occurring with unaccustomed snow shoveling might be anginal but could also be caused by strain on the pectoral muscle or sternoclavicular joint. Pain after meals can either be esophageal or myocardial in origin, while pain after vomiting implicates the esophagus.

Effects of Posture. Pain that worsens on bending over, lying down, or stooping should suggest gastroesophageal reflux, pericarditis, or pancreatitis. Pain worsened by standing suggests a pneumothorax or emphysema. Pain made worse by deep breathing, coughing, sneezing, or laughing and relieved by quiet breathing suggests pleuritis (pneumonia, infarction, infectious process), or it can suggest fracture of the ribs, cartilages, sternum, or vertebra, or muscle strain.

Pain-Relieving Factors. Pain relieved by antacids indicates an upper gastrointestinal pathophysiologic process. Nitroglycerin relieves the pain of stable angina completely, partially relieves the pain of unstable angina or esophageal spasm, but does not relieve the pain of myocardial infarction.

Preceding Symptoms of Disease. Preceding or concomitant symptoms should direct attention to various organs: heartburn to the esophagus, angina to the heart, and alcohol abuse to the pancreas (41). Dyspnea should suggest left-sided heart failure from myocardial infarction or right-sided heart failure from massive pulmonary embolism. Recent postoperative immobilization or the use of contraceptive drugs should raise the suspicion of pulmonary embolism (41).

Physical Examination

Central chest pain associated with shock should suggest the following, in approximate order of frequency: acute myocardial infarction, massive pulmonary embolism, pericarditis or tamponade, dissecting aortic aneurysm, and acute pancreatitis (41).

Jugular venous distension implicates the cardiovascular system (myocardial infarction, pericardial tamponade, pulmonary embolism). Kussmaul's sign (distension of the jugular veins on inspiration) is seen in tamponade caused by pericarditis or mediastinal tumor.

Significant pulsus paradoxus (marked decrease in the pulse volume during inspiration) should immediately raise suspicion of pericardial tamponade unless airway obstruction is present.

Asymmetric pulses in a patient with central chest pain suggest dissecting aneurysm as the first consideration (41). Cardiac arrhythmias and gallop rhythms are commonly seen in acute myocardial infarction. Moreover, the murmur of mitral regurgitation is heard in myocardial infarction, whereas the initial appearance of the murmur of aortic regurgitation is a clue to the presence of a dissecting aortic aneurysm.

Systemic hypertension is seen in both acute myocardial infarction and dissecting aneurysms, while subcutaneous emphysema indicates a ruptured viscus.

A pericardial friction rub occurring simultaneously with the onset of pain suggests a dissecting aortic aneurysm or acute pericarditis, whereas that beginning more than 24 hours after onset of pain suggests acute myocardial infarction.

Lateral Pleuritic, Orthopedic, and Neurologic Chest Pains

The most common structures that cause pain in the lateral chest wall are disorders of the chest wall, pleura, or thoracic spine.

History

Abrupt onset of lateral chest pain suggests a torn muscle, rib fracture, pulmonary embolism, or pneumothorax, in approximately that order (37). Aggravation of the pain by movement of the thorax during deep breathing or relief by immobilization suggests a rib fracture or torn muscle.

Purulent sputum accompanying the pain suggests bronchopulmonary infection, and bloody sputum suggests pulmonary embolism. Immobilization after recent operation and use of birth control pills can precede pulmonary embolism, whereas preceding symptoms of coryza or malaise suggest infection.

Segmental pain followed by a vesicular eruption suggests the onset of acute herpes zoster (see Chapter 22). Pain localized to the sternal region is usually caused by fracture of the sternum, chondritis, muscle strain, myofascial pain syndromes, mediastinal tumor, referred pain of herniated cervical disk, foreign body, or carcinoma of the tracheobronchial tree, or diseases of the esophagus (retroesophageal esophagitis, carcinoma, ulcer). Less common causes are necrosis of the sternum, multiple myeloma, mediastinal tumors, mediastinitis, or mediastinal abscess.

Localized pain in the side of the chest is usually caused by muscle strain, myofascial syndromes, fractured ribs (trauma, carcinoma, osteoporosis), pleuritis, pneumonia, infarction, carcinoma, deep axillary abscess, diaphragmatic pleurisy, subphrenic abscess, and empyema. Less common causes include uncommon lesions of the ribs such as actinomycosis, myeloma, and periostitis, neurofibromata, epidemic pleurodynia, distension of the colon (left side), cholecystitis (right side), disseminated lupus erythematosus, and neurosis.

Pain localized in the back of the chest is usually caused by postural deformities, postural osteoarthritis, facet syndrome, and other disorders of the vertebral column, osteoporosis of the vertebrae or ribs, fracture of the vertebrae or ribs, displaced ribs, myofascial syndromes (particularly levator scapulae, latissimus dorsi, multifidi, rhomboids, and iliocostalis thoracis), fracture of the scapula, tuberculosis of the spine (Pott's disease), tumors of the vertebrae or posterior portion of the ribs, congenital disorders of the spine or thorax, osteomyelitis of the vertebrae, infectious arthritis, Kümmell's disease (traumatic spondylitis), osteitis deformans (Paget's disease), infectious vertebral epiphysitis (Scheuermann's disease), and herniated thoracic disk.

Physical Examination

Acute tenderness to palpation of the painful site strongly suggests that the lesion is in the chest wall, the site of tenderness indicating the diagnosis. Lumps suggest fractures, rib tumors, or inflamed costochondral or chondrosternal joints. In patients with rib fractures, mild compression of the ribs both in the lateral and anteroposterior planes produces intense pain.

Palpation of the muscles of the chest wall can reveal the presence of trigger areas indicative of myofascial pain syndromes. Tensing and stretching of each of the various muscles of the chest wall will cause pain if there has been an acute muscle strain or tear.

Palpation of the trachea can reveal deviation (to the opposite side) in pneumothorax. Percussion at the site of pain can produce acute tenderness if one or more

underlying ribs are fractured. Dullness on percussion suggests consolidation of the lung or fluid in the pleural space. Hyperresonance suggests pneumothorax.

Auscultation can reveal clicking of the ribs or the grating of rib fractures. A pleural rub suggests irritation caused by infection or embolism, whereas rales at the site of pain suggest underlying lung disease.

Pain from nerves and nerve roots is almost always lateralized and has a segmental pattern. The most common cause is herpes zoster, although spinal arthritis and disorders of the neuraxis can also cause segmental pain (neuralgia).

Chest Pain Referred from Extrathoracic Disorders

Pathology in Cervical Spine

Unilateral sharp or deep aching pain in the pectoral region associated with pain in the neck and upper limb is frequently caused by compression of lower cervical nerve roots by posterolateral herniation of a disk, osteophyte fracture, or other pathologic process. Lesion of C-8 on the left side produces anginalike pain in the left chest and medial arm, but the pain is unaffected by effort if the arm and neck are not moved. Pain is aggravated by ipsilateral neck flexion, head compression, cough, sneezing, and straining; it is relieved by head traction associated with sensory and reflex changes in the limb.

Pain in the upper anterior chest can be also caused by thoracic inlet syndromes, but pain that is most severe in the shoulder and limb, unaffected by effort but aggravated by extreme abduction of the arm, is often associated with signs of vascular compression.

Pancoast's syndrome often causes pain in the scapular region and anterior chest, but the pain is most severe in the shoulder and in the medial aspect of the arm. The pain is associated with paresthesia, dysesthesia, hypesthesia, and weakness of the muscle supplied by the ulnar nerve. Fullness and tenderness may be noted in the medial supraclavicular and paravertebral regions.

Abdominal Disease

Gas entrapment syndrome produces abdominal pain with radiation to the lower chest. Gastric distension produces pain in the entire epigastrium and anterior and left lateral chest up to the xiphoid or the lower sternal region. Gas entrapment in the hepatic flexure produces pain in the right upper quadrant of the abdomen and right lateral anterior chest. Gas in the splenic flexure produces pain in the left upper abdominal quadrant and left anterior and lateral chest. Signs include abdominal distension, abdominal tympany, and positive radiographic evidence in the standing position.

Biliary colic produces pain in the epigastric or right subcostal regions, but the pain frequently extends to the back at the inferior angle of the scapula and sometimes into the low central anterior chest. Mild subcostal tenderness can be noted.

Biliary tract disease can provoke angina pectoris in patients with preexisting coronary disease associated with T-wave changes. Cholecystitis is associated with nausea, vomiting, fever, jaundice, and a tender mass in the right upper quadrant of the abdomen.

Gastric ulcer located in the cardia (this is an uncommon site) is a frequent cause of laterally radiating pain in the central anterior and lower part of the chest. Gastric ulcer at other sites is not associated with chest pain. Duodenal ulcer can produce pain that radiates to the xiphoid, but chest pain is rare.

Some patients with acute pancreatitis complain only of chest pain that simulates the pain of myocardial infarction and often is associated with transient electrocardiographic abnormalities. The pain often radiates to the back; it is relieved by forward bending. It may be associated with diaphragmatic irritation resulting in pleuritic chest pain.

Distension or inflammation of the liver or spleen produces pleuritic pain in the chest and often in the shoulder. The pain is aggravated by breathing but is unaffected by effort. Subphrenic abscess produces inflammation of the diaphragm with consequent pleuritic pain on the side of the chest, shoulder, or both. Usually, there is sign of infection.

Chest Pain Primarily of Psychological Origin

Anxiety, depression, hypochondriasis, and other psychological factors can produce chest pain that is atypical in location, quality, and duration. Pain is usually in the left precordial or cardiac apical region. Chest pain does not always keep the patient from sleep, but it is present on awakening. Acute anxiety is usually associated with dyspnea, hyperventilation, palpitation, dizziness, perspiration, weakness, increased muscle tension, and diffuse chest tightness.

Chronic anxiety may produce what has been called cardiac neurosis (*soldier's heart*), or neurocirculatory asthenia. The pain is usually dull and is felt at the cardiac apex; it can be associated with attacks of sharp pain. The pain varies in severity and location and is often related to physical activity. Patients complain of weakness, low energy level, dyspnea, and palpitation.

Pain can be caused by endogenous depression associated with signs of depressive illness, anorexia, weight loss, fatigue, low energy level, malaise, and insomnia.

A positive diagnosis of pain of psychological origin is made by exclusion of disease of the heart and lungs and positive evidence acquired through psychological tests.

SUMMARY

Pain in the chest can be caused by various factors (Table 60-2), and it is therefore most important for the physician to distinguish disorders that are not life-threatening from those that are serious. An incorrect diagnosis of a hazardous condition such as angina pectoris is likely to have harmful psychological and economic consequences and can lead to unnecessary complex procedures such as coronary arteriography. Failure to recognize a serious disorder such as coronary artery disease or mediastinal tumor could result in a dangerous delay of much needed treatment. The situation must therefore be carefully assessed. (The most important points in examining a patient with chest pain are listed in Table 60-1.)

TABLE 60-2. Pain in the chest: summary of differential diagnosis

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CHAPTER 61

Cardiac and Aortic Pain

Marshall A. Corson and Robert R. Phillips

Many types of cardiac diseases can produce pain in the chest, including coronary heart disease, valvular heart disease, cardiomyopathy, pericardial disease, and aortic disease. Of these, coronary heart disease is by far the most common cause of cardiac pain and is of the greatest public health importance. Coronary heart disease remains the leading cause of death in the United States, currently estimated to cause 1 in every 4.8 deaths (1). Cardiac death is preceded by symptoms referable to the cardiovascular system in most patients. Moreover, because only a minority of heart disease deaths are the result of progressive ventricular dysfunction, prevention strategies should favorably impact on the natural history of coronary atherosclerosis. The recognition of a cardiac pain or discomfort syndrome is the single most powerful diagnostic tool available for the diagnosis of coronary heart disease. The pain of chronic coronary heart disease can generally be relieved by medications or revascularization. Thus, not only is cardiac pain easily treatable, but it is also important as a diagnostic tool in the recognition of coronary heart disease and the prevention of death. Advances in diagnosis and treatment have continued to reduce morbidity and mortality, such that the primary goal in the contemporary evaluation of a chest pain syndrome is to use subjective and objective data to determine its risk potential. Diseases of the thoracic aorta are much less common causes of chest pain, but when they do occur, a prompt, correct diagnosis and appropriate therapy are highly effective. If left untreated, many patients die. These various cardiovascular disorders are among the most important causes of severe pain that require effective management, and therefore deserve detailed consideration.

This chapter contains a current and comprehensive overview of cardiac and aortic pain. The material is presented in four parts: Mechanisms of Cardiac Pain, including a historic overview of cardiac pain, characteristics of cardiac pain, and neuropathophysiology; Myocardial Ischemic Syndromes, including stable angina pectoris, variant angina, unstable angina, and acute myocardial infarction (AMI); Chest Pain from Other Cardiac Diseases, including aortic valvular disease, hypertrophic cardiomyopathy, and acute pericarditis; and Aortic Chest Pain, with emphasis on dissection of the thoracic aorta. The present work represents the revision of an original chapter in this textbook by Hammermeister and Bonica. Major cardiology textbooks provide more detailed consideration of both coronary heart disease and aortic dissection (2, 3 and 4).

MECHANISMS OF CARDIAC PAIN

Historical Overview of Cardiac Pain

The history of chest pain caused by disease of the heart goes back to the time of Hippocrates. In the *Corpus Hippocraticum*, specific reference is made to“palpation and piercing (pain) sensation felt in the breast and pain in the vertebral column” caused by“fluxions of humours in the heart” (5). In ancient Rome *angina* and *angor* were described by Celsus in his *De re Medicina* (30 AD) (6). A clear description of coronary pain is found in the work of Caelius Aurelianus, a Roman physician of the fifth century ad who used the term *passio cardiaca propria to* indicate pain of cardiac origin specifically. Like Celsus, he also used *angina* and *angor* to indicate acute disease characterized by a sense of choking and strangling (7). Although the condition was undoubtedly known throughout the Middle Ages, literary references to it were few until the Renaissance. Bartolomeo Castelli (8), in 1598, wrote that“angor est nativi caloris cordis contractio, et in centrum retractio, ad quam sequitur eiusdem cordis dolor, palpitatio et tristitia” (angor is a contraction, and a retraction toward the center, of the natural heat of the heart, which is followed by heart pain, palpitation and anguish). Some three decades later Girolamo Mercuriale, writing about diseases of the viscera, first used the term *cardialgia* to indicate heart pain (5). At the beginning of the eighteenth century, Bonet wrote in *Sepulchretum* that the *dolor pectoris* (chest pain) is a serious symptom and described the case of a patient with chest pain who died suddenly; on autopsy the coronary arteries were found to be occluded (9). During the ensuing seven decades, references to a relationship between recurrent heart pain and sudden death were frequent.

Notwithstanding these precedents, credit for the first description of angina pectoris goes to William Heberden who, in 1768, presented a lecture titled“Some Account of a Disorder of the Breast” before the Royal College of Physicians in London and published it 4 years later (10). Heberden's description is lucid, concise, and contains many important diagnostic clues used today:“There is a disorder of the breast . . . . they who are afflicted with it, are seized while they are walking (more especially if it be uphill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all this uneasiness vanishes.” Heberden also recognized the progressive nature of angina pectoris and its predilection for evolving into an unstable pattern:“After it has continued a year or more, it will not cease so instantaneously upon standing still; and it will come on not only when the persons are walking, but when they are lying down, especially if they lie on their left side, and oblige them to rise up out of their beds. In some inveterate cases, it has been brought on by the motion of a horse, or a carriage, and even by swallowing, coughing, going to stool, or speaking, or any disturbance of mind” (10).

The term *angina* was used by Heberden not only to signify a sense of choking and strangling (according to Celsus), but also to indicate a terrible anxiety and anguish experienced by the patient (*angor animi*). In fact, the word is derived from the Indo-European root *agh*, which means“to choke, to oppress, to suffer.” Although Heberden rightly deserves the recognition of being the first to describe the syndrome, it is not commonly recognized that he did not believe that angina originated in the heart, even though he implied this belief in the title of his monograph. Even in a later discussion, Heberden failed to associate angina pectoris with disease of the coronary arteries. This was surprising because toward the end of the eighteenth century, several British physicians strongly believed in a relationship between angina pectoris and myocardial ischemia. In 1786 Edward Jenner carried out a necropsy on the body of a patient whom he had treated for angina pectoris and noted that the coronary arteries were so severely calcified that cutting through them produced an intense grating sound. Subsequently, after observing other necropsies in which“cartilaginous” obstruction of the coronary arteries was noted, he became convinced that coronary artery disease was the cause of angina pectoris:“the importance of the coronary arteries and how much the heart must suffer from their not being able duly to perform their functions . . . it is possible that all the symptoms may arise from this one circumstance” (11).

Dr. Caleb Parry, a close friend of Jenner, was familiar with Jenner's belief about angina pectoris. Using personal clinical material and Jenner's account of his

experiences, as well as that of others, he published his monumental book on angina pectoris in 1799 (12). Parry wrote that “Though a quantity of blood may circulate through the arteries, sufficient to nourish the heart, as appears in some instances, from the size and firmness of the organ, yet there would probably be less than what is requisite for ready and vigorous action. Hence though a heart so diseased may be fit for the purposes of common circulation, during a state of bodily and mental tranquility, and of health otherwise good, yet when any unusual exertion is required, its powers may fail under the new and extraordinary demand.”

Even in the nineteenth century, controversy regarding the cause of angina pectoris persisted. Home, Warren, Desportes, and others (see 5 for references) proposed that cardiac spasm was the cause of angina pectoris. They noted that in some cases of angina pectoris no coronary sclerosis was demonstrated, whereas in other cases severe coronary sclerosis observed at autopsy had not induced any anginal attack. Despite all the efforts of these physicians, for more than 150 years angina was not related to myocardial ischemia by *mainstream* physicians, including such stalwarts as Sir Clifford Allbutt, Regius Professor of Medicine at Cambridge University, and probably also Sir William Osler, his fellow Regius Professor at Oxford. Allbutt, in 1915, in his two-volume *Diseases of the Arteries Including Angina Pectoris* (13), stated that“angina pectoris is anything you please . . . a very popular sentiment.” Allbutt and others attributed angina to disease of the aorta, perhaps distension. Beginning with Heberden, this discrepancy probably arose because the major cardiac diagnostic technique of that time, palpation of the pulse, often revealed no abnormalities in patients with angina; this was Heberden's observation during his own anginal episode (10). Nine years after Allbutt's proposal, Wenckebach (14) similarly postulated that the sudden distension of the aorta or distension of the coronary arteries proximal to the point of occlusion stimulated the nerve plexuses.

At about the time that Allbutt was contesting the basis for myocardial ischemia, Herrick's (15) experiments provided strong support to the concept of a causal relationship between coronary insufficiency and cardiac pain. This was reaffirmed by Keefer and Resnik (16) in 1928 in their classic paper on angina pectoris, in which they stated that this symptom“was due to anoxemia of the myocardium . . . the attacks occur when the oxygen supply to the heart is inadequate to meet the oxygen demands of the heart.” Further work in support of this theory was reported by Sutton and Lueth (17) and White and coworkers (18), who carried out experiments on dogs that manifested pseudoaffective reactions (signs of pain) by repeated and intermittent occlusion of the orifices of coronary arteries. These painful reactions could be produced by occluding the orifices of the coronary arteries without causing distension; in contrast, acute mechanical distension of the cavity of the left ventricle, the aortic ring, or the aortic arch produced no pain. At about the same time, Wood and Wolferth (19) clearly demonstrated a causal relationship by observing electrocardiographic (ECG) changes during angina; thus the concept of the ischemic origin of angina became widely accepted.

Paul Dudley White is generally credited with ushering in the *modern era* of twentieth century cardiology. Development of powerful new diagnostic techniques, such as electrocardiography (ECG) (20) and echocardiography (21), constituted the basis for current noninvasive evaluation of chest pain, whereas the advent of cardiac catheterization and selective coronary angiography (22) heralded the era of coronary artery bypass surgery (23) and percutaneous coronary revascularization (24). These technical innovations have been matched by progress in the development of pharmacologic agents, such as antagonists of the sympathetic nervous system (25), renin-angiotensin systems (26), and thrombolytic agents (27).

Characteristics of Cardiac Pain

The chest pain experienced by patients with coronary ischemic syndromes, aortic stenosis or regurgitation, and hypertrophic cardiomyopathy all have the common denominator of myocardial ischemia. Thus, the pains of each of these conditions may have similar characteristics. Cardiac pain is visceral in nature (i.e., initially the pain is often vague, diffuse, poorly localized, and referred to varying anatomic areas). Patients often find it difficult to describe. Many patients refuse to use the word *pain* in describing angina pectoris, preferring instead to call it a discomfort, a tightness, a constricting feeling in the chest,“a band across the chest . . .a weight on the center of the chest” or a strangling sensation. It was for this reason that Heberden chose the word *angina*, which means strangling. Ischemic myocardial pain often carries with it the feeling of impending doom or death; Heberden used the Latin phrase *angor animi* to express this feeling of terror (10).

Patients often feel the need to stand or sit absolutely motionless when they experience angina. Ischemic myocardial symptoms can also be described as paresthesia or a numbness or weakness, particularly in the arms. Ischemic myocardial pain is commonly mistaken for pain of gastrointestinal origin because it can be epigastric in location, similar to the *heartburn* of esophagitis, and accompanied by an intense desire for eructation. It is not uncommon for patients suffering from angina pectoris to feel that they could obtain relief if only they could belch. The pain of AMI shares many of these characteristics, although usually it is more severe and of longer duration. Pain of myocardial ischemia is not pleuritic, and it is not exacerbated by deep breathing or coughing. It generally does not vary with position, as does the pain of acute pericarditis. The identification of precipitating factors, such as exercise or emotion, is an essential part of the diagnosis of stable angina pectoris (see General Principles of Diagnosis, later in this chapter); unstable angina and variant angina, by definition, do not have recognizable external precipitating stimuli. It is also now recognized that more than 30% of patients with demonstrable coronary ischemia have either no symptoms or atypical symptoms, such as dyspnea only, so-called anginal equivalents.

The visceral nature of cardiac pain provides a basis for its clinical differentiation from chest wall pain or pain from superficial structures. These differences in pain perception and in the stimuli required to evoke pain are summarized in Table 61-1. Pain from the skin can be localized precisely and is superficial and often sharp in nature. Pain from the chest wall (e.g., muscles, ribs, ligaments, parietal pleura) is intermediate in localization, depth, and sharpness (see Chapter 12 and Chapter 60). Also, chest wall pain is often exacerbated by movement, such as with breathing or coughing.

Structure	Effective stimulus	Conscious pain perception
Skin	Discrete touch, pinprick, heat, cold	Precisely localized, superficial, burning, sharp
Chest wall	Deep pressure, movement	Intermediate in localization, aching, sharp or dull
Heart and thoracic viscera	Ischemia, distension, movement, muscle spasm	Vague, diffuse, deep, aching, usually dull

From Edmeads J, Billings RF. Neurological and psychological aspects of chest pain. In: Levene DL, Billings RF, eds. *Chest pain: an integrated diagnostic approach*. Philadelphia: Lea & Febiger, 1977, with permission.

TABLE 61-1. Differences in pain perception from heart, chest wall, and skin

Although ischemic myocardial pain can occur almost anywhere between the diaphragm and the mandible, it is commonly felt in the anterior chest, retrosternally, with radiation to one or both arms, to the throat and mandible, or to all these areas. Less commonly, the pain or discomfort is confined to the throat, arms, epigastrium, or even the interscapular region. Because of its visceral origin, ischemic myocardial pain or discomfort is generally referred to an area of substantial size, such as the patient's fist or a larger area. Pain that is discretely confined to a small area on the chest or that can be localized by the patient with a single finger is usually not pain of myocardial ischemia but is chest wall pain. It is generally believed that the intensity and size of the area of true visceral and referred visceral pain are influenced to a significant degree by the degree and size of the myocardial ischemia or myocardial necrosis. The greater the degree and area of myocardial ischemia, the greater the nociceptive barrage into the neuraxis, with consequent spread of neuropathophysiology into the spinal cord and probably the brainstem and, consequently, the greater the spread and intensity of the pain. In addition to the pain, the patient may develop hyperalgesia in the spinal segments involved.

Ischemic myocardial pain generally lasts 5 to 15 minutes for stable exertional angina, 15 to 30 minutes or longer for unstable angina and variant angina, and 1 to 8 hours or more for AMI. The acute pain of infarction is usually intense, often accompanied by a strong alarm reaction and a feeling of impending death, and not infrequently by nausea, vomiting, and profuse sweating. After a period of several hours, some AMI patients feel the pain to be localized more precisely, originating in the thoracic wall or upper limbs. Some authors consider this to be the second phase of AMI and have described (28) that, among their patients, many experienced muscle tenderness in the pectoralis major, the deep muscles of the interscapular region, the muscles of the forearm, and less frequently the trapezius.

Fleeting pain lasting from a few seconds to a minute is almost certainly not pain of myocardial ischemia. Likewise, pain that persists for days is unlikely to be ischemic myocardial pain. In typical angina pectoris, chest pain relief usually occurs within 2 to 5 minutes after taking sublingual nitroglycerin. Some patients might require a second nitroglycerin for complete relief, but the beginning of subsidence of the pain occurs within 3 to 5 minutes. Pain that takes 15 minutes or longer to be relieved by rest or nitroglycerin either is not caused by myocardial ischemia or is a more severe form, such as unstable angina or AMI. It is also true that nitroglycerin provides relief of noncardiac chest pain, due to its actions as a smooth muscle relaxant; therefore, its specificity for the conclusive diagnosis is low. Nitroglycerin is a somewhat

unstable compound, especially when exposed to heat or sunlight, and can lose its vasoactive potency. Use of old nitroglycerin is another reason for failure of prompt relief of angina. Many patients can recognize nonpotent nitroglycerin because it does not sting under the tongue or give a feeling of fullness in the head, as does fresh, potent drug.

Neuropathophysiology

The development of sophisticated electrophysiologic and histologic techniques since 1950 has permitted numerous studies that have greatly complemented and supplemented our knowledge of neuroanatomy (see Chapter 3 and Chapter 60). These studies, reviewed by Malliani (29), have formed the basis for our understanding of the location and function of the sympathetic and vagal afferent nerves and of their roles in activating homeostatic reflex mechanisms, as well as contributing to the pathophysiologic states caused by cardiac disease.

Agostini and colleagues (30) demonstrated that the heart has a substantial afferent innervation of A-d and C fibers from the vagus nerves. Others have shown that many of these afferent fibers respond to bradykinin and to ischemia, as well as to various mechanical stimuli (31,32). The precise role of these fibers in pain sensation (i.e., nociception) is still controversial (33). Evidence from animal studies since 1925 seemed to indicate that nociceptive information is transmitted primarily by sympathetic afferents (18,34), which are also involved in reflexes that control cardiovascular homeostasis. Whether sympathetic afferents transmit all ischemic pain sensations to the central nervous system has been called into question, however, by a number of clinical studies that reported the degree of anginal amelioration in patients treated in the early to mid-twentieth century with ablation of cervical, thoracic, or both sympathetic afferents (reviewed in 33). Thoracic sympathectomy or dorsal rhizotomy was poorly tolerated, with death rates approaching 10% in most series. Six studies, each inclusive of greater than or equal to 50 treated patients, all agreed in their findings of complete relief in only 50% to 60%, partial relief in 30% to 40%, and no relief in 10% to 15% of such treated patients. These consistent results suggest that the pain of cardiac ischemia may be transmitted at least in part through parasympathetic (vagal), as well as sympathetic, afferents. Vagal afferents may also play a role in modulation of cardiac pain (see Central Mechanisms, later in this chapter).

Roughly equal numbers of myelinated A-d and unmyelinated C fibers run in the cardiac sympathetic nerves. Direct recordings show that both fiber types are spontaneously active under ambient conditions (29,35). Single-unit recordings from white rami communicantes or dorsal roots of the thoracic sympathetics to the heart have shown that during coronary occlusion the activity of A-d and C fibers increases significantly (36,37 and 38). The responses of many A-d units are slow (mean, 80 seconds), appear to depend on myocardial stretching, and have spontaneous active discharge that occurs in synchrony with cardiac rhythm. Moreover, sympathetic afferent activity increases when the pressure within the heart increases (29,39). Responses of most C-fiber units are quicker, with a latency of 10 to 20 seconds following coronary occlusion, and the resulting irregular firing is unrelated to mechanical factors or to cardiac rhythm. These characteristics have led to the proposal that most A-d and a few C fibers serve a *mechanosensitive* function following either internally derived mechanical perturbation or on blunt probing or mechanical deformation of the heart or surrounding structures, and are concerned with the reflex regulation of circulation. Serotonin, histamine, bradykinin, and acids markedly excite both C and some A-d sympathetic afferents (40,41 and 42), and the effects of bradykinin are markedly enhanced by prostaglandins (42,43). It has thus been held that most C fibers and a few A-d fibers function in a *chemosensitive* mode (38). An evolving model emphasizes increasing recognition of *polymodal* fibers that may function in both mechanosensitive and chemosensitive modes (44). It has been suggested that cardiac pain is produced by the release of humoral (algogenic) agents from ischemic myocardial muscles, which sensitize or frankly activate the terminals of these afferent neurons. Because bradykinin and prostaglandins are formed and released in heart muscles following ischemia (45,46), and because prostaglandins have been shown to potentiate the algogenic effects of bradykinin in other tissues (see Chapter 3), a classical view is that angina results from the excitation of afferent terminals by the joint release of neurohumoral substances such as prostaglandins (43), serotonin (47), adenosine (38), bradykinin (43), or all of these.

The early work of investigators such as Brown and Malliani (48) postulated the existence of specific cardiac nociceptors, but with increasing characterization of afferent sympathetic fibers (presence of spontaneous baseline activity, responsiveness to hemodynamic events) an alternative explanation was needed. A modified version of the *intensive theory* (see Chapter 3) was proposed as a working hypothesis: Cardiac pain can result from the extreme excitation of a spatially restricted population of afferent sympathetic fibers, hence from an afferent code based on a peculiar spatiotemporal pattern (49).

The definitive explanation for the perception of ischemia remains elusive, however (50). While there appears to be agreement that both sympathetic and vagal afferents participate in the transmission of ischemic pain, the precise *sensor* of ischemia remains to be determined. Some answers may be forthcoming from the combination of classical physiology with molecular biology. The superfamily of degenerin/EnaC ion channels participates in mechanotransduction in phylogenetically diverse organisms ranging from *Caenorhabditis elegans* to mammals (51). A proton-gated ion channel member of this superfamily has been described (52), which is an intuitive candidate for nociception in the myocardium (53), given the known wide swings in pH under pathologic conditions of ischemia and infarction (54). Innovative methods of patch clamping with tissue culture may enable further characterization of an alternate candidate nociceptor family, the ATP-sensitive P2X3 ligand-gated ion channels (55).

Central Mechanisms

Myocardial ischemia, whether caused by atherosclerotic coronary artery disease or another cause of myocardial oxygen supply and demand imbalance, produces true visceral pain, felt deep in the chest and described as vague, poorly localized, and aching in character, and frequently radiating to sites outside of the chest, especially the inner aspects of the arms, neck, and occasionally the jaw. The mechanism(s) of visceral pain has not been precisely defined, but it is probably a result of nociceptive impulses passing to the upper thoracic spinal cord, where they excite cell bodies of spinothalamic tract (STT) neurons and possibly the neurons of other ascending systems. Although STT cells that respond specifically to visceral nociceptive impulses but not to cutaneous inputs have not been found, clinical evidence suggests that this is the mechanism for true visceral pain (56).

The mechanisms of *referred* visceral pain are discussed in Chapter 3 and Chapter 4. Some experimental studies concerning the neuropathophysiology of the referred pain produced by myocardial ischemia have been carried out. Foreman and associates (57,58) have studied the effects of electrical stimulation of sympathetic afferents, the application of bradykinin into the heart, and noxious stimulation of the skin and muscle and of coronary artery occlusion in monkeys. They noted that these interventions all excited high-threshold and wide dynamic range spinothalamic neurons located primarily in laminae IV and V (68%), but also in laminae VII (24%) and I (8%) of the upper four or five thoracic segments. Of these STT cells, 64% were high-threshold neurons, 26% were wide dynamic range neurons, and almost 10% were high-threshold inhibitory neurons. Those in the latter category consisted of cells that were excited by pinch of the skin but inhibited by blowing hair on the skin (59). The following results were obtained: (a) these STT cells respond to A-d and C sympathetic afferents but not to A-b afferents; (b) all the STT cells receive a convergent input from A-d and C nociceptors in the skin and underlying muscles, as well as from the heart; and (c) the receptive fields of the cutaneous and muscle afferents are located in the ipsilateral upper anterior and lateral chest and in the medial and lateral aspects of the ipsilateral forelimb. In one study it was found that approximately 40% of STT cells received input from both A-d and C sympathetic afferents, 50% received only A-d fiber input, and 10% received only C fiber input. These and other data support the *projection-convergence* theory of Ruch (Fig. 61-1), which provides an explanation for cardiac pain being felt in the anterior chest and arms (see Chapter 3 and Chapter 4 for detailed discussion of this and other theories of referred pain). Moreover, it has been shown that neurons in the thalamic nuclei, where the axons of STT cells terminate, respond to noxious cutaneous input and to noxious stimulation of the viscera. Viscerosomatic convergence has also been found in the somatosensory cortex.

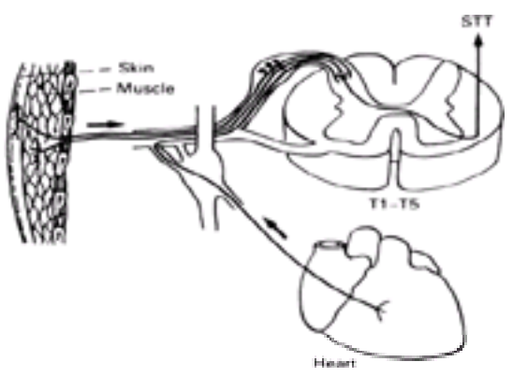

Figure 61-1. Schematic depiction of the projection-convergence theory of Ruch to explain the mechanism of cardiac pain. Afferent sympathetic fibers from the heart, skin, and muscles converge on the same spinothalamic tract (STT) cell and the cell of spinoreticulothalamic tract that transmits the impulses to the lateral and medial thalamus, respectively. Because the spinoreticulothalamic tract is a multisynaptic network, it mediates nociceptive impulses slowly and these are perceived as diffuse aching visceral pain. The spinothalamic tract cells project to the lateral thalamus that is concerned with the sensory discriminative function. (See Chapter 3, Chapter 4

and Chapter 5 for details.)

Ammons and associates (60) demonstrated that electrical stimulation of the left thoracic vagus nerve caused inhibition of the spontaneous activity of 61% of STT cells in the T-1 to T-5 segments. Moreover, left thoracic vagal stimulation inhibited 100% of the STT cells that responded to noxious somatic stimulation. Stimulation of the cardiac vagal branch could produce similar results, but stimulation of the vagal fibers below the heart could not produce inhibition. Effects of vagal stimulation completely disappeared after the vagi were transected in the cervical region. Vagal stimulation also inhibited the response of the STT cells to intracardiac injection of bradykinin (61). These results indicate that activation of descending pathways initiated by cardiac or cardiopulmonary vagal afferents is powerful enough to depress cell activity, even when the cell receives noxious input. It was also suggested that vagal inhibition of STT neurons was mediated by activation of descending systems that are part of the system for pain modulation (see Chapter 4). Stimulation of the nucleus raphe magnus inhibited all the STT cells in the upper thoracic segments that responded with an increased discharge to the intracardiac injection of bradykinin (60). It was postulated that the afferent vagal impulses that reach the nucleus of the tractus solitarius activate efferent fibers that project to the medial reticular formation and the hypothalamus, which in turn causes stimulation of the nucleus raphe magnus (58). These interactions may have implications for the high incidence of painless myocardial ischemia or infarction (see following discussion). One possibility is that vagal input into the brainstem powerfully activates descending inhibitory pathways, which in turn reduce the responsiveness of STT cells to the excitatory effects of sympathetic afferent fibers (62).

A limited amount of clinical data consistent with the previously mentioned observations is available. Studies indicate that as many as 70% of episodes of myocardial ischemia may be clinically silent, while 30% of AMIs are painless (63). Silent ischemia is clinically important because it is associated with an increased risk of adverse events subsequent to an episode of unstable angina (64) or AMI (65). Individual patients may have both painful and painless ischemic episodes that could be determined by the severity of ischemia but may be determined by other factors. To explore this issue, Rosen et al. used positron emission tomography as a measure of regional neuronal activation in a defined group of patients with two- or three-vessel coronary artery disease and silent ischemia, compared with a well-matched control group with clinical angina (66). Ischemia was induced and quantified by standard dobutamine stress echocardiography, using a graded infusion of the synthetic catechol to increase the determinants of myocardial oxygen consumption: heart rate, contractility, and blood pressure. In the silent ischemia group, seven of nine patients became aware of a forceful heartbeat, one experienced chest wall warmth, and one was asymptomatic, while ischemic ST segment depression was detected by ECG and wall motion abnormalities observed by echocardiography. In contrast, seven of seven of the symptomatic group experienced typical angina pectoris; both the time to significant ECG change and the extent of changes were similar between the groups. By positron emission tomography, both groups experienced equivalent dobutamine-dependent increases in thalamic activation, but the extent of cortical activation was significantly greater in the angina group. Cortical regions activated in the angina group included the bilateral anterior and ventral cingulate cortex, mesial orbitofrontal, and basal frontal cortex and left temporal lobe. This study has several implications. Equivalent ischemic stress in patients with or without angina pectoris was associated with a similar degree of thalamic activation; the absence of angina was thus unlikely due to the failure of peripheral sensing or transmission to the thalamus. The cerebral areas activated in the angina group may represent specific cortical projections within a pathway mediating the proprioception of cardiac pain. Failure of these areas to be activated in the silent ischemia group may have been due in part to differential gating of impulses at the thalamic level. Clarification of these mechanisms will require further study.

Effects of Myocardial Ischemia and Pain

Tissue damage from myocardial ischemia and mechanical changes of the ventricles consequent to an acute infarct produce local biochemical changes and stimulate vagal and sympathetic afferents to produce pain and segmental and suprasegmental reflex responses (67). In addition to the excitation of these sympathetic afferents by the algogenic substances that excite and sensitize the sympathetic afferents directly, they can also be stimulated directly by physiologic motion of ischemic myocardium to produce a further increase in sympathetic reflex activity. Cardiac vagal afferents are mechanoreceptors that can also become sensitized after AMI and provoke abnormal reflexes.

Reflexes elicited by AMI involve afferents and efferents of both cardiac vagi and cardiac sympathetic nerves, which produce symptoms and signs characteristic of vasovagal and sympathosympathetic reflexes (29,67). Under normal conditions these two extrinsic neurogenic controls of cardiac function have reciprocal neural organization, so that stimulation of sympathetic afferents not only elicits an increased action of sympathetic afferents but also, simultaneously, reduces the discharge of vagal efferents and vice versa. Under pathologic conditions, however, this typical response is disturbed. Consequently, in most AMI patients, both systems are overactive. The one that predominates is determined by many interrelated factors, including the presence and intensity of pain and the size and location of the infarct; sympathetic overactivity predominates in cases of anterior infarction, while parasympathetic overactivity predominates in patients with inferior infarctions (67,68).

An example of the potential danger of abnormal vasovagal reflexes is the Bezold-Jarisch reflex of severe bradycardia, atrioventricular (AV) block, peripheral vasodilation, and consequent severe hypotension. The concurrent sympathetic hyperactivity increases myocardiac contractility and can be considered to be an important mechanism for opposing ventricular dilatation and cardiogenic shock. On the other hand, these potentially protective sympathetic reflexes can be detrimental by imposing a demand for increased oxygen consumption on the myocardium (67). Moreover, animal experimentation has shown that the a-adrenergic portion of the sympathetic nervous system can exert a vasoconstrictor effect on the coronary vessels, with a consequent decrease in both coronary blood flow and myocardial oxygen supply (69,70). In addition to the sympathosympathetic reflexes, stimulation of sympathetic afferents by mediation of nociceptive (pain) impulses can elicit widespread cardiac, vascular, and hormonal changes.

Thus, it appears that segmental and suprasegmental sympathetic reflexes, anxiety, and psychological stress may increase the workload of the heart and its oxygen consumption. Moreover, increased coronary vasomotor tone can further decrease blood flow in the already compromised atherosclerotic coronary circulation, worsening supply and demand mismatch, leading to further ischemia and possibly expanding the infarction. One or more of these responses can be a critical factor in causing the death of the patient. Therefore, it is essential to relieve the pain, anxiety, and mental stress and decrease or eliminate the abnormal reflexes promptly and effectively.

MYOCARDIAL ISCHEMIC SYNDROMES

Etiology and Pathophysiology of Coronary Artery Disease

Manifestations of myocardial ischemia can be classified according to clinical presentation, pathologic anatomy, and pathophysiology. The pathophysiology of these *syndromes* is incompletely understood, and there may be overlap between clinical presentations (Table 61-2). This discussion concentrates on atherosclerotic coronary artery disease because it accounts for 95% or more of patients with a myocardial ischemic syndrome caused by coronary artery disease. Myocardial ischemia can occur in the absence of anatomic coronary artery disease because of an activated clotting system, abnormal vasoreactivity (spasm), or marked myocardial hypertrophy. The most common pathophysiologic substrate for myocardial ischemia in patients with normal coronary arteries is severe ventricular hypertrophy, such that the oxygen requirements of the myocardium exceed its capacity to increase its blood supply (e.g., aortic stenosis or regurgitation, severe hypertension, hypertrophic cardiomyopathy). Although the pathogenesis is different, the underlying biochemical mechanisms, symptoms, and ECG manifestations are often similar to those of ischemia resulting from coronary artery disease.

Syndrome	Clinical presentation	Pathoanatomy	Pathophysiology
Stable angina	Exertional chest pain	Atherosclerotic coronary stenosis ≥50%	Provoked by increase in myocardial oxygen demand
Unstable angina	Chest pain at rest	Atherosclerotic coronary stenosis with platelet thrombus	Reduction in coronary blood flow by partially occluding thrombus or enhanced vasoreactivity
Acute myocardial infarction			
Q-wave infarction ST elevation	Severe unprovoked chest pain	Atherosclerotic coronary stenosis completely occluded by thrombus	Precipitating event unknown, possibly rupture of plaque, platelet aggregation, hemorrhage into plaque, or all three
Non-Q-wave infarction	Severe unprovoked chest pain	Atherosclerotic coronary stenosis partially occluded	Reduction in coronary blood flow due to severe coronary spasm or partially occluding thrombus
Silent myocardial ischemia	Ischemic ST changes without pain	Uncertain; probably atherosclerotic coronary stenosis ≥50%	Defect in pain recognition versus subclinical ischemic episodes

TABLE 61-2. Classification of myocardial ischemia syndromes

Prior mantle radiation for mediastinal cancer or syphilis can produce obstruction at the origins of the coronary arteries, the latter through extension of the aortitis to the coronary ostia; the myocardial ischemic syndrome is the same as if the obstruction were produced by atherosclerosis. Collagen vascular diseases can produce obstruction of the coronary arteries, usually smaller branches, through an arteritis. Kawasaki's disease, a periarteritis-like disease of infants, can produce aneurysms of coronary arteries and other medium-sized arteries. Congenital anomalies of the coronary arteries can also produce myocardial ischemia; the most serious of these are the origin of a coronary artery from the pulmonary artery and the anomalous origin of the left coronary artery from the right coronary sinus with passage between the aorta and pulmonary artery.

Dissection of the aorta can produce acute occlusion of a coronary artery if the dissection extends proximally to include the orifice of a coronary artery. Acute embolic coronary occlusion can occur with endocarditis or in patients with prosthetic aortic valves. Rarely, blunt chest trauma, such as with a steering wheel injury, can produce damage to a coronary artery, usually the left anterior descending coronary artery. Rarely, coronary artery obstruction is caused by iatrogenic intimal damage by a catheter or cannula; this has been observed in coronary angiography, coronary angioplasty, and aortic valve replacement, in which the coronary arteries are often perfused with a cannula.

The pathophysiology of atherosclerosis involves the deposition of cholesterol and other lipids, the proliferation of smooth muscle cells, and the laying down of collagen in the subendothelial intima of medium-sized and large arteries. In large arteries the atherosclerotic process can damage the media and result in the formation of aneurysms, as occurs commonly in the abdominal aorta. In medium-sized arteries the atherosclerotic process more commonly results in obstruction through the heaping up of the atheroma to impinge on the vessel lumen, as in the coronary and cerebral arteries. Development of atheroma probably begins in childhood and usually takes 30 to 50 years to progress to the stage at which clinical manifestations are produced (71).

The pathogenesis of atherosclerosis has been the subject of intense research activity for the past 40 years, but the basic pathophysiologic mechanisms are still largely speculative. Three hypotheses have been proposed: the response to injury hypothesis, proposed by Ross and Glomset (72); the monoclonal hypothesis of Benditt and Benditt (73), who proposed that the atheroma is essentially a benign tumor; and the lipogenic hypothesis, which emphasizes altered lipid metabolism. Presently, the response to injury hypothesis seems best able to explain the available epidemiologic and biochemical data. According to this theory, the endothelium is damaged by any of various noxious stimuli (e.g., mechanical forces, hyperlipidemia, homocysteine, immunologic factors, toxins, such as those from cigarette smoke, or viruses), resulting in abnormal permeability or even denudation. If the stimulus ceases, healing of the intima can occur. If the intimal injury is sufficiently severe or prolonged, however, transudation of lipids occurs together with egress of abnormal cells (smooth muscle cells and macrophages) into the subintimal region. As the process continues, collagen is laid down and cholesterol and its esters are taken up by cells in the lesion. Studies demonstrate that the media enlarges to accommodate the developing plaque, but once the area within the media has increased by approximately 40%, the vessel can no longer enlarge and the plaque begins to significantly decrease the lumen area (74). Destabilization of such a plaque can then trigger an acute coronary syndrome, as discussed here.

General Principles of Diagnosis

History

The patient's history is the single most important diagnostic tool in the evaluation of coronary artery disease. The nature, location, duration of the pain, and the factors that provoke and relieve it constitute the most useful information obtained from the history. In the vast majority of patients with angina pectoris the diagnosis can be made from the history alone, provided that proper history-taking skills are combined with knowledge of the wide variation in symptoms that can occur. Historical (subjective) elements can then be combined with readily obtained objective data (physical examination and ECG) to formulate a provisional explanation for the occurrence of acute chest pain syndromes (Table 61-3). Ischemic myocardial pain can be located anywhere between the diaphragm and mandible; most often it is initially retrosternal (true visceral pain), but soon involves the anterior chest and radiates to both arms, neck, and occasionally the jaw. By its nature, ischemic myocardial pain is vague, diffuse, and ill defined, hence the *visceral nature*. Many patients find it difficult to describe such vague symptoms; this is the setting in which directed yes or no questions can easily result in an incorrect database. The importance of initiating the history taking with nondirected questions cannot be overemphasized. The question“Do you have chest pain?” invariably produces an affirmative response, because everyone has chest pain at one time or another, and a more productive line of inquiry may center on the nature of the patient's“chest discomfort.”

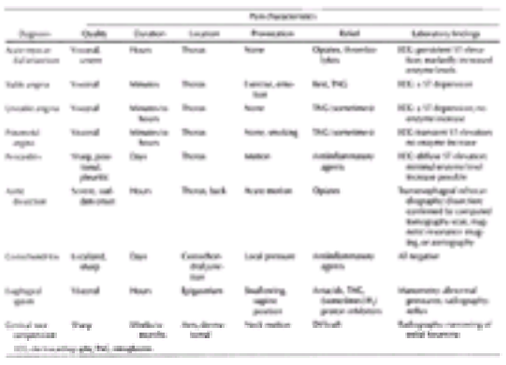

TABLE 61-3. Differential diagnosis of acute chest pain syndromes

It is useful to quantify the amount of exertion required to precipitate pain in patients with exertional angina. Even though the exertion required might vary within the same patient, a classification based on the level of precipitating activity is useful in assessing the severity of the disease, the patient's disability, the effects of therapy, and the progression of the disease. The guidelines of the Canadian Cardiovascular Society are particularly useful because they were designed specifically for angina (75):

- Class 1: Angina occurs only with strenuous or rapid or prolonged exertion at work or recreation. Ordinary physical activity, such as walking or climbing stairs, does not cause angina.
- Class 2: Angina results in slight limitation of ordinary activity. It can be produced by walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, exercise in cold or during emotional distress, or exercise in the first hours after awakening.
- Class 3: Angina results in marked limitation of ordinary physical activity. It can be produced by walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.
- Class 4: Angina results in the inability to carry on any physical activity without discomfort. Angina can be present at rest.

Physical Examination

The physical examination is often overlooked as an important and useful diagnostic tool in patients with coronary heart disease, because it is so often normal. Nevertheless, a careful physical examination is essential, even for the negative information it produces. Reversible risk factors for atherosclerosis can be detected by identifying hypertension, xanthomas of hyperlipidemia, or nicotine stains caused by cigarette smoking. The adequacy of myocardial function can be assessed by examining for evidence of congestive heart failure, such as elevated jugular venous pressure, pulmonary rales, gallop rhythm, cardiomegaly, or peripheral edema. Noncoronary causes of myocardial ischemia, such as aortic valve disease or hypertrophic cardiomyopathy, are usually detected on physical examination.

Routine Laboratory Studies

Routine laboratory studies are often normal, but still important, like the physical examination. Severe anemia must be excluded as a cause of angina. Diabetes as a risk factor for atherosclerosis needs to be identified and treated. Assessment of renal function is essential, particularly in patients being considered for coronary arteriography or coronary artery bypass surgery. Serum lipid measurements with determination of high-density lipoprotein and low-density lipoprotein are also

essential to identify risk factors and initiate treatment. The West of Scotland Coronary Prevention Study demonstrated that a high baseline high-density lipoprotein was a strong negative predictor of coronary events, and lowering the low-density lipoprotein using pravastatin prevented coronary events by 31% in men without prior AMI (76). Both the 4S and CARE trials demonstrated similar benefits for patients with hypercholesterolemia when statin therapy was initiated after AMI (77,78). The release of myocardial isoenzymes, such as the MB fraction of creatine phosphokinase or Troponin I, is particularly useful in detecting myocardial necrosis and is discussed further (see Acute Myocardial Infarction, later in this chapter).

Resting Electrocardiography

The resting ECG is a cost-effective tool in the evaluation of patients with chest pain, provided that its limitations are recognized. It is normal in approximately 50% of patients with angina but no previous AMI; thus a normal resting ECG does not exclude severe coronary artery disease (79). The presence of left ventricular hypertrophy or ST wave changes consistent with myocardial ischemia favors the diagnosis of angina pectoris; the presence of significant Q waves makes coronary artery disease very likely (80). The presence of arrhythmias and atrioventricular (AV) or conduction system blocks on the resting ECG generally increases the probability of coronary artery disease, but these findings are also prevalent enough with other forms of cardiac disease as to lack specificity in the prediction of ischemic heart disease likelihood. An ECG obtained from a patient actively experiencing angina is abnormal in approximately 50% of patients with coronary artery disease and a normal resting ECG. If the patient is at rest this finding may define an unstable coronary syndrome and indicate that early coronary angiography is appropriate for risk stratification (81).

Chest Roentgenography

Most patients with coronary artery disease and preserved left ventricular function have normal cardiovascular structures on the chest roentgenography. The primary value of the chest roentgenogram is in the assessment of heart failure. Important signs of heart failure are cardiomegaly, pleural effusions, redistribution of the pulmonary venous pattern to the upper lobes, and signs of interstitial edema and dilated lymphatics (Kerley B lines). The physical examination is notoriously insensitive in detecting cardiac enlargement; although less sensitive than echocardiographic or angiographic techniques, the chest roentgenogram is a cost-effective way of assessing cardiac chamber enlargement. Furthermore, the heart size on the chest roentgenogram is an important prognostic indicator (82). In the absence of severe valvular regurgitation an inverse relationship between left ventricular size and ejection fraction (fraction of end-diastolic volume ejected with each beat) can be seen. Thus, significant left ventricular enlargement in the absence of valvular regurgitation is almost always associated with severe, chronic left ventricular dysfunction; the status of left ventricular systolic function is one of the two most powerful predictors of survival in patients with coronary artery disease (83).

Calcification of the coronary arteries is an uncommon finding on the chest roentgenogram but almost always indicates severe coronary atherosclerosis and often obstruction. Calcification seen in the region of the left ventricle can represent a calcified thrombus in a ventricular aneurysm. The chest roentgenogram is insensitive in the detection of left ventricular aneurysms, but deviation of the midportion of the left ventricular silhouette superiorly and to the left on the posteroanterior film can be a sign of an anterolateral aneurysm.

Exercise Stress Test

The exercise stress test yields valuable information not only from serially obtained ECG traces, but also from other physiologic responses to exercise and the maximum exercise capacity. The exercise stress test has been the traditional noninvasive method for evaluating patients with chest pain syndromes and has also been widely applied as a useful indicator of subsequent risk following AMI. The stress test is also useful for assessing disability and evaluating the results of therapy. Exercise stress testing is frequently misused, however, either because the wrong questions are asked about it or because attention is focused on the ECG and the other important data available are overlooked.

The application of Bayes' theorem has been useful in deciding which patients are most likely to have the benefit of greater assuredness of diagnosis from the addition of exercise stress testing to the history, physical examination, and routine laboratory data, including the resting ECG (84). Patients whose pretest probability of coronary artery disease is in the intermediate range benefit most diagnostically from the performance of the test. Examples of such patients would be a middle-aged man with risk factors for coronary heart disease and a chest pain syndrome not fully typical of angina pectoris, or a postmenopausal woman with typical angina pectoris. In both of these examples the probability of coronary artery disease causing the symptoms from the information given is in the range of 30% to 60%.

An exercise stress test with greater than 1 mm horizontal or down-sloping ST-segment depression persisting 80 milliseconds after the J point (junction of terminal QRS component and the ST segment) significantly increases the probability of finding a significant coronary artery obstruction on angiography, whereas no significant ST-segment depression at maximal exercise significantly reduces this probability (85,86). In patients in whom the history and other data obtained before the exercise test provide a high degree of certainty regarding the diagnosis (i.e., the pretest probability of obstructive coronary artery disease is either extremely high or extremely low), exercise stress testing is not indicated for the sole purpose of establishing the diagnosis. For example, in the man with risk factors and typical angina who has a pretest probability of obstructive coronary disease of more than 90%, a positive ST-segment response on exercise testing increases this probability only minimally, whereas a negative ST-segment response is not sufficient to exclude obstructive coronary artery disease. In studies designed to eliminate workup bias, by commitment of intermediate probability patients with chest pain to both exercise treadmill testing and coronary angiography, the sensitivity of stress testing has ranged from 45% to 50% and the specificity from 85% to 90% (87,88).

Exercise testing is also important for assessing the severity of disease, assessing prognosis, and evaluating the results of therapy. Many patients with angina whose diagnosis is clear from the history and resting ECG should have exercise stress testing to assess the severity of the disease, to provide an estimate of the likelihood of future cardiac events, and to aid in determining the need for coronary angiography. Whereas the ST-segment response to exertion is the most commonly used diagnostic criterion (usually depression greater than or equal to 1 mm), the ST segment has more limited usefulness in the assessment of prognosis. In an analysis of patients in the Seattle Heart Watch Coronary Arteriography Registry, the duration of exercise or maximal workload achieved, maximum heart rate, and maximum systolic blood pressure were the most powerful predictors of prognosis in patients with known coronary artery disease (83). In a multivariate analysis, the rate-pressure product (the product of maximal heart rate and maximal systolic blood pressure during exercise) included all the prognostic information available in the exercise test. In other studies marked ST-segment depression (greater than or equal to 2 mm) has been shown to be a useful adverse prognostic indicator (89). Such functional information is also most useful in patients undergoing low-level post-AMI stress testing.

The absolute contraindications to exercise testing include AMI within 2 days, cardiac arrhythmias causing symptoms or hemodynamic compromise, symptomatic and severe aortic stenosis, symptomatic heart failure, acute pulmonary embolus or pulmonary infarction, acute myocarditis or pericarditis, and acute aortic dissection. Relative contraindications include known left main coronary stenosis (greater than or equal to 70%), moderate aortic stenosis, electrolyte abnormalities, systolic blood pressure greater than 200 mm Hg, diastolic blood pressure greater than 110 mm Hg, uncontrolled tachyarrhythmias or bradyarrhythmias, hypertrophic cardiomyopathy or other forms of outflow tract obstruction, mental or physical impairment leading to an inability to exercise adequately, and high-grade AV block (90). Unstable angina was previously considered to be a contraindication to exercise testing, but more recent studies have shown that both exercise treadmill (91,92), and pharmacologic (93,94), testing are safe in low- or intermediate-risk patients hospitalized with unstable angina who have had AMI ruled out and are free of angina and congestive heart failure.

Stress Imaging Modalities

Both the sensitivity and the specificity of ECG stress imaging for detection of coronary ischemia can be increased through the concomitant use of an imaging modality such as nuclear perfusion imaging (95) or echocardiography (96,97). Nuclear perfusion imaging typically uses intravenously injected agents that are taken up from the circulation by myocardial cells; both intact regional blood flow and viable myocardium are required for normal uptake. Agents used include thallium 201, a potassium analog that is avidly taken up and accumulated by normally perfused myocardium, and technetium 99m–tagged synthetic organic complexes such as tetrofosmin or sestamibi. The latter group of agents, in contrast to thallium, is maximally taken up during the first pass through the coronary circulation, lending itself to increasing use in the assessment and risk stratification of chest pain in the emergency setting. The technetium 99m–based agents decay with production of higher energy g-rays, improving the signal-to-noise ratio in large patients or those with obstructive airways disease, and enabling faster data collection.

Patients are usually exercised with a standard treadmill stress protocol or the infusion of a coronary vasodilator such as dipyridamole. At the time of development of angina or shortly before maximal stress has been achieved, the imaging agent is injected through a peripheral vein. Imaging of the myocardium commences immediately with a standard gamma camera or with a tomographic system, such as single photon emission computed tomography (SPECT), which yields three-dimensional computer-generated cardiac images. If an area of myocardium is supplied by a significantly (greater than or equal to 50% to 70%) stenotic coronary artery, it becomes transiently ischemic because the restricted coronary flow cannot meet the increased metabolic demands. This area does not take up the imaging

agent and is visualized as a defect on the image obtained immediately on completion of exercise. Over a period of several hours, thallium redistributes to the area that showed a defect on the early image; thus, an image obtained 3 or 4 hours after exercise shows normal uptake in the area of the defect on the early image. In contrast, scar caused by AMI cannot take up thallium either on the rest or stress image. Because technetium 99m–based agents do not redistribute, it is necessary to reinject the agent after a several-hour or overnight hiatus. An alternative used increasingly frequently is the stress dual isotope study, in which resting thallium SPECT images are compared with SPECT images obtained directly thereafter using a technetium 99m–based agent at peak stress (98). The scintigraphic window for technetium 99m imaging can be set so as to eliminate any signal from the weakly emitting thallium.

Coupling of two-dimensional echocardiographic imaging of the heart with physical or pharmacologic stress can also provide useful diagnostic and prognostic information regarding coronary heart disease. Stress echocardiography requires highly skilled and experienced sonographers and thus likely should be performed routinely in a practice setting or not offered. Current-generation echocardiographic equipment can typically display a series of resting cardiac cycles in each of a number of transducer projections through the heart. At maximal stress, imaging is repeated with attempts to recreate identical three-dimensional images, and the rest and stress images are then compared side by side. Sensitivity and specificity are greatest in younger, thin individuals with normal resting wall motion, who develop regional wall motion defects indicated by impaired systolic wall thickening (99). A purported advantage of the induction of ischemia with an inotropic agent (dobutamine) is the ability to administer graded stimuli (e.g., starting at 5 µg per kg per minute and increasing in increments of 5 to 10 µg per kg per minute to a maximal dose of 40 µg per kg per minute), with serial imaging at each infusion level. This protocol may be optimal for recreating the physiology of a graded exercise test response in patients who have noncardiac reasons for inability to exercise to an adequate stress level on a treadmill. The presence of significant wall motion abnormalities at rest limits the predictive value of changes observed with typical (exercise or pharmacologic) stress, in essence limiting the usefulness of the procedure to those with normal rest studies, with one exception. In patients with significant areas of viable but markedly hypoperfused (so-called hibernating) myocardium, the detection of improved wall motion with low doses (less than 10 µg per kg per minute) of dobutamine in areas that were at baseline markedly abnormal may indicate the potential for return to normal function with revascularization (100,101).

Cardiac Catheterization and Coronary Angiography

Selective coronary angiography, introduced by Sones in 1959, led to a totally new understanding of coronary anatomic pathology and made possible the development of surgical and percutaneous coronary revascularization. In this diagnostic procedure the coronary arteries (shown in Fig. 61-2) are selectively cannulated with separate preformed catheters for the right and left coronary arteries, introduced percutaneously through the femoral artery in the groin (Judkins' technique). Injecting 3 to 10 mL of iodinated radiographic contrast material and filming the output phosphor of a radiographic image intensifier provide excellent definition of the coronary arteries. In skilled hands the risk of coronary angiography is low, even in acutely ill patients such as those with AMI. The risk of coronary angiography is highest in the newborn, the elderly, the acutely ill, and those with severe left ventricular dysfunction. Selective coronary angiography is the only procedure currently available that accurately defines the location and severity of coronary arterial obstructions. As such, it is an invaluable tool in the evaluation of patients with chest pain syndromes. It is an essential prerequisite to consideration of coronary revascularization. It is useful in patients whose chest pain syndrome cannot be diagnosed noninvasively. In addition, it provides much vital prognostic information, because prognosis is strongly related to the amount of myocardium placed in jeopardy by severe proximal coronary arterial stenoses.

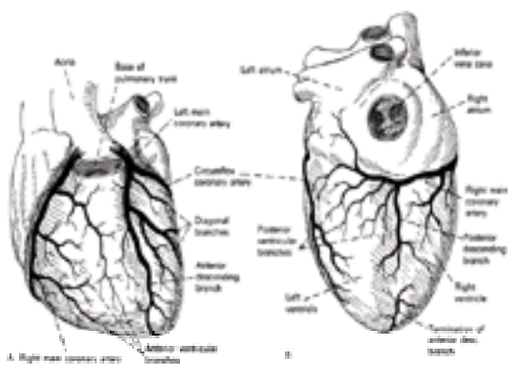

Figure 61-2. Anatomy of the coronary arteries and their branches. **A:** Anterior view. **B:** Posterior diaphragmatic view.

Stable Angina Pectoris

History

Angina pectoris can be defined as chest discomfort of a visceral nature precipitated by exertion or emotion and promptly relieved by rest or nitroglycerin. It is the most common symptomatic manifestation of stable coronary heart disease. Angina can occur in a stable pattern in many patients for a prolonged period of time (months to years). It differs from unstable angina in that a precipitating factor can generally be identified (usually exercise), and that relief occurs promptly with the removal of the precipitating factor or with the administration of sublingual nitroglycerin. The importance of angina pectoris is that it is often the most valuable clue to coronary artery disease, it is often disabling, and some patients with angina are at high risk for AMI or sudden cardiac death.

Stable angina pectoris occurs when the myocardial oxygen demand transiently exceeds the myocardial oxygen delivery because of an increase in a determinant of oxygen demand (Table 61-4). The pathologic substrate in the vast majority of patients is a significant coronary artery obstruction caused by an atherosclerotic plaque. The clinical syndrome of angina pectoris can also occur in patients who have hypertension (102), severe aortic valve disease (see Aortic Stenosis, later in this chapter), and hypertrophic cardiomyopathy. Most patients can be diagnosed on the basis of the history. The most important information to elicit from the history regarding angina regards the factors that precipitate the attack and how the patient relieves it. Typical precipitating factors are exertion and emotion. Isometric exertion, such as lifting over the head, is more likely to precipitate angina than isotonic exertion because of the marked increase in blood pressure that occurs with sustained isometric muscle contraction. Exertion performed after a large meal, during times of emotional distress, or on cold exposure is more likely to precipitate angina than exertion under other conditions. Angina tends to occur more frequently and with less provocation in the first hours after awakening. Stable angina is relieved within minutes by stopping exertion, alleviating the precipitating factor, or taking sublingual nitroglycerin.

Myocardial oxygen demand	Myocardial oxygen delivery
Heart rate	Coronary blood flow
	Transcoronary pressure gradient
Contractility	Aortic diastolic pressure
	Left ventricular diastolic pressure
Left ventricular wall stress	Coronary vascular resistance
Left ventricular systolic pressure	
Left ventricular size (radius)	Oxygen extraction
	Arterial saturation
	Arterial-coronary sinus oxygen difference

TABLE 61-4. Determinants of myocardial oxygen demand and delivery

The nature and location of angina also provide useful diagnostic clues. Angina is diffuse and vague; it is often described as a pressure sensation, a weight on the chest, or a constricting feeling in the chest and often in the neck. The patient may use a clenched fist to illustrate the constricting nature of the discomfort. Angina is not pleuritic and does not usually change with change in posture, as does pericardial pain. Angina is not fleeting; brief stabbing pains in the chest lasting only

seconds are probably neuritic in origin. The duration of angina is generally 5 to 15 minutes. Although angina can occur almost anywhere between the diaphragm and mandible, it is typically retrosternal with radiation into one or both arms, throat, and mandible. Occasionally, it can occur only in the arms, only in the mandible, or only in the interscapular region. Sometimes the pain can occur in the epigastrium and might be mistaken for gastrointestinal pain by the physician or patient, such as esophagitis or peptic ulcer. Because of its visceral nature, anginal pain generally encompasses a substantial area and is deep seated; pain that is localized to a small area on the chest wall (e.g., smaller than 1 to 2 inches in diameter) or that is superficial is generally not angina. Pain localized by the patient with a single finger is not likely to be angina. Table 61-5 lists historical features of angina.

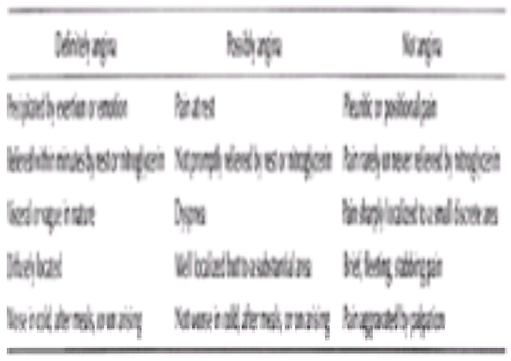

TABLE 61-5. Diagnostic clues of angina pectoris from the history

Physical Examination

Physical examination is typically the least useful of the diagnostic tools, but some helpful information can be obtained. Often, no cardiovascular abnormalities are detected. Particular attention to the major controllable determinants of myocardial oxygen consumption, heart rate, and systolic blood pressure is essential (see Table 61-4). Other causes of angina or anginalike pain, such as aortic valve disease, hypertrophic cardiomyopathy, or mitral valve prolapse can be excluded by careful examination for the appropriate murmurs or midsystolic click. Reproduction of the pain by firm palpation of the chest or by pressing on the ribs is useful in diagnosing chest wall pain. Costochondritis, a specific but uncommon inflammation of the costochondral junction, is best diagnosed by eliciting exquisite pain with light pressure over the costochondral junction approximately 1 to 2 inches lateral to the sternum. Symptoms and signs of congestive heart failure, such as elevated jugular venous pressure, pulmonary rales, or gallop rhythm, should be sought. Treatment of heart failure can also improve angina by lowering the left ventricular diastolic pressure, thereby improving the perfusion gradient for coronary blood flow and reducing the wall stress.

Routine Laboratory Testing

The resting ECG is often normal. Q waves provide evidence of old AMI and thereby of coronary heart disease but do not necessarily help to identify the cause of the presenting chest pain. An ECG taken during an anginal episode may be diagnostically useful when it shows ST-segment depression. The chest roentgenogram is helpful to the extent that it permits assessment for cardiomegaly and evidence of congestive heart failure. Routine blood tests exclude severe anemia (hematocrit below 25%) as a precipitating factor for angina and examine for risk factors of atherosclerotic heart disease such as diabetes or hyperlipidemia, but are of little direct value in determining whether the presenting complaints are the result of myocardial ischemia.

Stress Testing

The exercise stress ECG has been the traditional noninvasive diagnostic tool for the evaluation of angina pectoris, as was discussed previously. This study can often provide unique information such as objective documentation of a patient's exercise tolerance, the threshold for ischemia, and the efficacy of vasoactive and antianginal therapy in controlling the blood pressure and heart rate response to strenuous exercise. Most diagnostic laboratories use the protocol developed by Dr. Robert Bruce at the University of Washington, which is a graded protocol using 3-minute stages at increasing speed and walking grade. Each successive stage requires a defined amount of work from the patient, which has been correlated with many activities of daily life. Exercise testing should be considered for two principal indications: for diagnosis of the presence or absence of coronary artery disease and for the assessment of prognosis in patients with known coronary artery disease. Large-scale studies, such as the prospective Duke series (103), demonstrate the utility of treadmill stress testing for the detection of high-risk patients such as those with left main coronary artery disease, severe triple-vessel disease, and critical aortic stenosis. For example, in this series, patients who demonstrated inducible ischemic ECG changes and were unable to complete the first or second stage of the Bruce protocol had a prevalence of significant coronary artery disease of 98% and a prevalence of severe three-vessel coronary artery disease of 50% to 70%. Nearly 25% of these patients had left main coronary disease. Furthermore, the CASS registry found that the prognosis of patients who developed greater than or equal to 2 mm of ST depression in the first stage of the Bruce protocol is poor, with an annual mortality greater than 5% (104). In contrast, patients with a normal ECG at high workload carry a very favorable prognosis. Those completing stage III or higher with less than 1-mm ST depression were found to have an annual mortality of less than 1%. Thus, exercise testing is important for assessing severity of disease, prognosis, and response to therapy. Many patients whose diagnosis is suggested by the history should undergo exercise testing to determine whether further diagnostic tests, such as coronary angiography, are indicated or if coronary artery bypass grafting needs to be performed. Whereas the ST-segment response to exertion is the most commonly used diagnostic, the ST-segment response has more limited usefulness in prognostication (83). It is similarly underpowered to predict the stenotic vessel(s), for reasons that are unclear.

Stress Testing with Cardiac Imaging

Combining stress testing with imaging of the heart has also been useful both in establishing the diagnosis and assessing prognosis (105). Commonly combined modalities include exercise or pharmacologic stress testing with radionuclide perfusion SPECT imaging or echocardiographic wall motion analysis. These techniques are most useful in patients whose baseline ECG precludes obtaining diagnostic ST-segment changes with exercise testing (e.g., left ventricular hypertrophy with repolarization abnormalities or left bundle branch block). Such imaging techniques are required for the assessment of perfusion (or its surrogate cardiac wall motion by echocardiography) in patients undergoing pharmacologic stress.

Coronary Angiography

Despite major advances in sophisticated noninvasive diagnostic procedures, coronary angiography is the only technique that can reliably determine the location, number, and severity of coronary artery obstructions. It can be performed with relatively low morbidity and mortality (0.1%), but it is expensive, uses ionizing radiation, and does carry a small risk. For patients with stable angina, the following indications for diagnostic angiography have been included in the current guidelines: patients with angina pectoris who have been successfully resuscitated after an episode of sudden cardiac death; patients who cannot undergo noninvasive testing, or in whom such assessment has resulted in uncertainty of diagnosis; patients suspected of having a nonatherosclerotic cause of myocardial ischemia not revealed by noninvasive testing; and those with high pretest probability of left main or three-vessel coronary artery disease (81).

Treatment

Medical Therapy. Following diagnosis and assessment of risk for a major coronary event through noninvasive and invasive studies, if appropriate, the first step in therapy of stable angina should involve minimizing coronary artery disease risk factors and eliminating factors that aggravate angina. Hyperlipidemia (see Acute Myocardial Infarction, later in this chapter), cigarette smoking, and hypertension are the major controllable risk factors. Pipe and cigar smoking have also been associated with an increased risk of AMI or death, but to a lesser degree than cigarette smoking, probably because the dose is lower as a result of less inhalation of the pollutants. Weight reduction in obese patients, control of hyperglycemia in diabetics, correction of arterial hypoxemia in patients with pulmonary disease, control of tachycardia (particularly that caused by b-agonists used as bronchodilators), and a program of moderate isotonic exercise such as walking are also appropriate initial measures. Other medical conditions that aggravate angina, such as severe anemia, thyrotoxicosis, or congestive heart failure, should be diagnosed and treated.

Aspirin. Because the primary mechanism for events in patients with coronary atherosclerosis is destabilization of a plaque with formation of mural thrombus, it is

intuitive that all patients with atherosclerosis in general, and chronic stable angina in particular, use aspirin regularly if tolerated (106). The antithrombotic effects of aspirin are due to the inhibition in platelets of thromboxane A_2 synthesis (107). Although the benefits of aspirin therapy were initially demonstrated in the context of AMI and unstable angina, more recent studies have shown that risk of coronary events is reduced by aspirin use. The Physicians' Health Study included approximately 300 male physicians with chronic angina, but without prior AMI, who were shown to have an 87% reduction in the risk of AMI during 5 years of follow-up with the use of 325 mg of aspirin every other day (108). Similar reductions in the risk of AMI and sudden death were also observed in a mixed gender population (109) with the use of low-dose aspirin (75 mg per day).

b-*Adrenergic Blockers.* b-Adrenergic blockersare highly effective in reducing the frequency of anginal attacks and in improving exercise tolerance in patients with stable exertional angina (25). Their primary mechanism of action is most likely the reduction of myocardial oxygen demand by decreasing resting and exercise heart rates and, to a lesser extent, systolic blood pressure. More recent data indicate that b-blockade may also improve myocardial oxygen supply; continuous ambulatory ECG and blood pressure monitoring reveals a reduction in transient ischemic events (110). The most common side effects are fatigue, mental depression, exacerbation of congestive heart failure in patients with severe left ventricular dysfunction, and bronchoconstriction. b- Adrenergic blockers should be used cautiously in patients with a history of severe congestive heart failure or who have a left ventricular ejection fraction lower than 0.30, although studies suggest that such patients who can tolerate b blockade have a significant survival advantage (111,112). Nonselective b-adrenergic blockers are also relatively contraindicated in patients with severe obstructive airways disease resulting in arterial desaturation or CO_2 retention. b_1-Selective agents such as metoprolol have been developed to minimize bronchoconstriction, but in the larger doses often required for control of angina they lose their selectivity and can cause bronchospasm. b-Adrenergic blockers are also relatively contraindicated in patients with insulin-dependent diabetes because they block the sympathetic response to hypoglycemia, thereby prolonging the episode and impairing its recognition.

Nitroglycerin. Nitroglycerin has been a mainstay of treatment of symptomatic anginal attacks ever since the first description of the response to amyl nitrate by Brunton in 1867 (113) and to nitroglycerin by Murrell in 1879 (114). The mechanism of action of nitroglycerin is still the subject of some debate. It reduces myocardial oxygen demand through reducing left ventricular wall stress by decreasing afterload, and may increase coronary blood flow to ischemic myocardium through dilation of the coronary stenoses (115). Sublingual nitroglycerin (0.4 mg) can be used therapeutically for exertional angina or prophylactically prior to performing exercise likely to precipitate angina, such as climbing stairs or sexual intercourse. If complete relief is not obtained with a single tablet, a second can be used in 5 to 10 minutes. Ischemic myocardial pain not responding to three nitroglycerin tablets within 15 to 20 minutes requires immediate medical attention. The duration of action of sublingual nitroglycerin is brief, usually 15 to 30 minutes; therefore, its use is not practical as a long-term prophylactic drug. A number of long-acting nitrate preparationswith mechanisms of action similar to that of sublingual nitroglycerin are available. Among the most commonly used are the oral organic nitrates, isosorbide dinitrate and isosorbide mononitrate, and various types of topical nitrates. Isosorbide dinitrate can be begun at a dose of 10 mg three times a day and increased at 5- to 7-day intervals to 40 mg of the sustained-release form three times a day. Isosorbide mononitrate in sustained-release form has the theoretical advantage of much less first-pass metabolism in the liver. At 120 to 240 mg daily, it has been shown to reproducibly increase treadmill exercise in patients with chronic stable angina as effectively after 6 weeks of use as on the first day of use (116). This sustained benefit is important because of the phenomenon of nitrate tolerance, by which the sensitivity of the vasculature to the antiischemic effects of nitroglycerin is lost without a 10- to 12-hour daily nitrate-free period (117).

Calcium Channel Blockers. There is considerable controversy about the use of calcium channel blockers in patients with coronary artery disease (118). Immediate-release nifedipine is contraindicated in patients with coronary artery disease or suspected acute coronary syndrome. Amlodipine, diltiazem, and verapamil are effective at reducing angina and do not cause excess mortality in those with coronary artery disease or acute coronary syndrome in the absence of significant congestive heart failure. These drugs cause vascular smooth muscle relaxation by selectively inhibiting the inward calcium current through the conventional L-type calcium channel in the cell membrane, and they have proven to be effective in the treatment of angina (119). Although their mechanisms of action at the cellular or organ level are similar to those of the nitrates, their biochemical site of action is different; therefore, these agents can be synergistic with nitrates in the treatment of angina. In contrast to nitrates these agents are also myocardial depressants, with verapamil being the most potent. Verapamil should be used cautiously or not at all in patients with severe congestive heart failure or left ventricular dysfunction. Amlodipine has proved safe in patients with congestive heart failure (120). Both verapamil and diltiazem slow AV conduction and are relatively contraindicated in patients with advanced degrees of AV block or sick sinus syndrome. Calcium channel blockers commonly produce minor ankle edema that can usually be easily controlled with a diuretic. Because these are potent vasodilators, headache and orthostatic hypotension are common side effects, particularly when used in combination with large doses of nitrates.

The history is useful in choosing the first antianginal agent to initiate treatment. In patients whose angina is primarily exertional or is provoked by other stresses that increase myocardial oxygen demand, b-adrenergic blocking agents are highly effective, as are the nitrates and calcium channel blockers. In patients with angina at rest, in whom the mechanism might be a spontaneous reduction in coronary blood flow caused by normal coronary vasoreactivity or spasm, nitrates or calcium channel blockers are probably preferable over b-adrenergic blockers; the latter could theoretically exacerbate coronary spasm by leaving the a-constrictor tone unopposed. These three classes of antianginal drugs are useful in combination in patients with severe angina. Medical therapy is often not considered to be *maximal* unless the patient is receiving a drug from all three classes in therapeutic doses.

Surgical Revascularization. Various surgical procedures were tried for relief of severe angina in the 1950s, but none was demonstrated to be more effective than a placebo or sham operation (121). With the description of the aortocoronary bypass operation by Favalaro in 1969, a truly effective way of improving myocardial blood flow at an acceptable risk was introduced (23). The operation is based on the angiographic observation that, in the earlier phases of symptomatic coronary artery disease, the atherosclerotic obstructions are in the proximal portions of the coronary arteries, leaving the distal portions of the vessels relatively free of disease. Direct surgical attack on the obstructive lesions (i.e., endarterectomy) did not work because of the small size of the arteries. The construction of a bypass conduit of saphenous vein from the ascending aorta to the coronary artery distal to the obstruction has been shown to be highly effective in relieving anginal symptoms and improving exercise tolerance. The operation, which requires the use of cardiopulmonary bypass to allow the delicate anastomoses to be made on the arrested heart, can now be performed with an operative mortality of approximately 1% to 3%. The probability of early graft patency is high (90%), as is the initial relief of symptoms (80%). As atherosclerosis progresses in the native coronary arteries and develops in the saphenous veins, however, symptoms return at a rate of 3% to 4% per year so that by 5 years after surgery approximately 30% of operated patients are again symptomatic. The internal mammary artery is now used as the bypass conduit of choice to coronary arteries on the anterior surface of the heart because it does not appear to develop atherosclerotic obstruction, resulting in better late patency rates (122).

Whereas the beneficial symptomatic results of coronary bypass surgery in patients who are severely limited by angina preoperatively are quite clear, the effect of surgery on survival has been more controversial. With the publication of three large randomized trials comparing survival of surgically and medically treated patients (123,124 and 125), it was established that survival is improved with surgical therapy in patients with significant obstruction of the left main coronary artery (123) and in patients with three-vessel coronary artery disease and left ventricular dysfunction (125). No study has shown improved survival in patients with single-vessel coronary artery disease. A European randomized trial showed substantially improved survival in symptomatic patients with three-vessel disease and normal left ventricular function (124). The Coronary Artery Surgery Study conducted in the United States and Canada, however, showed no survival benefit for minimally symptomatic patients with three-vessel disease and normal left ventricular function (125). Although neither the Veterans Affairs Cooperative Study nor the Coronary Artery Surgery Study showed improved survival in patients with two-vessel disease, some data from the European study suggest that, if one of the two involved vessels is the anterior descending coronary artery, survival might be prolonged with surgery (124). These classic studies performed in the 1970s and 1980s were of great value in demonstrating the benefits of surgical revascularization in high-risk groups. However, with the technical improvements of shorter bypass pump runs, increasing use of arterial conduits, and early (within 12 to 24 hours) postsurgical patient mobilization, the applicability of these large trials to current decision making has been somewhat reduced (126). The concomitant improvements in catheter-based revascularization continue to redefine the options for patients with symptomatic coronary atherosclerosis.

Percutaneous Coronary Intervention. In selected patients, percutaneous coronary intervention procedures such as percutaneous transluminal coronary angioplasty (PTCA) provide effective revascularization without a surgical procedure. This catheterization procedure, developed by Gruntzig in the late 1970s (127), consists of passing a flexible guidewire across the coronary artery stenosis and following with a balloon catheter over the guidewire. The balloon is inflated and the stenosis is dilated. In skilled hands, the procedure promptly relieves the obstruction in approximately 90% of attempts, but a small risk of occluding the artery or damaging it is involved, so that emergency surgery is sometimes required. A major unresolved problem is the recurrence of the stenosis in approximately 30% of patients within 6 months of the procedure. The introduction of intracoronary stents has reduced the frequency of complications requiring emergent surgery and reduced the rate of stenosis recurrence by approximately 50%. The addition of aggressive antiplatelet regimens, with a combination of aspirin, ticlopidine (or, more recently, clopidogrel), and abciximab (a glycoprotein IIb/IIIa inhibitor), has reduced the incidence of early thrombotic occlusion and may also contribute to a reduction in recurrent stenosis (128). Catheter-based interventions have become the treatment of choice for single- or double-vessel disease, and increasingly for patients with three-vessel disease (129). The need for repeat intervention and sometimes coronary artery bypass graft remains the major problem for catheter-based interventions.

Variant Angina

Clinical Description and Pathophysiology

Variant angina is a useful descriptor for chest pain syndromes that may have both typical and atypical features. The two primary pathophysiologic mechanisms of variant angina are epicardial coronary artery spasm (Prinzmetal's angina) and microvascular angina. Prinzmetal's angina was described as anginal pain at rest accompanied by ST-segment elevation in the absence of an exertional component (130). Prinzmetal postulated that it might be caused by transient narrowing as the result of changes in the vasomotor tone of proximal coronary artery stenoses. Subsequent angiographic investigation of patients fitting this definition has shown findings that vary from normal coronary arteries to severe atherosclerotic coronary artery disease; thus, it is not a single disease entity, with the latter group overlapping with unstable angina patients. Nevertheless, it appears that a small group of patients has predominantly unprovoked, at-rest angina, with dramatic ST-segment changes and sometimes malignant ventricular arrhythmias. Many patients are premenopausal women who smoke cigarettes. Anginal attacks are most frequent in the morning hours, with marked variability over time in the disease activity. The mechanism of the coronary spasm is unknown, although in approximately 25% of patients evidence has been found of a more generalized vasospastic syndrome, such as Raynaud's phenomenon or migraine headaches. Microvascular angina is often said to be present in patients with exertional chest pain, abnormal measures of myocardial perfusion under physical or pharmacologic stress (with or without adjunct imaging), and angiographically normal coronary arteries (131). Microvascular angina, also known as *syndrome X*, may be part of a continuum of disorders, characterized by some or all of the following symptoms: abnormal sensitivity to cardiac stimulation (enhanced visceral nociception), esophageal dysmotility, and various types of psychosocial disorders, including panic disorder (132).

Diagnosis

The diagnosis of Prinzmetal's angina is best made by demonstrating marked ST-segment shifts during episodes of unprovoked angina in a patient who otherwise has normal exercise tolerance. Coronary angiography during an anginal episode usually shows spasm in the coronary artery predicted by the ECG ST-segment changes. Because anginal episodes occur unpredictably, however, such an episode might not occur spontaneously during coronary angiography. Provocative testing with ergonovine, a serotonin- and a-adrenergic receptor agonist, has been used in the past for diagnosis in the catheterization laboratory, and more recently has been replaced in some centers by methylergonovine (Methergine). The diagnosis of microvascular angina may be somewhat more difficult to prove, given that it requires a clinical component, abnormal noninvasive studies, and angiographically normal epicardial coronary arteries.

Treatment

Both nitrates and calcium channel blockers are generally effective in these patients, either separately or in combination. Of course, cessation of smoking should be advised. The prognosis in patients with angiographically normal coronary arteries is good, although rarely AMI can occur.

Unstable Angina

Clinical Description and Pathophysiology

Unstable angina can be defined as angina occurring at rest or with little or no provocation. Previously, patients with new-onset angina and patients with a crescendo pattern to their exertional angina were included with those in the unstable angina group, but these two subgroups probably have differing pathophysiologies and prognoses.

Patients with unstable angina generally have a severe stenosis (greater than or equal to 90% in one or more major coronary arteries), but the vessel is still patent. The angina occurs without any change in the determinants of myocardial oxygen demand, and therefore must be the result of a reduction in coronary blood flow caused by an increase in coronary vascular resistance (see Table 61-4). The increase in resistance is thought to occur primarily at the severe atherosclerotic stenosis because of partial occlusion by a platelet thrombus, by an increase in vasomotor tone producing a small reduction in lumen area that can effect a large increase in resistance, or by a combination of both these mechanisms. Rarely, an unstable angina pattern can occur in patients with angiographically normal coronary arteries; in these patients coronary spasm must be the primary mechanism.

Diagnosis

As with stable angina, the history provides most of the diagnostic information required. The pain is similar to that of stable exertional angina; within the same patient, the nature and location of the pain are usually the same as those experienced with exercise. The major difference is that the pain comes on at rest with no change in heart rate or blood pressure preceding the onset of pain. The pain can be more severe than that of the exertional pain and can last 30 minutes or longer. In a patient without previous objective evidence of coronary heart disease, such as prior AMI or typical exertional angina, the presenting complaint of chest pain at rest can be difficult to distinguish from noncardiac pain on the basis of the history alone. The pain is often less responsive to sublingual nitroglycerin than exertional angina.

As in stable angina, the physical examination is often unrevealing. Nevertheless, evidence of congestive heart failure, aortic valve disease, uncontrolled hypertension, tachycardia, fever, severe anemia, and marked anxiety should be sought. Most patients with unstable angina have transient ST-segment depression or elevation or T-wave inversion with the anginal episode. The absence of ECG changes with the pain, however, does not exclude the diagnosis. Frequently, unstable angina can only be differentiated from a non–Q-wave infarction by the absence of an increase in serum enzyme levels. The pain pattern and ECG changes alone do not distinguish unstable angina from a non–Q-wave infarction. In view of this consideration, a newer conceptualization of the continuum of unstable angina and non–Q-wave AMI is represented by characterizing such patients as experiencing an acute coronary syndrome. Excluded from this classification are patients with persistent ST elevation, and a high clinical priority is to further exclude from this category patients with noncardiovascular causes of chest pain.

Thallium myocardial imaging during an episode of unstable angina reveals a perfusion deficit that returns to normal following relief of pain. This observation forms the basis for our understanding of the pathophysiology (i.e., transient reduction in coronary flow), but thallium imaging is generally not required to establish the diagnosis. Exercise testing is generally contraindicated in patients having chest pain at rest. In most patients whose age and general medical condition make them potential candidates for revascularization, coronary angiography should be performed during the same hospital admission for two reasons. First, the incidence of severe coronary artery disease requiring surgery for prolongation of survival (e.g., left main coronary artery obstruction or three-vessel disease) is higher in patients with unstable angina than in those with other manifestations of coronary heart disease. Second, failure of medical therapy resulting in readmission for recurrent unstable angina or AMI has been relatively common.

Treatment

Patients with unstable angina should be admitted to the hospital and placed at bed rest in a quiet, anxiety-free environment. If arterial hypoxemia is present, oxygen should be administered. Factors that increase myocardial oxygen demand or coronary artery resistance should be vigorously treated; the most important of these are hypertension and cigarette smoking. Because of the difficulty in distinguishing unstable angina from non–Q-wave AMI, and because their pathophysiologies are similar, with acute thrombus formation causing partial or temporary occlusion, it is logical that antiplatelet therapies are effective in reducing the incidence of AMI and recurrent angina in patients presenting with unstable angina.

Aspirin, intravenous heparin, and nitrates have been the mainstays of medical therapy. If oral or topical nitrates are unsuccessful in providing prompt relief of pain, nitroglycerin should be given intravenously starting at 10 µg per minute, increasing by 10 µg per minute every 10 minutes until the initial rate of 50 µg per minute is achieved. If the pain persists or recurs, nitroglycerin can be titrated upward to a maximal dose of 300 µg per minute, provided that the systolic arterial blood pressure does not fall below approximately 100 mm Hg. If the patient has been on a b-blocker at the time of admission, it should be continued unless congestive heart failure or marked bradycardia is present. Sudden withdrawal of b-adrenergic blockers has been associated with a rebound phenomenon, resulting in more severe angina or AMI. If the patient is not already on a b-blocker, consideration should be made for initiating therapy at the time of admission.

Randomized trials have shown a marked beneficial effect of aspirin in the prevention of AMI and death over the subsequent several months (133). Intravenous heparin use has also been associated with a reduction in combined outcome of death, AMI, and recurrent angina in other studies (134). More recently, low-molecular-weight heparin has been shown to be at least as good if not better than unfractionated heparin (135). Current clinical practice includes some form of heparin for the first 24 to 48 hours of hospitalization for unstable angina. Finally, there is much enthusiasm about the possible role of glycoprotein IIb/IIIa inhibitors for the treatment of unstable coronary syndromes. Initial studies demonstrate a reduction in the composite end point of death and AMI that has been durable for up to 60 days. The ultimate role of these new therapies will be determined by the results of several recent trials (136,137). High-risk unstable angina patients with significant

ST depression, low-grade positive troponin levels, or prior AMI may have incremental benefit from treatment from the use of glycoprotein IIb/IIIa inhibitors (138).

Revascularization is the therapy of choice for patients whose angina cannot be controlled by antianginal agents and for those in whom surgery prolongs life (see Stable Angina: Surgical Therapy, previously in this chapter). The decision to pursue surgical versus catheter-based revascularization depends on the number of diseased vessels and the patient's comorbidities. The intraaortic balloon is highly effective for the temporary control of pain and can probably prevent infarction until coronary angiography and surgery can be performed for those patients whose angina cannot be controlled by intravenous nitroglycerin. The mechanism whereby the intraaortic balloon affords myocardial protection involves augmentation of diastolic aortic pressure, increasing coronary flow, and reducing systolic pressure, thus reducing myocardial oxygen demand.

Acute Myocardial Infarction

Approximately 1,500,000 patients experience AMI annually in the United States, and approximately 250,000 die before reaching the hospital (139). Approximately 50% of deaths caused by AMI occur within 1 hour of onset of symptoms, mostly the result of malignant ventricular arrhythmias and ventricular fibrillation. Many of these *electrical* deaths are preventable with better public education regarding the symptoms of AMI, as well as improved access to cardiopulmonary resuscitation and defibrillation. The challenge has been to bring medical care to the patient quickly enough, or vice versa. Of patients hospitalized with AMI, approximately 6% to 10% die during hospitalization (most of left ventricular failure) and another 5% die in the first year after hospitalization of recurrent infarction or arrhythmia. These figures represent substantial improvement in prognosis of AMI, based on advances in reperfusion therapies, risk stratification, and risk factor modification.

Pathophysiology

AMI is irreversible myocardial cell death resulting from ischemia. The key diagnostic feature of AMI for rapid assessment purposes is the finding of sustained regional ST elevation by ECG. Based on subsequently obtained cardiac enzyme studies and evolution of the ECG, AMI may be classified as *Q-wave infarction* (formerly known as *transmural*) and *non–Q-wave infarction* (formerly known as *subendocardial*). Further classification can be made according to location, as determined from the ECG. Q- wave infarctions are most often (greater than 80%) the result of total occlusion of a proximal coronary artery by a recent thrombus superimposed on a severe atherosclerotic lesion (140). In non–Q-wave infarctions the artery is usually still partially patent but severely obstructed by an atherosclerotic plaque, with or without superimposed thrombus. The basic mechanisms leading up to the acute infarction are still controversial. Two main theories have been proposed: (a) hemorrhage into a plaque, causing expansion of the plaque and further obstruction of the lumen; and (b) denuded or damaged endothelium over the plaque, leading to attachment of a platelet thrombus, which in turn leads to more thrombus formation and total occlusion of the artery.

Symptoms and Signs

The clinical presentation is usually that of severe oppressive chest pain accompanied by diaphoresis and lasting from 20 minutes to several hours. Up to 50% of patients have a prodrome of intermittent anginalike pain lasting up to several days, but with onset at rest (i.e., unstable angina). The prodromal pain can be so mild or transient that patients do not seek medical attention. The discomfort of AMI is sometimes epigastric, accompanied by a desire to belch, and often mistaken by both patient and physician for gastrointestinal upset. The pain can occasionally be interscapular, only in the arms, or only in the mandible. Data from the Framingham study, however, showed that AMI can be clinically silent in approximately 25% of patients. Other commonly associated symptoms are dizziness and weakness from low cardiac output, marked diaphoresis from autonomic discharge, and palpitations or syncope from ventricular arrhythmia.

Despite relatively typical and severe symptoms in most cases, the average delay from onset of symptoms to arrival at a hospital is 1 to 3 hours in a number of studies (139); during this period the acutely ischemic myocardium is most unstable electrically and ventricular fibrillation is most likely to occur. Further patient and public education is needed to make at-risk patients knowledgeable of symptoms and aware of the danger of delay in seeking attention. Physicians must also be prepared to deal with false alarms in emergency rooms and some ultimately unnecessary hospital admissions.

When a complete database is available (history, ECG, and serum enzymes) the diagnosis is usually not difficult, but the pain is sometimes atypical or even absent in 25% of AMI patients. Other diseases that should be considered in the differential diagnosis are acute pericarditis, mitral valve prolapse, acute pulmonary embolism, aortic dissection (which can cause AMI by occluding the coronary ostium), stable angina, unstable angina, variant (Prinzmetal's) angina, costochondritis and other chest wall pain, esophageal spasm, biliary disease, cervical root compression, and psychosomatic pain. Acute pulmonary embolism can occasionally be particularly difficult to distinguish from AMI because it can produce visceral pain, acute decrease in cardiac output, an autonomic response to this decrease, and ECG changes, all of which can resemble those of AMI.

The presenting physical signs can be surprisingly few. Either hypotension from low cardiac output or hypertension from sympathetic discharge can be present. Similarly, either bradycardia from vagal discharge (common in inferior infarction) or heart block or tachycardia from reduced stroke volume or sympathetic stimulation can be observed. In a minority of patients pulmonary congestion can be manifested by tachypnea, dyspnea, rales, or even frank pulmonary edema with frothy sputum. Examination of the heart is often normal; some patients, though, might have an S_3 gallop, a murmur of mitral regurgitation caused by papillary muscle dysfunction, or a precordial bulge reflecting dyskinetic myocardium (left ventricular wall moving outward with systole).

Diagnosis

The clinical approach to the patient must usually be chosen on the basis of rapid assessment of history, cardiac risk factors, and ECG data. For this reason a focus on the presence or absence of prolonged ST elevation by ECG is critical in determining whether the patient should receive medical or catheter-based coronary reperfusion. Current American Heart Association/American College of Cardiology guidelines advocate institution of revascularization therapy within 30 minutes of presentation for thrombolytic agents or 60 minutes by percutaneous coronary revascularization (141).

In patients with prolonged ischemic chest pain who do not have ST elevation, hospitalization and antiischemic and antithrombotic measures are instituted as described previously (see Unstable Angina). Some of these patients are found to *rule in* for AMI on the basis of serial measurements of cardiac enzymes. The dying myocardial cell releases some of its enzymatic contents into the bloodstream; the detection of these enzymes in serum is diagnostically useful. Creatine phosphokinase (CPK) is usually detectable within a few hours of the onset of symptoms, peaks at 12 to 24 hours, and is fully renally excreted within 48 to 72 hours. CPK-MB isozyme increases the specificity, and most criteria for enzymatic confirmation of AMI include a twofold rise in total CPK and an increased CPK-MB with CPK-MB percentage typically greater than 5% to 7% of the total CPK. Alternatively, a distinct rise above the normal range of CPK-MB mass by radioimmunoassay correlates highly with myocardial necrosis and may be used in tandem with one of the newer troponin assays. Serum lactate dehydrogenase (LDH) is now rarely used diagnostically; it is first detectable in serum 24 to 48 hours after onset of symptoms, peaks at 3 to 6 days, and is present at elevated levels for as long as 8 to 14 days. It is this latter characteristic that makes determination of the serum LDH level useful diagnostically in patients who do not seek medical care for several days after the onset of symptoms. Additional predictive value is conferred by the finding of an LDH1/ LDH2 isozyme reversal (142). Cardiac troponins offer the advantage of higher specificity. Cardiac troponin T (cTn-T) and cardiac troponin I (cTn-I) are currently used in clinical practice (143). Since very little cTn-T and no cTn-I is produced by skeletal muscle or other tissues, they are the most specific markers of myocardial necrosis. Levels of cTn-T and cTn-I on admission correlate with hospital and 30- to 45-day mortality data. The troponins first appear in the serum approximately 3 hours after infarction and peak in 12 to 24 hours. They have the advantage of lasting 7 to 14 days, allowing diagnosis of distant AMI and thus precluding the need for measurement of LDH.

Imaging of the heart by echocardiography, radionuclide SPECT, or magnetic resonance reveals abnormalities in AMI. These modalities may be used to confirm the clinical impression of AMI, and an emerging strategy receiving increasing support is to use these diagnostic methods for their negative predictive value (i.e., to assist in ruling out acute myocardial ischemia/injury) (144). One additional imaging modality occasionally used is technetium 99m pyrophosphate scanning. This is the same radiopharmaceutical used for bone scans; the pyrophosphate complexes with calcium in the bone and carries with it the attached technetium 99m radionuclide. The mechanism of uptake by infarcting myocardial cells is presumably similar to that of uptake by bone. Infarcting myocardial cells collect large amounts of calcium in their mitochondria, to which the technetium 99m pyrophosphate complexes. This technique has its greatest use in patients with an atypical history and a preexisting ECG abnormality that precludes a diagnosis (e.g., left bundle branch block or paced rhythm).

Treatment

Treatment of AMI has evolved from a historically passive supportive role aimed primarily at prevention and treatment of lethal ventricular fibrillation to an aggressive interventional approach aimed at reestablishing myocardial perfusion and minimizing myocardial necrosis. The primary reason for the evolution in treatment is the contemporary recognition that AMI is most frequently the result of coronary thrombosis. Three approaches have been used in humans to restore myocardial blood

flow promptly: emergent coronary bypass graft surgery, thrombolytic therapy, and percutaneous coronary intervention. Although emergency bypass surgery can be performed in selected patients and has acceptable morbidity and mortality, it has never been adequately scrutinized with a controlled clinical trial; moreover, it is expensive and is extraordinarily demanding on acute care resources. Intravenous administration of thrombolytic agents, alone or in combination with antiplatelet agents, has been shown to significantly reduce the mortality and complications resulting from AMI. Thrombolytic therapy or percutaneous coronary intervention is now an accepted standard of care for a patient presenting with ST elevation within 12 hours of the onset of continuous symptoms (141).

Thrombolytic therapy has been demonstrated to be effective in multiple randomized controlled trials for treatment of AMI. Trials have demonstrated the efficacy of streptokinase (SK), anistreplase (APSAC), tissue plasminogen activator (t-PA), and recombinant plasminogen activator (r-PA). Initial studies, including GISSI and ISIS-2, demonstrated the efficacy of SK versus placebo and that acetylsalicylic acid is required in conjunction with SK therapy (145). They also demonstrated that early therapy is required if mortality benefit is to be achieved. Subsequent trials have compared various treatment regimens to SK. Initial comparisons suggested similar efficacy for SK, APSAC, and t-PA. With refinement of the treatment strategies, it now appears that front-loaded t-PA is superior to SK or APSAC, which are equivalent. GUSTO-I randomized 41,021 patients to (a) SK and subcutaneous heparin, (b) SK and intravenous heparin, (c) t-PA and intravenous heparin, and (d) t-PA and SK and intravenous heparin. Acetylsalicylic acid was given to all patients. Thirty-day mortality was (a) 7.2%, (b) 7.4%, (c) 6.3%, and (d) 7.0%. t-PA therefore produced a 14% benefit of reduced mortality over SK and heparin (146). GUSTO-III has since demonstrated equal efficacy for r-PA and t-PA (147).

Current recommendations for treatment of AMI with thrombolytic therapy state that treatment should be considered for those with ST elevation of 0.1 mV in two contiguous leads, or for those with new left-bundle branch block and a typical clinical history for AMI, with symptom duration of greater than 20 minutes and less than 12 hours (141). Once these criteria are met, careful consideration of absolute and relative contraindications must be made prior to therapy. Absolute contraindications include recent surgery or major trauma within 14 days, active internal bleeding, aortic dissection (must be excluded if significant clinical suspicion), any hemorrhagic stroke ever, or an ischemic stroke within the past year, and known AV malformation. Relative contraindications include severe hypertension at presentation, with systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg; cardiopulmonary resuscitation for more than 10 minutes, severe liver disease, oral anticoagulants with prothrombin time greater than 15 seconds; puncture of a noncompressible vessel; and traumatic endotracheal intubation (141). The decision regarding the appropriate regimen must take into account the patient's age and symptom duration, because the risk of intracerebral hemorrhage increases with age and benefit decreases with time.

An alternative to thrombolytic therapy is primary PTCA. Because of the benefit of early restoration of coronary flow and the common existence of contraindications to thrombolytic therapy, primary PTCA has been increasingly used. PTCA has since proven to be superior to thrombolytic therapy when both are immediately available. In the PAMI-1 trial, primary PTCA was compared with t-PA; in the PTCA group, the composite end point of reinfarction or death was reduced during hospitalization (12.5% versus 5.1%) and at 6 months (17% versus 8.2%) (148). The indications for primary PTCA are similar to those for thrombolytic therapy and can usually be performed when thrombolysis is immediately available and when thrombolytic therapy is contraindicated.

Adjunctive Medical Therapy. Established forms of therapy for AMI include hospitalization in a coronary care unit with continuous ECG monitoring, treatment of pain with narcotic analgesics, administration of supplemental oxygen, and attempts to minimize myocardial oxygen demand through attention to the determinants of myocardial oxygen consumption (see Table 61-4). The use of oxygen is now accepted as a routine measure for all patients with acute coronary syndromes. Oxygen therapy may limit both the size of myocardial injury as well as reduce the ST elevations in AMI. After initial stabilization, oxygen therapy can be discontinued for those with uncomplicated AMI. For those with oxygen saturation less than 90% or with complications such as pulmonary edema or hypotension, oxygen therapy should be continued.

Aspirin should be administered in a dose greater than or equal to 160 mg to all patients (provided they have no known hypersensitivity) with suspected acute coronary syndrome or AMI. The second International Study of Infarct Survival (ISIS-2) demonstrated that acetylsalicylic acid alone reduced the mortality of evolving AMI by 23% (145). Acetylsalicylic acid inhibits platelet aggregation by an almost complete inhibition of thromboxane A_2 production. The benefit is additional to those of thrombolytic therapy.

Morphine sulfate given intravenously in 2- to 4-mg increments is the preferred analgesic agent because of its potency, safety when given intravenously, lack of myocardial depressant effects, and generally minimal hemodynamic changes in the supine patient (149).

b-Blockers have been shown to reduce mortality both in the early (hospital) and chronic post-AMI periods. In ISIS-1 atenolol was administered within 12 hours of diagnosis and reduced hospital mortality from 4.3% to 3.7%. Similar results were seen in the MIAMI trial and in TIMI-II, where early intravenous metoprolol (within 2 hours) followed by oral dosing reduced mortality, reinfarction, and recurrent ischemia. The benefits were evident by day 1 and were sustained throughout the follow-up period. Three large well-done randomized trials have demonstrated that institution of a b-blocking agent prior to discharge for AMI reduces subsequent mortality significantly over the next several years (150,151).

Early treatment with inhibitors of the angiotensin-converting enzyme has been shown in several studies to decrease the incidence of future mortality and recurrent AMI. The only trial that did not demonstrate a mortality benefit used intravenous enalapril, which caused excessive hypotension, especially in the elderly. Current recommendations are to start treatment within 24 to 48 hours of all AMIs, especially anterior AMIs, with an angiotensin-converting enzyme inhibitor, as tolerated by blood pressure greater than 100 mm Hg (141). Intravenous angiotensin-converting enzyme inhibitor should be avoided in the acute period. Those with persistent left ventricular dysfunction receive continued benefit from its long-term use (152).

Nitrates are also commonly used in the treatment of AMI. They are indicated in patients with AMI and congestive heart failure, large anterior AMI, recurrent angina, persistent ischemia, or pulmonary edema. Caution should be used in those with right ventricular infarction, systolic blood pressure less than 90 mm Hg, or bradycardia. Nitrates act by dilating the capacitance veins, and coronary and peripheral arteries. Anginal pain is likely relieved by a combination of increasing myocardial blood flow, decreasing ventricular preload, and reducing left ventricular afterload (thus reducing myocardial O_2 demand). Intravenous nitrates are preferred because they are easily titrated to effect and systolic blood pressure.

The use of anticoagulants following AMI is still subject to debate and investigation. Studies using two-dimensional echocardiography showed that intraventricular thrombus is seen with moderate frequency in patients with anterior AMI. Thus, it seems reasonable to anticoagulate patients with anterior AMI for approximately 1 month, provided that no contraindications exist. Others would anticoagulate those patients in whom a thrombus can be detected by echocardiography; these patients are generally anticoagulated for 3 to 6 months.

Risk Assessment

Patients with uncomplicated AMI are hospitalized for 3 to 7 days. Near the end of the hospitalization, it has become accepted practice in patients who did not receive early coronary angiography to perform a low-level exercise test to look for symptoms or signs of ischemia at a low workload. Provided that patients with severe left ventricular dysfunction or severe congestive heart failure, or patients manifesting myocardial ischemia at rest or on minimal activity are excluded, the low-level exercise test can be performed safely. Some studies have shown a markedly increased risk for a future coronary event in patients who exhibit ischemia in the form of angina or ST-segment depression, or hemodynamic instability (lack of adequate heart rate or blood pressure increase) on the low-level exercise test. Thus, it has become accepted practice to recommend coronary angiography in patients exhibiting symptoms of myocardial ischemia either spontaneously or on the low-level exercise test following AMI. Such patients generally have multivessel coronary artery disease, and well-controlled clinical trials in this subgroup of patients have been performed to demonstrate that coronary artery bypass surgery or percutaneous coronary intervention improves outcome compared with medical therapy.

Complications

The most common complication of AMI is ventricular arrhythmia, which occurs in some form in more than 90% of patients in the first 72 hours following onset of the infarction. Premature ventricular beats are almost universal; more complex forms, such as couplets, triplets, and nonsustained ventricular tachycardia, are also commonly seen early after AMI. The value of treatment for these rhythms when asymptomatic has not been demonstrated; however, ventricular tachycardia (or ventricular fibrillation), when hemodynamically destabilizing, must be treated aggressively, with intravenous lidocaine and direct current cardioversion. Accelerated idioventricular rhythm also occurs relatively commonly in those with AMI. It must be distinguished from ventricular tachycardia (on the basis of a rate between 50 and 110 beats per minute) because the former is generally benign and requires no treatment.

AV conduction disturbances are relatively common and important complications of AMI. First-degree AV block (PR interval greater than 0.20 seconds) occurs in approximately 10% of patients and is almost always intranodal and benign. Progression to complete AV block only occurs in the small proportion of patients in whom

the first-degree AV block is below the bundle of His; this is generally associated with a wide QRS caused by bifascicular block. Mobitz type I second-degree AV block or Wenckebach block occurs in 4% to 10% of patients with AMI (usually inferior), is associated with a narrow QRS complex, is usually transient (up to 72 hours), is presumably caused by ischemia of the AV node, rarely progresses to complete AV block, and generally does not require pacing. Mobitz type II second-degree AV block is rare in those with AMI (less than 1% of all cases), is caused by disease below the bundle of His, is associated with a wide QRS, often progresses to complete AV block, is more often associated with anterior infarction, and generally requires pacing. When complete AV block occurs in patients with inferior infarction, it is caused by relatively well-localized ischemia of the AV node, the escape rhythm is most often nodal with a rate of 40 to 60 beats per minute, and generally well tolerated (141).

The mortality of acute inferior infarction complicated by complete AV block (20% to 25%) is moderately increased over that of inferior infarction alone. This is in contrast to anterior infarction complicated by complete AV block; there the block is a result of interruption of each of the three major fascicles below the bundle of His, meaning that the mass of infarcting myocardium is large. The escape rhythm is idioventricular, slow (less than 40 beats per minute), and subject to asystole. The mortality of anterior infarction complicated by complete AV block is high (70% to 80%), mostly as a result of the extent of the infarction. Although some have argued that pacing does not improve the relatively benign prognosis of AV block in inferior infarction, and nothing short of myocardial salvage can improve the disastrous prognosis of anterior infarction complicated by AV block, temporary ventricular pacing is generally recommended for all AMI patients with complete AV block.

Cardiogenic shock is another major complication of AMI, which occurs in 10% to 15% of hospitalized AMI patients when greater than or equal to 40% of the left ventricular myocardium has been destroyed by new and old infarction. Cardiogenic shock is defined as a cardiac output insufficient to meet the needs of vital organs despite an adequate intravascular volume and ventricular filling pressures. The hemodynamic findings in cardiogenic shock are hypotension (systolic pressure less than 80 mm Hg), left ventricular filling pressure greater than or equal to 18 mm Hg, and cardiac index less than 1.8 L per minute per m^2. Peripheral manifestations of inadequate end-organ perfusion are oliguria, cool diaphoretic skin, and altered mental status. When caused by left ventricular dysfunction, cardiogenic shock has a mortality of over 90% and is the most common cause of death in hospitalized AMI patients. It is essential to exclude hypovolemia when presented with a patient with signs of shock because it is easily treatable. Physical signs, such as venous pressure and pulmonary rales, and radiographic findings, such as Kerley B lines, correlate poorly with left ventricular filling pressure, so nothing can substitute for direct invasive measurement of left and right ventricular filling pressures in patients with suspected cardiogenic shock. The Swan-Ganz catheter can generally be passed percutaneously through a vein (usually the internal jugular) at the bedside without fluoroscopic guidance through the right side of the heart to the pulmonary artery to measure the pulmonary artery wedge pressure, which is a good approximation of left atrial pressure and left ventricular diastolic pressure.

Another correctable cause of cardiogenic shock is right ventricular infarction, which often requires intravascular volume overexpansion to right atrial pressures greater than or equal to 10 mm Hg to achieve an adequate cardiac output. Ventricular septal rupture and papillary muscle rupture each occur in 1% to 3% of hospitalized AMI patients and generally result in cardiogenic shock. These can be corrected surgically, although with a high operative mortality. When hypovolemia, right ventricular infarction, and rupture of the septum or papillary muscle have been excluded, acute left ventricular dysfunction involving 40% or more of the left ventricle is the likely cause of the cardiogenic shock. Temporary improvement in hemodynamic status can be obtained with the use of a mechanical support device such as the intraaortic balloon; by inflating in diastole and deflating in systole this balloon can reduce left ventricular afterload and increase coronary perfusion pressure. The intraaortic balloon alone, however, is rarely sufficient. The best chance for short-term survival is conferred by early cardiac catheterization with primary angioplasty of the culprit stenosis for early reperfusion. In patients who undergo such treatment successfully, several weeks after recovery significant residual ischemia should be treated by appropriate means to favorably impact on long-term survival (141).

CHEST PAIN FROM OTHER CARDIAC DISEASE

Aortic Stenosis

Pathophysiology

Aortic stenosis is a disease state resulting from increasing left ventricular outflow tract obstruction that results in pressure overload and hypertrophy of the left ventricle, with symptoms of angina, dyspnea, and syncope (153). Critical aortic stenosis constitutes a high risk for sudden cardiac death. In the middle-aged adult, aortic stenosis may become manifest as a result of a congenitally abnormal valve. The valve might have been originally bicuspid, one of the most common congenital cardiac anomalies, or might have had three unequal sized cusps. The valve functions with little or no hemodynamic derangement for the first three or four decades of life. The abnormal anatomy predisposes to fibrotic thickening and deposition of calcium, however, until the valve becomes severely stenotic in middle life. This is a disease that is more common in men. Also presenting in middle age is rheumatic aortic stenosis. The inflammatory process of rheumatic fever produces thickening and shortening of the leaflets with commissural fusion; this usually results in the hemodynamic findings of mixed stenosis and regurgitation. In almost all cases the mitral valve is also affected by the rheumatic process. In the past 20 years the incidence of senile calcific aortic stenosis has increased to the point where it is the most common cause of aortic stenosis (154). A spectrum of disease severity is seen, ranging from the combination of a moderate systolic ejection murmur and mildly thickened leaflets seen on echocardiography, to a more severe and progressive variety that ultimately requires surgical valve replacement.

The thickening and calcification of the aortic valve leaflets progressively impede the ejection of blood from the left ventricle. The left ventricle hypertrophies (increases its wall thickness) in response to this *pressure overload* and can only maintain a normal stroke volume by markedly increasing the intraventricular systolic pressure from the normal 120 mm Hg to (frequently) over 200 mm Hg. The normal aortic valve produces no measurable pressure gradient between the left ventricle and aorta, but in severe aortic stenosis this pressure gradient can be as high as 100 mm Hg (Fig. 61-3). The left ventricle might be able to compensate for this marked pressure overload for many years, but eventually myocardial failure may develop (155). The left ventricle increases its preload (filling pressure) to maintain the falling stroke volume. With increasing preload come ventricular dilatation and a falling ejection fraction. The rising diastolic pressure required to maintain cardiac output results in pulmonary venous hypertension, decreased pulmonary compliance, and the sensation of dyspnea. Natural history studies performed before the era of valve replacement surgery showed that once the full syndrome of congestive heart failure is present, the prognosis of untreated aortic stenosis is guarded; 50% of such patients die within 2 years if the valve is not replaced (156).

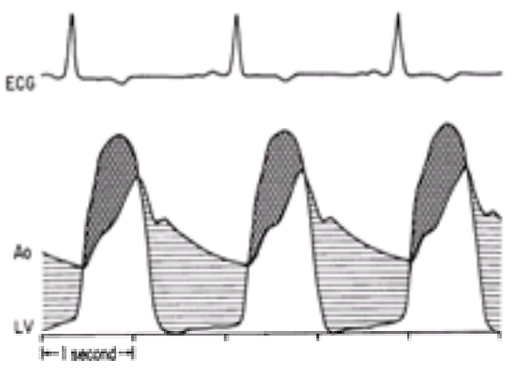

Figure 61-3. Electrocardiographic and pressure recordings from a patient with moderately severe aortic stenosis (calculated valve area = 1.0 cm^2). The cross-hatched area indicates the pressure gradient between the aorta (Ao) and the left ventricle (LV); normally, no gradient is measurable. The area marked by horizontal lines represents the diastolic pressure gradient across the coronary bed (i.e., the head of pressure driving blood through the coronary arteries). Because of the low aortic diastolic and increased left ventricular diastolic pressures, this driving gradient is reduced.

Symptoms and Signs

The symptoms of aortic stenosis vary considerably from patient to patient. Dyspnea is common, resulting from increased left ventricular diastolic pressure producing pulmonary venous hypertension, which in turn results in transudation of fluid into the pulmonary interstitium. This transudation reduces pulmonary compliance and impairs oxygen transport, with both resulting in the symptom of dyspnea. Angina is a relatively common symptom in patients with severe aortic stenosis. The pathophysiology is similar to that of angina caused by atherosclerotic coronary artery disease in that it is the result of myocardial ischemia (157). It differs in that significant coronary artery disease is present in 50% or less of adult patients with aortic stenosis. In patients without obstructive coronary artery disease, the

myocardial ischemia is the result of increased oxygen demand caused by the high left ventricular wall stress resulting from the high left ventricular systolic pressures required to overcome the obstructed valve. The impaired coronary blood flow is caused by the reduced driving pressure across the coronary bed as a result of the elevated left ventricular diastolic pressure and reduced aortic diastolic pressure. Finally, the myocardial fiber hypertrophy can exceed the capillary growth, worsening ischemia. Even in patients with obstructive coronary artery disease, similar pathophysiology of angina may pertain, because aortic valve replacement alone usually relieves the angina.

Diagnosis

The most common clinical presentation is that of a relatively asymptomatic middle-aged man with a systolic ejection murmur and possibly evidence of left ventricular hypertrophy on the ECG (158). Although the symptoms of angina, congestive heart failure, and syncope were emphasized in the past, dyspnea on exertion is the most common early symptom. Because the anginal pain of aortic stenosis is the result of myocardial ischemia, it shares many characteristics with that of angina caused by obstructive coronary artery disease. It is vague, diffuse, retrosternal, often exertional, and promptly relieved by rest. Although it can be promptly relieved by nitroglycerin, the administration of nitroglycerin might present some risk to patients with left ventricular outflow obstruction. The drop in peripheral resistance cannot be compensated for by increased left ventricular ejection; hence, the arterial pressure can fall precipitously and produce dizziness or syncope.

Physical Examination

Physical signs are useful in determining that aortic valve disease is present, but are less useful in assessing the severity of the stenosis. The characteristic finding is a systolic ejection murmur in the aortic area, with radiation to both carotid arteries. Often, however, the ejection murmur is clearly heard, or even is loudest, at the apex. In severe stenosis the peripheral pulses can have reduced amplitude and slowed upstroke, described as *pulsus parvus et tardus*. Abnormal peripheral pulses are often modulated by the compliance of the vascular system, however, and have not been consistently useful in judging severity. The left ventricular impulse is often sustained, a sign of hypertrophy, but is in the normal location if dilatation has not occurred. A thrill palpable over the upper sternum is uncommon but, when present, usually indicates severe stenosis. Because the thickened calcified leaflets are relatively immobile they do not make a sound when closing, so splitting of the second sound is not heard in adults with aortic stenosis. Similarly, a systolic ejection click is almost never heard in adults but is often present in children with aortic stenosis, in whom it is caused by the valve's snapping upward at the onset of ejection.

Electrocardiography and Chest Roentgenography

The ECG provides important clues to the presence of left ventricular hypertrophy, which in the absence of systemic hypertension often means significant stenosis. The chest roentgenogram is generally of little help in assessing the severity of the stenosis. It is useful in evaluating for the presence of left ventricular dilatation and pulmonary vascular congestion, both signs of myocardial failure. Rarely, evidence of calcification can be seen on the chest roentgenogram. The absence of valve calcification in the adult means that the stenosis is not severe; obviously this is not the case in children with congenital aortic stenosis.

Echocardiography

Two-dimensional and Doppler echocardiography have become the imaging modalities of choice for diagnosing aortic stenosis and estimating its severity. Two-dimensional echocardiography is useful for differentiating valvular aortic stenosis from the relatively uncommon (in the adult) cases of supravalvular or subvalvular stenosis. Additional information regarding ventricular wall thickness and motion as well as atrial size can be obtained using this modality. The measurement of blood velocity by the Doppler principle has proven to be so useful in the noninvasive assessment of the severity of aortic stenosis as to form the basis for therapeutic decisions regarding surgical valve replacement. To maintain a normal stroke volume the blood passing through the narrowed aortic orifice must do so at an increased velocity. Using the Bernoulli equation relating pressure drop across a stenosis to change in velocity, the instantaneous aortic valve gradient can be reliably estimated from blood velocity in the aortic root measured by Doppler ultrasound (159). Meticulous attention must be directed toward ensuring that the Doppler beam is parallel to the stenotic jet to ensure that the severity of the stenosis is fully recognized.

Cardiac Catheterization

Cardiac catheterization has in the past been the procedure of choice for defining the severity of aortic stenosis, assessing ventricular function, and determining whether associated coronary artery disease is present. Now, with accurate echocardiographic techniques for quantitating the severity of aortic stenosis and radionuclide or echocardiographic techniques for assessing ventricular function, some younger patients can undergo valve replacement without prior cardiac catheterization. Cardiac catheterization is still the preferred definitive diagnostic study in older patients with a substantial risk of concomitant coronary artery disease (over the age of 40 years), however, because it is the only reliable technique for identifying and localizing coronary artery obstructions.

Treatment

Medical therapy has little to offer in symptomatic patients other than minimizing the risks of valve replacement by optimizing hemodynamic status. It is now widely believed that all patients with angina, syncope, or congestive heart failure caused by aortic stenosis should be offered valve replacement if their general medical condition makes the risk of surgery acceptable and allows a meaningful life following valve replacement (158). In patients with symptomatic aortic stenosis, cardiac catheterization usually shows a mean aortic valve gradient of 40 mm Hg or more and an estimated valve orifice area of 1 cm^2 or less. It is still controversial whether asymptomatic patients with severe aortic stenosis should also be offered valve replacement (160).

Aortic valve replacement can be accomplished with an average operative mortality of less than 5% (158). Reparative procedures on the aortic valve have been tried but are not effective, either because of failure to relieve the stenosis or because of rapid recurrence of the stenosis. Several types of prosthetic valves are currently in common use and are generally of two types, mechanical prosthetic valves (tilting-disk and bileaflet) and bioprosthetic valves (stented or stentless heterografts or homografts). Because both homograft and heterograft valves are avascular, and perhaps because of their sterilization and treatment with glutaraldehyde, they are nonantigenic. Nevertheless, each is a nonliving biological structure; the stresses imposed by millions of openings and closings under pressure result in gradual disintegration of the collagen and elastic fibers in the valve. Thus, biological valves are expected to have a finite lifespan, ranging from 10 years (porcine heterograft) to perhaps 15 to 20 years (cadaveric homograft). On the other hand, they are relatively nonthrombogenic and generally do not require anticoagulation, with its attendant risk of bleeding (161). Mechanical prostheses are durable but are thrombogenic and require permanent anticoagulation with warfarin. An increasingly used procedure with advantages to the younger aortic stenosis patient is the Ross procedure. A pulmonary autograft is performed, in which the patient's own native pulmonary valve and main pulmonary artery are excised and grafted into the aortic position, with reimplantation of the coronary arteries. Typically, a heterograft is placed in the pulmonic position. Postsurgical anticoagulation is not required, early results indicate better graft survival relative to aortic homograft, and the valve and root can continue to grow if the patient is a child or adolescent (162).

Prognosis

Patients with aortic stenosis who are asymptomatic and maintain normal exercise tolerance probably have a good prognosis (160). On the other hand, the prognosis changes precipitously with the onset of symptoms; 25% die in the first year and 50% within 2 years of the onset of symptoms. The prognosis is worst if the symptoms are those of congestive heart failure, with nearly all patients dying within 2 years. Unfortunately, although valve replacement improves prognosis in patients with congestive heart failure caused by aortic stenosis, the prognosis is worse than in aortic stenosis patients without heart failure undergoing valve replacement.

Aortic Regurgitation

Pathophysiology

Aortic regurgitation has many causes; some of the more common are a congenitally bicuspid valve, rheumatic heart disease, endocarditis, many connective tissue disorders, and collagen vascular diseases. To compensate for the loss of a portion of left ventricular ejection back into the left ventricle, the left ventricle increases its stroke volume by dilating to as much as five times its normal volume. Rarely, patients with pure aortic regurgitation and no coronary artery disease experience angina pectoris (163). The pathophysiology is analogous to that presented for aortic stenosis. The marked left ventricular dilatation that represents the compensation for significant chronic volume overload results in increased left ventricular wall stress. Although left ventricular systolic pressures are usually normal, the increased radius of the left ventricle results in increased wall stress (and, thereby, increased myocardial oxygen demand) according to the Laplace relationship. Coronary blood flow can be impaired both by a low aortic diastolic pressure from the low-resistance runoff back into the left ventricle and by an increased left ventricular diastolic pressure,

leading to relative tissue ischemia.

Symptoms and Signs

Aortic regurgitation can be asymptomatic for many years, even if it is severe. Like aortic stenosis, the most common symptom is dyspnea on exertion. Late in the course of the disease the full picture of congestive heart failure can be seen, including marked fatigue, orthopnea, paroxysmal nocturnal dyspnea, and edema.

Diagnosis

The diagnosis is usually easily made from the physical examination, which reveals the typical diastolic, decrescendo, high- pitched murmur at the left sternal border, wide pulse pressure, bounding peripheral pulses, and a displaced cardiac impulse caused by the left ventricular dilatation. Echocardiography and Doppler ultrasound are useful in confirming the diagnosis and in assessing left ventricular size and function and the severity of the regurgitation. Echocardiography is now considered appropriate for decision making regarding aortic valve replacement (164). Cardiac catheterization is helpful in assessing coronary artery disease, quantitating the severity of the regurgitation, evaluating for other valve involvement, and assessing left ventricular function.

Treatment

Medical therapy should include prevention of endocarditis with prophylactic antibiotics. Afterload reduction with nifedipine was shown to be of benefit in delaying the need for valve replacement in one series (165); whether inhibition of the renin-angiotensin system will be of equal or greater benefit is unknown. Even more than is the case with aortic stenosis, the timing of aortic valve replacement in patients with severe aortic regurgitation is critical (166). Because in many patients the left ventricle is capable of sustained compensated function, premature valve replacement may unnecessarily expose the patient to increased thrombotic or bleeding complications. However, if surgery is unduly delayed, left ventricular dysfunction may become irreversible. Therefore, current indications for aortic valve replacement in aortic regurgitation include symptoms of left heart failure, impaired exercise tolerance and falling exercise ejection fraction, or end-systolic diameter larger than 55 mm by echocardiography (166).

Prognosis

Valve replacement in appropriately selected patients is usually associated with amelioration of cardiac symptoms and enhancement of survival.

Mitral Valve Prolapse

Pathophysiology

Chest pain is frequently associated with mitral valve prolapse, although the exact pathogenesis of chest pain is unclear. Mitral valve prolapse is one of the most frequent cardiovascular abnormalities, occurring in 3% to 5% of the population, with female subjects affected approximately twice as frequently as male subjects (167). In the milder forms the distinction from normal is often unclear. The full syndrome consists of typical auscultatory findings of a midsystolic click and late systolic murmur, atypical chest pain, and arrhythmias (168). Although there are multiple causes, the common denominator appears to be a mitral apparatus that is too large. In early systole the valve might be competent, but as the ventricle becomes smaller with systolic ejection, the mitral leaflets prolapse into the left atrium, resulting in mitral regurgitation and a late systolic murmur. The chordae are too long, and the mitral leaflets large and redundant. Histologic examination of the leaflets reveals a loose myxomatous material in the leaflets. Haphazard arrangement and disruption of the collagen can be seen on electron microscopy. Although mitral valve prolapse can be seen in those with known connective tissue disorders such as Marfan's and Ehlers-Danlos syndromes, most patients with prolapse do not have another identifiable connective tissue disorder. Nevertheless, it is thought that mitral valve prolapse can be a specific genetic syndrome because it is inherited in many patients, often with a characteristic body habitus including pectus excavatum and an asthenic appearance (169).

Symptoms and Signs

Mitral valve prolapse should be considered in the differential diagnosis of most types of chest pain, especially if the pain is not typical of angina and the patient is female. The pain often is sharp, stabbing, and nonexertional. It usually does not respond to nitroglycerin. The pathophysiology of the pain is unknown. Some have attributed it to abnormal tension on the papillary muscles, but proof is lacking. Palpitations from the cardiac arrhythmias associated with this syndrome are also common. Rarely, the arrhythmias can produce alterations in cardiac output resulting in dizziness, syncope, or even sudden cardiac death (170).

Diagnosis

The diagnosis can be made from the physical examination alone if the typical findings of midsystolic click and late systolic murmur are present. Only a portion of the classic findings can be present, however, and the physical signs are dynamic, varying greatly with the hemodynamic state. Some patients can have a pansystolic murmur indistinguishable from that of other forms of mitral regurgitation. Thus, a set of diagnostic criteria has been developed, based on the presence of symptoms, signs, and findings on echocardiography (171). Cardiac catheterization is rarely required unless the mitral regurgitation is severe enough to lead to consideration of mitral valve replacement or repair. If the patient has palpitations or symptoms of transient cerebral ischemia, evaluation for arrhythmias should be done. The 24-hour ambulatory ECG is the most useful tool, although sometimes the arrhythmias can be identified on the resting or exercise ECG. The full range of arrhythmias from atrial or ventricular premature beats to supraventricular and ventricular tachycardias has been observed.

Treatment

Most patients have an excellent prognosis and require no treatment. Patients who have mitral regurgitation should receive endocarditis prophylaxis for dental and other procedures in which bacteremia is likely to occur (172). For those with significant chest pain, b-adrenergic blockers can be effective therapeutically as can long-acting calcium channel antagonists. These agents can also ameliorate palpitations in mitral valve prolapse due to supraventricular or nonsustained ventricular tachycardia. However, individuals with hemodynamically significant ventricular arrhythmias should be treated aggressively with amiodarone or implantable defibrillator. Mitral valve prolapse is a manifestation of myxomatous valve disease, a syndrome now most frequently etiologically implicated as the cause of mitral regurgitation requiring valve replacement surgery in the elderly population (173).

Hypertrophic Cardiomyopathy

Pathophysiology

Hypertrophic cardiomyopathy is an uncommon, genetically mediated disease with a heterogeneous presentation, including angina, dyspnea, syncope, and, in a small high-risk subset, sudden cardiac death. Contemporary molecular genetic studies have demonstrated that mutations of many of the contractile protein genes (e.g., b-myosin heavy chain, a-tropomyosin, and troponin T) are associated with the bizarre myofiber disarray, endocardial plaquing, and interstitial fibrosis that characterize the myocardium in patients with this disease (174). The pathophysiologic features of hypertrophic cardiomyopathy are mediated by regional (septal more than basal more than lateral) ventricular hypertrophy resulting frequently in dynamic, and less commonly in fixed, obstruction to flow through the left ventricular outflow tract (175). Systolic function of the ventricle is preserved or even supernormal in the earlier stages of the disease. The dyspnea and exercise intolerance are the result of diastolic dysfunction secondary to abnormal ventricular compliance caused by the massive hypertrophy of the ventricular walls. Some patients have disproportionate hypertrophy of the interventricular septum (asymmetric septal hypertrophy) that may result in displacement of the anterior leaflet of the mitral valve, further contributing to left ventricular outflow tract obstruction.

Symptoms and Signs

Many patients with hypertrophic cardiomyopathy are asymptomatic. The diagnosis may be suspected by a family history of sudden cardiac death or hypertrophic cardiomyopathy, by an ECG showing unexplained left ventricular hypertrophy, or by the murmur in those patients with the obstructive variety of the disease. Physical examination is notable for a markedly sustained apical impulse, which may be accompanied by a palpable presystolic augmented atrial contraction. Jugular venous pressure may be increased with a prominent A wave, reflecting abnormal diastolic function of the right ventricle. Ventricular gallops, S_4 more commonly than S_3, may

be heard and the carotid upstroke has a distinctive bifid character. The most distinctive physical finding is a harsh systolic murmur heard across the entire precordium, which may be accompanied by a separate mitral regurgitation murmur. The ejection murmur is unique in being augmented by maneuvers (squat-to-stand or strain phase of Valsalva) that decrease venous return and reduce ventricular loading, worsening the obstruction. The most common symptom among symptomatic patients is dyspnea on exertion. The chest pain is anginal in character and is usually the result of myocardial ischemia that can often be demonstrated objectively by perfusion. Although the epicardial coronary arteries are typically large and free of obstructive disease, an imbalance exists between myocardial oxygen demand and supply due to narrowing of small intramyocardial coronary arteries (176). Other factors predispose to the finding of frank ischemia in obstructed patients: increased left ventricular wall stress because of the high systolic pressures, high diastolic pressure in the left ventricle, and outstripping of capillary growth by the marked myocardial fiber hypertrophy. Besides dyspnea and chest pain, both atrial and ventricular arrhythmias are relatively common and can produce palpitations, dizziness, syncope, or sudden cardiac death.

Diagnosis

The ECG is nearly always abnormal, most commonly showing the QRS voltage and repolarization abnormalities of left ventricular hypertrophy. Also, abnormal Q waves, which are sometimes confused with AMI, are seen in 30% to 50% of patients (177). The diagnostic procedure of choice is the echocardiography (178). The increased left ventricular wall thicknesses and normal ventricular cavity size are usually easily identified. Systolic anterior motion of the anterior mitral valve leaflet can be visualized and the degree of obstruction characterized in response to diagnostic maneuvers (e.g., Valsalva's). Risk stratification and treatment of arrhythmia in these patients are complex due to the underlying myocardial substrate, and probably should be performed in centers with extensive experience in this evaluation (179).

Treatment

No specific therapy is required for asymptomatic patients, unless mitral regurgitation is present, indicating the need for antibiotic prophylaxis. Echocardiography of family members and genetic counseling, however, should be recommended for all patients with this disorder. Current therapeutic approaches include medications [b-adrenergic antagonists, nondihydropyridine calcium channel blockers, and occasionally potent negative inotropic medications such as disopyramide (180)], dual-chamber pacing to reverse the pattern of ventricular contractile activation (181), and resection of the disproportionately increased myocardium, a procedure known as myotomy-myectomy (182). Although useful in aggregate for symptom control, no form of therapy has been clearly shown to reduce the risk of sudden cardiac death.

Acute Pericarditis

Pathophysiology

Acute pericarditis is caused by inflammation of the pericardium and produces a characteristic pain syndrome, pericardial friction rub, and ECG changes. Other forms of pericarditis, such as subacute effusive pericarditis and constrictive pericarditis, are not discussed here, because these usually do not produce pain but cause hemodynamic abnormalities.

Pathologic examination reveals acute inflammatory cells within both the visceral and parietal pericardium. The inflammation can invade the myocardium beneath the visceral pericardium, which probably accounts for the characteristic ECG changes (see following discussion). Fibrin becomes deposited on the pericardium, giving it a shaggy, reddened appearance; an accompanying pericardial effusion may be present. Most cases of acute pericarditis heal, leaving little in the way of residual changes except for a few clinically insignificant adhesions between the visceral and parietal pericardium. In a few cases, however, acute pericarditis leaves marked fibrotic changes in both layers of adherent pericardium, resulting in constriction of the heart.

The following are some common causes of acute pericarditis:

- Idiopathic
- Infection: viral; pyogenic bacteria
- Immunologic disorders: acute rheumatic fever; rheumatoid arthritis; systemic lupus erythematosus; scleroderma; post-AMI (Dressler's syndrome; postpericardiotomy syndrome)
- AMI
- Drugs: procainamide; hydralazine; isoniazid.

It is thought that viral infection (particularly coxsackie B and echovirus type 8) accounts for a large percentage of cases of acute pericarditis, although documentation of viral infection is often not possible. Uremia and drugs (procainamide and hydralazine) are other common causes of acute pericarditis. Bacterial infection is a rare but potentially lethal form of acute pericarditis that requires immediate diagnosis and treatment with drainage and antibiotics (183).

Symptoms and Signs

Acute pericarditis characteristically produces severe sharp chest pain that worsens in the supine position and is partially relieved by sitting. It is often markedly exacerbated by deep breathing, leading to confusion with pleuritis (which can accompany acute pericarditis). Some patients experience a pulsating nature to the pain with each heartbeat. The pain is more often retrosternal but can radiate to the anterior neck, the mandible, and the trapezius ridge (184). Patients can be dyspneic because of the marked increase in severity of the pain with normal respiration. The prime physical sign is the pericardial friction rub. Since the time of Laennec, the rub has been described as sounding like creaking leather. Typically, three separate components to the rub have been noted: systole, rapid ventricular filling in early diastole, and atrial contraction. Often only one or two components are present, however, with the systolic component usually being the last to disappear. In its complete form the rub is easily distinguishable from cardiac murmurs but, if only the systolic component is present, this distinction is often unclear. The rub often changes with position; to exclude a pericardial friction rub the patient must be examined in multiple positions, including on hands and knees.

Diagnosis

The diagnosis can generally be made by the history of typical positional pain, as described previously, the physical signs, and the ECG. The typical ECG finding is widespread ST-segment elevation associated with upright T waves, observed in more than 90% of cases (185). Besides the noncoronary distribution of ST elevation, it is usually more saddle-shaped or concave than in AMI. Later, T- wave flattening, inversion, or both can develop. New Q waves never develop; this is a feature that distinguishes acute pericarditis from an acute Q-wave AMI. The distinction from non–Q-wave infarction is much more difficult, however, and requires the identification of the rub, no or minimal changes in cardiac enzyme levels, and a rapid response to antiinflammatory agents. ST-segment elevation in this context is nonspecific; in addition to occurring in the early stages of AMI, ST-segment elevation can be a normal variant known as *early repolarization*, a sign of a ventricular aneurysm, or a sign of coronary artery spasm.

The chest roentgenogram is of relatively little value. If an accompanying pericardial effusion is present, the cardiac silhouette can be enlarged. Levels of cardiac enzymes, creatine kinase and LDH, are most commonly within the normal range, but occasionally minor elevations with positive isozymes can be found. The echocardiogram, although commonly ordered, provides little specific information. Whereas the echocardiogram is the best diagnostic tool available for pericardial effusion, effusion is often absent in acute pericarditis.

Treatment

The pain of acute pericarditis usually promptly responds to institution of antiinflammatory agents. If the pain is mild, aspirin, 650 mg three or four times a day, can be adequate. For more severe cases, a nonsteroidal antiinflammatory agent should be used at effective doses; indomethacin, 25 to 75 mg three or four times a day, seems to be highly effective in most cases. In fact, the pain relief can be dramatic and rapid, within 4 to 8 hours. If no relief has been obtained in 24 to 48 hours, prednisone may be started at a dose of 60 to 80 mg daily in divided doses; this can usually be tapered and stopped after about 2 weeks of therapy. The response to antiinflammatory agents is so characteristic that failure to respond to the above regimen should lead to questioning of the diagnosis. If the pain is severe, narcotic analgesic agents should be used until relief is obtained with antiinflammatory agents.

In a minority of patients acute pericarditis can recur weeks or months after completion of the initial course of therapy, requiring repeat treatment. In a few patients

pericardiectomy might be required to control the pain of multiple recurrence and avoid the side effects of sustained prednisone therapy. Recent studies suggest that colchicine may be of benefit in this setting (186). In most patients the pericarditis heals without recurrence or late sequelae. A few patients, however, develop chronic constrictive pericarditis.

AORTIC CHEST PAIN

Fortunately, acute emergency room presentations of aortic chest pain are relatively uncommon. However, due to their high-risk potential they need to be aggressively sought in at-risk patients. The major aortic causes of chest pain include dissection, aneurysm, and ulcer. Of these, the most commonly encountered is acute aortic dissection, accounting for approximately 2,000 cases annually in the United States (187).

Aortic Dissection

Clinical Description and Pathophysiology

Aortic dissection is the most common clinical catastrophe involving the aorta, far exceeding rupture of the abdominal aorta. It is characterized by severe, sharp chest pain in 75% to 90% and hypertension in 60% to 75% of patients. This uncommon but potentially lethal event begins with an intimal tear followed by progressive formation of a plane within the media of the aorta, consisting of extravasating blood intermixed with evolving thrombus. Untreated, it is lethal in most patients because of rupture of the aorta. In a large natural history series 21% died within 24 hours of onset of symptoms, 37% by 48 hours, and 74% within 2 weeks (188). Dissection occurs in all adult age groups, but has its greatest incidence in middle age and older. Other than a history of hypertension, patients are often completely healthy right up to the acute event, which in some cases may be precipitated by abrupt motion. Male subjects predominate over female by a ratio of 2 to 3:1. The most common associated risk factor is hypertension. The incidence of aortic dissection appears to be increased in pregnant women and in patients with congenitally bicuspid aortic valves, Marfan's syndrome, or Ehlers-Danlos syndrome.

Cystic medial necrosis is a common pathologic finding in aortic dissection. It is seen in the unaffected aortic wall of many patients dying of aortic dissection; both elastic and collagen fibers degenerate, with cystic spaces developing within the media. Although a similar pathologic picture is seen in patients with Marfan's syndrome, an autosomal dominant connective tissue disorder susceptible to aortic dissection, an inherited biochemical defect cannot be identified in most patients with dissection. The cystic medial necrosis can be the result of excessive mechanical stress and strain, because it increases in frequency in patients with systemic hypertension or hypertension of the ascending aorta caused by coarctation of the aorta. This observation is the source of the controversy regarding the role of cystic medial necrosis because it seems to occur with equal frequency in hypertensive patients without dissection as in patients with dissection, most of whom have also had hypertension (188). Nevertheless, many authorities believe that the weakening of the media of the aorta through degeneration of elastic and collagen is an important factor in the pathogenesis of dissection of the aorta (189).

A tear of the intima of the aorta can be identified in most but not all autopsied cases of aortic dissection; this tear can also frequently be seen by imaging methods used clinically (see following discussion). The intimal tear is seen twice as frequently in the ascending aorta, where the hydrodynamic forces of left ventricular ejection are the greatest, than elsewhere in the aorta. Variables that seem to be important are the rate of rise of aortic pressure (dP/dT), the systolic pressure, and the pulse pressure (systolic pressure minus diastolic pressure). The stress within the wall of the aorta is a function of both the intraluminal pressure and the radius (the Laplace relationship). Thus, for a given aortic pressure, the stress in the wall of the aorta is greater in a dilated aorta than in a nondilated one. Similarly, the increased stroke volume and decreased vascular resistance of pregnancy, resulting in a widened pulse pressure and increased aortic dP/dT, might be why dissection appears with increased frequency in pregnant women. Once the intimal tear allows intraluminal blood access to the media of the aorta, the hydrostatic forces of each heartbeat result in further tearing and separation of the media. The dissection can extend as far distally as the iliac arteries and proximally to the aortic valve cusps and ostia of the coronary arteries. A second lumen to the aorta is formed, known as a *false lumen*, which can be detected by angiography, transesophageal echocardiography (TEE), and CT scanning. Sometimes the false lumen can rejoin the true lumen distally through a second tear in the intima; this can relieve some of the pressure in the false lumen and slow or stop the dissecting process. As the dissection passes the orifice of a side branch of the aorta, the displaced intima can result in obstruction of that branch. Thus, loss of distal limb pulses or occlusion of a coronary artery resulting in AMI is frequently seen in aortic dissection. Also, the blood supply to other vital organs, such as the kidney and bowel, can be disrupted by this process. If the dissection extends retrograde to the aortic valve, the support of the valve leaflets can be altered so that aortic regurgitation ensues. Although the interruption of blood supply to vital organs can be devastating, the usual cause of death is external rupture, either into the pleural space or the pericardial space.

Aortic dissection has been classified according to several schemes. The DeBakey classification was based on point of origin of the medial tear and encompassed three variants: type I, involving ascending aorta, arch, and descending aorta; type II, involving ascending aorta only; and type III, involving descending aorta only. Because of the implications for treatment, the Stanford criteria have become more commonly used in recent years (190). By this scheme type A dissection involves proximal (ascending) aorta, with or without involvement of arch, descending aorta, or both, whereas type B dissection involves the descending aorta only. As discussed, the signs and symptoms of each type may be distinctive.

Symptoms and Signs

Pain, which is usually excruciating, is a presenting symptom in over 90% of patients with dissection and the predominant presenting symptom in over 75% (191). The pain is usually maximal in intensity at its onset in contrast to the pain of myocardial ischemia or infarction, which often waxes and wanes. The pain is sometimes described as a tearing or ripping sensation. The pain can migrate from an anterior retrosternal location to posterior or back pain as the dissection propagates. The location of the pain is of some value in localizing the dissection (191). Two-thirds of patients with dissection in the ascending aorta have anterior chest pain, compared with only 27% of patients with dissection in the descending thoracic aorta. Nearly all (94%) patients with dissection in the descending thoracic aorta have pain in the back, but 50% of patients with dissection in the ascending aorta also have back pain. Commonly associated with the pain are symptoms and signs of autonomic nervous system hyperactivity such as diaphoresis, bradycardia or tachycardia, apprehension, nausea, and vomiting. Other presenting symptoms are syncope, stroke, paraplegia from interruption of the spinal arteries, pulse loss with resultant limb ischemia, and congestive heart failure from aortic regurgitation. In the large series from Massachusetts General Hospital, only 8 of 124 patients had no pain: four presented with congestive heart failure, two with stroke, and two with an abnormal chest roentgenogram (191).

Hypertension, sometimes severe, is commonly present, more frequently with dissection of the descending thoracic aorta than the ascending. In one series 60% of patients with dissection of the descending aorta had a diastolic pressure exceeding 120 mm Hg, and in 42% it exceeded 140 mm Hg. Conversely, up to 20% of patients with ascending aortic dissection can be hypotensive. Loss of one or more arterial pulses is common, having been reported in 50% of patients with dissection involving the ascending aorta and in 16% of those with dissection of the descending thoracic aorta (188). This sign is particularly useful if the state of the pulses has been carefully recorded previously. One-half to two-thirds of patients with dissection of the ascending aorta develop the high-pitched decrescendo murmur of aortic regurgitation. It may be heard along the right sternal border in contrast to the more common types of aortic regurgitations, which are best heard along the left sternal border. The other well- known signs of severe aortic regurgitation (e.g., bounding peripheral pulses, wide pulse pressure, left ventricular heave), however, might not be present early in the course of dissection because not enough time has passed for left ventricular dilatation and increased stroke volume to occur.

Although rupture of the dissection into the pericardial space is usually promptly fatal and is the most common cause of death from dissection, a few patients can have a limited leak into the pericardium. These patients can exhibit a pericardial rub or hypotension and pulsus paradoxus from pericardial tamponade. Approximately 20% of patients have neurologic deficits on presentation. Hemiparesis with or without change in consciousness occurs most commonly in patients with dissection of the ascending aorta, while neurologic compromise of the lower extremities (e.g., paraparesis) is seen more commonly with dissection of the descending thoracic aorta (192).

Diagnosis

The definitive diagnosis of aortic dissection is based on demonstration of the separation of the aorta into true and false lumens. Given the overlap of sensitivity and specificity of several useful diagnostic approaches, the technique of choice is often defined by local clinical practice. Aortography by selective injection of radiographic contrast material into the ascending aorta accurately distinguishes aortic dissection from other types of aortic aneurysms and is still considered the gold standard diagnostic procedure in many centers. The combination of transthoracic and TEE can identify virtually all the major features of dissection, including the intimal flap, communications between the false and true lumina, aortic root dilation, thrombus formation, aortic regurgitation and pericardial effusion or tamponade. Multiplane ultrasound imaging has greatly enhanced the value of TEE, allowing practitioners to take advantage of its safety, portability and rapidity of application in unstable patients to yield a definitive diagnosis (193). Alternative techniques, including magnetic resonance imaging and contrast-enhanced chest CT scanning, are reported to

be as sensitive as TEE with slightly enhanced sensitivity. Thus, a common-sense approach may be to choose the diagnostic approach based on the clinical and hemodynamic stability of the patient: Unstable patients may be most rapidly assessed with TEE and triaged to early operative intervention if appropriate, while those who are more stable may be more effectively evaluated with MRI, CT or angiography (192).

Treatment

Pharmacologic therapy should be initiated as soon as the diagnosis of aortic dissection is suspected. The goals are to reduce aortic pressure and dP/dT, to reduce the likelihood of acute rupture. For this purpose, intravenous nitroprusside to reduce blood pressure and an intravenous b-blocking agent (intermittent bolus metoprolol or continuous infusion esmolol) are appropriate. Typically, reduction of systolic blood pressure to the 110 to 120 range is the objective. This can also be achieved in some cases with intravenous use of the combined a-, b-blocker labetalol.

For patients in whom a type B dissection is confirmed, continued antihypertensive therapy with close observation for complications such as increasing aortic diameter, saccular aneurysm formation, or persistent chest pain is appropriate. For patients experiencing these complications surgical intervention is most safe and effective after 2 to 3 weeks of medical stabilization, if possible. The surgical procedure involves replacement of a relatively short segment of the descending thoracic aorta by a left lateral thoracotomy, obliterating the false lumen at both the distal and proximal anastomoses in the process. Surgery is recommended for type A dissections provided that the status of other organ systems does not impose an excessive surgical mortality and provides the possibility of satisfactory quality of life. This surgery consists of resection of the ascending aorta from just above the sinus of Valsalva to the origin of the innominate artery, followed by replacement with a Dacron prosthesis. The false lumen is obliterated while making the distal anastomosis if the dissection extends beyond, as it often does. Generally, no attempt is made to resect all of the involved aorta if the dissection involves the arch or the descending aorta. If coronary occlusion or significant aortic regurgitation has occurred, however, the aortic valve is also replaced and the coronary arteries are reattached to the aortic prosthesis. Improvements in operative technique have improved surgical survival rates to the range of greater than or equal to 95% at 30 days postsurgery (194).

Aortic Ulcer

Clinical Description and Pathophysiology

A clinical entity that has been increasingly recognized as a cause of acute chest pain, and which may have distinct implications for therapy, is the penetrating aortic ulcer (195). An aortic atheromatous plaque may ulcerate, with progressive disruption of the internal elastic lamina and burrowing through the intima into the media. As a consequence, localized intramedial dissection may occur, in association with a variable degree of intramural hematoma formation and the possibility of pseudoaneurysm formation in the adventitia or frank rupture with hemothorax. Virtually all patients with aortic ulcer have severe aortic atherosclerosis as the predisposing factor.

Diagnosis

The majority of cases of penetrating aortic ulcer occur in the descending aorta. Characteristic features most commonly encountered include midscapular pain affecting an elderly person with hypertension. Frequently, an abdominal aortic aneurysm is also present, perhaps serving as a marker of the severity of the atherosclerotic process within such patients. As is the case with aortic dissection, the diagnostic methods of choice include TEE, contrast CT, magnetic resonance imaging, or contrast angiography. These studies reveal an ulcer crater and variable amounts of intramural hematoma but no evidence of intimal flap. The natural history and risk of penetrating aortic ulcers may be greater than for more typical forms of aortic dissection, possibly because of the involvement of more layers of the aorta by penetrating ulcer in comparison with the usual occurrence of dissection within the middle to outer third of the media. Penetrating ulcers of the ascending aorta are therefore considered an absolute indication for urgent surgical repair, whereas the approach to descending aorta–penetrating ulcer is more controversial. A higher index of suspicion for complications must be maintained for penetrating ulcer of the descending aorta, and in patients in whom other factors would predict intermediate-term survival and good functional status, operative intervention after an initial period of stabilization is appropriate (195).

Aortic Aneurysm

Clinical Description and Pathophysiology

Aneurysm of the thoracic aorta is an uncommon cause of chest pain that most often presents in a subacute fashion related to its size and location within the thorax. Ascending thoracic aneurysms are typically not due to atherosclerosis, but rather to other forms of aortopathy, such as cystic medial necrosis, giant cell arteritis, or following chest trauma. Descending aortic aneurysms, in contrast, usually are associated with severe atherosclerosis. Patients with dilation of the ascending aorta may experience left-sided heart failure as a result of aortic annular dilation and aortic valvular insufficiency. Alternatively, enlargement of the sinuses of Valsalva due to aortic root dilation may be associated with direct compression of the coronary arteries or coronary arterial thromboembolism. Such a sinus of Valsalva aneurysm may rupture into the right ventricular cavity, the right atrium, or the pulmonary artery causing heart failure. Thoracic aortic aneurysms may exist in a clinically quiescent state for a long time but eventually may cause symptoms on the basis of compression of thoracic structures, such as dyspnea or cough due to airway compression, superior vena cava syndrome, or pulmonary artery stenosis. Such aneurysms may also rupture into the mediastinum, pleural space, or esophagus.

Diagnosis and Treatment

As with other forms of thoracic aorta disease, contemporary imaging methods including TEE, contrast CT scan, magnetic resonance imaging, and aortography are diagnostically useful. It is generally agreed that primary prophylactic operation is indicated in cases in which the aneurysm has reached 6 cm in maximal diameter or 5 cm in patients with Marfan's syndrome (192). Recurrent symptoms or progressive enlargement are probably indications for more urgent operative intervention.

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CHAPTER 62

Painful Disorders of the Respiratory System

David D. Ralph

This chapter includes discussion of painful disorders of the trachea, bronchi, lungs, and pleura. Because the primary focus of this book is on pain, many nonpainful respiratory disorders are not considered here. Examples of disease not included are chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, asthma, and pulmonary fibrosis. Moreover, because disorders of the upper airway (nose and mouth, pharynx and larynx) are discussed in Chapter 47 and Chapter 52, they are not considered here. The information is presented in five parts: basic considerations, painful disorders of the tracheobronchial tree, pain caused by diseases of the lung, disorders of the pulmonary circulation, and chest pain caused by disorders of the pleura. As with most other chapters in the book, only key references are included. More detailed discussion can be found elsewhere (1,2). Cancer of the lung is discussed in Chapter 35, Chapter 36, and 64.

BASIC CONSIDERATIONS

Anatomic and Neurologic Aspects

This section contains a summary of the anatomy of the trachea, bronchi, lungs, and pleura and is presented as a review. This supplements the information in Chapter 60. More detailed discussion can be found elsewhere (3,4,5 and 6).

Anatomy of the Trachea, Bronchi, and Lungs

Trachea and Bronchi. The trachea is a cartilaginous membranous tube that extends from the larynx on a level with the C-6 vertebra to the upper border of the T-5 vertebra, where it divides into the right main bronchus and the left main bronchus. The trachea is nearly but not quite symmetric and is flattened posteriorly. It is approximately 11 cm (10 to 12 cm) long and its diameter from side to side ranges from 2.0 to 2.5 cm, being greater in the male than in the female. The trachea is smaller, more deeply placed, and more movable in the child than in the adult (3,6).

The right main bronchus is wider, shorter, and less abrupt in its divergence from the trachea than the left main bronchus. It usually continues approximately 2.5 cm before the right upper lobe bronchus branches off laterally, but in a study of approximately 20 cadavers, Bonica and Hall (7) found that the right main stem bronchus varied from 0.3 to 2.5 cm long. The left bronchus is smaller in caliber but longer than the right bronchus, usually being approximately 5 cm long. Each main bronchus gives off secondary bronchi for each lobe of the lung, and these in turn give off tertiary bronchi for each lobule of the lung. Figure 62-1 depicts the anatomy of the tracheobronchial tree.

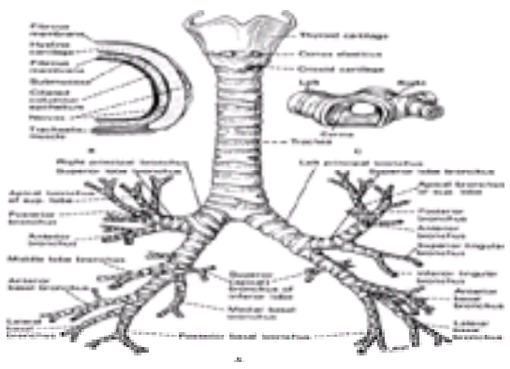

Figure 62-1. Anatomy of the tracheobronchial tree. **A:** Anterior view of the trachea and primary and secondary bronchi and tertiary bronchial tubes. The right main stem bronchus makes an angle of approximately 20 degrees with the midsagittal plane, whereas the left main stem bronchus makes an angle of 40 degrees. **B:** Cross-section of the adult trachea showing the nerves that supply the submucosa and mucosa. **C:** Bifurcation of the trachea viewed from above. The interior shows the carina as it would be seen through a bronchoscope. (Modified from Clemente CD. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985.)

Lungs and Pleura. The two lungs and the parietal pleura are shown in Figure 62-2. Each lung is invested by two layers of serous membrane, the pulmonary, or visceral, pleura and the parietal pleura. The visceral pleura covers the surface of each lung and dips into the fissures between its lobes. The parietal pleura lines the inner surface of the chest wall, covering the diaphragm, and is reflected over structures occupying the middle of the thorax. The two layers are contiguous with each other and on and below the root of the lung; normally they are in actual contact with each other, with a small amount of liquid in the potential pleural space, permitting movement of the two layers without friction (see Chest Pain Caused by Disorders of the Pleura).

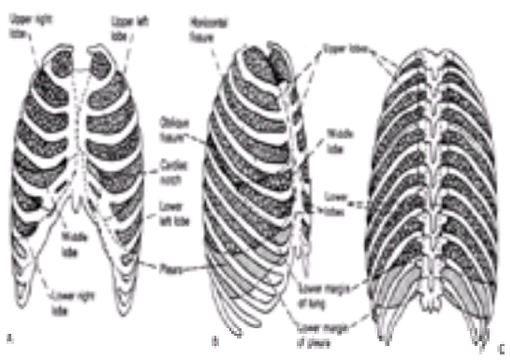

Figure 62-2. Anterior **(A)**, lateral **(B)**, and posterior **(C)** views of the thorax showing the relationship of the pleurae and lungs to the chest wall. The pleura from each side approaches the other behind the midportion of the manubrium. The extension of the caudal portion of the pleurae is seen in **B** and **C**.

When the lung collapses, or when air or fluid collects between the two layers, the cavity becomes apparent. The right and left pleural sacs are entirely separate from each other; between them are the thoracic viscera (see Fig. 62-2A). The parietal pleural sacs touch each other only for a short distance anteriorly behind the upper part of the body of the sternum. In the center of the chest cavity the two pleural sacs are separated by the mediastinum.

Different portions of the parietal pleura have special names to indicate their position: The costal pleura lines the inner surface of the ribs and the intercostal muscles; the diaphragmatic pleura covers the convex (superior) surface of the diaphragm; the mediastinal pleura covers the medial aspects of the lungs and is in contact with other thoracic viscera; and the cupola of the pleura (cervical pleura) arises in the neck and overlies the apex of the lung.

Neurophysiology

Trachea, Bronchi, and Lungs. Chapter 60 contains a description of the nerve supply to the tracheobronchial tree, the pulmonary vessels, the lungs, and the pleura. Figure 62-3 and Figure 62-4 are reproduced here from Chapter 60 for the convenience of the reader. Figure 62-5 is a schematic depiction of the segmental nerve supply to the lungs.

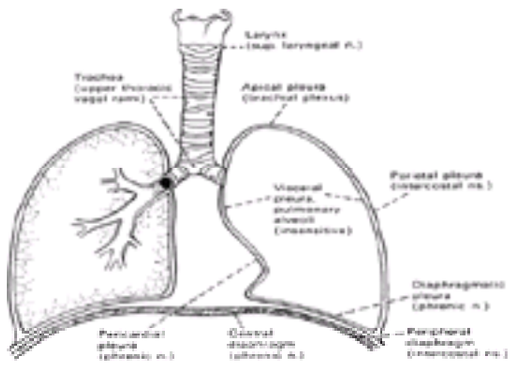

Figure 62-3. Schematic representation of the sensory nerve supply to the tracheobronchial tree, parietal pleura, and upper surface of the diaphragm, as well as to the diaphragmatic pleura. (Modified from White JC. Sensory innervation of the viscera. In: Wolff HG, Gasser HS, Hinsey JC, eds. *Res Publ Ass Nerv Ment Dis: Pain.* Vol 23. Baltimore: Williams & Wilkins, 1943: Fig. 97, p. 377.)

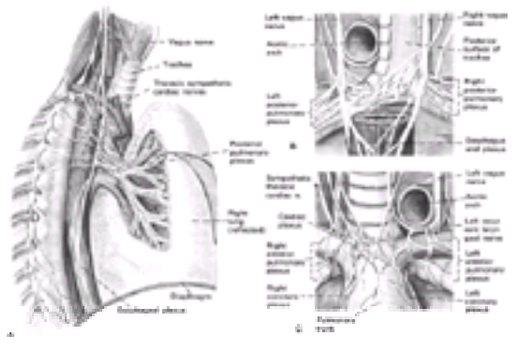

Figure 62-4. Anatomy of the pulmonary plexuses and their distribution. **A:** Right parasagittal view showing origin, course, and termination of the nerves that contribute to the right pulmonary plexus. **B,C:** Posterior and anterior views of the trachea and two primary bronchi to show the relation of the pulmonary plexus to these structures. (Developed from data in Mitchell GAG. *Cardiovascular innervation*. London: E & S Livingstone, 1956:196–238; and Netter FH. *The CIBA collection of medical illustrations.* Vol 7, The respiratory system. West Caldwell, NJ: CIBA Pharmaceuticals, 1979:28.)

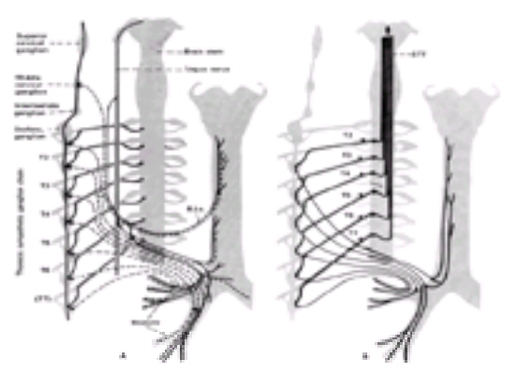

Figure 62-5. **A:** Schematic representation of the segments of the spinal cord and sympathetic chain that provide sympathetic efferent and afferent nerves and of the vagal nerves that supply parasympathetic efferent and afferent fibers to the tracheobronchial tree, the lungs, and their blood vessels. Preganglionic sympathetic and parasympathetic fibers are shown as solid lines, and postganglionic sympathetic fibers are shown as dashed lines. **B:** The sympathetic afferents are depicted with their cell bodies in the dorsal root ganglia, their proximal branches synapsing in the dorsal horn of the spinal cord, and the distal branches accompanying the sympathetic nerves. Both sympathetic efferents and afferents pass through the white rami communicantes, the thoracic sympathetic chain, the thoracic cardiac and aortic nerves, and the esophageal nerves and then proceed to their destination. (R.l.n., recurrent laryngeal nerve; STT, spinothalamic tract.)

The tracheobronchial tree receives contributions from the vagus, which contains preganglionic parasympathetic and afferent fibers, and also from the sympathetic postganglionic fibers derived from the T-2 to the T-6 or T-7 sympathetic ganglia and occasionally the stellate or middle cervical ganglia. The trachea receives some vagal afferent and efferent fibers through the recurrent laryngeal nerve, which is frequently joined by fibers from the middle cervical sympathetic ganglion. The lower part of the trachea receives vagal fibers directly from the vagus nerves and postganglionic sympathetic fibers from the stellate and T-1 ganglia.

The two bronchial trees and the pulmonary vessels derive their nerve supply from a larger posterior pulmonary plexus and a smaller anterior pulmonary plexus located at the beginning of each pulmonary artery on each side (4). Each pulmonary plexus contains vagal efferent and afferent fibers, as well as sympathetic efferent and afferent fibers, which leave the root of the lung and proceed distally. Immediately after entering the lungs the nerve filaments become partially segregated into groups that accompany the main bronchi, the pulmonary vessels, and the bronchial arteries. At the level of the main bronchi is a subepithelial plexus, located between cartilaginous plates and the bronchial musculature, and a deep plexus, located between cartilaginous plates in the submucous and mucous membranes.

From the walls of the smaller bronchi the two plexuses blend into a single plexus that can be traced as far as the respiratory bronchioles, but nerve fibers running either singly or in small bundles continue still further into the walls of the atria (4). Afferent fibers extend distally as far as the proximal end of the alveolar duct (Fig. 62-6).

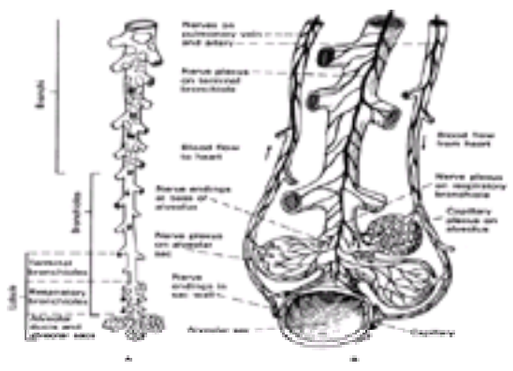

Figure 62-6. **A:** Anatomy of the distal part of a tertiary bronchus and of the bronchioles, alveolar ducts, and alveolar sacs. **B:** Nerve supply to the terminal portion of the pulmonary artery, the pulmonary vein, and respiratory bronchioles, all of which contribute to the nerve supply of the alveolar ducts and alveolar sacs. The number of alveolar sacs has been greatly reduced for the sake of clarity. Note the nerve endings within the wall of the alveolar sac that has been cut. (**A** and part of **B**modified from Netter FH. *The CIBA collection of medical illustrations.*Vol 7, The respiratory system. West Caldwall, NJ: CIBA Pharmaceuticals, 1979:28. Distal part of **B** was developed from data of Fillenz M, Widdicombe JG. Receptors of the lungs and air-ways. In: Neil E, ed. *Handbook of sensory physiology*. Vol 3/1. Berlin: Springer-Verlag, 1972:81–112.)

The nerve supply to the various vessels within the lungs varies in richness: The small bronchial arteries have the best supply, the pulmonary arteries are less richly innervated, and the pulmonary veins have a poor supply, limited to their extrapulmonary parts and the large intrapulmonary branches (5). The larger bundles of the pulmonary arteriolar nerve fibers are located on the side of the vessels, facing the bronchi, and can be traced to the extremities of these vessels; some extend beyond them to the visceral pleura. Filaments passing through the bronchial arteries come from the adjacent extrachondrial parts of the bronchial nerve plexus.

Both myelinated and unmyelinated fibers have been found in pulmonary nerves and plexuses. Many of these have sensory receptors in the pulmonary blood vessels and are involved in the reflex control of the pulmonary circulation, with vasoconstrictor and vasodilator fibers supplied by the sympathetic and parasympathetic efferent nerves, respectively. The lungs have two types of receptors that probably have a nociceptive function: type J receptors of C afferents and“lung irritant” receptors with afferents in the A-d range, all running in the vagus nerves (4,8). The type J receptors are located within the interstitial space, close to the capillaries, whereas the lung irritant receptors are found in the epithelial lining of the lung and its airways. These receptors are activated by various stimuli that produce mechanical distortion within the lung, such as pulmonary congestion, microembolism, atelectasis, and pneumothorax, and biochemical irritants. Pain caused by mechanical or chemical damage of the lung is probably mediated by these A-d and C fibers. The sympathetic afferents might have a role in the transmission of nociceptive impulses and are involved in reflex control of the circulation and of the tracheobronchial tree.

The sensory nerves that transmit nociceptive impulses from the trachea and bronchi are afferents of the vagus nerves and their branches (see Chapter 60; also see Fig. 60-17). It appears that each side of the tracheobronchial tree derives its sensory supply from the ipsilateral vagus nerve because, when the mucous membrane of the tree is noxiously stimulated, the area of pain reference is ipsilateral to the site of stimulation. Section of the vagus nerve below the recurrent laryngeal nerve but above the pulmonary plexus has been found to abolish the pain caused by carcinoma of the bronchus.

Pleura. The visceral pleura is supplied by sympathetic fibers that have a vasomotor function; these have afferent fibers that apparently have no nociceptive function because noxious stimulation of the visceral pleura does not result in pain. As previously mentioned, the visceral pleura also receives parasympathetic fibers through the pulmonary plexuses. In contrast, the parietal pleura is richly supplied by nerves containing sensory fibers that carry nociceptive information. The costal pleura is supplied by the intercostal nerves. The cupola of the pleura (cervical pleura) is supplied by the first thoracic spinal nerve, while the mediastinal pleura and diaphragmatic pleura are supplied by sensory fibers contributed by the phrenic nerves (see Fig. 60-8).

Evaluation of the Patient

Evaluation of patients who present with pain in the chest suspected of being caused by disease of the tracheobronchial tree, lung, or pleura requires a detailed history, physical examination, and, frequently, chest imaging studies. The history and physical examination should be carried out as discussed in Chapter 12 and Chapter 60. Pulmonary function tests; arterial blood gas analysis; chemical and microbiological tests; or special studies such as computed chest tomography (CT), magnetic resonance imaging scan, endoscopy, biopsy, or radionuclide scanning might also be necessary. Because disorders of the respiratory system are frequently a manifestation of a systemic process, attention must be focused not only on the chest but also on the comprehensive evaluation of the patient's entire health status.

History taking provides essential information and initiates the physician's understanding of the patient as a person, the patient's environment, and the type and place of work, as well as the patient's expectations and fears. As discussed in Chapter 12, data should include past and present history; information on previous illnesses, medications, and other therapies; a family history; and history of the occupation. If warranted, information should be obtained about travel history; exposure to pets or other animals; or exposure to such hazards as tobacco, smoke, asbestos, coal, silica, beryllium, iron oxide, tin oxide, cotton dust, titanium, silver, and nitrogen dioxide (9).

Obviously, much time should be devoted to obtaining a detailed description of the presenting chest pain and other major respiratory symptoms, such as cough, dyspnea, wheeze, and hemoptysis. The most important respiratory system disorders that produce pain include inflammation of the tracheobronchial tree or of the pleura, as in pneumonia, pulmonary thromboembolism, and malignancy. Pleuritic pain is usually localized to one side of the chest and is related to movements of the thorax and to respiration. Lesions confined to the pulmonary parenchyma do not produce pain except as previously mentioned, when pathophysiologic processes stimulate the J or the lung irritant receptors. Detailed information must be obtained about the various characteristics of the pain, including the speed of onset, location, radiation, intensity, duration, and factors that aggravate and relieve the pain (see Chapter 60) (9). A detailed history and a comprehensive physical examination, carried out along the lines summarized in Table 60-1, together with a review of Chapter 60C, permit a presumptive diagnosis. Important diagnostic points (see Table 60-2) should also help the physician to make a differential diagnosis among pain caused by respiratory disorders, pain of the chest wall resulting from orthopedic or neurologic problems, and pain referred to the chest from diseases of the abdominal viscera or from neck and upper limb disorders.

Epidemiology

Acute respiratory disorders afflict more Americans than any other group of acute conditions. The 1992 estimates published by the National Center of Health Statistics based on the National Health Interview Survey, indicated that, of a total of 445 million acute conditions, 209 million (47%) involved the respiratory system (Table 62-1) (10). Because the survey excluded those conditions that did not involve restricted activity or medical attention, the actual figure is even larger. The next most frequent group of acute conditions included approximately 62 million injuries and 54 million infectious and parasitic diseases. As noted in Table 62-1, these respiratory disorders caused 707 million days of restricted activity, 345 million days of bed disability, and nearly 129 million days lost from work among those 18 years of age or older who were fully employed outside the house. In addition, respiratory disorders caused more than 82 million days of school absence in those younger than 18 years of age.

Conditions	Total number	Restricted activity (days)	Bed disability (days)	Work loss (days)	Attended by physicians: Percentage of conditions	Attended by physicians: Total physician visits
Common cold	66.8	148.5	42.4	21.6	41.9	27.9
Other upper respiratory infections	30.9	74.9	11.6	10.8	80.9	25.0
Influenza	90.4	195.4	170.1	69.3	36.2	32.7
Acute bronchitis	12.1	67.2	27.9	11.5	90.7	11.0
Pneumonia	4.2	64.3	40.0	11.0	90.7	4.1
Other acute respiratory conditions	5.2	23.3	13.6	3.2	89.1	4.6
All	208.9	757.5	345.6	129.4	50.1	104.4

From National Center for Health Statistics. Current estimates from the National Health Interview Survey: United States 1992. Vital Health Stat 10:190. DHHS Pub. No. (PHS)93-1518. Hyattsville, MD: National Center for Health Statistics, 1993.

TABLE 62-1. Incidence and impact of acute respiratory disorders (numbers in millions)

Table 62-1 lists the percentage of acute respiratory conditions that resulted in at least one visit to a physician. As might be expected, the highest percentage of medical attention was obtained for upper respiratory infections, acute bronchitis, and pneumonia. The number of physician visits for each condition (last column) was computed by multiplying the total number for each condition by its percentage. The total was nearly 105 million visits.

With regard to chronic respiratory conditions, 1994 information for certain disorders is available (11): chronic bronchitis, 14.0 million; asthma, 14.6 million; emphysema, 2.0 million; chronic sinusitis, 34.9 million; and other chronic respiratory conditions, 26.1 million (12). This does not include data on neoplasms (see Chapter 64). No figures are available about the number of restricted activity days, bed disability days, and days of lost work, but it is likely that the numbers are significantly larger because of the chronicity of these disorders.

PAINFUL DISORDERS OF THE TRACHEOBRONCHIAL TREE

Acute Tracheobronchitis

Acute inflammation of the upper respiratory tract causes mild to moderate pain, which is perceived as soreness and irritability of the airway. The patient can also experience retrosternal burning or soreness, often associated with a sore throat or laryngeal irritation. The condition is generally self-limiting, with eventual complete healing and return of function. Although often mild, bronchitis can be serious in debilitated patients and in those with chronic lung or heart disease. Bacterial pneumonia can be a critical complication (13).

Etiology

Acute bronchitis can be caused by an infectious process or by various irritants. An acute infectious process, most prevalent in winter, is often part of an acute upper respiratory infection. Not infrequently this develops after a common cold or other viral infection of the nasopharynx, throat, or tracheobronchial tree and is often complicated by a secondary bacterial infection. Exposure to air pollutants and possibly chilling, fatigue, or malnutrition are predisposing or contributing factors (13). Recurrent attacks often complicate chronic bronchopulmonary disease, and impair bronchial clearance mechanisms. Repeated infections can be associated with chronic sinusitis or bronchiectasis.

Various irritating gases can also cause inflammation of the tracheobronchial tree. Acute irritative bronchitis can also be caused by various mineral and vegetable dusts and by fumes from strong acids, ammonia, certain volatile organic solvents, chlorine, hydrogen sulfide, sulfur dioxide, or chlorine. Polluted air can settle over an area, and highly irritant gases such as sulfur dioxide and nitrogen peroxide can increase in concentration until clinical symptoms result. Inhalation of extremely hot air produces a burning in the upper airway that is exceedingly painful and slow to heal (13). When associated with inhalation of soot and burning particles, such a burn can be rapidly fatal.

Pathophysiology

Acute infectious tracheobronchitis initially causes hyperemia of the mucous membranes followed by desquamation, edema, leukocytic infiltration of the submucosa, and production of a sticky or mucopurulent exudate. The protective function of the bronchial cilia, phagocytes, and lymphatics is disturbed, and bacteria can invade the normally sterile bronchi and cause accumulation of cellular debris and mucopurulent exudate. Coughing, although distressing, is essential to eliminate bronchial secretion. Airway obstruction can result from edema of the bronchial walls, retained secretions, and, in some cases, spasm of the bronchial muscles. Direct thermal injury from inhalation of hot air, if not fatal, causes the patient to cough up eschar before recovering. The healing process is prolonged and difficult.

Symptoms and Signs

Acute infectious bronchitis is often preceded by symptoms of upper respiratory infection: coryza, malaise, chills, slight fever, back and muscle pain, and sore throat (13). The onset of tracheobronchitis is signaled by a cough that is initially dry and nonproductive but raises small amounts of viscid sputum for a few hours a day and then becomes more abundant and mucopurulent. At this time patients can feel retrosternal irritation and discomfort or frank pain. Patients with frequent coughing episodes can experience pain due to strains of the intercostal or abdominal muscles. In severe or complicated cases, fever up to 38.3°C or 38.9°C (101°F or 102°F) can be present for 2 to 5 days, after which a few symptoms subside while the cough can continue for several weeks. Some patients continue to cough and some bring up abundant mucoid or mucopurulent sputum. Dyspnea, which is secondary to the underlying obstruction, can be experienced.

Auscultation in patients with uncomplicated acute bronchitis reveals scattered high- or low-pitched rhonchi, occasional crackling or moist rales, or both at the base of the lungs. Wheezing after coughing is commonly noted. Patients with acute irritative bronchitis usually have a dry nonproductive cough, but with invasion of bacteria, patients develop the same symptoms and signs as those of acute infectious bronchitis.

Patients who manifest persistent or increased fever may be developing bronchopneumonia, which can produce persistent localized signs of consolidation. This and other serious complications are seen most commonly in patients with underlying chronic respiratory disorders. In such patients, acute bronchitis can lead to worsening blood gas abnormalities.

Diagnosis

Diagnosis is presumptively made through a detailed history and physical examination. If the symptoms and signs are serious or persist, a chest roentgenogram should be taken to rule out other diseases or complicating pneumonia. When serious underlying chronic respiratory disease is present, arterial blood gases should be monitored at frequent intervals. Microbiological smears and cultures can be obtained in an attempt to determine the infective organism.

Treatment

Treatment consists of rest until pain subsides, fluids in amounts of 3 to 4 L per day during the febrile course, and the administration of nonsteroidal antiinflammatory drugs (NSAIDs) to reduce the fever and relieve the muscle pain that most of these patients have. NSAIDs should be given in sufficient doses to provide effective analgesia and achieve an antipyretic effect. For example, aspirin in doses of 600 mg every 4 hours should be given, but if this does not provide effective relief, the dose should be increased to 1,000 mg every 4 hours. Of course, in patients who are allergic to aspirin, other NSAIDs should be used. In any case patients should be monitored closely for any adverse side effects (see Chapter 83). If the patient has a severe cough that continues to produce muscle pain and interferes with sleep, codeine in doses of 32 to 64 mg should be added to NSAIDs. Care should be taken if patients also have COPD. Other measures include steam inhalation or a vaporizer for coughing and bronchodilators for wheezing.

In patients in whom a high fever persists and who have purulent sputum or in those who have a concomitant underlying disorder such as COPD, antibiotics should be

given (13,14). A chest film should be obtained to exclude the development of pneumonia. Oral amoxicillin, 250 mg every 6 hours, or trimethoprim-sulfamethoxazole is adequate for most patients without underlying diseases. In COPD patients it is important to cover *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis*. Cefaclor, azithromycin, or clarithromycin are alternative effective antibiotics in COPD patients (14). Sputum smear evaluation and culture plus chest imaging can guide antibiotic choice if symptoms persist or recur or in patients with unusually severe disease.

Bronchiectasis

Bronchiectasis is an irreversible focal dilation of the bronchioles, often accompanied by infection. Although pain is not the most severe symptom, many patients experience some retrosternal and general chest pain (15,16).

Etiology and Pathophysiology

Acquired bronchiectasis results from direct bronchial wall destruction after infection, inhalation of bronchial chemicals, immunologic reaction, or vasculopathy that interferes with bronchial nutrition, or alternatively from mechanical alterations secondary to atelectasis or loss of parenchymal volume that leads to bronchial dilation and secondary infection. Acquired conditions commonly leading to bronchiectasis include the following: (a) severe pneumonia (especially complicating measles, pertussis, or certain adenovirus infections in children); (b) necrotizing infection at any age caused by *Klebsiella*, staphylococci, influenza virus, fungi, mycobacteria, and perhaps *Mycoplasma*; and (c) bronchial obstruction from any cause such as foreign bodies, enlarged lymph nodes, mucous infection, or lung cancer. Inherited causes of bronchiectasis include conditions such as cystic fibrosis and ciliary dyskinesis syndromes (17).

Bronchiectasis can be localized or extensive and is most common in the lower lobes in conditions other than tuberculosis. Upper lobe involvement is common with tuberculous bronchiectasis. Pathologic examination of the airway reveals extensive inflammatory destruction, chronic inflammation, increased mucus, and loss of cilia.

Symptoms and Signs

Although patients might be completely asymptomatic, chronic cough and sputum production are the most characteristic and common symptoms in infected patients; these usually begin insidiously after a respiratory infection and tend to worsen gradually over a period of years (15,16,18). As the condition progresses, the cough eventually becomes more productive, occurring with typical regularity in the morning on arising, late in the afternoon, and on retiring, but many patients are affected with cough during intervening hours. Concurrent pneumonia and hemoptysis are common, and the latter can be the first and only symptom in so-called dry bronchiectasis. Physical findings are not specific, but persistent rales can occur over the affected part of the lungs. Pulmonary functional and hemodynamic changes depend on the extent of the accompanying pathologic changes, such as diffuse chronic bronchitis, pulmonary emphysema, or pulmonary fibrosis, and can include reduction in lung volumes and air flow rates, ventilation or perfusion defects, hypoxemia, and, in severe cases, pulmonary hypertension.

Pain is not a common symptom but it can occur and produces significant discomfort, particularly in patients in whom the bronchiectasis is associated with osteoarthritis, so-called rheumatic bronchiectasis. Such patients have pain not only in the chest but also in the limbs. Teodori and Galletti reported a number of cases (19) in which patients with bronchiectasis had pain in the chest and in the arms that was moderate and poorly localized. Ten of 18 patients with bronchiectasis had deep marked diffuse pain of variable location. Figure 62-7 depicts the most frequent sites of the pain, cutaneous hyperalgesia, and deep hyperalgesia. It was concluded that the pain was a referred phenomenon from stimulation of the tracheobronchial tree, whereas the cutaneous and deep hyperalgesia were caused by viscerocutaneous reflexes (19).

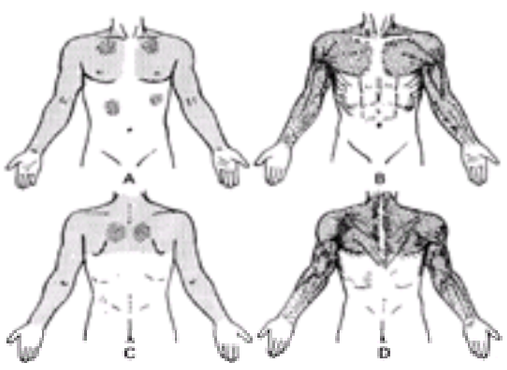

Figure 62-7. Distribution of pain and of cutaneous and deep hyperalgesia in patients with bilateral bronchiectasis. **A,B:** Anterior views of distribution of the pain, indicated by heavy stipples and of the cutaneous hyperalgesia, indicated by the cross-hatched areas. **C,D:** Posterior views showing the distribution of deep hyperalgesia involving muscles of the chest. (Modified from Teodori U, Galletti R. *Il dolore nelle affezioni degli organi interni del torace*. Rome: L Pozzi, 1962:262.)

Diagnosis

Diagnosis of bronchiectasis is made by history and physical examination and by symptoms and signs as described above. Standard chest radiographs can show increased bronchovascular markings, areas of honeycombing, or cystic areas with or without fluid levels, but often the radiographs are nondiagnostic in early stages of disease. CT scanning of the chest is necessary to confirm the diagnosis and extent of the lesions, especially if surgery is being contemplated (15,16).

Treatment

Treatment consists of appropriate antibiotics, other drugs, and physical therapy to promote bronchial drainage. In patients without cystic fibrosis, the flora in the sputum are usually mixed gram-positive and gram-negative microorganisms, and anaerobes commonly inhabit the bronchiectatic cysts. A broad-spectrum antibiotic such as amoxicillin, 250 to 500 mg orally every 6 hours, or trimethoprim-sulfamethoxazole is continued until the sputum is nonpurulent and less voluminous, usually for 1 to 2 weeks. Antibiotics should be repeated at the first sign of returning infection; if it recurs frequently, prolonged chemoprophylaxis with amoxicillin or trimethoprim-sulfamethoxazole can be tried but is often disappointing. If bronchopneumonia or serious respiratory infection occurs, a parenteral antibiotic guided by Gram's stain and culture/sensitivity studies is indicated. Cystic fibrosis patients may develop early staphylococcal colonization and as their course progresses will eventually become colonized with mucoid *Pseudomonas*species, which require intermittent active treatment (17). Effective methods to improve drainage of secretions in cystic fibrosis patients include exercise, chest percussion with postural drainage, positive expiratory pressure devices, vest/compressor oscillation systems, and possibly hand-held oscillation flutter devices (20).

The mild to moderate pain that is usually present in a number of patients should be managed with NSAIDs in moderate to high doses (650 to 1,000 mg aspirin every 4 hours). If these are not effective and the patient has a persistent cough, moderate doses of codeine can be added to the NSAIDs. If physical examination reveals the presence of a superimposed myofascial syndrome, trigger points should be injected with a local anesthetic and other therapy should be carried out (see Chapter 29 and Chapter 64).

PAIN CAUSED BY DISEASES OF THE LUNG

Lung tissue is generally considered to be insensitive to noxious stimuli; accordingly a large number of common lung diseases are not discussed in this chapter. However, under certain pathophysiologic conditions, the J receptors in the interstitial space near the capillaries, the lung irritant receptors in the epithelial lining of the lung and its airways, or both types of receptors are excited by stimuli that produce mechanical distortion within the lung tissue, such as pulmonary congestion. In addition, infectious diseases such as pneumonia or lung abscess can extend to produce inflammation of the pleura and cause pleuritic pain. Disorders of the pulmonary circulation such as pulmonary hypertension and pulmonary embolism can also be a source of chest pain.

Pulmonary Infections

Pneumonia

Pneumonia is defined as an inflammation in the lung parenchyma in the portion distal to the terminal bronchioles and composed of the respiratory bronchioles, alveolar ducts, alveoli, and interstitial tissues (21,22). Patterns of pneumonia can be classified based on roentgenographic or pathologic evidence. In lobar pneumonia the infection is confined to an entire lobe; in segmental or lobular pneumonia it is confined to a segment of the lobe; in bronchopneumonia it is confined to alveoli contiguous to the bronchi; and in interstitial pneumonia it is confined to the interstitial tissues.

Etiology and Epidemiology. The most common causes of pneumonia in adults are bacteria: *S. pneumoniae*, *Staphylococcus aureus*, *H. influenzae*, *Klebsiella pneumoniae*, and other gram-negative bacilli. Legionella can occur in several serotypes; the frequency of legionella infection varies from community to community. *Mycoplasma pneumoniae* can cause pneumonia, especially in older children and young adults. Various other types of bacteria can also cause specific types of pneumonia.

Predisposing factors include respiratory viral infection, alcoholism, age extremes, debility, immunosuppressive diseases and immunosuppressive therapy, compromised consciousness, pulmonary aspiration, and exposure to transmissible agents (22). The usual mechanism is either inhalation of droplets small enough to reach the alveoli or aspiration of secretions from the upper airways. Other mechanisms include hematogenous dissemination or through the lymphatics or directly from contiguous infection. An important contributing factor is postoperative or posttraumatic decrease in chest wall and pulmonary compliance, with consequent hypoventilation, impairment of the cough reflex, bronchial spasm, and dehydration. All these cause retention of bronchial secretions, which lead to segmental atelectasis and in turn to lung infection.

Another unusual but important cause of pneumonia is aspiration of gastric contents (Mendelson's syndrome), which causes chemical pneumonitis with serious lung pathophysiology. This disorder is the most frequent cause of anesthetic morbidity and mortality among patients who receive general anesthesia (23).

Other contributing factors are weakness from malnutrition or neuromuscular diseases, thoracic deformities such as severe kyphoscoliosis, or severe lung disease that prevents the full inspiration and brisk expiration necessary to generate an effective cough (22).

In the United States 3 to 4 million people develop community-acquired pneumonia annually; approximately 16% require hospitalization, and of these 75,000 to 125,000 die from pneumonia (24). Pneumonia is the most common lethal infection and ranks sixth among all disease categories as cause of death; it is the most frequently occurring fatal hospital-acquired infection. In addition to diarrheal illnesses, lower respiratory tract infections are a major cause of death in developing countries. Despite this impressive prevalence, few infections have causative agents that are so frustratingly difficult to identify. In up to 50% of patients no pathogen can be identified, despite a strong clinical impression of bacterial pneumonia (25).

Pathophysiology. The earliest stage of pneumonia is congestion characterized by extensive serous exudation, vascular engorgement, and rapid bacterial proliferation. The next phase is called *red hepatization*, reflecting the liverlike appearance of the consolidated lung or lobule. The air spaces are full of polymorphonuclear cells, with vascular congestion; extravasation of red blood cells provides the basis for the reddish discoloration on gross examination (21). The parenchyma can be intact, but the usual air-containing spaces change into a solid organ with a dense inflammatory response; hence, the term *hepatization*. The next stage is *gray hepatization*, in which accumulation of fibrin is associated with inflammatory white and red blood cells in various stages of disintegration, and the alveolar spaces are packed with an inflammatory exudate. The final stage is resolution, characterized by resorption of the exudate, often with little or no permanent scarring or loss of function.

Symptoms and Signs. The major symptoms of pneumonia occur in varying combinations of cough, fever, chest pain, dyspnea, and the production of sputum, which can be mucoid, purulent, or even bloody. In some patients extrapulmonary features such as confusion or disorientation are prominent features. Occasionally, in elderly, alcoholic, or neutropenic patients, respiratory symptoms and signs are absent altogether.

Chest pain occurs predominantly in lobar pneumonia that involves the peripheral lung tissues, frequently sparing the airways (22). The inflammation involves the pleura early and thus pleuritic pain is an initial symptom. The onset of pain may be fairly rapid, occurring over a few hours and mimicking the pain associated with pulmonary embolism. Pleurisy is frequent with pneumococcal lobar pneumonia, occurs not infrequently with *Klebsiella* pneumonia, but is noted infrequently in mycoplasmal and viral pneumonia. Because the pleura is unaffected in bronchopneumonia and interstitial pneumonia, pain is usually not a prominent symptom in these conditions.

The common physical findings are fever, tachycardia, and tachypnea; patients with severe hypoxemia appear cyanotic. Chest examination usually reveals a decreased respiratory excursion on the affected side because of the pleuritic pain and dullness to percussion from pneumonic consolidation or an accompanying pleural effusion (22). Among the earliest auscultatory findings is the presence of high-pitched end-inspiratory crackles originating from fluid-filled alveoli. Consolidated lung surrounding a patent bronchus produces bronchial breath sounds. Examination of the skin with a pinprick or pinch reveals cutaneous hyperalgesia in the same segments supplying the pleura. If the diaphragmatic pleura is involved, the hyperalgesia is found in dermatomes C-3 to C-5 and perhaps in T-9, T-10, and T- 11 (see Chapter 60 for details of innervation of the pleura).

Patients with lower lobe involvement also have hyperalgesia of the chest, whereas if the pneumonia involves the upper lobes, the hyperalgesia is present in T-2 to T-5 or T-6. In addition, pinch reveals deep hyperalgesia and increased muscle tension. Both the cutaneous and deep types of hyperalgesia are present on the side ipsilateral to the pneumonia (19).

Diagnosis. A presumptive diagnosis is usually made through a detailed history, physical examination, and roentgenographic studies, which invariably show the pulmonary infiltrate. Culture and staining of appropriate specimens are unfortunately often of limited usefulness in identifying the pathogen (25). A complete blood cell count, electrolytes, and renal and hepatic function testing have prognostic significance but rarely point to a specific pathogen. For definitive diagnosis it is necessary to demonstrate the pathogen in pleural fluid, blood, or lung or transtracheal aspirate (21,25).

Treatment

General Therapy. Treatment of patients with pneumonia includes general measures such as rest, fluids, and antibacterial agents for the bacterial pathogen. Initial antibiotic therapy usually must be chosen before the infectious etiology is definitively known. One commonly used set of guidelines for the initial antibiotic choice in treating community-acquired pneumonia was developed by the American Thoracic Society (25). These guidelines define four patient categories and directed therapy toward the pathogens most commonly occurring in each category. The first category includes patients age 60 years or younger who have no comorbid conditions. *S. pneumoniae*, *M. pneumoniae*, and *Chlamydia pneumoniae* are common etiologic agents in this group. A macrolide such as erythromycin, clarithromycin, or azithromycin is the first choice for such patients, with tetracycline the alternative choice for those allergic to or intolerant of the macrolides. The second group includes patients older than 60 years of age or patients of any age with comorbid conditions who are not sick enough to require initial hospitalization. Antibiotic coverage in these patients is broadened to include greater coverage of *H. influenzae*, other aerobic gram-negative bacilli, and *S. aureus*. Appropriate antibiotic choices include either a second- generation cephalosporin or trimethoprim-sulfamethoxazole or a b-lactam/b-lactamase inhibitor combination with optional addition of a macrolide. The third group of patients are ill enough to require hospitalization (mortality rate of 5% to 25%). Polymicrobial infections can occur in this group. Recommended initial antibiotic coverage is similar to the second group but without the option of trimethoprim- sulfamethoxazole. The fourth group contains patients with severe pneumonia (mortality up to 50%). These patients may have a severe pneumonia caused by the common pathogens (*S. pneumoniae*, *S. aureus*) or by aerobic gram-negative bacteria and so need treatment with a macrolide plus either an antipseudomonal third-generation cephalosporin, such as ceftazidine, or with other antipseudomonal agents, such as imipenem/cilastatin or ciprofloxacin.

Nosocomial pneumonias have a high mortality, as they often occur in patients with short- or long-term immune defects and often are caused by gram-negative organisms; accordingly they must be presumptively treated with potent broad-coverage antibiotics. With either community-acquired or nosocomial pneumonia, the antibiotic coverage should be narrowed to more specific coverage if a recognized pathogen is clearly identified through cultures (25).

Pain Therapy. The treatment of pain associated with pneumonia depends on its severity. Patients with mild pain should be given NSAIDs in the medium range of dosages listed in Chapter 83. For moderate pain it might be necessary to give high doses (e.g., 1,000 mg of aspirin together with 64 to 128 mg of codeine or other narcotics). Because the pain is severe in many of these patients, it may be necessary to combine NSAIDs with morphine or other potent narcotics. A highly effective

way of providing good pain relief with potent narcotics is by the use of patient-controlled analgesia (see Chapter 84).

In patients with severe pain that is not adequately relieved by systemic analgesics, consideration should be given to having an anesthesiologist carry out posterior intercostal block of the segments involved with pain using a long-acting local anesthetic, such as bupivacaine. To obviate the minimal discomfort from the needle punctures, a bolus of 150 mg of thiopental sodium will produce amnesia (not anesthesia) for 3 to 5 minutes, during which time the needles are inserted. This procedure provides complete pain relief for 8 to 12 hours and also eliminates the reflex segmental and suprasegmental responses described in Chapter 9.

An alternate technique for managing severe pain is the use of epidural opioid analgesia, which is achieved by placing a catheter in the lower thoracic epidural space and injecting appropriate doses of a narcotic. Although this is not as effective in blocking nociceptive impulses as the use of local anesthetic, it usually provides excellent pain relief and has the advantage over the use of intercostal block of involving only one puncture. Because the pain only lasts 3 or 4 days with effective antibiotic therapy, all these therapeutic procedures to manage pain are practical and are associated with only minimal adverse side effects. An epidural catheter can be placed to provide many days of pain relief with local anesthetics and opioids.

Lung Abscess

A lung abscess consists of a localized pus-containing cavity resulting from necrosis of lung tissue and surrounding pneumonitis. It can be a cause of chest pain, especially if the inflammation extends to the parietal pleura.

Etiology and Pathophysiology. Lung abscesses are usually caused by aspiration of infected material from an upper airway when a patient is unconscious or obtunded from alcoholism, central nervous system disease, general anesthesia, or excessive sedation. Lung abscesses are usually produced by anaerobes and are not infrequently associated with periodontal disease. Sometimes multiple organisms act synergistically. Bacteria cultured from a lung abscess include the common pyogenic bacteria and nasopharyngeal flora, particularly anaerobes and, less often, aerobic bacteria and fungi. Bronchogenic carcinoma can obstruct an airway and cause a distal lung abscess (26).

A single abscess is most common, but multiple abscesses that are usually unilateral also occur and can develop simultaneously or spread from a single focus (26). In abscesses caused by aspiration, the superior segment of the lower lobe and the posterior segment of the upper lobe are most frequently affected because these locations are connected to airways that are gravitationally dependent in a person who is supine. The solitary abscess consequent to bronchial obstruction or an infected embolus starts as necrosis over the major portion of the involved bronchopulmonary segment, with its base adjacent to the chest wall and the pleural space; the affected part is often obliterated by inflammatory adhesions. Abscesses occurring in multiple sites in noncontiguous parts of the lung are usually a result of hematogenous spread and are frequently caused by *S. aureus* (22,26).

An abscess usually ruptures into a bronchus and its contents are expectorated into the air and fluid-filled cavity. With adequate drainage, the walls usually collapse and contract, eventually obliterating the cavity. If drainage is inadequate the abscess becomes fibrotic and rigid, and healing does not occur. Occasionally an abscess ruptures into a pleural cavity, resulting in empyema and not infrequently in a bronchopleural fistula. If the abscess ruptures into the airway, acute suffocation or diffuse pneumonia may result.

Symptoms and Signs. Symptoms can develop acutely or be insidious. Early symptoms are often those of pneumonia, characterized by malaise, anorexia, sputum-producing cough, and fever. Unless the abscess is completely walled off, the sputum is purulent and is frequently blood-streaked. Approximately 60% of patients with abscess caused by anaerobic bacteria develop a putrid odor discernible at some distance from the patient (26). Some patients manifest severe prostration and a temperature of 39°C to 40°C.

Chest pain occurs invariably with pleural involvement. Teodori and Galletti (19) carefully studied the location, quality, and intensity of pain in 15 patients with lung abscess. They noted that all but two patients had pain that was dull and aching in character, and it was mild in two, moderate in eight, and severe in three. Pain caused by abscess in the superior lobe was usually referred to the ipsilateral scapula, pain from the midportion of the lung was usually referred to the ipsilateral shoulder and arm and mammary region, and pain that involved the lower part of the lung was usually referred to the shoulders bilaterally. In the latter case it is likely that the diaphragmatic pleura was involved in the inflammatory reaction. Pain was continuous in eight of the patients and occurred at intervals during the day in the rest. All the patients had cutaneous hyperalgesia, and 12 had deep muscular hyperalgesia. Figure 62-8 shows the distribution of spontaneous pain and the cutaneous hyperalgesia in one patient who had unilateral pain.

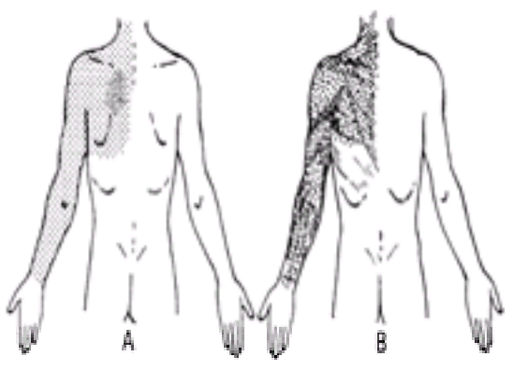

Figure 62-8. Distribution of pain and of cutaneous hyperalgesia in patients with an abscess in the left lung. **A,B:** Posterior views showing the distribution of the pain, indicated by *heavy stipples*, and of the cutaneous hyperalgesia, indicated by the *cross-hatched areas*. (Modified from Teodori U, Galletti R. *Il dolore nelle affezioni degli organi interni del torace*. Rome: L. Pozzi, 1962:72.)

Physical signs of lung abscess include a small area of dullness indicating localized pneumonic consolidation, suppressed rather than bronchial breath sounds, and fine or medium moist rales.

Diagnosis. The presumptive diagnosis can be made through a history and physical examination that reveals the aforementioned signs (9). Chest roentgenography initially shows a segmental or lobar consolidation that becomes globular as it distends with pus. After a rupture into a bronchus, a cavity with a fluid level appears on the film. Failure of an area of pneumonia to resolve should always suggest abscess formation or an obstruction such as a tumor in the airway. The patient should be followed with roentgenography or CT scanning at 1- to 2-week intervals in search of central areas of diminished density. The sputum should be examined by smear and cultured for bacteria, including mycobacteria. If anaerobes are suspected as the causative agents, consider obtaining a specimen of bronchial secretions by transtracheal aspiration to avoid contaminating the specimen with oral anaerobic organisms. If there is a mass within the radiographic cavity, the sputum should be examined for *Aspergillus*.

Treatment. Prompt and complete healing of a lung abscess depends on prolonged adequate antibiotic treatment and drainage; most patients recover without surgical intervention. As soon as the sputum and blood have been collected for culture and sensitivity testing, antibiotic therapy should be initiated promptly. Clindamycin, 600 mg intravenously three or four times a day, or the combination of a penicillin plus a b-lactamase inhibitor or metronidazole has replaced penicillin alone as the initial antibiotic choice based upon data that 15% to 20% of patients do not respond to penicillin alone (26). Treatment should be continued until the pneumonitis has resolved and the cavity has disappeared or stabilized on serial roentgenograms. Cavity closure often requires 2 to 3 months of treatment. Postural drainage can be a helpful adjunct but can also cause spillage to other bronchi, with extension of the process or acute obstruction. If the patient is too weak to cough up secretions, suctioning or intubation should be considered. Occasionally, bronchoscopic aspiration might be required to remove tenacious sputum. Pulmonary resection is the procedure of choice for an abscess resistant to medical therapy, particularly if bronchogenic carcinoma is suspected. Management of the chest pain associated with the lung abscess is similar to that described above for pneumonia.

DISORDERS OF THE PULMONARY CIRCULATION

Pulmonary Arterial Hypertension

Pulmonary hypertension can develop acutely, as in the patient with a large pulmonary embolism, or gradually, as in the patient with primary pulmonary hypertension or pulmonary hypertension secondary to progressive systemic sclerosis or other systemic diseases. Acute pulmonary hypertension can cause severe pain, often in the center of the chest, which is crushing or gripping in quality and is easily confused with the pain of acute myocardial infarction (27,28). In contrast to the pain of myocardial infarction, however, the pain of acute pulmonary arterial hypertension does not radiate to the jaw or to the arms, and seldom to the back. The gradual development of chronic pulmonary hypertension is less likely to be associated with chest pain, but these patients can develop a form of exertional anginalike pain associated with right ventricular ischemia (29).

Etiology and Pathophysiology

When pulmonary hypertension occurs acutely, such as in an acute pulmonary embolism in a patient with previously normal right heart function, the pulmonary artery systolic pressure usually cannot rise acutely to more than 50 mm Hg, after which the pressures does not rise further but right heart failure ensues. Davies (27) suggested that chest pain can be produced by acute dilatation of the main pulmonary artery or its major branches because acute distension of a large blood vessel anywhere in the body can cause pain, and this is also true of pulmonary arteries. A fall in Pa O_2 is a potent and immediate cause of rapid small pulmonary arterial constriction, leading to a rise in pulmonary arterial pressure with consequent distension of the larger vessels, which in turn may cause pain. Davies believed that pain can occur in a previously healthy patient with an acute rise in pressure or in a patient with chronic pulmonary hypertension when an extra load raises pressure still further (27).

The mechanisms causing pulmonary hypertension in primary pulmonary hypertension and many cases of secondary pulmonary hypertension are poorly understood, but some possible factors have been suggested. Destruction of vessels is one factor in emphysema and pulmonary fibrosis. In addition, neurohumoral vasoconstrictor mechanisms may be involved in some disorders. Support for this view is provided by the observation that the pulmonary vascular resistance can be acutely reduced in some patients by administration of vasodilators or by breathing oxygen (28). The anorexic agents that can cause pulmonary hypertension may do so through a serotoninlike effect on vascular growth (29). A role for immune mechanisms is suggested by the association and occurrence of Raynaud's disease or scleroderma, disseminated lupus erythematosus, rheumatoid arthritis, and dermatomyositis.

Pathologic examination of patients with chronic primary pulmonary hypertension will usually reveal findings confined to the right side of the heart and lungs, with the right atrium often enlarged and right ventricle hypertrophy present. Frequently, the large pulmonary arteries exhibit atherosclerotic plaques. The small pulmonary arteries (30 to 300 µm in diameter) exhibit muscular hypertrophy and intimal hyperplasia, sometimes with fibrosis (29).

With the development of severe pulmonary vascular disease, abnormal elevation of pulmonary arterial pressure occurs, often to a striking degree, and the pulmonary arterial pressure can be equal to that of the systemic arterial pressure. The cardiac output increases inadequately with exercise and eventually decreases even at rest. The pulmonary capillary pressure is normal, as the vascular restriction is upstream (except in pulmonary venoocclusive disease or left heart disease), and no intracardiac shunts are detected unless the patient develops a stretched foramen ovale because of the high right atrial pressure (29). In patients with advanced disease, the mean right atrial pressure is increased and the *a* wave in the right atrium is markedly elevated, which is an indication of the forceful atrial contraction necessary to fill the hypertrophied right ventricle. Mild systemic arterial oxygen desaturation is quite common, even in the absence of heart failure, and is a result of ventilation-perfusion mismatching within the lungs. Results of spirometry and lung volume measurements are often normal but the diffusion capacity is often reduced. Chronic hyperventilation may be present.

Symptoms and Signs

Patients with acute pulmonary hypertension may have severe central chest pain located retrosternally, often associated with anxiety and sense of impending death (27). Patients with chronic primary pulmonary hypertension relate a history of gradual onset of symptoms dominated by exertional dyspnea and fatigue; 50% to 60% may have angina-type chest pain (28). Hoarseness or dry cough caused by compression of the left recurrent laryngeal nerve by the enlarged pulmonary artery occurs in approximately 6% to 8% of patients (29).

Patients with acute pulmonary arterial hypertension can be in shock from low cardiac output. Cyanosis is usually present with acute pulmonary hypertension. The jugular pulse shows a prominent *a* wave, a right ventricular heave is present, and a pulse can be felt in the region of the main pulmonary artery. The pulmonary closure sound is markedly accentuated and often palpable (28). An atrial valve sound is heard at the lower left sternal border, and in some patients, an ejection murmur at the pulmonic area or the early diastolic murmur of pulmonic regurgitation is heard. Chest roentgenograms can show cardiac enlargement of the right ventricle and right atrial prominence, with marked dilatation of the pulmonary artery segments.

Diagnosis

Acute pulmonary hypertension can be confirmed by echocardiography with measurement of the elevated velocity of tricuspid regurgitation, allowing calculation of the degree of pulmonary hypertension, and examination of the degree of inferior vena cava dilation, examination of the right atrial size, and examination of the right ventricular size and systolic function, yielding an assessment of the components of cardiac function. The diagnosis is best confirmed by right heart catheterization with concomitant measurements of oxygen contents so that intracardiac shunts can be excluded. Measurement of pulmonary artery wedge pressure and cardiac output allows the best characterization of the degree of hemodynamic compromise and will help guide therapy.

The pathology of many types of pulmonary hypertension is similar. Accordingly, many clinicians group with primary pulmonary hypertension forms of pulmonary hypertension related to the use of diet pills or related to cirrhosis and portal hypertension. Secondary causes of pulmonary hypertension include progressive systemic sclerosis and other so-called collagen vascular diseases, left-to-right cardiac shunts, diffuse pulmonary diseases such as emphysema, chronic left heart disease, and chronic pulmonary thromboembolism. Diagnosis requires not only a thorough history but also a complete physical examination and special tests, including pulmonary function tests, cardiac catheterization, angiography, and radioactive lung scanning studies.

Treatment

Acute pulmonary hypertension is a medical emergency best treated by eliminating the causative factor. For pulmonary embolism, treatment would include anticoagulant or thrombolytic therapy. Inhalation of high concentrations of oxygen can sometimes be effective in decreasing the pulmonary arterial pressure and, consequently, the pain.

In patients with chronic primary pulmonary hypertension, the downward course is progressive in many patients, despite treatment. Right-sided heart failure should be treated with cardiotonic and diuretic regimens. If the patient is hypoxemic, oxygen therapy is essential to remove any component of active hypoxic vasoconstriction. Based upon studies of patients with primary pulmonary hypertension, the response to direct vascular smooth muscle relaxants (e.g., nitroprusside, diazoxide, and hydralazine), to b agonists, and to a-adrenergic blockers is often disappointing. High-dose calcium channel–blocker therapy is well established but effective in a minority of patients (29). Effective in the majority of patients is the constant infusion of epoprostenol (prostacyclin), which has led to successful therapy of many patients who are unresponsive to all other treatments (29). Before instituting long-term therapy, measurements of the acute responses of the pulmonary artery pressure, pulmonary vascular resistance, cardiac output, and systemic arterial pressure are indicated to guide the selection of therapy and to aid in prognosis.

The management of pain depends on the severity and duration. In patients with severe and excruciating central pain caused by acute pulmonary hypertension, avoidance of exertion or elimination of the causative factor, such as giving oxygen to patients who have pain at high altitudes, is usually sufficient. If the severe, excruciating pain persists after a reasonable trial period, intravenous narcotics should be administered. In patients with chronic pulmonary hypertension, the pain is usually not severe and can be managed with NSAIDs given alone or in combination with codeine.

Pulmonary Embolism

Acute pulmonary embolism is a relatively common event, particularly in hospitalized, acutely ill patients (30,31). The incidence of symptomatic pulmonary embolism in the United States has been estimated at 600,000 annually (30). Evidence of acute or chronic pulmonary emboli can be found in up to 60% of autopsies, but most are probably clinically insignificant (31). However, pulmonary emboli cause or contribute to approximately 5% of deaths and yet only 30% of these emboli are diagnosed

or suspected premortem. Acute pulmonary embolism might be the most common cause of acute pulmonary disease in hospitalized patients and is one of the most common causes of sudden unexpected death in this population (32).

Etiology

The pulmonary embolus can consist of thrombus, air, amniotic fluid, fat, or bone marrow (30). Ninety-five percent of pulmonary emboli arise from thrombi forming in the leg or pelvic veins (30,31). Thrombi occur in the right cardiac chambers or other veins and account for most of the remaining 5% of pulmonary emboli. Amniotic fluid, fat, or bone marrow emboli represent less than 1% of all cases of pulmonary embolism. The most significant risk factor for the formation of thrombus and subsequent pulmonary embolism is venous stasis, such as that which occurs postoperatively, with prolonged periods of bed rest, with low cardiac output from any cause, and with prolonged immobility during lengthy travel.

Other predisposing factors include the use of oral contraceptives, pregnancy and the postpartum period, obesity, malignancy, hematologic disorders (e.g., polycythemia vera), vascular injuries from minor trauma, and prolonged immobilization of patients with chronic disease states (33). When a patient seems to have inadequate risk factors for embolism or repeated episodes of embolism, a hypercoagulable state should be sought. Examples of hypercoagulable states include resistance to activated protein C (abnormal factor five), antiphospholipid syndromes, antithrombin 3 or protein C or S deficiency, and dysfibrinogenemias (30,33). Several studies have shown that patients undergoing hip surgery with general anesthesia have a significantly greater incidence of thromboembolism than those undergoing the same surgery with regional anesthesia (33).

Once released into the venous circulation, emboli are distributed to both lungs in 65% of cases, unilaterally in 35%. The lower lobes are involved four times more often than the upper lobes, probably because of their greater blood flow.

Pathophysiology

Most of the consequences of pulmonary embolism can be explained by obstruction of the pulmonary vasculature to produce hypoxemia, acute pulmonary hypertension, right ventricular failure, and reduced cardiac output or cardiogenic shock. Hemodynamically significant pulmonary embolism is associated with obstruction of approximately 30% or more of the segments of the pulmonary arterial tree (34). Acute obstruction of the right or left main pulmonary artery with a balloon, however, produced relatively few hemodynamic changes or symptoms (34). Therefore, it is generally thought that the acute pulmonary embolism leads to the release of humoral substances such as serotonin, prostaglandins, and histamine, resulting in constriction of the pulmonary arterial bed (30,34).

The combined effect of the mechanical obstruction by thrombus and vasoconstriction leads to ventilation-perfusion mismatching, resulting in the arterial hypoxemia that is common but not universal. Pulmonary vascular resistance, pulmonary arterial pressure, right ventricular systolic and diastolic pressures, and right atrial pressure are increased, whereas the cardiac index is decreased. If pulmonary vascular resistance increases acutely to the extent that the right ventricle cannot generate sufficient pressure to maintain cardiac output, arterial hypotension results, and this can progress to shock. In patients without preexisting cardiopulmonary disease, this occurs only after massive embolization involving at least 50% and usually 75% of the pulmonary vascular bed (31). In patients with prior cardiopulmonary disease, shock can occur with a lesser extent of embolization.

Symptoms and Signs

The most common symptoms of pulmonary embolism are chest pain, dyspnea, and tachypnea (35,36). The frequency of these and other symptoms and signs reported by 327 patients in large clinical trials of thrombolytic therapy for pulmonary embolism (37) is shown in Table 62-2. The chest pain was pleuritic in more than 75% of patients. The pleurisy is often caused by pulmonary infarction, which produces inflammation on the pleural surfaces, a pleural rub, and pleuritic pain. The pleuritic pain can be a relatively late finding because it can take several days for pulmonary infarction and pleural inflammation to develop. The pleuritic pain is characteristically severe and persistent, lasting several days longer than that of pneumonia, for example (27). Indeed, the persistence of pleuritic pain for more than 7 days in an acutely ill patient should suggest pulmonary embolism (Fig. 62-9).

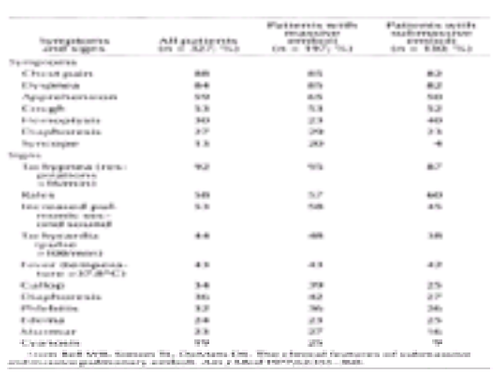

TABLE 62-2. Symptoms and signs in 327 patients with acute pulmonary embolism

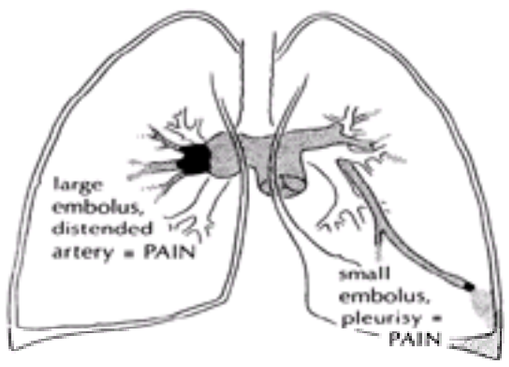

Figure 62-9. The origin of pain in pulmonary embolism. (From Levene DL, Billings RF, eds. *Chest pain: an integrated diagnostic approach*. Philadelphia: Lea & Febiger, 1977:77.)

Patients with large pulmonary emboli usually experience a severe, visceral, retrosternal (deep) crushing pain at the time of the embolism, similar to that of myocardial ischemia, except that the pain does not radiate. This is thought to be caused by sudden distension of the pulmonary artery, right ventricle, or both, or even by right ventricular ischemia resulting from sudden increase in wall stress and myocardial oxygen demand. When this type of pain occurs together with T-wave or S-T segment changes, distinction from unstable angina or acute myocardial infarction can be difficult. Unfortunately, the clinician is often not alert to the diagnosis, as the classic triad of hemoptysis, pleuritic chest pain, and a pleural rub is uncommon (36).

In patients with massive pulmonary artery obstruction, consequent marked increase in pulmonary artery pressure can cause right ventricular failure, with resultant distension of cervical veins and other signs of right ventricular failure. In such patients auscultation reveals a right ventricular heave and a right ventricular presystolic and protodiastolic gallop. Cyanosis is usual with massive pulmonary embolism, but not with a lesser degree of obstruction. Examination of the lungs is usually normal in the absence of pulmonary infarct. Wheezing is sometimes heard, particularly if underlying bronchopulmonary or cardiac disease is present.

Tachypnea, often with dyspnea, almost always occurs after an embolic episode; it appears to be of reflex origin, most likely caused by stimulation of juxtacapillary

receptors in the alveolar membrane by swelling of the alveolar interstitial space (31,33). This stimulation increases vagal afferent activity that in turn stimulates medullary respiration, with consequent alveolar hyperventilation manifested by a lower Pa CO_2.

Diagnosis

All the symptoms, signs, and routine laboratory data in acute pulmonary embolism are nonspecific; their usefulness lies in leading to a suspicion of the diagnosis. The diagnosis rests on establishing a defect in pulmonary artery perfusion that cannot be explained by coexisting lung disease. The gold standard for the diagnosis of pulmonary embolism remains a technically adequate pulmonary arteriogram (30,33,38). The passage of a catheter to the main pulmonary artery and the angiogram can be performed by a trained angiographer, with minimal risk (approximately 0.2% mortality rate). The use of perfusion imaging to guide the angiographer in performing subselective angiography with small doses of contrast material reduces this risk even further. The identification of filling defects within the pulmonary arteries or abruptly cut-off terminated arteries establishes the diagnosis of pulmonary embolism. Thrombi lyse over a period of 7 to 10 days; therefore, pulmonary angiography (and radionuclide imaging) are most sensitive in the first few days after the onset of symptoms.

Pulmonary angiography is now the initial diagnostic test in only a minority of patients with suspected pulmonary embolism because of greater confidence in the use of radionuclide ventilation-perfusion scintigraphy (39,40) or helical CT scanning (41). At most hospitals, $\dot{V}/\dot{Q}$ scanning is the primary diagnostic tool for most patients with suspected pulmonary embolism. The Prospective Investigation of Pulmonary Embolism Diagnosis study was critical in defining the uses and limitation of $\dot{V}/\dot{Q}$ scanning (38,39). Many clinicians will proceed to treat for embolization if the $\dot{V}/\dot{Q}$ scan and clinical suspicion indicate a greater than 85% chance of embolism and will forego further workup or treatment if the combined scan and clinical impression indicate less than a 10% chance of embolism (38,40). Unfortunately, a large number of patients still have an intermediate chance of embolism after these studies. In these patients, some clinicians go straight to angiography for a definitive diagnosis, whereas others scan the legs for clots because a positive finding of clots in the leg would lead to a decision to initiate anticoagulant therapy in any case. Because the decision making can become complex, it is often important to have the decisions as to the steps in the diagnostic workup guided by a clinician very experienced with pulmonary embolism. The newer technique of spiral CT scans can be highly reliable in detecting central clots (41). To what extent spiral CT may eventually replace ventilation-perfusion scanning in the initial workup of a patient with suspected pulmonary embolism will depend on the sensitivity of the CT technique when applied to large populations of previously unscreened patients.

Electrocardiographic changes in acute pulmonary embolism are nonspecific and do not aid in differentiating from other causes of chest pain and acute dyspnea. The typical electrocardiographic pattern of right heart strain (right axis deviation of the QRS wave and T- wave inversion in the right precordial leads) is seen in only approximately 19% of patients with pulmonary embolism. T-wave inversion and S-T segment shifts that might suggest myocardial ischemia are seen in 30% to 40% of patients (31).

The chest roentgenogram is similarly nonspecific. The most common finding is no acute change because most pulmonary emboli do not cause pulmonary infiltrates. The classic pleural-based wedge-shaped infiltrate is uncommon. When preexisting pulmonary infiltrates are present the diagnosis becomes more difficult because the ventilation-perfusion scan is less reliable. These are patients in whom pulmonary angiography might be necessary if establishment of the diagnosis is required.

Treatment

Prophylaxis. The most important aspect of treatment is prevention. Early ambulation after surgery or acute myocardial infarction is thought to be effective. Alternatively, a number of studies have shown that subcutaneous low-dose heparin (5,000 U two times a day) is highly effective in preventing venous thrombosis, pulmonary embolism, or both (42,43). Patients undergoing hip or knee replacement or prostatic surgery need more aggressive anticoagulation (44). Guidelines generated by professional societies for prophylactic therapy have been published and are updated periodically (43). With the use of these prophylactic measures, the incidence of clinically significant pulmonary embolism has decreased substantially. As previously mentioned, several studies have shown that patients undergoing hip replacement operations under regional anesthesia have significantly less incidence of thromboembolism than those managed with general anesthesia (43).

General Therapy. Treatment of the acute event is usually primarily aimed at preventing further pulmonary embolism, supporting the circulation, and administering oxygen until the natural lytic processes result in dissolution of the emboli. If the diagnosis is strongly suspected and no significant contraindication to anticoagulation is present, therapy with heparin should be started even before the diagnosis is established by ventilation-perfusion scanning or pulmonary angiography. Heparin can be given as a loading dose of 80 units per kg, followed by a weight-adjusted continuous intravenous infusion of approximately 18 U per kg per hour or by a dose sufficient to prolong the activated partial thromboplastin time (aPTT) twofold. Anticoagulation to a therapeutic aPTT within the first 24 hours of treatment lessens the risk of recurrent embolization. Following a weight-based algorithm results in attaining a prolongation of the aPTT to over 1.5 times control within the first 12 to 24 hours in 96% of patients (45). Several algorithms for dose adjustments have been published. Oral anticoagulation with warfarin is then instituted for a period of 3 to 6 months. If no prior embolism has occurred and the inciting cause has resolved (e.g., recent surgery), it seems to be of little benefit to continue anticoagulation therapy beyond 3 to 6 months (46). A few patients with recurrent pulmonary embolism and persisting risk factors need to remain on chronic anticoagulation indefinitely.

Thrombolytic therapy has been carefully studied (47). The administration of urokinase or streptokinase results in more rapid lysis of the emboli and restoration of normal hemodynamics but produces no overall decrease in the mortality rate. Presently, thrombolytic therapy is therefore reserved for patients with massive emboli with marked hemodynamic compromise or little reserve. Pulmonary embolectomy using cardiopulmonary bypass has also been used in patients in cardiogenic shock from pulmonary emboli but carries a high operative mortality rate (48); it is rarely used at present. If contraindications to anticoagulation exist or if pulmonary embolism recurs while patients are adequately anticoagulated with heparin or warfarin, interruption of the inferior vena cava by the percutaneous placement of an umbrella should be considered. Because sizable collateral channels develop with time around the site of the filter, a few patients will eventually have recurrent embolization even after a filter is placed.

Pain Therapy. The management of the pain associated with pulmonary embolism depends on the rate of onset, severity, duration, and quality. The patient who experiences sudden, severe crushing central pain caused by a large pulmonary obstruction should be given morphine or another potent narcotic intravenously slowly. The initial dose of 4 to 5 mg diluted in 5 mL of saline solution is injected over a period of 2 or 3 minutes. This should produce some relief in 5 minutes and good relief in 10 to 15 minutes. If the patient still experiences severe pain a second dose of 5 mg should be administered and the patient monitored closely. Usually the second dose provides ample pain relief, but if it does not within 15 to 20 minutes of the injection, a third dose should be given; after this the patient can be managed with a continuous infusion of opioids or patient-controlled analgesia.

An even more effective alternative is the use of a cervicothoracic sympathetic block with a long-lasting local anesthetic, provided, of course, that a physician expert in its administration is available in the hospital. This procedure produces complete pain relief ipsilateral to the injection within 5 to 8 minutes of injection, and the pain relief will last for 6 to 10 hours. Leriche and colleagues (49) were the first to suggest the use of this procedure in the treatment of pulmonary embolism; they believed that it not only relieved pain by blocking afferent impulses from the lungs but that it also interrupted efferent impulses taking part in the production of sympathetic reflex mechanisms thought to be involved in the pathophysiology. More recent data did not substantiate this claim but suggested that reflexes involved in the pathophysiology are mediated primarily by the vagus nerves (50). Nevertheless, the procedure is effective in relieving the central type of pain (51). Moreover, because it blocks some of the sympathetic afferent input to the neuraxis, it should decrease the segmental and suprasegmental reflex responses that are invariably associated with severe pain and nociceptive input (see Chapter 9). Another relatively new procedure for relief of the pain is the use of intraspinal narcotics.

Patients who develop pleuritic pain can usually be relieved with NSAIDs combined with a potent narcotic agent given orally or parenterally. If the patient has experienced severe pleuritic pain unrelieved by systemic analgesics, however, a posterior intercostal block with bupivacaine should be considered (see Chapter 102). The procedure is carried out in the manner described for the pleurisy of pneumonia.

CHEST PAIN CAUSED BY DISORDERS OF THE PLEURA

The most important disorders of the pleura that produce chest pain are either of inflammatory origin, as in pleuritis, or from mechanical distortion, as in pneumothorax.

Pleuritis

Inflammation of the pleura can occur with underlying pulmonary diseases, including pneumonia, lung abscess, pulmonary infarct caused by an embolus, and neoplasm (52). As discussed above, pleuritis is associated with localized chest pain. Pleural pain in the absence of physical and radiographic findings or underlying

disease suggests the diagnosis of epidemic pleurodynia, infection of the pleura, or a connective tissue disorder such as systemic lupus erythematosus.

Pleurodynia, also known as *Bornholm disease* and *epidemic myalgia*, is characterized by malaise, sore throat, and anorexia, followed by increased debility; fever; and sudden onset of muscle, pleuritic, and abdominal pain (52). The pain is sharp, severe, and paroxysmal over the lower ribs or substernal area. It is markedly aggravated by moving, breathing, coughing, sneezing, and hiccuping and can be referred to the shoulders, neck, scapula, or chest. In approximately 50% of patients pain and spasm of the anterior abdominal muscles occur in combination with chest pain. Many patients complain of cutaneous hyperalgesia, hyperesthesia, and paresthesia in the area of the pain.

Pleurodynia usually occurs as an epidemic and lasts 3 to 7 days, but relapses can occur (52). Coxsackie B viruses were isolated from the striated muscle of patients with pleurodynia during an epidemic (53). Occasionally the pleuritis is accompanied by pleural effusion, and the virus has been isolated from the pleural fluid. Bornholm disease can occur in those of any age but is most common in children and young adults. Early in the course of the illness meningitis, myocarditis, or hepatitis can ensue. Later, jaundice or orchitis may appear.

Treatment

Because of the absence of effective antibiotics, the treatment of pleuritis is directed toward the underlying disease and relief of pain. In patients with mild to moderate pain, NSAIDs given alone or in combination with codeine in optimal doses usually suffice. For more severe pain, potent narcotics with NSAIDs should be tried. Systemic analgesics, even in optimal doses, do not, however, completely relieve the pain associated with deep breathing and coughing. Untreated pain can prevent the patient from bringing up secretions and increase the risk of a subsequent bacterial pneumonia. In such patients, serious consideration should be given to the use of posterior intercostal blocks or segmental epidural analgesia with long-lasting anesthetic agents such as bupivacaine. Intraspinal opioids, although not quite as effective, are a good alternative. These procedures require the skills of an anesthesiologist.

Occasionally, acute pleuritis leads to chronic adhesive pleuritis as a sequela of empyema, hemothorax, or tuberculosis. Adhesive pleuritis is characterized by marked thickening of the pleura, which can interfere with pulmonary function. Under these circumstances, the thickened pleura encases the lung and“traps” it so that the lung behaves as if it were small and stiff, despite having intrinsically normal mechanical processes. If symptoms such as dyspnea are severe, surgical removal of the thickened pleura (decortication) might be indicated (52).

Pleural Effusion

Although not usually painful, pleural effusion is discussed briefly here for the sake of completeness. The visceral and parietal pleurae form a continuous membrane that encloses a potential space that normally contains only a small amount of liquid. This liquid is dynamic, and as with all movements of liquid between vascular and extravascular compartments, the principle of Starling's equation applies (52). Under normal circumstances the liquid is filtered out of the parietal pleura, which is supplied by systemic capillaries at a mean pressure of 30 cm H_2O; most of this is taken up at the visceral pleura, supplied by the pulmonary circulation with a mean capillary pressure of 11 cm H_2O. For the removal of macromolecules plus some liquid, there are in addition lymphatic stomata in the diaphragmatic and vascular portions of the parietal pleura.

An abnormal accumulation of liquid, designated as pleural effusion, occurs with changes in hydrostatic and oncotic forces (transudation) or with an alteration in membrane permeability (exudation), such as with inflammation or neoplastic involvement. The finding of pleural effusion in the absence of parenchymal disease suggests primary tuberculosis, subdiaphragmatic abscess, mesothelioma, or primary bacterial infection of the pleural space. Many pleural effusions, even large ones, are asymptomatic, but patients can complain of dyspnea, pleuritic chest pain, or a dull, uncomfortable sensation in the chest (51). Physical signs include deviation of the trachea to the contralateral side, dullness on percussion, and diminished breath sounds over the affected side.

Empyema is the presence of infected liquid or frank pus in the pleural space and is usually a complication of pneumonia, abscess from the lung, or diaphragmatic or esophageal perforation. Chest pain, fever, cough, night sweats, and weight loss are common complaints.

Treatment of symptomatic pleural effusion or empyema includes adequate drainage of the pleural space, directed antimicrobial therapy, and the control of pain as discussed in previous sections.

Pneumothorax

In pneumothorax a collection of gas in the pleural space occurs that results in complete or partial collapse of a lobe or entire lung. When air enters the pleural space, pleural pressure in the affected hemithorax tends to approach atmospheric pressure, thus eliminating the normal negative pressure that keeps the lung expanded (54). The less negative the pleural pressure, the greater the degree of lung collapse. The normal elastic recoil of the unaffected lung causes a shift of the mediastinum from the affected to the unaffected side. If pressure inside the pneumothorax increases above atmospheric pressure, as with a one-way leak into the pleural space (“ball valve leak”), or when a pneumothorax occurs as a complication of positive pressure ventilation, a tension pneumothorax is present. Under these circumstances the affected lung is compressed, the mediastinum is further shifted toward the unaffected side, and cardiac output can be severely compromised because of the positive intrathoracic pressure that decreases venous return to the heart.

Tension pneumothorax is a medical emergency (54). Pneumothorax can occur spontaneously or can be secondary to underlying lung disease, chest trauma, mechanical ventilation, or perforated esophagus. Spontaneous pneumothorax most commonly occurs in previously healthy adults between 20 and 40 years of age. In many of these patients air leaks into the pleural space as a result of rupture of small blebs on the surface of the visceral pleura. The cause of the blebs is unclear, but they tend to be located around the apex of the lung.

Symptoms and Signs

Spontaneous pneumothorax usually manifests itself by sudden chest pain of pleuritic type, localized to one side and associated in most cases with a sensation of dyspnea. The most helpful feature of the pain is its sudden onset, so that often patients can describe their activities at the moment it appeared (27,52,54). The severity of pain and degree of dyspnea at onset are not indicative of the size of the pneumothorax. Usually both pain and dyspnea disappear within 2 to 3 hours after a small pneumothorax in healthy people. Persistence of dyspnea and pain that increases in severity suggest a large pneumothorax and perhaps intrapleural hemorrhage.

The sudden change in volume of the lungs with shift of the mediastinum is likely to cause a visceral-type deep central pain, retrosternal pressure, or heaviness, but this usually does not persist and is overshadowed by the pleuritic pain.

Physical examination reveals tachypnea, asymmetric expansion of the chest on the affected side (because of outward recoil of the chest wall as the lung collapses), mediastinal shift with deviation of the trachea, cardiac dullness and apex beat away from the pneumothorax, hyperresonance to percussion, and diminished breath sounds over the affected side. Chest roentgenograms reveal a visible visceral pleural edge with no lung markings between this edge and the chest wall (54). It is important to take the chest roentgenograms with the patient in the upright position because, in a supine posture, upward movement of air with approximation of the visceral and parietal pleura can obscure the presence of a pneumothorax. A pneumothorax may be easier to detect on an expiratory film because expiration makes the lung appear darker due to crowding of the parenchymal element, leading to greater contrast with the air-containing pneumothorax space. Inspiratory films, however, are better for estimating or serially following the size of a pneumothorax because the lung volume of the film in inspiration is more reproducible.

Treatment

Treatment depends on the size of the pneumothorax. A small spontaneous pneumothorax in a stable patient is best managed by reassuring the patient and close observation, because the air leak has usually sealed by the time the patient presents to the physician. The pain is generally managed easily with systemic analgesics given orally. Large pneumothoraces are usually accompanied by moderate to severe pain that requires therapy in the form of evacuation of air and the use of a combination of an NSAID and a narcotic. Aspiration of air can be accomplished with a small needle attached to a one-way flutter valve or with closed thoracostomy tube drainage (54). Spontaneous tension pneumothorax is unusual but, if present, should be treated as an emergency by immediate aspiration through a wide-bore needle placed in the pleural space at the level of the second intercostal space anteriorly in the midclavicular region.

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CHAPTER 63

Chest Pain of Esophageal Origin

Charles E. Pope, Jr.

Although the esophagus normally transports solids, liquids, and gas to—and occasionally from—the stomach without discomfort, it can generate pain indistinguishable from the pain experienced from myocardial infarction as well as other less threatening kinds of unpleasant sensations. Chest pain in the Western world is usually interpreted by both patient and physician as a manifestation of coronary artery insufficiency and often leads to worry, multiple tests, and inappropriate hospitalizations. Chest pain of esophageal origin is quite common; of 204 consecutive patients admitted to a coronary care unit and found not to have an acute myocardial infarct, the pain was attributed to the esophagus in 76 (32%) of these patients (1). This would suggest that after heart disease has become unlikely as a result of appropriate testing, it is well to consider the esophagus as a potential pain source. This chapter discusses some of the clinical features and diagnostic/therapeutic tests that establish the esophagus as the source of the discomfort. As is discussed, such establishment is not a simple matter.

It has long been suggested that esophageal pain can arise both from the esophageal mucosa and from the esophageal muscle. A third possibility is currently under active investigation—that pain can be experienced by abnormal central nervous system (CNS) processing of afferent impulses from the esophagus that are normally not perceived. Mucosal disease can be recognized and documented; there are often specific forms of therapy that allow confirmation of a diagnostic impression by a therapeutic trial. In contradistinction, attributing chest pain to malfunction of esophageal muscle is a more uncertain task. The therapeutic options for esophageal muscle problems are less precise, and the opportunity for a therapeutic trial may not be possible because of the lack of effective forms of therapy. Determining the potential role of aberrant CNS function in the genesis of esophageal chest pain has only just begun. Most studies of CNS-esophageal relationships are still confined to control subjects.

The information in this chapter is divided into six sections: basic considerations, including the anatomy and physiology of the esophagus; esophageal mucosal disorders; esophageal muscular disorders; role of the CNS in the generation of esophageal pain; other painful disorders of the esophagus; and approach to the patient with chest pain. More detailed information can be obtained from review articles (2,3 and 4).

BASIC CONSIDERATIONS

Anatomy of the Esophagus

General Structure

The esophagus is a tube consisting of striated muscle in the upper one-third and smooth muscle in the remainder of the organ. It is approximately 35 cm long, 3.0 cm in lateral diameter, and 1.9 cm in anterior-posterior diameter (Fig. 63-1). It begins at the cricopharyngeus muscle, which separates the esophagus from the pharyngeal muscle, with which the esophagus is closely tied functionally. It passes through the mediastinum, traverses the hiatus of the diaphragm, and ends in the lower esophageal sphincter (LES) muscle, which separates the esophageal lumen from the gastric lumen. Careful dissections in human cadavers show a thickening of the circular, but not longitudinal, muscle in the LES zone as well as an unusual distribution of the circular muscular fibers (5). The esophagus is lined with stratified squamous epithelium that is lubricated by specialized mucous glands located in the submucosal layer. The esophagus contains no specialized adventitial layer, which accounts for some of the difficulties encountered by surgeons making anastomoses in the esophagus.

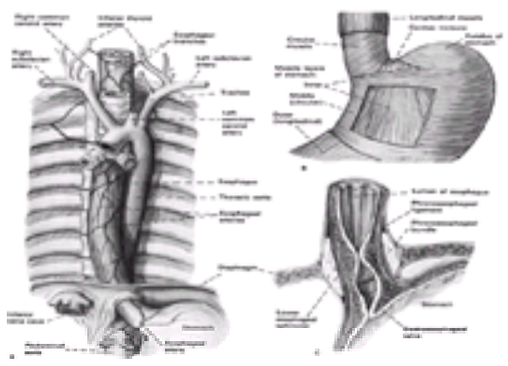

Figure 63-1. Anatomy of the esophagus. **A:** Relationship of the esophagus (except the uppermost part, which has been resected) to the lower trachea, the proximal bronchi, and the aorta, and its arterial blood supply. **B:** Lower esophagus and upper stomach showing the direction of the longitudinal and circular muscle fibers of the lower esophagus and the upper part of the stomach. **C:** Coronal section depicting the component parts of the gastroesophageal junction and the component parts of the antireflux barrier, including the lower esophageal sphincter, made up of thick circular musculature. The phrenoesophageal ligament arises from the circumference of the hiatus as an extension of the inferior fascia of the diaphragm and breaks up into an ascending and descending leaf; the former passes cephalad for several centimeters above the hiatus, where it is inserted circumferentially into the adventitia of the esophagus, and the descending leaf passes downward and is inserted around the cardia deep to the peritoneum. Within the cavity, thus formed by the phrenoesophageal ligament and below the diaphragmatic hiatus, lies a ring of dense fibroareolar and fatty tissue that together with the ligament make up the phrenoesophageal bundle. Also, the gastroesophageal valve is created by the acute angle of His and consists of a flat lateral leaf approximating against the mucosa of the lesser curvature of the stomach. (**A** and **B** modified from Netter FH. *The CIBA collection of medical illustrations.* Vol 3, Digestive system. Part I, Upper digestive tract. Caldwell, NJ: CIBA Pharmaceuticals Co., 1959:38– 41. **C** was developed from data in Hill LD, Thor K, Mercer D. Surgery for hiatal hernia and esophagitis. In: Hill LD, ed. *The esophagus: medical and surgical management*. Philadelphia: WB Saunders, 1988:98.)

Blood Supply

The arterial supply to the cervical esophagus comes from the terminal branches of the inferior thyroid artery. The thoracic portion is supplied mainly from bronchial arteries at the level of the carina (6). Branches of the left gastric and splenic arteries supply the lower thoracic and abdominal portions of the esophagus.

The venous drainage of the cervical esophagus is into the inferior thyroid vein, which empties into the brachiocephalic veins. The thoracic esophagus is drained by the periesophageal plexus, which empties into the azygos system. The lowest portion of the thoracic and abdominal esophagus drains into the gastric veins which, in turn, empty into the portal vein.

Nerve Supply

Studies in animals and humans have made it necessary to alter this section of the chapter markedly from previous editions. The present description is based on the chapters by Sengupta and Gebhart (7), Cervero and Foreman (8), Conklin and Christensen (9), and Clouse and Diamant (10). More specific details can be found in these references.

Two systems mediate sensation from the esophagus. Vagal fibers arise in the submucosa and muscle layers and run to the CNS with their cell bodies in the nodose ganglion. The fibers terminate in the nucleus tractus solitarius, which sends input to the thalamus, the limbic cortex, and the primary somatosensory cortex. Visceral afferent fibers arise in the same location and travel with the sympathetic nerves to the dorsal root ganglia, where their cell bodies are located. They may make contact with some somatic afferent nerves in the dorsal root ganglia or go on to the spinal cord, where they make contact with secondary neurons whose cell bodies are in the gray matter (lamina I and V) and that travel to the brain via the spinothalamic tract, the spinoreticular tract, and the spinomesencephalic tract.

Motor nerves of the esophagus arise in the pons and medulla from the dorsal motor nucleus and the nucleus ambiguus. They travel down the vagal trunks and contact second-order neurons located in the myenteric plexus. Axons from these second order neurons innervate the smooth muscle of the esophagus as well as other nerve bodies within the myenteric plexus.

Another command and control center is located within the wall of the esophagus: the enteric nervous system of the esophagus. This consists of a sensory portion; the submucosa, or Meissner's plexus; and the myenteric, or Auerbach's plexus. Neurons in the myenteric plexus have both excitatory and inhibitory activity on the esophageal smooth muscle. A great deal of intrinsic capability is built in to this system so that it can function without any external input. The relative importance of the intrinsic control system and the modifications produced by vagal motor input is not thoroughly worked out at the present time. Figure 63-2 presents a simplified block diagram of the system.

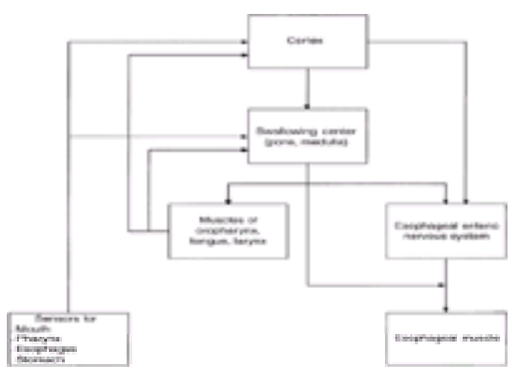

Figure 63-2. Block diagram of afferent and efferent connections between esophagus and brain.

Physiology of the Esophagus

Motor function

In the resting state, the cricopharyngeus muscle is tonically contracted by impulses from the CNS. Constant electrical spike activity is recorded from the muscle, which is inhibited when swallowing commences. The sphincter is physically opened by the laryngeal muscles lifting the larynx and the cricoid cartilage upward and forward, literally pulling the sphincter open. Changes in bolus volume and viscosity alter the timing of upper esophageal closure.

A stripping peristaltic wave begins just below the cricopharyngeus and traverses the striated muscle, creating a relatively high intraluminal contraction amplitude with a rapid rate of rise of pressure to the peak. Contraction of the smooth muscle portion of the esophagus seems to follow without a break, and for many years, the peristaltic wave was considered to be continuous. Some studies, however, suggest that the wave in the striated muscle actually ends, and the presence of the bolus in the esophagus causes a separate contraction to begin in the smooth muscle and proceed down to the area just above the LES, where a third wave may be generated (11).

Intraluminal pressure measurements taken from the LES zone show a resting pressure of 15 to 20 mm Hg that falls at the same time as laryngeal elevation during swallowing. There is still a physical barrier between the esophagus and the stomach after this relaxation, as the negative intraesophageal pressure does not equilibrate with the positive intragastric pressure. Two other types of LES relaxation are recognized. One, transient LES relaxation, is associated with belching and with reflux (12). The other type of relaxation can be produced by injection of small quantities of water into the pharynx; its physiologic role remains to be defined (13).

This motor activity of the esophagus is controlled by a “swallowing center” located in the pons and the medulla. This center receives input from the cerebral cortex and from afferent vagal and visceral fibers. The center also organizes efferent impulses to the tongue, larynx, pharynx, and esophagus so that the act of swallowing can be tightly coordinated. The striated muscle of the cricopharyngeus and the proximal esophageal musculature receive fibers from the nucleus ambiguus of the swallowing center.

Peristaltic organization of the esophageal smooth muscle is more complex. There is sequential activation of progressively more distal smooth muscle by efferent vagal fibers from the dorsal motor nucleus of the swallowing center acting on the cell bodies of the enteric nervous system; there is intrinsic control from the enteric nervous system itself; there may be a myogenic component to the peristaltic wave, which is resident in the muscle. The methods by which these complex systems interact have not been defined. Certain nerves in the enteric nervous system that probably release nitric oxide can inhibit the muscle of the distal esophagus when a proximal contraction is present. In humans, inhibition of nitric oxide production by recombinant hemoglobin can lead to disorganization of peristalsis, increase in peristaltic amplitude, and chest pain (14).

Intramural excitatory nerves that release acetylcholine and are sensitive to atropine set the tone and function of the LES. Inhibitory nerves in the same location that release nitric oxide and possibly vasoactive intestinal polypeptide balance their action.

Sensory Function

The esophagus can respond to distension, to change in wall tension, to changes in chemical or osmotic concentrations, and to alterations in temperature. A great deal of afferent information is produced by normal peristalsis and intraluminal contents and transmitted by vagal fibers. There do not appear to be specialized nerve endings to sense tension or pH; it is still not certain whether afferent neurons can respond to a variety of different stimuli or whether specific nerves mediate specific sensations.

In the opossum, an animal with both striated and smooth muscle in the esophagus (but rather distant from humans phylogenetically), individual fiber studies have demonstrated vagal afferent fibers that respond both to distension and to the presence of normal peristalsis (15). In the same animal, there are visceral afferent fibers

that travel with the sympathetic fibers (16). Single-fiber recordings show two types of these fibers responding to distension. One type fires in response to both balloon distension and to normal peristalsis and is called a *wide-dynamic-range mechanonociceptor*. The other type responds only to elevated intraluminal pressures. Both types are believed to be specific nociceptors. Fibers could also be categorized as rapidly adapting or slowly adapting to prolonged balloon distension. Both are sensitive to bradykinin, a substance released during ischemia and inflammation (17).

Studies of afferent spinal single neurons have been undertaken in cats (18). Most fibers responded with an increase in firing rate to balloon distension; a significant minority decreased their rate of firing during stimulation. Of interest was the observation that somatic stimulation also caused increased rates of firing of the visceral afferent neurons, suggesting cross-talk between somatic and visceral receptors. Chemical inflammation of the esophagus decreased the balloon volumes necessary for excitation of these neurons.

Such studies are not possible currently in humans, but evidence obtained by brain positron emission tomography (PET)scans of central excitation by balloon excitation has been reported (19). When esophageal balloon inflation is just enough for the subject to be aware of a sensation, there is increased blood flow activity along the central sulcus, insular cortex, and the operculum. When inflation is increased to a level perceived as painful, activity in these areas increases. In addition, the anterior insular cortex on the nondominant side is activated, as is the anterior cingulate gyrus. Preliminary studies in control subjects using functional magnetic resonance imaging to measure changes in cerebral blood flow show that areas in the occipital, parietal, and superior frontal lobes are activated by the perfusion of acid but not saline (20). Balloon distension in the same patients activates separate areas than those stimulated by acid (parietal-occipital areas).

Sites of Pain Reference

Perhaps because of the overlap in the dorsal root ganglia between somatic sensory nerves and visceral afferent nerves, pain due to disease of the esophagus is referred to the chest, epigastrium, and, occasionally, to the back. Numerous investigators have attempted to delineate the areas of pain referenced by mechanical distension of the esophagus with a balloon; electrical or chemical stimulation has also been used. Jones carried out a series of experiments in which he distended the esophagus at different levels (21). He noted that moderate distension produced substernal pain experienced at the level of the balloon (Fig. 63-3). Pain arising from the upper esophagus was felt in the midline over the upper portion of the manubrium, whereas that produced by distension at the cardiac end of the esophagus was felt at the level of the xiphoid cartilage.

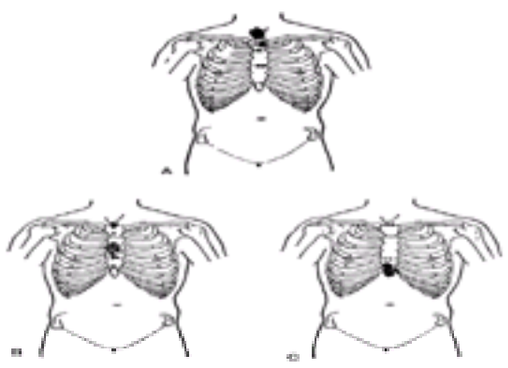

Figure 63-3. Sites of referred pain from inflation of a balloon in the upper **(A)**, middle **(B)**, and lower **(C)** esophagus. Each dot represents one subject. Compare with Fig. 63-4. (From Jones CM. *Digestive tract pain*. New York: Macmillan, 1938:11, with permission.)

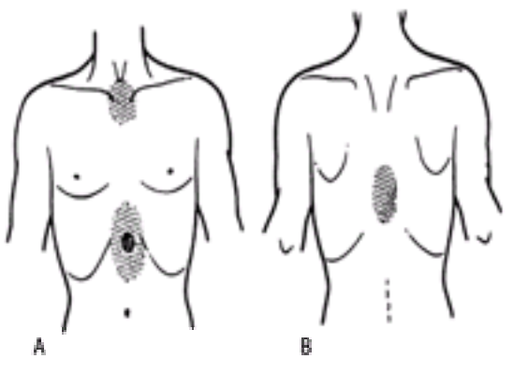

Figure 63-4. **A:** Anterior view showing reference of pain caused by inflation of the upper third and lower third of the esophagus. **B:** Posterior view showing reference of pain in the back from mechanical stimulation of the lower esophagus. (From Teodori U, Galletti R. *Il dolore nelle affezioni degli organi interni del torace*. Rome: L. Pozzi, 1962:169–178, with permission.)

Teodori and Galletti, in studies using an esophageal balloon, determined not only the site of pain but also changes in electric skin resistance at those sites (22). They reported that rapid inflation of the balloon with 30 to 50 mL of air produce moderate to severe pain, the site of which depended on the level of distension. Distension in the upper third of the esophagus produced pain referred to the area of the manubrium and upper part of the sternum without producing any pain in the back. In contrast, stimulation of the lower third of the esophagus produced pain in the xiphoid process and the epigastric area. Posteriorly, the pain was felt in the midline at the level of the sixth to seventh thoracic vertebrae (Fig. 63-4). They noted that the referred pain produced by stimulation of the middle third of the esophagus usually was less intense and more variable in location. In some subjects, the pain was felt in both the manubrium and xiphoid processes; in others, in one or the other; and, in still others, in the retrosternal region. The areas of decreased electrical resistance were consistently in the same sites as the area of referred pain (Fig. 63-5). Cutaneous hyperalgesia developed in most subjects in the epigastric region and in the skin overlying the lower portion of the sternocleidomastoid muscles bilaterally.

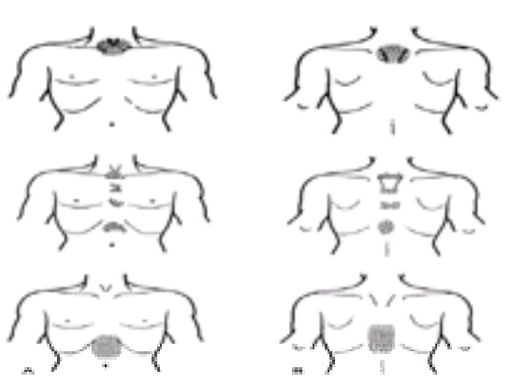

Figure 63-5. Zones in which there was a reduction in the cutaneous electrical resistance (RCER) consequent to mechanical stimulation of the esophagus with an inflated balloon that produced pain in the anterior **(A)** and posterior **(B)** portion of the chest. The top panel shows the areas of RCER from stimulation of the upper third of the esophagus. Posteriorly the area of the pain overlies the midline and paravertebral region at the level of the seventh cervical to the first thoracic vertebrae, inclusive. The middle panel shows the area of RCER from stimulation of the middle third of the esophagus. Note the variability. The bottom panel shows the area of RCER from stimulation of the lower third of the esophagus. Posteriorly this area overlies the paravertebral region at the level of the sixth to the eleventh thoracic vertebrae. (From Teodori U, Galletti R. *Il dolore nelle affezioni degli organi interni del torace*. Rome: L. Pozzi, 1962:169–178, with permission.)

PAINFUL ESOPHAGEAL MUCOSAL DISORDERS

Gastroesophageal Reflux Disease

Etiology and Pathophysiology

The most common inciting agent for painful esophageal mucosal disease is pathologic gastroesophageal reflux. All humans have some esophageal reflux, usually in the postprandial period, but when the exposure time of the esophageal mucosa becomes too long, reflux damage can occur. The increase in exposure time in turn is determined by an increased number of transient relaxations of the LES (12). Reflux into the esophagus during such unguarded moments of transient relaxation can be facilitated by the presence of a hiatus hernia, which serves as a storage area for gastric acid close to the sphincter zone (23). Decreased gastric emptying, found in approximately one-half of patients with severe reflux, also allows an increased amount of gastric contents to be potentially available for reflux. Once refluxed, defects in peristalsis may retard clearance and increase contact time of this fluid.

The increased contact time of gastric contents may not produce any grossly visible endoscopic evidence of reflux, but well-oriented biopsies of the esophageal mucosa show basal cell hyperplasia and extension of the papillary pegs toward the surface (24). Careful examination of the basal cell zone shows that there are increased spaces between these cells, perhaps allowing hydrogen ions access to bare nerve endings below the epithelium, which might mediate the sensation of heartburn or of chest pain (25).

Once the acid has penetrated the epithelium and stimulated nervous elements, the subsequent pathways in humans have not been fully worked out. In animals, production of rather severe esophagitis by chemical means decreases the threshold of spinal nerves for other stimuli such as balloon distension (18). A similar lowering of the threshold for balloon stimulation has been shown in humans as well (26). Thus, acid can produce a direct effect or sensitize the esophagus so that other stimuli may reach perception.

Effects of esophageal mucosal stimulation by acid on production of pain by other organs must also be considered. In patients with fixed coronary artery narrowing and S-T changes associated with angina, exercise capability can be sharply limited by acid perfusion of the esophageal mucosa (27). Intraesophageal acid perfusion can also lower coronary blood flow in patients with exertional chest pain, normal coronary arteries, and electrocardiographic changes during exercise (syndrome X) (28).

Symptoms

The most common symptom of reflux is heartburn. This term is used by lay individuals to refer to a disparate group of symptoms; further questioning is always in order if the patient volunteers that he or she is troubled by heartburn. Reflux-induced heartburn is usually substernal, with radiation up into the neck. Usually, it is described with an open hand moving up and down over the sternum. The most common phrase used to describe the sensation of heartburn is “burning.” “Pain” is not a common descriptor. Heartburn may come in waves and be accompanied by increased salivation and swallowing. Relief by swallowed antacids, albeit transiently, is an essential feature of heartburn. Patients with untreated achalasia, for instance, who would not be expected to have much reflux because of their hypertensive nonrelaxing LES, occasionally complain of substernal burning. However, they do not find relief of this burning by ingestion of antacids.

Chest pain due to reflux is usually described as an oppressive weight on the chest that tends to spread laterally more than the sensation of heartburn usually does. It may radiate to the back, neck, jaw, shoulder, or arm. “Pressure,” “boring,” or “aching” are adjectives often used. Unlike the discomfort of heartburn, which usually responds to a dose of antacids, chest pain due to reflux remains after a single dose of an acid-neutralizing compound. Only prolonged acid suppression is of benefit.

Sometimes the symptoms of heartburn and chest pain coexist in the same patient. Heartburn can increase in intensity until it passes from a sensation of burning to a sensation of pain. More commonly, an individual patient reports both sensations, but states that they often occur independently from one another rather than merging from one sensation to the other.

Other clinical manifestations of gastroesophageal reflux disease may be present, such as regurgitation of gastric contents when bending over or when lying supine. Extraesophageal manifestations of reflux, such as hoarseness, persistent cough, or repeated clearing of the throat, may signal laryngeal irritation. Mild dysphagia is a common result of pathologic reflux. It usually does not cause the patient to have to regurgitate the bolus, but only to reswallow or wash the bolus down with liquids.

Diagnosis

There have been four basic approaches to attempt to establish the diagnosis of chest pain due to gastroesophageal reflux. The first approach attempts to measure the prevalence of abnormal reflux in patients with chest pain of unknown origin. The second approach is to correlate episodes of chest pain with periods of esophageal acidification, as detected with a pH electrode. The third approach instills acid into the esophagus to provoke chest pain; the fourth approach is to perform a therapeutic trial by inhibiting the retrograde flow of gastric acid into the esophagus by either pharmacologic or surgical methods.

Table 63-1 lists the prevalence of pathologic reflux detected by prolonged pH monitoring in patients with chest pain of unknown origin (29,30,31,32,33 and 34). Most of the patients enrolled in these studies were thought not to have coronary artery disease on the basis of either invasive or noninvasive cardiac tests. It can be seen that reflux is quite commonly found in such patients. This does not automatically demonstrate that there is a direct causal relationship between mucosal acid exposure and the production of pain. Perhaps acid exposure sensitizes the esophagus to other stimuli such as distension. Such sensitization has been demonstrated in patients with noncardiac chest pain and normal esophageal function tests (26).

Reference	n	%
DeMeester et al. 1982 (29)	50	46
Hewson et al. 1991 (30)	100	48
Hick et al. 1992 (31)	46	70
Lux et al. 1995 (32)	45	31
Adamek et al. 1995 (33)	95	52
Chillebert et al. 1995 (34)	287	21

TABLE 63-1. Prevalence of pathologic reflex in chest pain

The technological advances in pH monitoring that allow 24-hour recording in ambulatory patients have allowed attempts to correlate episodes of chest pain with episodes of reflux. Table 63-2 shows some results from the literature of such correlation (30,33,35,36). These estimates are probably high, as some authors accept even one episode of simultaneous pain and reflux as showing a causal relationship. If there are many episodes of reflux but only a few episodes of chest pain, the relationship may well have occurred by chance. It has been suggested that an attempt to document the relationship more firmly can be done by dividing the period of monitoring into 2-minute epochs and then creating a 2 × 2 table of the relationship between chest pain and reflux (37).

Reference	n	%
Peters et al. 1988 (35)	22	69
Vantrappen et al. 1987 (36)	33	64
Hewson et al. 1991 (30)	100	50
Adamek et al. 1995 (33)	22	2

TABLE 63-2. Correlation of reflux with pain

Simultaneous recording of chest pain and reflux episodes has allowed another important subgroup of acid-sensitive patients to be described. These individuals have normal total acid exposure values, yet they respond to their infrequent episodes of reflux with chest pain. These patients respond as well to acid-suppressive therapy as do patients with abnormally increased reflux times.

Acid infusion tests (Bernstein test) would be expected to pick out patients with chest pain due to an acid-sensitive esophageal mucosa. However, as Table 63-3 demonstrates, fewer patients have a positive acid perfusion test than have abnormal acid exposure times (34,38,39 and 40). When both studies are done in the same patient, discordant results are often found. In one study, 18 patients had a positive acid perfusion test; only nine had abnormal 24-hour pH results (41). Conversely, ten additional patients had abnormal 24-hour pH exposure but negative acid perfusion studies.

Reference	n	%
Katz et al. 1987 (40)	910	7
Hewson et al. 1989 (38)	71	23
Chilliebert et al. 1995 (34)	287	39
Frobert et al. 1996 (39)	63	16

TABLE 63-3. Provocation of pain with acid infusion

With the advent of powerful acid suppressive medications, the proton pump inhibitors, the possibility of a therapeutic trial to discover the place of acid reflux in the production of chest pain became a reality. The results of a placebo-controlled trial of such agents show a significant decrease in both the intensity and occurrence of chest pain on those patients receiving active medication (42). However, it is equally important to realize that none of the treated patients became totally asymptomatic.

Treatment

The choice of treatment modality depends on the strength of the evidence that acid is the culprit responsible for chest pain. The choice is also dictated by other factors such as concurrent endoscopic or laryngoscopic evidence for reflux and by the preferences of both the patient and the health care resources available.

If medical therapy is thought to be the best choice, current practice would suggest that proton pump inhibitors in adequate dose be used. Omeprazole, 40 mg daily, or lansoprazole, 30 mg daily, should be the starting dose. If these doses eliminate the chest pain, attempts to lower the dose of medication can be made. Alternatively, if the evidence that acid has played a role in the chest pain (e.g., erosive esophagitis on endoscopy) is strong, but this dose of medication does not solve the problem, the dose can be doubled. Failure of a double dose might lead to a reevaluation of the place of acid reflux in the production of chest pain. If the patient has had a positive 24-hour pH test result before therapy, it might be worthwhile to repeat the monitoring while the patient takes full-dose medication, as there are a few patients in whom the proton pump inhibitors do not suppress acid.

Antireflux surgery has become more acceptable now that laparoscopic techniques have decreased the morbidity of the procedure. However, the choice of whether to offer such surgery to someone with chest pain depends on several factors. If the patient complains of ordinary heartburn and has erosive esophagitis or Barrett's epithelium, surgery can be offered to treat these manifestations with the hope that chest pain will also vanish postoperatively. If chest pain is the only manifestation of reflux, a positive therapeutic trial of acid suppression should be sought before surgery is offered.

How effective is antireflux surgery? In a large surgical experience, 11 patients were specifically operated on because of chest pain documented to occur with bursts of acid reflux. Total relief of chest pain was found in ten of these patients (29). In a series in which chest pain was specifically sought for both before and after Nissen fundoplication, 46 of 88 patients with preoperative chest pain became totally asymptomatic (43). In one laparoscopic series, 49 of 66 patients lost their chest pain postoperatively (44).

Infections and Physical Agents

Infections and physical agents primarily affect the esophageal mucosa and produce a characteristic symptom that helps to guide the clinician to the correct diagnosis. The symptom is odynophagia, or pain on swallowing. The pain is not necessarily bolus related; even a “dry swallow” containing only a small amount of saliva can cause exquisite pain. The mucosa usually has visible lesions that allow endoscopy to be useful in diagnosis. Therapy depends on the inciting agent. This topic has been thoroughly reviewed by Baehr and McDonald (45).

Infections

Etiology and Pathogenesis. The immunocompromised host is the most common individual attacked by the agents shown in Table 63-4. Herpes simplex is the only virus that can produce symptoms in the completely normal host. The immunologic lesion can be subtle (diabetes, malignancy) or marked (acquired immunodeficiency syndrome, radiation therapy, chemotherapy). Steroid use, even topical therapy, can allow some of these infections to occur.

Agent	Immunocompromised	Appearance
Candida albicans	Yes	Adherent glaques
Herpes simplex	Usually	Ulcers, raised edges
Cytomegalovirus	Yes	Deep serpiginous ulcers
Varicella zoster	Yes	Ulcers, raised edges
Human immunodeficiency virus	Yes	Giant deep ulcer

TABLE 63-4. Infectious agents

Symptoms and Signs. Odynophagia is the hallmark of symptomatic infection, although occasionally other symptoms, such as unexplained nausea, lead to the endoscopy that establishes the diagnosis. Oral thrush can suggest contiguous esophageal involvement in a patient with human immunodeficiency virus infection and is probably evidence enough for a therapeutic trial. Pharyngeal vesicles (early) and shallow ulcers (later) can suggest herpes simplex infection in both normal and immunocompromised patients.

Diagnosis. Endoscopy is the preferred method of evaluating the esophageal lining and obtaining adequate samples for definitive culture or immunodiagnosis. Blind scraping with a sheathed cytology brush occasionally obtains diagnostic material in patients with *Candida* or viral illnesses if endoscopy is not feasible. Double-contrast radiology can show small lesions, but it is not sensitive or specific enough when compared with the results obtained by endoscopy. All ulcerated lesions should be biopsied for histologic and cultural diagnosis. Biopsies should be directed both at the edges of the ulcer and at the base of an ulcer in the case of cytomegalovirus infection.

Treatment. Adequate treatment depends on adequate diagnosis. Several of these infections have indistinguishable appearances from one another, so cultural, immunodiagnostic, and histologic criteria are essential in establishing a cause for infection. Treatment suggestions are given in Table 63-5.

Infection	Treatment
Candida albicans	
Light infection	Nystatin, 50,000 units q4h p.o.
	Clotrimazole, 10 mg 5 times/day p.o.
Moderate infection	Fluconazole, 100 mg/day for 10 days, p.o.
Severe infection	Amphotericin B, 0/5 mg/kg q8h for 7–10 days, i.v.
Herpes simplex	Acyclovir, 250 mg/m^2 q8h for 7–10 days, i.v.
Varicella zoster	Same as herpes simplex
Cytomegalovirus	Ganciclovir, 5 mg/kg q12h for 14 days, i.v.
Human immunodeficiency virus	Prednisone, 40 mg qd for 2 weeks

TABLE 63-5. Treatment of esophageal infections

Physical Agents: Radiation

Etiology and Pathogenesis. The esophageal mucosa is sensitive to ionizing radiation and is often included in the fields used to treat lung and thyroid cancers. Odynophagia often appears after 25 to 30 Gy and usually lasts until the radiation is stopped. Biopsies of the mucosa show shrunken pyknotic nuclei. In animals and sometimes in humans, there is disturbance in peristalsis, as the muscles and nerves of the esophagus are also sensitive to radiation.

Symptoms. Patients complain of both pain and dysphagia, usually for solid boluses. Pain tends to be constant and is exacerbated by attempts to swallow food. This often leads to poor nutrition for the patient and can become a real clinical problem.

Diagnosis. A clinical history is all that is necessary to make the diagnosis. Endoscopy does not offer added information; it will increase the patient's discomfort.

Therapy. Topical anesthetic agents and pain medication will be necessary to control symptoms. There are currently no agents that will protect the esophageal mucosa from ionizing radiation.

Physical Agents: Pill Esophagitis

Etiology and Pathogenesis. Studies in control patients show that even young healthy individuals will have temporary (and unrecognized) arrests of swallowed gelatin capsules. Several swallows of water are often necessary for complete transport into the stomach. Transit is even worse if the pills are swallowed in a recumbent position. When motor abnormalities of the esophagus or luminal obstruction such as a stricture are added, transport becomes even more perilous. Sometimes pills containing timed-release granules are opened by the patients and mixed with food. This can cause quite a burn to the esophageal mucosa.

Table 63-6 lists the most common offenders; however, the list is long and should be consulted if pill esophagitis seems to be in the differential diagnosis.

Antibiotics	Doxycycline, tetracycline
Nonsteroidal antiinflammatory drugs	Aspirin, ibuprofen
Quinidine	–
Alendronate	–
Potassium chloride	Especially sustained-release capsules
Iron preparations	–

TABLE 63-6. Pills causing frequent esophageal damage

Symptoms. The usual clinical syndrome is characteristic enough to be easily recognized. A previously healthy individual will suddenly develop rather severe chest discomfort that is steady and exacerbated by swallowing. Additional history will reveal that the patient has recently started a new pill preparation.

Diagnosis. A characteristic history is sometimes all that is necessary to offer a firm diagnosis of pill esophagitis. If the situation is not clear, esophagoscopy will usually demonstrate a circumscribed ulcer at the level of the aortic arch or just above the LES. Cases have been reported in which adherent material from the offending capsule(s) still remain in the bed of the ulcer.

Treatment. Reassurance and stopping the offending medication or giving it in a noncapsule liquid form will alleviate the distress within 3 or 4 days. Preventive medicine is best. Encourage patients to take a drink of water before the pill is taken, swallow the pill with a large mouthful of water, and then take two to three additional swallows of water. All this should be done in the upright position, not lying down in bed. The practice of taking a handful of pills at once is to be discouraged.

Physical Agents: Caustics

Etiology and Pathogenesis. The esophagus can be exposed to caustic agents, either accidentally in the case of children or alcoholics, or with suicidal intent. Injury with lye is instantaneous; attempts to neutralize the alkali should not be made. Some of the granular bowl cleaners contain strong caustics.

Symptoms and Signs. There is often poor correlation between signs of burns in the oral cavity and damage to the esophagus. The patient may spit out the caustic before swallowing it, which will produce oral damage without esophageal damage. Conversely, a normal oropharynx does not guarantee a burn-free esophagus. Respiratory stridor suggests a laryngeal burn and the possible need for airway control.

Diagnosis. Although earlier articles on this subject suggested that endoscopy should not be done after caustic ingestion for fear of perforation, the advent of modern small-caliber flexible endoscopes has allowed safe inspection of the esophagus in this situation. If the mucosa appears normal, further therapy directed toward the esophagus is not necessary and the appropriate social or psychiatric therapy can be started. Signs of a severe burn with a necrotic appearance might prompt rapid surgical consultation, especially if liquid lye has been the ingestant.

Therapy. The acute pain of ingestion will need to be controlled with appropriate intravenous narcotics. Both antibiotics and steroids have been advocated for caustic injury of the esophagus; there are no controlled trials showing benefit of either form of therapy. A controlled trial of steroid therapy in children showed no benefit; stricture formation was a function of extent of injury and not the presence or absence of steroids (46).

PAINFUL ESOPHAGEAL MOTOR DISORDERS

The concept of chest pain arising from disturbances in esophageal muscle function has long been held by clinicians. Osler mentioned esophagismus and spasm in the late 1800s (47). The first objective confirmation that esophageal motor abnormalities could cause pain was provided by Evans, who demonstrated radiologically disordered peristalsis in 40% of patients with chest pain; two control groups (n = 1,400) had only a 1% to 5% prevalence of such motor disturbances (48). When manometric techniques were introduced, patients with chest pain were found to have diffuse esophageal spasm (49) and high-amplitude long-duration contractions associated with pain (50). This section examines the role of abnormal esophageal muscle contractions as an etiologic agent in chest pain.

Etiology and Pathophysiology

Several possibilities exist that might explain how motor abnormalities of the esophagus could cause chest pain.The most obvious one is that increased tension during a contraction might activate receptors in the esophageal wall. Contractions of the uterus during labor are perceived as painful—why not “labor pains” of the esophagus? This possibility, although attractive, will have to await methodology that can sample the intensity of afferent nerve impulses arising in the wall of the esophagus.

Prolonged high-amplitude contractions might interfere with the blood flow in the esophageal wall and produce ischemic pain. It is not possible to measure blood flow directly in the esophageal musculature, nor is it possible to examine the esophageal venous effluent to look for biochemical indicators of ischemia. Disturbances in blood flow were inferred from an experiment that measured esophageal rewarming after a short infusion of cold water (51). It was found that there was a significant delay in rewarming in patients with esophageal contraction abnormalities and chest pain. Other investigators producing chest pain with edrophonium stimulation noted no change in rewarming time in patients who developed chest pain when compared with those who did not develop chest pain (52).

A change in muscle compliance has been demonstrated with a balloon system in which a cross-sectional area of stimulation could be constantly monitored (53). This study showed that balloon volume alone did not necessarily measure cross-sectional distension dimensions and that the esophageal muscle of patients with chest pain of unknown origin was stiffer than the esophageal muscle of control patients.

Another provocative preliminary finding is that the longitudinal muscle of the esophagus, demonstrated by intraluminal ultrasound, contracts before the onset of chest pain (54). These changes were not detected by intraluminal pressure measurements, which showed no changes when the pain occurred.

Symptoms and Signs

Pain associated with contraction abnormalities is usually described by the patient as a sense of pressure—a boring or aching sensation. This can range in intensity from a feeling of slight constriction to an intense pressure associated with diaphoresis, a gray color, and a feeling of impending death. This pain is usually felt substernally but rarely can be felt only in the neck or epigastric area (Fig. 63-6). Radiation through to the back is a clinical clue that the pain under consideration might be of esophageal origin. Radiation into the neck, jaw, teeth, and shoulder is common. Occasionally, pain radiates to the left arm or to both arms as it does in myocardial ischemia.

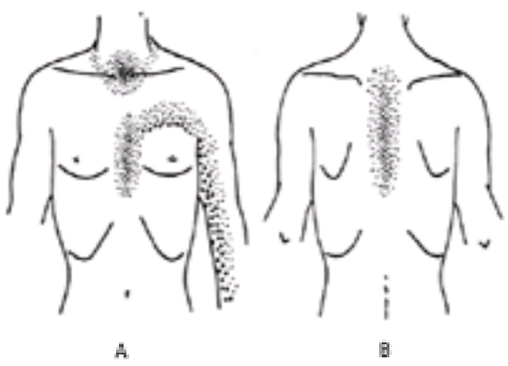

Figure 63-6. Area of pain reference from esophageal colic. The pain is usually felt substernally, but it can be felt also in the neck or the epigastric area **(A)** and almost always in the back **(B)**. Radiation occurs into the neck, jaw, teeth, and shoulder and occasionally to the left or both arms.

The duration of motor pain can be from a few seconds to many hours. It can be clinically indistinguishable from the pain due to coronary artery disease, not only in location but also in the factors that aggravate or relieve it. An exercise-related component is present in approximately one-half of the patients whose pain is eventually found to be of esophageal origin. It tends to be quite variable in the amount of exercise related to stimulate pain from day to day. Sometimes the ingestion of cold beverages produces an attack.

Patients with esophageal motor disorders producing pain also often give a history of intermittent dysphagia, usually not during attacks of pain. Most patients will not eat or drink during an attack. If they do take liquid, and it regurgitates back into the nasopharynx, a motor disorder of the esophagus is most probably present. It is

uncommon for bolus ingestion to produce chest pain due to contraction abnormalities of the esophageal muscle.

Diagnosis

Intraluminal manometry remains the most common method of searching for abnormalities of motor function. Interpretation of tracings is more objective than interpretation of radiographic images. During the 1990s, many hospitals and clinics obtained the equipment necessary to perform esophageal manometry.

A discussion of manometric techniques is beyond the scope of this chapter, but it is available in the comprehensive book by Castell and Castell (55). There is still a lack of uniformity in the performance and interpretation of esophageal manometric tests. Some of this is due to different forms of catheters and recording apparatus; operator interpretation is also not uniform.

When patients with chest pain thought not to be due to coronary artery disease are investigated with manometry, esophageal motor abnormalities are present in 23% to 63% of the patients (Table 63-7) (40,56,57,58 and 59). These estimates exclude patients with achalasia, a motor disorder of the esophagus in which chest pain can be present at the beginning of the illness. In most series, high-amplitude waves, often of increased duration, are the most common finding, present in approximately one-half of those with abnormal findings (Fig. 63-7). Diffuse esophageal spasm (Fig. 63-8) is quite an uncommon finding.

Reference	n	Any motor disorder	High-amplitude waves
Brand et al. 1981 (56)	145	57 (39%)	29 (20%)
Traube et al. 1983 (57)	112	35 (31%)	13 (12%)
Benjamin et al. 1983 (58)	30	19 (63%)	9 (30%)
Katz et al. 1987 (40)	910	255 (28%)	123 (13%)
Cannon et al. 1990 (59)	87	20 (23%)	11 (13%)

TABLE 63-7. Motor disorders in patients with chest pain

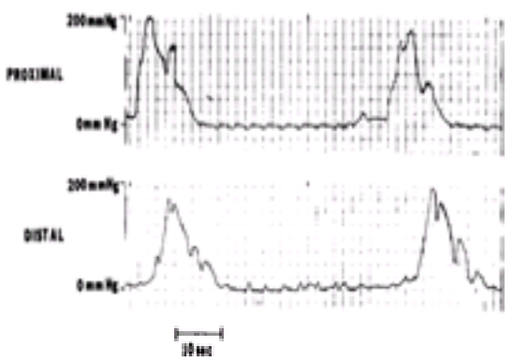

Figure 63-7. Manometric record of high-amplitude peristaltic contraction. Tracings obtained for two tips 5 cm apart shows waves of very high amplitudes (175 to 200 mm Hg, compared with normal values of 60 to 100 mm Hg), long duration (14 to 16 sec, compared with normal values of less than 6 sec), and slow velocity of propagation (50 to 60 cm/sec, compared with a normal value of 4 cm/sec). Pain can be present throughout the duration of such waves.

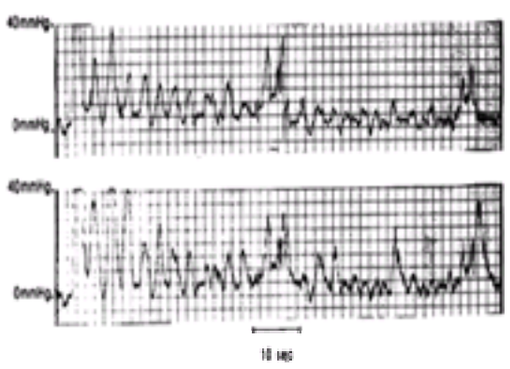

Figure 63-8. Manometric record of diffuse spasm of the esophagus. Note elevation of the baseline pressure on the left side of the tracings with superimposed simultaneous contractors. The baseline pressure returns to normal in the center of the tracings. A peristaltic contraction is recorded on the far right portion of the tracings. Pain, if present, would be experienced during the period of baseline elevation.

The mere presence of a motor abnormality does not establish a causal relationship between the abnormal pattern and the chest pain. If the patient can be studied during an episode of pain and the onset, intensity, and disappearance of discomfort predicted by watching the manometric tracing, a relationship has been established. This is an uncommon event; in one early study, 38 of 160 patients had discomfort during testing; of these, 14 had abnormal motor patterns that correlated with the chest discomfort (56). This is only a yield of approximately 9%. Another group of investigators found no correlation between chest pain and manometric abnormalities when the patient was studied in the middle of an attack (60).

When the technology of ambulatory manometry became available, it was hoped that the increased period of observation with the patient in his or her own environment would increase the yield of positive studies. Even when patients with daily pain were investigated, this hope was not fulfilled. Table 63-8 shows the number of patients demonstrating pain-related esophageal motor patterns (31,32 and 33,35,39,41,61). There is a wide range, from no relationship whatsoever to a 29% positive yield. The best results seem to be obtained when the testing is undertaken soon after a patient enters a coronary care unit and is ruled out for myocardial ischemia (62). Ambulatory motility units are quite expensive, and the low sensitivity shown in the reported studies does not inspire confidence in this technique.

Peters et al. 1988 (35)	7/24 (29%)
Ghillebert et al. 1990 (41)	7/50 (14%)
Stein et al. 1991 (61)	13/108 (12%)
Hick et al. 1992 (31)	0/47
Adamek et al. 1995 (33)	11/84 (13%)
Lux et al. 1995 (32)	12/45 (27%)
Frobert et al. 1996 (39)	0/63

TABLE 63-8. Correlation of abnormal motility with chest pain

Provocative Tests

The relatively low yield of esophageal motility monitoring has led to attempts to find a good provocative test that might uncover abnormal motility. Table 63-9 lists some of the agents that have been used for this purpose. Unfortunately, none of these agents has been found to increase the yield of pain-related motility abnormalities to any great extent. In one series, when a group of 62 patients with chest pain of unknown origin was exposed to acid, edrophonium, and bethanechol, only 9 of the 62 responded with pain and a positive-related manometric pattern (63).

Agent	Dose
Ice water	–
Acid infusion	0/1 N hydrochloric acid, 30 gtt/min for 30 min
Edrophonium (Tensilon)	100 μg/kg i.v.
Bethanechol	40 or 80 μg/kg s.q.

TABLE 63-9. Provocative agents for motor disorders

Even more confusing is the relationship between provocative testing and the occurrence of reflux-related pain and motor abnormality–related pain. In a series of 33 patients investigated with prolonged as well as standard manometry, pH monitoring, acid perfusion, and edrophonium testing, there was no consistent relationship between spontaneous pain and induced pain (36). All combinations were possible (Fig. 63-9). Some patients (labeled as those with an irritable esophagus) would respond with identical pain to either motor disorder (spontaneous or provoked) or to acid reflux/infusion.

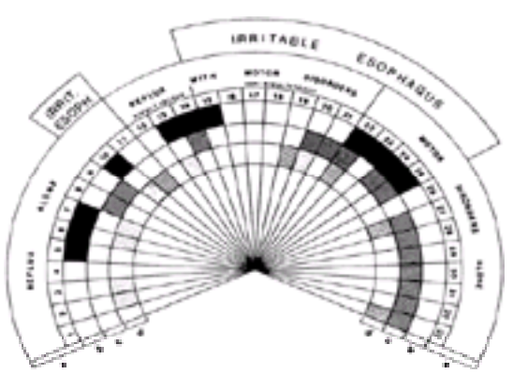

Figure 63-9. Diagram to show results in 33 patients with anginalike chest pain of esophageal origin. *a*, 24-hour pH and pressure results; *b*, positive acid-perfusion test; *c*, conventional manometry; *d*, edrophonium stimulation test. It can be seen that 24-hour tests do not always predict the results of provocative tests. Some patients ("irritable esophagus") respond to multiple agents. (IRRIT. ESOPH., irritable esophagus.) (From Vantrappen G, Janssens J, Ghillebert G. The irritable oesophagus—a frequent cause of anginalike pain. *Lancet* 1987;I:1232–1234, with permission.)

In a position paper on the diagnostic usefulness of esophageal manometry, this lack of diagnostic yield has led to a recommendation that provocative tests not be used (64). This report also suggests that contraction abnormalities are not clearly the cause of esophageal pain; thus, their demonstration does not lead to therapeutic decisions. My own opinion is that in the rare situation when motor abnormalities can be directly associated with pain, an esophageal origin is established. Even the existence of contraction abnormalities suggests an esophageal origin—this suggestion can lead both patient and physician to reduce the use of medical resources (65).

Treatment

The sentence used in the second edition of this textbook (1990) is still correct: "No uniformly effective forms of medical therapy for esophageal motor disorders are available at the present time." Drugs that have been used to treat esophageal motor disorders are listed in Table 63-10.

Agent	Dose
Nitroglycerin	0/4 mg sublingual prn
Isosorbide dinitrate	10 mg q6h p.o.
Dicyclomine	20 mg qid p.o.
Diltiazem	30 mg qid to 60 mg qid to 90 mg qid p.o.
Trazadone	50 mg qd to tid p.o.
Imipramine	50 mg qhs

TABLE 63-10. Pharmacologic treatment of motor disorders

Nitroglycerin

The ease with which nitroglycerin can be taken at the onset of chest pain is an advantage; the accompanying headache often limits its clinical use. Long-acting forms, such as isosorbide or nitropaste, can be tried if the short-acting form provides relief. There may be a selection bias in the patients referred for esophageal testing. If a patient responds to nitroglycerin, that patient may receive a cardiac label, and a contraction abnormality of the esophagus is not considered. Failure of nitroglycerin therapy may predispose to referral to an esophageal laboratory. Therefore, the true prevalence of patients with pain of esophageal origin responding to nitroglycerin may be underestimated.

Calcium Channel–Blocking Drugs

Because high-amplitude waves are a major part of those contraction abnormalities associated with pain, attempts have been made to decrease the amplitude of the peristaltic wave with calcium channel–blocking drugs. Although nifedipine decreases peristaltic amplitude, it does not decrease chest pain (66). One small double-blind trial suggests that diltiazem may offer some relief (but not complete relief) of chest pain (67).

Antidepressive Drugs

Impressed by the degree of psychological problems in patients with chest pain of unknown origin, Clouse et al. undertook a double- blind trial of low-dose trazadone (68). Although the patients on therapy had better quality of life, the amount of chest pain and contraction abnormalities did not change. In a trial of low-dose imipramine in patients with chest pain of unknown origin (41% had abnormal esophageal motility tracings), treatment led to alleviation (but not disappearance) of chest pain (69).

Botulinum Toxin

After botulinum toxin (Botox) injected into the LES zone of patients with achalasia was shown to decrease the intrasphincteric pressure and to increase esophageal emptying, this medication was tried in other motor disorders. In a heterogeneous group of esophageal motor disorders, pain was relieved in 30% of the patients and improved in the rest of them (70). Further controlled trials of this approach would seem to be in order.

Surgical Therapy

Although there have been scattered case reports of alleviation of chest pain by long myotomy in patients with varying contraction disorders of the esophageal muscle, only a few series with more than four or five patients have been published. Ellis reported on 42 patients operated on in the period from 1970 to 1991; relief of pain was experienced in all but five patients (71). DeMeester's group reported alleviation of pain in 14 of 17 patients subjected to a long myotomy (72). Eight of ten patients treated with a thoracoscopic myotomy had their chest pain disappear or markedly improve (73). The decreased morbidity of minimally invasive surgery may lead to larger series of patients in the future.

CHEST PAIN AND THE CENTRAL NERVOUS SYSTEM

Lack of a clear-cut relationship between either mucosal acid sensitivity or esophageal motor activity and the production of chest pain has led to the examination of the role of afferent nerve input and its central processing in the genesis of chest pain of esophageal origin. Several lines of investigation suggested this possibility. The concept of the “irritable esophagus” put forward by Vantrappen and his colleagues takes note of the fact that several different stimuli can produce identical pain syndromes (36). Could this mark use of the same nervous pathways by different stimuli, or does this suggest central processing of different inputs leading to a common sensation?

Balloon stimulation demonstrated a clear increased sensitivity to lower balloon volumes in patients with chest pain of unknown origin when compared with control subjects (74). This led to the concept that there was altered visceral sensitivity in these patients, although it did not differentiate between peripheral and central processing. Repeat balloon distensions caused increased pain in chest pain subjects but not in controls or patients with dysphagia, suggesting changes in either afferent nerve sensitivity or differences in central processing (75).

Is balloon distension merely a convenient form of esophageal stimulation, or does it suggest a possible mechanism for the production of pain? The latter possibility is supported by experiments that infused air into the esophagus to produce distension (76). It was found that most control subjects and patients with chest pain would belch easily to remove the infused air. There were a few patients who could not belch easily; they were the same patients who had their chest pain reproduced by balloon distension. In a subset of these nonbelching patients, their pain was reproduced when gastric distension with gas-forming compounds led to esophageal regurgitation of air and chest pain.

Can the set point at which distension is perceived be changed? Acid infusion into the esophagus of control subjects can sensitize the esophagus so that it responds to smaller balloon volumes (26). Patients with chest pain and ongoing reflux disease do not show a response to acid infusion by a drop in balloon volume; they presumably have already been sensitized. The set point can also be affected by installation of benzocaine, a lipid-soluble anesthetic, into the esophagus of volunteers (77). This installation causes an increase in the balloon volumes necessary to reach thresholds of both perception and pain.

To study possible central differences in processing, cerebral-evoked potentials were measured in chest pain patients and in controls with either balloon (78) or electrical (79) stimulation. Both groups noted a decrease in the amplitudes of the evoked potential (Fig. 63-10), suggesting CNS modification in the chest pain patients. Caution must be used in interpreting amplitude changes of cerebral-evoked potentials, as they can be influenced by levels of attention, external stimuli, and other factors that might be difficult to control (80). A change in the amplitude of the evoked potential can also be caused by neuropathy in the visceral afferent supply, commonly present in diabetic patients (81).

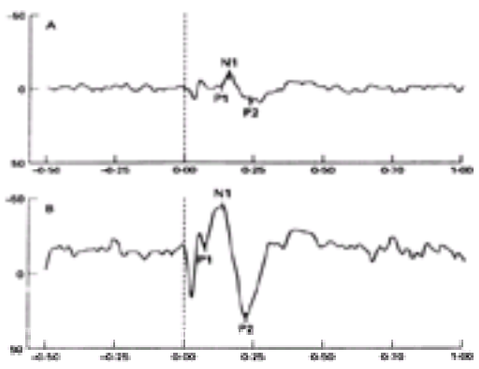

Figure 63-10. Brain-evoked potentials after stimulation of the esophageal mucosa. The stimulus was delivered at time 0.00. P1, N1, P2 are the inflection points of the potentials. Note the reduced voltages in the chest pain patient **(A)** as compared with those recorded from the control subject **(B)**. (From Frobert O, Arendt-Nielsen L, Bak P, et al. Pain perception and brain evoked potentials in patients with angina despite normal coronary angiograms. *Heart*1996;75:436–441, with permission.)

Brain function during balloon stimulation in control subjects has been investigated with PET scanning (19), which showed activation in the insular and primary somatosensory cortex areas for nonpainful stimuli. An increase in balloon diameter to a level producing pain caused increased blood flow in these same areas, as well as activation of the right anterior insular cortex and the anterior cingulate gyrus. No similar studies have yet been reported in patients with chest pain of unknown

origin.

PET scanning has also shown that areas of activation of the brain are important in whether pain is perceived. Some patients with narrowed coronary arteries do not develop chest pain when exercised (82). They are classified as having “silent ischemia.” When such patients have PET scans during stress, they show activation of the thalamic areas, as do patients who develop angina during exercise. Those with “silent ischemia” do not activate areas in the anterior and ventral cingulate cortex and left temporal pole, as do patients with ordinary angina. Cause and effect are not indicated in these studies, but pain is reported only when anterior cingulate cortex is activated.

It is an attractive hypothesis that changes in visceral sensitivity can explain why some patients with chest pain and normal esophageal tests can develop chest pain. An increase in normal visceral information carried either in the vagal nerve or in the visceral afferents might be amplified even further centrally so that impulses that would not normally be perceived would produce a sensation interpreted as pain. Acid reflux might decrease the threshold values at which distending or contraction abnormalities might be felt. Abnormal motor activity might produce increased visceral afferent activity that would be produced as pain. Alternatively, abnormal cortical activity might cause a decrease in inhibitory motor neurons, which would produce abnormal motor activity similar to that seen in volunteers whose normal inhibitory neurons were blocked by a nitric oxide inhibitor (14). Methodology is being developed that might allow some of these possibilities to be investigated in human subjects. A great deal remains to be learned.

Are there any therapeutic possibilities in attempting to modulate CNS activity? As has been pointed out, low-dose imipramine has been of some value in patients with chest pain and contraction abnormalities (69). Trazadone has also been shown to allow patients to cope with their disease (68). Three trials of cognitive therapy in the treatment of chest pain show that coping behavior increased, although the actual amount of chest pain was not much decreased (83,84 and 85).

OTHER PAINFUL DISORDERS OF THE ESOPHAGUS

Effort Rupture of the Esophagus (Boerhaave's Syndrome)

Etiology and Pathogenesis

The act of vomiting is a very violent one indeed; it is amazing that more injuries to the esophagus do not result from this athletic endeavor. Vomiting is rather a coordinated activity between diaphragm, abdominal muscles, the LES, and the upper esophageal sphincter. Studies in animals and a few humans show that there are a few preliminary twitches of the diaphragm during the phase of nausea. A sudden descent of the diaphragm rapidly increases gastric pressure. The LES is presumably inhibited, as are the central muscular fibers of the diaphragm that normally support the LES. The rapid rise in gastric pressure and contraction of the abdominal musculature propel the gastric contents forcefully up the passively distended esophagus and through the presumably relaxed upper esophageal sphincter. If there is incoordination of these various actions, pressure builds up in the esophageal lumen to the point of a through-and-through tear of the esophageal muscle, allowing gastric contents to enter the pleural space. This tear is usually directed to the left lateral aspect of the esophagus in the distal portion. Classically, this is most likely to occur in the postprandial period, especially after alcohol ingestion.

Symptoms and Signs

The classic presentation of Boerhaave's syndrome is to have a patient develop postprandial nausea and vomiting, followed by the onset of crushing chest pain. In truth, patients found later to have a rupture of the esophagus do not always give a history of proceeding vomiting. The pain may be overwhelming, leading to the diagnosis of a myocardial infarct, a large pulmonary infarct, or a suspected dissecting aneurysm. The patient may be short of breath, directing attention to the lungs and heart rather than to the esophagus. Subcutaneous emphysema may be noted and suggest a perforation with accompanying mediastinal air. This is not an easy clinical diagnosis; delayed recognition of the perforation can occur in up to one-half of the cases.

Diagnosis

A chest film done because of pulmonary problems often suggests a rupture when a pleural effusion is seen or mediastinal or subcutaneous air is recognized. Unless the diagnosis is clinically obvious, a contrast study of the esophagus using water-soluble dye usually provides evidence of a free perforation. In one series, 23 of 24 contrast studies showed evidence of a perforation (86). It is preferable to begin the examination with water-soluble dye rather than barium sulfate, as extravasation of the former agent will not lead to long-term consequences as will the spilling of barium into the pleural cavity. A diagnostic thoracentesis usually shows acidic fluid; rarely, food particles will be aspirated by the needle.

Treatment

Surgical repair of the esophageal rent is in order—it is hoped within 12 hours of the original insult. Unlike perforations due to instrumentation, delay in diagnosis and therapy does not seem to be too harmful (86). The defect in the wall is identified, sutured, and occasionally covered with a flap of thickened pleura or with a gastric patch to protect the suture line. Nonoperative management has occasionally been tried with success, but surgical control of the rupture is still the preferred treatment.

Paraesophageal Hernias

Etiology and Pathogenesis

There is a grading system of gastric herniation. The common sliding hernia is considered to be grade I. A hernia in which the gastroesophageal junction remains below the diaphragm and the fundus or antrum passes through the diaphragmatic hiatus is considered to be grade II. A combined type, in which both the gastroesophageal junction and the fundus are up into the mediastinum but the fundus is higher than the gastroesophageal junction, is considered to be grade III. Grades II and III are interchanged often in the literature. Classically, the grade II hernias do not have an increased incidence of reflux, as the gastroesophageal junction functions normally. Grades I and III have reflux; grade III may in addition have obstructive symptoms similar to those seen with a grade II hernia. Volvulus of a portion of the herniated stomach may lead to ischemia and pain. Volvulus may also lead to obstruction with colic.

Symptoms and Signs

Pain from a paraesophageal hernia can come in two forms. The more common form is a postprandial fullness and pressure. It may be accompanied by a gurgling sensation as the patient moves in bed. The patient may complain of shortness of breath after a particularly large meal. The other type of pain is more severe and may resemble that experienced during a myocardial infarct. It may be due to ischemia of the stomach as the blood supply is compromised by a partial or complete volvulus. The pain is not relieved by antacids; belching may signal the return of the herniated stomach to a more normal position.

Diagnosis

A plain film of the chest may show a retrocardiac mass with an air-fluid level contained within it. A barium esophagram shows the esophagus disappearing behind a displaced fundus (Fig. 63-11). An esophagoscopy can present a truly confusing appearance, as the normal relationships of gastroesophageal junction, fundus, and antrum are not present. The endoscopic view will be of two separate passages, one leading to the pylorus, the other to the fundus.

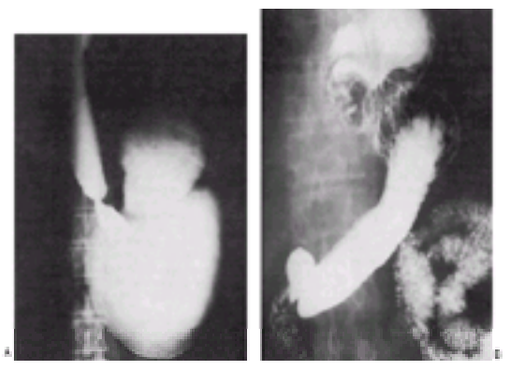

Figure 63-11. **A:** Paraesophageal hernia. Note that the esophagogastric junction is located well down in the abdomen and that the fundus rises into the chest. **B:** Large hiatus hernia. The impression of the diaphragm is seen in the midfundal region. The gastroesophageal junction is located high in the mediastinum. (Radiographs courtesy of C.A. Rohrmann, M.D.)

Therapy

This anatomic defect requires an anatomic solution—corrective surgery. However, there is still disagreement as to the place of corrective surgery when a totally asymptomatic hernia is picked up on a chest x-ray. Chest pain, especially the type resembling a myocardial infarct, would suggest the need for corrective surgery even though these hernias tend to occur in elderly patients with many other medical problems. Symptoms of fullness and obstruction call for a more individualized approach. Most patients will be better off when the hernia is corrected. If there has been blood loss in the patient, another indication for surgery is present. Hernias can be repaired either with an open operation or laparoscopically. The latter less morbid procedure is gradually gaining popularity. However, it is more demanding than the ordinary laparoscopic antireflux repair.

APPROACH TO THE PATIENT WITH CHEST PAIN

Clinical judgment is still the most important tool when investigating a patient with chest pain. In the immunocompromised patient, viral or yeast infection is a strong possibility and should lead to immediate endoscopy, with procurement of adequate samples for viral and fungal study. In the standard patient, the scheme shown in Fig. 63-12 might be used.

Figure 63-12. Algorithm for the approach to a patient presenting with chest pain. See text for definition of steps. (PPI, proton pump inhibitor; R/ O, rule out.)

A cardiac evaluation would seem to be the best place to begin the evaluation in view of the anxiety produced both in patient and physician by the symptom of chest pain. The intensity of the evaluation depends on the age of the patient and risk factors for coronary artery disease such as hypertension, smoking, hyperlipidemia, and diabetes (see Chapter 61).

A careful examination by palpation of the spine and chest wall will be productive in 10% to 15% of patients presenting to a cardiac clinic or general internist (87). Pressure over the spinous processes of T-3 and T-4, which reproduces the anterior chest pain, strongly suggests a musculoskeletal origin of the pain, and physiotherapy can then be used for relief.

Ultrasound scanning for gallstones may uncover the reason for chest pain of unknown origin, as colic from the gallbladder may be perceived as chest pain instead of the more common right upper quadrant location. A finding of gallstones leads to their removal; it is hoped the chest pain will be removed with the stones.

A 24-hour pH test would seem to be the next best step. This allows both the quantitation of the amount of reflux present as well as an evaluation of the frequency of coincident reflux with pain. If this is positive, a therapeutic trial with high doses of proton pump inhibitors such as omeprazole, 20 mg twice a day, or lansoprazole, 30 mg twice a day, can be done for 8 weeks. If this is effective, a clinical choice between continuing the medication or consideration of antireflux surgery can be made.

If the trial fails, it is probably worth repeating the 24-hour pH monitoring while the patient continues to take medication to make certain that the patient is not one of the small group of patients who do not respond to proton pump inhibitors at this dose. If reflux is still shown at this dose, the dose can be raised even higher or antireflux surgery can be considered.

If the initial 24-hour pH probe result is negative, an endoscopy can be done to make certain that the period of monitoring is not a false-negative response. My own experience is that such an endoscopy is usually negative, although there is support for the concept of finding signs of erosive esophagitis even without the usual symptoms of reflux (88).

Standard manometry can then be used to discover if a contraction abnormality of the esophagus is present, especially if the patient also complains of dysphagia. Should there be evidence of high-amplitude waves or the more uncommon diffuse esophageal spasm, a trial of diltiazem, 30 mg four times a day, rising to 60 and then 90 mg four times a day, can be done. Should the patient respond, the drug may be continued. If standard manometry is normal and the frequency of chest pain is daily, ambulatory manometry can be considered. If the drug trial has failed, endoscopic ultrasound can be used to look for an increase in thickness of the esophageal wall. If positive, the patient might be considered for myotomy, especially if dysphagia is also present. If negative, cognitive therapy can be tried.

Although this is a plan, it must be stated that it is not one that has been tested in the real-world situation. With the exception of controlling acid and, it is hoped, the accompanying chest pain, the remainder of the algorithm is on uncertain ground. To improve it, major advances in technology still will be necessary before a good understanding of chest pain of esophageal origin will be obtained.

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CHAPTER 64

Chest Pain from Other Disorders Including Cancer

Jonathan R. Gavrin

This chapter covers chest pain not caused by the specific disorders addressed in the preceding chapters of Section C, Part IV. It is divided into two parts: Neoplastic Chest Disease and Nonneoplastic Chest Disease. Lung and breast cancers make up the overwhelming majority of thoracic neoplasms; except for metastases to lung, which are common, thoracic cancers other than primary lung and breast are rare. Nonneoplastic chest disease is a large and varied collection of syndromes that often present a perplexing set of diagnostic and therapeutic dilemmas.

NEOPLASTIC CHEST DISEASE

In developed countries, cancer continues to be the second leading cause of death, behind cardiovascular disease. Cancers account for approximately one-third of all deaths yearly and equal or exceed the death rates for coronary artery disease, exclusive of other cardiovascular diseases such as stroke, high blood pressure, or rheumatic heart disease (1) (http://www.americanheart.org/). Lung cancer and breast cancer each account for approximately 14% of the 1.2 million estimated new cancer cases per year, and together account for roughly 30% of all cancer deaths annually (1) (Table 64-1). Sadly, the age-adjusted death rate for lung cancer in female subjects has been rising since the late 1980s, rapidly approaching the death rate for men with lung cancer (1,2 and 3). For male subjects, even though the total death rate from lung cancer remains unacceptably high, in 1990 there began a slow but consistent decline (1) (Fig. 64-1).

Parameter	All cancers	Lung cancer	Breast cancer
New cases			
Total	1,228,600	171,500	180,300
Female	600,700	80,100	178,700
Male	627,900	91,400	1,600
Deaths			
Total	546,800	160,100	43,900
Female	270,600	67,000	43,500
Male	294,200	93,100	400

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TABLE 64-1. Estimates of new cases and deaths from lung cancer and breast cancer

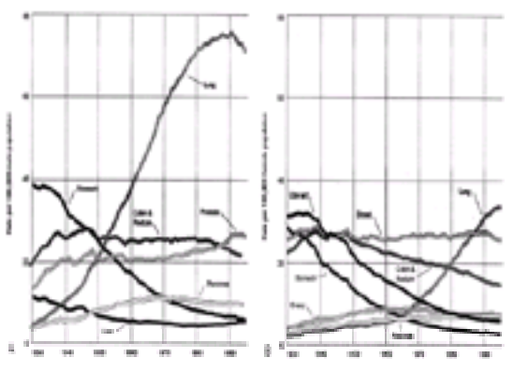

Figure 64-1. Age-adjusted death rates for males **(A)** and females **(B)** in the United States from cancer of selected sites, 1934 through 1994. Rates are per 100,000 and are age adjusted to the 1970 U.S. standard population. Due to changes in International Classification of Diseases coding, numerator information has changed over time. Rates for cancers of the liver, lung, and colon and rectum are affected by these coding changes. (Reprinted with permission of the American Cancer Society, Inc.)

Together, breast and lung malignancies not only make up a huge proportion of lethal cancers, but also lead to myriad painful and other aversive symptoms, be they from primary disease, metastasis, or treatment. The ensuing discussion highlights general characteristics and then explores the specific chest symptoms related to these two diseases; it does not consider global principles of cancer pain management or palliative interventions that previous chapters address (see Chapter 36 and Chapter 40). For completeness, a brief review of other thoracic neoplasms follows the material on breast and lung cancers.

Cancer of the Lung

Basic Considerations

The term *lung cancer* properly refers to tumors of respiratory epithelial origin (bronchi, bronchioles, and alveoli) (4). This chapter also includes discussions of mesothelioma and metastatic lung disease. The former, of pleural origin, is frequently associated with chest pain, cough, and other symptoms associated with primary lung tumors. Metastatic lung disease, the symptomatology of which resembles primary lung cancers, is exceedingly common, occurring in approximately 30% of all cancer patients (nearly 20% of patients dying from pulmonary metastases have no other detectable focus of disease) (5).

The bronchogenic carcinomas [squamous cell (epidermoid), adenocarcinoma, bronchioalveolar carcinoma, large cell carcinoma, and small cell (oat cell) carcinoma] account for approximately 90% of primary lung tumors; undifferentiated carcinomas, carcinoids, bronchial gland, and other rare tumors account for the remaining 10% (4). Adenocarcinoma has now replaced squamous cell (epidermoid) cancer as the most frequent lung tumor (6). Histologic subtyping into small cell lung cancers and non–small cell lung cancers has major clinical importance, determining treatment decisions. Typically, small cell lung cancers have spread by the time of diagnosis; chemotherapy and radiation are the only realistic treatment options and sometimes are effective. For non–small cell lung cancers that are localized at the time of

diagnosis, surgery or radiation may be curative, but metastatic disease is resistant to chemotherapeutic interventions (4).

Smoking is the single most important etiologic factor in pulmonary tumors (7,8) and is present in 90% of patients. The causal relationship between other environmental exposures and lung cancer is also well established, including passive smoke inhalation (9,10 and 11), asbestos, silica dust, dichlorodiphenyltrichloroethane (DDT) (12), certain occupations, and living situations, including poverty and proximity to industrial regions (1213,14,15,16,17,18,19,20,21,22, and 23). Asbestos-related disease, most importantly pleural mesothelioma, should peak in the next two decades and then decline, due to control of industrial exposures.

No truly satisfactory curative treatment exists for any of the lung-related tumors, primary, metastatic, or pleural (24,25,26 and 27). Five- year survival rates for all but the most localized disease are dismal, and half of those people with local disease will be dead within 5 years (1) (Table 64-2). Therapeutic advances in the past three decades have made only modest improvements in overall survival with lung cancer, from 8% to 14%. However, many efforts to improve the quality of supportive and palliative measures have developed. Pain and other somatic symptom management, along with psychological support, are central to quality care and have improved significantly in this time period (28,29, and 30).

Malignancy	All stages (%)	Local disease (%)	Regional disease (%)	Distant disease (%)
Breast (female)	84	97	76	21
Lung	14	49	18	2

TABLE 64-2. Five-year survival for lung cancer and breast cancer

Clinical Features

The overwhelming majority of patients with lung cancer present with some sign or symptom, with only 5% to 15% of patients asymptomatic at diagnosis, usually by routine chest radiograph. Typically, at the onset of tumor growth or invasion, lung cancers produce signs and symptoms arising from local enlargement, invasion of adjacent structures, regional growth, lymphatic spread, or growth in distant metastatic sites from hematogenous dissemination. Clinical manifestations may also occur from remote effects of lung tumors, in particular paraneoplastic syndromes that may result from ectopic secretion of peptide hormones (4,31). Except for pleural pain and vague pains thought to be of visceral origin and typically involving the ipsilateral hemithorax, chest pain in lung cancer patients is not common. Rather, cough, dyspnea, hemoptysis, and syndromes associated with compression or obstruction of vascular and airway structures are the predominant symptoms (32) (Table 64-3). The approach to patients with lung cancer, therefore, is of a general palliative nature, encompassing much more than just pain relief (see Chapter 40).

Symptoms secondary to central or endobronchial growth of the primary tumor
Cough
Hemoptysis
Wheeze and stridor
Dyspnea from obstruction
Pneumonitis from obstruction (fever, productive cough)
Symptoms secondary to peripheral growth of the primary tumor
Pain from pleural or chest wall involvement
Cough
Dyspnea on a restrictive basis
Lung abscess syndrome from tumor cavitation
Symptoms related to regional spread of the tumor in the thorax by contiguity or by metastases to regional lymph nodes
Tracheal obstruction
Esophageal compression with dysphagia
Recurrent laryngeal nerve paralysis with hoarseness
Phrenic nerve paralysis with hemidiaphragm elevation and dyspnea
Sympathetic nerve paralysis with Horner's syndrome
Eighth cervical and first thoracic nerves with ulnar pain and Pancoast's syndrome
Superior vena cava syndrome from vascular obstruction
Pericardial and cardiac extension with resultant tamponade, arrhythmia, or cardiac failure
Lymphatic obstruction with pleural effusion
Lymphangitic spread through lungs with hypoxemia and dyspnea
(Adapted from Carbone KKH. Signs and symptoms of bronchogenic carcinoma. In: Straus AM, ed. Lung cancer: clinical diagnosis and treatment. New York: Grune & Stratton, 1967:85–98.

TABLE 64-3. Common signs and symptoms of lung cancer

In patients with superior pulmonary sulcus syndrome, metastatic plexopathy, or bone involvement, pain is caused by peripheral (nociceptive) mechanisms or peripherocentral (deafferentation) mechanisms. Nociceptive pain is usually localized and continuous and increases with time, caused by tumor invasion of the nearby vertebrae, the cupola of the pleura, and other soft tissue. Deafferentation pain is caused by compression, infiltration, and destruction of the involved spinal nerves, which produces burning pain with allodynia, hyperalgesia, hyperesthesia, dysesthesia, and hyperpathia in a segmental distribution. In patients with costopleural syndrome, the pain is predominantly caused by a peripheral mechanism, but if intercostal nerves are involved, deafferentation pain may play a prominent role in the patients' discomfort.

Symptoms Due to Intrathoracic Spread. Intrathoracic spread of lung cancer, either by direct extension or by lymphatic metastasis, produces regional disease symptoms in the thorax; the same is true for metastatic disease to the lung from other primary carcinomas. Involvement of the superior pulmonary sulcus, for example, produces Pancoast's syndrome (see Pancoast's Syndrome, later in this chapter) (Fig. 64-2). Tracheal obstruction and irritation can be associated with retrosternal and anterior chest wall pain, as well as with cough and hemoptysis (4,31,33). Entrapment of the recurrent laryngeal nerve produces vocal cord paralysis with hoarseness and, because of the longer intrathoracic course of the left nerve, these symptoms more commonly occur on the left side than on the right side. Involvement of the phrenic nerve can lead to paralysis and elevation of the hemidiaphragm, with resulting dyspnea.

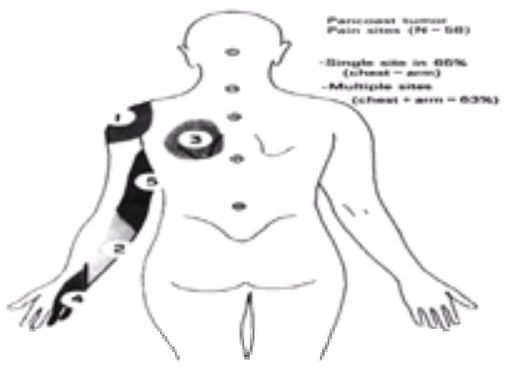

Figure 64-2. Sites of pain in Pancoast's syndrome in order of frequency. Of 58 patients, 28 (49%) had pain in the shoulder, 24 (41%) in the medial forearm, 23 (40%) in the scapula, 9 (15.5%) in the fourth and fifth fingers, and 4 (7%) in the medial part of the upper arm. (Reprinted from Watson PN, Evans RJ. Intractable pain with lung cancer. *Pain* 1987;29:163–173, with permission.)

Compression of the esophagus by the tumor can lead to dysphagia, odynophagia, and, not infrequently, deep visceral pain caused by the involvement of sensory nerves to the esophagus. Also, dysphagia of both solids and liquids can result with recurrent laryngeal nerve paralysis; because this nerve supplies part of the cricoid musculature and proximal esophagus, aspiration of gastric contents can result. Compression of the thin-walled low-pressure system of the superior vena cava by a right-sided tumor or large lymph nodes in the mediastinum produces the superior vena cava syndrome (see Superior Vena Cava Syndrome, later in this chapter).

Tumor extension into the pericardium and heart can produce pericardial tamponade or congestive heart failure. Other problems of regional spread include lymphatic obstruction with resulting pleural effusion, and lymphangiectatic spread to the lungs, with production of hypoxemia and dyspnea. Bronchioalveolar carcinoma can spread transbronchially with tumor growing along the multiple alveolar surfaces, resulting in impairment of oxygen transfer, respiratory insufficiency, dyspnea, hypoxemia, and production of large amounts of sputum. Some of these patients have deep, retrosternal, diffuse visceral-type pain.

Symptoms Due to Extrathoracic Metastatic Disease. Metastatic disease, found in 50% to 90% of autopsies of patients with lung cancer, can involve nearly any organ, but most commonly affects pleura, lung, bone, pericardium, and liver. Other sites of metastasis include adrenals, central nervous system, meninges, gastrointestinal tract, esophagus, and thyroid gland (4,31).

These produce common clinical problems, which include neurologic deficit from brain metastasis, pain from bone metastases and pathologic fractures, biochemical liver dysfunction, anorexia and cachexia, and biliary obstruction with pain. Some patients with metastases to the lymph nodes in the supraclavicular region, and occasionally in the axilla and groin, have pain and ulceration. Extension of tumor into the vertebral column frequently causes spinal cord compression, with consequent neurologic signs and symptoms.

Paraneoplastic Syndromes. Paraneoplastic syndromes, which are remote effects of cancer, are common in patients with lung cancer and can be the initial finding or the first sign of recurrence of the lung cancer. In addition, a paraneoplastic syndrome can mimic metastatic disease and, unless detected, might lead to inappropriate palliative rather than curative treatment. Successful treatment of the tumor can relieve paraneoplastic syndromes, so this is the basis for therapy (4,31,33).

Pancoast's Syndrome (Superior Pulmonary Sulcus Tumor). First discussed in the English literature by E. S. Hare in 1838 (34), it was Pancoast's classic 1932 paper that described the clinical features of superior pulmonary sulcus tumor as “pain around the shoulder and down the inner side of the arm and often the ulnar side of the forearm, loss of power and wasting of the muscles of the hand, Horner's syndrome, and signs mainly of dullness in the apex of the chest” (35). In fact, Pancoast's syndrome can result from a variety of conditions affecting the apex of the lung (Table 64-4A; see Fig. 64-2); it is associated with 3% to 5% of pulmonary tumors and probably occurs more frequently in men (36). The superior pulmonary sulcus is located just below the lower trunk of the brachial plexus. A growing mass irritates and eventually compresses nerve roots C-7 through T-2, causing the characteristic pain and motor and sensory disturbances in the distribution of the ulnar and intercostobrachial nerves. Frequently, the discomfort becomes excruciating, often associated with the lancinating pains of deafferentation. Although all of the patients in Pancoast's original report exhibited Horner's syndrome, subsequent published reports suggest an incidence closer to 60%. Less frequently, there is hoarseness from involvement of the recurrent laryngeal nerve or symptoms of spinal cord compression secondary to extension along the nerve roots into the epidural space (37,38,39 and 40) (Table 64-4B).

Bronchogenic carcinomas
Tuberculosis
Pulmonary abscess
Laryngeal tumors
Branchial cleft tumors
Myeloma
Cervical rib
Neoplasms of the cervical sympathetic ganglia

TABLE 64-4A. Conditions associated with Pancoast's syndrome

Parameter	Source		
	Bentivoglio (40)	Kiernan et al. (38)	Watson and Evans (39)
Number of patients	400	38	32
Symptoms and signs (% of total patients)			
Pain	98	95	100
Horner's syndrome	42	48	34
Brachial plexopathy	45	17 (72)*	41
Spinal cord compression	16	28	5
Vocal cord paralysis	16	3	11
Bone invasion	45	7	NS
Cough, hemoptysis	34	3	NS

NS, not stated.
*Seventeen percent at presentation, but 72% eventually developed plexopathy.

TABLE 64-4B. Signs and symptoms of Pancoast's tumors in percentage of patients studied

Other Brachial Plexopathies. Brachial plexopathy is a well-known complication of cancers, most frequently from metastatic disease (metastatic brachial plexopathy), but also associated with radiation therapy (radiation brachial plexopathy), surgery, or regional tumor growth. In metastatic brachial plexopathy, pain is the most common presenting symptom, while radiation brachial plexopathy typically presents as dysesthesia or weakness of the arm. In patients with brachial plexopathy from tumor infiltration, approximately 70% have primary lung or breast cancer (41,42).

Costopleural Syndrome. The costopleural syndrome results from tumor invasion of the pleura, soft tissue, and ribs, often with involvement of the intercostal nerves. Costal pleural irritation causes a sharp aching or burning sensation usually overlying the pathologic process. Central lesions of the diaphragmatic pleura typically cause well-localized sharp or aching pain in the shoulder or ridge of the trapezius, while lesions in the pleura overlying the muscular portion of the diaphragm tend to cause a referred dull and aching pain to the upper lumbar region of the back and the upper two-thirds of the abdomen. Tumor infiltration of the cupola of the lung usually produces pain in the upper interscapular or vertebral area and in the medial aspect of the arm. Mediastinal pleural invasion produces pain felt deep in the central portion of the chest and also in the shoulder and trapezius region. Deep breathing, coughing, and movement all exacerbate pleural pain. Metastatic lesions to soft tissue and ribs cause somatic nociceptive pain; compression, irritation, or damage to intercostal nerves produces a continuous neuropathic pain with accompanying burning, dysesthesia, and sensory loss that is unilateral and segmental (Fig. 64-3).

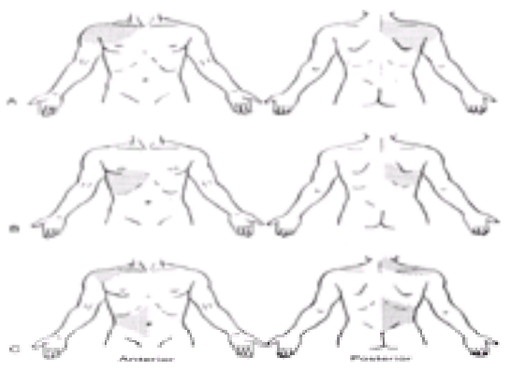

Figure 64-3. Sites of pain in various costopleural syndromes. **A:** Pain pattern from pathology in the right upper part of the thoracic cage, or apical parietal pleura. **B:** Pain pattern of the right middle part of the chest and parietal pleura. **C:** Pain pattern from irritation of the right portion of the diaphragmatic pleura producing pain in the shoulder, outer abdomen, and back (parts supplied by the phrenic nerves and the lower thoracoabdominal intercostal nerves), respectively.

Superior Vena Cava Syndrome. Obstruction of venous drainage in the upper part of the chest, the superior vena cava syndrome, is associated with malignancy approximately 90% of the time; of those malignancies, lung cancers make up roughly 85%. Its overall incidence in cancers is 3% to 8%. The superior vena cava, a thin-walled, low-pressure vessel, lies in a tight compartment of the anterior-superior mediastinum behind the rigid sternum, adjacent to the right mainstem bronchus, and completely encircled by the chains of lymph nodes that drain the entire right chest and the lower portion of the left chest cavity. Clinical diagnosis is relatively easy. Venous engorgement in the thorax and neck, with consequent facial edema and tachypnea, are the hallmarks. Chest pain, cough, dysphagia, edema of the upper extremity, and signs and symptoms of increased intracranial pressure, including severe intractable headache, are variably present (43,44 and 45) (Table 64-5).

Sign or symptom	Approximate incidence (%)
Dyspnea	65
Venous distension in the thorax	55
Venous distension in the neck	65
Facial edema	50
Cough	25
Facial plethora	20
Cyanosis	20
Upper extremity edema	15
Chest pain	15

Modified from Yahalom J. Oncologic emergencies. In: DeVita VT, Hellman S, Rosenberg A, eds. *Cancer: principles and practice of oncology.* 5th ed. Philadelphia: Lippincott–Raven, 1997:2869–3476.

TABLE 64-5. Signs and symptoms of superior vena cava syndrome

Pain Syndromes Caused by Vertebral Metastases. The vertebral column, particularly the thoracic and lumbar regions, is the most frequent site of bone metastasis from primary lung, breast, and prostate tumors (46) (Fig. 64-4). Almost all patients with vertebral metastases have local or radicular pain, or both, depending on the extent of vertebral body or nerve root involvement. In extreme cases, epidural spinal cord compression can occur.

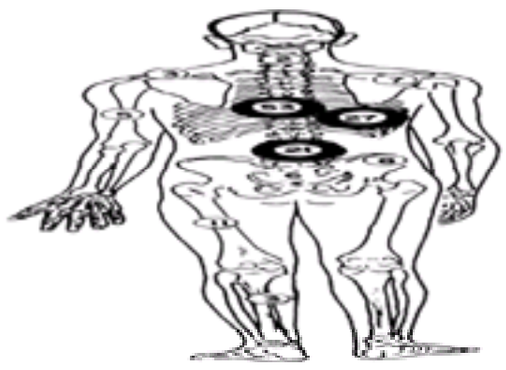

Figure 64-4. Sites of intractable pain caused by skeletal metastasis in 64 patients consequent to lung cancer. The circles contain the number of metastases at various sites. The most frequently involved regions of the 101 painful sites were the thoracic vertebrae, the ribs, and the lumbar vertebrae. The sites indicated do not relate to lateralization. (Reprinted from Watson PN, Evans RJ. Intractable pain with lung cancer. *Pain* 1987;29:163–173, with permission.)

Postthoracotomy Syndrome. Moderate to severe pain in the distribution of one or more intercostal nerves, persisting beyond the usual course of postoperative pain, characterizes the postthoracotomy syndrome. Even though incisional nerve injury (traumatic neuroma) appears to play a minor role compared with ongoing pain from recurrent or persistent tumor in the distribution of the thoracotomy scar (38), nerve block or local anesthetic injection of suspected neuromas carries minimal risk and may aid greatly in diagnosis and treatment planning. Pain due to direct tumor involvement may respond to palliative antitumor therapies, but proper management of systemic or regional analgesic techniques remains the linchpin of pain relief. If systemic medications are ineffective or cause unacceptable side effects, posterior multidermatomal intercostal nerve or thoracic epidural blocks may provide prolonged relief. Thoracic paravertebral block is also a safe technique for unilateral pain relief in chronic postthoracotomy pain (47).

Epidural Spinal Cord Compression. Epidural spinal cord compression is the second most common neurologic complication of systemic cancer, occurring in 5% to 10% of patients. Although usually associated with advanced cancers, spinal metastases can occur any time during the disease; in as many as 8% of patients with spinal involvement, it is the first manifestation of the underlying malignancy (48,49). Epidural spinal cord compression occurs most commonly in the thoracic spine, and pain is the initial symptom in 90% of patients, typically occurring days or weeks before other neurologic signs and symptoms (50). It is, therefore, imperative to make this diagnosis as early as possible and intervene preemptively when feasible. Corticosteroids for acute symptoms and radiotherapy to prevent or delay progression are the mainstays of treatment. Response to systemic chemotherapy generally is poor. Surgical decompression by laminectomy or vertebral body resection seems to be as effective as radiation and may have value in patients who are relatively healthy systemically (49,50 and 51). When a patient is not known to have cancer, misdiagnosis as pain of musculoskeletal origin can occur. If recumbent position exacerbates thoracic pain, and it is progressive and unremitting despite appropriate interventions for musculoskeletal pain, the practitioner should obtain appropriate imaging studies, which usually establish the diagnosis.

Benign Neoplasms of the Lung. Less than 5% of all lung neoplasms are benign. Adenomas and hamartomas account for approximately 90% of such lesions, the remainder being a collection of uncommon neoplasms (chondromas, fibromas, lipomas, hemangiomas, leiomyomas, teratomas, pseudolymphomas, and endometriosis). Similar to malignant lung neoplasms, these syndromes typically present with cough, hemoptysis, obstruction, infection, or asymptomatically as a pulmonary nodule on radiography (4). Pain is uncommon. Cure is by surgical removal.

Mediastinal Tumors. Various benign and malignant tumors and cysts occur within the mediastinum. Although one-third to one- half of these tumors are asymptomatic, found on routine chest radiography, the remainder produce chest pain or tightness, dyspnea, hoarseness, general malaise, anorexia and cachexia, and other symptoms and signs secondary to compression of mediastinal structures. Severity and character of the manifestations are related to tumor size and location

(44,52,53). Mediastinal tumors produce a wide variety of systemic syndromes, many due to ectopic hormone secretion (Table 64-6A and B, Fig. 64-5 and Fig. 64-6).

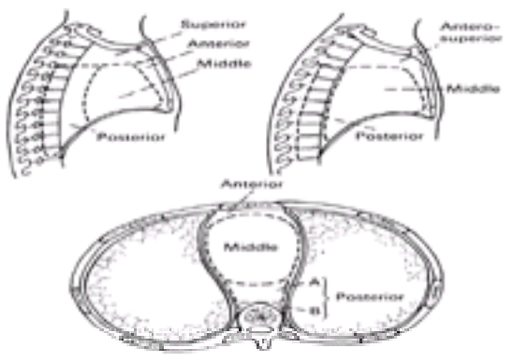

Figure 64-5. **A,B:** Two different classifications of the compartments of the mediastinum. **C:** Cross-section showing the compartment including the posterior compartment as classified in **A** and **B**.

TABLE 64-6A. Symptoms and signs of mediastinal tumors

Type of tumor	Incidence (%)
Neurogenic tumor	21
Thymoma	19
Lymphoma	13
Germ cell neoplasm	10
Primary carcinoma	5
Mesenchymal tumor	6
Endocrine tumor	6
Other	3
Cysts	18
Pericardial	6
Bronchogenic	6
Enteric	2
Other	4

Adapted from Davis RD Jr, Sabiston DC Jr. The mediastinum. In: Sabiston DC, Jr, Lyerly HK, eds. Textbook of surgery: the biological basis of modern surgical procedures. Philadelphia: WB Saunders, 1997:1905–1942.

TABLE 64-6B. Type and incidence of primary mediastinal tumors and cysts

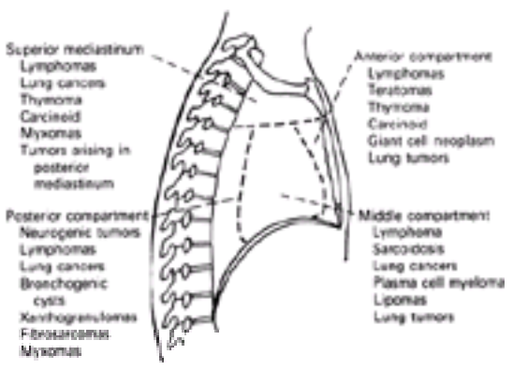

Figure 64-6. Locations of the most frequently occurring mediastinal neoplasms.

Cancer of the Breast

Basic Considerations

Breast malignancies arise from the epithelial cells lining the ducts or lobules of the breast and are the most common cancer in women, exclusive of skin cancers (54). Malignant breast disease accounts for approximately 30% of all new cancer cases and a little more than 15% of all cancer-related deaths in women each year; it occurs in more than twice as many women as lung cancer, although lung cancer now causes more deaths annually (1) (see Table 64-1). Mammography is the only reliable test for detecting nonpalpable early breast cancer, at which time 90% are curable (55). Approximately 75% of women with newly diagnosed breast cancer have no identifiable risk factors, the most obvious of which is age; there is a straight line increase in incidence with every year of life until menopause, at which time the incidence slope begins to decrease (54,56). The genetics of breast cancer is a topic of intense inquiry (57), but only approximately 10% currently are linked directly to genetic mutations (54). No proof exists that environmental factors, including diet, play a major role and, although administration of exogenous estrogen has long been thought to contribute to breast cancer risks, evidence is still inconclusive (58,59 and 60). The endogenous hormone-dependent nature of the disease, however, is clear; early menarche, delayed first full-term pregnancy, and late menopause (natural or surgical) are major factors. There is consensus that ". . . length of menstrual life—particularly the fraction occurring before the first full-term pregnancy—is a substantial component of the total risk (and) can account for 70–80% of the variation in breast cancer frequencies in different countries" (54).

Infiltrating ductal carcinomas comprise the vast majority of invasive breast cancers (approximately 70% to 75%), while medullary carcinomas, lobular carcinomas, and mucin-producing tumors each account for 3% to 6% of breast cancers. Worth special mention are two cutaneous manifestations, Paget's disease, occurring in 1% to 4% of all patients with breast cancer, and inflammatory breast cancer, characterized clinically by skin redness and warmth with an erysipeloid margin on the underlying skin (54,61).

Management of primary cancers localized to the breast or regional lymph nodes has changed since the mid-1980s. Many randomized, controlled clinical trials have demonstrated that breast-conserving surgery (i.e., lumpectomy) is as effective, based on 10-year survival, as more extensive procedures such as mastectomy or

modified radical mastectomy. Adjuvant radiation may reduce rates of local or regional recurrence and is indicated for women with high-risk primary tumors (positive margins, positive nodes). Breast-conserving surgery is not appropriate for large tumors, tumors involving the nipple-areolar complex, intraductal cancers involving multiple quadrants, for women with collagen vascular disease, for women who lack motivation for breast conservation, or in those cases where adjuvant radiotherapy is indicated but not readily available. Systemic chemotherapy, although imperfect, is life-saving in more than one-fourth of women who would otherwise die from metastatic breast cancer (54).

The natural history of malignant breast disease remains poorly understood. Indeed, one-half of all recurrences appear more than 5 years after initial therapy, and nearly one-half of all patients treated for local disease develop, and ultimately succumb to, distant metastases, primarily soft tissue, bone, and viscera (lung and liver) (54).

Clinical Features

Breast pain is a common and highly nonspecific symptom, usually caused by a benign cyst, but it does not preclude malignancy. Failure to recognize the significance of a painful breast mass is a frequent cause of delayed diagnosis and demands careful clinical evaluation and mammography. If these are negative for cancer, the most likely explanation for breast pain is *fibrocystic* change or influence of menstrual cycle (56). Small breast malignancies rarely cause pain or other symptoms, underscoring the importance of routine mammographic screening in patients at risk. Larger tumors (greater than 2 cm in diameter), however, often are the basis for a dull aching pain, in proximity to the breast, probably caused by compression or irritation of nociceptors in the underlying soft tissues. Regional lymph node involvement can cause localized, nociceptive pain in the axilla. More important, irritation or compression of the intercostobrachial nerve or nerves of the brachial plexus causes burning neuropathic syndromes, frequently accompanied by episodic lancinating pain. Patients who neglect seeing a physician can present with necrosis and ulceration of the skin and deeper tissues of the breast associated with a severe burning and aching pain that is predominantly in the affected region, but that can radiate to the anterior chest and axilla.

Metastases to bone and various viscera are associated with pain and other symptoms and signs, depending on the site. Of particular importance are metastases to the ribs, which produce localized chest pain frequently associated with intercostal neuralgia, and metastases to the vertebral column, which often produce localized back pain or signs and symptoms of spinal cord compression. Radicular pain also occurs with metastatic vertebral fracture and sudden compression of the spinal nerves. Invasion of the brachial plexus results in metastatic brachial plexopathy.

Postmastectomy Pain Syndrome. Postmastectomy pain syndrome consists of persistent pain in the anterior chest, axilla, and medial and posterior parts of the arm that follows any surgical procedure on the breast. It can occur after a relatively simple procedure, such as lumpectomy, but more commonly occurs following radical procedures, especially those involving extensive axillary node dissection. Onset varies from 2 weeks to 6 months after operation and has a reported incidence from 5% to 20% (62,63). The syndrome develops from damage to the intercostobrachial nerve, which is a branch of the second intercostal nerve, with frequent contribution also from the third intercostal nerve. Radical mastectomy can also damage cutaneous branches of the fourth and fifth nerves. Postmastectomy pain syndrome occurs more frequently in patients who have had postoperative complications, such as wound infection or fluid retention (62,64,65).

The pain of postmastectomy syndrome is tight, constricting, and burning, often associated with bouts of lancinating pain, paresthesia, dysesthesia, hyperpathia, hypesthesia, and hyperesthesia in the distribution of the injured nerves. Movement of the arm exacerbates the pain; immobilization relieves pain but enhances lymphedema of the arm due to impaired venous return, making movement even more uncomfortable. Sometimes the allodynia and hyperesthesia are so intense that even contact with undergarments triggers pain. Without adequate pain relief and active physical therapy, patients are at risk for a variety of upper extremity problems, including frozen shoulder and varying manifestations of chronic nociceptive and neuropathic pain syndromes. To preserve upper extremity function, posterior multidermatomal intercostal nerve block, thoracic paravertebral block, or epidural analgesia may be necessary, the same techniques used for postthoracotomy pain syndrome (47).

Brachial Plexopathy. Brachial plexopathy in breast cancer is more likely to be radiation induced than the brachial plexopathies associated with lung cancers, which tend to be from metastatic disease (see previous discussion). Treatment is as for other radiation-induced plexopathies or those associated with tumor invasion (see Chapter 36).

Phantom Breast Pain. Phantom breast syndrome (PBS) is a significant problem after radical or modified mastectomy, occurring in one-fourth to one-half of women undergoing such procedures (66,67,68,69 and 70). PBS can be painful, can manifest as itch, or can be a nonpainful sensation that the missing breast is still present. PBS typically develops within 3 months after surgery, with duration varying from a few seconds to a few minutes (70).

Studies suggest that psychosocial factors, such as poor emotional support from the surgeon, damaged body image, impaired sexual function, and occupation outside the home, may be important risk factors for development of PBS (66,67); at operation, women who later develop PBS tend to be younger and premenopausal with children, and have a history of preoperative breast sensations including pain (69,70). External radiation, iridium implantation, adjuvant chemotherapy, site, side, and even extent of surgery seem to play little role in the development of PBS (66,68,69).

NONNEOPLASTIC CHEST DISEASE

The number and variety of pain disorders in the chest are huge. Lesions or diseases of the upper six segments of the thoracic spinal cord; pathology that affects the rootlets, roots, or short formed nerve trunks of the upper six spinal nerves; or lesions and diseases limited to the anterior primary division of these nerves, referred to as the *thoracic intercostal nerves*, can cause chest pain. If the pathologic process affects the lower six segments of the thoracic spinal cord or the rootlets, roots, or formed nerve, the pain distributes in the affected segments of the abdomen, lower thoracic and lumbar spines, and paraspinal regions. Diseases or lesions of the thoracoabdominal intercostal nerves produce pain in the anterior abdominal wall and the lateral aspect of the trunk, depending on the site of the pathologic process (Table 64-7).

TABLE 64-7. Chest pain caused by neuropathic, musculoskeletal, and other disorders

Many chest pain syndromes have characteristics not specifically related to the thorax except by accident of location. Neuropathic pain from herpes zoster in the T-4 dermatome and musculoskeletal pain from strained pectoralis muscles, for example, do not differ intrinsically from similar pathology elsewhere, except that they occur in the chest. Other chapters of this book address diagnosis and treatment of such syndromes, so it suffices here to list them without detailed discussion. Other syndromes are specific to the chest, because they relate to unique anatomic structures, are referred to the chest from extrathoracic sites, or have psychological ramifications; these are worthy of more extensive description.

Chest Pain of Neuropathic Origin

Virtually any process that impinges on or damages nerves that distribute to the thorax results in neuropathic pain in the chest (Table 64-8). Thoracic myelopathy,

radiculopathy, neuropathy, and intercostal neuralgia belong in the differential diagnosis of chest pain without an obvious visceral etiology.

TABLE 64-8. Chest pain primarily of neuropathic origin

Thoracic Myelopathy

Contrary to general belief, disorders of the spinal cord are common causes of pain in the chest as well as in the abdomen and back. The lesion or disease can be intrinsic within the spinal cord, extramedullary but within the meninges, located in the epidural space, or a combination of these (see Chapter 60).

Radiculopathy and Neuropathy (Segmental Neuralgia)

Irritation of sensory (dorsal) rootlets or roots produces radiculalgia. Neuropathy of the short formed thoracic spinal nerves before they divide and form the primary anterior and posterior divisions produces segmental neuralgia. Patients experience discomfort in the skin and subcutaneous tissue supplied by part or all of the affected nerve(s); usually it has a sharp burning or constricting quality, sometimes accompanied by brief bouts of stabbing or lancinating pain. Often the pain is worse at night. Movements of the thoracic spine (twisting and bending) and changes in intraspinal pressure from coughing, sneezing, or straining exacerbate the pain. Hyperalgesia, hyperesthesia, and hyperpathia of the affected segments usually accompany the pain. The extensive overlap of adjacent thoracic spinal nerves can make clinical demonstration of sensory loss impossible; involvement of several contiguous roots allows the careful practitioner to demonstrate hypesthesia in the dermatome(s) in the middle of the band of hyperalgesia.

Intercostal and Peripheral Neuropathy

Trauma, surgery, infection, and compression can injure one or more intercostal nerves. Postthoracotomy and postmastectomy syndromes (discussed previously) are specific examples of such conditions.

The intercostal nerves, in their positions immediately inferior to each rib, are vulnerable to rib trauma. Fracture of a rib can cause injury to the subjacent nerve, followed by a sharp superficial burning pain in its distribution. Respirations or movements of the rib cage aggravate the pain and mimic pleurisy. There is not much sensory deficit unless there is injury at several contiguous levels because there is significant overlap of the intercostal nerves. Palpation usually elicits superficial and deep tenderness, particularly over the site of the rib fracture. If the fracture becomes displaced, it can lacerate the pleura and damage the lung.

When the history and physical examination reveal evidence of chest wall trauma, it is easy to make the diagnosis. If the trauma is remote and forgotten, the examiner will not be able to elicit rib tenderness and the diagnosis can be extremely difficult. In such cases, an appropriately located fracture line or rib callus on chest radiography can aid in diagnosis.

Systemic analgesics usually suffice for pain management, but patients with severe intercostal neuralgia may benefit from posterior intercostal block with a long-acting local anesthetic, such as 0.25% to 0.50% bupivacaine.

Chest Pain of Musculoskeletal Origin

Musculoskeletal conditions cause at least 10% of all cases of noncardiac chest pain (71). In patients with chest pain and angiographically normal coronary arteries (less than 30% stenosis in all arteries), the incidence of musculoskeletal disorders is much higher, in the 40% to 70% range (72,73). Table 64-9) lists the most important musculoskeletal disorders that produce pain in the chest. Arthritis of the rib articulations with sternum and thoracic spine, chest wall trauma, benign overuse myalgia, and fibrositis are some of the most common syndromes (74), as well as myofascial pain syndromes. More general discussion of muscular pain syndromes, including those of the spine, is found in Chapter 28 and Chapter 29. The discussion here focuses primarily on the skeletal structures unique to the chest (i.e., ribs, costal cartilages, and the sternum) (Fig. 64-7).

TABLE 64-9. Chest pain primarily of musculoskeletal origin

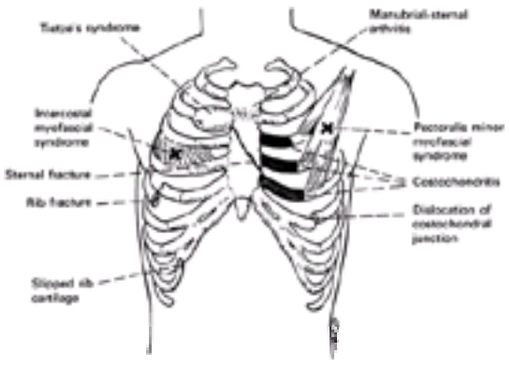

Figure 64-7. Schematic diagram of the chest showing some of the most important musculoskeletal disorders that cause chest pain.

Pain Associated with Disorders of the Ribs

Costovertebral Arthritis. Arthritis of the costovertebral and costotransverse joints is uncommon, but may be associated with osteoarthritis, ankylosing spondylitis, and, infrequently, other arthritides. Deep breathing, coughing, or direct compression of the chest typically makes the pain worse (74). The anatomic characteristics and increased mobility of the first, eleventh, and twelfth costovertebral joints make them more susceptible to degenerative changes than other levels. Rarely, arthritis of the first costovertebral joint causes thoracic outlet syndrome (75).

Rib Trauma and Fractures. Fracture of one or more ribs is one of the most common causes of acute musculoskeletal chest pain. In most cases, fractures result from direct trauma, but they can also occur as so-called tussive fracture during severe paroxysms of coughing, a condition first described in 1773 (76). Patients with severe osteoporosis or metastatic cancer may experience spontaneous rib fracture.

Several investigators have shown that epidural analgesia is more effective, and may result in better outcome, than systemic opioids for treatment of rib fracture after major trauma (77,78 and 79). The optimum combination of epidural local anesthetic and opioid is unknown, and the superiority of epidural over other intrapleural or extrapleural regional techniques remains to be seen (80,81, and 82). In chest wall trauma with less than three ribs involved, there is no evidence to suggest that epidural techniques are superior to carefully titrated systemic analgesia.

Rib trauma without fracture is fairly common, resulting in point tenderness and occasionally local swelling at the site of injury. Movement, deep breathing, and cough aggravate the pain, and radiographs are normal. Metastatic disease from lung, breast, prostate, and other solid tumors may present as isolated rib swelling and tenderness. Radiographs and other imaging techniques confirm the presence of bony pathology (see Fig. 64-7).

Slipping Rib Syndrome. Davies-Colley first described the slipping rib syndrome in 1922 (83). Other names for the syndrome include clicking rib, rib gliding, rib-tip syndrome, slipping rib cartilage, displaced ribs, and nerve nipping at the costal margin. The syndrome, thought to be of traumatic origin, is characterized by chest or abdominal pain at the costal margin due to irritation of the intercostal nerve. It is associated with increased mobility of the sternal tip of the costal cartilage, most often of the tenth rib, but occasionally that of the eighth and ninth ribs. The syndrome occurs most often in middle-aged adults, equally in men and women, and with no predilection for either side; uncommonly, there is bilateral pathology (84). It is an unusual cause of pain in children (85,86).

The upper seven ribs articulate directly with the sternum by their respective cartilages, but the cartilages of the eighth, ninth, and tenth ribs articulate with the cartilage above by endochondral synovial membrane surrounded by fibrous tissue; this is the weakest point in the chest, particularly vulnerable to trauma (see Fig. 64-7). Injury in the area can cause separation of the costal cartilages, following which the cartilaginous ends curl upward, creating an up and down slipping with respiration or other chest movement. The rib can also slip anteriorly and posteriorly over the border of the upper cartilage, with a click and pain that are diagnostic.

The *hooking maneuver* is the pathognomonic test (87). The examiner places curled fingers under the inferior rib margin and pulls anteriorly. A positive test produces a clicking noise and exacerbates the pain. The same maneuver on the contralateral side, except in the rare instances of bilateral slipping rib, is negative. Infiltration of local anesthetic (e.g., 5 mL of 0.5% lidocaine) into the space between the detached cartilage and rib renders the hooking maneuver painless.

Conservative treatment of slipping rib syndrome consists of reassurance and nonopioid systemic analgesics. Serial injection of the painful site with local anesthetic plus corticosteroid often provides prolonged relief. Surgical excision of the affected rib and costal cartilage is a reasonable alternative in those patients who do not respond to conservative measures (88,89).

Tietze's Syndrome. This syndrome, first described by Tietze in 1921 (90), consists of a nonspecific, benign, self-limiting, nonsuppurative, painful swelling of the costal cartilages, most often the second and occasionally the third. The swelling can progress to an irregular mass that obliterates the adjacent intercostal spaces. True Tietze's syndrome is a relatively rare condition affecting young people (including children), with a predilection for those in their second and third decades without preponderance of either gender. The causes are unknown, but rheumatic conditions often precede the onset of chest pain (91) and respiratory straining, such as severe cough, heavy manual work, and deficient nutrition, have been suggested as causative factors (92).

There is isolated involvement of the second costochondral junction in 60% of patients with Tietze's syndrome (93). Involvement of the chondrosternal, manubriosternal, sternoclavicular, and xiphisternal articulations is less frequent. Lesions are unilateral and single in more than 80% of patients (94). The disorder usually runs a self-limited course of remissions and exacerbations (90,91,94,95 and 96). The pain can cease spontaneously within 2 to 3 weeks, but not infrequently it lasts months, and the residual swelling can persist for much longer, even several years (92).

The predominant symptom of Tietze's syndrome is pain of variable intensity in the anterior chest wall. It is usually localized to the involved synchondrosis but can radiate widely over the anterior chest wall, occasionally to the shoulder and neck. In some patients the pain is similar to that produced by a heavy weight pressing on the chest, reminiscent of cardiac or esophageal pathology, but in others it is a vague soreness or tightness. Coughing, deep breathing, and lying prone typically aggravate the pain. Tenderness and swelling are present in the affected costal cartilage(s), but the overlying skin shows no alteration and moves freely over the tender bulbous or fusiform swelling. Heat, erythema, and constitutional symptoms are absent.

Careful history and thorough examination of the chest and exclusion of other conditions affecting the costal cartilages, such as rheumatoid arthritis, pyogenic arthritis, tumors, and relapsing polychondritis, make the diagnosis (97). Although plain radiographs are normal, x-ray tomography may be a useful confirmatory examination (98,99). Bone scan may show abnormal accumulation of radionuclide at the involved costochondral joint, but is nonspecific, as this is also found in costochondritis (93). Laboratory tests may exclude other conditions but are not helpful in diagnosing this syndrome.

Costochondritis (Anterior Chest Wall Syndrome). Costochondritis, also called *anterior chest wall syndrome*, *chest wall syndrome*, *costosternal syndrome*, and *costosternal chondrodynia* (100,102,103 and 104), is a relatively frequent cause of anterior chest pain, both as a primary condition and in combination with coronary artery disease. It simulates cardiac pain and thus is a great source of confusion and concern among clinicians; its etiology is unknown.

Pain of the anterior chest wall that often radiates widely, sometimes into the back and abdomen, is the primary characteristic of costochondritis. Palpation of the affected portions of the thoracic cage elicits local tenderness at multiple sites and also reproduces radiation of the pain. In contrast to Tietze's syndrome, in which only one level is involved in 80% of patients, multiple sites are present in 90% of patients with costochondritis. The second to fifth costal cartilages are most frequently affected (94,100). Usually, the pain and tenderness are located more easily than with Tietze's syndrome and, in contrast to Tietze's syndrome, no local swelling is present. The condition occurs more frequently in women (a ratio of 3:1) and at a later age in life (two-thirds of patients are over the age of 40). Respiratory symptoms occur only in approximately 12% of patients with costochondritis, as compared with approximately 85% of those with Tietze's syndrome. Movement of the chest and body can frequently aggravate the pain (Table 64-10).

Feature	Tietze's syndrome	Costochondritis
Frequency	Rare	More common
Age group most commonly affected	<40 yr	≥40 yr
Number of sites affected	One in 80%	More than one in 90%
Costochondral junctions most commonly involved	Second (occasionally third)	Second to fifth
Local swelling	Present	Absent
Associated conditions	Respiratory tract infections	Cervical strain syndrome, coronary artery disease, myofascial syndrome

Modified from Fam AG, Smythe HA. Musculoskeletal chest wall pain. CMAJ 1980;122:379–88.

TABLE 64-10. Tietze's syndrome and costochondritis

Inflammation of the upper costal cartilages can cause intense chest pain that clinicians often mistake for that of cardiac disease, initiating referral to a cardiologist (100,104). When the condition involves the lower costal cartilages, the pain is in the upper abdomen, which may prompt referral to a gastroenterologist (105).

This condition is important in causing chest or abdominal pain in adolescents. In a study of 100 patients in an adolescent outpatient clinic who complained of chest or upper abdominal pain, 79 had only tender costal cartilages. In this group the pain usually was located in the anterior chest, but in a number of patients, it radiated to the back and abdomen. The condition was more often unilateral than bilateral, affecting the left side more often than the right side, the left fourth sternocostal cartilage being most frequently involved. A simple program of mild analgesics and reassurance was sufficient treatment for all patients (106).

Comprehensive history and physical examination, including complete neurologic and musculoskeletal evaluation, are essential in making the diagnosis of costochondritis, because this syndrome can mimic more serious conditions in the chest and abdomen. Several maneuvers reproduce pain similar in quality and location to the spontaneous pain and are useful in establishing the diagnosis of anterior chest wall syndrome (105). Firm, steady pressure applied to the sternum and to the left and right parasternal junctions, the intercostal spaces, the ribs, the inframammary area, and the entire pectoralis major muscle elicits the pain of costochondritis. The *horizontal flexion test* consists of having the arm flexed across the anterior chest and applying steady prolonged traction in a horizontal direction, while at the same time the patient's head is rotated as far as possible toward the ipsilateral shoulder. The *crowing rooster maneuver* involves having the patient extend the neck as much as possible by looking toward the ceiling while the clinician, standing behind the patient, exerts traction on the posteriorly extended arms (105). Epstein and coworkers used radionuclide cineangiography performed at rest and during symptom-limited exercise to visualize regional wall motion abnormalities in the heart. Eleven of the 12 patients studied experienced pain at rest, and eight had episodes of pain that awakened them from sleep. One patient with isolated chest wall syndrome described what was considered to be classic angina pectoris. All patients had chest wall tenderness, the location of which is shown in Figure 64-8. The most common site of tenderness was the left parasternal region, followed by the inframammary region, the left pectoral muscles, including their insertions, and the sternum. Of the 12 patients, 11 had a positive horizontal flexion test and four had a positive crowing rooster test. All patients with the chest wall syndrome had a normal ejection fraction and normal regional wall motion at rest and during exercise. The investigators concluded that the radionuclide cineangiographic test, which is invariably positive in patients with coronary artery disease, is a sensitive method for differentiating between anterior chest wall syndrome and cardiac pathology (105).

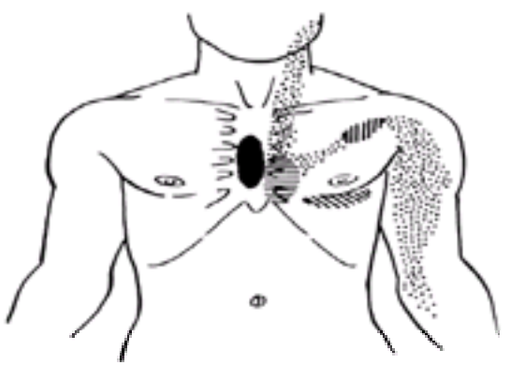

Figure 64-8. Pattern of pain in patients with anterior chest wall syndrome showing the regions in the anterior chest in which spontaneous pain was most frequently experienced and where tenderness could be elicited. The black and striped areas represent primary sites of pain and of tenderness and the stippled areas represent radiation of the pain. (Modified from Epstein SE, Gerber LH, Borer IS. Chest wall syndrome: a common cause of unexplained cardiac pain. *JAMA* 1979;241:2793–2797.)

In patients who have the chest wall syndrome in association with organic heart disease, the characteristics of the pain and tenderness also help in differentiating between the two conditions (see Fig. 64-8). In most patients with anterior chest wall syndrome, the pain is localized mainly in the precordium or the left parasternal region, usually at the level of the left third or fourth intercostal space, and often radiating superiorly toward the left shoulder and down the left arm, characteristics that differ from the more generalized pain of myocardial ischemia. Moreover, the pain usually occurs at rest and lasts for many minutes to hours, which also distinguishes it from pain of cardiac origin. In the relatively small percentage of patients in whom the pain is indistinguishable from that of typical angina pectoris caused by coronary disease, careful questioning often discloses that the pain has atypical precipitating features more closely related to postural changes and to stresses imposed on chest wall structures than to physical exertion *per se*. Although the prompt pain-relieving effect of nitroglycerin is usually considered good evidence that the pain is a result of myocardial ischemia, some patients with chest wall pain and no evidence of any organic heart disease have reported relief after taking sublingual nitrate.

The most critical finding establishing the diagnosis of chest wall syndrome is the detection of chest wall tenderness on physical examination, which is present in all patients. Tenderness located in the region of origin of spontaneous pain, particularly when the quality of the pain evoked by the physician reproduces the spontaneous pain, together with a negative radionuclide test, provides the strongest evidence of chest wall syndrome.

A highly reliable and effective differential diagnostic procedure in such patients is producing intercostal block at the posterior axillary line. This provides complete relief of pain from chest wall pathology, but has little or no effect on cardiac pain because the nociceptive pathways from the heart are in the sympathetic afferents located in the paravertebral region. Bone scintigraphy helps delineate the extent and location of costochondral lesions (107).

Treatment of costochondritis, or chest wall syndrome, consists of reassurance, the use of nonsteroidal antiinflammatory drugs (NSAIDs), alone or in combination with an opioid as needed, heat application, and other physical therapeutic measures. Reassurance that the pain is of benign origin is probably the most important intervention, thus avoiding the emotional and financial burdens often associated with an erroneous diagnosis of organic heart disease. Admission to coronary care units is common, and patients may exhibit chronic anxiety, largely because they believe the chest pain of costochondritis, particularly when it radiates into the anterior chest or even down the left arm, is a harbinger of imminent death (105). Reassurance that the pain is from a non– life-threatening condition can often lead to dramatic symptomatic improvement and rehabilitation. Intercostal block at the posterior costal margin provides complete pain relief for several hours; the procedure demonstrates to patients that the condition is in the chest wall and not from the heart (see Table 64-10).

Tumors of the Costal Cartilages. Cartilaginous tumors of the ribs are rare, usually noticed because of a growing mass rather than the onset of an obscure chest pain. Conditions such as tuberculosis, fungal abscess, gumma, malunited fractures, deformities, and Tietze's syndrome are part of the differential diagnosis. When a tumor mass is felt, diagnosis is easy. Pain can be a heavy, chronic, boring distress but may also be pleuritic in nature, referred along the course of the intercostal nerve. Surgical excision is the primary treatment.

Costochondral Dislocation. Dislocation at the costochondral junction, secondary to trauma, causes pain at the site of injury. The condition, frequently seen in people younger than 30 years of age, typically produces a continuous, dull, aching, and burning pain, with discomfort localized to an area of the costal margin and occasionally referred to the back. Sometimes the pain exhibits the sharp and lancinating character of radicular pathology. Local tenderness invariably is present, and palpation may reveal a mass probably due to accumulation of excess cartilaginous material at the site of injury. In some cases, the pain is more disabling than that associated with simple rib fracture.

Treatment consists of reduction of the dislocation with subsequent pain relief. Infiltration of the area with local anesthetic or, more effective, intercostal nerve block above and below the site of dislocation permits manipulation and reduction; the injection site may be at the anterior axillary or midclavicular line.

Chest Pain Caused by Pathology of the Sternum and Its Articulation

Trauma and Arthritis of the Sternoclavicular Joint. Pain arising from the sternoclavicular joint can radiate to the anterior chest wall simulating pain of visceral origin. The major causes of sternoclavicular joint arthritis include osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and infection (74,108,109). Infectious etiologies are diverse (108,110,111) and have been reported after subclavian vein catheterization (112) and in intravenous drug users (113). Traumatic subluxation or dislocation, as well as tumor metastases, also can cause pain in the sternoclavicular joint. Shrugging of the shoulders aggravates the pain, and

palpation of the joint elicits severe tenderness. Treatment consists of NSAIDs with or without an opioid. Infectious cases require antibiotic therapy, while noninfectious cases may respond well to local injection with anesthetic and corticosteroid.

Sternocostoclavicular Hyperostosis. Sternocostoclavicular hyperostosis (or sternoclavicular hyperostosis) is a peculiar syndrome manifested by bilateral chronic painful swelling of the clavicles, sternum, and first ribs, with associated aseptic joint destruction and arthritis. The condition frequently occurs in association with palmoplantar pustulosis, a seronegative arthrosteitis (114,115,116 and 117). Abnormalities on plain radiograph may take years to evolve despite the frequent occurrences of clinical symptoms (118). However, bone scintigraphy and computerized tomography are sensitive in the early stages of the syndrome (119,120 and 121). Previously thought to be a specific disorder of the sternoclavicular joint, studies using computed tomography suggest that the sternoclavicular joint is not primarily involved; hyperostosis develops around the costal cartilage including periosteum, perichondrium, and ligamentous structures with sparing of the sternoclavicular joint space (119). Laboratory values are usually normal except for occasional persistent elevation of erythrocyte sedimentation rate. Rarely, the syndrome involves the cervical spine and may manifest as a swelling in the neck (122,123).

Sternocostoclavicular hyperostosis follows a relapsing course; bone enlargement and extension of the inflammatory process can lead to occlusion of the subclavian vein or can cause thoracic outlet syndrome (116). Treatment is symptomatic, consisting of antiinflammatory medications, including NSAIDs and corticosteroids. In severe cases, radiotherapy may be beneficial (101).

Manubriosternal Arthritis. Arthritis of the manubriosternal joint can cause localized pain in the upper sternal region. The condition occurs in association with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, gout, and palmoplantar pustulosis (124,125,126,127,128,129 and 130). Trauma from sports injury (131) or even due to seizures (132) can predispose to arthritis in this joint. Infectious causes are rare (133,134) but intravenous drug use, as with other septic arthritides, appears to be a risk factor (135). The pain may localize to the joint or it may radiate widely along the upper ribs to the shoulders, mimicking anginal pain. Pain may be constant or intermittent (92). Motion of the chest, including deep breathing, coughing, sneezing, and yawning, aggravate the discomfort.

Diagnosis should include identification of the pathologic process. Imaging studies of the chest may be helpful (136). Treatment consists of NSAIDs, and the pain control may require opioid analgesics. In noninfectious cases, infiltration with local anesthetic and corticosteroids may provide prolonged relief.

Trauma to the Sternum. Blunt injury to the sternum can cause strain or even partial subluxation of the manubriosternal joint. At the time of or soon after injury, the patient experiences sharp pain localized to the area of the angle of Louis. Pain can also radiate into a broader area. Conservative management of simple joint sprain with systemic analgesics and the application of heat usually suffices. If the patient has severe pain, local infiltration of the joint with local anesthetic and corticosteroid produces effective relief. Occasionally, the displacement is sufficient to require surgical intervention in which case neural blockade of the intercostal nerves (at the level of the second and third ribs in the midclavicular line) provides excellent postoperative analgesia.

Xiphoidalgia Syndrome. Spontaneous pain in the anterior chest associated with discomfort and tenderness of the xiphoid process defines the xiphoidalgia syndrome. This relatively rare condition also goes by the names *painful xiphoid syndrome*, *hypersensitive xiphoid*, and *xiphoid cartilage syndrome*. Little is known about the etiology and pathophysiology of this ailment, but it sometimes occurs concomitantly with coronary artery disease, intestinal disease, arthritis, and neurologic or metabolic disorders, making diagnosis somewhat confusing when it occurs independently (92). The xiphoid receives its nerve supply from the phrenic nerves and the T-4 to T-7 intercostal nerves, so that pain is usually widespread. Typical pain is intermittent, low substernal or epigastric radiating into the precordium or abdomen, often making it difficult to distinguish from serious visceral pathology by history. However, examination reveals tenderness at the xiphoid, and palpation duplicates the pain and its radiation. Lipkin and colleagues described the pain as “a deep slightly nauseating ache, somewhat like that experienced after a blow to the celiac plexus” (137). The intensity varies considerably from an annoying, slight, aching discomfort to an agonizing pain that can be terribly frightening (92).

Movements that act on the xiphoid, such as bending, stooping, and turning, precipitate or aggravate the pain of xiphoidalgia, particularly after a full meal, which itself increases the pressure behind the xiphoid (92). Usually, exercise does not aggravate the pain, but careful questioning may be necessary to determine whether a particular movement rather than general exertion brings on the pain. Unlike many other types of chest pains, the discomfort of xiphoidalgia does not subside immediately after an aggravating movement has ceased. The frequency of pain is variable but can occur several times a day. Its duration varies from minutes to several hours, but it usually lasts for an appreciable time after it is provoked. In addition to reproducing the spontaneous pain and its radiation, externally applied pressure can cause patients to feel pain deep in the chest (retrosternal), shoulder, and back.

The disorder ordinarily persists for weeks or months, but usually disappears spontaneously without special treatment. Nonopioid systemic analgesics, with or without the addition of an appropriate opioid, control mild to moderate pain. If these prove ineffective in patients with severe pain, injection of a local anesthetic and a corticosteroid into the xiphosternal joint usually provides effective relief for hours and sometimes days. In extreme cases one could consider surgical resection, but this rarely is necessary.

Chest Pain Caused by Myofascial Pain Syndromes

Myofascial pain syndromes are discussed in Chapter 29. Myofascial pains in the chest usually develop gradually, but the occasional sudden onset may cause patients and physicians to mistake the symptoms for those of cardiac ischemia. Trauma or repetitive use of a muscle can result in a myofascial pain syndrome, which can vary from a slight ache to severe, unrelenting, and disabling discomfort. It is critical to identify myofascial pain syndromes in the patient with chest pain to avoid the emotional and financial costs of cardiac evaluation. Table 64-11) lists the various myofascial pain syndromes of the chest. Figure 64-9,Figure 64-10,Figure 64-11,Figure 64-12,Figure 64-13,Figure 64-14 and Figure 64-15 illustrate pain patterns and trigger points for various myofascial pain syndromes in the chest.

Location of pain	Muscle involved
Anterior chest	Sternalis; pectoralis major; pectoralis minor; scaleni muscle; sternocleidomastoid (sternal head); subclavius; iliocostalis cervicis
Upper thoracic back	Levator scapulae; trapezius multifidi
Midthoracic back	Latissimus dorsi; rhomboid; serratus posterior superior; trapezius serratus anterior
Low thoracic back	Serratus posterior inferior; iliocostalis thoracis multifidi

TABLE 64-11. Myofascial syndromes causing chest pain

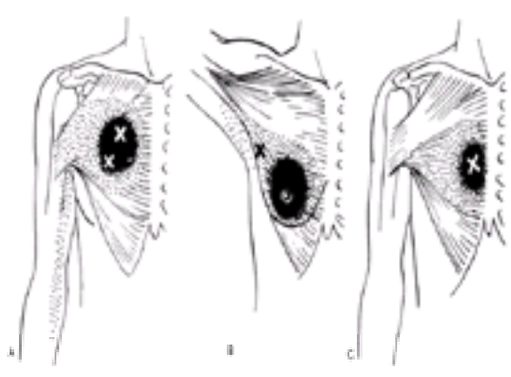

Figure 64-9. Patterns of pain provoked by trigger points in different parts of the right pectoralis major muscle. **A:** Pattern provoked by trigger points (*X*) in the intermediate sternal section of the muscle. **B:** Pain and trigger points in the lateral margin of the muscle. **C:** Trigger point (*X*) in the medial margin of the muscle. The

black area depicts the essential zone of pain, while the stippled area shows the spillover zone.

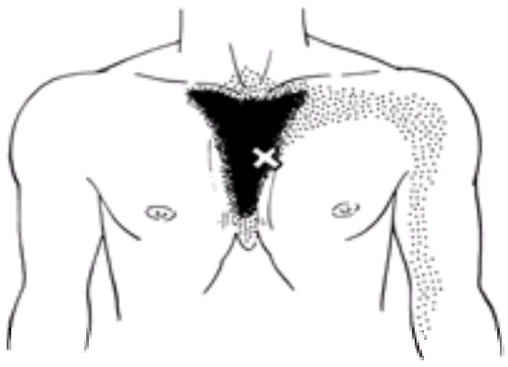

Figure 64-10. Pattern of pain and trigger point (*X*) in the sternalis muscle. See text for details.

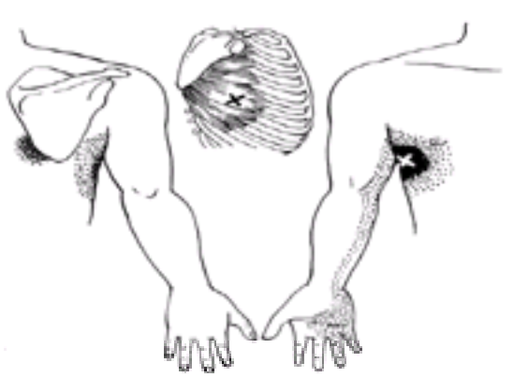

Figure 64-11. Areas of pain and sites of trigger points (*X*) of the serratus anterior myofascial syndrome. **A:** Site of trigger point. **B:** Anterior view showing pain pattern. **C:** Posterior view showing spillover zone. See text for details.

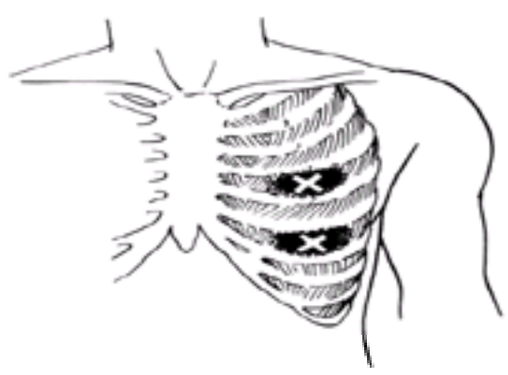

Figure 64-12. Pattern of referred pain provoked by trigger points (*X*) in the intercostal muscles. This is a frequent cause of anterior chest pain.

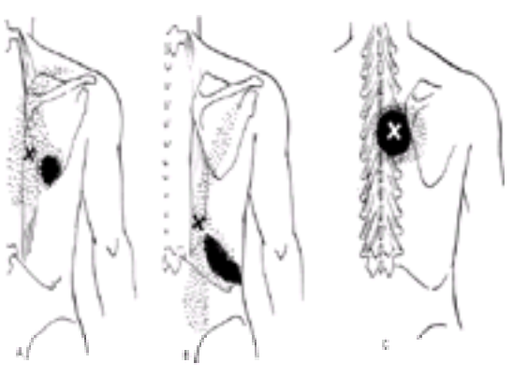

Figure 64-13. Pain patterns with their corresponding trigger points (*X*) in the iliocostalis and multifidus thoracis muscles. **A:** Trigger point in the iliocostalis muscle just medial to the medial edge of the scapula. **B:** Trigger point in the lower portion of the iliocostalis thoracis. **C:** Posterior chest pain pattern provoked by trigger point in the upper part of the multifidus thoracis muscle.

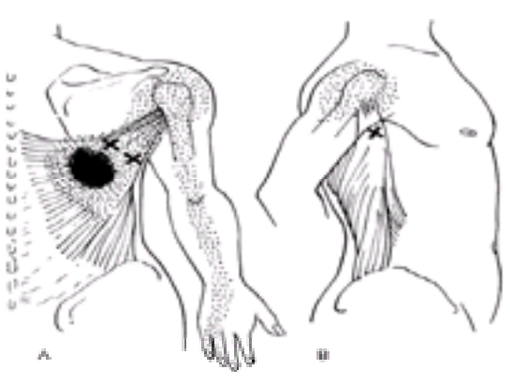

Figure 64-14. Pain in the posterior part of the chest with spillover into the shoulder and arm caused by trigger points (*X*) in the right latissimus dorsi muscle. **A:** Posterior view. **B:** Lateral view.

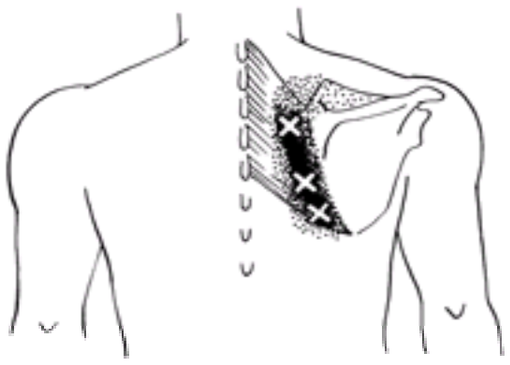

Figure 64-15. Posterior chest pain caused by trigger points in the rhomboid muscles.

Other Painful Muscular Disorders

Traumatic Muscle Strain. Trauma to muscles of the chest can cause injury to fibers throughout the entire muscle. Repeated stress or excessive muscular activity, such as lifting, painting a ceiling, chopping wood, coughing, or exercising untrained muscles may result in traumatic strain. These are the same causative factors that produce myofascial syndromes with trigger points; in some patients, however, widespread *strained* muscles may be painful and tender over their entirety. Maneuvers that tense or stretch the muscle usually make the pain worse. Careful examination of the muscle does not reveal any localized tender or trigger points but indicates generalized tenderness over the entire muscle. Treatment consists of reassurance, local application of heat or ice, use of systemic analgesics, rest of the injured muscles, and avoidance of the precipitating activities. In patients who have severe pain, infiltration of a dilute solution of a long-acting local anesthetic (e.g., 0.125% bupivacaine) throughout the muscle produces prompt pain relief.

Precordial Catch Syndrome. The precordial catch syndrome is an unusual, benign, self-limited condition that does not radiate and is characterized by sudden, brief, periapical pain. Pain occurs randomly, without warning or obvious precipitant. Onset of the syndrome usually is in adolescence or childhood in otherwise healthy individuals. The pain can occur at rest or during mild activity but does not occur on exertion (138,139,140 and 141).

The sharp stabbing pains known as *catches* or *stitches* typically are in the anterior chest wall, usually in the left parasternal area or near the cardiac apex. Duration is from 30 seconds to 3 minutes. Some patients report the onset of pain while slouching or bending over. Deep breathing aggravates the pain, and shallow breathing provides relief. Moderate activity and correct posture may also relieve the catch. No local tenderness is associated, such as that with most other chest wall pain syndromes.

The cause is unknown. Treatment consists of reassurance. The unpredictability, short duration, and benign nature of precordial catch syndrome make analgesics unnecessary and ineffective.

Chest Pain Caused by Diseases of the Mediastinum

In addition to the tumors discussed previously in this chapter, two other mediastinal disorders deserve mention, mediastinal emphysema and mediastinitis.

Mediastinal Emphysema

Air within the planes of the mediastinum can appear spontaneously or can be secondary to chest trauma; perforation of the esophagus, trachea, or bronchus; or spread from fascial planes of the nasopharynx or dissection from the retroperitoneal space. Spontaneous mediastinal emphysema or spontaneous pneumomediastinum occurs with no apparent cause. Air probably dissects from the alveoli to the interstitial space into the vascular adventitia and into the hilum, from where it moves into the mediastinum, neck, or retroperitoneal space.

If the volume of air reaching the mediastinum is small, the resulting pain can be severe while other physiologic disturbances might be minimal. Occasionally, the condition is self-limited, with spontaneous recovery. When great volumes of air accumulate, as in what Wehrmacher (92) called “malignant mediastinal emphysema,” profound physiologic disturbances result. Compression of the great veins to the heart causes circulatory shock, impaired gas exchange across the alveoli, and cardiovascular collapse that can progress to death if there is not prompt intervention to relieve increased mediastinal pressure.

Spontaneous pneumothorax produces rather sudden onset of pain in the absence of effort while the patient is quietly standing, sitting, or lying. The pain usually begins beneath the sternum and sometimes radiates to the back, neck, or shoulders, but rarely to the arms. Physical examination can reveal subcutaneous crepitus in the upper body, and one can often hear a crunching sound over the precordium synchronous with the heartbeat (Hamman's sign). Fever and mild leukocytosis are common with uncomplicated mediastinal emphysema.

A radiograph of the chest in a patient with spontaneous mediastinal emphysema demonstrates air in the mediastinum and usually a small pneumothorax. It is much more difficult to demonstrate mediastinal air than pneumothorax; identification usually is easiest along the pleural line parallel to the left heart border on films made during full expiration (92).

Therapy for the benign type of mediastinal emphysema is purely symptomatic, but for malignant emphysema, surgical drainage of the mediastinum is essential to release the entrapped air. Oxygen therapy might be necessary to relieve dyspnea and cyanosis. Systemic analgesics or thoracic epidural and sedatives control the pain; appropriate monitoring of the patient is essential to detect any adverse side effects.

Mediastinitis

Acute mediastinitis occurs as an extension from a mediastinal lymphadenitis secondary to pulmonary or pleural infections, from inflamed neighboring structures, such as sternotomy incision, or from rupture of the esophagus or trachea. The infection can be nonsuppurative, phlegmonous, or suppurative, and an abscess can result. Wehrmacher described a rather peculiar chronic cicatrizing mediastinitis of uncertain origin that manifests extensive fibrosis with retraction and displacement of various mediastinal structures (92).

The usual symptoms of acute mediastinitis are those referable to the underlying infection. Rupture of the esophagus usually produces severe, excruciating, retrosternal pain simulating that of acute myocardial infarction. Esophageal perforation is a surgical emergency. Esophageal diseases are discussed in Chapter 63.

Systemic manifestations often overshadow other causes of mediastinitis. Treatment varies according to the cause of mediastinitis but invariably requires antibacterial therapy. Pain management is contingent on the severity of the pain, usually requiring systemic opioids.

Chest Pain Caused by Disorders of the Diaphragm

The diaphragm can be the site of inflammatory diseases, tumors, hemorrhage, edema, and degeneration. Previous chapters have discussed the various causes of pleuritis involving the diaphragmatic pleura, including viral infection (pleurodynia) and other infectious processes involving the thoracic viscera, diaphragmatic hernia, and many causes of diaphragmatic peritonitis. Here, the discussion focuses on three conditions: acute primary diaphragmatitis, sustained diaphragmatic spasm, and diaphragmatic flutter.

Acute Primary Diaphragmatitis

Acute primary diaphragmatitis, also known as *Heddron's syndrome*, is manifested by moderate to severe pain in the lower chest, upper abdomen, and shoulder. The

cause of this condition is unknown, but some (92) have suggested that it can follow chilling or acute nasopharyngeal infection and is attributed to a primary myositis of the diaphragm, bearing no relationship to lesions of the pleura, lungs, or subphrenic organs.

Clinically, the pain limits the respiratory effort beyond a fixed depth, invariably with spasm of the abdominal muscle below the costal margin, associated with pain in the upper quadrants but no deep tenderness. The costal margins flare and remain relatively immobile; fluoroscopy shows the diaphragm to be immobilized in midposition during the acute phase. As the myositis subsides and fibrous tissue replaces the muscles, flattening of the diaphragm persists. Symptoms usually subside within 1 or 2 weeks, but can recur during inclement weather (92). Treatment of this condition is symptomatic and should include encouragement, reassurance, and effective pain control with systemic analgesics.

Sustained Spasm of the Diaphragm

Rare cases of persistent contraction of the diaphragm can cause chest pain (92). In each instance, a characteristic disorder of diaphragmatic function is demonstrable by fluoroscopic observation: Inspiration becomes jerky, and the excursion of the diaphragm during inspiration is extended, so that during expiration the structure assumes a progressively lower position. When the state of contracture of the diaphragm is such that adequate respiratory excursions are no longer possible, dyspnea occurs, with the feeling of inability to take a breath. During attacks of sustained diaphragmatic contractions, patients experience pain in the pericardium or elsewhere in the chest, with radiation to the shoulder. In some cases, pallor, sweating, hypotension, and angor animi, simulating that of acute myocardial infarction, accompany the attacks. In others, diaphragmatic spasm causes occlusion of the esophagus, with consequent dysphagia and odynophagia.

Such patients require a thorough workup to exclude severe thoracic visceral disorders. Because emotional conflicts may provoke attacks, psychological management is especially important. If patients have severe dyspnea, supplementary oxygen is helpful. Pain control is with systemic analgesics. In patients who have severe contraction, unilateral or bilateral phrenic nerve blocks might be necessary to relieve the spasm.

Diaphragmatic Flutter

Diaphragmatic flutter is a rare but disturbing cause of chest pain that usually escapes recognition for a long time. The cause of the condition is frequently unknown, but some have reported it to be precipitated by excitement, emotional tension, severe cough, pressure on the upper abdomen, exercise, and sneezing. Deep inspiration, swallowing, or supraclavicular pressure sometimes can suppress symptoms, as can a period of natural sleep (92).

Diaphragmatic flutter causes pain in the chest, shortness of breath, and palpitations. The pain occurs along the diaphragmatic attachment, in the epigastrium, and over the precordium, and radiates into the neck, shoulder, and down the arm. Clocklike sounds and plethysmographic oscillation at the base of the lung as visualized by fluoroscopy demonstrate the rapid movement of the diaphragm.

Management should be conservative for patients in whom the condition does not cause significant emotional or physiologic disturbances. In those in whom the condition persists, or does cause severe emotional and physiologic disturbances, injection of 5 to 10 mL of local anesthetic on the anterior surface of the scalenus anticus establishes a phrenic nerve block. Unilateral block may be sufficient, but occasionally bilateral block is indicated. If effective, and if the patient has no respiratory difficulties, one should consider a continuous infusion block.

Chest Pain of Tegumentary Origin

Table 64-7 lists a number of skin disorders that can cause chest pain, including burns and scars. This section describes three rather unusual conditions that one should consider in the differential diagnosis of chest pain.

Idiopathic Chronic Mastalgia

Chronic severe pain in the entire breast that persists for years without a demonstrable cause characterizes idiopathic mastalgia. Onset is typically in the third or early fourth decade of life. Although many clinicians believe the condition has a psychological basis, clinical reports reveal no emotional or psychological abnormality (142,143). Pain can be unilateral or bilateral and is usually cyclical, but upward of 25% of women experience noncyclic pain (144,145 and 146). Approximately 85% of women respond to adequate reassurance, but 10% to 20% of patients require medical therapy (147). A hormonal event such as menopause, pregnancy, or use of oral contraceptives often provides relief (146). Treatment with danazol appears to be the most effective therapy, followed by bromocriptine, tamoxifen, and evening primrose oil (145,148,149 and 150). Cyclical mastalgia responds better to drug treatment than does the noncyclic variety (147,148,151).

Adiposis Dolorosa (Dercum's Disease)

In 1892 Dercum described a syndrome characterized by painful subcutaneous fatty tumors in various parts of the body, especially the lower extremities (152). If present in the breast, adiposis dolorosa can cause long-term pain. No truly satisfactory treatment exists for this condition, but reports suggest that intravenous lidocaine, oral mexiletine, and liposuction may offer relief (153,154 and 155).

Mondor's Disease

Mondor's disease is a form of phlebitis of the anterior lateral chest usually due to thrombosis of the superficial vein of the thoracic wall, primarily affecting middle-aged women with pendulous breasts (92,156,157 and 158). Intravenous drug use is another risk factor (159). Typically there is a palpable painful cord within the skin. Many practicing physicians are unaware of this condition, leading to considerable patient anxiety, especially when it involves the breast (160).

The initial inflammatory phase consists of the rather sudden appearance of a painful, tender, subcutaneous cord running somewhat obliquely across the thorax in the distribution of one or more of the superficial subcutaneous veins. The cord can be linear or Y-shaped, corresponding to the linear or branching course of the affected vein. During the inflammatory phase the lesion can grow as if a worm were crawling beneath the skin (92). After the initial inflammatory phase, usually lasting several weeks, an indolent phase follows with little or no discomfort, and only the palpable cord, extending like a catheter beneath the skin, remains as evidence of the disorder.

Laboratory studies are of little value, although the eosinophils in the peripheral blood might be slightly increased. Biopsy usually reveals a white indurated cord that macroscopically appears as a small caliber vessel.

The most important feature in the management of this disorder is its recognition so that the patient can be spared unnecessary anxiety and apprehension. The disease is self-limited and requires nothing more than symptomatic relief of the pain with systemic analgesics, including NSAIDs (161).

Referred Chest Pain from Extrathoracic Disorders

Many diseases or lesions outside the thoracic cavity can refer pain to the chest. Included are disorders of the neck, cervical disk syndromes, thoracic outlet syndrome, and disorders of the abdominal viscera. These conditions are discussed in greater detail in Chapter 54, Chapter 55, Chapter 56 and Chapter 57 and Chapter 65, Chapter 66, Chapter 67, Chapter 68 and Chapter 69; brief comments relevant to the chest follow here.

Cervical Disk Disease

Herniation of intervertebral disks in the lower part of the cervical spine can cause pain in the anterior upper part of the chest. Cervical roots C-5 to C-7 form the lateral and C-8 to T-1 form the medial pectoral nerves that supply the pectoral muscles and fascia. Posterolateral herniation of a cervical intervertebral disk causes anterior chest pain that is deep, aching, steady, and, at times, severe. The pectoral muscles can be tender when they are the seat of the referred pain and there is almost always referred pain in the shoulder and upper limb. Coughing, sneezing, straining, and lateral flexion to the affected side aggravate the pain (see Chapter 56).

Thoracic Outlet Syndrome

In addition to neurovascular conditions in the upper extremity, thoracic outlet syndromes can refer pain to the chest. Careful history and physical examination allow the diagnosis to be made (see Chapter 55).

Disorders of the Abdominal Viscera

Gas entrapment syndromes, biliary tract disease, pancreatitis, peptic ulcer disease, tumors of the gastric cardia, subphrenic abscess, hepatic abscess, enlarged spleen, and a variety of other disorders of abdominal visceral can give rise to pain in the chest. These are discussed in Chapter 65, Chapter 66, Chapter 67, Chapter 68 and Chapter 69.

Chest Pain and Psychological Factors

The heart deceives, because it is never anything but the

expression of the mind's miscalculations.

. . .

I don't know what the heart is, not I:

I only use the word to denote the mind's frailties.

Marquis de Sade (1740–1814)

The affective dimension of chest pain is enormously complex; the symbol of the heart and its representation in culture and art truly place it at the core of human emotions. The stark connection between the health of the pump inside the thorax and life or death amplifies reactions to chest pain and creates a whole genre of disease and disability. It is well beyond the scope of this chapter to explore the psychological factors associated with chest pain in great detail. Instead, the following brief discussion addresses generally the emotional reactions to organic chest pain and describes the most common psychological contributors to nonorganic chest pain.

Emotional Reactions to Organic Chest Pain

Patients with sudden acute chest pain, regardless of the cause, experience varying degrees of anxiety, apprehension, and fear, depending on their interpretation of the cause of pain. Those who believe that they are experiencing a heart attack become extremely frightened of possible impending death. Many patients who have acute myocardial infarction pass through reactions of denial, anxiety, depression, and, finally, acceptance (162). In acute myocardial infarction patients, anxiety and apprehension provoke a marked increase in general neural sympathetic tone and produce an increase in the neuroendocrine response to stress that can aggravate the existing pathophysiology and prove deleterious to the patient. It is therefore essential to relieve the pain and also the associated anxiety and apprehension promptly to minimize or prevent these serious psychophysiologic responses.

Patients with persistent angina pectoris frequently develop reactive depression as a consequence of the limitation imposed by the illness, which is seen as a threat affecting the patient's lifestyle, self-image, status, family relationships, and security (162). The depression frequently aggravates the physical disability and, if it remains untreated, it sets up a vicious circle that produces progressive physical and psychological deterioration. Reactive depression is an even greater problem in patients with chronic cancer- related chest pain, not only because of the significance of the pain but also because of the progressive physical and psychological deterioration that these patients undergo.

Chest pain caused by nonmalignant musculoskeletal or neuropathic disorders provokes a great deal of anxiety and apprehension until patients have been reassured about the *benign* nature of the painful condition. In most patients, reassurance about the nonthreatening nature of the pain decreases or eliminates the depression. Some patients, however, in whom pain persists because its cause remains unknown or because the pain remains unrelieved, are also likely to develop reactive depression if the pain is intense enough to affect work and lifestyle.

In addition to assessing the patient to diagnose the primary cause, it is also important to assess the emotional reactions to, and psychological impact on, the patient's pain and pathologic process. Comprehensive treatment aims at both the pain and the emotional reactions to it.

Chest Pain Primarily Resulting from Psychological Mechanisms

Precise epidemiologic data are absent, but chest pain with no evidence of physical pathology often results from psychological mechanisms. The most common causes are anxiety disorders, affective disorders, operant mechanisms, psychophysiologic factors, and somatoform disorders.

The assessment of psychological factors is not easy when a patient first presents at the physician's office or in the emergency room. The diagnosis of chest pain primarily of psychological origin demands systematic exclusion of organic pathology and positive findings for positive psychological factors. Because of the potential seriousness of a physical cause of the chest pain, a complete and thorough history, physical examination, and full investigative procedures are essential prerequisites to the diagnosis. When pain primarily of psychological origin is suspected, the examiner should proceed in a reassuring way to avoid undue concern in the patient.

Billings (162) suggested the following as indications that the patient's complaints are primarily of psychological origin:

- The pain is usually located in the precordial region at the apex of the heart and is rarely central (Fig. 64-16).

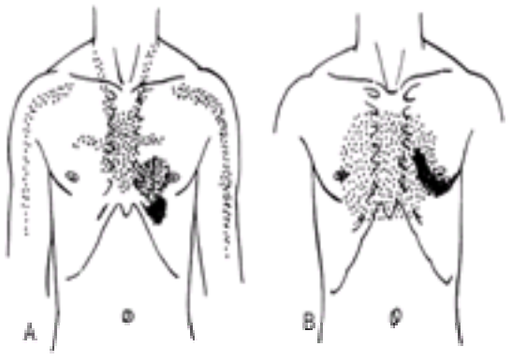

Figure 64-16. Patterns of pain provoked by psychological factors. **A:** Pattern of pains in a patient who has true angina (*light stipple*) coexisting with psychological pain usually felt at the cardiac apex or over the area where the patient thinks the heart lies (*heavy stipple*). **B:** Pattern of pain in acute anxiety felt diffusely throughout the chest or precordially. In patients with conversion pain, it is usually also felt precordially at the cardiac apex or along an operative scar if one is present.

- Description of the pain is atypical and stated in dramatic terms, such as “tearing pain through the chest wall” or “stabbing pain like a knife cutting through the heart.” Thus, it does not fit an organic syndrome nor does it follow a physiologic pattern.
- The distribution is not anatomically explicable and the development of the pain involves events that are not physiologically related.
- Often, more than one system is involved or several different pain patterns are noted on different occasions.
- *Psychogenic* pain does not awaken patients from sleep but can be present on awakening or soon thereafter.

- In most patients, an emotional precipitant usually precedes the development of acute pain, and patients manifest symptoms and signs of anxiety, depression, or other neurotic patterns.
- In contrast with pain of organic origin, which responds consistently to appropriate analgesics or other forms of therapy, pain primarily of psychological origin is more likely to show a variable response on different occasions.

Practitioners should tailor treatment of patients who have acute or persistent chest pain primarily of psychological origin according to the primary psychological disorder involved. In patients with an acute anxiety attack, reassurance, relaxation techniques, anxiolytic drugs, sedatives, tranquilizers, and time reduce anxiety. In patients with chronic anxiety, winning and retaining their confidence and providing reassurance are the most important therapeutic measures. In addition to obtaining a detailed history and physical examination, it is important to demonstrate a complete understanding of, and an interest in, patients' symptoms. Reassurance should not stop with the exclusion of organic heart disease but should include an emphasis on a good prognosis for life expectancy and a low incidence of disability. The practitioner should identify precipitating factors and deal with them in terms of patients' lifestyle, attitudes, and emotional reactions.

Acute Anxiety Attack. An acute anxiety attack usually begins as a sudden unexpected sense of terror, a feeling of apprehension, which increases in severity, leads to dyspnea, and is associated with a sense of choking or smothering, palpitations, and chest pains that are often so severe patients believe they are having a heart attack or dying. Dyspnea, or a feeling of air hunger, can produce the hyperventilation syndrome, characterized by a marked increase in ventilation producing severe respiratory alkalosis that leads to marked cerebral vasoconstriction and decreased blood flow. As a result of these changes, patients experience tachycardia, sweating, tremor, dizziness, and increased muscle tension, which can be accompanied by a diffuse chest tightness and paresthesia, a feeling of tingling in the hands, feet, face, or throat, feelings that cause patients to conclude that their initial fears are substantiated and they are suffering from a fatal heart attack (162).

The chest pain associated with an acute anxiety attack can occur even without hyperventilation and is described by patients as a severe, sharp, precordial pain or pain in the left inframammary region (see Fig. 64-16). The pain can be diffuse in the chest but is rarely retrosternal. The pain does not occur during physical effort but can develop after the effort has ceased. After the acute pain subsides, patients may have a dull ache or mild pain that persists. Chest pain may become the focus of concern and the complaint that initiates a trip to the physician or emergency room.

An acute anxiety attack usually lasts for a few minutes, rarely for more than 30 minutes. Following the attack, people can feel fatigued and exhausted. As the attacks recur, some of the symptoms mentioned previously become the focus of the patient's attention. Frequently, this focus comprises the sensation of palpitations, dyspnea, and chest pain, which can become recurrent complaints.

Chest pain caused by an acute anxiety attack is clinically important. Hurst, a world authority on heart disease, once stated that “The most common cause of chest pain is not related to cardiovascular disease, but is associated with anxiety” (163). Moreover, because elevated plasma catecholamine levels often accompany acute anxiety, it is a common precipitant of angina. Indeed, in patients who have some degree of coronary artery disease, myocardial infarction can occur during periods of sustained anxiety (162). Early diagnosis and treatment of the anxiety attack are critically important and crucial in the prevention of chronicity.

Chronic Anxiety State. In patients with chronic anxiety, chest pain and various other symptoms and signs are present in a common pattern that has been called the syndrome of *cardiac neurosis*, in which cardiovascular, respiratory, and nervous symptoms are prominent features in the absence of an explanatory diagnosis. This syndrome has been known for more than a century; in 1871 Da Costa referred to it as *irritable heart syndrome* (164). Since then, this condition has undergone many name changes, including *soldier's heart* (165), *Da Costa's syndrome* (166), *effort syndrome* (167), *neurocirculatory asthenia* (168), and *vasoregulatory asthenia* (169).

Patients with this syndrome complain of a moderate to severe shortness of breath, usually described as an inability to fill the lungs, palpitations, chest pain, nervousness, anxiety, fatigue, generalized weakness, and low energy level. Among the most important precipitating or aggravating factors are emotion-provoking situations, illness, hard physical labor, pregnancy, and military service (162). Billings (162) theorized that this syndrome tends to develop in patients who have problems relating to dependency needs and who are attempting to function in a situation that is taxing their coping ability. Anxiety and concern about the heart can develop in response to this stress, and one symptom is precordial pain. Physician uncertainty about the diagnosis and the use of unnecessary tests may refocus attention on the heart, thereby exacerbating the situation.

Patients feel pain at the cardiac apex, often described as a dull ache, with or without attacks of sharper pain in the same area (162) (see Fig. 64-16). The patient might relate the pain to physical exertion, but it usually occurs after the physical exertion has ceased and is associated with fatigue rather than effort. The shortness of breath, usually described as an inability to fill the lungs, is a prominent symptom, as are generalized weakness and low energy levels. Other manifestations of anxiety can be present but are not prominent.

This condition tends to persist for years, with periods of exacerbation and remission. A number of patients can recover entirely and some show improvement (162,170). The prognosis for disappearance of symptoms is poor if a serious psychiatric background and a long history of symptoms are present or the syndrome appears after relatively brief and minor physical strain (170). Cardiophobia is an extreme form of chronic, recurring anxiety focused on the heart (171).

Other Psychiatric Disorders. Depression, conversion reactions, hypochondriasis, and operant (learned) behavior sometimes manifest as chest pain. Specific therapy aimed at the underlying psychiatric condition is the only sensible approach to patients with these disorders. Chapter 24, Chapter 25 and Chapter 26 discuss these conditions in greater detail.

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CHAPTER 65

General Considerations of Abdominal Pain

John J. Bonica and Daniel O. Graney

The abdomen is one of the most frequent sites of regional acute pain; there are numerous chronic pain syndromes caused by disorders of the abdominal viscera or referred to this region by diseases of the thoracic viscera. Pain in the abdomen can also be neuropathic due to disease of the spinal cord or of the lower six thoracic nerves. Injury and disease of muscles and the fascia and other somatic structures that are part of the abdomen are also causes of abdominal pain. This chapter, like others that introduce pain in various body regions, is intended to provide information on the anatomic, neurologic, and pathophysiologic bases of pain in the abdomen and a general approach to its diagnosis. Although the pelvis is considered to be part of the abdominal cavity, the various pain syndromes in this region are discussed separately in Section E (Part IV) to emphasize their importance and also because pain in the pelvis is often related to diseases of the perineum and external genitalia.

The information in this chapter is presented in four major sections: Basic Considerations, including an overview of the most common causes of pain in the abdomen and their mechanisms, and a brief discussion of the epidemiology of abdominal pain; Anatomy and Neurologic Aspects of the abdomen and viscera contained therein, including anatomy of the muscles of the abdomen, a brief description of the peritoneum, the nerve supply to these structures, and a general description of the autonomic and afferent nerve supplies to the abdominal viscera; Summary of Evaluation of the Patient and Differential Diagnosis of patients presenting with abdominal pain; and a table that presents all possible causes of abdominal pain, the characteristics of the pain, and other symptoms and signs that should help to make a differential diagnosis. The subsequent four chapters are more detailed and present specific information on these various aspects as they pertain to the disease of each viscus.

BASIC CONSIDERATIONS

Classification of Abdominal Pain

Pain in the abdomen is usually caused by disorders of the viscera contained within the abdominal cavity, including the pelvic viscera. Referred pain to the abdomen from diseases of the chest is the next common cause and often is a source of difficulty in differential diagnosis, because the lower thoracic cavity and the abdomen, other than the pelvis, can be considered as one neurologic unit: The somatic and visceral nerve supplies of both regions have a common segmental distribution in the spinal cord. To be more specific, the lower half of the thoracic parietal pleura, the periphery of the diaphragmatic pleura, and approximately the upper 85% of the abdominal wall are supplied by the lower six or seven thoracic (and the first lumbar) somatic spinal nerves. Moreover, the proximal ends of the afferent nerves, mediating nociceptive and other sensory impulses from the abdominal viscera (except the pelvis), synapse in the same spinal cord segments as the somatic spinal nerves. It is not surprising, therefore, that lesions of these various structures produce pain with similar localization in the trunk. These neuroanatomic and neurophysiologic factors also explain the common features of pain in the chest and abdomen caused by neuropathic disorders. The same neurologic lesions of the spinal cord or of the lower six or seven thoracic and first lumbar spinal nerves or their roots frequently produce a similar type of pain in the lower chest or the abdominal wall, depending on the level of the lesion. Less common causes of abdominal pain are disorders of muscles and certain systemic diseases.

Abdominal Visceral Disease

The characteristics and mechanisms of pain caused by abdominal visceral disease are discussed in detail in Chapter 9. To briefly recapitulate, cutting and tearing or crushing of the viscera does not result in pain or in other perceptible sensation (1). Tension or stretching of the walls of hollow viscera, traction or stretching of the peritoneum, and increased tension caused by rapid stretching of the capsule of solid viscera constitute the *adequate stimulus* for visceral pain, specifically the following (2,3,4 and 5): (a) spasm of the smooth muscle of a hollow viscus; (b) sudden abnormal distension, stretching, or tearing of any part of the gastrointestinal tract (including the biliary ducts) or of the genitourinary system (including the ureters, urinary bladder, and uterus); (c) contraction of a hollow viscus under isometric conditions (i.e., the outlet of the viscus is obstructed); (d) rapid abnormal stretching of the capsule of such solid organs as the liver, spleen, or kidney; (e) traction, compression, or twisting of the mesentery, parietal peritoneum, ligaments, or blood vessels; (f) rapidly developing ischemia of the viscera; and (g) inflammation and necrosis of the pancreas or other viscera.

Inflammation, whether of bacterial or chemical origin, or ischemia of a viscus liberates algogenic (pain-producing) substances such as bradykinin, serotonin, histamine, and prostaglandins that stimulate and sensitize nerve endings and thus lower their threshold for the adequate stimulus to activate sensory nerve endings. Thus, whereas pinching the wall of the healthy gastric mucosa or applying faradic stimulation or chemical irritants to it produces no pain, such procedures do produce pain of considerable intensity when done to inflamed, congested, and edematous gastric mucosa (5). Severe ischemia has a similar effect by increasing the concentration of these algogenic substances in the region of nerve endings.

Pain in the abdomen can be separated into two types according to the origin of the nociceptive impulses: visceral pain and parietal (somatic) pain. Based on localization, either type can be felt in or near the structure from which it arises or can be felt at a region that is removed from the structure that is the seat of noxious stimuli. Thus, four types of pain are associated with visceral disease: (a) unreferred or true visceral pain; (b) referred visceral pain; (c) unreferred or local parietal pain; and (d) referred parietal pain.

Unreferred Visceral Pain. Unreferred or true visceral pain is dull, poorly localized in the epigastrium, periumbilical region, or lower midabdomen, and usually felt around the midline, because with few exceptions the abdominal organs are supplied with afferents bilaterally. Exceptions to this are the kidneys, ureters, cecum, ascending colon, and descending and sigmoid colon, which have unilateral innervation. The poor localization of the pain occurs because innervation of most viscera is multisegmental and the viscera contain fewer nerve endings than the skin. The quality of the pain is usually gnawing, cramping, and associated with nausea, sweating, vomiting, perspiration, and pallor. When the nociceptive input is intense, the pain is referred to the skin and deeper somatic tissue.

On the basis of the lack of evidence for a sensory channel specifically concerned with the transmission of visceral sensory impulses and the considerable amount of experimental data on viscerosomatic convergence in the central nervous system, Cervero and Tattersall (6) dispute this century-old classic concept of true visceral pain.

Referred Visceral Pain. Referred visceral pain is somewhat more localized than true visceral pain. It is located in the dermatomes and myotomes that are supplied by the same spinal cord segments as the affected viscus and is the result of the convergence-projection mechanism (see Chapter 9). Thus, distension of the intestine with a balloon causes a vague, aching, poorly localized discomfort at first but, with greater distension, the pain is referred to the abdominal wall and back (7).

Unreferred Parietal Pain. Parietal pain is considered to be unreferred or local when the inflammation of the parietal peritoneum produces pain localized in the body wall directly over the site of the inflammation, such as the localized pain in acute appendicitis produced by inflammatory involvement of the parietal peritoneum at

McBurney's point. The pain results from stimulation of nociceptive fibers in the parietal peritoneum in the right lower quadrant.

Referred Parietal Pain. Referred parietal pain is characterized by pain felt in an area that is remote from the site of nociceptive stimulation. A typical example is the pain felt in the shoulder when the parietal peritoneum of the middle portion of the diaphragm is inflamed and stimulated.

Pain of Neuropathic Origin

Lesions of the spinal cord, such as primary or metastatic tumors, or spinal cord compression causes pain in the abdomen when the lesion involves one or more of the lower six thoracic segments of the spinal cord. The pain can be dull, aching, and not well localized or radicular, depending on the lesion. Compression or inflammation of the rootlets and roots of the lower six or seven thoracic nerves, such as in herpes zoster, tabes dorsalis, or compression from vertebral tumors or herniated disks, produces sharp, burning, segmental pain in the abdomen and is associated with hyperalgesia, hyperesthesia, and other sensory disturbances. Intercostal neuropathy produced by mechanical or inflammatory processes can also cause pain in the anterior abdomen.

Pain Caused by Musculoskeletal Disorders

In addition to producing radiculopathy or neuropathy with segmental pain, disorders of the lower thoracic spine can cause local or regional pain in the back or occasionally referred to the side of the trunk. Fracture or dislocation of the lower ribs or their cartilages causes localized pain on the side of the injury. Fracture or subluxation of the cartilages causes sharp localized epigastric pain that is aggravated by movement and pressure. Myofascial pain syndromes involving muscles of the abdomen are much less frequent causes of pain from the abdomen than from other parts of the body. Trauma with hemorrhage to the anterior abdominal wall can cause localized pain. In all these conditions, the pain is fairly well localized and sharp and is associated with tenderness. Postoperative pain is a source of moderate to severe discomfort, especially following operation in the upper abdomen. This type of pain is markedly aggravated by movement, coughing, and straining and is often associated with reflex muscle spasm and other segmental and suprasegmental responses (see Chapter 41).

Other Causes of Abdominal Pain

Various systemic, toxic, allergic, hematologic, and endocrine disturbances can cause episodes of severe, deep abdominal pain that can simulate that of visceral disease. The pain of porphyria or lead colic is usually difficult to distinguish from that of intestinal obstruction because severe hyperperistalsis is a prominent feature of both (8). The pain of uremia or diabetes is nonspecific, and the pain and tenderness frequently shift in location and intensity. Black widow spider bites produce pain and rigidity of abdominal muscles and of back muscles, an area not frequently involved in disease of intraabdominal origin.

Disease of intraabdominal arteries and veins can cause severe, diffuse pain as in embolism or thrombosis of the superior mesenteric artery or rupture of abdominal aortic aneurysm, or it can cause mild continuous diffuse pain for 2 or 3 days before vascular collapse or evidence of peritoneal inflammation appears (8). The early, seemingly insignificant, discomfort is caused by hyperperistalsis rather than by peritoneal inflammation. The absence of tenderness and rigidity and the presence of continuous diffuse pain in a patient likely to have vascular disease are characteristic of occlusion of the superior mesenteric artery (8).

Pain primarily caused by psychological or emotional factors varies enormously in type, location, and other characteristics, usually has no relation to meals, and is often accentuated during the night; nausea and vomiting are rarely observed and no reflex spasm of abdominal muscles is seen. Frequently, the site of the pain varies from visit to visit.

Table 65-1 presents the most common causes of abdominal pain. (A more detailed listing is given later in Table 65-6, which contains the important diagnostic features of each condition.)

TABLE 65-1. Major causes of abdominal pain

TABLE 65-6. Summary of etiology and differential diagnoses of abdominal pain

Epidemiology

The precise incidence and prevalence of abdominal pain are not known, but data from the 1986 National Health Interview Survey (9) suggest that nearly 15 million Americans suffered acute disorders of the digestive system, and approximately 2 million had acute disorders of the kidney and ureters in 1986. These conditions resulted in more than 105 million days of restricted activity, approximately 44 million days of bed disability, and approximately 25 million days of lost work. In addition, more than 30 million people were listed as having “selected chronic digestive conditions,” including 4.5 million patients with ulcers, nearly 3 million patients with gastritis or duodenitis, 2.5 million patients with enteritis or colitis, 5.3 million patients with frequent recurrent periods of pain caused by indigestion, and more than 1.6 million patients with spastic colon associated with abdominal pain.

The 1986 National Hospital Discharge Survey (10) indicated that approximately 5.8 million patients were hospitalized for digestive and kidney diseases in 1986, resulting in nearly 38 million days of hospitalization. Moreover, approximately 6.7 million operations were performed to diagnose and treat digestive and renal disorders (Table 65-2).

	Inpatient Discharges			Operations	
Disease	No. of patients (in thousands)	Average length of stay (days)	Total hospital days (in thousands)	Type	Total (in thousands)
Digestive tract				Digestive tract	
Peptic ulcer	395	7.1	2,805	Endoscopy	442
Gastritis or duodenitis	196	4.5	882	Gastrectomy	79
Appendicitis	250	4.9	1,225	Appendectomy	271
Inguinal hernia	184	5.0	912	Cholecystectomy	382
Enteritis or colitis	439	4.8	2,059	Repair of inguinal hernia	179
Cholelithiasis	494	6.9	3,409	Division of adhesions	125
Other disorders	2,047	4.2	8,771	Hemorrhoidectomy	114
				Other	1,348
Subtotal	3,715	4.7	17,743	Subtotal	3,720
				Renal or ureteral	181
Renal or ureteral					
Calculi	113	3.6	1,192		
Other	1,703	5.2	8,856		
Subtotal	1,816	4.9	10,048		
All	5,531	4.5	27,811	All	6,712

Source: Adapted from National Center for Health Statistics. Advance data, 1986 summary; national Hospital discharge survey. Hyattsville, MD: National Center for Health Statistics, 1987. (Publication No. 10).

TABLE 65-2. Hospitalizations and operations performed for digestive and renal diseases in 1986

The 1987 estimates of the American Cancer Society (11) included 224,000 new cases of cancer of the digestive organs and 22,000 new cases of cancer of the kidney and ureters, while the total deaths from each group of cancers were 125,000 and 9,400, respectively (Table 65-3). The total of new cases and deaths from cancer of the digestive system is the highest of any organ system or cancer site.

	Estimated new cases			Estimated deaths		
Site	Male	Female	Total	Male	Female	Total
Digestive organs						
Esophagus	6,000	2,900	8,900	6,400	2,400	8,800
Stomach	15,000	9,600	24,600	8,900	5,900	14,800
Small intestine	1,300	1,200	2,500	400	400	800
Large intestine	47,000	51,000	98,000	25,000	27,000	52,000
Rectum	23,000	20,000	43,000	4,000	3,900	8,000
Liver and biliary passages	7,000	4,900	14,000	5,000	5,000	10,000
Pancreas	13,000	13,200	26,200	12,500	12,000	24,500
Other cancers	2,000	1,200	4,000	600	600	1,200
Subtotal	114,000	110,000	224,000	62,600	57,500	125,100
Kidney	13,000	8,000	21,000	5,700	3,700	9,400

Adapted from American Cancer Society: Cancer facts and figures, 1987. New York: American Cancer Society, 1987.

TABLE 65-3. Estimates of new cancer cases of the digestive and renal systems and cancer deaths in 1987

Computations based on the incidence of pain with these various abdominal and renal conditions, and data on the incidence of cancer pain with various types of cancers (see Chapter 35), suggest that in 1986 approximately 20% of Americans had abdominal pain that required medical attention. The Nuprin Pain Report suggested that these numbers underestimate the actual figures and noted that in 1985, 46% of Americans had abdominal (*stomach*) pain (12).

ANATOMIC AND NEUROLOGIC ASPECTS

Anatomy of the Abdomen

The abdomen, the region of the trunk below the diaphragm, is composed of an upper part, the abdomen proper, and a lower part, the lesser pelvis (13,14). The anatomy of the pelvis is described in Chapter 70. The abdomen is largely bounded by muscles, and its shape and size can thus be altered under different conditions, such as varying degrees of distension of the hollow organs contained therein and the different phases of respiration. Moreover, the tone of the muscles is important in maintaining the abdominal (and pelvic) viscera in position.

The abdomen proper is bounded anteriorly by the rectus abdominis muscles, the pyramidalis, and the aponeurotic parts of three muscles: the external oblique, internal oblique, and transversus abdominis. It is bounded at its sides by the fleshy parts of these three muscles and by the iliac muscles and iliac bones and posteriorly by the lumbar part of the vertebral column, the crura of the diaphragm, the psoas and quadratus lumborum muscles, and the posterior part of the iliac bones. Superiorly it is bounded by the diaphragm and inferiorly by the superior aperture of the lesser pelvis. Because of the dome shape of the diaphragm, a considerable part of the abdominal cavity extends superiorly and is inside the framework of the thorax. The abdomen proper contains the greater part of the gastrointestinal tract as well as the liver, pancreas, spleen, kidneys, part of the ureters, supraadrenal glands, and numerous blood vessels, lymph vessels, lymph nodes, and nerves.

For purposes of location of the viscera, especially in clinical practice, the abdomen is divided into nine regions by imaginary planes. Two horizontal and two sagittal planes pass through the cavity, with the edges of each plane being indicated by lines projected onto the surface of the body (Fig. 65-1). Figure 65-2 depicts the relationship of various abdominal viscera and other structures to the dermatomes and to the ribs.

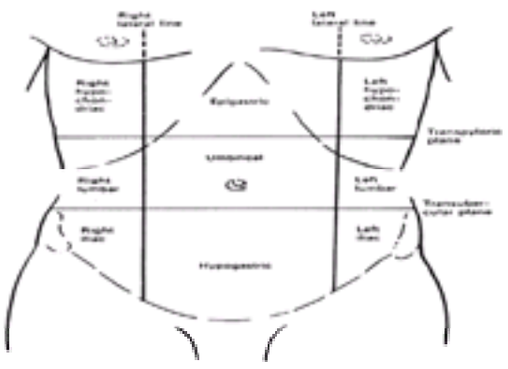

Figure 65-1. Regions of the abdominal wall. The wall is divided into nine regions by four imaginary lines, of which two pass horizontally around the body and two vertically. The upper horizontal line or plane, also called the *transpyloric plane*, is at a level midway between the suprasternal notch and the symphysis pubis, intersects the front of the body of the first lumbar vertebra near its lower border, and meets the costal margin at the tip of the ninth costal cartilage. The lower transtubercular plane is at the level of the top of the crests of the iliac bones and intersects the front of the body of the fifth lumbar vertebra near its upper border. The vertical lines, one on each side of the body, descend from the cartilages of the eighth rib to the center of the inguinal ligament.

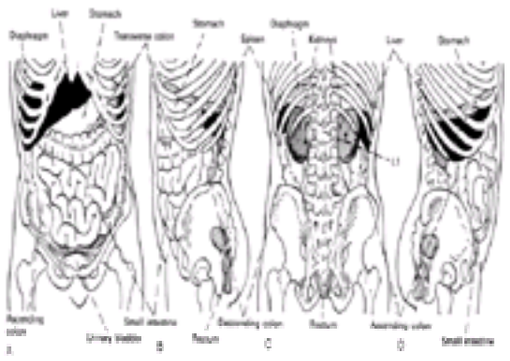

Figure 65-2. Abdominal viscera shown in their normal relationship in the skeleton. **A:** Anterior view. **B:** View from the left side. **C:** View from the back. **D:** View from the right side. (Modified from Clemente CD, ed. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985.)

Muscles

The muscles of the abdomen are conveniently divided into an anterolateral group and a posterior group. The anterolateral group consists of four large, flat muscular sheets that form the anterior abdominal wall, including the internal and external oblique, the transversus and rectus abdominis, and two smaller elements, the cremaster and pyramidalis, which are involved in the suspension of the testes and in the tensing of the midline tendinous raphe of the abdominal wall. The posterior muscles of the abdomen include the psoas major and minor, the iliacus, and the fasciae covering them, as well as the quadratus lumborum muscle. The superior part of the abdomen is composed of the inferior surface of the diaphragm, which, although discussed briefly in connection with the chest, is considered in some detail here; the other muscles are then described briefly.

Diaphragm. Figure 65-3 depicts the inferior surface of the diaphragm with the various nerves and some of the major vessels, but without any of the other structures. This dome-shaped musculofibrous sheet, which separates the thoracic from the abdominal cavities, consists of the central tendon, which consists of a thin but strong aponeurosis of closely interwoven fibers situated near the center of the dome, and the peripheral part, which consists of muscular fibers that are attached to the circumference of the thoracic outlet and converge into the central tendon (13,14).

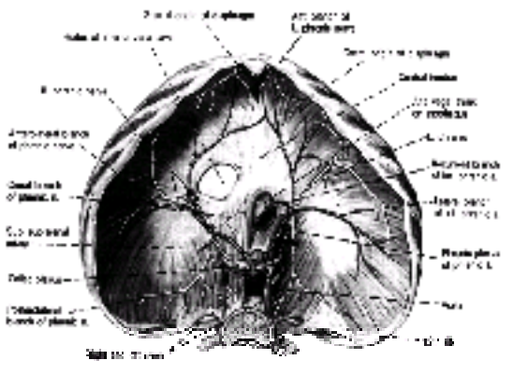

Figure 65-3. Abdominal surface of the diaphragm depicting the phrenic nerves (n.) and arteries (a.) and the phrenic plexus, as well as the major openings. See text for details. (Modified from Netter FH. *The CIBA collection of medical illustrations.* Vol 2, Digestive system. Part III, Lower digestive tract. Summit, NJ: CIBA, 1979:21.)

The musculofibers are grouped into three portions: the sternal part, arising from two fleshy slips from the back of the xiphoid process; the costal part, arising from the internal surface of the cartilage and from adjacent parts of the lower six ribs on each aide and interdigitating with the transversus abdominis muscle; and the lumbar part, arising from two aponeurotic arches, from the medial and lateral arcuate ligaments, and from the lumbar vertebrae by two pillars, or crura.

The diaphragm has three large openings—the aortic, esophageal, and vena caval—and a number of smaller ones that transmit the greater and lesser splanchnic nerves. The aortic aperture is the lowest and most posterior of the large openings and is situated at the level of the lower border of the T-10 vertebra and the thoracolumbar intervertebral disk, slightly to the left of the median plane. In addition to being an opening for the passage of the aorta, the aortic aperture also transmits the thoracic duct and occasionally the azygos and hemiazygos veins.

The esophageal aperture is an elliptic opening in the muscular part of the diaphragm at the level of the T-10 vertebra that is formed by the splitting of the medial fibers of the right crus (14). In addition to transmitting the esophagus, it allows the passage of the vagal and sympathetic nerves that surround the lower esophagus and then proceed to the stomach, the esophageal branches of the left gastric vessels, and some lymphatics. The fascia on the inferior surface of the diaphragm, which is continuous with the transversalis fascia and is rich in elastic fibers, extends upward into the opening in a conical fashion to be attached to the wall of the esophagus approximately 2 cm above the gastroesophageal junction, with some of the elastic fibers penetrating to the submucosa of the esophagus. This fascial extension, often called the *phrenico-esophageal ligament*, is an important structure in the treatment of esophageal reflux (see Fig. 65-12). The vena caval aperture is the highest of the three large openings and is situated at approximately the level of the disk between the T-8 and T-9 vertebrae. It transmits the inferior vena cava and some branches of the right phrenic nerve, which is the major motor nerve supply to the diaphragm and also contains some sensory fibers (see Chapter 60).

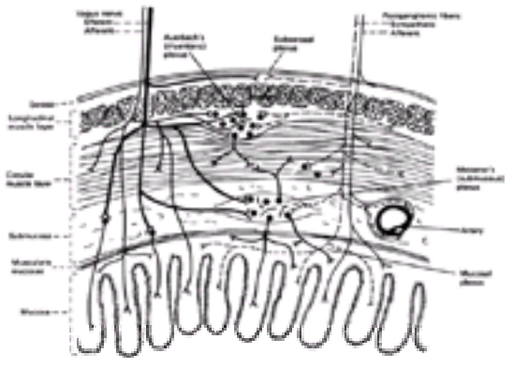

Figure 65-12. Arrangement of nerve cells and nerve fibers in the intramural plexuses in the intestine. The axonal endings of the parasympathetic preganglionic neurons synapse in the wall of the intestine, whereas the axonal endings of postganglionic sympathetic neurons are largely distributed to the intramural ganglia and the blood vessels. (Modified from Kuntz A. *Autonomic nervous system*, 4th ed. Philadelphia: Lea & Febiger, 1953:215.)

Anterolateral Muscles

The anterolateral group of muscles of the abdomen is covered by a fascia that is divisible into two layers, between which are superficial vessels, nerves, and superficial inguinal lymph nodes. The superficial layer of the fascia is thick, is areolar in texture, and contains a varying quantity of fat in its meshes. Below, it passes over the inguinal ligament and is continuous with the superficial fascia of the thigh. The deep layer of the fascia is more membranous than the superficial, contains

elastic fibers, and is loosely connected by areolar tissue to the aponeurosis of the external oblique muscle except in the medial plane, where it adheres intimately to the linea alba and to the symphysis pubis (Fig. 65-4).

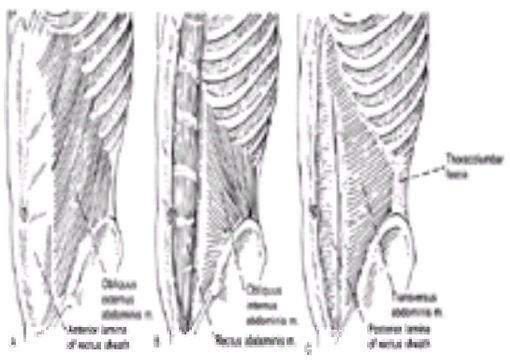

Figure 65-4. Muscles and fascia of the abdominal wall. **A:** External oblique muscle and anterior lamina of the rectus sheath. **B:** Rectus abdominis and internal oblique muscle. **C:** Transversus abdominis, thoracolumbar fascia, and posterior lamina of the rectus sheath.

External Oblique Muscle. The external oblique muscle, the largest and most superficial of the three flat muscles, arises by eight fleshy slips from the external surfaces and inferior borders of the lower eight ribs; these slips interdigitate with the serratus anterior and latissimus dorsi (see Fig. 65-4A). The fibers diverge from these attachments as they pass into their insertion: Those from the lower two ribs pass inferiorly to become attached to the outer lip of the iliac crest, whereas the middle and upper fibers are directed inferiorly and anteriorly, and end in an aponeurosis that is a strong tendinous sheath and whose fibers are directed downward and medially. In the medial plane its fibers end in the linea alba, which is a tendinous raphe that stretches from the xiphoid process to the symphysis pubis. At the raphe it is continuous with the aponeurosis of the opposite muscle, and together these two cover the anterior part of the abdomen. The margin of the aponeurosis between the anterior superior iliac spine and the pubic tubercle is a thick band formed and then turned on itself to present a grooved upper surface. This is the inguinal, or Poupart's, ligament.

Internal Oblique Muscle. The internal oblique muscle is internal to and is thinner and less bulky than the external oblique muscle. It arises by muscular fibers from the lateral two-thirds of the grooved upper surface of the inguinal ligament, from the anterior two-thirds of the intermediate line of the iliac crest, and from the thoracolumbar fascia (see Fig. 65-4B). The posterior fibers pass cephalad and laterally to the inferior border of the lower three or four ribs and are continuous with the internal intercostal muscles. The fibers from the inguinal ligament arch across the spermatic cord in the male and the round ligament of the uterus in the female, become tendinous, and attach to the corresponding part of the aponeurosis of the transversus abdominis muscle to the crest in the medial part of the pecten ossis pubis, forming the conjoint tendon or falx inguinalis. The rest of the fibers pass anteriorly and anterosuperiorly, ending in an aponeurosis that gradually broadens from below upward. In its upper two-thirds, this aponeurosis splits at the lateral border of the rectus abdominis into two layers, which pass around it and reunite in the linea alba that they help to form.

Transversus Abdominis. The transversus abdominis is the innermost of the flat muscles of the abdominal wall and is internal to the internal oblique abdominis. It arises from the lateral third of the inguinal ligament, the anterior two-thirds of the inner lip of the iliac crest and thoracolumbar fascia between the iliac crest and the twelfth rib, and the internal aspects of the lower six costal cartilages, where it interdigitates with the diaphragm (see Fig. 65-4C). The muscle fibers pass anteriorly and end in its aponeurosis. The lower fibers of the aponeurosis pass inferiorly and medially, together with those of the aponeurosis of the internal oblique, to the crest and pecten of the pubis; these contribute to the falx inguinalis, while the rest pass horizontally over the aponeurosis toward the medial plane and blend with the linea alba.

Rectus Abdominis. The rectus abdominis muscle is a long, thick, rather narrow muscle that extends along the whole length of the front of the abdomen and is separated from its counterpart by the linea alba. It arises by two tendons, a lateral and larger tendon attached to the crest of the pubis and a medial tendon that interlaces with the larger one and becomes connected with ligamentous fibers of the symphysis pubis (see Fig. 65-4B). Superiorly, each muscle is inserted by three fascicles of unequal size to the fifth, sixth, and seventh costal cartilages. The muscle fibers of the rectus are interrupted by three fibrous bands called *tendinous intersections*. The rectus abdominis is enclosed in the rectus sheath, which is the aponeurosis of the oblique and transverse muscles. Figure 65-5 depicts a transverse section through the anterior and posterior abdominal walls showing the termination of the abdominal muscles and the fascia that covers them.

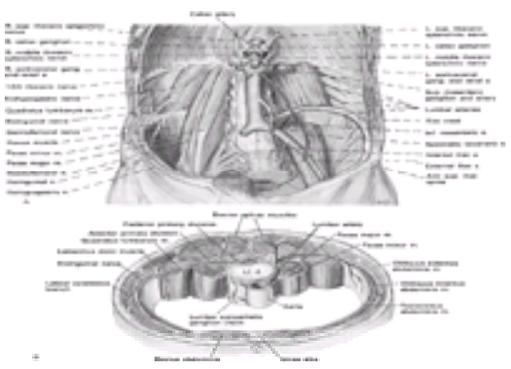

Figure 65-5. **A:** Posterior wall of the abdomen showing the blood vessels on the right (*black*) and the lumbar nerves on the left (*white*), as well as the muscles that make up the posterior boundary of the abdomen proper. **B:** Cross-section of the trunk depicting the anterior and posterior abdominal muscles and course of the lumbar artery (the reader's right) and the first lumbar nerve on the reader's left. (**A** modified from Netter FH. *The CIBA collection of medical illustrations*. Vol 3, Digestive system. Part II, Lower digestive tract. Summit, NJ: CIBA, 1979:35, 43.)

Only the quadratus lumborum is described here because the other posterior muscles of the abdomen are muscles of the lower limb and are described in Chapter 75. The quadratus lumborum is an irregularly quadrilateral-shaped muscle that is broader inferiorly (see Fig. 65-5). It arises below by aponeurotic fibers of the iliolumbar ligament and by the adjacent portion of the iliac crest for approximately 5 cm, while above it is inserted into the medial half of the lower border of the last rib and to the apices of the transverse processes of the upper four lumbar vertebrae by four small tendons. Anterior to the quadratus lumborum are the colon, kidney, psoas major and minor, and diaphragm.

Peritoneum

The peritoneum is the largest and most complexly arranged serous membrane of the body. In men, it consists of a closed sac; part of this lines the abdominal wall and the remainder is reflected over viscera. In women, the lateral ends of the uterine tube open into the peritoneal cavity. The part that lines the abdominal wall is called the *parietal peritoneum*, while that reflected over the viscera is the *visceral peritoneum*. The free surface of the membrane is covered with a layer of flattened mesothelium and is kept moist and smooth by a thin film of serous fluid, so that the viscera can glide unrestricted over each other on the wall of the cavity.

A fairly large amount of areolar connective tissue intervenes between the parietal peritoneum and the abdominal wall, blending with the fascia lining. This structure, known as the *extraperitoneal tissue*, varies in quantity and contains a varying amount of fat in different regions. The areolar connective tissue is loosely connected to parietal peritoneum in the abdominal wall but is dense in adherence on the inferior surface of the diaphragm and behind the linea alba. It is especially loosely arranged in some places to allow alteration in size of certain organs, such as the urinary bladder. The extraperitoneal tissue is usually heavily laden with fat on the posterior abdominal wall in relation to the kidney. The visceral peritoneum, on the other hand, is firmly united to the viscera that it covers and cannot be easily stripped off. Indeed, the connective tissue layer, the subserous fascia of the visceral peritoneum, is directly continuous with the fibrous tissue stroma of the viscera.

The parietal and visceral layers of the peritoneum are in actual contact, the peritoneal cavity being the potential space between them. The peritoneal cavity consists of a main region, called the *greater sac*, and a diverticulum from this called the *omental bursa*, or *lesser sac*. The neck or communication between the greater and lesser sacs is the *epiploic foramen*, or *foramen of Winslow* (13).

Omenta

Lesser Omentum The lesser omentum is the fold of peritoneum that extends to the liver from the lesser curvature of the stomach and the beginning of the duodenum. It is continuous with the two layers that cover the anterosuperior and posteroinferior surfaces of the stomach and approximately the first 2 cm of the duodenum. A portion of the lesser omentum that extends between the liver and stomach is known as the *hepatogastric ligament*, and that between the liver and duodenum is known as the *hepatoduodenal ligament*.

Greater Omentum. The greater omentum is the largest peritoneal fold. It consists of a double sheet folded on itself so that it is made up of four layers. The two layers that descend from the stomach and the beginning of the duodenum pass downward in front of the small intestine for a variable distance. They then turn on themselves and ascend as far as the anterosuperior aspect of the transverse colon. They adhere to but are separable from the peritoneum on the upper surface of the transverse colon and the upper layer of the transverse mesocolon.

Mesenteries

The peritoneal fold, collectively known as the *mesenteries*, includes the mesentery of the small intestine, called the *mesentery proper*, and the mesoappendix, the transverse mesocolon, and the sigmoid mesocolon. The mesentery of the small intestine is a broad, variably shaped fold of peritoneum that connects the convolutions of the jejunum and ileum to the posterior abdominal wall. The part attached to the posterior wall of the abdomen is called the *root of the mesentery*. The mesoappendix is a triangular fold of peritoneum around the vermiform appendix that is attached to the back of the lower end of the mesentery close to the ileocecal junction. Its layers include the blood vessels, nerves, and lymph vessels of the appendix, together with a lymph node. The transverse mesocolon is a broad fold that connects the transverse colon to the posterior abdominal wall. Its two layers pass from the anterior surface of the head and the anterior border of the body of the pancreas to the posterior surface of the transverse colon. The sigmoid mesocolon is a fold of peritoneum that attaches the sigmoid to the pelvic wall. These structures are important because they contain blood vessels, nerves, and lymph vessels and, when stretched, provoke nociceptive impulses.

Vessels and Nerves

The parietal and visceral layers of the peritoneum are developed from the somatopleural and splanchnopleural layers of the lateral plate mesoderm, respectively. Correlated with their embryologic origin is the fact that the parietal peritoneum derives its nerve supply from the spinal nerves, which also supply the muscles and skin of the parietes (the same applies to its arterial supply and to drainage of the venous systems). The visceral peritoneum, which is considered to be an integral part of the viscera themselves, derives its nerve supply from the autonomic nerves supplying the viscera. The difference in the sensibility of the two layers of the peritoneum is thus correlated with the different innervation. In conscious patients, pain can be elicited by noxious stimuli applied to the parietal peritoneum, but these stimuli are ineffective when applied to the visceral peritoneum or to the viscera themselves. The region of the gastrointestinal tract that is insensible to stimuli that are normally painful when applied to the skin and other than somatic structures extends from approximately the middle of the esophagus down to the junction of the endodermal and extradermal parts of the anal canal. Conversely, tension or stretch applied to the viscera or the visceral peritoneum, such as overdistension of the hollow viscera or traction of the mesentery that stretches the nerve plexus in the walls of the organs or the nerves in the mesentery, produces pain. Other effective stimuli are spasm or contraction of the visceral muscle, particularly under isometric conditions, ischemia, and inflammation, which lowers the threshold of nerve endings.

The somatic nerve supply of the parietal peritoneum also supplies the corresponding segmental area of the skin and trunk muscles, and noxious stimuli applied to these structures produce pain and reflex muscle contraction or spasm. The parietal peritoneum of the undersurface of the diaphragm is supplied centrally by both phrenic nerves and peripherally by the lower six intercostal and subcostal nerves, so that inflammation or irritation of the peripheral part of the diaphragmatic peritoneum causes pain, tenderness, and muscular rigidity in the distribution of the lower intercostal nerves, whereas stimulation of the central portion produces pain in the distribution of the cutaneous branches of the C-3 to C-5 nerves (neck and shoulder regions). (Chapter 60 and Figure 60-9 describe the thoracoabdominal intercostal nerves in more detail.)

Autonomic and Sensory Nerve Supply to the Abdominal Viscera

This section presents a general overview of the anatomy of the parasympathetic, sympathetic, and afferent (sensory) nerves to the viscera of the abdomen proper. The information that follows is an extension of the description of the nerves to the thoracic viscera to the abdomen, which includes a discussion of the origin and course of the thoracic splanchnic nerves (see also Figure 60-11). The nerves to the pelvic viscera and the nerves to the structures of the pelvis are described in Chapter 70.

Figure 65-6,Figure 65-7,Figure 65-8,Figure 65-9,Figure 65-10,Figure 65-11,Figure 65-12 and Figure 65-13 depict the anatomy of the parasympathetic, sympathetic, and sensory nerves that supply the viscera in the abdomen proper. The parasympathetic efferent (motor) and afferent (sensory) fibers are contributed by branches of the vagus nerves and by the sacral splanchnic nerves (nervi erigentes). The sympathetic supply is provided by thoracic and lumbar splanchnic nerves as described in Chapter 60. Descriptions of the course and distribution of the vagus nerves, splanchnic nerves, and celiac and subsidiary plexuses are given below.

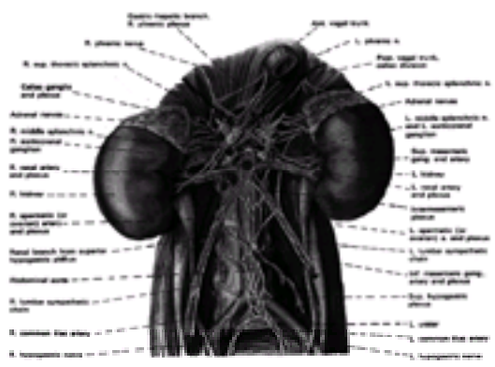

Figure 65-6. Anterior view of the abdomen showing the celiac plexuses and the ganglia as well as the subsidiary plexuses, including the phrenic, suprarenal, renal, testicular, and superior and inferior mesenteric plexuses. (Modified from Mitchell GAG. *Cardiovascular innervation*. Edinburgh, UK: Livingstone, 1956:258.)

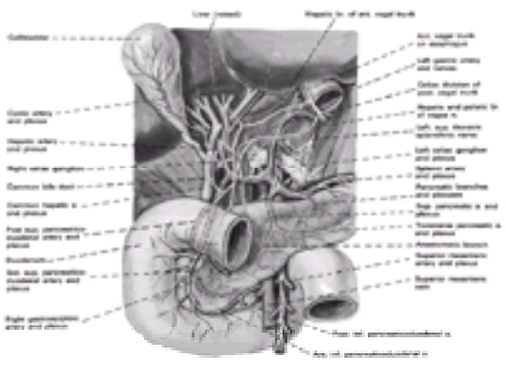

Figure 65-7. Hepatic plexus and its various subsidiary plexuses. For the sake of clarity, the celiac ganglia in this and other illustrations in this chapter are shown as two large masses instead of several separate portions scattered on each side.

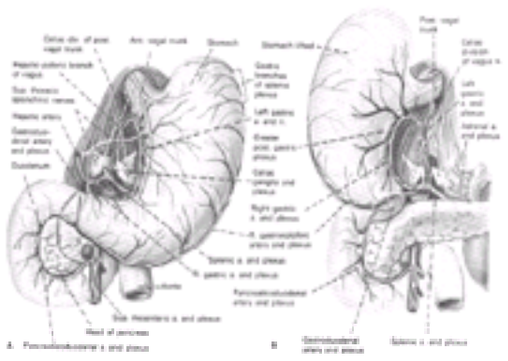

Figure 65-8. Autonomic nerve supply to the stomach and duodenum. **A:** Anterior view showing the anterior vagal trunk and its direct contribution to the hepatic plexus and the celiac plexus, which gives off the left gastric plexus that meets with the right gastric plexus; all of these supply the lesser curvature of the stomach. The gastroduodenal plexus supplies the duodenum and head of the pancreas; the greater curvature of the stomach is supplied by the right gastroepiploic plexus and gastric branches of the splenic plexus. **B:** The stomach has been shifted to the right to show the celiac, gastric, right gastroepiploic, and other plexuses and nerves that supply the stomach. (Modified from Mitchell GAG. *Cardiovascular innervation*. Edinburgh, UK: Livingstone, 1956:242.)

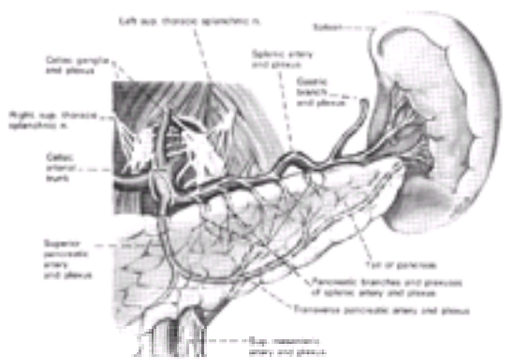

Figure 65-9. Splenic plexus. Note its origin and distribution to the pancreas, spleen, and stomach. (Modified from Mitchell GAG. *Cardiovascular innervation*. Edinburgh, UK: Livingstone, 1956:249.)

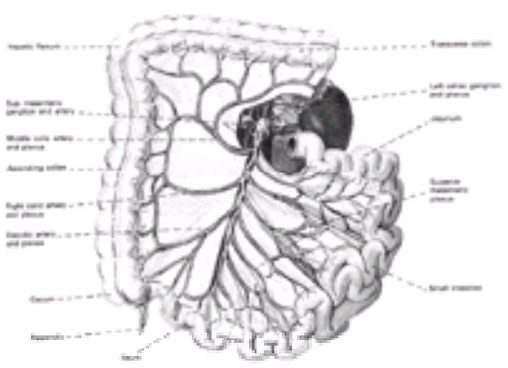

Figure 65-10. Superior mesenteric plexus. (Modified from Mitchell GAG. *Cardiovascular innervation*. Edinburgh, UK: Livingstone, 1956:251.)

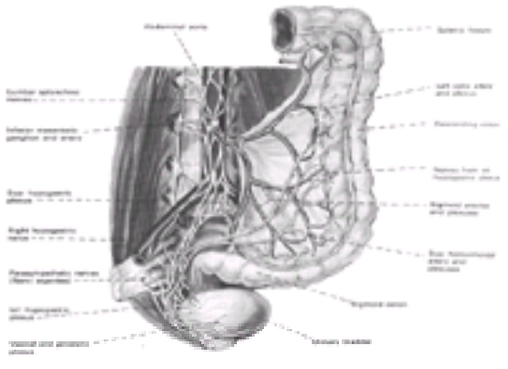

Figure 65-11. Inferior mesenteric plexus. (Modified from Mitchell GAG. *Cardiovascular innervation*. Edinburgh, UK: Livingstone, 1956:245.)

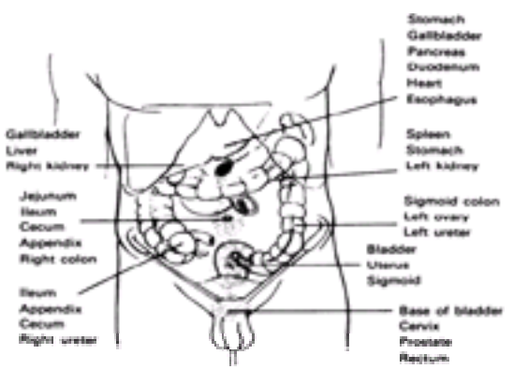

Figure 65-13. Abdominal pain according to site. Visceral pain occurs mostly in the midline epigastric, periumbilical, and hypogastric regions. Parietal pain occurs because of involvement of the parietal peritoneum that causes reference to the right and left lateral regions. (From Currie DJ. *Abdominal pain*. New York: McGraw-Hill, 1979:188.)

Vagus Nerves

The vagus nerves supply parasympathetic preganglionic fibers and sensory nerves to the viscera of the abdomen proper, except the left half of the transverse colon and the descending colon, which are supplied by the sacral parasympathetic nerves. As discussed in Chapter 8 and Chapter 60, the cell bodies of the parasympathetic preganglionic fibers are located in the dorsal motor nucleus of the vagus in the medulla of the brainstem, while the cell bodies of the sensory nerves are located in the inferior (nodose) ganglion, with the proximal processes entering the medulla and the distal processes incorporated into the vagus nerves. The two vagus nerves pass vertically from the base of the skull down the neck within the carotid sheath until they reach the root of the neck. The further course of the nerve differs on the two sides of the body.

Right Vagus Nerve. On the right side, the vagus descends posteriorly to the internal jugular vein. It crosses the first part of the subclavian artery, enters the thorax, and descends through the superior mediastinum, lying posterior to the right brachiocephalic vein. It then passes to the right of the trachea posteromedially to the superior vena cava and medially to the pleura and lung, passing posteriorly to the right principal bronchus to reach the posterior aspect of the root of the right lung, where it breaks up into posterior pulmonary branches that unite with filaments from the thoracic sympathetic nerves to form the right posterior pulmonary plexus. From the lower part of the posterior pulmonary plexus two or three branches descend on the posterior aspect of the esophagus and, with a branch from the left vagus, form the posterior esophageal plexus.

From the posterior esophageal plexus a trunk is formed that continues posteriorly to the esophagus to enter the abdomen through the esophageal opening in the diaphragm. This is the *posterior vagal trunk*, which contains fibers from both vagus nerves. In the abdomen, the posterior vagal trunk divides into a small gastric branch, which supplies the posteroinferior surface of the stomach with the exception of the pyloric canal, and a large celiac branch, which ends chiefly in the celiac plexus but also sends fibers directly to the splenic, hepatic, renal, suprarenal, and superior mesenteric plexuses.

Left Vagus Nerve. The left vagus nerve enters the thorax between the left common carotid and left subclavian arteries, posterior to the left brachiocephalic vein, and then descends through the superior mediastinum and crosses the left side of the aortic arch to pass behind the root of the left lung, where it divides into posterior pulmonary branches that unite with the sympathetic fibers and form the left posterior pulmonary plexus. Two branches descend from this left posterior pulmonary plexus in front of the esophagus, where they form the anterior esophageal plexus with a twig from the right posterior pulmonary plexus.

From the anterior esophageal plexus a trunk containing fibers from both vagus nerves continues in front of the esophagus, enters the abdomen through the esophageal opening of the diaphragm, and becomes the anterior vagal trunk. In the abdomen, the *anterior vagal trunk* sends branches to the cardiac antrum and then divides into right and left branches. The fibers of the left group follow the lesser curvature of the stomach and supply the anterosuperior surface of this viscus. The right group consists of three main branches. One proceeds between the layers of the lesser omentum toward the porta hepatis. Here, it divides into an upper branch that enters the porta hepatis and a lower branch that chiefly supplies the pyloric canal, pylorus, superior and descending parts of the duodenum, and the head of the pancreas. The second branch is distributed to the anterosuperior surface of the body of the stomach, and the third branch follows the lesser curvature of the stomach as far as the angular notch.

Sympathetic Nerves

The viscera of the abdomen proper are supplied by sympathetic efferent (motor nerves) whose cell bodies are located in the T- 5 to L-2 spinal cord segments and whose axons pass through the anterior nerve roots, short formed nerves, and white rami communicantes to reach the sympathetic chain. These axons pass through the chain without synapsing and pass through the splanchnic nerves to end in the three prevertebral ganglia—the celiac, aorticorenal, and inferior mesenteric ganglia—where they synapse with cell bodies of postganglionic neurons (see Chapter 8). The axons of the postganglionic neurons, together with axons of preganglionic parasympathetic fibers and afferent fibers, make up the celiac plexuses and then proceed as subsidiary plexuses that supply the various abdominal viscera. Although the origin and course of the thoracic splanchnic nerves are described in Chapter 60 and depicted in Figure 60-11, a brief discussion of their course and origin, their contribution to the celiac and subsidiary plexuses, the origin and course of the lumbar splanchnic nerves, and the anatomy of the celiac plexus and its subsidiary plexuses is presented here.

Greater Splanchnic Nerve. The greater thoracic splanchnic nerve, consisting mainly of myelinated preganglionic sympathetic and afferent fibers, is formed by three or four roots that are given off by the T-5 or T-6 to the T-9 or T-10 ganglia inclusively. These roots run inferiorly, anteriorly, and medially on the anterolateral aspect of the vertebral column and come together at the level of the ninth or tenth vertebra to form the nerve. Near the origin of the formed nerve is usually found (70% of cases) an enlargement called the *splanchnic ganglion of Lobstein* (14). Its downward course in the thorax is described in Chapter 60 (see Figure 60-8). It passes through the diaphragm within the space that separates the internal from the external crus and enters the abdominal cavity. In the abdomen it has a short course in an anteromedial and inferior direction before it breaks up into its terminal branches, which spread out like a fan and terminate in the celiac ganglia; some also terminate in the ipsilateral aorticorenal ganglion. In its course it gives off fine collateral filaments that join the esophageal and aortic plexuses, intercostal vessels, azygos veins, and aortic plexus. Some filaments supply the diaphragm and contents of the spinal canal, and some filaments join the middle thoracic splanchnic nerve.

Lesser Splanchnic Nerve. The lesser splanchnic nerve is usually formed by two roots that arise from the tenth and eleventh ganglia and soon thereafter converge into one trunk that descends inferiorly, anteriorly, and medially on the anterolateral aspect of the vertebral column. This then passes through the diaphragm accompanied by the superior thoracic splanchnic nerve to terminate in the ipsilateral aorticorenal ganglion, although some fibers can terminate in the celiac ganglia, and one or two filaments pass to the renal plexus, or superior mesenteric plexus.

Least Splanchnic Nerve. The least splanchnic nerve is usually formed by one fine root that arises from the last thoracic ganglion and then passes anteriorly, medially, and a little inferiorly below the middle thoracic splanchnic nerve. It perforates the diaphragm along with the other two thoracic splanchnic nerves to enter the abdominal cavity, where it proceeds to and ends in the posterior renal ganglion and the adjacent part of the renal plexus.

Lumbar Splanchnic Nerves. The lumbar splanchnic nerves, usually four, arise from the lumbar portion of the paravertebral sympathetic chain and pass anteriorly to join the celiac intermesenteric (abdominal aortic) and superior hypogastric plexuses. The L-1 splanchnic nerve arises from the uppermost lumbar ganglion and joins the celiac, renal, and intermesenteric (aortic) plexuses (see Fig. 65-6). The L-2 splanchnic nerve arises from the second (and sometimes third) ganglia and joins the lower part of the aortic plexus. The L-3 splanchnic nerve arises as two or three stouter roots from the second, third, or fourth ganglia and passes in front of the common iliac vessels to join the superior hypogastric plexus. The lowest (usually the L-4) splanchnic nerve arises from the lowest lumbar ganglion and passes posterior to the common iliac vessels to join the lower part of the superior hypogastric plexus or the hypogastric nerve. On one or both sides it supplies twigs to the aorta, inferior vena cava, and common iliac artery and communicates with the gonadal (spermatic or ovarian) and ureteral plexuses.

Celiac Plexus and Subsidiary Plexuses

The celiac plexus, also called the *solar plexus* and sometimes the *epigastric plexus*, is the largest prevertebral plexus. It is composed of two or more large aggregates of ganglion cells, the right and left celiac ganglia, a number of smaller ganglia, and a dense network of parasympathetic and sympathetic efferent and afferent fibers that enmesh these ganglia (see Fig. 65-6). The plexus is situated in the epigastrium just anterior to the crura of the diaphragm and the body of the first lumbar vertebra, surrounding the celiac artery and the root of the superior mesenteric artery. The entire plexus lies posterior to the stomach and the omental bursa. The right half of the plexus lies behind the upper part of the head of the pancreas, the small part of the duodenum, the lower end of the portal vein, and the inferior vena cava. The left half is also covered by the pancreas and splenic vessels. In the midline, the plexus rests anterior to the beginning of the abdominal aorta. The inferior phrenic arteries are superior and the renal vessels inferior to the plexus, while the suprarenal vessels often pass through interstices in the plexus (14,15,16 and 17).

The celiac plexus and ganglia are joined by the superior and middle thoracic splanchnic nerves of both sides, which contain sympathetic preganglionic and afferent fibers, and also by branches of the vagus nerves, composed of preganglionic parasympathetic and afferent fibers as well as sensory fibers from the phrenic nerves. Many of these fibers cross from one side to the other to form a dense network. Numerous secondary or subsidiary plexuses are derived from the celiac plexus; these follow the branches of the celiac artery and also surround neighboring arteries.

The celiac plexus occupies an area approximately 3 cm long and 4 cm wide. In the transverse plane, it occupies the region between the two adrenal glands and extends beyond the lateral borders of the aorta on both sides. In the longitudinal plane, it occupies the area delineated by the celiac artery above and the renal arteries below. It is thus situated in front of the entire L-1 vertebra and often even the upper portion of the L-2 vertebra. The plexus lies in loose areolar tissue, which

is rich in fat.

Prevertebral Ganglia. The ganglia associated with the celiac plexus and its subsidiary plexuses are, according to the classic description, in three pairs: the celiac, the aorticorenal, and the superior mesenteric. According to Hovelacque (18), however, such a description, although serving the purpose of simplicity, is merely schematic, because the actual number and shape of the ganglia are variable (see Fig. 65-6).

Celiac Ganglia. The celiac ganglia, usually described as two large masses, semilunar in shape and located on each side of the origin of the celiac artery, in reality vary in number, shape, and size (18). In most cases their surfaces are irregular and reddish gray, and they are flattened anteroposteriorly. Sometimes they are semilunar in shape with the concavity facing superomedially or inferolaterally, whereas at other times they are quadrilateral or stellate in shape. Frequently, one or both are divided into several small portions that are scattered around the celiac axis.

Because of the variability in size and shape, it is difficult to give exact measurements. On average, the celiac ganglia collectively are 20 to 25 mm by 10 to 15 mm and 3 to 5 mm in thickness (14,16). The distance separating them also varies, ranging from 6 or 7 mm up to as much as 20 to 25 mm. The ganglia receive the terminations of the ipsilateral superior and middle thoracic splanchnic nerves that synapse with cell bodies of postganglionic neurons contained within the ganglia. The celiac ganglia are covered by a dense network of fibers that cross from one side to the other, some passing anteriorly to the celiac artery and others passing posteriorly to it.

Aorticorenal Ganglia. The aorticorenal ganglia can be regarded as the detached lower and outer portions of the celiac ganglia, to which they are almost always united by one or more bands containing nerve fibers and ganglion cells (16). They are intermediate in size between the celiac and superior mesenteric ganglia and are fusiform or irregular in shape. Usually, they are situated above the origin of the renal arteries, although sometimes they are anterior or anterosuperior to the arteries. Each ganglion receives fibers from the middle and inferior thoracic splanchnic nerves. The two aorticorenal ganglia are often connected by fibers that cross in front of the aorta.

Superior Mesenteric Ganglion. The superior mesenteric ganglion is a small irregular mass approximately 5 mm in diameter that lies on the anterior surface of the aorta just above, or occasionally below, the origin of the superior mesenteric artery.

Secondary (Subsidiary) Plexuses. The secondary plexuses arising from or connected with the celiac plexus include the phrenic, gastric, hepatic, splenic, adrenal, renal, superior mesenteric, intermesenteric (abdominal aortic), spermatic (ovarian), and inferior mesenteric plexuses.

Phrenic Plexus. The phrenic plexus arises from the upper part of the celiac plexus and from some sensory filaments contributed by the phrenic nerves (see Fig. 65-3). Both sets of nerves accompany the inferior phrenic arteries to become distributed to the diaphragm and send a few filaments to the suprarenal glands by way of the suprarenal plexus (see Fig. 65-6). On the right side the plexus closely accompanies the inferior phrenic artery. In addition, the left plexus sends some filaments to the esophagus, while the right plexus sends filaments to the inferior vena cava and to the hepatic plexus. At the point of junction of the right phrenic plexus with the phrenic nerve is a small mass called the *phrenic ganglion* (see Chapter 60). Because this plexus contains sensory fibers that pass to the phrenic nerves and into the spinal cord at the C-3 to C-5 level, it has special clinical importance in regard to referred pain caused by disease in the upper abdomen.

Hepatic Plexus. The hepatic plexus, the largest of the subsidiary plexuses, receives fibers directly from the left and right vagus nerves that do not traverse the celiac plexus and also receives sensory fibers from the right phrenic nerve (see Fig. 65-7). The plexus accompanies the hepatic artery, portal vein, and their branches into the liver; in the liver the nerves are confined to the vicinity of blood vessels. Branches from the hepatic plexus form tertiary plexuses that accompany all the branches of the hepatic artery, including the right gastric, gastroduodenal, and cystic arteries.

The *right gastric plexus* is reinforced by filaments from the pyloric branches of the vagal trunks and supplies sympathetic, parasympathetic, and sensory fibers to the upper parts of the anterior and posterior surfaces of the stomach and also the pylorus (see Fig. 65-8).

The *gastroduodenal plexus* accompanies the gastroduodenal artery and its branches, the right gastroepiploic and superior pancreaticoduodenal arteries. Branches from the gastroduodenal plexus pass to the pylorus and superior part of the duodenum, while many of the nerves that pass with the right gastroepiploic artery supply the right part of the stomach and its greater curvature.

The *superior pancreaticoduodenal plexus* supplies the descending part of the duodenum, head of the pancreas, and lower part of the bile duct. Fibers passing to the gallbladder arise from the cystic plexus, with some branches also passing to the bile ducts. These various plexuses contain both afferent and efferent sympathetic and parasympathetic fibers that supply the liver, gallbladder, stomach, duodenum, and pancreas. The functions of the sympathetic and parasympathetic fibers in these structures are presented in Table 65-4. The sensory fibers associated with the vagus probably constitute the afferent limb of subconscious reflexes, while the sympathetic afferents mediate nociceptive and other sensory impulses.

Structures or organs	Sympathetic stimulation	Adrenergic receptors	Parasympathetic stimulation
Stomach:			
Motility	Decreased	α,β	Increased
Sphincters	Contracted	α	Relaxed
Secretion	Inhibited	α	Increased
Liver	Glycogenolysis Gluconeogenesis	β	
Gallbladder and biliary ducts	Relaxed	β	Contracted
Pancreas	Vasoconstriction		
Insulin secretion	Reduced	α	Increased secretion
Spleen	Contraction of capsule	α	
Intestines			
Motility	Decreased	α,β	Increased
Sphincters	Relaxed	β	Contracted
Secretion	Decreased	α	Increased
Suprarenal glands	Secretion of 80% epinephrine, 20% norepinephrine	α	
Kidneys	Arteriolar constriction	α	Controls glomerular secretion
Ureters, bone and motility	Decreased	α	Increased

TABLE 65-4. Physiologic responses to autonomic stimulation

Left Gastric Plexus. The left gastric plexus is derived from the celiac plexus and from both vagal trunks that pass directly to it. It accompanies the left gastric artery along the lesser curvature of the stomach (see Fig. 65-8B). The plexus supplies fibers to the stomach and to the abdominal portion of the esophagus through the subsidiary plexuses that accompany the two or three esophageal branches of the left gastric artery. The gastric sympathetic nerves are motor to the pyloric sphincter but are inhibitory to the muscular coat of the stomach.

Splenic Plexus. The splenic plexus is formed by branches from the celiac plexus, left celiac ganglia, and posterior vagal trunk. It accompanies the splenic, pancreatic, short gastric, and left gastroepiploic arteries (see Fig. 65-9). The small plexus around the left gastric or left gastroepiploic artery communicates with gastric branches of the posterior vagal trunk and with gastroesophageal branches of the left phrenic plexus that run to the gastroesophageal junction (16,17). The plexus around the pancreatic branch supplies the pancreas. The fibers that terminate in the spleen are principally, if not wholly, sympathetic efferents and afferents, with the efferents terminating on blood vessels and unstriated muscle of the splenic capsule and trabeculae (14,15 and 16). The sympathetic afferents convey nociceptive impulses provoked by rapid distension of the splenic capsule.

The subsidiary plexus that surrounds the pancreatic branches of the splenic artery supplies the neck, body, and tail of the pancreas. The subsidiary plexus that surrounds the short gastric branches of the splenic artery is distributed to the fundus of the stomach, while the plexus around the posterior gastric branch contributes fibers to the fundus and posterior wall of the stomach. The subsidiary plexus surrounding the left gastroepiploic branch contributes fibers to the upper third of the greater curvature of the stomach. The plexuses that continue along the omental branches of the left gastroepiploic artery, and those of the right gastroepiploic artery, supply nerve fibers to the greater omentum.

Suprarenal Plexuses. The suprarenal plexuses are formed by branches from the celiac plexus, celiac ganglia, phrenic plexus, and ipsilateral superior thoracic splanchnic nerves (see Fig. 65-6). The plexuses supply the suprarenal glands, which, relative to their size, have a larger autonomic nerve supply than any other organ (16). Most of the nerve fibers are preganglionic sympathetic fibers that terminate and synapse with the large chromaffin cells, the pheochromocytes, which are

analogous with postganglionic sympathetic neurons. The suprarenal plexuses also have parasympathetic preganglionic fibers and afferent fibers (15).

Renal Plexuses. The renal plexuses are formed by filaments from the ipsilateral celiac ganglion, celiac plexus, aorticorenal ganglion, inferior thoracic splanchnic nerve, L-1 splanchnic nerve, aortic plexus, and superior hypogastric plexus (14,15,16,17 and 18) (see Fig. 65-6). Collections of nerve cells (ganglia) are found in each plexus, with the largest, the renal ganglion, usually lying posteriorly or posterosuperiorly to the commencement of the renal artery. The plexus continues into the kidney around the branches of the renal artery to supply the vessels and renal glomeruli and tubules, particularly the tubules in the cortex of the kidney (19). Most fibers of this plexus are sympathetic efferents that have vasomotor function and sympathetic afferents that transmit nociceptive information. The plexus also has parasympathetic preganglionic fibers that synapse in small ganglia in the hilum of the kidney, but not within its parenchyma (16,17). The renal plexus gives off fibers that contribute to the upper third of the ureteric plexus that supplies the ureter and also contributes to the testicular or ovarian plexuses. The middle third of the ureteral plexus is derived from the superior hypogastric plexus and hypogastric nerve, while the lower part is derived from the hypogastric nerve and inferior hypogastric plexus (these are discussed in detail in Chapter 68, and the testicular and ovarian plexuses are discussed in Chapter 70, which introduces the section on pain in the pelvis).

Superior Mesenteric Plexus. The superior mesenteric plexus is a continuation of the lower part of the celiac plexus but also receives fibers directly from the posterior vagal trunk and from the celiac and aorticorenal ganglia of both sides. The superior mesenteric ganglion is often incorporated into the origin of the plexus (see Fig. 65-10; also see Fig. 66-8). The plexus surrounds the superior mesenteric artery, accompanying it into the mesentery, and divides into a number of secondary plexuses that are distributed to all structures supplied by the artery. These include the following plexuses: (a) the pancreaticoduodenal plexus, which contributes to the nerve supply of the pancreas; (b) the jejunal and ileal plexuses, which supply the small intestine; and (c) the ileocolic, right colic, and middle colic plexuses, which supply the corresponding parts of the large intestine. The sympathetic efferent fibers decrease motility, relax the sphincters, and inhibit secretions of the intestine, while the parasympathetic fibers have opposite effects. The parasympathetic afferents have a subconscious reflex function, while the sympathetic afferents participate in the reflexes but also convey nociceptive information (see Table 65-4).

Abdominal Aortic Plexus. The abdominal aortic plexus, also known as the *intermesenteric plexus*, is formed by fibers contributed by the celiac plexus and ganglia and by the L-1 and L-2 splanchnic nerves (see Fig. 65-6). The plexus is situated on the anterior and lateral parts of the aorta between the origins of the superior and inferior mesenteric arteries. It is continuous above with the celiac plexus and celiac and aorticorenal ganglia and below with the superior hypogastric plexus. Fibers derived from this plexus contribute to the formation of the adrenal, renal, spermatic, inferior mesenteric, iliac, and superior hypogastric plexuses and also supply the inferior vena cava.

Inferior Mesenteric Plexus. The inferior mesenteric plexus is derived chiefly from the aortic plexus but also receives fibers from the L-2 and L-3 splanchnic nerves (see Fig. 65-11). Below the origin of the artery, the plexus is connected by oblique bundles with the superior hypogastric plexus and with parasympathetic fibers from the sacral splanchnic nerve (16,17). Usually, the parasympathetic supply to the distal colon and its vessels runs in fine long nerves that arise on each side by several rootlets from the inferior hypogastric (pelvic) plexus and hypogastric nerves or as direct offshoots from the sacral splanchnic nerves (nervi erigentes), passing upward to join the inferior mesenteric plexus (for a more detailed description of these nerves see Chapter 70). The plexus surrounds the inferior mesenteric artery and then forms a subsidiary plexus. Near its beginning at the origin of the artery, the inferior mesenteric ganglion, or a number of small discrete ganglia, is found. Through its subsidiary plexuses around the superior and inferior left colic arteries it supplies the left part of the transverse colon and the descending colon, and through the superior rectal plexus it supplies the sigmoid colon.

Superior and Inferior Hypogastric Plexuses

The superior hypogastric plexus, considered a continuation of the abdominal aortic plexus with contributions from other parts; the hypogastric nerve; and the inferior hypogastric plexuses are discussed in Chapter 65 because they contribute sympathetic, parasympathetic, and afferent nerves to the pelvic viscera. Illustrations depicting the nerve supply for each of the major organs within the abdomen proper are presented in the respective chapters.

Intrinsic (Enteric) Nervous System

The gastrointestinal tract is supplied by the extrinsic nerves mentioned previously and also by an intrinsic nervous system consisting of cell bodies and short axons. Two major and three minor networks or plexuses of neurons and their axons form the intrinsic nervous system (20,21,22 and 23). The two main ganglionated plexuses are the myenteric (Auerbach's) plexus and the submucosal (Meissner's) plexus (see Fig. 65-12).

Auerbach's plexus lies between the longitudinal and circular muscle layers and consists of three plexiform networks (20,21). The primary network is a coarse structure consisting of large bundles of unmyelinated fibers that link various ganglia. Although its meshes vary within relatively wide limits in regard to size and form, they exhibit primarily a longitudinal arrangement (20). The secondary plexus is intimately connected with the primary one but is made up of more slender bundles of nerve fibers, with few neurons interspersed. This secondary plexus is, in turn, continuous with the tertiary plexus and lies in intimate contact with the circular muscle. Nerve fibers extend from this plexus into the muscles that terminate in relation to muscle cells.

The submucous, or Meissner's, plexus consists of a meshwork of relatively slender fiber bundles, with small ganglia located at nodal points (20). It is not confined to a definitively limited zone in the submucous layer; some fiber bundles lie near the circle of muscle layer and others lie close to the muscularis mucosae. Mechanical separation of the mucosa and submucosa from the outer muscular layer usually effectively removes the submucous from the circular muscle layer.

In addition to these two main plexuses are three variably developed plexuses (22): (a) the subserosal plexus, situated beneath the serosa and consisting of bundles of nerve fiber with few ganglia; (b) the deep myenteric plexus, situated within the circular muscle coat, similar in structure to the tertiary network of Auerbach to which it is continuous, and also connected with the adjacent submucous plexus; and (c) the mucous plexuses, which are widely distributed and are further named according to their positions in the mucosa—namely, subglandular, intraglandular, and intravillous mucous plexuses. These plexuses usually contain no neurons and are mere extensions of submucous plexuses.

Auerbach's plexus is associated with smooth musculature of the gut from the esophagus to the internal anal sphincter, including the biliary tract, and is also present in the striated muscle of the upper esophageal pharynx (21). The function of Auerbach's plexus in the striated muscle is not known, but it might innervate the muscularis mucosae, glands, and blood vessels (22). The density of ganglia in the myenteric plexus varies in different parts of the gut (24). In the esophagus the ganglia are scantier than in the stomach, small bowel, or colon. In the colon, the greatest concentration of neurons occurs in relation to the tenia. Few ganglia are found in the distal 2- to 3-cm segment of the rectum. This should be borne in mind to avoid making a wrong diagnosis of Hirschsprung's disease (25).

The ganglia in the submucous plexus are more abundant in the small bowel than in other parts of the gut. No ganglia are in the submucous plexus in the esophagus or in the anal canal distal to the pectinate line. During development the enteric ganglia first appear in the proximal gut wall and then migrate caudally toward the anus.

Enteric nerves are of three types (26). Type I cells have numerous thick dendrites and a single slender axon that enters one of the fasciculi to reach the target cells. These neurons are thought to have a motor function. Type II cells have long smooth dendrites that arise from the mucosa and are thought to be sensory neurons. Type III cells have dendrites of intermediate length that terminate in the same or neighboring ganglia; they might serve as interneurons or integrating neurons. It is thought that the submucous plexus contains only type II (sensory) neurons.

Electrophysiologic studies have found several distinct types of enteric neurons (27,28): (a) neurons that respond to sensory stimuli; (b) neurons that generate patterned outputs of spontaneously discharged action potential; and (c) neurons that show temporal coupling of firing with other neurons, suggestive of synaptic interaction between neurons. These results suggest that the enteric nervous system is capable of intrinsic integration and is involved in local reflex mechanisms (20).

The axons from the efferent intramural neurons are distributed to various effector cells, including the smooth muscle cells, secretory cells, absorptive cells, and endocrine cells. The axons branch and rebranch as they proceed to their target cells, and as they come into contact with the target cells, they end in a swelling that contains vesicles of neurotransmitters and they make synaptic contacts with the effector cells.

The intrinsic nervous system has contacts with the endings of axons of postganglionic sympathetic and parasympathetic neurons and afferent fibers that connect the intrinsic system with the central nervous system. This makes possible independent function by the intrinsic system; also, however, it can influence and be influenced by the extrinsic nervous system, which of course is under the influence of the central nervous system.

The gastrointestinal tract is rich in various cells that contain hormones and transmitter substances (22,29,30). A number of hormones are found together in the gut and in the brain, including gastrin, somatostatin, substance P, vasoactive intestinal polypeptide, and gastrin-releasing peptide. The gut also contains various chromaffin cells, particularly enterochromaffin cells. Some of these have a common origin in the neural crest and are included in a series of amine precursor uptake and decarboxylation (APUD) cells that share the common property of synthesizing and storing amines such as dopamine, histamine, and serotonin. These cells are probably innervated by the intrinsic autonomic nerves and thus might also influence the function of the intramural system, which appears to play a key role in the neuroendocrine regulation of the function of the gastrointestinal tract (22,31,32).

Summary of Neurologic Function

Parasympathetic and Sympathetic Nerves

The roles of the parasympathetic and sympathetic nerves are summarized in Table 65-4.

Afferent (Sensory) Innervation. The afferent fibers associated with the parasympathetic and sympathetic nerves are widely distributed throughout the gastrointestinal tract and other viscera in the abdomen. Approximately 90% of fibers in the vagus are afferents, and of these 80% to 90% are unmyelinated fibers (33). The rest are myelinated afferents of which the majority are A-d and a smaller percentage are A-b fibers. Studies in cats have shown that each greater splanchnic nerve contains 3,000 to 3,500 afferent fibers, which are less than 20% of the total numbers of fibers in this nerve (the remainder are preganglionic fibers) (6,33,34). The majority of these afferent fibers (2,000 to 3,000) are unmyelinated (C) fibers, 250 to 400 are A-d, and approximately 120 to 350 are A-b fibers. The lesser and least thoracic splanchnic nerves contain another 1,000 to 2,000 afferents, the lumbar splanchnic nerves contain approximately 4,600, and the sacral parasympathetic innervation contains approximately 7,300 afferents. Thus, it appears that a total of 22,000 to 25,000 spinal afferents (associated with splanchnic nerves and the sacral parasympathetics) are responsible for signaling afferent information from the abdominal and pelvic viscera of the cat.

Afferent fibers convey information about mechanical, chemical, thermal, and osmotic changes, which are transduced into impulses that are transmitted to integrating neurons in the neuraxis. In the neuraxis they are subjected to modulating influences and are transmitted either to efferent neurons at segmental levels or to the brainstem to provide information to the hypothalamus, limbic system, thalamic nuclei, and finally the cortex (see Chapter 3, Chapter 4 and Chapter 5).

Under physiologic conditions, these afferent fibers are involved in the regulation of visceral functions, in sensations, and in various spinal and supraspinal reflexes.

The mechanoreceptors consist of two types, those with a slowly adapting response able to detect static and dynamic events and those with a rapidly adapting response able to detect dynamic events only (35,36).

Slowly adapting mechanoreceptors have been shown to exist in the walls of the esophagus, stomach, and intestine; are *in series* with muscle fibers, and act as tension receptors rather than length receptors (37). They are stimulated by balloon distension and by spontaneous or drug-induced muscle contraction. These receptors lie in the muscle layer, and those in the stomach are of two types: receptors with a low-tension threshold that excite gastric centers in the neuraxis and cause reflex gastric activity, and those with a higher threshold that have inhibitory effects (37). It has been speculated that low-tension-threshold receptors help to set the level of smooth muscle contraction in the quiescent stomach, and when the stomach starts to contract, input from these receptors controls the timing and force of contraction. When the contraction becomes strong it can be inhibited by the high-threshold mechanoreceptors. The slowly adapting tension receptors also signal sensations of gastric distension and can mediate hunger pains resulting from gastric contraction in an empty stomach (22,37).

Rapidly acting mechanoreceptors are those that give an *on* and an *off* response when a steady mechanical stimulus is applied and later removed, but give no response while the stimulus is held steady. Rapidly adapting receptors have been found in the mesentery and include pacinian corpuscles beneath the serosa of the small intestine (e.g., movement receptors) and receptors in the muscularis mucosa of the intestine (muscularis mucosa receptors) and in the mucosa (mucosal receptors). The rapidly adapting receptors serve various functions. Mesenteric pacinian corpuscles located at the root of the mesentery and next to the branches of the mesenteric arteries stabilize blood flow through the splanchnic bed. The movement receptors located beneath the submucosa signal distortion of the intestine and the dynamic phase of inflation or deflation of an intraluminal balloon. The muscularis mucosa receptors are thought to act as the flow receptors, while some mucosal receptors are sensitive to tactile stimulation. The transitional epithelium in the anal canal possesses sensitive receptors that can distinguish between gas and liquid (36). They serve to let the flatus pass while retaining the feces.

Chemoreceptors can be activated by a chemical substance that acts as a stimulus either by its structural configuration or by its physical characteristics. Most of the chemoreceptors in the gastrointestinal tract, such as acid receptors and osmoreceptors, are activated by the physical characteristics of chemical substances (35,36,38). Acid receptors have been described in the gastric mucosa and duodenal mucosa and osmoreceptors have been identified in the duodenal mucosa (22,35).

In Chapter 3 and Chapter 7, mention is made of Cervero's experiments on the biliary duct of the ferret, in which he found low-threshold and high-threshold fibers and concluded that the high-threshold biliary afferents probably have a nociceptive function (39). His viewpoint was summarized in 1988 (40). JGnig and Morrison, however, in a comprehensive review (41), concluded that no evidence exists for a population of high-threshold afferents that would qualify as visceral nociceptors. Their analysis of an immense number of data on the functional and morphologic properties of spinal afferent neurons supplying the abdominal viscera led them to conclude that these neurons are functionally homogeneous (i.e., that the same population of afferents encodes various events that give rise to nonnoxious and noxious sensations, a number of reflexes, and to the regulation of viscera).

Most of the available data dispute both concepts and suggest that visceral sensory receptors encode nociceptive events by peripheral recruitment of receptors showing a wide range of threshold (summation). While this interpretation denies the existence of two distinct and separate populations of sensory receptors (nociceptive and nonnociceptive), it also does not support a notionally single population of afferent fibers with a narrow range of excitability threshold as claimed by JGnig and Morrison. Instead, it is based on the existence of different kinds of afferent fibers whose thresholds form a continuum ranging from anoxious to noxious levels. Thus, as the stimulus intensity increases, more and more of these receptors are activated and pain is felt by a process of central summation (38).

SUMMARY OF EVALUATION OF THE PATIENT

This section presents a general approach to the assessment of patients with abdominal pain. Each of the subsequent four chapters contains a more detailed description of the evaluation of patients presenting with disease suspected to involve specific organs. Obviously, other than in patients who are hemorrhaging and require urgent operative intervention, it is essential to obtain a detailed history and carry out a comprehensive physical examination, including a neurologic and orthopedic evaluation, as discussed in Chapter 12 and summarized in Table 60-1. In many cases it is also necessary to obtain laboratory data, including a complete blood count and urinalysis and, in specific cases, roentgenographic studies to detect free air and other soft tissue pathology. The text by Weiner is particularly useful in the differential diagnosis of acute abdominal pain (42).

History

As emphasized in Chapter 12 and elsewhere in this book, an orderly, systematic, and painstakingly detailed history is the most important aspect of the patient's assessment, and often the correct diagnosis can be made on the basis of the information obtained. Particularly important is inclusion of information about the rapidity of onset of the pain, its quality, intensity, duration, and temporal characteristics, and factors that relieve and aggravate it. If the pain has been present for several days before the patient seeks a physician's counsel, it is important to ascertain whether any of its features have changed and what time of the day the pain is better and what time it is worse. The patient should be asked specifically what effects the following activities or functions have on the pain: eating, swallowing, belching, deep breathing, coughing, straining, release of flatus, defecation, urination, lateral or forward flexion of the trunk or other movements, and supine and prone positions. Specific information should be obtained about associated symptoms and signs or phenomena such as nausea, vomiting, dyspnea, hematemesis, hemoptysis, melena, and the presence of weakness or numbness in various parts of the body. Details about the history of the pain are presented below.

Physical Examination

The physical examination should begin with a simple critical inspection of the patient regarding the facies, color, degree of hydration, respiratory movements, and the various other parts of the examination listed in Table 60-1, beginning with the abdomen and then the chest. In regard to the examination, Silen (8) emphasized that the amount of information to be gleaned from the physical examination is directly proportional to the gentleness and thoroughness of the examiner. In a patient

suspected of having peritonitis, one should avoid palpating deeply and eliciting rebound tenderness because this markedly aggravates the pain and increases reflex muscle spasm. The same information can be obtained by gentle percussion of the abdomen (rebound tenderness on a miniature scale, a maneuver that can be far more precise and localizing). Asking the patient to cough elicits true rebound tenderness without the need for placing a hand on the abdomen. Moreover, the brusque illustration of rebound tenderness startles and induces protective spasm in a nervous or worried patient in whom true rebound tenderness is not present. It is especially important to carry out a rectal (and vaginal, if appropriate) examination in every patient with abdominal pain. Similarly, it is essential to examine the chest and spine to exclude referred abdominal pain caused by disorders in these structures.

Laboratory Studies

The results of the laboratory examination, including a complete blood count, should be integrated with the information obtained from the history and physical examination. The urinalysis is helpful in providing some indication of the state of hydration and in ruling out severe renal disease, diabetes, and urinary infection. Determination of blood urea nitrogen, blood sugar, and serum bilirubin levels can also be helpful. Silen (8) emphasized that the serum amylase determination is overrated in helping to reach a diagnosis of acute pancreatitis because many other conditions, such as perforated ulcer, strangulating intestinal obstruction, and acute cholecystitis, can be associated with a marked increase in its value.

Plain and upright or lateral decubitus roentgenograms are useful in helping to reach a diagnosis of intestinal obstruction, perforated ulcer, and various other conditions that can be associated with pneumoperitoneum. Other specialized tests can be used in connection with disease of the gastrointestinal tract, liver, gallbladder, and kidney (see Chapter 66, Chapter 67, Chapter 68 and Chapter 69). There is little question that modern imaging techniques, such as ultrasound, computed tomography, and magnetic resonance scanning and radionuclide studies have led to major improvements in diagnostic accuracy.

Key Points to the Differential Diagnosis

The following points given here, as in Chapter 60, can help the physician in making a differential diagnosis. These include the various characteristics and location of the pain at the time of onset and during the interval between onset and the time the patient is being evaluated, as well as at the time of evaluation, its relation to other bodily functions, and associated signs and symptoms. Much of the information contained in this section is taken from the first edition of this book (43), from material by Currie (44) and others (45,46), and from material contained in the next four chapters.

Characteristics of Pain at Onset

Site of the Pain. The patient should be asked to point to the site of pain when the pain began. It is important to determine, if the pain was in the midline, whether it was located in the epigastrium, periumbilical area, or hypogastric region and, if it was felt on the side, whether it was in the upper or lower part of the side. The conditions that produce pain in these regions are listed in the following sections.

Time Course and Circumstances. Sudden severe pain that occurs instantaneously is a sign of perforated ulcer; rupture of an abscess or hematoma; rupture of the esophagus; rupture of ectopic pregnancy; rupture of infarct of an abdominal organ, heart, or lung; spontaneous pneumothorax; ruptured or dissecting aortic aneurysm; or ruptured spleen. Table 65-5 lists these and other conditions according to the rate or time course of onset (43).

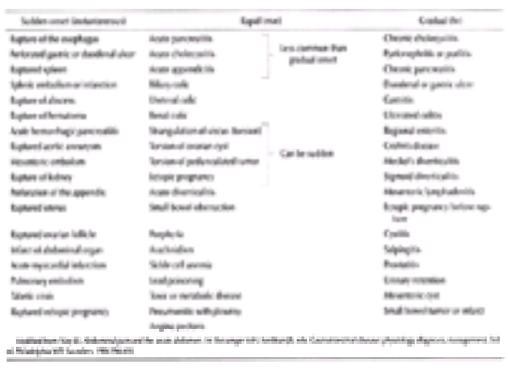

TABLE 65-5. Classification of abdominal pain according to the rate of onset

A clear statement of what the patient was doing at the time of onset of the pain is important (44). Did the pain follow an injury or intake of food, fluids, or alcoholic beverages? Did the pain occur while doing heavy work or carrying out a special movement? An injury to the upper abdomen, or to the lower chest and left flank, followed by sudden pain, should suggest rupture of the spleen. Pain that follows drinking alcohol should suggest pancreatitis, gastritis, peptic ulcer, or esophagitis. Sudden epigastric and lower chest pain that occurs with severe vomiting immediately after a large meal suggests perforation of the esophagus. If the pain developed during sleep and awakens the patient it is usually of organic rather than of psychological origin. Pain following endoscopic examination of any part of the gastrointestinal tract should immediately raise the suspicion of injury and possible perforation. Cramps followed by diarrhea are expected after a laxative, but cramps without diarrhea might indicate an obstruction (44). Sudden pain caused by straining, such as coughing, sneezing, or bearing down, suggests a neuropathic process if the pain is segmental or renewed enlargement of an abdominal aneurysm if the pain does not have a segmental distribution.

Quality. Sharp pain suggests pain of superficial cutaneous and somatic structural origin or pain that is being produced by a neuropathic lesion, such as radiculopathy of herpes zoster or that caused by compression of one or more of the lower seven thoracic spinal nerves. Segmental burning pain felt in the abdominal wall and lower part of the chest can be a result of postherpetic neuralgia or chronic neuropathic lesions of the spinal cord. Burning epigastric pain suggests peptic ulcer, gastritis, or esophagitis. Severe tearing abdominal pain suggests a dissecting aneurysm, while pain of the same quality in the anal region during defecation is caused by an anal fissure. Poorly localized, diffuse, *sickening* abdominal pain, difficult for the patient to describe, suggests abdominal visceral disease.

Intensity and Rate of Onset. The intensity or severity of the pain depends partly on the rate of change and the intensity of the stimuli. If the rate of change is slow, little or no pain is felt even though a pathologic process has progressed to a marked degree, whereas if the rate of change is rapid the pain is intense. Therefore, severe pain occurs with sudden obstruction of hollow organs, abrupt impairment of blood supply, chemical peritonitis caused by a ruptured viscus or hemorrhage, or acute inflammation. Moderate pain occurs with localized or chronic inflammatory disease and with progressive chronic obstruction by tumors or gradual enlargement of the liver, spleen, or kidney, with a consequent progressive increase in tension on the capsule. It is critically important to evaluate the patient's assessment of the intensity or severity of the pain within the framework of the psychological evaluation of the patient, as well as noting the specific manner (e.g., facial expression, pallor, frowning, clenched jaws, body position, movements) and the types of words the patient uses.

Time of Day or Month. Information should be obtained about the time of day and perhaps month that the pain is aggravated or relieved. Peptic ulcer pain, especially that caused by duodenal ulcer, tends to occur several hours after breakfast, at midmorning coffee time, just before lunch, several hours after lunch, immediately before supper, a few hours after supper, and during the night (44). Pain that awakens the patient at night is more frequently seen with duodenal ulcer disease. The pain of peptic ulcer rarely begins before breakfast, which is in contrast to the pain of irritable colon that usually starts early in the morning.

Back pain, especially if it causes the patient to awaken, is significant and usually indicates significant disease. Currie (44) attributed this to the fact that sleep allows increased autonomic activity so that the pain of peptic ulcer and cramping pain can be bothersome at night. Burning retrosternal pain, felt when the patient first lies down, is typical of heartburn caused by esophageal reflux. The constant pain of an infiltrating tumor can also be more distressing to the patient once the distractions of the day cease. Pain of primarily psychological origin rarely awakens the patient but, if such a patient has insomnia, it can produce troublesome discomfort at night (44).

Lower abdominal pain occurring 2 weeks before expected menstruation can be caused by bleeding at ovulation. The problem is not likely to occur in women who take contraceptive pills because these generally suppress ovulation and, consequently, pain from such bleeding is unlikely to occur. Currie (44) stated that a venereal infection can become established more readily during menstruation than at other times, and therefore acute salpingitis associated with lower abdominal pain occurs

more frequently soon after menstruation than at other times in the menstrual cycle.

Characteristics of the Pain since Onset and at Present Time

Any change in location, quality, intensity, and duration of the pain during the interval between onset and the time the patient is being evaluated is important in deciding on the diagnosis. In most diseases of the gastrointestinal tract the initial pain is true visceral pain and is felt as a poorly localized, diffuse, sickening pain in the midline. Spread of the infection and inflammation to the parietal peritoneum causes more localized and rather sharp burning pain in one region of the abdomen. The classic example is the steady or cramping periumbilical pain with acute appendicitis that changes to a well-localized pain at McBurney's point in the right lower quadrant of the abdomen. Similarly, biliary colic initially produces pain usually in the midline but, when this is complicated by acute cholecystitis, the patient begins to have pain in the right upper quadrant and often in the inferior angle of the right scapula (referred parietal pain). If the pathologic process worsens, empyema, gangrene, and perforation with diffuse peritonitis produce diffuse parietal pain and referred parietal pain in the right shoulder and trapezius region.

Steady visceral pain suggests increasing distension or ischemia, whereas cramping pain indicates exaggerated intestinal activity. Most patients with visceral pain are likely to experience change with time and therefore require repeated evaluation. This is especially true of patients with an undiagnosed abdominal pain because of possible changes in the quality and location of the pain and with probable changes in abdominal physical signs, any of which can help in the diagnosis (44). With each examination it is important to assess the location, quality, intensity, and temporal characteristics of the pain, as well as to determine factors that make the pain worse or better. These include such factors as the type and amount of food intake, changes in bodily functions, and, most important, the associated symptoms and signs.

Temporal Features. Acute continuous pain is encountered with peritonitis secondary to a ruptured viscus, impairment of blood supply, hemorrhage into the abdominal cavity, and an increase in the tension of the supporting elements of organs (capsules, ligaments, or mesentery). Intermittent or colicky pain is usually caused by intermittent and recurrent disturbances of the function of a hollow viscus. This can be produced by the following conditions: (a) intrinsic lesions, such as tumors, stones, intussusception, segmental enteritis, or extrinsic factors, such as hernias, tumors, bands, or torsion; and (b) metabolic ileus, which can either be spastic (e.g., lead intoxication, porphyria, uremia, diabetes, arachnidism, endocrine disorders) or mesenteric embolism or thrombosis, hypoxemia secondary to pneumonia, or potassium and sodium deficit. Constant chronic pain suggests a progressively developing or static lesion such as cancer. Constant pain felt in different parts of the abdomen usually implies a functional or emotional disorder rather than a progressive disease such as neoplasm.

Aggravating and Relieving Factors. Food or Fluid Intake.

The type, quality, and quantity of food eaten aggravate various pathophysiologic processes and consequently the intensity, character, and duration of the pain. Appealing and tasty foods, including sweets and such irritants as hot and cold foods, spices, acids, and alcoholic beverages, increase gastric acidity and thus aggravate the pain of peptic ulcer, gastritis, and reflux esophagitis (44). Food roughage is also said to increase the pain of peptic ulcer. Peptic ulcer pain becomes worse several hours after eating, when gastric acid is unbuffered because food has left the stomach. Intake of fatty food delays gastric emptying and thus delays the onset of the peptic ulcer pain that occurs after meals. Fatty foods stimulate the gallbladder to contract and can precipitate or aggravate biliary colic. Protein stimulates pancreatic secretion so that foods rich in protein can exacerbate the pain of pancreatitis. Food or alcoholic beverages tend to aggravate pancreatitis regardless of its cause. Lactose contained in dairy products causes bloating, cramps, and diarrhea in lactase-deficient individuals. Aerophagia, or air swallowing, can cause gastric distension with consequent abdominal distress within a few minutes of eating. Because eating stimulates the gastrocolic reflex that produces stimulation of the lower intestine, pain that might exist in the lower bowel is intensified by eating.

Relieving Factors. Factors that relieve abdominal pain are often opposite to those that aggravate it, although some exceptions to this rule have been noted (44). Fasting does not relieve but rather aggravates the pain of peptic ulcer; this can be relieved by bland, soft, unstimulating foods. Peptic ulcer pain is best controlled by food ingestion and antacid medication. The time that it takes for the medication to relieve burning pain is of significant diagnostic importance (44). Immediate relief on swallowing a liquid antacid localizes the site of irritation to the esophagus, whereas in patients with gastric or stomal ulcer relief occurs within 10 to 15 minutes, and that of duodenal ulcer takes 7 to 15 minutes (44). Avoiding fatty foods does not relieve biliary colic but might prevent some attacks.

Avoiding large meals or food altogether affords some relief in patients with painful lower intestinal disorders. The partial small bowel obstruction in Crohn's disease improves with starvation. Avoidance of lactose-containing dairy products can relieve abdominal bloating, cramps, and diarrhea. Similarly, belching relieves the distress of early postprandial pain caused by air swallowing. Pain from lesions of the lower bowel is relieved by a bowel movement, and urgent defecation followed by relief of periumbilical visceral pain occurs frequently in patients with regional ileitis. Unplugging a colonic obstruction by enemas or intubating a sigmoid volvulus produces immediate relief with passage of flatus and liquid feces. Temporary relief of abdominal pain might not indicate improvement but can be followed by worsening of the patient's condition. Frequent examples are the temporary relief of local pain consequent to rupture of an empyema of the appendix or gallbladder or to rupture of an acute paracolic abscess or other intraabdominal abscess into the peritoneal cavity.

Relation to Other Bodily Functions. Pain intensified by movement of the diaphragm suggests thoracic visceral disease, diaphragmatic disease, or subphrenic abscess or disease of the upper abdominal viscera. Pain aggravated by factors such as movement of the trunk, coughing, or sneezing suggests a radiculopathy or neuropathy caused by tumor or compression in the spine. Pain made worse by the supine position and improved by forward bending suggests acute pancreatitis or cancer of the pancreas. Recumbency, straining, or stooping aggravates the pain of esophageal reflux disease, whereas standing or forward bending relieves it. Back pain or upper abdominal pain that appears while the patient is standing an hour or so after drinking fluids, and is relieved soon after lying down, suggests poor drainage from the renal pelvis. Pain made worse by contraction of abdominal muscles suggests myofascial pain syndromes or trauma with hemorrhage into the muscle.

Associated Symptoms and Signs

Symptoms. The time relation of nausea, vomiting, diarrhea, and obstipation is an important point to aid the differential diagnosis between abdominal visceral disease and extraabdominal causes of pain (43,44,45 and 46). Vomiting without nausea suggests central nervous system disease (4). In patients with abdominal visceral disease, nausea and vomiting are usually accompanied by autonomic reactions such as sweating, pallor, palpitation, weakness, and fainting. Fainting alone can indicate the presence of severe pain. Other than diseases of the central nervous system, vomiting is preceded by anorexia and nausea. Nausea and vomiting occur readily in children with gastroenteritis, in alcoholics, and in adults with peptic ulcer disease. However, recurrent vomiting in children between ages 1 and 10 is more likely to be associated with a posterior fossa brain tumor than diseases of the abdominal viscera. Pyloric obstruction, with which the stomach is greatly distended, causes vomiting of large volumes. The large vomitus can contain recognizable vegetable matter eaten several meals prior to the vomiting but does not contain bile if the pylorus is completely occluded, whereas the presence of bile indicates that the pylorus and biliary ducts are open. Early and frequent vomiting occurs with small bowel obstruction. Toxic vomiting complicates pancreatitis, gastritis, peritonitis with advanced ileus, and high small bowel obstruction.

Signs. The presence of hyperalgesia or hyperesthesia that has a segmental distribution is of diagnostic value because it suggests a neuropathic origin of the pain. Marked localized tenderness to palpation indicates inflammation of visceral disease and, because it usually occurs directly over the involved organ, its diagnostic value is obvious. Reflex spasm of the abdominal muscles occurs with neuropathic and musculoskeletal disorders as well as with intraabdominal visceral disease but, in the latter, the spasm is more marked and is aggravated by deep pressure. In acute abdominal conditions, such as appendicitis, cholecystitis, and acute pancreatitis, spasm of the rectus muscle occurs over the involved structure. It is important to differentiate between voluntary and involuntary (reflex) spasm. The presence of distension indicates obstruction of the gastrointestinal tract (see Table 65-1 for causes). An abdominal mass associated with the pain is of course diagnostically significant because it could be the direct or indirect cause of the pain.

Location and Distribution. The location and distribution of pain at the time of assessment are important diagnostic characteristics. Segmental pain suggests radiculopathy or neuropathy, whereas pain that does not conform to dermatomal or peripheral nerve distribution is either visceral or musculoskeletal in origin. Abdominal visceral diseases have relatively specific areas of pain reference. For example, the pain of hepatic or biliary disease is in the epigastrium or right hypochondrium with radiation to the right posterior chest, lumbar region, and scapula. It is obviously important to know the possible causes of pain in the various regions of the abdomen (see Fig. 65-1).

Generalized Abdominal Pain. Generalized abdominal pain occurs with acute or chronic peritonitis caused by bacteria, tuberculosis, fungal infection, parasitic disease, granulomatous peritonitis, widespread neoplasm of the peritoneum such as primary mesothelioma, secondary carcinomatosis, vasculitis, Henoch-Schönlein purpura, eosinophilic peritonitis, Whipple's disease, and sclerosing peritonitis, as well as with acute intestinal obstruction, gastroenterocolitis, chronic ulcerative colitis, dysentery, epidural spinal cord compression, acute rheumatic fever, brucellosis, typhoid fever, sickle cell anemia, lead poisoning, and other generalized processes that cause metabolic disturbances of the gastrointestinal tract. Psychological and environmental factors are often primary causes of pain in the abdomen, especially in

children and women. This pain can be generalized or frequently can be in the periumbilical region.

Pain in the Epigastrium. Pain in the epigastrium is produced mainly by lesions of the stomach, gallbladder, duodenum, pancreas, liver, lower esophagus, heart, lungs, and certain nervous system disorders (see Fig. 65-13). The most important include chronic peptic ulcer, perforated ulcer, acute gastritis, pylorospasm, gastric carcinoma, acute and chronic pancreatitis (early), cholecystitis with lithiasis (early), perforation of the lower esophagus, chemical or bacterial esophagitis, myocardial infarction, pericarditis, congestive heart failure, and epigastric hernia. Less common causes include ulcer of the lower esophagus, aneurysm of the abdominal aorta, primary or metastatic tumors of the lower thoracic spinal cord, gastric crisis (tabes dorsalis), diaphragmatic hernia, acute hepatitis, diabetic acidosis, myofascial syndromes, pleurisy, and pericarditis.

Pain in the Right Hypochondriac Region. Pain in the right hypochondriac region is usually produced by diseases of the liver and gallbladder, hepatic flexure of the colon, diseases of the right chest or right hemidiaphragm, and disorders of the nervous system, muscle, and bone. The most important diseases include acute and chronic cholecystitis, biliary colic, cancer of the liver or gallbladder, abscess of the liver or pancreas, acute or chronic hepatitis, right hemidiaphragmatic pleurisy, subphrenic abscess, duodenal ulcer, right segmental or intercostal neuralgia, postcholecystectomy syndrome, right-sided slipped costal cartilage, pneumonia, and pleurisy. Less common causes include tender postoperative or posttraumatic scar, gas entrapment at the hepatic flexure of the colon, carcinoma of the hepatic flexure of the colon, and carcinoma of the bile ducts.

Pain in the Left Hypochondriac Region. Pain in the left hypochondriac region is usually caused by disease of the spleen, splenic flexure of the colon, lesion of the left chest, cancer of the tail of the pancreas, and neurologic and musculoskeletal disorders. The most common are embolism or thrombosis of the splenic vessels, splenic infarction, splenic abscess, splenomegaly, colitis, carcinoma of the splenic flexure of the colon, ruptured spleen, left-sided pneumonia, pleurisy, segmental or intercostal neuralgia, gas entrapment syndrome in splenic flexure of the colon, left-sided slipped costal cartilage, diaphragmatic hernia, pericarditis, and angina pectoris. Less common causes include contusion of the spleen, perisplenitis, abscess of the spleen, tuberculosis or amyloid disease of the spleen, congestion of the spleen, and neoplasm of the cardia of the stomach.

Pain in the Right or Left Lumbar Regions. Pain in the right or left lumbar (lateral) region is caused by disease of the kidney, ureters, head or tail of the pancreas, and colon. The most common causes include carbuncle or furuncle of the kidney, perinephritic abscess, pyelitis, pyelonephritis, renal abscess, tuberculosis of the kidney, tumor of the kidney, postnephrectomy pain syndrome, and segmental or intercostal neuralgia of one or more of the T-8 to T-11 nerves resulting from mechanical compression by tumors or vertebral disease.

Pain in the Periumbilical Region. Pain in the periumbilical region is usually a result of disease of the small intestine, appendix, cecum, body of the pancreas, or of neurologic or musculoskeletal disorders. The most common causes are acute intestinal obstruction, acute diverticulitis, chronic intestinal obstruction, Meckel's diverticulitis, embolism of the superior mesenteric artery, metabolic ileus, enterocolitis, regional enteritis, umbilical hernia, tabes dorsalis, bilateral segmental (T-9 to T-11) neuralgia, myofascial syndromes, and postoperative scars. Periumbilical pain in children and women is frequently caused by psychological and environmental factors. Less common causes include peptic ulcer, cholelithiasis, epithelioma of the umbilicus, pancreatic calculi, omphalitis, omental cyst or carcinoma, aneurysm of the abdominal aorta, tumors of the spinal cord, and segmental or intercostal neuralgia.

Pain in the Right Iliac Region. Pain in the right iliac region of the abdomen is usually caused by disorders of the appendix, small intestine, cecum, right kidney and ureter, and right uterine tube or ovary or by neurologic or musculoskeletal disorders. The most important include acute appendicitis, acute salpingitis, ruptured ectopic pregnancy, chronic salpingitis, oophoritis, twisted ovarian cyst, ruptured graafian follicle, acute oophoritis, Meckel's diverticulitis, renal colic (see Table 65-6 for causes), acute pyelitis, carcinoma of the cecum, inguinal hernia, Crohn's disease, iliac adenitis, acute epididymitis, right psoas or midabdominal abscess, segmental neuralgia of T-12 to L-1 nerves, and postoperative scar. Less common causes include inguinal adenitis, ileocecal adenitis, sarcoma of the ilium, suppurative periostitis of the ilium, strangulated retroperitoneal hernia, sigmoid volvulus, and aneurysm of the iliac artery.

Pain in the Left Iliac Region. Pain in the left iliac region is usually caused by disease of the sigmoid colon, left urinary tract, and internal genitalia (female) or by neurologic or musculoskeletal disorders. The most common causes include acute salpingitis, chronic salpingooophoritis, ectopic pregnancy, twisted ovarian cyst, ruptured graafian follicle, acute oophoritis, ulcerative colitis, midabdominal or psoas abscess, acute diverticulitis, carcinoma of the sigmoid colon, sigmoid volvulus, intussusception (children), intestinal obstruction, fecal impaction, inguinal hernia, acute epididymitis, left lower ureteral calculus, radiation of pain from disease of the kidney and pelvis, segmental neuralgia (e.g., herpes zoster, herniated disk, spinal tumor), segmental neuralgia of lower thoracic nerves (e.g., vertebral disease, osteoarthritis, tumors, deformity), iliohypogastric and ilioinguinal neuralgia (e.g., retroperitoneal tumor, infections), lumbar myofascial syndrome, left psoas abscess, and postoperative scar. Less common causes include disease of the hip and sacroiliac joints, aneurysm of the left iliac artery, strangulated retroperitoneal hernia, rectal polyp, and cyst of the canal of Nuck.

Pain in the Hypogastric Region. Pain in the hypogastric region is usually caused by urinary bladder, internal genitalia, and intestinal diseases or by neurologic or musculoskeletal disorders. The most common causes include acute cystitis, urinary bladder distension, prostatitis, seminal vesiculitis, hypertrophy of the prostate, calculi in the urinary bladder, carcinoma of the urinary bladder, ulcer of the urinary bladder, various diseases of female genitalia (including dysmenorrhea, acute salpingitis, ruptured ectopic pregnancy, acute or chronic endometritis, retrodisplacement of the uterus, carcinoma of the uterus, pelvic peritonitis, and prolapse of the uterus), acute diverticulitis, volvulus, intussusception, chronic colitis, rupture of the urinary bladder, tumors of the rectosigmoid, Meckel's diverticulum, chronic constipation, regional enteritis, various neuralgias (see previous discussion), myofascial syndromes, and occasionally postoperative scar.

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CHAPTER 66

Painful Diseases of the Gastrointestinal Tract

Richard W. Tobin and Michael B. Kimmey

Pain is an important and common symptom of gastrointestinal tract disease. It can be the first indication of a new pathologic process, or it can signify a change in a known condition. The recognition of the pain pattern and its significance is crucial to the early diagnosis and treatment of these problems. The relief of pain is frequently of diagnostic importance and is often the best indicator of successful treatment.

Abdominal pain is a common complaint. One survey of more than 1 million adults selected randomly from the U.S. population found current complaints of “stomach pain” in 13% and “pain in lower abdomen” in 11% of men and in 17% of women who responded to the questionnaire (1). Because abdominal pain caused by diseases of the gastrointestinal tract can be mimicked by painful conditions of other abdominal and extraabdominal structures, the evaluation of this symptom often requires physicians to use the full breadth of their medical knowledge.

A patient with abdominal pain of gastrointestinal origin can be completely disabled by this symptom. This disability involves all aspects of the patient's life, including bodily functions, employment, and family relations. These problems can be continuous, as in a patient with unresectable cancer or, more commonly, can be intermittent, as in inflammatory bowel disease or the irritable bowel syndrome. The complex interaction between the course of inflammatory bowel disease and psychological factors is a good example of the importance of the patient's family and social environment (2). Recurrent pain can cause the disruption of employment or family structure; psychosocial influences can affect the activity of the inflammatory bowel disease.

Painful gastrointestinal diseases have a large economic impact as well. For example, irritable bowel syndrome is a leading cause of absence from work and is the basis of extensive use of diagnostic facilities; drugs for peptic ulcer disease (PUD) and gastroesophageal reflux, such as the H_2-receptor blockers and proton pump inhibitors (PPIs), are among the most widely prescribed prescription medications.

In this chapter, the diagnostic and therapeutic principles outlined previously are applied to painful diseases of the gastrointestinal tract. The information is presented in four sections: General Considerations of Diagnosis and Management; Diseases of the Stomach and Duodenum; Diseases of the Small and Large Intestines; and Diseases of the Anus and Rectum. The beginning of each section contains a brief discussion and illustrations of the anatomy and nerve supply of each specific viscus, contributed in part by Bonica.

GENERAL CONSIDERATIONS OF DIAGNOSIS AND MANAGEMENT

The management of abdominal pain caused by gastrointestinal disease is based on accurate diagnosis. The history, physical examination, and use of selected laboratory tests and procedures usually yield the correct diagnosis and a list of differential diagnoses, and help to determine further management. The severity and acuteness of pain often determine the pace of further diagnostic testing. This chapter does not discuss extraintestinal or extraabdominal causes of abdominal pain because they are presented in Chapter 65, Chapter 67, Chapter 68, and Chapter 69.

History

The character and location of the pain often help to suggest the mechanism of the pain. The location, intensity, rate of onset, quality, duration, frequency, time of day, and relationship to factors that increase or decrease the pain should be determined for each pain described by the patient. The sudden onset of severe pain that does not diminish, for example, is characteristic of a perforated viscus, embolism, torsion, or hemorrhage. Crampy intermittent pain is commonly caused by intestinal disease, but urinary system and fallopian tube problems can also cause crampy pain. Pain severity can be a misleading feature because of individual differences in pain perception or responses to painful stimulation. Nonetheless, the most severe pains of abdominal origin are caused by intestinal infarction, perforated ulcer, dissecting aortic aneurysm, and ureterolithiasis. Associated symptoms are also useful in diagnosis. Upper gastrointestinal symptoms of nausea, vomiting, anorexia, and bleeding should be sought. Useful lower digestive tract symptoms include diarrhea, constipation, flatulence, and bleeding, as well as stool color and caliber. A review of urinary and gynecologic symptoms should also be obtained. Other systemic symptoms, such as weight loss or fever, are also helpful.

Physical Examination

Physical examination of the patient with abdominal pain often determines the immediate management course. General examination can reveal signs of increased autonomic activity that are associated with visceral pain, such as flushing, diaphoresis, tachycardia, and mydriasis. Body posture can suggest certain diagnoses. Patients with intestinal or renal colic move frequently in an attempt to decrease the pain, often in a writhing fashion; on the other hand, patients with peritonitis lie quietly on their back, usually with knees and hips flexed to reduce pain. Abdominal examination must be thorough and include inspection, auscultation, palpation, percussion, and rectal examination. Signs of peritonitis on examination dictate a more expedient evaluation, usually culminating in surgical exploration of the abdomen.

Laboratory Evaluation

Laboratory evaluation should be directed by the diagnoses suggested by the history and physical examination. Hematocrit, white blood cell count, and urinalysis are useful and inexpensive tests that are obtained on most patients with abdominal pain. Serum liver function tests (e.g., bilirubin, alanine aminotransferase, alkaline phosphatase), creatinine, and amylase or lipase can be useful for excluding diseases of the liver, bile ducts, kidney, and pancreas. Abdominal roentgenograms are useful in the acute setting in patients with moderate or severe abdominal tenderness, after abdominal trauma, and when the clinician suspects bowel obstruction, ischemia, perforation, or renal and biliary calculi (3). *Helicobacter pylori* infection in the stomach has been found to be closely associated with PUD. Evidence for *H. pylori* infection can be obtained by serum antibody testing, urease-based testing (of gastric biopsy specimen or by urea breath test), or by histopathologic examination of gastric mucosa (4).

Contrast radiography and fiberoptic endoscopy of the gastrointestinal tract are complementary in the diagnosis of diseases of the stomach, proximal small intestine, and colon (5,6). The choice of test depends on the clinical situation and on local availability and expertise. A study comparing upper endoscopy and the double-contrast barium meal in patients with upper gastrointestinal symptoms found endoscopy to be particularly useful in patients who were unable or unwilling to cooperate with the maneuvers required for a radiologic examination (5). Several studies have suggested that endoscopy is more specific and sensitive than

roentgenography. Diagnosis of small intestinal disease depends primarily on radiographic examination, although small bowel enteroscopy can be helpful in certain circumstances. Plain abdominal radiographs, contrast examinations, arteriography, ultrasound, and computed tomographic (CT) scanning are useful in the diagnosis and management of intestinal causes of abdominal pain (7).

Pathophysiology

Understanding the mechanism of gastrointestinal tract pain is diagnostically useful. Most pain from the gut begins with stimulation of visceral pain receptors (see Chapter 3). Relatively little is known about the anatomy and physiology of gut pain receptors (8). Mucosal and serosal inflammation, traction on the mesentery, rapid luminal distension, ischemia, and forceful smooth muscle contraction under isometric conditions (i.e., with obstruction distal to the contraction) are known stimulants of these pain receptors (8). These receptors are endings of the A-d and C afferent nerve fibers that accompany the sympathetic nerves from the stomach and small and large intestine, which pass through the celiac plexus and subsidiary plexuses, the splanchnic nerves, the sympathetic chain, and the white rami communicantes and have their cell bodies in dorsal root ganglia of spinal nerves. Pain fibers from the rectum accompany the parasympathetic fibers to the dorsal root ganglia of the S-2 to S-4 spinal nerves. Central nervous system pathways for visceral afferent (nociceptive) fibers are similar to those of somatic afferent nerves. Cortical areas receiving visceral pain sensations are intermixed with those receiving somatic pain input (see Chapter 5).

The characteristics of visceral pain have been described in Chapter 3 and Chapter 12. Visceral pain caused by distension, inflammation, or ischemia of the gut can be a continuous aching or gnawing, or can be of a burning character (9,10). An intermittent cramping sensation is produced when a strong smooth muscle contraction is the source of pain. Forceful gut contraction can be a result of increased peristalsis without obstruction, as in gastroenteritis, or it can be stimulated by distal mechanical obstruction. Visceral pain is generally poorly localized, is often described as deep within the abdomen, and can be associated with signs of autonomic overactivity. This type of pain is most commonly felt in the midline because most areas of the gut have bilateral spinal connections. Some healthy subjects and many patients with the irritable bowel syndrome, however, have lateralizing pain in response to luminal distension (11).

Gastrointestinal diseases cause somatic pain when they involve the parietal peritoneum or the anus. Peritoneal irritation can either be localized or diffuse. When an inflamed organ, such as the appendix, or a colonic diverticulum touches the peritoneum, a well-localized and usually severe somatic pain is felt by the patient. A perforated ulcer, on the other hand, causes a generalized peritonitis with severe diffuse abdominal pain. Either of these pains is usually aggravated by any movement of the patient. The anal canal is also innervated by somatic nerves, so inflammatory and infiltrating diseases in this area can produce a severe, well- localized pain.

Treatment

Management of gastrointestinal pain involves both treatment of the underlying disorder causing the pain and the use of nonspecific pain-relieving measures. Specific treatment of the underlying disease usually leads to improvement of symptoms, which is often the best indicator of successful therapy. On the other hand, use of nonspecific measures, such as systemic analgesics and nerve blocks, is also an important part of the therapeutic approach to patients with abdominal pain. Nonspecific pain relief is indicated in situations in which specific corrective therapy is not available, such as patients with advanced gastric or colon cancer. Nonspecific pain control measures should also be used for patients with benign disease while they are awaiting specific therapy.

Pain relief is an important part of patient management during therapy for gastrointestinal disease. The selection of nonspecific analgesic measures depends on the severity of pain and on the nature of the underlying disease. Simple measures, such as the application of heat or change in diet, are effective in some situations. Potent narcotic analgesics are required in other circumstances. Caution should be exercised, however, in the use of potent analgesics before a diagnosis or specific diagnostic plan is made. Pain might be the only symptom of a significant underlying disease; masking pain could thus delay diagnosis and definitive therapy (12). However, we are unable to locate other references or personal experience to scientifically address the validity of this standard shibboleth.

Complete pain relief should be a management priority in patients awaiting surgical treatment. The use of adequate quantities of narcotic analgesics to relieve pain should not be deterred by concerns of respiratory depression and addiction (see Chapter 84). Pain is a powerful respiratory stimulant, and the short-term use of narcotics does not cause psychological or physical dependence. Pain that is not relieved by parenteral narcotic analgesics can often be managed with subarachnoid or epidural narcotics. Splanchnic and celiac plexus blocks with long-acting local anesthetic agents are also useful in the management of intractable pain while patients are awaiting specific therapy.

DISEASES OF THE STOMACH AND DUODENUM

Basic Considerations

Anatomy

An understanding of the anatomy and embryology of the stomach and duodenum is useful in the diagnosis and management of painful diseases of these organs (Fig. 66-1). The stomach is fixed proximally at its attachment to the distal esophagus, where the esophagus penetrates the diaphragm. This esophagogastric junction is just to the left of midline at the level of the T-10 vertebra. The stomach has a variable shape but lies predominantly in the left upper quadrant. The distal end of the stomach crosses the midline at approximately the level of the L-1 vertebra and is separated from the duodenum by a band of connective tissue and muscle fibers, which constitute the pyloric sphincter. The portion of the duodenum proximal to the papilla of Vater originates from the embryonic foregut. The distal duodenum is derived from the midgut and passes posterior and to the left of the midline to become the jejunum at the ligament of Treitz.

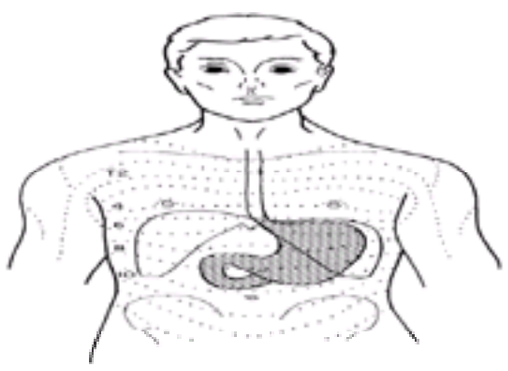

Figure 66-1. Location of the stomach and duodenum in relationship to the diaphragm and the dermatomes.

Nerve Supply

As in the rest of the gastrointestinal tract, pain receptors in the stomach and duodenum are stimulated by distension, traction, and direct pressure generated by contraction of the muscles of these structures. Local inflammation and ischemia lower the receptor threshold to nociceptive stimuli. These nociceptive stimuli are transmitted through afferent pathways that accompany the visceral sympathetic fibers through the celiac plexus, the greater splanchnic nerves, the paravertebral sympathetic chain, and the white rami communicantes, and have their cell bodies in dorsal root ganglia of spinal nerves, which in turn transmit the impulse to the dorsal horn of the spinal cord. Nociceptive impulses from the stomach and proximal portion of the duodenum are transmitted primarily through the T-6 to T-10 roots inclusively, although in some individuals the T-5 or T-10 root (or both) is also involved (10). Nociceptive impulses from the distal portion of the duodenum are transmitted to the spinal cord through the T-8 to T-10 spinal nerves, although T-11 and, rarely, T-12 can also be involved. The nerve supply of the stomach and duodenum is illustrated in Figure 66-2.

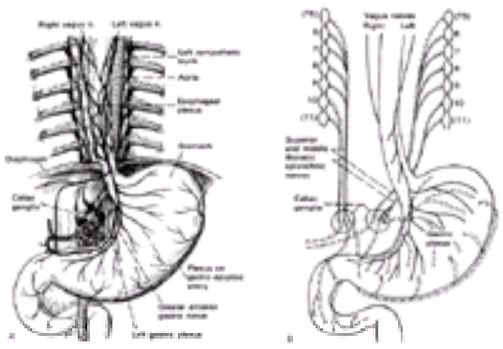

Figure 66-2. Innervation of the stomach and duodenum. **A:** Relationship of the vagus nerves and the thoracic sympathetic chain and their distribution to the lower esophagus and to the stomach and duodenum. As noted, both vagus nerves continue from the esophagus to the stomach, where the anterior vagus trunk passes along the lesser curvature to the stomach, supplying the anterior surface of this viscus as far as the pylorus. The posterior vagus gives off branches that are distributed to the posterior part of the stomach. Both nerves give off one branch that is greater than the others, and hence are called the *greater anterior gastric nerve* and *greater posterior gastric nerve*, respectively. The various gastric branches can be traced for some distance before they sink into the muscle coat, where they synapse with postganglionic parasympathetic neurons. The vagus nerves also give off celiac branches that pass along the left gastric artery and reach the celiac plexus, where they intermingle with sympathetic fibers. Vagal fibers from the celiac branches are distributed to the pylorus and duodenum. Both vagi have afferent fibers that transmit sensory information, except nociception. The sympathetic preganglionic fibers derive from the paravertebral sympathetic chain, pass peripheralward as the superior (greater) thoracic splanchnic nerves, and end in the celiac ganglia, where they synapse with postganglionic neurons. The axons of the latter pass to the stomach and duodenum along the side of the various branches of the celiac and superior mesenteric arteries, around which they form plexuses. These arterial plexuses are comprised mainly of sympathetic efferent and afferent (nociceptive) fibers but also contain some parasympathetic fibers, which, as mentioned previously, reach the celiac plexus by way of the celiac branches of the two vagal trunks. The celiac plexus breaks up into subsidiary plexuses that follow the various arteries to the stomach and duodenum to supply these structures. **B:** Innervation of the stomach and duodenum by the vagus nerves and by the segmental sympathetic and sensory nerve supplies. The solid lines for the vagus and sympathetic nerves indicate preganglionic fibers, the dashed lines indicated postganglionic fibers, and dotted lines indicate the nociceptive pathways. The parentheses for T-5 and T-11 indicate that these are inconstant segments. Frequently, the celiac ganglia are composed of more than two, as shown here. (See Chapter 65 for more details of the origin and relation of these nerve pathways.) (Modified from Netter FH. Innervation of the stomach and duodenum. In: *CIBA collection of medical illustrations.* Vol 3, Digestive system. Part II, The digestive tract. West Caldwell, NJ: CIBA Pharmaceutical Co., 1959:64, 65, and Bonica JJ. *The management of pain*. Philadelphia: Lea & Febiger, 1953:395, 397.)

Characteristics of the Pain

Visceral pain originating in the stomach is usually felt in the midepigastric area (9). Gastric diseases that involve the overlying parietal peritoneum can cause pain in the left upper quadrant alone or can be combined with epigastric pain. Diseases of the duodenal bulb cause visceral pain that is usually felt in the epigastrium, but occasionally also in the right upper quadrant. Diseases of the distal duodenum cause pain that is usually felt in the periumbilical region.

Clinical Considerations

Anatomic Abnormalities

Most congenital abnormalities of the stomach and duodenum present in infancy or early childhood with symptoms of gastric outlet obstruction. Epigastric pain that is exacerbated by eating and relieved by vomiting is characteristic. Hypertrophic pyloric stenosis is most commonly seen in infants, but can rarely be found in adults who present with vomiting, epigastric pain, and weight loss. Partial or complete duodenal obstruction caused by webs or atresia, malrotation, or an annular pancreas can also present with similar symptoms. Treatment by surgical correction of the underlying abnormality is usually successful in these conditions.

Paraesophageal hiatal hernias are caused by a diaphragmatic defect adjacent to the esophagogastric junction, which allows herniation of large portions of the stomach into the thorax. Patients with this disorder often complain of epigastric fullness or mild discomfort. The most feared complication of this anatomic defect is acute gastric volvulus caused by rotation of the stomach on its longitudinal axis (13). Patients with acute gastric volvulus usually present with epigastric pain and forceful vomiting. This diagnosis should be suspected when these symptoms are present, and there is difficulty in passing a nasogastric tube. Radiographic contrast examination should confirm the diagnosis of a paraesophageal hiatal hernia and acute gastric volvulus, if present. Emergency surgery is required in the latter situation. Some surgeons recommend elective surgery in all cases of paraesophageal hernia to prevent the development of a volvulus (13).

Dyspepsia, Nonulcer Dyspepsia, Gastritis, and Duodenitis

In the past, the term *dyspepsia* has been used to describe multiple upper gastrointestinal tract symptoms, including bloating, nausea, belching, and indigestion, but this term is most appropriately used when the predominant symptom is abdominal discomfort centered in the upper abdomen. Dyspepsia is a common complaint in the United States. Approximately one in four persons reports recurrent pain or discomfort centered in the upper abdomen in any 1 year (14), and in 1985 it was estimated that 2% to 5% of all primary care visits in the United States were for dyspepsia, with a cost of more than $1.4 billion (15). Studies that have investigated the cause of dyspepsia in large numbers of patients presenting to their primary care physician with this complaint have revealed that the most common diagnosis in these patients is nonulcer dyspepsia (see Nonulcer Dyspepsia, later in this chapter). Other common diagnoses in patients with dyspepsia include gastroesophageal reflux disease and PUD.

Nonulcer dyspepsia refers to the symptom of dyspepsia for which no organic cause can be identified. Patients with nonulcer dyspepsia may or may not have evidence of gastritis or duodenitis (see Duodenitis, later in this chapter). Nonulcer dyspepsia is a common diagnosis made in patients with chronic upper abdominal pain, particularly in those younger than 40 years of age (16).

Gastritis refers to inflammation of the stomach detected by histologic evaluation of mucosal biopsy specimens. However, this term has also been used to describe erythema or friability seen on endoscopic examination of the stomach, mucosal irregularity seen on radiologic contrast examination of the stomach, and upper abdominal complaints in patients seen by health care providers. However, these endoscopic, radiologic, and clinical uses of gastritis do not correlate well with histologic gastritis. Therefore, it is most appropriate for the endoscopist and radiologist to simply describe what they see, and for the clinician to use the term *dyspepsia* when describing a patient with upper abdominal discomfort. In fact, most patients with gastritis are asymptomatic, and there are no symptoms characteristic of gastritis. In patients with upper abdominal symptoms, it is usually difficult to assign a clear cause and effect relationship between symptoms and the presence of gastritis. Therefore, most patients with upper abdominal discomfort and gastritis without other findings are considered to have nonulcer dyspepsia. Gastritis is commonly classified into acute and chronic (predominantly mononuclear cell infiltrate) forms. The most common types of acute gastritis include acute hemorrhagic and erosive gastritis and acute *H. pylori* gastritis. Common forms of chronic gastritis include *H. pylori* gastritis, chemical gastritis, autoimmune atrophic gastritis, and hypertrophic gastritis (Ménétrier's disease).

Duodenitis is also a histologic diagnosis made on duodenal biopsies. Endoscopic findings of erythema and friability of the duodenal bulb are also frequently termed *duodenitis*. Histologic and endoscopic duodenitis does not correlate well with symptoms (17). Duodenitis can in some cases be part of the spectrum of duodenal ulcer disease (18). The clinical significance of duodenitis without symptoms is unknown. Patients with upper abdominal symptoms and endoscopic or histologic evidence of duodenitis without ulceration are considered to be in the category of nonulcer dyspepsia.

Etiology and Pathophysiology

Dyspepsia. Dyspepsia can arise from several etiologies. The most common diagnoses are nonulcer dyspepsia, gastroesophageal reflux disease, and PUD. Other etiologies are less likely, but include lactose intolerance, irritable bowel syndrome, biliary or pancreatic disease, or gastric cancer (less than 1% in the United States).

Nonulcer Dyspepsia. Nonulcer dyspepsia refers to the complaint of dyspepsia without clearly identifiable organic etiology, and it is likely a syndrome of multiple

causes (16). Possible factors contributing to nonulcer dyspepsia include altered gastric motility (19), psychosomatic disorders (20), and increased sensitivity to gastric distension (21). Whether chronic gastritis secondary to *H. pylori* infection (see following section) could be a cause of nonulcer dyspepsia is a topic of intense debate. Multiple studies examining whether patients with nonulcer dyspepsia improve after eradication of *H. pylori* infection have come to different conclusions, although these studies are often fraught with methodologic difficulties (22). Many prescription and nonprescription medications also cause dyspepsia. These include aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors, bisphosphonates, and others. Endoscopy is usually normal in patients with drug-induced dyspepsia.

Helicobacter pylori *Gastritis.* The understanding of gastritis changed remarkably in the 1990s. The most common cause of gastritis is now known to be *H. pylori* infection. *H. pylori* is a curved gram-negative rod with several specialized properties that allow it to colonize the relatively hostile environment of the stomach. These specialized properties include multiple flagella, release of chemotactic and cytotoxic substances, and presence of urease, an enzyme that converts urea to ammonia and carbon dioxide. *H. pylori* only colonizes gastric mucosa, but may be the most common infection in the world, with an estimated 50% of the world's population harboring this organism (23). The presence of *H. pylori* in the gastric mucosal mucous layer is always associated with mucosal inflammation. Ingestion of the organism can cause an acute gastritis and clinical symptoms of upper abdominal pain, nausea, and vomiting that may last up to a few weeks (24). However, reports of acute *H. pylori* gastritis are uncommon, and the vast majority of patients acquired the infection in childhood and have chronic gastritis. Chronic *H. pylori* gastritis has been associated with the development of PUD, mucosa-associated lymphoid tissue tumors (MALT lymphoma), and gastric adenocarcinoma (23). However, it is unclear whether chronic *H. pylori* gastritis, without one of the previously mentioned complications, can cause symptoms. Certainly, the majority of patients with chronic *H. pylori* gastritis are asymptomatic.

Other Types of Gastritis. Several other types of gastritis are recognized but are not clearly associated with dyspepsia, nausea, or abdominal pain. These include acute hemorrhagic or erosive gastritis, which is seen in association with stressful illnesses such as burns, intracranial diseases, trauma, sepsis, and ingestion of certain drugs, especially aspirin and other NSAIDs (25). *Chronic chemical gastritis* refers to the histologic pattern seen after recurring exposure to extrinsic or intrinsic chemical agents. The most common extrinsic agents are NSAIDs, and the most common intrinsic culprit is bile. Autoimmune atrophic gastritis is an inherited disease in which an immune response is directed against parietal cells of the oxyntic mucosa. With the destruction of parietal cells, intrinsic factor production is decreased, and vitamin B_{12} deficiency, with or without pernicious anemia, may result. Hypertrophic gastropathy (Ménétrier's disease) is a type of nonerosive gastritis of unknown cause characterized by large gastric folds with loss of protein through the gastric mucosa (26). Gastritis can also develop in patients with Crohn's disease, postgastrectomy patients, and in patients with peripheral eosinophilia, allergic conditions, and eosinophilic infiltration in the stomach wall (eosinophilic gastritis). In addition, other bacteria, fungi, and viruses have been associated with the development of gastritis.

Symptoms and Signs. Dyspepsia, by definition, refers to the symptom of upper abdominal discomfort. In 25% of patients the pain radiates to the back. Episodic pain of longer than 3 years' duration is described by more than 90% of patients. Most report no relation of pain to meals, but approximately 25% describe some relief with antacids. Nausea is present in many patients whereas weight loss, nocturnal pain, and a change in bowel pattern are uncommon. Symptoms of depression or psychological tension are frequent. *Nonulcer dyspepsia* refers to dyspepsia without clear organic etiology. There are no clear symptoms or signs that reliably distinguish dyspepsia from nonulcer dyspepsia.

Acute infection with *H. pylori* can cause a syndrome of upper abdominal discomfort, nausea, and diarrhea that can last for a few weeks; this is a rare syndrome.

Upper gastrointestinal hemorrhage and abdominal pain are the most frequent symptoms in patients with acute hemorrhagic or erosive gastritis. Bleeding is the predominant finding in stress-associated gastritis. In the absence of perforation, epigastric pain is present in fewer than 10% of patients. Pain is more commonly reported when erosive gastritis is caused by aspirin and other NSAIDs than when caused by stress. When pain is present with drug-induced erosive gastritis, it is usually epigastric and is frequently relieved by meals and antacids.

Most patients with nonerosive gastritis are asymptomatic. A minority of the subset with atrophic mucosa can develop neurologic symptoms caused by vitamin B_{12} deficiency. Paresthesias, loss of sensation, and dementia can be the only complaints because abdominal pain does not occur in this disease. Symptoms of anemia can also be present with vitamin B_{12} deficiency.

Approximately 75% of patients with hypertrophic gastropathy have abdominal pain. This pain is usually epigastric and is occasionally relieved by meals (26). Anorexia, weight loss, and peripheral edema are frequently associated symptoms. Most patients have a long history of abdominal pain before the diagnosis of hypertrophic gastropathy is made.

Diagnosis. The symptom of dyspepsia alone is not sufficient to separate the diagnosis of nonulcer dyspepsia from gastroesophageal reflux disease, PUD, or gastric cancer. The most efficacious and cost-efficient evaluation and management strategy in patients presenting with dyspepsia is currently in debate. If a patient presents with dyspepsia and warning symptoms, such as bleeding, dysphagia, weight loss, or severe vomiting, then further evaluation should clearly be pursued. If a dyspeptic patient does not have any associated warning symptoms, however, then strategies of empiric acid suppression (27), empiric *H. pylori* testing and treatment (28), and initial endoscopic evaluation have all been advocated (29). Because the risk of gastric cancer increases after age 50 years, initial endoscopic strategies may be more appropriate in this group. If a patient is treated empirically and does not respond, then further evaluation is required. Given current data and resources, a reasonable approach is suggested in Figure 66-3. If a diagnostic procedure is required, upper endoscopy is a more sensitive technique for detecting mucosal abnormality than radiography. Although high-quality air-contrast barium radiography usually excludes significant gastric and duodenal ulcerations and a gastric mass, it may miss smaller mucosal lesions and does not allow for biopsy and histopathologic correlation.

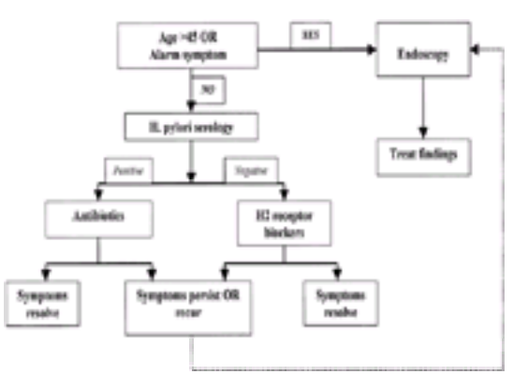

Figure 66-3. Approach to a patient with dyspepsia.

Other diagnostic tests might be required in patients with atypical symptoms or if the diagnosis is unclear after an endoscopy. Patients with low serum albumin levels and large folds on radiographic or endoscopic examination may require endoscopic ultrasonography and large particle gastric biopsy to diagnose hypertrophic gastropathy. Dyspeptic symptoms can be similar to those caused by cholecystitis and chronic pancreatitis. If symptoms are persistent and troublesome, abdominal ultrasonography should be used to evaluate the pancreas, gallbladder, and bile ducts.

Whether to look for and treat *H. pylori* infection in patients with uninvestigated dyspepsia or patients with nonulcer dyspepsia remains controversial. The diagnosis of *H. pylori* can be made by serology, urease-based tests (including the noninvasive urea breath test and urease testing on endoscopic biopsy specimens), and histology. Because of its low cost and excellent sensitivity, serology is the current initial diagnostic test of choice in most patients. The urea breath test is the current noninvasive method of choice to document eradication. Culture of *H. pylori* is expensive and difficult compared with the previously mentioned tests and thus is not generally performed.

Treatment. A key to treating patients with nonulcer dyspepsia remains making a positive diagnosis and providing reassurance (see Fig. 66-3). Many patients do not require medical therapy after a confident diagnosis has been made. In general, patients should be asked to avoid foods that exacerbate their symptoms, eat smaller and more frequent meals, and avoid excessive use of ethanol, caffeine, tobacco products, and NSAIDs. However, attempts to find medications that help relieve the discomfort of patients with nonulcer dyspepsia have been frustrating. Antacids have not been clearly shown to be better than placebo, even though antacids and

placebo lead to temporary relief in a large proportion of these patients. A metaanalysis has suggested that H_2-receptor antagonists may result in symptom improvement of 20% over placebo (30). Preliminary trials with PPI therapy have also shown significant improvement in nonulcer dyspepsia compared with placebo. Prokinetic agents have also been used to treat patients with nonulcer dyspepsia. Studies with metoclopramide, domperidone, and cisapride have suggested that these medications are more effective than placebo. In patients with visceral hyperalgesia and nonulcer dyspepsia, agents that modify the transmission of nociceptive inputs from the gut to the brain are of therapeutic interest, but their clinical efficacy remains unproved (31). Varying with the population studied, approximately 50% of patients with nonulcer dyspepsia have evidence for *H. pylori* infection. Multiple studies evaluating the effect of *H. pylori* eradication in patients with *H. pylori* infection and nonulcer dyspepsia have shown mixed results, and these studies are often fraught with methodologic difficulties (22). Although more research should be done before definitive conclusions can be made, the general guideline of *H. pylori* eradication in these patients cannot currently be supported by available clinical trials. Nonulcer dyspepsia can be chronic and is not associated with decreased longevity. Therefore, any treatment attempted should be monitored and stopped if side effects occur. Systemic analgesics are never indicated for treatment of this category of gastric disorders.

The objectives of therapy of acute and chronic hemorrhagic or erosive gastritis are pain relief and the prevention of complications. The development of acute erosive gastritis and ulceration in patients with serious underlying disease can be prevented if the intragastric pH is kept above 3.5. Oral antacids, H_2-receptor antagonists, and PPIs can all be used to attain a pH of greater than 3.5. Use of these agents to treat erosions is less successful but is generally attempted. Patients with erosive gastritis caused by aspirin and other NSAIDs should stop taking their NSAIDs if possible. When NSAID medication must be continued, NSAIDs that more selectively inhibit the cyclooxygenase-2 enzyme may be less harmful to the gastric mucosa (32) (see Chapter 83).

Patients with hypertrophic gastropathy can do well for years without therapy (26). If pain or hypoalbuminemia from gastric protein loss is disabling, relief can be obtained with gastrectomy. Patients with infectious gastritis other than *H. pylori* should be treated with specific antimicrobial agents whenever possible.

Peptic Ulcer Disease

Despite advances in the understanding of PUD, ulceration of the stomach and duodenum continues to be one of the most important diseases of the gastrointestinal tract. Because PUD results in significant pain and a high morbidity, it is a leading cause of health care expenditures. In the United States, there are approximately 500,000 new cases and 4 million recurrences each year, with an estimated annual direct cost of $3 to $4 billion per year (33). New diagnostic and therapeutic techniques have contributed to this expense, but also dramatically changed the management of patients with ulcers during the 1990s. Gastric and duodenal ulcers are considered together here because of similarities in symptoms, diagnostic approaches, and therapies.

Etiology and Pathophysiology. An ulcer is a localized loss of the normal gastric or duodenal mucosa. Granulation tissue and inflammatory exudate are found in the base of an ulcer, which extends into or through the submucosal layer of the gastrointestinal wall (Fig. 66-4). Ulcers are formed because of an imbalance between ulcerogenic factors and defensive factors that usually protect against mucosal damage (34). *H. pylori* infection and use of NSAIDs are the two most common conditions associated with the development of peptic ulcers. *H. pylori* has been identified in up to 90% to 95% of patients with duodenal ulcer and 60% to 80% of patients with gastric ulcer compared with a 25% to 30% incidence in control groups (35,36). Eradication of *H. pylori* infection in patients with PUD has been shown to dramatically decrease the chance of PUD recurrence (37). However, the exact mechanism by which *H. pylori* is involved in causing PUD remains unclear. Colonization of the gastric antral mucosa by *H. pylori* is known to result in higher levels of gastrin as a result of decreased somatostatin release. Somatostatin normally inhibits gastrin synthesis and release, and lack of this braking mechanism can lead to increased gastrin-mediated acid secretion. *H. pylori* is also known to produce cytotoxins; however, whether these cytotoxins actually play a significant role in producing ulcers remains unknown. Use of aspirin and other NSAIDs has also been associated with PUD. These medications inhibit the production of prostaglandins, which are important in mucosal defense.

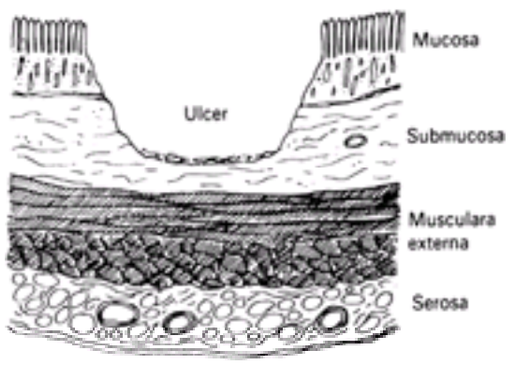

Figure 66-4. Schematic diagram of a peptic ulcer.

The role of gastric acid in the pathogenesis of PUD has long been appreciated. The presence of gastric acid is necessary for the development of a peptic ulcer. Excessive acid can be present in absolute terms, as in the Zollinger-Ellison syndrome, in which a gastrin-producing tumor causes a marked increase in gastric acid production, or the acid might only be increased relative to the ability of the gastric or duodenal mucosa to protect itself.

Symptoms and Signs. Symptoms alone do not differentiate reliably among the diagnoses of duodenal ulcer, gastric ulcer, and nonulcer dyspepsia. In all of these diseases, pain is most often felt in the epigastrium, although right upper quadrant pain is seen in some patients with duodenal ulcer and left upper quadrant pain can be seen with gastric ulcer (Fig. 66-5). The pain is variously described as gnawing or burning, and a sense of fullness is common. Radiation of pain to the back occurs in 20% to 30% of patients. Pain relief by food or antacid ingestion is described by one-half of patients with a duodenal ulcer and by less of those with gastric ulcer and nonulcer dyspepsia. Pain that awakens the patient at night is more frequently seen with duodenal ulcer disease. Nausea, vomiting, heartburn, and anorexia are reported in a significant number of patients with these diseases. Although patients with gastric ulcer tend to be older and patients with nonulcer dyspepsia have milder degrees of pain, these findings do not help to distinguish among these diagnoses in an individual patient. Patients with ulcers associated with NSAID consumption are often asymptomatic until they present with a complication (38). Symptoms also correlate imperfectly with ulcer healing. Patients who become asymptomatic can still have an ulcer crater approximately 15% of the time. Furthermore, two-thirds of patients who are still symptomatic after a 6-week course of antacid therapy are found to have healing of their ulcer at endoscopy.

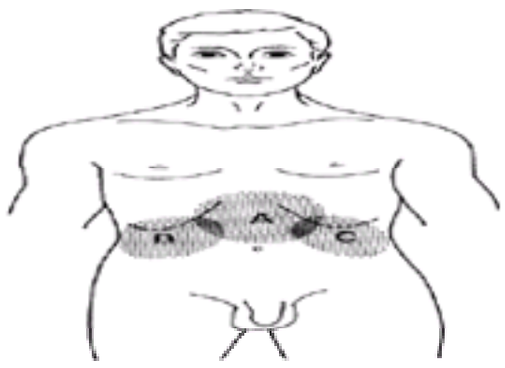

Figure 66-5. Locations of referred pain from peptic ulcer. Most commonly, the pain is referred to the epigastrium (A). In some patients, the pain of duodenal ulcer is referred to the right upper quadrant (B) or left upper quadrant in patients with gastric ulcer (C).

Bleeding, perforation, penetration, obstruction, and intractable pain are the most common complications of PUD. Gastrointestinal bleeding, presenting either as melena or hematemesis, complicates PUD in 10% to 20% of patients. Bleeding can be associated with pain, or it can be the first and only manifestation of the ulcer.

Approximately 5% of patients with ulcers experience perforation. Perforation presents with the sudden onset of severe epigastric pain that quickly spreads to involve the entire abdomen as peritonitis ensues. If a duodenal ulcer perforates and partially seals, it can present as right lower quadrant pain because of the accumulation of gastric contents in the right paracolic gutter. Penetration of a duodenal or gastric ulcer into the pancreas, adjacent omentum, or hepatobiliary system is usually suspected if the patient has severe continuous pain that resists medical therapy. Radiation of pain to the back occurs in more than one-half of patients with posterior penetration. Somatic pain with a radicular quality is also frequently described in this situation, probably because of inflammation of retroperitoneal structures. Gastric outlet obstruction should be suspected in patients with ulcers who develop frequent vomiting, particularly if the vomiting occurs at night or if the emesis contains food residue eaten several hours earlier. Patients who develop pyloric obstruction frequently have a long history of ulcer pain that has recently changed character. With the onset of obstruction, pain can become more continuous and be relieved by vomiting. Intractable pain can be caused by penetration or by inadequate therapeutic regimen.

Surgery for PUD is much less frequent because of improved medical treatments for PUD. Postoperative symptoms occur in 10% to 50% of patients after PUD surgery, depending on the type of operation and the population studied. Abdominal pain, diarrhea, vasomotor phenomena, vomiting, weight loss, anemia, and metabolic bone disease are the most commonly encountered problems. Abdominal pain caused by alkaline reflux gastritis is usually a continuous burning pain, often similar to the initial ulcer pain, and frequently exacerbated by eating. Antacids do not relieve the pain. Vomiting of bitter bile-stained material is frequently described. Crampy or steady epigastric pain occurring 30 to 60 minutes after eating and associated with flushing, diaphoresis, and lightheadedness is referred to as the *dumping syndrome*. Other considerations in the patient with chronic postoperative pain are recurrent ulceration, obstruction of the gastric outlet, and malfunction of the afferent loop in a patient with a Billroth II anastomosis.

Diagnosis. Physical findings and laboratory tests are often not specific for PUD. For example, epigastric tenderness is found just as frequently in patients with ulcers as in those without ulcers (39). The serum amylase level is normal in patients with uncomplicated PUD but may be elevated if the ulcer has penetrated into the pancreas. The serum gastrin level should be measured in patients with multiple ulcers, recurrent ulcers, when ulcers are present in the distal duodenum, or are refractory to medical or surgical therapy, because this picture suggests Zollinger-Ellison syndrome. Zollinger-Ellison syndrome is characterized by the presence of upper gastrointestinal ulcer, marked increase in secretion of gastrin, and a non–beta islet cell tumor of the pancreas, known as a *gastrinoma*.

Demonstration of an ulcer requires radiographic contrast examination or endoscopy. Contrast examinations are less expensive, but endoscopy is more sensitive and has the capability of biopsy. The choice of tests often depends on clinical situation and local availability of these two procedures.

All gastric ulcers should be examined endoscopically. Six to eight biopsies and brush cytology of the ulcer rim should be obtained. Nonhealing gastric ulcers and those ulcers that have a suspicious appearance on initial examination should be reexamined and rebiopsied to exclude malignancy.

Evidence for *H. pylori* infection should be sought in all patients with PUD by serologic tests, urease-based testing, or histologic examination of gastric mucosa (discussed previously).

Postgastrectomy syndromes should be considered in all patients with upper abdominal pain and a history of gastric surgery. A diagnosis of dumping or alkaline reflux gastritis is often based on the characteristic clinical presentation. Recurrent ulceration is best detected by endoscopy because postsurgical changes make radiographic findings difficult to interpret. On the other hand, gastric and afferent loop obstruction are best demonstrated radiographically.

Treatment

Medical Therapy. Historically, therapeutic strategies for PUD have primarily focused on decreasing acid exposure in the stomach. However, with the recognition of the role of *H. pylori*, current strategies involve the use of antibiotics in combination with antisecretory medications to eradicate *H. pylori* and achieve enhanced ulcer healing with decreased recurrence rates.

However, no easy regimen for eradication of *H. pylori* currently exists. Several effective therapies are listed in Table 66-1. In most patients in the United States, a triple-therapy regimen with a PPI, clarithromycin, and metronidazole or amoxicillin is a reasonable choice, with relatively high success rates and good compliance (36,40,41). One downside to PPI-based triple therapies is high cost. Bismuth-based therapies are cheaper and effective; however, compliance with these regimens is often more difficult. A reasonable second-line therapy is ranitidine-bismuth subcitrate, metronidazole, and clarithromycin or amoxicillin.

Regimen	Dose/mg	Schedule	Days of treatment	Success rate	Cost
Proton pump inhibitor	¶	b.i.d.	10–14		
Clarithromycin	500	b.i.d.	10–14	>80%	$$$
Metronidazole or	500	b.i.d.	10–14		
Amoxicillin	2 × 500	b.i.d.	10–14		
Bismuth subsalicylate	2 tablets	q.i.d.	10–14		
Tetracycline	500	q.i.d.	10–14	>80%	$
Metronidazole or	250	t.i.d.	10–14		or
Clarithromycin	500	b.i.d.	10–14		$$
Ranitidine bismuth subcitrate	400	b.i.d.	14		
Clarithromycin	500	b.i.d.	14	>80%	$$
Tetracycline or	500	b.i.d.	14		
Metronidazole	250	t.i.d.	14		

¶Omeprazole 20 mg, or lansoprazole, 30 mg

TABLE 66-1. Triple-therapy regimens for *Helicobacter pylori* eradication

In terms of acid suppression alone, antacids, H_2-receptor blockers, and PPIs have all been shown effective at healing ulcers. Antacids have been shown to heal 80% to 90% of both gastric and duodenal ulcers in 6 to 12 weeks (42,43). Liquid antacid preparations should be taken 1 hour after each meal and at bedtime in doses of 15 to 30 mL. The H_2-receptor antagonists cimetidine, ranitidine, famotidine, and nizatidine are attractive alternatives to antacids because they are equally effective (42), generally have fewer side effects, and are easier to administer. Administration of H_2-receptor antagonists, cimetidine (1,600 mg), ranitidine (300 mg), famotidine (40 mg), or nizatidine (300 mg), given once daily after dinner, are effective at healing PUD. PPIs (such as omeprazole and lansoprazole) inhibit the H^+/K^+ ATPase acid secretory pump in the gastric parietal cell membrane. These medications produce more sustained and robust acid suppression than H_2-receptor antagonists and have been shown to heal ulcers faster than H_2-receptor blockers (44,45), a property that may be important in patients with complicated (e.g., bleeding) ulcers.

Agents that bind to ulcers have also been shown to promote healing. Sucralfate is the only one of these drugs presently available in the United States. Given in a dose of 1 g four times a day, sucralfate is as effective as cimetidine for healing duodenal ulcers. Constipation is an infrequent side effect of sucralfate. Sucralfate should not be taken at the same time as other medications to avoid interference with absorption of the other drugs.

Aspirin, other NSAIDs, and alcohol should be avoided by patients with ulcers. For patients who must continue on NSAID therapy, maintenance therapy with a prostaglandin analog (misoprostol), high-dose H_2-receptor antagonists, and PPIs have been shown to be effective at decreasing the likelihood of ulcer recurrence (46,47 and 48). Other dietary limitations are not associated with improved healing. Patients should be encouraged not to smoke, because smoking impairs ulcer healing. Avoidance of unnecessary stress is always commendable, but too much emphasis on this aspect cannot be recommended on the basis of available information concerning the effects of stress on ulcer formation and healing.

Surgical Therapy. The use of surgical therapy for PUD has dramatically declined with the advent of more effective medical therapy and identification and eradication of *H. pylori*. However, surgery for PUD is indicated for refractory PUD (Zollinger-Ellison syndrome should be excluded), persistent bleeding, obstruction, penetration, and perforation (49). Parietal cell vagotomy by a surgeon experienced in this procedure is the operation of choice for intractable pain. Dumping, diarrhea, and alkaline reflux gastritis are all less frequent with this operation, although recurrent ulcers are more common than with other ulcer surgery and occur in 5% to 10% of patients. Vagotomy with pyloroplasty, and vagotomy with antrectomy and either gastroduodenostomy or gastrojejunostomy, are alternative ulcer operations. Repeat surgery might be needed for complications of severe alkaline reflux gastritis or for obstruction of surgical anastomoses.

All patients with ulcer pain should be managed with the medical and surgical treatments outlined previously. Acid-suppressive medications, and acetaminophen if necessary, generally provide sufficient pain relief during the healing phase. Narcotic analgesics or anesthetic blocks should be used in patients with severe pain caused by perforation or penetration after diagnosis has been made and surgery is planned. Patients should not be left in pain while awaiting surgery.

Neoplasms of the Stomach

Gastric cancer is a leading cause of cancer deaths worldwide. Adenocarcinoma accounts for more than 80% of malignant gastric neoplasms, with lymphoma and malignant stromal tumors making up the remainder. Although the incidence of gastric cancer is decreasing in the United States, this malignancy remains a cause of upper abdominal pain and a therapeutic challenge to physicians. An update on most aspects of gastric neoplasms is available (50). Further discussion about pain associated with cancer can be found in Chapter 35, Chapter 36 and Chapter 37.

Etiology and Pathophysiology. Infectious, environmental, and genetic factors have significant roles in the pathogenesis of gastric cancer. *H. pylori* infection has been implicated as a predisposing factor in the development of gastric adenocarcinoma (excluding cardia tumors) as well as in the development of MALT lymphomas arising in the stomach (51,52). Dietary salt and nitrates have been linked epidemiologically to gastric cancer. An increased incidence of gastric cancer occurs in patients with autoimmune atrophic gastritis and in patients with large adenomatous gastric polyps.

Symptoms and Signs. Patients with early gastric cancer can be asymptomatic, experience a sensation of fullness, or have vague epigastric pain. The pain can be similar to the pain of gastric ulcer. Weight loss, anorexia, vomiting, and occult or overt gastrointestinal bleeding can be present. Local invasion can cause pancreatitis, gastrocolic fistulas, or severe continuous abdominal or back pain. Metastases from gastric cancer can be responsible for ascites, pleural effusions, or jaundice. Physical examination may reveal an epigastric mass, enlarged liver, ascites, or enlarged supraclavicular, axillary, and umbilical lymph nodes.

Diagnosis. A combination of diagnostic procedures is used in the detection of gastric cancer. Upper gastrointestinal roentgenography can reveal a mass or suspicious ulcer. Gastroscopy provides direct visualization and an opportunity to biopsy an ulcer or mass lesion and to brush it for cytology. Biopsies and brushings for cytology should be taken of gastric ulcers and of any irregular appearing mucosa. Endoscopic ultrasound is the most accurate method to establish the depth of wall invasion and the presence of local lymph nodes (53). Endoscopic ultrasound can also direct fine needle aspiration of submucosal lesions or lymph nodes. CT scanning is currently the most useful nonsurgical method for detection of metastatic spread.

Treatment

Cancer Therapy. Treatment of gastric cancer traditionally includes surgery and chemotherapy. Patients who have no evidence of spread of the neoplasm outside the stomach should have a subtotal or total gastrectomy and lymph node dissection. Palliative surgery is also indicated for luminal obstruction and hemorrhage. Patients with locally advanced or metastatic disease can benefit from chemotherapy using combinations of 5-fluorouracil, doxorubicin, mitomycin C, triazinate, and methotrexate (54). Radiotherapy has not been useful in the treatment of locally advanced gastric cancer, but can relieve pain caused by metastases to bone.

Pain Therapy. The treatment of severe pain in patients with advanced gastric cancer is a significant problem and challenge and is discussed in detail in Chapter 36 and Chapter 40. Both visceral and somatic pain mechanisms are usually involved because of abdominal wall or retroperitoneal invasion. For such patients, available therapies include narcotic analgesics, orally or parenterally, intraspinal narcotics, block of the splanchnic nerves or celiac plexus alone or combined with intercostal block, neurostimulation techniques, and ablative neurosurgical operations. Two or more of these techniques are frequently used to provide relief.

Pain can be controlled in most patients with maximum life expectancy of less than 3 months by appropriate use of narcotic analgesics. In patients with mild to moderate pain, NSAIDs are used initially and, if necessary, can be combined with codeine or more potent narcotics such as morphine. Regularly scheduled oral administration of a pain cocktail containing methadone is often effective. A dose of 10 mg every 8 hours is prescribed initially but must then be titrated to the patient's needs. The addition of hydroxyzine (25 to 50 mg every 6 hours) or prochlorperazine to the cocktail is useful for the treatment of nausea and vomiting, which is frequent in these patients. Moreover, hydroxyzine potentiates the analgesic action of narcotics. Intraspinal narcotics are increasingly being used and are effective in many of these advanced cancer patients (see Chapter 102).

Neurolytic blocks are used for the management of a subset of patients with advanced gastric cancer and severe pain. This therapy is usually reserved for situations in which the overall condition of the patient is fairly good and the pain is localized and severe. Significant pain relief has been reported in more than 90% of patients with gastric cancer who have had bilateral celiac plexus block with 50% alcohol solution (55). Pain relief often lasts for months after this procedure. Recurrent pain sometimes responds to repeated injections, but, when these fail, extension of the cancer to the peritoneum or abdominal wall is likely. This requires neurolytic blocks of the involved intercostal nerves. Neurolytic blocks are often combined with pharmacologic therapy or psychological techniques, or both.

Neurostimulation and ablation procedures are sometimes used for the treatment of severe intractable pain in patients with advanced gastric cancer. These procedures should be used when life expectancy is greater than 3 months and when pharmacologic therapy is not effective or is associated with unacceptable side effects (see Chapter 100, Chapter 101, Chapter 105, and Chapter 106).

DISEASES OF THE SMALL AND LARGE INTESTINES

Basic Considerations

Anatomy

The small intestine begins at the distal end of the stomach, the pyloroduodenal junction, and ends as it joins the colon at the ileocecal valve. The proximal 10 in. of small bowel make up the duodenum (the duodenum was discussed previously, with the stomach, because of similarities in the clinical presentation of diseases of these two organs). The remainder of the small intestine, suspended on its mesentery, is approximately 10 ft long and occupies most of the abdomen (Fig. 66-6).

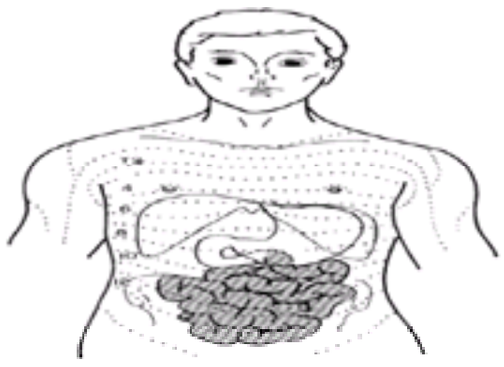

Figure 66-6. Location of the small intestine in relationship to the dermatomes.

The large intestine, or colon, begins at the ileocecal valve and ends at the anus. The cecum is the most proximal aspect of the colon and usually lies in the right lower quadrant. The ascending and descending portions of the colon do not have a mesentery and are relatively fixed in the retroperitoneum. The transverse colon has a mesentery and can form variable-sized loops across the midabdominal cavity. The sigmoid colon also has a mesentery and can stretch to a great length, particularly in the elderly. The rectum, which is fixed in the retroperitoneum, forms the most distal 12 to 15 cm of large intestine. Some disease processes of the distal rectum are clinically similar to anal diseases (see Diseases of the Anus and Rectum, later in this chapter). The positions of the small and large intestines within the abdomen are

shown in Figure 66-6 and Figure 66-7.

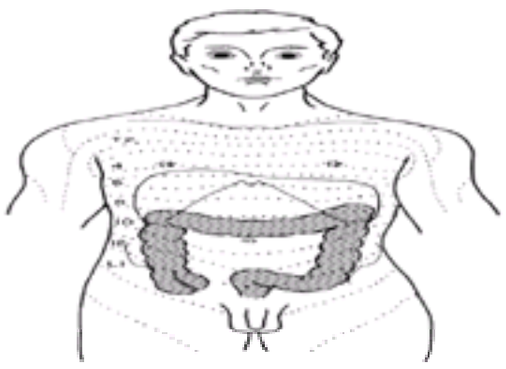

Figure 66-7. Location of the large intestine in relationship to the diaphragm and the dermatomes.

The embryologic development of the intestine accounts for some of the abnormalities encountered clinically. During normal fetal development, the small bowel is transiently occluded by proliferating epithelial cells. Defective recanalization can result in the formation of gut duplications, cysts, and webs, which all can cause problems subsequently. Another embryologic remnant that might be clinically relevant later in life is a Meckel's diverticulum, which forms at the junction of the primitive gut and the vitelline duct. This diverticulum often contains gastric mucosa and can cause abdominal pain and intestinal bleeding.

Nerve Supply

Visceral sensation, including pain from the jejunum and ileum, is carried by sympathetic afferent nerves through the least and lesser splanchnic nerves, and from there through the superior mesenteric and part of the celiac plexuses to enter the spinal cord at the T-8 to T-12 levels (Fig. 66-8). Sensation from the cecum, ascending colon, and right half of the transverse colon is carried by sympathetic afferent fibers that pass through the least and lesser splanchnic nerves, and from these through the inferior mesenteric and superior mesenteric plexuses to enter the spinal cord at the T-10 to L-2 levels. Pain sensation from the left half of the transverse colon and from the descending colon and rectum is mediated by afferent fibers; some of these accompany sympathetic fibers to the lower thoracic and lumbar sympathetic trunks and others course with the parasympathetic nerves through the pelvic plexus and pelvic nerves (nervi erigentes) and then enter the spinal cord at the S-2 to S-4 levels (Fig. 66-9; see Fig. 66-8). In a few persons, afferent sensation can also be carried by the vagus nerve because midgut visceral pain can be felt after spinal cord transection above T-1 as well as after bilateral splanchnic nerve resection (12).

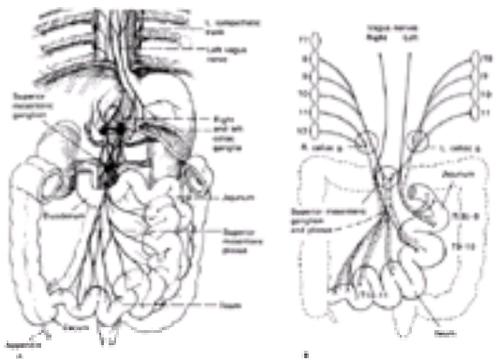

Figure 66-8. Innervation of the small intestine. **A:** Relationship of the vagus nerves, sympathetic trunk, celiac ganglia, superior mesenteric ganglion, and superior mesenteric plexus supplying the small intestine. **B:** Schematic depiction of the nerve supply to the small intestine. The vagus nerves supply the small intestine with parasympathetic preganglionic fibers, which end in the wall of the gut and synapse with short postganglionic fibers. These also contain sensory fibers that convey sensations other than nociception. The small intestine received sympathetic supplies through preganglionic sympathetic fibers (*solid lines*) derived from T-8 to T-12 on the right and T-8 to T-11 on the left. These synapse in the celiac and superior mesenteric ganglia with postganglionic fibers (*dashed lines*). Sensory fibers, which transmit nociceptive information (*dotted lines*), follow the sympathetic nerves and enter the spinal cord at T-8 to T-12 on the right and T-8 to T-11 on the left. The segments that supply sympathetic and sensory fibers to different parts of the small intestine are indicated by numbers. The segments in parentheses in the sympathetic chain are inconstant. (For more detailed information of the origin and course of these nerve pathways, see Chapter 65.) (Modified from Netter FH. Innervation of the stomach and duodenum. In: *The CIBA collection of medical illustrations*. Vol 3, Digestive system. Part II, Lower digestive tract. Summit, NJ: CIBA Pharmaceutical Co., 1979:76–79, and Bonica JJ. *The management of pain*. Philadelphia: Lea & Febiger, 1953:395, 397.)

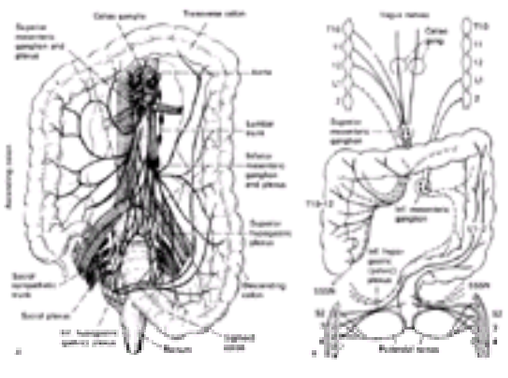

Figure 66-9. Innervation of the large intestine. **A:** Anatomic relationship of the nerve supplying various parts of the colon and rectum. **B:** Schematic depiction of the innervation of the vagus, sympathetic, and sensory fibers. The right and transverse colon up to the splenic flexure is supplied by preganglionic parasympathetic fibers of the vagus nerves, which synapse in the wall of the viscus with short postganglionic fibers. The sympathetic supply is through preganglionic fibers derived from T-10 to T-12 (*solid lines*), which synapse with postganglionic fibers (*dashed lines*) in the superior mesenteric ganglion. This portion of the gut also receives postganglionic fibers from the L-1 ganglion. This part of the colon is supplied by sensory (nociceptive) fibers that accompany the sympathetic nerves and enter the spinal cord at T-10 and L-1 inclusively. The descending colon receives preganglionic sympathetic fibers from L-1 to L-2, which synapse in the inferior mesenteric ganglion with the postganglionic fibers that supply the viscus as far as the sigmoid colon. Postganglionic sympathetic fibers to the rest of the colon from the rectosigmoid junction and rectum are derived from sacral sympathetic splanchnic nerves (SSSN), which are derived from the sacral portion of the sympathetic chain. The descending colon is supplied with parasympathetic preganglionic fibers, which originate in spinal cord segments S-2, S-3, and S-4 and pass through the inferior hypogastric (pelvic plexus) and from there to the colon and rectum, where they end in the wall of the viscus and synapse with short postganglionic fibers. The sensory fibers that conduct nociceptive impulses accompany the parasympathetic nerves and enter the spinal cord in the S-2, S-3, and S-4 segments. Sensory supply to the rectum is through the pudendal nerve. (See Chapter 65 for a more detailed description of the origin and course of these nerve pathways.) (Modified from Netter FH. Innervation of the small intestine. In: *The CIBA collection of medical illustrations*. Vol 3, Digestive system. Part 2, Lower digestive tract. Summit, NJ: CIBA Pharmaceutical Co., 1979:76–79, and Bonica JJ. *The management of pain*. Philadelphia: Lea & Febiger, 1953:395, 397.)

Characteristics of the Pain

Pain from the small intestine is usually felt as a periumbilical cramp or colic. This pain can be triggered by luminal distension or by excessive motor activity. In patients with functional abdominal pain, experiments with balloon distension of the jejunum and ileum produced pain that was felt in various quadrants of the abdomen by different patients (56,57). Steady visceral pain can be caused by intestinal distension or ischemia. Inflammatory and infiltrative processes that extend to the parietal peritoneum can cause localized somatic pain from the involved area of peritoneum. Traction on the root of the mesentery can cause a similar type of somatic pain but usually produces a periumbilical visceral type of pain (58).

Distension of the ascending and right half of the transverse colon generally causes periumbilical pain, although a significant number of patients also have suprapubic pain. Because the right colon is fixed to the retroperitoneum, severe distension causes right-sided pain, similar to that of infiltrating and inflammatory processes. Stimulation of somatic nerves in the underlying peritoneum is the probable mechanism of this type of pain.

Distension of the left half of the transverse colon and descending colon usually produces pain in the midline below the umbilicus and in the suprapubic region. Severe distension causes left-sided pain localized over the region of distension. Sigmoid colon lesions that involve the overlying peritoneum can cause right lower quadrant, suprapubic, or left lower quadrant pain because of the long mesentery from which the sigmoid colon is suspended, which enables it to touch a wide area of abdominal wall. The common positions of referred pain from the small and large intestines are shown in Figure 66-10.

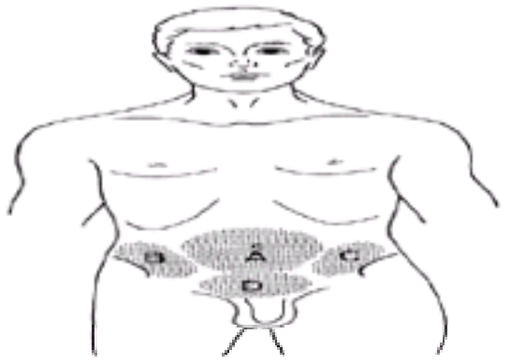

Figure 66-10. Sites of referred pain from diseases of the small and large intestine. Periumbilical pain (A) is caused by distension of disease of the ascending and right half of the colon, but a significant number of patients also have suprapubic pain (D). Pain in the right lower quadrant (B) is caused by severe distension or disease of the appendix and small intestine, as well as of the beginning of the ascending colon. Pain in the left lower quadrant (C) is caused by disease of the descending or sigmoid colon.

Clinical Considerations

Anatomic Abnormalities

Etiology and Pathophysiology. Most congenital anatomic derangements of the intestine that cause abdominal pain do so by producing luminal obstruction. Incomplete canalization of the gut lumen or *in utero* ischemia can cause atresia or stenosis of any part of the intestine. Failure of the intestine to rotate on its mesentery when it reenters the abdomen in the second trimester can result in malrotation of various portions of the bowel. Malrotation can be present without any symptoms. Pain is produced by this anomaly only if intestinal obstruction results from associated fibrous (Ladd's) bands, internal herniation, or formation of a volvulus. Meckel's diverticula are embryologic remnants of the connection of the vitelline duct and terminal ileum. Intestinal obstruction can be induced by these diverticula either by formation of a volvulus or by intussusception. An ulcer can occur in the diverticulum if ectopic gastric mucosa is present.

Symptoms and Signs. Symptoms caused by anatomic abnormalities of the gut are similar to those produced by other causes of intestinal obstruction (see Intestinal Obstruction, later in this chapter). Most congenital abnormalities present in infancy or early childhood. Occasionally, symptoms of these disorders first appear in adults. Therefore, these anomalies should be considered in the differential diagnosis of abdominal pain in adults as well as in children.

Continuous burning or aching abdominal pain can also be caused by anatomic defects. Intestinal duplications usually occur in the ileum and can contain acid-producing gastric mucosa. This can lead to local intestinal ulceration that causes pain directly or after perforation of the gut wall. Ectopic gastric mucosa is also responsible for the pain associated with a Meckel's diverticulum, which is often postprandial. The mucosal ulceration can cause lower gastrointestinal bleeding (59). Inflammation of a Meckel's diverticulum can cause right lower quadrant pain that mimics that of appendicitis.

Diagnosis and Treatment. Most cases of congenital intestinal anomalies are first detected when laparotomy is performed for the relief of intestinal obstruction. Surgical resection of the area of stenosis or duplication is curative. Areas of internal herniation should be reduced and repaired. Meckel's diverticula should be resected.

Patients with less severe symptoms can have their anatomic abnormality diagnosed before laparotomy, usually by radiographic contrast examination. Many of these anomalies are asymptomatic, and thus the challenge is to be certain that the symptoms are actually caused by the anomaly and not by another condition.

Appendicitis

Appendicitis is the most common cause of acute severe abdominal pain that requires surgery. Approximately 10% of the population develops appendicitis at some time (60). Although appendicitis can occur in the very young and the elderly, the peak incidence is in the second and third decades of life.

Etiology and Pathophysiology. More than one-half of appendicitis cases are caused by obstruction of the appendiceal lumen by fecaliths, calculi, or other material. This blockage leads to swelling, mucosal ischemia, and bacterial invasion. Other pathogenic mechanisms can be involved but are largely unknown. Within 24 to 36 hours after luminal obstruction, perforation can occur, leading to peritonitis or abscess formation.

Symptoms and Signs. Patients with acute appendicitis have moderate to severe pain that begins in the epigastric or periumbilical region (61). This initial pain is of a visceral type and is caused by luminal obstruction and distension of the appendix. Pain is most often steady, but some patients have cramping or colicky pain. Movement does not seem to affect this initial pain. The pain generally increases in severity over several hours and then can subside before localizing in the right lower quadrant.

When inflammation extends to the appendiceal serosa, stimulation of overlying parietal peritoneal somatic nerves results in well-localized right lower quadrant pain. This pain is usually severe, continuous, and exacerbated by bodily movement and coughing. Vomiting and defecation do not affect the quality or severity of this pain.

Most patients with appendicitis have anorexia, nausea, and vomiting. A useful diagnostic feature is that nausea and emesis follow the onset of pain. Diarrhea is reported by less than 25% of patients. Some patients report a sensation of constipation.

Diagnosis and Treatment. Diagnosis and treatment of appendicitis requires surgical intervention when symptoms, physical examination, and laboratory findings suggest the diagnosis. Physical examination reveals a temperature of higher than 38°C in 50% of patients. Rebound tenderness and involuntary guarding, usually in the right lower quadrant, are common findings. Tenderness on rectal examination is frequently present. Peripheral leukocytosis is seen in more than 90% of patients. An appendiceal fecalith is seen on plain abdominal roentgenography in less than 10% of patients. Other laboratory findings are nonspecific. Laparotomy must be

done early in the course of the illness to prevent the significantly increased morbidity and mortality associated with perforation.

The physician must also be aware of atypical presentations of acute appendicitis caused by unusual locations of the appendix. Inflammation of a retrocecal appendix causes less severe pain that can remain poorly localized and not cause discrete localized abdominal tenderness. Ureteral irritation can lead to urinary frequency and pyuria. An appendix that hangs down over the pelvic brim can cause severe pain that localizes to the low midline or left abdomen after beginning in the periumbilical region. Rectal and pelvic tenderness is more commonly seen in this group.

In the majority of patients, the diagnosis of appendicitis can be made at the bedside based on clinical suspicion elicited by the patient's history, the physical examination, and the results of laboratory analysis (elevated white blood cell count). In most cases, the decision to operate is made at the bedside, and no further workup is needed. In patients who present with symptoms that are not clearly due to appendicitis, ultrasonography and CT scan can be useful tests. Ultrasonographic criteria have been found to have a 68% sensitivity and a 98% specificity in making an accurate diagnosis (62). CT can also be used in the evaluation of patients with suspected appendicitis. Unenhanced helical CT of patients presenting to the emergency room with suspected appendicitis has been found to have up to 98% accuracy and be cost effective by reducing the number of unnecessary operations (63).

Many diseases that simulate acute appendicitis can sometimes only be excluded by laparotomy. Infectious gastroenteritis, lymphadenitis, ureterolithiasis, and, in women, salpingitis, ruptured ovarian cysts, and ruptured ectopic pregnancy must be considered in the differential diagnosis. Intravenous urography, culdocentesis, and laparoscopy obviate the need for laparotomy in some patients.

The role of laparoscopic surgery versus laparotomy in patients with suspected appendicitis is still debated. A review of studies comparing the two approaches suggests that laparoscopic appendectomy is associated with a reduced risk of postoperative infection, a minimal reduction in hospital stay, and a faster return to normal activity, but longer intraoperative time than laparotomy (64). Once the decision has been made to perform laparoscopy or exploratory laparotomy in a patient with presumed appendicitis, all efforts should be made to relieve the abdominal pain. Parenteral narcotics and segmental epidural analgesic blocks are useful in this situation.

Infectious Enterocolitis

Infections of the small and large intestines are a common cause of self-limited abdominal pain. Infectious enterocolitis should be suspected in any person who develops diarrhea and abdominal cramping.

Etiology and Pathophysiology. Infectious agents that cause enterocolitis include bacteria, protozoans, and viruses. These organisms produce intestinal dysfunction and pain by mucosal invasion, toxin production, or both (65). Specific organisms are considered in the section Diagnosis and Treatment.

Symptoms and Signs. Symptoms of infectious enterocolitis are similar for all organisms that cause this problem. Abdominal cramps are usually intermittent and can be localized to the periumbilical region or lower in the hypogastrium. Rectal urgency is frequent when the rectum is involved. Diarrhea can be watery, bloody, or mucoid; associated symptoms of nausea, vomiting, and fever can be present.

Diagnosis and Treatment. Identification of the causative infectious organism depends on using the known epidemiologic associations to determine appropriate culture media and other laboratory tests. A specific diagnosis is critical to direct appropriate treatment of enterocolitis. Invasive infections are most commonly caused by bacteria and typically cause severe pain and bloody diarrhea. The presence of fecal leukocytes suggests the presence of invasive organisms, but both false-positive and false-negative test results are common. Evaluation of the stool with culture or molecular techniques remains the best initial method to identify the specific organism responsible.

Invasive Organisms. Campylobacter jejuni is the most common cause of invasive infections. *Campylobacter* enterocolitis is treated with erythromycin, 500 mg four times a day for 7 days, if symptoms are persistent, but usually the disease remits spontaneously. Some cases have been associated with household pets, but the source of infection in most patients is unknown. *Salmonella*, *Shigella*, *Yersinia*, and enteroinvasive *E. coli* can cause a similar clinical illness, sometimes associated with eating contaminated foods. Antimicrobial therapy of these infections is usually unnecessary, but might be warranted in selected instances.

Food-Borne Organisms. Food-borne organisms cause enterocolitis that is usually self-limited and requires no treatment. *Staphylococcus aureus*, *Bacillus cereus*, and *Clostridium perfringens* often produce severe abdominal pains and watery diarrhea, which begin several hours after eating contaminated food and last less than 24 hours. *S. aureus* and *B. cereus* infections are frequently associated with severe vomiting.

Traveler's Diarrhea. Travelers to developing countries with tropical climates can develop enterocolitis (66). Contaminated food and water are responsible for transmitting the organism. In addition to the bacterial pathogens mentioned previously, other forms of *E. coli*, and the protozoan organisms *Entamoeba histolytica* and *Giardia lamblia* should also be considered in this setting. Diagnosis of these protozoal agents depends on finding characteristic cysts and trophozoites in the stool of infected patients or by immunofluorescent studies and antigen detection in the stool. Diarrhea and abdominal cramping usually persist for 2 to 7 days. Treatment of traveler's diarrhea includes nonspecific agents to reduce diarrhea (see following discussion) and empiric antibiotics such as quinolones or trimethoprim-sulfamethoxazole. Use of other specific antimicrobial agents requires recovery of a pathogenic agent from the stool.

Enterohemorrhagic Colitis. A specific strain of *E. coli* identified as *E. coli* 0157:H7 has been found to be responsible for numerous sporadic and food-borne outbreaks of bloody diarrhea. Other strains of *E. coli* have subsequently been found to cause this syndrome. This infection is becoming increasingly recognized as a cause of bloody diarrhea (67). Recovery without sequelae is the usual outcome; however, the infection can be associated with the development of hemolytic-uremic syndrome and thrombocytopenic purpura. These complications most often occur in children and older adults, in whom they can be fatal. Treatment is supportive.

Antibiotic-Associated Colitis. Patients who develop abdominal cramping and diarrhea, and who have been on antibiotics in the previous 6 weeks, should be suspected of having pseudomembranous colitis (68). This condition has been associated with the use of nearly all antibiotics, but cephalosporins, ampicillin, and clindamycin are most frequently implicated. Overgrowth of the toxin-producing organism *Clostridium difficile* causes this syndrome by destruction of the colonic epithelium. Diagnosis depends on identifying characteristic pseudomembranes on the rectal mucosa at sigmoidoscopy and by detecting the presence of the *C. difficile* organism and cytotoxin in the patient's stool. Treatment with metronidazole (Flagyl), 250 mg three times a day for 7 days, or oral vancomycin (Vancocin), 250 to 500 mg four times a day for 7 days, is usually curative. A severe colitis can result from this syndrome, producing a serious life-threatening situation.

Diarrhea in Immunocompromised Patients. Patients who are immunocompromised are at risk to develop abdominal pain and diarrhea from other organisms, including cytomegalovirus, mycobacteria, cryptosporidium, *Microsporium*, *Isospora*, and *Blastocystis hominis* among others (69). Diagnosis is usually made by stool examination, or, if necessary, by endoscopy. In neutropenic patients, right lower quadrant abdominal pain and watery or bloody diarrhea can occur as a result of mucosal denudation and bacterial invasion of the proximal colon and distal small intestine in a process called *neutropenic typhlitis*. Diagnosis is made by typical symptoms in an appropriate clinical setting. Treatment is with broad-spectrum antibiotics or surgery.

Supportive Therapy. Supportive therapy for the patient with abdominal cramping and diarrhea caused by an infectious agent is important. Maintenance of hydration with liquids and oral electrolyte solutions is important. Cramping and diarrhea can often be reduced by using bismuth subsalicylate (Pepto-Bismol) in a dose of 30 mL each half hour, up to 8 oz, or until diarrhea and cramps subside. Antiperistaltic agents, such as loperamide, diphenoxylate, and codeine, reduce the severity of diarrhea but should be used cautiously in patients with a fever or bloody diarrhea because of the risk of increasing the severity and prolonging the illness.

Radiation Enterocolitis

Etiology and Pathophysiology. Patients undergoing abdominal or pelvic irradiation for the treatment of neoplasia can develop intestinal complications. These can occur while the radiation is being administered, immediately after completion of treatment, or many months or years after treatment has been discontinued. Most patients so affected have received a total radiation dose of more than 4,000 rads (70). Patients undergoing recent radiation therapy have symptoms produced by mucosal edema and ulceration. Late symptoms after abdominal radiation are usually caused by partial small bowel obstruction from radiation-induced intestinal fibrosis. Diarrhea, when present, is caused by malabsorption, fistulas, or bacterial overgrowth.

Symptoms and Signs. Patients can have gastrointestinal symptoms while undergoing a course of radiation treatment. Nausea, vomiting, and diarrhea can occur, beginning at the end of the first week of treatment. A sensation of incomplete rectal evacuation and tenesmus indicates rectal and lower colonic mucosal involvement.

Increased mucus and blood can be present in the stool. Mid- and lower abdominal cramping is present with significant small intestinal involvement.

Abdominal symptoms can present months to years after radiation therapy has been completed. Symptoms of proctitis, including rectal burning, urgency, and mucoid diarrhea, are most frequent. Decreased stool caliber often indicates the presence of a rectal stricture. Periumbilical cramping pain suggests the presence of partial small or large bowel obstruction caused by stricture formation. If significant obstruction is present, progressive abdominal distension, nausea, and vomiting occur. Rectal bleeding, malabsorption, fistula formation, and perforation can also be late manifestations of radiation injury (71).

Diagnosis. The diagnosis of radiation enterocolitis should be considered in patients with abdominal pain who have a history of undergoing abdominal radiation therapy. The presence of the clinical syndrome described previously is usually sufficient for diagnosis if other causes of pain are excluded. Proctosigmoidoscopy should be done to exclude other diseases, such as colonic cancer. Typical mucosal changes of radiation proctitis, including friability, ulceration, and telangiectasias, can be seen. Infectious enterocolitis needs to be ruled out using stool cultures, particularly in recently treated and potentially immunosuppressed patients with diarrhea. The diagnosis of partial mechanical intestinal obstruction is best made by plain abdominal roentgenography and contrast radiography.

Treatment. Treatment of radiation enterocolitis is directed at the patient's most distressing symptoms. Pain associated with ongoing radiation can respond to a decrease either in radiation dose or frequency of treatments. Stool-bulking agents such as psyllium, 1 to 2 tablespoons daily, anticholinergic drugs such as dicyclomine, 10 to 20 mg four times a day, and antiperistaltic drugs such as loperamide, 2 mg four times a day, can also be helpful in reducing diarrhea and cramping. Rectal symptoms can respond to warm sitz baths and topical 2% lidocaine ointment. Diarrhea and pain in patients with a history of remote radiation treatment can sometimes be reduced by sulfasalazine. More recent treatments have included short-chain fatty acid enemas (72), hyperbaric oxygen (73), and sucralfate enemas (74). Bleeding from radiation proctitis can often be controlled endoscopically using electrocoagulation or laser therapy (75). Surgery can be hazardous in the patient with radiation enterocolitis because of a reduced vascular supply that results in impaired wound healing. Laparotomy is required, however, if tight strictures, complete obstruction, or symptomatic fistulas are present.

Diverticulitis

Etiology and Pathophysiology. Herniation of a small piece of intestinal mucosa and submucosa through the muscular wall of the bowel forms a diverticulum. These diverticula can be caused by increased colonic intraluminal pressure from chronic constipation. Diverticula are frequent in populations whose diets contain low quantities of fiber. Approximately 50% of people in the United States develop colonic diverticula by the ninth decade of life (76). The diverticula are usually multiple and are most frequently found on the left side of the colon. Diverticula rarely cause abdominal pain unless they become inflamed; this condition is called *diverticulitis* and occurs at some time in approximately 10% to 20% of patients with diverticula (76).

Symptoms and Signs. Most patients with diverticulitis are older than 60 years and complain of lower abdominal pain and fever. The pain is generally of moderate severity, can be either steady or cramping, and is frequently associated with nausea, vomiting, and a change in bowel habit (i.e., diarrhea, constipation, or mucus in the stool). Although diverticula are most commonly seen in the left colon, pain is frequent in the right as well as the left lower quadrants, possibly because of a redundant sigmoid colon that loops to the right of midline in many of these patients. Pain sometimes radiates to the back. Fever is usually present, and a peripheral leukocytosis with left shift is seen in most patients. Lower abdominal tenderness is a frequent finding, but significant rigidity and rebound tenderness are unusual. The sigmoid colon can sometimes be felt as a firm, tender cord in the left lower quadrant.

Diagnosis. The clinical diagnosis of diverticulitis can be made without difficulty in most cases. Gentle proctosigmoidoscopy with minimal air insufflation is useful in excluding other mass lesions, such as carcinoma, and diffuse mucosal diseases, such as inflammatory bowel disease and infectious colitis. Ischemic colitis must be considered in this group of patients, particularly when abdominal tenderness and pain are extreme and when antibiotic therapy has little effect. In the majority of patients, radiographic contrast examination is best delayed until patients have clinically improved. However, if the diagnosis is in doubt, the patient is not responding to appropriate treatment, or there is suspicion of a complication (e.g., abscess, fistula), then CT scanning is appropriate. Barium enemas have been reported to cause perforation when performed in patients with acute diverticulitis; however, gentle water-soluble contrast enemas can be helpful in some cases. The presence of diverticula can be confirmed, and areas of luminal narrowing safely defined when the radiographic examination is performed after the fever and pain have subsided.

Treatment. Most patients with diverticulitis respond to medical treatment with broad-spectrum antibiotics, correction of fluid and electrolyte losses, and general supportive care. Severely ill patients should initially be given nothing by mouth and then advanced slowly to a low-residue diet as symptoms improve. Use of parenteral narcotics is best avoided whenever possible to lessen the risk of masking a diverticular perforation or some other process, such as colonic ischemia. Surgical or percutaneous drainage is necessary when radiography shows abscess formation. Surgical intervention may also be required if the patient is not responding to medical therapy, or if colonic obstruction does not resolve. In the latter case, surgical decompression with a colostomy might be necessary. Later, when the area of diverticulitis is less inflamed, the segment can be resected as part of a two- or three-stage surgical procedure.

Crohn's Disease

Crohn's disease is a frequent cause of both acute and chronic abdominal pain, particularly in young people. Crohn's disease is an idiopathic inflammatory disease of the intestine. Either the small or large intestine, or both, are involved with a transmural inflammatory process. Areas of normal mucosa, referred to as *skip areas*, can be present between the inflamed regions of bowel.

Etiology and Pathophysiology. The cause(s) of Crohn's disease remains unknown. More recent theories revolve around the concept of genetically determined defective downregulation of inflammation driven by ubiquitous antigens present in the intestinal lumen (77). Varying bacteria and viral antigens have been postulated to be the triggering agent. More recent work has focused on the possible role of *Mycobacteria paratuberculosis* in Crohn's disease (78). However, it appears likely that Crohn's disease represents a heterogeneous group of diseases that shares similar mechanisms of tissue damage but may have different initiating events and immunoregulatory abnormalities (77).

Symptoms and Signs. Pain in patients with Crohn's disease is caused by either obstruction or inflammation. Inflammatory pain can be found anywhere in the abdomen, depending on the location of the inflamed bowel. Right lower quadrant pain is most frequent because of the common involvement of the terminal ileum and cecum. This pain is a continuous ache and occasionally radiates to the right upper thigh. It can be severe enough to cause the patient to limp. The pain is not necessarily associated with bowel movements but can be exacerbated by eating. Often superimposed on this continuous aching discomfort is a more severe crampy pain, which is located in the periumbilical region and is often relieved by bowel movements. This type of pain is usually a sign of partial intestinal obstruction induced by the inflammatory process and can be associated with nausea and vomiting. Diarrhea, which can be bloody, fever, and weight loss are other frequent symptoms.

Symptoms of anal and rectal involvement can also be prominent in patients with Crohn's disease. Rectal involvement causes a sensation of urgency or tenesmus (a feeling of rectal irritation or discomfort that makes the patient feel that a bowel movement is about to occur, when, in fact, only a small amount of diarrhea might be present, or no stool at all). Perianal pain caused by fistula, fissure, or abscess is found in approximately one-half of patients with Crohn's disease at some time in their illnesses. Severe pain localized to the anus and perianal area, accompanying or following bowel movements, is characteristic of these complications (these anorectal problems are discussed in more detail in Diseases of the Anus and Rectum, later in this chapter).

Patients with Crohn's disease can also have symptoms caused by extraintestinal complications (79). These problems are most common during periods of active inflammation and often respond to medical or surgical treatment of the bowel disease. Arthritis is seen in approximately 25% of patients with Crohn's colitis, but is less frequent when Crohn's disease is limited to the small bowel. A few large joints or multiple smaller joints can be affected. Skin involvement in the form of erythema nodosum, pyoderma gangrenosum, and other rashes is also seen in patients with colonic inflammation. Conjunctivitis, uveitis, and oral aphthous ulcerations are seen in 5% to 10% of patients with colitis. Liver disease, including pericholangitis, fatty liver, and, less commonly, sclerosing cholangitis, is also seen in patients with Crohn's disease.

Diagnosis. The diagnosis of Crohn's disease is usually made by a suggestive history and physical examination, with the aid of radiographic contrast examination endoscopy, and endoscopic biopsies. Small intestinal involvement is best detected with barium radiography. Colonic involvement can be defined by both roentgenography and colonoscopy. It is sometimes difficult to distinguish between Crohn's disease limited to the colon and ulcerative colitis.

Patients presenting with complaints of abdominal pain and diarrhea must have infectious enterocolitis ruled out by appropriate cultures and serologic tests. *Campylobacter*, *Shigella*, *Mycobacteria*, and *Amoeba* can all cause a clinical picture similar to that of Crohn's colitis. Pseudomembranous colitis should be considered

in all patients who have been taking antibiotics. *Yersinia* infection can also cause right lower quadrant pain and diarrhea that mimic Crohn's disease.

Appendicitis, ischemic enterocolitis, and intestinal malignancy should also be considered in patients thought to have inflammatory bowel disease. Patients who have an abrupt onset of ileitis are frequently operated on for presumed appendicitis. Appendectomy should not be done in these patients if the cecum is grossly involved with Crohn's disease at the time of surgery because enterocutaneous fistulas could form at the appendectomy site. Intestinal ischemia should be considered in elderly patients with intestinal inflammatory disease, especially in patients with a history of other atherosclerotic cardiovascular diseases. Colonic cancer and small intestinal lymphoma must be ruled out when a mass is present on radiographic studies of the intestine.

Treatment. Treatment of the patient with Crohn's disease involves a multidisciplinary approach. The gastroenterologist, surgeon, psychologist, and nutritionist all have valuable roles, but it is crucial that the patient maintain close contact with one physician. The emotional support, provided by a trusted and concerned physician, is invaluable over the long course of illness. The role of stressful life events in the exacerbation of inflammatory bowel disease is well recognized and underlines the role of the primary physician for major psychological support. Formal psychotherapy is indicated in selected patients with prominent psychological problems.

Pain is best controlled by appropriate management of the underlying inflammatory disease. Systemic corticosteroids, such as prednisone in a dose of 1 mg per kg, are useful in treating acute exacerbations of Crohn's disease. These drugs must be used cautiously and should be tapered rapidly because of their long-term side effects and the difficulty some patients have in discontinuing the medication. Systemic corticosteroids do not prevent relapses of Crohn's disease, and, thus, long-term use is discouraged. Hydrocortisone enemas are useful in the treatment of rectal and left colonic inflammation. This can be particularly helpful in reducing the troublesome symptom of tenesmus. Newer oral and topical corticosteroids (budesonide, beclomethasone, tixocortol) have been shown to be effective with few or no systemic side effects (80). These agents are either poorly absorbed or rapidly metabolized by the liver.

Oral aminosalicylate agents can also be useful in the management of Crohn's disease. Sulfasalazine (Azulfidine) in a dosage of 2 to 4 g per day is useful in treating flares of Crohn's colitis, but has not been shown to prevent relapse in the patient with quiescent disease. Newer aminosalicylate agents, including mesalamine (Asacol, Pentasa, Rowasa), olsalazine (Dipentum), and balsalazide (Colazide), do not have some of the intolerance or allergic complications of sulfasalazine. These newer aminosalicylate agents are effective in Crohn's ileocolitis and colitis, and, in addition, mesalamine has been shown to be effective in maintaining remission in patients with Crohn's disease (81,82).

Immunosuppressive medications, such as 6-mercaptopurine, azathioprine, and methotrexate, can prevent relapse and decrease corticosteroid requirements in patients with Crohn's disease. Cyclosporin A and tacrolimus may also be useful in patients with chronic active Crohn's disease and in healing fistulae secondary to Crohn's disease (83,84). Metronidazole in a dosage of 15 to 20 mg per kg per day, ciprofloxacin, or both can be helpful in patients with Crohn's disease, particularly for perianal disease (85,86). Other novel therapies under investigation include the use of lipoxygenase inhibitors, interleukins, free radical scavengers, and antibodies to tumor necrosis factor (80).

Narcotic analgesics should be used judiciously in the management of patients with inflammatory bowel disease. The decreased intestinal motility associated with the use of these agents can precipitate toxic megacolon in patients undergoing severe attacks of Crohn's colitis. Paradoxically, narcotics can increase pain in some patients by increasing intestinal spasm. Nevertheless, the less potent narcotics are helpful in managing the chronic diarrhea and cramping. Four to eight tablets daily of codeine, loperamide, or diphenoxylate with atropine are commonly used. Anticholinergic drugs, such as propantheline, 15 mg four times a day, and dicyclomine, 20 mg four times a day, also relieve intestinal cramping in some patients.

Dietary manipulation can benefit some patients with inflammatory bowel disease. Patients with significant obstructive symptoms can obtain relief by eating low-residue foods. Many patients with Crohn's disease are lactose intolerant; a trial of eliminating dairy products from the diet can decrease pain and diarrhea. Other dietary manipulations should aim at providing adequate amounts of protein and calories.

Resective surgery should be avoided whenever possible because the disease can recur in previously uninvolved segments of bowel. Nevertheless, significant intestinal obstruction and unhealed fistulas remain a common indication for surgery in this disease. Surgery is also indicated for the drainage of abscesses and for repair of intestinal perforation. Massive intestinal hemorrhage and toxic dilatation of the colon unresponsive to medical therapy are other rare indications for surgery in Crohn's disease.

Ulcerative Colitis

Etiology and Pathophysiology. Ulcerative colitis is another common type of idiopathic inflammatory bowel disease. Inflammation is limited to the mucosal surface of the colon, beginning at the anus and extending proximally for variable distances. Unlike Crohn's disease, the inflammatory process does not involve the more proximal gastrointestinal tract. Like Crohn's disease, the cause is unknown; the same pathogenic factors discussed in the previous section might also be involved in ulcerative colitis.

Symptoms and Signs. Most patients with ulcerative colitis have some combination of abdominal pain, diarrhea, and hematochezia during active flares of the disease. Bloody diarrhea is a more common complaint than pain. Pain is usually not as severe as that seen in some patients with Crohn's disease. Pain is usually located in the left lower quadrant of the abdomen, is cramping in character, and is generally accompanied by an urge to defecate, which often relieves the pain. A minority of patients have a fulminant onset of ulcerative colitis, known as *toxic megacolon*. In this situation, the colon distends to a large diameter and can produce severe diffuse abdominal pain and fever.

Perianal pain is not as common in ulcerative colitis as it is in Crohn's disease. Patients with ulcerative colitis can have anal fissures that cause pain during bowel movements, but perianal fistulas are not part of this disease.

Diarrhea is often a prominent symptom. Stools can be soft but formed, watery, full of mucus, or frankly bloody. Diarrhea can be present, with or without abdominal pain. Stools can be as frequent as every half hour and often awaken the patient at night.

Extraintestinal manifestations of ulcerative colitis are similar to those seen in Crohn's disease (79). Joint, skin, eye, and liver involvement can be indistinguishable from that seen in Crohn's disease.

Diagnosis. The diagnosis of ulcerative colitis is usually made when sigmoidoscopy is performed to investigate diarrhea and abdominal pain. The rectal mucosa is red, friable, and sometimes ulcerated in patients with active disease. Crohn's disease, infectious colitis, and ischemic colitis can give a similar clinical and sigmoidoscopic appearance and should be considered as other diagnostic possibilities. Stool cultures and serology for amebiasis should always be done in this setting to rule out an infectious cause. In chronically immunosuppressed patients, the diagnosis of cytomegalovirus infection should also be excluded. Rectal mucosal biopsies can sometimes help to distinguish among infectious colitis, Crohn's colitis, and ulcerative colitis.

Patients with ulcerative colitis have an increased risk for the development of colon carcinoma. Patients with disease that has involved the entire colon for longer than 10 years are at highest risk. Those with a change in the character of their diarrhea or abdominal pain should be investigated for this complication. Colonoscopy with multiple biopsies is the procedure of choice for detecting colon cancer or dysplasia in patients with ulcerative colitis.

Treatment. The same multidisciplinary approach used in the management of patients with Crohn's disease should be followed for patients with ulcerative colitis. Medical, surgical, psychological, and nutritional therapies all have roles in the management of patients with this disease. The specific treatment selected depends on the severity, extent, and duration of the disease.

Pain in patients with ulcerative colitis is best managed by controlling the colonic inflammation. Sulfasalazine (Azulfidine), in a dosage of 2 to 4 g per day orally, is usually effective in inducing remission and preventing relapse in patients with mild to moderate disease. Approximately 25% of patients taking this drug have nausea, epigastric pain, or headache; these side effects can be reduced by lowering the dose of Azulfidine or by switching to a newer aminosalicylate medication such as mesalamine, olsalazine, or balsalazide (see previous discussion). These newer aminosalicylate medications have also been shown to be effective in a dose-dependent manner for treating mild to moderately active ulcerative colitis as well as in maintaining remission (80). For patients with rectal or left-sided colonic involvement, aminosalicylate enemas can be effective in achieving clinical remission and preventing relapse.

Corticosteroids are effective in controlling colonic inflammation and the resultant abdominal pain and diarrhea. Patients with disease limited to the rectum and

descending colon often benefit from the daily administration of hydrocortisone enemas (Cortenema) or hydrocortisone suppositories. These preparations are especially helpful in patients with rectal urgency and tenesmus. More severe and diffuse colonic disease usually requires systemic corticosteroids. Prednisone, 40 to 60 mg per day, rapidly controls the symptoms of pain and diarrhea in most patients. Because disease relapse is not prevented by systemic corticosteroids, however, these drugs should be tapered rapidly and discontinued whenever possible.

Immunosuppressive medications, including 6-mercaptopurine and azathioprine, have been shown to be effective in refractory ulcerative colitis as well as in maintenance therapy. These medications are often useful for their steroid-sparing effect. Cyclosporine has been shown to be effective in avoidance of emergent colectomy in patients with severe ulcerative colitis refractory to corticosteroids (87), and tacrolimus (FK506) my also be useful in this circumstance (88). Long-term benefit is still under investigation.

Nicotine patches have been shown to be superior to placebo in treating patients with mild to moderately active ulcerative colitis (89); however, long-term studies are not available. This agent may be most useful in the patient whose colitis presents or flares with smoking cessation.

Antiperistaltic drugs are useful in decreasing the frequency of diarrhea in patients with ulcerative colitis. Diphenoxylate with atropine and loperamide are the most frequently used agents. A dosage of four to eight tablets per day is commonly used. These drugs can also decrease some of the lower abdominal cramping pain associated with bowel movements. Opiates should not be used in patients with severe disease because they have been associated with the development of toxic megacolon (90).

Colectomy is indicated in patients with ulcerative colitis for intractable disease and for specific complications. Colectomy is life saving in patients with toxic megacolon unresponsive to medical management. Others with continued abdominal pain and bloody diarrhea that is only controlled by high-dose corticosteroids should also be offered surgery. Total proctocolectomy cures ulcerative colitis and prevents the sequelae of long-term corticosteroid use in these patients. Colectomy is also indicated to prevent the development of carcinoma when mucosal biopsies show dysplasia in patients with long-standing disease.

Proctocolectomy with ileostomy and proctocolectomy with ileoanal anastomosis and ileal reservoir are the most commonly performed operations in patients with ulcerative colitis. The choice of operation depends on the medical condition, preference of the patient, and experience of the surgeon.

Intestinal Obstruction

Etiology and Pathophysiology. Mechanical or nonmechanical obstruction to the normal passage of intestinal contents from the stomach to the anus is another common cause of abdominal pain. Interruption of the luminal pathway can be a result of several different mechanisms, all of which produce the symptoms of abdominal pain, distension, vomiting, and failure to pass flatus. The causes and mechanisms of intestinal obstruction are listed in Table 66-2. In adults, adhesions most commonly cause mechanical small bowel obstruction, and cancer is the most frequent cause of large bowel obstruction. Nonmechanical obstruction of the intestine is caused by abnormal intestinal motor function, which can be either a primary intestinal abnormality, as in primary intestinal pseudoobstruction (91), or more commonly, secondary to other problems.

Mechanical obstruction	Nonmechanical obstruction
Luminal contents	Pseudoobstruction
Foreign bodies	Primary
Gallstones	Secondary: drugs, endocrinopathy, systemic illness
Bezoars	Paralytic ileus
Feces	Surgery
Intrinsic lesions	Trauma
Neoplasms	Infection
Strictures	Metabolic
Atresia	
Extrinsic compression	
Neoplasms	
Adhesions	
Abscess	
Intussusception	
Volvulus	
Herniation	

TABLE 66-2. Causes of intestinal obstruction

Symptoms and Signs. Abdominal pain resulting from intestinal obstruction is usually caused by intestinal distension proximal to the area of obstruction. Crampy periumbilical pain is characteristic of small bowel obstruction. The interval between cramps is approximately 5 minutes when the blockage is proximal and longer with more distal obstruction. Abdominal distension is usually present, except with the most proximal obstructions. Vomiting is bilious with upper intestinal obstruction and becomes darker and even feculent as the area of blockage is increasingly distal. Patients with colonic obstruction usually have more distension, pain, and vomiting occurring later. The pain caused by large bowel obstruction is often infraumbilical, in the midline, or on either side. Patients might continue to pass feces after the onset of obstruction because of preserved colonic motility, but they cease to pass flatus. Patients with nonmechanical obstruction generally have less severe pain than those with mechanical obstruction. Further diagnostic tests are required to distinguish between those in the two groups.

Diagnosis. Physical examination of the obstructed patient is important for diagnosis and for determining management. Measurement of the orthostatic blood pressure and assessment of mucous membranes help to guide fluid resuscitation. These patients are usually dehydrated. Bowel sounds are generally decreased, possibly with high-pitched rushes, but these findings are neither sensitive nor specific for obstruction. Although abdominal distension with mild diffuse or periumbilical tenderness is often present, marked localized or rebound tenderness and fever should raise the suspicion that intestinal infarction or perforation has complicated the obstruction.

Plain abdominal roentgenography is the single most useful test in the diagnosis of intestinal obstruction. Dilated bowel, filled with air and fluid, is seen except with early or extremely proximal intestinal obstruction. The location and appearance of dilatated bowel help both to localize the obstruction and to determine whether a mechanical or nonmechanical mechanism is involved. Elevated peripheral white blood cell counts increase the suspicion of perforation or strangulation. Whereas radiographic contrast examinations help to localize the point of obstruction, they are best used when the patient has been decompressed, especially with small bowel obstruction. Barium or water-soluble contrast enemas are useful in defining a colonic obstruction and can even be therapeutic if a volvulus or intussusception is present.

Treatment. The management of the patient with intestinal obstruction includes general supportive care, treatment of the underlying abnormalities, and avoidance of complications. Initially, dehydration should be corrected with intravenous fluids, and the bowel decompressed with nasogastric suction. When clinical findings and plain films suggest complete mechanical obstruction, early laparotomy both defines the cause of obstruction and allows intestinal diversion or definitive correction of the abnormality. Parenteral narcotics are indicated for relief of pain while the patient is awaiting surgery. The major complications of intestinal obstruction are perforation and strangulation or infarction. Both problems carry high morbidity and mortality, require immediate surgery, and could be masked by analgesic use. Therefore, analgesics should be withheld in this situation if the diagnosis is unclear and if surgical intervention is not yet planned. Significant pain relief is often obtained by bowel decompression alone.

Treatment of nonmechanical obstruction involves supportive care, correction of underlying electrolyte or hormonal abnormalities, minimizing the use of constipating medications, and nasogastric suction if required. Surgery is rarely indicated. Paralytic ileus secondary to the postoperative state, infections, and electrolyte imbalance usually resolve with time and treatment of the causative factors. However, in patients not responding to conservative management, use of the anticholinesterase agent neostigmine has shown promise in treating selected patients with acute colonic pseudoobstruction (91). Supportive care and fluid therapy are also helpful in patients with acute exacerbations of chronic pseudoobstruction, but definitive therapy for these patients is not generally available (92).

Intestinal Neoplasms

Etiology and Pathophysiology. Benign and malignant neoplasms of the colon, including polyps and cancers, are common. Adenocarcinoma of the colon is the second most common cause of cancer deaths in the United States and is the most common type of gastrointestinal cancer. Most carcinomas of the colon are thought to begin as small growths of neoplastic tissue, known as *adenomatous polyps*. These polyps have an increasing degree of malignant potential with increasing size. Other

types of polyps, with little or no malignant potential, are also commonly found in the colon, including hamartomatous and hyperplastic polyps. The cause of colonic adenomas and adenocarcinomas is unknown, but both genetic and dietary factors are probably involved. Certain patients have conditions that place them at high risk of developing colon cancer, such as ulcerative colitis, familial polyposis syndromes, nonpolyposis family cancer syndromes, and general family history of colon cancer. Neoplasms of the large intestine other than adenocarcinoma are rare; these include carcinoid tumors, lymphomas, and stromal tumors.

Tumors of the small intestine are uncommon. Adenocarcinoma, lymphoma, carcinoma, and malignant stromal tumors all occur in the small bowel but overall account for less than 5% of all intestinal neoplasms.

Symptoms and Signs. Most neoplasms of the intestine are painless until they produce luminal obstruction or extend to adjacent structures. When obstruction is present, the cancer is often incurable; the tumor must reach a large size before it causes obstruction. Occasionally, a small polyp presents with pain caused by intussusception. The characteristics of pain caused by intestinal obstruction and intussusception are similar to those described in the preceding section. Locally advanced carcinomas can cause abdominal pain by erosion into adjacent organs, such as the retroperitoneum and sacrum. Carcinomas can perforate and cause acute abdominal pain and signs of peritonitis. Other symptoms of neoplasms include bleeding, which is often occult, and changes in bowel habits, such as constipation. A reduction in stool caliber is often noted if the tumor is in the rectum or distal colon. Metastatic colon cancer frequently causes profound inanition, weight loss, and pain.

Diagnosis. Selection of diagnostic tests to detect intestinal cancer is based on the patient's clinical presentation. Patients with pain caused by complete intestinal obstruction usually require laparotomy, both for diagnosis and for treatment of the obstruction. Intermittent abdominal pain caused by partial bowel obstruction should be investigated by contrast radiography. Upper gastrointestinal roentgenography with a small bowel follow-through examination or abdominal CT scanning can detect small intestinal mass lesions, but laparotomy is sometimes required for diagnosis of these lesions. If symptoms or plain abdominal films suggest the presence of large bowel obstruction, rigid or flexible sigmoidoscopy followed by a barium enema should delineate the level of obstruction. Colonoscopy is necessary to biopsy mass lesions detected by roentgenography and can also reveal small polyps or cancers missed by radiography (93).

Patients with gross or occult blood in their stools, or a change in stool character and frequency, should have a colonoscopy to detect polyps and cancers. These lesions may be missed by barium enema. Blood tests (e.g., the level of carcinoembryonic antigen) can be useful in following patients with a history of resected colon cancer to monitor for recurrence.

Treatment. Treatment of intestinal neoplasms involves several types of therapies, including surgery, radiation therapy, and chemotherapy. Polyps can usually be removed by colonoscopy, but colectomy is needed if an invasive carcinoma is present. Surgical resection provides the best chance for cure of colon cancer; prognosis is directly related to the degree of invasion and spread. Radiation therapy decreases pain caused by spinal metastases and advanced pelvic tumors. In patients with stage III colon carcinoma, postsurgical adjuvant chemotherapy (5-fluorouracil with levamisole) has been shown to decrease tumor recurrence and prolong survival (94). The use of 5-fluorouracil with leucovorin may be as effective as 5-fluorouracil with levamisole. In patients with stage II colon adenocarcinoma, adjuvant treatment with 5-fluorouracil and levamisole may produce a decreased recurrence rate without a significant benefit in survival (94). In patients with limited liver metastasis, surgical resection may be possible. Hepatic arterial infusion of floxuridine can also decrease the size of liver metastases and thus decrease right upper quadrant pain caused by distension of the liver capsule, but survival might not be prolonged by this procedure (95). This therapy should be used in patients with symptomatic liver metastasis who are in otherwise good condition.

Treatment of pain in patients with advanced colorectal cancer is a challenging problem that often requires multiple medical disciplines. Many of these patients can be managed with narcotic analgesics, using the principles outlined in Chapter 36, Chapter 84, Chapter 102, Chapter 103, and Chapter 104. When narcotics are not well tolerated or are ineffective, other procedures should be attempted. Upper abdominal pain can be relieved by celiac plexus block with alcohol (55). Because pain is more commonly seen in the lower abdomen and pelvis in these patients, however, subarachnoid injection of alcohol to interrupt the affected segments can be used; epidural administration of morphine or some other narcotic can be alternatives to neurosurgical procedures in patients with intractable lower abdominal, pelvic, and sacral pain caused by colorectal cancer (96,97). Detailed discussions of these high-technology and surgical aspects of managing cancer pain can be found in Chapter 35 and Chapter 102, Chapter 103, Chapter 104, Chapter 105 and Chapter 106.

Irritable Bowel Syndrome

Etiology and Pathophysiology. Irritable bowel syndrome is a frequent cause of abdominal pain in the general population and is the most common diagnosis among patients referred to gastroenterologists (98). The cause of this disorder is unknown but most likely is multifactorial and may be related to altered visceral sensitivity or intestinal motility (99,100). Emotional stress is often associated with exacerbations of the irritable bowel syndrome. Patients with this disorder also perceive pain produced by small and large intestinal distension in more diverse abdominal and extraabdominal sites than do healthy people (11,56). Irritable bowel syndrome is twice as common in female than male subjects, can be associated with a history of prior physical or sexual abuse, most often begins in the third or fourth decade of life, and commonly recurs for the lifetime of the patient.

Symptoms and Signs. Most patients with irritable bowel syndrome have abdominal pain, a cramping or aching pain below the level of the umbilicus that is relieved by a bowel movement or by passing flatus (101). Pain lasts from a few minutes to hours and is usually recurrent. Some patients with irritable bowel syndrome have predominantly epigastric pain and are part of the nonulcer dyspepsia spectrum.

Alteration of bowel habits occurs in 90% of patients with irritable bowel syndrome. Constipation, diarrhea, or alternating episodes of constipation and diarrhea can occur. Individual patients often have a typical pattern of bowel evacuation that is constant over their lifetimes. Stools are often loose with an episode of pain, but the pain is usually relieved by the bowel movement (101). Abdominal distension, mucus in stools, nausea, vomiting, and excessive flatus are frequently associated symptoms. Symptoms are recurrent and are often associated with stressful life events.

Diagnosis. Diagnosis of irritable bowel syndrome requires recognition of the positive clinical features outlined previously, as well as exclusion of other known causes of the patient's symptoms (101). Lactose intolerance, giardiasis, inflammatory bowel disease, and intestinal obstruction should be considered in patients with recurrent abdominal pain and altered bowel habits. A trial lactose-free diet; examination of stool for blood, ova, and parasites; sigmoidoscopy; and barium enema examinations are usually needed to exclude these possibilities. Patients who have blood in their stool, fever, weight loss, progressive symptoms, nocturnal pain, or nocturnal diarrhea are more likely to have an illness other than irritable bowel syndrome; those in this group should have a more thorough investigation for other causes of their symptoms.

Treatment. No cure is available for irritable bowel syndrome, but patients can be helped in several ways. The concerned and supportive physician can do much to relieve patients' concerns about their symptoms. The importance of a supportive role is illustrated by the beneficial effects of placebos in reducing pain in these patients. Stress management techniques can also be useful in decreasing the frequency of symptoms. Tricyclic antidepressants have been shown to reduce abdominal pain and nausea significantly more than placebo in patients with irritable bowel syndrome (102).

Other medical therapies for irritable bowel syndrome can benefit individuals, but controlled trials have not proven their efficacy in large groups of patients. A high-fiber diet is usually helpful in reducing constipation, but abdominal pain might not be relieved. Loperamide or diphenoxylate with atropine, one or two tablets in the morning and evening, can be used to control diarrhea. Anticholinergic agents such as dicyclomine, 10 to 20 mg, hyoscyamine, 0.125 to 0.25 mg, and propantheline, 15 to 30 mg given before meals, can decrease abdominal pain that is induced by eating. Narcotic analgesics for pain in this syndrome have not, in our experience, been useful, nor are there published studies that indicate the utility of narcotics for this syndrome. Moreover, the risk of psychological and physical dependence from long-term opiates is real. Reassurance that symptoms usually resolve with time and that the patient's longevity is not decreased in irritable bowel syndrome is critical to successful long-term management.

DISEASES OF THE ANUS AND RECTUM

Basic Considerations

Anatomy

The rectum constitutes the distal 12 to 15 cm of the large intestine, beginning at approximately the level of the S-3 vertebra. Many diseases of the rectum are part of the spectrum of other colonic diseases and have been considered in the previous section (e.g., carcinoma, inflammatory bowel disease, and various obstructive

lesions). Other disease processes involving the rectum produce symptoms that are similar to those of anal disease and are included here to facilitate clinical recognition. The terminal 3 cm of the rectum pass through the anal canal, which is made up of an internal sphincter of smooth muscle and an external sphincter of striated muscle. The rectum is lined with columnar mucosa as far distally as the pectinate line, which is approximately 2 cm inside the anal verge.

Nerve Supply

Sensory innervation of the rectum is through visceral afferent nerves that course with parasympathetic nerves by way of the pelvic splanchnic nerves and the pelvic plexus to enter the spinal cord at the S-2 to S-4 levels (see Fig. 66-9). Rapid distension, inflammation, and infiltration of the rectum produce a sensation of aching in the region of the rectum or a poorly localized deep central pelvic pain. Patients with rectal diseases also often report a dull or aching pain in the region of the midsacrum (103).

The anal canal distal to the pectinate line is covered with stratified squamous epithelium and is innervated by somatic sensory nerves. These nerve fibers are carried by the inferior hemorrhoidal nerve and synapse in the dorsal root ganglion at the S-2 to S-4 levels. Unlike other parts of the rectum and intestine, the anal canal is sensitive to cold, heat, and touch. Pain from the anus is well localized and often severe. The pain is usually continuous and can be of a burning, throbbing, or aching nature (103).

Clinical Considerations

Anatomic Abnormalities

Anal stenosis and atresia with fistula formation to other perineal structures are common congenital defects caused by incomplete development of the hindgut. They are generally diagnosed by inspection in early infancy and thus are not considered further here.

Hirschsprung's disease, or congenital megacolon, is caused by the absence of the intramural neural plexuses of a segment of the colon and results in dilation of the bowel proximal to the abnormal segment (103). More than two-thirds of cases involve only the rectum and distal sigmoid colon. Most patients present in infancy with abdominal distension and vomiting, suggesting intestinal obstruction. If the problem remains undetected until later in childhood, constipation, failure to gain weight, and diffuse abdominal pain can result. The diagnosis is usually suspected when a dilatated colon is seen on plain abdominal radiographs or with barium enema. Diagnostic confirmation requires the demonstration of the absence of intramural nerve plexuses by rectal biopsy. Surgical resection of the rectosigmoid usually corrects the problem.

Foreign Bodies

Numerous types of foreign bodies have been known to be introduced into the rectum, causing local pain and irritation. Perforations and lacerations can also occur, resulting in severe pain and sometimes peritonitis. Blood or mucus might be seen in the stool. The presence of foreign bodies and the extent of mucosal damage can usually be assessed by sigmoidoscopy. Most foreign objects in the rectum can be removed through the sigmoidoscope, although anesthesia may be required for this procedure. Laparotomy is required for foreign bodies that cannot be removed endoscopically and for intestinal perforation.

Hemorrhoids

Etiology and Pathophysiology. Hemorrhoids are dilatated blood vessels of the anal canal. They are classified as internal if above the pectinate line and external if below the pectinate line. Several theories have been proposed to explain the formation of hemorrhoids (104). Increased venous pressure in the pelvis, high anal sphincter tone, low-residue diets with resulting hard stool, and prolonged straining with defecation can all contribute to hemorrhoid pathogenesis.

Symptoms and Signs. Internal hemorrhoids are usually painless and cause symptoms either by bleeding or by prolapsing into the anal canal (104). Most patients with internal hemorrhoids reveal a history of anal discomfort at some time, although this might only be a mild irritation. If prolapsed hemorrhoids become incarcerated and thrombose, however, intense pain can be produced. The pain is localized to the anal area and is made worse by bowel movements, sitting, and walking. Hemorrhoidal bleeding is usually bright red and painless and can be seen on the surface of the stool, on the toilet tissue, or in the toilet bowl.

External hemorrhoids are usually asymptomatic. They are frequently seen in young people as small perianal bluish masses covered with normal perianal skin. These hemorrhoids can be painful if they thrombose or rupture into the surrounding skin, causing traction on adjacent nerves. This usually follows an episode of constipation and straining with defecation. The patient presents with well-localized perianal pain that is continuous and exacerbated by sitting and defection. External hemorrhoids usually do not cause rectal bleeding.

Diagnosis. Hemorrhoids are usually diagnosed by inspection of the anus and by use of simple maneuvers. Internal hemorrhoids can be seen at anoscopy, but the best way to detect them is with a stress test. The patient is asked to sit on the toilet and strain as one would during defecation. After 30 seconds, and while the patient continues to strain, the examiner inspects the anal region by placing a handheld mirror under the patient's buttocks. Internal hemorrhoids are visualized as bluish structures that protrude from the anus. Incarcerated internal hemorrhoids can be seen directly without patient straining as erythematous masses in the anal canal, covered with pink rectal mucosa. These lesions are tender and might not easily reduce back into the rectum. Thrombosed external hemorrhoids are bluish masses outside the anus that are covered with normal perianal skin and are usually tender to palpation.

Patients with anorectal pain or bleeding should have nonhemorrhoidal causes of the symptoms ruled out. Infectious proctitis, inflammatory bowel disease, anorectal neoplasms, and anal fissures should be considered in these patients. Sigmoidoscopy usually excludes these problems in patients younger than the age of 35 years. If pain or bleeding persists after treatment, colonoscopy should be performed to exclude lesions in more proximal areas of the colon (104). Care must be taken so that bleeding caused by a colon cancer above the area of sigmoidoscopy is not incorrectly attributed to hemorrhoids.

Treatment. Most patients with mild bleeding and discomfort caused by hemorrhoids can be managed medically. An increase in dietary fiber is often sufficient to soften stools, resulting in decreased straining with defecation. Topical application of ointments containing local anesthetics, such as 2.5% lidocaine or 1% pramoxine, can be soothing to patients with thrombosed external hemorrhoids. Hydrocortisone ointment 1% is also sometimes helpful for this condition. Warm water baths can decrease painful spasms of the anal sphincter.

Surgical therapy of hemorrhoids should be used in patients with persistent pain, bleeding, and prolapse. Rubber band ligation is a simple outpatient procedure that is quite effective in patients with internal hemorrhoids that are reducible and not too large (105). This ligation is more efficacious and has fewer complications than cryosurgery or injection of sclerosing solutions. Infrared coagulation and laser therapy for hemorrhoids are also available (106). Surgical resection of hemorrhoids is the treatment of choice for large and unreducible prolapsing hemorrhoids. Incarcerated hemorrhoids can usually be reduced after 1% lidocaine is injected around the anus and under the protruding hemorrhoid. Pain usually subsides within several days. Early surgical hemorrhoidectomy should be performed if thrombosis or gangrene is present. Patients with persistent pain, despite medical treatment of thrombosed external hemorrhoids, should have the associated clot excised. A single elliptical incision after injection of a local anesthetic, such as 1% lidocaine, allows clot evacuation. The procedure is safe, effective, and well tolerated.

Proctitis

Etiology and Pathophysiology. Inflammation of the anus and rectum has both infectious and noninfectious causes. Infectious proctitis is seen most frequently in homosexual men in whom frequent and widespread anogenital and orogenital contact is common (107). Infectious causes of proctitis are listed in Table 66-3. Inflammatory bowel disease limited to the rectum, trauma from foreign bodies and anal intercourse, radiation therapy, and allergies to lubricants and enemas are noninfectious causes of proctitis.

Symptoms and signs	Causative organism
Pain and anal discharge	*Neisseria gonorrhoeae*
	Herpesvirus hominis
	Treponema pallidum
	Chlamydia trachomatis
Pain and diarrhea	*Entamoeba histolytica*
	Campylobacter jejuni
	Shigella species
	Chlamydia trachomatis

TABLE 66-3. Causes and symptoms and signs of infectious proctitis

Symptoms and Signs. Bleeding, mucous or purulent discharge, pain, burning, and rectal urgency are the chief symptoms produced by anorectal inflammation; these symptoms are similar for all causes of proctitis. Diarrhea can be present if inflammation extends to more proximal areas of the colon (see Table 66-3). Pain is often increased by bowel movements and by wearing tight clothing. The most severe pain occurs when inflammation is present distal to the pectinate line.

Diagnosis. Specific diagnosis of the cause of proctitis is important for directing therapy and determining prognosis. Sigmoidoscopy usually reveals erythematous and friable rectal mucosa, with or without ulcerations, and areas of adherent purulent material. Herpes simplex infections can show characteristic grouped vesicles. Cultures for bacterial, chlamydial, and herpes organisms should be obtained from swabs obtained at sigmoidoscopy. Rectal ulcers should be swabbed for darkfield microscopic examination, and a serum serologic test for syphilis should be obtained if the patient has a history of anal intercourse. Rectal biopsies should be obtained when symptoms are persistent and cultures are negative to rule out inflammatory bowel disease.

Treatment. Treatment of proctitis is directed at the specific cause as well as symptomatic relief. Antibiotic therapy should be based on the results of appropriate cultures. Treatment of inflammatory bowel disease has been discussed previously. Sitz baths, warm compresses applied to the perianal region, and local analgesic ointments, such as lidocaine, can provide some relief. If maceration is present, all lubricants and ointments should be avoided and the area kept as dry as possible. Oral narcotic analgesics are sometimes necessary in severe cases.

Anorectal Abscess

Etiology and Pathophysiology. Localized abscesses are common in the perianal and anorectal areas. These infections can arise in preexisting tears, fissures, or thrombosed hemorrhoids, or can be seen in systemic illnesses such as Crohn's disease, ulcerative colitis, and leukemia. An underlying cause, however, often cannot be found. Abscesses can be superficial and in the perianal region, or they can be deep, in any of several potential spaces around the rectum (108).

Symptoms and Signs. Perianal abscesses, the most common type of anorectal abscess, present as painful localized masses. Pain is usually throbbing and constant until the abscess bursts.

Symptoms of deep anorectal abscesses are often not as well defined as those of the more superficial lesions. An aching sensation in the rectum, or poorly defined lower abdominal and pelvic pain, can be present. Fever is common in these deep perirectal infections.

Diagnosis. Physical examination in patients with anorectal abscesses usually reveals the diagnosis. Superficial abscesses are easily recognized by the presence of a red, tender, localized swelling near the anus. Deeper abscesses are detected by an exquisitely tender area of rectum found on digital examination. If deeper abscesses have burst into the rectal lumen, a purulent discharge is present. Peripheral leukocytosis is common, especially with deeper abscesses. Anorectal abscesses are distinguished from pilonidal, Bartholin's, and periurethral abscesses by their anatomic relationships to other perineal structures.

Treatment. Treatment of all anorectal abscesses centers around surgical drainage (108). It is not necessary to wait for fluctuance before carrying out incision and drainage. Antibiotics are useful when cellulitis is present around the abscess. The patient should have a follow-up examination for the detection of complications, such as fistula formation.

Anal Fissures

Etiology and Pathophysiology. Fissures of the anus are one of the most frequently seen painful anal conditions. These superficial tears of the anal epithelium are localized to the posterior midline of the anus in more than 90% of cases (103). Most commonly found in young adults with a recent history of constipation, fissures are probably formed by a tearing force associated with the passage of a large firm stool (104). Most fissures heal spontaneously within a few weeks. Chronic fissures, which are less likely to heal, occur in patients with high internal anal sphincter pressures. Other chronic fissures are seen in patients with Crohn's disease, ulcerative colitis, carcinoma, syphilis, and tuberculosis.

Symptoms and Signs. Most patients can relate the acute onset of pain caused by a fissure to defecation. Pain is localized to the anal area. The pain is continuous but is exacerbated by sitting and further defecation. Secondary constipation often occurs because of the fear of provoking pain with further bowel movements. A small amount of rectal bleeding and discharge can be present.

Diagnosis. The diagnosis of an anal fissure can usually be made by physical examination. Inspection of the anus often reveals an edematous skin tag adjacent to the distal aspect of the fissure. Rectal examination, with the examiner's smallest finger lubricated with lidocaine jelly, confirms the localized indurated anal wall and excludes associated mass lesions. Anoscopy and sigmoidoscopy must usually be postponed until the fissure has healed, but should eventually be done to exclude other rectal lesions.

Treatment. Treatment of anal fissures involves local analgesics and stool softeners to avoid pain and recurrent tears (104). Orally administered mineral oil or bulk agents such as psyllium usually loosen the stool, which facilitates stool passage and results in decreased straining. After the fissure has healed, additional fiber in the diet in the form of bran is often all that is needed to prevent recurrence. Local application of a lubricant containing a local anesthetic is helpful before bowel movements. This is best applied into the anal canal with the patient's little finger. Surgical resection or lateral subcutaneous sphincterotomy is usually required to treat chronic idiopathic fissures (109). However, more recent trials suggest that topical nitrates or botulinum toxin injection are also effective (110,111).

Anorectal Neoplasms

Etiology and Pathophysiology. Neoplasms of the anal canal and perianal region account for less than 5% of lower gastrointestinal malignancies. Approximately 50% of the neoplasms that present as anal masses are adenocarcinomas of the rectum, with distal growth through the anal canal. Most of the remainder are squamous cell carcinomas of the anal canal. Melanomas, basal cell carcinomas, and cloacogenic carcinomas are other rare neoplasms of this region.

Anal squamous cell carcinomas are associated with the presence of benign anorectal disorders, although the exact role of these conditions in the pathogenesis of the carcinoma is unknown. More than 50% of patients with these cancers have a history of hemorrhoids, fistulas, fissures, leukoplakia, abscesses, or anal warts (112).

Symptoms and Signs. Neoplasms of the anus and distal rectum present with symptoms different from those of more proximal colorectal cancers. These tumors are first detected either as an anal mass, because of bleeding or mucous discharge, or because of painful defecation. Continuous localized pain unassociated with defecation can also occur. Narrowing of stool caliber is often noted. Symptoms of large bowel obstruction can be seen with advanced cases. Weight loss and inguinal adenopathy usually indicate the presence of metastases.

Diagnosis. The diagnosis of an anorectal neoplasm is usually obvious after visual inspection of the anus and a gentle rectal examination. Any firm or indurated lesion

of the anal canal should be suspected as being neoplastic. These mass lesions can be biopsied through the anoscope to obtain a histologic diagnosis. If the patient can tolerate the procedure, the proximal extent of the tumor should be assessed by sigmoidoscopy.

Treatment. Therapy of anorectal neoplasms can involve radiotherapy, surgery, or chemotherapy. Radiotherapy or combined chemoradiotherapy of squamous cell carcinoma of the anus provides excellent control in approximately 80% of patients. Abdominoperineal resection is the operative treatment of choice for large rectal and anal cancers. Wide local excision should be reserved for anorectal tumors smaller than 4 cm^2. Postoperative chemoradiation therapy in patients with stage II or stage III anorectal adenocarcinoma can lead to a significant improvement in local control and survival (113). Preoperative radiation alone or chemoradiation for advanced local rectal cancers may also be effective while also improving resectability, decreasing morbidity, and increasing the chance that a sphincter-sparing operation may be performed (114). Novel therapies using interferons, monoclonal antibodies, and autologous tumor vaccines are being pursued (114).

Palliative treatment of anorectal neoplasms involves multiple therapeutic procedures. Radiation therapy of unresectable rectal cancer relieves symptoms of pain, bleeding, and discharge in approximately 75% of patients (115). Narcotic analgesics should be used liberally during radiation and in patients with pain unresponsive to radiation. The use of intraarterial chemotherapy, chronic intrathecal morphine administration, and ablative neurosurgical procedures in patients with intractable pain caused by anorectal neoplasms is similar to the use of these treatments for intestinal neoplasms. Pain management in patients with advanced cancer remains a challenging problem (see Chapter 36 and Chapter 40).

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CHAPTER 67

Painful Diseases of the Liver, Biliary System, and Pancreas

D. David Graham and John J. Bonica

Pain is a frequent concomitant of diseases of the liver, biliary system, and pancreas. Pain is important both as a diagnostic symptom to be interpreted and as a clinical management problem. Because of the high frequency of hepatobiliary and pancreatic disease in clinical practice, familiarity with hepatic, biliary, and pancreatic pain syndromes is essential.

In this chapter, pain syndromes associated with hepatic disorders, biliary disorders, and pancreatic disorders are presented. The causes and pathophysiology of primary disease processes involving each of these organ systems are discussed. Painful symptoms are examined from the viewpoint of underlying disease mechanisms. An outline of essential diagnostic tests is provided. Discussion of treatment options focuses on therapy of primary disease processes and on palliation of accompanying organic pain. Pathologic processes are examined to determine mechanisms of pain production as a guide to rational pain management.

LIVER

Basic Considerations

In humans, branches of both vagus nerves and branches of splanchnic nerves innervate the liver (1). Two separate but intercommunicating plexuses are formed by the sympathetic and parasympathetic nerve fibers (Fig. 67-1 and Fig. 67-2). An anterior plexus composed of parasympathetic fibers from the anterior vagus and of sympathetic fibers from the celiac ganglion surrounds the hepatic artery. The posterior plexus is located behind the bile duct and portal vein and is derived from the posterior vagus and right celiac ganglion. Hepatic nerves enter the liver in association with blood vessels and bile ducts and parallel these structures as they arborize within the liver parenchyma.

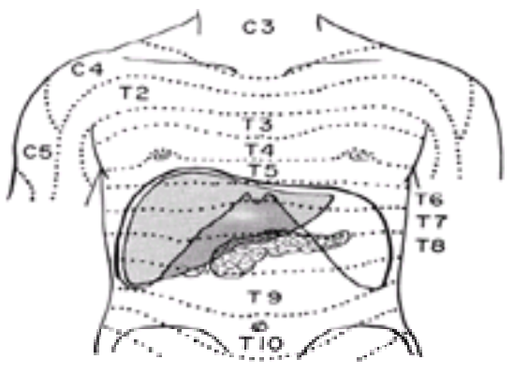

Figure 67-1. Schematic depiction of the position of the liver and pancreas in relation to body wall and dermatomes. The liver extends from T-5 to T-9, whereas the pancreas is located within T-7 to T-9.

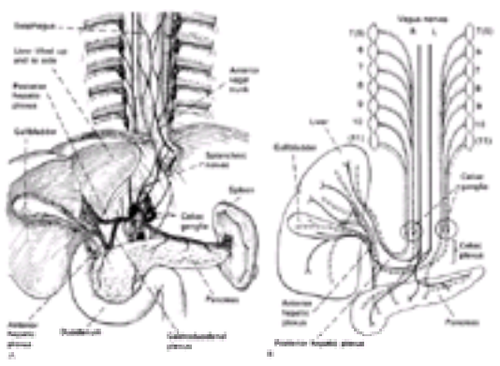

Figure 67-2. Anatomy of nerve supply to the liver, biliary system, and pancreas. **A:** Relationship of the vagus and sympathetic nerves contributing to the celiac plexus and the subsidiary plexuses, which follow vessels supplying the viscera. **B:** Schematic depiction of the course and distribution of two vagal nerves consisting primarily of preganglionic fibers, which synapse in the wall of the viscera with short postganglionic fibers (not shown). Preganglionic sympathetic fibers passing primarily from T-6 to T-9 (but also possibly from T-5, T-10, and T-11) pass through the superior and middle thoracic splanchnic nerves to the celiac ganglia, where they synapse with postganglionic fibers (*dashed lines*). Segments in parentheses in the sympathetic chain are variable. The afferent fibers are shown by the dotted lines. See text for details.

Hepatic pain is not transmitted by the vagi, although the liver receives a substantial vagal innervation and approximately 90% of vagal fibers are primary afferents. Vagotomy does not eliminate the perception of hepatic pain. Hepatic pain is believed to be transmitted to the central nervous system by afferent sympathetic fibers. In the cat, approximately 50% of visceral sympathetic fibers are afferent (2).

Clinical experience has attributed hepatic pain to stretch of Glisson's capsule by parenchymal swelling. The rate of hepatic enlargement can be the important variable in the production of pain; gradual hepatic enlargement is often painless. Morphologic evidence suggests that hepatic nerves might also be sensitive to changes in hepatic venous pressure (3). Nerve fibrils have been demonstrated in humans in association with intimal endothelial cells of hepatic veins that are structurally similar to known sensory nerves (4).

Hepatic inflammatory processes can produce well-localized somatic pain if the parietal peritoneum is involved. Sharp, intense, upper abdominal or lower thoracic discomfort is characteristic. Typically, inspiration intensifies such pain, and referred hepatic pain is usually noted in the right shoulder and scapular regions (Fig. 67-3).

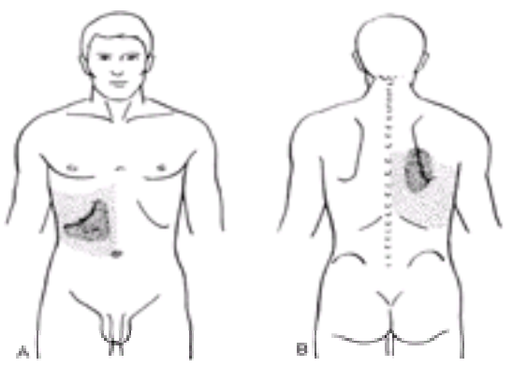

Figure 67-3. Areas of referred hepatic pain in the anterior **(A)** and posterior **(B)** regions of the body. The heavy stipple indicates the area of pain reference, whereas the light stipple indicates the extensive cutaneous hyperalgesia often associated with the pain.

Clinical Considerations

Viral Infection

Symptoms and Signs. Hepatic enlargement and pain resulting from capsular stretching frequently accompany acute viral hepatitis. During the early prodromal stage of the illness, pain is usually absent and physical findings are minimal. Fatigue, anorexia, arthralgias, and nonspecific constitutional complaints predominate. By the time jaundice appears, more than half of affected patients are symptomatic with hepatic pain. The discomfort is often described as a dull, heavy, unpleasant sensation, localized to the right upper abdomen. Hepatomegaly is common; the liver edge is usually smooth and tender to palpation just beneath the right costal margin.

Diagnosis. In the presence of appropriate symptoms, acute viral hepatitis can be diagnosed by determination of progressively elevated serum transaminase levels. The serum alkaline phosphatase levels can be normal or moderately elevated. Increases in the serum bilirubin level are variable. Assays to detect circulating viral antibodies and antigens should be performed to characterize the disease further.

Treatment. Treatment of uncomplicated acute viral hepatitis is largely supportive, consisting of nutritional care, pain relief, and avoidance of hepatotoxic drugs or agents. The accompanying hepatic discomfort is usually not a difficult management problem, but caution should be exercised in the administration of sedatives or analgesics. Agents with significant hepatic metabolic effects such as narcotics should be avoided, because the liver's ability to metabolize these substances may be compromised.

Bacterial Infection

Symptoms and Signs. Hepatic abscess should be suspected when hepatic pain is present in a patient with systemic sepsis. The most frequent localizing symptom is a constant dull pain in the right upper quadrant of the abdomen, present in 50% to 90% of such patients (5,6). Referred pain to the right shoulder and scapula is common. Most patients with hepatic abscess have a large, tender liver on physical examination. Jaundice is unusual, occurring in only 10% of patients (5). Ascites is rare. Systemic signs of sepsis predominate. Fevers, chills, rigor, and tachycardia are usually present. Malaise, anorexia, weight loss, nausea, and headache are frequent, nonspecific complaints.

Pathophysiology. Bacterial infection of the liver usually manifests as a parenchymal abscess. Hepatic abscesses can develop after bacterial contamination from several routes: (a) by direct extension from an adjacent suppurative process such as gangrenous cholecystitis; (b) by portal venous bacteremia from a distant septic focus such as appendicitis or diverticulitis; (c) through the biliary system via obstruction and cholangitis from either benign or malignant conditions; (d) from systemic infection such as endocarditis via the hepatic artery; or (e) due to secondary infection of blunt or penetrating hepatic trauma. The microbiology of hepatic abscesses reflects their common association with other gastrointestinal inflammatory diseases as well as biliary tract disease. Enteric organisms are recovered from cultures of the abscess in 80% of cases. *Escherichia coli, Streptococcus viridans*, and *Klebsiella* species are most prevalent and are discovered in greater than 50% of hepatic abscesses; anaerobic bacteria are frequent copathogens (7). Multimicrobial abscesses are common. More recently, fungal abscesses have become more common, likely due to the increased number of immunocompromised patients. Earlier this century, the majority of hepatic abscesses were the result of intraabdominal infections and subsequent extension to the liver, presumably via the mesenteric circulation and portal vein. However, with the advent of newer antibiotics, endoscopic biliary procedures, and percutaneous biliary tract manipulation, this etiology profile is changing. Currently, it is believed that biliary tract disease accounts for some 40% of liver abscesses. Interestingly, 20% to 40% of pyogenic liver abscesses have no identifiable cause (8). Hepatic abscesses are solitary in 60% of cases and multiple in the remainder. The right lobe is affected in 60% of cases, the left lobe is affected in 10% to 15% of cases, and 20% of cases are bilobar.

Diagnosis. Radiologic evaluation is essential to diagnose hepatic abscesses, to define the disease process anatomically, and to detect other foci of intraperitoneal sepsis. Ultrasonography is useful to rule out biliary tract disease. It is also a useful screening procedure for locating hepatic masses and to differentiate solid and cystic processes (6). Computed tomography (CT) scanning, however, currently provides the most detailed and accurate anatomic information for hepatic abscesses and has a higher overall diagnostic accuracy (95% to 100% sensitivity) than ultrasound. In most cases, CT scanning should be used in planning definitive therapy (9). ^{99}Technetium sulfur colloid scans have been used on a limited basis for some four decades. Such scans cannot detect lesions less than 2 cm in diameter, which limits their usefulness. Newer nuclear medicine technologies using gallium and indium have added little to the evaluation of these lesions. Magnetic resonance imaging (MRI) has not proven to be superior to CT scan in the diagnosis of hepatic abscess and does not allow for interventional techniques.

Treatment. The treatment of hepatic abscesses requires long-term (6-week) antibiotic therapy and percutaneous drainage of the abscess under CT or ultrasound guidance. Antibiotic therapy is usually started before detection of the abscess, because most patients have signs of systemic sepsis. The choice of antibiotic should reflect the polymicrobial enteric flora commonly associated with hepatic abscess; broad coverage of aerobic gram-negative organisms, *Streptococcus* species, and anaerobes should be achieved. Antibiotic therapy should include a 2-week intravenous course followed by oral antibiotics for an additional month. Once culture results return, antibiotics can be tailored for specific organisms. Percutaneous catheter drainage of hepatic abscesses is often successful if the infection is solitary and not associated with other intraperitoneal pathology, and it is most often the treatment of choice over operative therapy. In the case of multiple abscesses, percutaneous drainage is of little value. Operative therapy of accompanying foci of infection (e.g., suppurative cholangitis requiring cholecystectomy), however, is frequently required. Operative therapy may be required in the case of (a) patients in whom percutaneous drainage is not feasible, (b) a failed percutaneous drainage, and (c) patients with concomitant gastrointestinal disease requiring operation. Recently, laparoscopic drainage of hepatic abscesses has been introduced, which is also useful in addressing the primary disease process. Treatment of the pain associated with hepatic infection depends on successful treatment of the abscess. Chronic pain syndromes have not been associated with parenchymal hepatic infection.

Gonococcal Perihepatitis

Pathophysiology. Gonococcal perihepatitis, described in women as a cause of right upper quadrant pain, is known as the *Fitz- Hugh-Curtis syndrome*. The gonococcal organism is transmitted venereally and has an affinity for the urogenital epithelium. Ascending infection presumably enters the peritoneal cavity through the fallopian tubes and reaches the perihepatic space via the right paracolic gutter. Pelvic infection may not be clinically obvious. *Chlamydia* can also cause the syndrome in women in the presence or absence of gonococci.

Symptoms and Signs. Acute gonococcal perihepatitis begins as sudden right upper quadrant pain with radiation to the right shoulder. Inspiration intensifies the pain. Fever, tenderness, and rebound are common. Acute gonococcal perihepatitis can be suspected when these symptoms are present in sexually active women with clinical evidence of pelvic inflammatory disease or gonococcal organisms demonstrated on cervical culture.

Treatment. Treatment of acute gonococcal perihepatitis requires antibiotic therapy appropriate for treatment of the underlying pelvic inflammatory disease. Painful

symptoms should resolve promptly (10).

Chronic or incompletely treated perihepatitis has been reported to result in formation of adhesions from the liver to the surrounding parietal peritoneum. A chronic upper abdominal pain syndrome can result from traction of such adhesions on the parietal peritoneum. Laparoscopy can be used to identify this process. Lysis of offending adhesions usually eliminates the pain (11).

Neoplastic Disease

Involvement of the liver by primary and metastatic neoplasms remains a great challenge to those interested in the treatment of pain. The magnitude of this problem can be appreciated by considering that in total approximately 40% of patients dying with a solid tumor develop liver metastases (12). In addition, hepatocellular carcinoma is the most prevalent cancer in the world, killing more than 1 million annually. Furthermore, the incidence of hepatocellular cancer has doubled in the United States during the past 30 years. Without treatment, up to 70% of patients with hepatic metastases die within 1 year of diagnosis and nearly 100% die within 3 years. Results of a study by Jaffe and colleagues (13) suggested that metastatic replacement of the liver is the aspect of visceral cancers that most directly contributes to mortality. Because cure of primary or metastatic hepatic tumors is not common, palliation, including palliation of painful symptoms, is a major clinical goal.

Primary hepatic tumors cause approximately 1% of cancer deaths in the United States and are the twenty-second most common cancer in the United States (14). In parts of Africa and Asia, however, hepatocellular carcinomas cause up to 20% to 40% of cancer-related deaths. Hepatoma frequently develops in the setting of preexisting severe liver disease and often is related to hepatitis B and C infection. More than 50% of patients who develop hepatocellular carcinoma have histologic evidence of cirrhosis. Approximately 5% of patients with alcoholic cirrhosis in the United States develop hepatocellular carcinoma. The frequency is even greater in individuals with postnecrotic cirrhosis (10%), untreated hemochromatosis (20%), or cirrhosis caused by a ¡-antitrypsin deficiency. Because of the high absolute number of patients with alcoholism, the majority of patients in most reported series have Laënnec's cirrhosis, typical of alcohol abuse (15), although the number of cases related to chronic viral infection is increasing.

Symptoms and Signs. Most authors, although emphasizing that symptoms caused by hepatoma are vague and nonspecific, have reported that pain is a prominent symptom when patients first seek medical attention. Ihde and associates (16) noted that more than 70% of hepatoma patients have right upper quadrant or epigastric pain of a chronic nature, most commonly associated with a hepatic mass, weight loss, or ascites. The pain is frequently described as an epigastric pressure, fullness, or heaviness. Associated symptoms are nonspecific and include weakness, malaise, anorexia, and weight loss. The onset of symptoms is usually insidious. An abdominal mass is the main complaint in 10% to 20% of cases. Jaundice is present in some 25% of cases of primary hepatocellular carcinoma. A second relatively common presentation, noted in 8% of patients with hepatoma, consists of acute right upper quadrant pain, fever, and jaundice, mimicking that of acute cholecystitis.

Because hepatocellular carcinomas tend to develop in patients with hepatic functional impairment, systemic symptoms can be prominent and rapidly progressive. Cachexia and wasting, development of jaundice or worsening of preexisting jaundice, and intractable ascites are common. Hemorrhagic phenomena are frequent. Hemorrhage, including gastrointestinal bleeding from esophageal varices and rarely hemoperitoneum caused by intraperitoneal rupture of tumors, is a proximate cause of death in 50% of hepatocellular cancer patients. Hepatomas are among the tumors most frequently associated with paraneoplastic syndromes. Secondary paraneoplastic syndromes include polycythemia, thrombocytosis, hypoglycemia, hypercalcemia, and production of ectopic adrenocorticotropic hormone.

Treatment. Hepatocellular carcinoma is usually a relatively slow-growing tumor; resection, in the absence of cirrhosis, has often resulted in cure. Resection in the face of cirrhosis is much more likely to result in recurrence, although this may take several years to occur. In the United States, average survival after resection is 3 years, with 5-year survival rates in recent large series ranging from 11% to 46%. Resection is the only therapy that currently significantly prolongs survival. The response of hepatocellular carcinoma to intravenous single-agent and multiagent chemotherapy remains unimpressive. The most consistent response rates with respect to systemic chemotherapy have been reported with doxorubicin (Adriamycin). Response rates of 25% or less have been reported, without significant increase in survival time (17). The continuous infusion of chemotherapeutic agents into the hepatic artery has recently been described for the treatment of hepatomas, as well as other methods such as hepatic artery ligation, arterial embolization and chemoembolization, targeting irradiation, and direct tumor injection. Initial results suggest a modest improvement in palliation compared with those obtained with intravenous chemotherapy (12). Cryoablation is a new technique that has been shown to prolong survival slightly in otherwise unresectable patients (18). Pain during therapy is controlled with nonsteroidal antiinflammatory drugs and potent narcotics. In hospitals in which qualified personnel are available, severe pain can be temporarily relieved with segmental epidural analgesia (see Chapter 102) or intraspinal narcotics (see Chapter 103). See Chapter 35, Chapter 36 and Chapter 37 for a comprehensive summary of the management of cancer pain.

Hepatic Adenoma

In a woman of childbearing age who has been taking birth control pills and presents with chronic right upper quadrant pain, the diagnosis of hepatic adenoma should be seriously considered.

Diagnosis. Up to 80% of patients with adenoma will have symptoms related to the lesion (7). Biliary tract disease is first excluded by ultrasonography, which can also show the presence of a solid tumor in the liver. If the ultrasonography does not reveal biliary tract disease, the liver should be examined for masses. CT scanning or laparoscopic examination of the liver surface might be required. CT scan will show a solid, hypovascular mass that may contain hemorrhagic areas. Adenomas are composed of sheets of hepatocytes with thin-walled venous lakes lacking bile ducts or portal triads. Biopsy is generally considered safe but not often helpful.

Treatment. If the diagnosis of adenoma is suggested, the first step in treatment is to stop oral contraceptives. Smaller lesions may regress with 6 months of cessation of hormonal therapy. If the tumor is larger than 6 to 8 cm in diameter, and thus not likely to regress, or pain is not rapidly relieved, surgical excision is necessary. Pain rapidly resolves after excision. In patients for whom discontinuation of birth control medication and follow-up is decided on, gradual resolution of pain and tumor regression should occur. Otherwise, surgical excision should be considered. Because pregnancy increases the growth potential of adenomas, patients considering pregnancy are advised to undergo resection.

Hepatic adenomas can also present acutely, either with severe right upper quadrant pain or with spontaneous hemorrhage into the peritoneal cavity. Emergency surgery is indicated in these situations.

Metastatic Tumors

Metastatic tumors occur with 20 to 30 times the frequency of primary hepatic cancers. Hepatic metastatic disease is a particular problem for cancers drained by the portal venous system, being seven times more likely to occur than tumors arising outside the portal bed (19). In a series of 8,455 autopsies reported from the Roswell Park Cancer Center, 39% of adult patients with solid tumors had hepatic involvement (19).

Symptoms and Signs. Many patients with hepatic metastases are asymptomatic. Asymptomatic hepatic metastases are discovered in 15% to 20% of patients with colorectal carcinoma during staging of the cancers before operation or during laparotomy. Most patients with hepatic metastases are symptomatic, however, with pain as a prominent complaint. The pain associated with hepatic metastases is usually constant, dull, and localized to the epigastrium. Accompanying anorexia, weight loss, fatigue, fever, and epigastric fullness are common. Occasionally, acute episodes of right upper quadrant pain can herald hemorrhage into a hepatic metastasis or tumor necrosis. In contrast to primary hepatomas, jaundice and ascites are uncommon until the advanced stages of hepatic metastatic disease. When jaundice occurs as an initial finding, malignant biliary obstruction by enlarged nodes in the porta hepatis or by direct growth of biliary or pancreatic carcinomas is the usual finding. Death usually occurs as a result of liver failure from progressive replacement of the liver parenchyma.

Prognosis. The survival pattern in cases of hepatic metastasis depends on patients' functional status, the extent of hepatic replacement by the metastatic tumor, the presence or absence of an extrahepatic tumor, and the histology of the tumor type. Without treatment, 70% of patients with colorectal metastases to the liver die within 1 year and nearly 100% die within 3 years. Patients who undergo resection of a solitary metastatic lesion from a colorectal primary tumor may have a 40% 5-year survival rate. Metastatic gastric cancer is the second most common gastrointestinal tumor for which hepatic resection has been used for metastatic disease. Carcinoid tumor and islet cell or neuroendocrine tumors of the pancreas are somewhat favorable gastrointestinal tumor types for which hepatic resection is used. Other gastrointestinal cancers, especially pancreatic and esophageal cancers, are poor candidates because of unfavorable histology and rapid growth rates. Survival is markedly decreased in patients who are nutritionally debilitated when metastases are discovered or if extrahepatic tumor is also present.

Treatment. Selected patients with metastatic hepatic neoplasms (primarily colorectal cancers) can be candidates for curative surgery. They must meet rigorous

criteria: control of the primary cancer, absence of extrahepatic metastases, adequate functional hepatic reserve, and confinement of disease to one hepatic lobe. Less than 10% of all patients with hepatic metastases fulfill these criteria, and only 30% of potential candidates for surgical excision have resectable disease at the time of exploration. Sarcomas, neuroendocrine tumors, and endocrine tumors such as thyroid cancer and breast cancer are included among those nongastrointestinal tumor types for which hepatic resection is indicated. Some 20% to 40% of patients who undergo resection survive for 5 years postoperatively (7). Response to systemic chemotherapy depends on the site of the primary neoplasm, the extent of hepatic involvement, and the route of administration. Long-term palliation is occasionally possible (20).

Because cure of hepatic neoplasms is somewhat uncommon, symptomatic palliation is of cardinal importance. Measures to control the secondary manifestations of hepatic dysfunction are important therapeutic adjuncts. Relief of ascites by pharmacologic or mechanical means, treatment of the pruritus accompanying biliary obstruction, and attention to nutrition are examples of measures that make palliation of pain much more effective.

A commitment should be made to maintain patients with hepatic neoplasms on oral medications for as long as possible. It is generally possible and practical to maintain most patients with hepatic tumors on oral opioids and nonopioids plus adjuvants until the last few days of their lives (21). Sedation, the major adverse side effect, must be monitored but is generally not debilitating. Most patients remain ambulatory and can retain some independence. A discussion of specific agents, routes of administration, and dosage schedules is found in Chapter 36. If large doses of oral opioids are ineffective in relieving severe pain, intraspinal opioids should be given a trial. In patients with severe excruciating pain unaffected by the aforementioned procedures, a celiac plexus block with alcohol should be considered if a physician skilled in its administration is available.

BILIARY SYSTEM

Basic Considerations

In humans, the biliary system is supplied by sympathetic afferent fibers originating from the T-6 through T-10 dermatomes (see Fig. 67-2). Although sympathetic afferent innervation of the biliary system is bilateral, most fibers transmitting visceral pain traverse the right splanchnic nerves. The gallbladder and bile ducts receive extensive parasympathetic innervation, both through the hepatic branches of the left vagus and the celiac division of the posterior vagus. Visceral biliary pain, however, is not transmitted by afferent vagal fibers. Vagotomy does not alter the perception of biliary pain.

Visceral pain fibers in the biliary system are primarily sensitive to distension of the gallbladder or bile ducts and to forceful muscular contraction of the gallbladder in the presence of distal ductal obstruction (see Chapter 3 for details). Distension of the gallbladder or common bile duct most often causes pain when the distension occurs acutely; gradual enlargement usually does not cause painful symptoms. In humans, experimental dilatation of these structures causes an intense crampy pain in the epigastrium or right upper quadrant (22). The pain can be referred to the back at the level of the right scapula (Fig. 67-4). Active contraction of the gallbladder accompanying complete or nearly complete duct obstruction causes the pain of biliary colic. Colic is initiated when gallbladder contraction is stimulated by the hormone cholecystokinin. Cholecystokinin release, in turn, is stimulated by intraduodenal fats (23) or amino acids (24). Biliary visceral pain is usually not dramatic if the obstruction develops gradually within the common bile ducts, perhaps because of the capacity afforded by the extrahepatic and intrahepatic biliary systems.

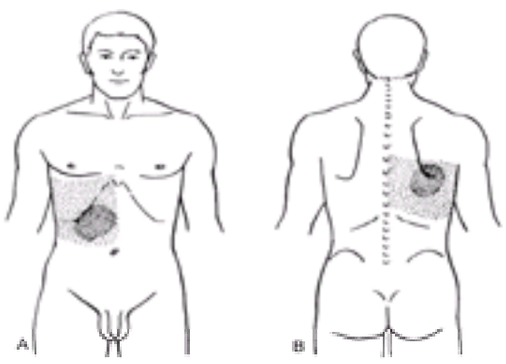

Figure 67-4. Areas of referred biliary pain in the anterior **(A)** and posterior **(B)** regions of the body. The heavy stipple indicates the area of pain reference, whereas the light stipple indicates the extensive cutaneous hyperalgesia often associated with the pain.

Inflammatory disease of the gallbladder can cause stimulation of the afferent nerve fibers of the parietal peritoneum, which is experienced as somatic pain. Nerve fibers that are activated by stimulation of the parietal peritoneum are distributed in the areolar connective tissue beneath the parietal mesothelium. These myelinated fibers are organized in dermatomes; biliary inflammation generally stimulates somatic afferents that reach the spinal cord through the sixth to ninth intercostal nerves, corresponding to dermatomes T-6 through T-9. Somatic pain associated with biliary disease is intense, easily described, and well localized to the right upper quadrant. When present, somatic pain tends to obscure accompanying visceral pain.

Clinical Considerations

Gallstones (XXI2)

Calculous biliary tract disease is a major problem in the United States. Approximately 12% of adults in this country are prone to the development of symptomatic gallstones. Approximately 1 million people annually in the United States develop symptoms attributable to their gallstones. More than 500,000 biliary tract operations are performed each year in the United States, and the numbers are increasing since the advent of laparoscopic cholecystectomy (25). Of those with symptoms from biliary calculi, 60% to 75% have colic as their initial symptom.

Symptoms and Signs. An episode of biliary colic usually begins with poorly localized pain in the midepigastrium. The pain can eventually move to the right upper quadrant. The discomfort is constant and may become severe. Often beginning 15 to 60 minutes after a meal, symptoms can persist for 4 to 8 hours before gradually abating. Accompanying anorexia, nausea, and vomiting, which may be bilious, magnify the unpleasant visceral sensations. Somatic pain is absent unless obstruction is complicated by inflammation. Referral of biliary visceral pain to the scapular area is frequently observed. Right upper quadrant tenderness and guarding are usually absent, as are systemic signs of inflammation.

The completeness of obstruction and the promptness of relief of obstruction probably determine whether gallbladder inflammation will occur to complicate biliary colic. In most people (90%) the obstruction relents and inflammatory changes are minimal and nonprogressive. If obstruction is not relieved, continued distension can result in the progressive inflammation of the gallbladder wall, which characterizes acute cholecystitis.

Pain associated with acute cholecystitis is usually well localized by history and physical examination to the right upper quadrant. Somatic pain can be present if the inflammatory process is in contact with the parietal peritoneum. Referred pain to the right shoulder due to diaphragmatic irritation can also be noted. Localized tenderness is noted in the right upper quadrant beneath the costal margin on physical examination and may be associated with muscle rigidity and rebound tenderness. Gentle, deep palpation heightens the discomfort, and Murphy's sign, inspiratory arrest during deep palpation in the right upper quadrant, may be elicited. In one-third of patients a palpable mass representing gallbladder and adherent omentum and bowel is noted. Low-grade fever (less than 101° F) is seen in 80% of patients with acute cholecystitis but does not reliably distinguish biliary colic and acute cholecystitis.

Diagnosis. Mild to moderate cases of acute cholecystitis are accompanied by modest leukocytosis, approximately 12,000 to 15,000 white blood cells per µL with a left shift. Serum bilirubin values are reported to be mildly elevated in 33% of patients with acute cholecystitis (usually lower than 4 mg per 100 mL). Serum alkaline phosphatase and serum amylase levels can also be modestly and nonspecifically elevated.

Radiopaque gallstones are visible on plain abdominal radiographs in 5% to 15% of patients. Ultrasonography has become the method of choice for demonstrating the presence of gallstones within the gallbladder. Using modern equipment and a real-time technique, several authors have reported that gallstones can be detected with

sensitivity and specificity of diagnosis that exceed 90% (26). The presence of acute cholecystic inflammation can be implied by the sonographic presence of a thickened gallbladder wall, pericholecystic edema or fluid, and tenderness during compression by the ultrasonic transducer (sonographic Murphy's sign). Occasionally, radionuclide scanning of the biliary system with hepatobiliary iminodiacetic acid scan can be useful in demonstrating cystic duct obstruction when the presentation is atypical. Hepatobiliary iminodiacetic acid scans are a highly sensitive (greater than 95%) but less specific (90%) measure of acute inflammation of the gallbladder (7). Alternative examinations, such as oral cholecystography, endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography, have limited usefulness in uncomplicated cases.

Treatment. Initial therapy of acute cholecystitis includes administration of intravenous antibiotics, fluid resuscitation, restriction of oral intake, and parenteral analgesics. Elective laparoscopic cholecystectomy is the recommended treatment for patients with symptomatic cholelithiasis. In the presence of gallstones, the typical visceral pain associated with biliary tract disease is permanently relieved in 95% of patients (27). Nonspecific dyspeptic symptoms associated with definite gallbladder calculi are relieved in 75% of patients.

Postcholecystectomy Pain (XXI3)

In certain patients, cholecystectomy can be one of the most effective operations used for relief of pain. Nonetheless, up to 20% of patients continue to have abdominal pain that is severe enough to prompt medical evaluation after surgery (28)—the so-called postcholecystectomy syndrome. Often, the pain complex is similar to that for which surgery was recommended and may occur months to years after the initial surgery. These patients represent difficult diagnostic and therapeutic problems. They are frequently evaluated and cared for by physicians interested in chronic pain.

Pathophysiology. Several factors have been identified that place patients at increased risk of postcholecystectomy pain. For example, those patients who have noninflamed gallbladders or gallbladders without calculi have a high incidence of postcholecystectomy pain. In addition, the risk of developing postoperative symptoms increases the longer the symptoms were present preoperatively.

Possible causes of postcholecystectomy pain can be separated into four general categories: (a) incorrect preoperative diagnosis such as peptic ulcer disease; (b) unrecognized accompanying hepatobiliary disease, such as a stricture or a common duct stone; (c) incomplete cholecystectomy or retained gallbladder; and (d) papillary obstruction (Table 67-1).

General category	Histopathologic diagnosis	Method of investigation
Incorrect preoperative diagnosis	Peptic ulcer	Upper gastrointestinal endoscopy
	Pancreatitis	Serum amylase determination, ultrasonography
	Functional bowel disorders	Barium enema, colonoscopy
Unrecognized hepatobiliary disease	Retained common duct stone, biliary stricture, neoplasm	ERCP
Incomplete cholecystectomy	Gallbladder remnant, cystic duct remnant	ERCP
Papillary obstruction	Sphincter of Oddi dyskinesia, ampulla of Vater dysplasia	ERCP and biliary manometry

ERCP, endoscopic retrograde cholangiopancreatography

TABLE 67-1. Causes of postcholecystectomy pain syndromes

Incorrect Diagnosis. In patients with persistent abdominal pain after cholecystectomy, the possibility of an incorrect preoperative diagnosis must always be considered. Unrecognized peptic ulcer, pancreatitis, and irritable bowel syndrome are the disturbances most frequently misidentified as calculous biliary disease. The possibility of incorrect diagnosis is greatest for those patients who are found to have noninflamed or acalculous gallbladders at the time of operation. Patients with persistent symptoms after cholecystectomy should be evaluated for these as well as other possibilities using appropriate endoscopic, radiologic, and laboratory tests.

Unrecognized Diseases. The second general category of disorders that cause persistent pain after operation includes coexistent unrecognized hepatobiliary disorders originating in a portion of the biliary system separate from the gallbladder. The most frequent pathologic entities identified in this category are retained common bile duct stones, postoperative biliary strictures, and unrecognized biliary or pancreatic neoplasms.

Retained stones constitute the most common cause of recurrent biliary-type pain after cholecystectomy. Residual common bile duct stones have been reported in approximately 2% of patients after cholecystectomy (29), and calculi are found in 80% of patients who undergo secondary biliary operations after cholecystectomy (28). Retained bile duct stones should be suspected in patients with biliary pain and biochemical evidence of cholestasis or pancreatitis. A history of previously performed common bile duct exploration should heighten suspicion because this maneuver is associated with a five- to tenfold increase in the risk of retained or recurrent stones. ERCP is the preferred method for demonstrating suspected common duct stones. Endoscopy also provides the options of therapeutic papillotomy and endoscopically guided stone extraction (30). If endoscopic stone removal is not possible or successful, reoperation might be recommended, often with formation of a biliary-enteric anastomosis to prevent recurrence.

Postoperative biliary strictures are second in frequency to retained biliary stones as causes for postcholecystectomy pain caused by residual hepatobiliary disease. In more than 90% of patients, biliary stricture results from iatrogenic injury to the extrahepatic bile ducts during cholecystectomy (31). In most of the remaining patients, ductal obstruction occurs because of cicatrization of the intrapancreatic common bile duct as a result of pancreatitis. Clinical symptoms can appear months to years postoperatively. Typical biliary-type pain and laboratory evidence of cholestasis are common findings. Endoscopic cholangiography is essential for identifying the injury and for defining the extent of damage anatomically. Postoperative biliary strictures have been treated by operative repair, stenting, balloon dilation, and combinations of these techniques. Experience, familiarity with available options, and clinical judgment dictate the most appropriate approach for individual patients.

Malignancy. Because symptoms caused by biliary, periampullary, and pancreatic malignancies can sometimes mimic pain from calculous biliary disease, these cancers, if not recognized at operation, can cause persistent postoperative distress. The treatment of pain resulting from retained biliary stones or biliary strictures consists of treating the residual disease. Restoration of anatomic and functional normality results in relief of pain. Treatment of malignancy-associated pain is covered later in this chapter.

Remnant Structures. Two frequently cited causes of persistent symptoms after cholecystectomy are remnants of gallbladder or remnant cystic ducts (32). A cystic duct remnant is generally defined as a residual ductal structure longer than 2 cm. Such remnants have been hypothesized to cause symptoms by harboring residual calculi, by allowing new stones to form in an area of relative stagnation, and by continued chronic inflammation. The causal relationship of cystic duct remnants to symptoms has been difficult to prove. There is now general agreement that a long cystic duct remnant is in and of itself innocuous. This has been supported by the now widespread use of the laparoscopic method of gallbladder removal in which the cystic duct is purposefully left long. Several large studies have shown that most patients with long cystic duct remnants are asymptomatic and that symptomatic patients generally have other possible explanations for their pain, such as residual common duct stones (33). A stone trapped in a cystic duct remnant may be a source of crystal or stone formation in patients with a propensity to develop gallstone pancreatitis or stenosing papillitis.

The best treatment for the retained cystic duct syndrome, of course, is prevention. The routine use of operative cholangiography for detecting long cystic ducts permits removal at the first operation. Removal of a cystic duct remnant by a second operation may be recommended if residual calculi are demonstrated by postoperative cholangiography. The reported results do not support removal of cystic duct remnants in the absence of demonstrable calculi if pain relief is the therapeutic objective (34).

Functional Disorders. The last general category of causes of postcholecystectomy pain includes functional disorders of biliary emptying. Two different mechanisms have been suggested to account for biliary pain and apparent biliary obstruction. In one group, the continued presence of chronic inflammation of the ampulla of Vater has been postulated to result in fibrosis and fixed stenosis of the ampulla. Sphincter of Oddi dyskinesia has been suggested in the absence of inflammation, with

spasm of the sphincter raising intraductal pressure and impeding emptying.

These two mechanisms are the basis for the “postcholecystectomy syndrome,” a nonspecific and poorly defined term. *Biliary dyskinesia* is a preferable appellation, but this term is best reserved for clinical situations in which typical biliary-type pain, biochemical evidence of cholestasis, and cholangiographic and manometric evidence of papillary dysfunction exist in the absence of one of the previously described causes of postoperative symptoms.

Diagnosis. Biliary dyskinesia is a diagnosis of exclusion. Patients who may be considered for an attempt at surgical relief for their biliary dyskinesia or stenosing papillitis require an extensive evaluation for other sources of their pain. A CT scan of the abdomen with fine cuts at the level of the pancreas is required. In addition, ERCP is an important part of the workup of these patients. Biliary manometry, when available, is confirmatory. Diagnostic manometry uses single-lumen or multilumen perfused catheters positioned across the sphincter of Oddi and recording pressures in the common bile duct, the sphincter, and the duodenum. In humans, common bile duct pressure is approximately 10 mm Hg above duodenal pressure (35,36). In turn, the sphincter of Oddi basal pressure is 5 to 10 mm Hg greater than the common bile duct pressure. Phasic high-pressure contractions occur periodically within the sphincter at a rate of four to six per minute. These contractions appear to be peristaltic, moving in antegrade fashion from the common bile duct to the duodenum. Intravenous infusion of cholecystokinin decreases the basal sphincter of Oddi pressure as well as the frequency and amplitude of phasic contractions (37). The effects of morphine are opposite to those of cholecystokinin; morphine increases resting sphincter pressure and increases the frequency of phasic contractions (38).

It has been suggested that a subset of patients with pain after cholecystectomy have identifiable manometric abnormalities and demonstrable obstruction to ductal emptying. In affected patients, manometrically measured basal sphincter of Oddi pressure is elevated to approximately twice control values (39) and is in excess of 40 cm H_2O. In addition, in those patients with suspected biliary dyskinesia, propagation of phasic pressure waves is frequently retrograde, in an antiperistaltic direction. Furthermore, provocative testing with cholecystokinin infusion suggests that some patients with this disorder respond to the hormone not with the expected ampullary relaxation, but with a paradoxic increase in sphincter pressure (40). The functional significance of manometric abnormalities is confirmed by observing delayed emptying either of endoscopically injected radiographic contrast medium or hepatically excreted radionuclide (41).

Only those patients with manometric abnormalities and documented delayed biliary emptying, in whom other pathophysiologic processes have been excluded, should be considered to have biliary dyskinesia (Table 67-2). It is not currently possible to distinguish between fixed fibrotic stenosis and spasm; elements of each can be present in any one patient.

Feature	Findings characteristic of biliary dyskinesia
Associated hepatobiliary disease	Absence of retained or recurrent biliary stones, biliary stricture, neoplasms; transient elevation of alkaline phosphatase and parenchymal liver enzyme levels with symptomatic episodes
Cholangiographic results	Mild to moderate dilatation of extrahepatic bile ducts; delayed emptying of cholangiographic contrast medium
Biliary manometry	Increased basal sphincter pressure; retrograde propagation of phasic pressure waves; paradoxic response to cholecystokinin
Response to therapy	Symptomatic improvement after sphincterotomy in 85% of patients

TABLE 67-2. Distinguishing features of biliary dyskinesia

Treatment. Endoscopically performed sphincterotomy or surgical transduodenal sphincteroplasty is currently the recommended treatment for patients with suspected biliary dyskinesia who meet the above criteria. Symptomatic improvement has been reported in up to 85% of patients treated in this fashion (41). Less invasive forms of therapy might be possible for mildly symptomatic individuals. Nitrates relax the sphincter of Oddi and can prove helpful if sphincteric spasm is present (42) but are of limited utility in the case of stenosis or stricture. Narcotics, particularly morphine, should not be used in these patients because of their known contractile effects on the sphincter of Oddi. Patients with severe, persistent pain may be considered for surgical chemical splanchnicectomy after several prognostic blocks have indicated that interruption of these nociceptive pathways provides complete pain relief (see Chapter 102 and Chapter 105). Intrathecal opioids can also be useful for such patients (see Chapter 103).

PANCREAS

Basic Considerations

The pancreas is subject to a number of disease processes, both inflammatory and neoplastic, in which pain is a major clinical feature. Patients with pancreatic disorders constitute a large proportion of those seen by physicians interested in pain control. The location of the pancreas in the retroperitoneum of the upper abdomen, its anatomic relationships to surrounding organs, and its complex physiologic functions present difficulties in the diagnosis and management of pancreatic pain syndromes. An understanding of pancreatic pathophysiology is essential to all physicians caring for such patients.

The pancreas is a roughly triangular organ that lies transversely in the upper retroperitoneum between the duodenum on the right and the spleen on the left. The pancreas is related anteriorly to the pylorus, stomach, gastrocolic omentum, and liver. Inferiorly, the pancreas is in contact with the transverse portion of the duodenum, the jejunum, and the transverse mesocolon. The transverse colon can also form a portion of the inferior border.

The pancreas receives both sympathetic and parasympathetic innervation. Sympathetic innervation is derived from the upper thoracic splanchnic nerve, which is composed of preganglionic fibers from the T-5 through T-10 spinal segments (see Fig. 67-2). Additional pancreatic sympathetic fibers travel in the lesser splanchnic nerve and are derived from the T-9 through T-11 segments. Before reaching the pancreas, fibers from the upper and middle thoracic splanchnic nerves traverse the celiac plexus and ganglion. The cell bodies of efferent nerves to the pancreas are in the celiac ganglion. Cell bodies of afferent pancreatic sympathetic nerves are located in dorsal root ganglia. Sympathetic afferent connections with the central nervous system are bilateral; some afferent fibers cross the midline on traversing the celiac ganglion.

Parasympathetic innervation of the pancreas is derived from the celiac division of the posterior vagal trunk. The cell bodies of afferent vagal fibers are located in the nucleus ambiguus of the medulla of the brain. Efferent vagal fibers are dendrites of neurons with cell bodies in the dorsal motor nucleus. Both efferent and afferent parasympathetic fibers pass through the celiac ganglion. Neither type of parasympathetic nerve fiber synapses within this ganglion.

Pancreatic visceral pain is usually sensed as a severe constant discomfort localized to the upper midabdomen. Although intensely unpleasant and often intractable, pancreatic pain is often difficult to describe. “Stabbing,” “burning,” and “boring” are commonly used adjectives. Radiation of pancreatic pain to the back in the area of the lower thoracic spine is common (Fig. 67-5). Because the pancreas does not contact the somatically innervated parietal peritoneum, somatic pain is not associated with pancreatic disorders unless peripancreatic inflammatory complications extend beyond the lesser sac.

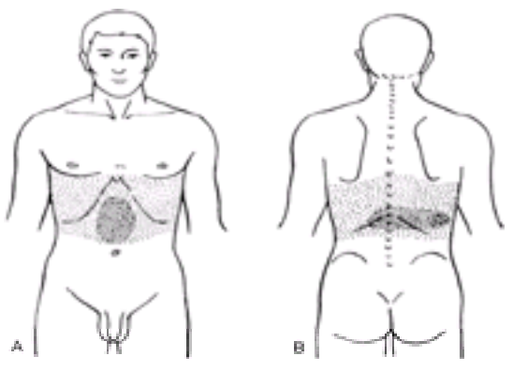

Figure 67-5. Areas of referred pancreatic pain in the anterior **(A)** and posterior **(B)** regions of the body. The heavy stipple indicates the pain reference, whereas the light stipple indicates the extensive cutaneous hyperalgesia often associated with the pain.

Vagal afferents do not appear to mediate pancreatic pain. Vagotomy alone is ineffective in the relief of pancreatic pain (43). Sympathetic afferents have been shown to transmit painful impulses from the pancreas. The use of sympathectomy in the treatment of pancreatic pain is discussed in Chapter 105.

Clinical Considerations

Acute Pancreatitis

Acute pancreatitis is one of the most common causes of acute abdominal pain requiring hospitalization. The disorder can vary in its clinical presentation, ranging from a transient mildly symptomatic illness in 90% of cases to a rapidly fatal abdominal catastrophe. Acute pancreatitis has proven difficult to diagnose reliably and to treat specifically. Palliation of the pain that accompanies acute pancreatic inflammation remains a major clinical challenge.

Etiology and Pathophysiology. Although the pathogenesis of acute pancreatitis in many cases is not definitely established, a number of factors are clearly associated with this disease (Table 67-3). In 80% to 90% of cases, the cause is related to excessive alcohol intake or biliary tract disease. Chronic alcohol abuse is the most common metabolic cause of acute pancreatitis in the United States, particularly in urban settings. Histologic evidence of antecedent pancreatitis has been reported in up to 45% of alcoholics in autopsy studies (44), but acute pancreatitis is recognized in less than 10% of such patients premortem. Individuals who develop acute alcoholic pancreatitis have abused alcohol for an average of 11 to 18 years before becoming symptomatic (45), with the mean ethanol consumption in these patients approximating 150 g per day. The triggering mechanism that initiates an episode of acute pancreatitis in the midst of chronic heavy alcohol intake is not known. The acute toxicity of ethanol for pancreatic acinar cells is believed to be the pathogenetic factor. Ethanol and its primary metabolite, acetaldehyde, have been shown to be toxic to pancreatic acinar cells. Cellular damage is postulated to occur by altering cellular membrane fluidity and composition (46), reducing mitochondrial protein synthesis (47) and enhancing abnormal amylase, trypsinogen, and chymotrypsinogen secretion (48). Several theories exist to explain alcohol- related acute pancreatitis. Currently, the most widely accepted theory suggests that pancreatic parenchyma is injured by pancreatic enzyme extravasation, which is facilitated by an increase in pancreatic ductal permeability and occurs in the presence of exocrine hypersecretion and partial ampullary obstruction (12).

Factor	Examples
Metabolic	Alcohol, hyperlipoproteinemia, hypercalcemia
Mechanical	Gallstones, posttraumatic, postoperative, after pancreatography
Vascular	Shock, cardiopulmonary bypass, polyarteritis nodosa
Drugs	Steroids, azathioprine, thiazide, estrogens, tetracycline, furosemide
Miscellaneous	Familial, viral infections, idiopathic

TABLE 67-3. Causative factors in acute pancreatitis

Acute pancreatitis has been reported in patients with both familial and acquired forms of hypertriglyceridemia. Individuals with Fredrickson type I hyperlipoproteinemia have a 30% risk of developing clinical pancreatitis. Pancreatitis occurs in 15% of those with type IV disease and in approximately 40% of those with type V hyperlipoproteinemia. A severe form of pancreatitis has been noted in association with the chylomicronemia syndrome (49).

Pancreatitis has been reported in association with hypercalcemia caused by hyperparathyroidism (50), multiple myeloma, and intravenous administration of calcium (51). Pancreatitis has been most clearly related to hyperparathyroidism that is long-standing and symptomatic. Acute pancreatic necrosis has been reported during hyperparathyroid crisis. The mechanism of hypercalcemia related to pancreatitis may involve calcium-induced trypsinogen activation with subsequent parenchymal autodestruction, calcium-associated stone formation in the pancreatic duct causing ductal obstruction, or calcium stimulated pancreatic exocrine hypersecretion.

Gallstones are recognized in more than 50% of nonalcoholic patients with acute pancreatitis. It is likely that passage of a gallstone through the ampulla of Vater is responsible for initiating pancreatitis in these patients. Gallstones can be retrieved from the stool of 85% to 95% of patients recovering from gallstone pancreatitis (52). In patients who underwent laparotomy within 48 hours of the onset of biliary pancreatitis, gallstones were reported to be present in the ampulla of Vater in 75% (53). In some patients, but not all, the anatomic structure of the ampulla of Vater can be a factor in the induction of gallstone pancreatitis by permitting transient obstruction of the pancreatic duct or obstruction of a common pancreatic-biliary channel. Cholangiographic studies have demonstrated a common channel between the common bile duct and the pancreatic duct in up to 90% of patients with a history of gallstone pancreatitis, compared with only a 20% to 30% incidence of a common channel in patients with calculous biliary disease and no history of pancreatitis. Mechanical disruption of primary or secondary pancreatic ducts by trauma, operative complications, or forceful ductal injection during pancreatography can also result in pancreatitis.

Numerous drugs have been reported to cause acute pancreatitis. The most compelling evidence supports estrogens and azathioprine (Imuran) in the direct causation of pancreatitis. Less common causes of pancreatic inflammatory disease include trauma, vasculitis, viral infections (Coxsackie and mumps viruses), pancreas divisum, ischemic pancreatitis, neoplasm, and familial pancreatitis.

Although a number of associations with acute pancreatitis have been clearly identified as causative factors, the mechanism of injury is not known in most cases. The pancreas responds to a spectrum of injuries in a stereotyped fashion. The essential pathogenetic feature of this response is the extravasation of activated pancreatic enzymes into pancreatic and peripancreatic tissues. Tissue necrosis, edema, and local and systemic inflammatory reactions result from this extravasation.

Symptoms and Signs. Abdominal pain is the hallmark symptom in patients with pancreatic inflammation. The abdominal pain begins acutely and usually increases gradually over several hours before reaching maximum intensity. The pain is most severe in the upper abdomen with penetration through to the back, often radiating to the chest and flanks. The pain of acute pancreatitis usually persists without relenting for hours to days. It is often aggravated by recumbency. If abdominal pain fluctuates markedly in intensity or ceases for periods of time, acute pancreatitis should be suspected. The rapid onset of symptoms and the severity of pain associated with acute pancreatitis can mimic those of other acute inflammatory processes such as gangrenous cholecystitis, perforated peptic ulcer, and intestinal ischemia. Nausea and vomiting are nearly constant accompanying symptoms in acute pancreatitis. Vomiting does not relieve the pain and is not progressive. Fever, tachycardia, and evidence of dehydration are present in most patients.

Acute pancreatitis usually results in intense nociceptive input that not only produces severe pain but also reflex responses that are usually inherent in serious tissue damage (see Chapter 9). Many patients develop severe reflex skeletal muscle spasm of the abdominal and lower chest walls, with a consequent marked decrease in chest wall compliance. Moreover, visceral reflexes also produce a decrease or inhibition of gastrointestinal tone with varying degrees of ileus, and also reflex bronchiolar constriction. The pain and reflex responses markedly impair ventilation, which frequently becomes rapid and shallow and produces hypercapnia and hypoxemia caused by increased physiologic shunting. As a result, the arterial oxygen tension falls steadily. In one series, 40% of patients with acute pancreatitis developed an arterial oxygen tension of less than 60 mm Hg while breathing room air some time during the first week of the ileus (54). Unless aggressively treated, this may contribute to a complex systemic response that may result finally in circulatory failure, respiratory failure, and death.

Diagnosis. Acute pancreatitis is a clinical diagnosis, suspected in susceptible individuals with acute abdominal pain and confirmed by appropriate laboratory and radiologic investigations. The diagnosis can be subtle. Pancreatic symptoms can be deceptive. In one report from a teaching institution, experienced clinicians correctly diagnosed severe pancreatitis in only 35% of patients at the time of admission (55). After 24 hours of hospitalization, 73% of patients had the disease correctly identified as pancreatitis. Even after 48 hours of hospitalization, however, only 83% of patients with severe acute pancreatitis had been diagnosed correctly.

Diagnostic confusion might be a result of the frequently nonspecific nature of pancreatic symptoms and of difficulties in physical examination. In addition, commonly used laboratory examinations, although sensitive, are relatively nonspecific. A serum amylase determination is the most useful indicator of pancreatic inflammation, with elevated serum amylase levels present in approximately 90% of cases of acute pancreatitis; however, increased amylase levels are fairly nonspecific, with both false-positives and false-negatives occurring. Unfortunately, hyperamylasemia often persists for only 24 to 48 hours after the initiation of pancreatitis, and the degree of hyperamylasemia does not correlate with the severity of pancreatic damage. Only 65% of patients with elevated serum amylase levels have pancreatitis. Normal serum amylase values are found in 10% to 15% of patients with acute pancreatitis. Urinary amylase measurements do not improve diagnostic capabilities, and the calculation of the urinary amylase to creatinine clearance ratio is generally not helpful.

Radiographic studies are often useful for evaluating the pancreas and supporting the clinical diagnosis of pancreatitis. In the setting of acute pancreatitis, CT scanning and ultrasonography have largely replaced other radiologic procedures in evaluation of the pancreas. These methods can provide useful anatomic information about the pancreatic gland, biliary system, and surrounding organs.

Newer CT scanners, with improved resolution and faster scanning times, have become the preferred study in most patients. The accuracy of CT scanning is improved with administration of both oral and intravenous contrast. CT scanning has been reported to demonstrate pancreatic abnormalities in 90% of patients with acute pancreatitis (56). The most common finding on CT examination is diffuse enlargement of the gland. The most frequent complication of acute pancreatitis detected by CT scanning is an extrapancreatic fluid collection. Pancreatic pseudocysts and pancreatic abscesses that occur frequently as sequelae of acute pancreatitis are readily identified by CT scanning.

Ultrasonography is only slightly less effective than CT scanning for demonstrating pancreatic edema, phlegmons, and pseudocysts. Because of the absence of ionizing radiation, ultrasound is a superior procedure to use for pregnant women. Ultrasound is also well suited to young children who might not be cooperative. Although CT scanning is superior to ultrasound in providing anatomic information about the pancreas, ultrasound is more sensitive for detecting biliary calculi as a cause for pancreatitis. Both MRI and spectroscopy are newer modalities that may hold promise as valuable tools for the evaluation of pancreatitis in the future. In addition, ERCP may be useful in the evaluation of the occasional patient with recurrent attacks of pancreatitis without an obvious etiology. ERCP may identify correctable etiologies in up to 50% of patients, such as pancreas divisum, stenosis of the ampulla of Vater, and focal pancreatic duct abnormalities.

Treatment. The clinical management of patients with acute pancreatitis combines measures to control the pancreatic inflammatory process with efforts to minimize pain and discomfort. The therapy of pancreatitis can be considered to have three phases: efforts to resuscitate and support the patient during the initial illness; attempts to limit pancreatic inflammation and abort development of complications; and measures to treat the complications that do occur. Physicians treating patients with acute pancreatitis must be aware that the process evolves, often unpredictably, often over a long period of time; therapeutic objectives must thus be reevaluated periodically. Relief of painful symptoms is a prime aspect of therapy throughout the course of the illness.

Patients with severe acute pancreatitis are at greatest risk of dying during the initial few days of the illness. Shock, respiratory failure, and hemorrhage are the main causes of mortality during this phase of the disease (57). Vigorous patient support has proven effective in preventing death during the early phase of acute pancreatitis. Maintenance of tissue perfusion by the appropriate restoration of intravascular volume is crucial. Respiratory support, prophylaxis against gastric stress ulceration, and appropriate transfusion have been shown to be effective measures in these patients. Intravenous nutritional supplementation is also essential and should be instituted early.

Numerous therapeutic measures and agents have been investigated in attempts to limit pancreatic inflammation and to prevent complications. Most proposed therapies have been empiric and based on an incomplete understanding of the pathophysiology of pancreatitis. Not surprisingly, most of the proposed therapies have not been found to be efficacious when subjected to controlled trials. The following are proposed measures for limiting pancreatic inflammation and preventing complications: (a) nasogastric suction, (b) hypothermia, (c) pancreatic irradiation, (d) steroids, (e) enzyme inhibitors (e.g., Trasylol), (f) early biliary operations, and (g) drugs (e.g., anticholinergics, cimetidine, antibiotics, octreotide, glucagon, calcitonin). Nasogastric suctioning prevents the accumulation of fluid and air in the gastrointestinal tract and treats the ileus that occurs with pancreatitis, but nasogastric suctioning has not been shown to result in a more rapid symptomatic or biochemical resolution of the pancreatic inflammatory process (58). Pancreatic inflammation is not positively influenced by steroid administration, trypsin inhibitors (59), or various other drugs, from anticholinergics to cimetidine (60). The administration of antibiotics prophylactically has been shown by a number of authors to decrease infection rates (61). Decrease in mortality has not been clearly demonstrated with the use of prophylactic antibiotics. Because food normally increases pancreatic secretion, fasting has been used to minimize pancreatic stimulation. Withholding food is logical and is usually effective in promoting pancreatic quiescence.

Because the passage of common bile duct stones is so frequently associated with the initiation of pancreatitis, it has been postulated that the length of the period of ampullary obstruction and the completeness of obstruction determine the severity of the resultant pancreatitis. Early biliary operation with disimpaction of the offending stone has been proposed as a means of limiting pancreatic inflammation. In a controlled trial of early operation reported by Stone and colleagues, no amelioration of pancreatic inflammation was noted (62). Because of the lack of positive effect on the pancreatic inflammatory process and because of the increased risk of infecting a sterile pancreatic phlegmon by operative manipulations, laparotomy during the early phase of acute pancreatitis is discouraged. An important exception to this recommendation exists for patients in whom serious coexistent pathology cannot be excluded. Positive evidence of acute pancreatitis does not exclude the presence of concomitant duodenal perforation, mesenteric infarction, or gangrenous cholecystitis. For similar reasons, including risk of exacerbation of acute pancreatitis, hemorrhage, perforation, and papillary stenosis, ERCP is generally to be avoided in the early stages of acute pancreatitis. An exception here is the use of ERCP for urgent decompression in the septic patient with an obstructed common bile duct.

Management of the pain associated with acute pancreatitis is an important aspect of patient care. Because of the severity of pancreatic symptoms, narcotic analgesia is the usual method of providing relief. Before narcotics are used, however, certainty of diagnosis is important. Relief of abdominal pain could remove an important diagnostic clue of some other nonpancreatic disease that might be mimicked by pancreatitis.

Morphine should be avoided in patients with pancreatitis because of its contractile actions on the sphincter of Oddi. Meperidine (Demerol) also produces spasm of the biliary tract, but its spasmogenic effect is less than that caused by morphine and thus is the preferred parenteral systemic analgesic for pancreatic pain. Epidural opioids produce better pain relief with less spasmogenic effects. Segmental epidural (T-5 to T-10) analgesia with a dilute solution of local anesthetic relieves pain, markedly improves ventilation, and decreases or eliminates the reflex muscle spasm and neuroendocrine response. Of course, hypovolemia should be treated before this procedure is initiated to minimize the hypotension caused by vasomotor blockade (see Chapter 9 and Chapter 102).

Chronic Pancreatitis

Chronic pancreatitis is an inflammatory disorder of the pancreas that includes recurrent or persistent abdominal pain and evidence of exocrine and endocrine pancreatic insufficiency. It is a distinct clinical entity frequently encountered by those caring for patients with chronic pain. Chronic pancreatitis differs markedly from acute pancreatitis in pathogenesis, sequelae, and response to treatment. Numerous experimental studies in animals and clinical observations in humans suggest that, for most patients, chronic pancreatitis does not evolve from recurrent episodes of acute pancreatitis with progressive, additive inflammatory changes. Most investigators agree that the mechanisms of injury for the two disease processes are fundamentally different. Support for this view has been provided by Sarles et al.

(63), who noted that the average age of onset for chronic pancreatitis is 38 years, whereas the average age of onset for acute pancreatitis is 51 years.

Etiology and Pathophysiology. Although numerous causative factors have been associated with chronic pancreatitis, pathogenic mechanisms are largely unknown. Therapy continues to be empiric and limited to management of symptoms, side effects, and complications of the disease. For most patients, chronic abdominal pain is the most prominent symptom and the most difficult complication of chronic pancreatitis to treat.

In the United States, the cause of chronic pancreatitis in 70% to 80% of patients is alcoholism. For most of the remaining patients the cause is not known, and the disease is labeled “idiopathic” chronic pancreatitis. Malnutrition is one of the major causes worldwide. Biliary calculi, so common as a cause of acute pancreatitis, are rarely a factor in the development of chronic pancreatitis. Other known causes include benign or malignant duct obstruction, cystic fibrosis, hereditary pancreatitis, hyperparathyroidism, hyperlipidemia, trauma, and pancreas divisum.

The histologic changes that characterize chronic pancreatitis usually develop in the setting of prolonged periods of excessive alcohol intake. Chronic alcohol ingestion, by mechanisms that are incompletely understood, causes sustained secretion of protein by pancreatic acinar cells. Increased secretion of protein, without a proportionate increase in secretion of pancreatic water and bicarbonate, has been postulated to cause precipitation of protein within the pancreatic ducts. Obstruction of primary and secondary pancreatic ducts by the precipitate can cause the damage to pancreatic acini, with the accompanying inflammation and fibrosis that typify chronic pancreatitis. Persistent ductal obstruction and lobular destruction result in the progressive loss of pancreatic exocrine tissue that characterizes chronic pancreatitis histologically. Although the islets of Langerhans are not initially involved in the inflammatory process, gradual loss of endocrine tissue occurs as well.

Symptoms and Signs. Pain is the central feature of chronic pancreatitis. Virtually 100% of patients suffer from chronic abdominal pain. Approximately 50% of patients with chronic pancreatitis experience a constant, gnawing epigastric pain. The pain can vary in intensity but never subsides completely. The discomfort frequently radiates to the back. Pain is frequently worsened by eating, and weight loss is a prominent accompaniment. Narcotic tolerance is frequent. Steady employment is rarely achieved. In a second group of patients, severe attacks of epigastric pain are episodic, with the affected individual pain free between attacks. Painful episodes might or might not be associated with signs of acute pancreatitis superimposed on chronic pancreatitis. The pain from episodic attacks can last for days to weeks. Constant pain is most frequently associated with alcoholic chronic pancreatitis, whereas intermittent pain is more common with nonalcoholic pancreatitis.

In addition to various pain syndromes, most patients with chronic pancreatitis have evidence of endocrine insufficiency. Of patients with chronic pancreatitis, 15% are insulin-dependent; most non–insulin-dependent patients have abnormally low basal insulin levels and abnormal glucose tolerance tests (64). Even when insulin dependence does occur, the patients have some circulating endogenous insulin and are not prone to diabetic ketosis. Nonetheless, the chronic complications of diabetes mellitus are significant causes of death in patients with chronic pancreatitis.

Exocrine insufficiency is detectable in approximately 50% of patients when they seek medical attention and occurs with increasing frequency over time. The repetitive cycles of tissue destruction result in a significant reduction in the ability of the pancreas to secrete amylase, lipase, and proteolytic enzymes. Steatorrhea and malabsorption result and contribute to chronic weight loss.

The natural history of chronic pancreatitis is not known with certainty. Most reported series have been retrospective and confounded by including patients undergoing pancreatic operations or patients with significant accompanying illnesses. A prospective report suggested that only 20% of patients with chronic pancreatitis die from causes directly related to pancreatitis or its complications (65). Malignancies, cardiovascular diseases, and severe infections were common nonpancreatic causes of death.

Diagnosis. Chronic pancreatitis should be suspected in all individuals with intractable abdominal pain. Chronic pancreatitis is a clinical diagnosis, based on appropriate signs and symptoms in susceptible individuals. Determination of serum enzyme values is usually of little value; serum amylase and serum lipase levels are infrequently elevated in patients with chronic abdominal pain and are nonspecific in their interpretation. Findings of endocrine or exocrine insufficiency strengthen the clinical impression.

When attempting to confirm the clinical suspicion of chronic pancreatitis, plain abdominal radiographs should be obtained because demonstration of pancreatic calcifications virtually assures the diagnosis. CT scanning, ultrasound, and endoscopic pancreatography have improved the diagnostic evaluation of chronic pancreatitis in recent years and help differentiate between chronic pancreatitis and malignancy. ERCP is most accurate, but it is invasive and is frequently reserved for patients in whom the diagnosis is unclear or in whom intervention is planned. Approximately 50% of patients with chronic pancreatitis have ductal abnormalities that can be demonstrated by these techniques. In these patients, pseudocysts or strictures, obstructions or stones in the pancreatic duct, or alternating areas of dilatation and narrowing are demonstrated. In the other half, normal biliary and pancreatic ducts are demonstrated. Ductal abnormalities constitute strong positive evidence for chronic pancreatitis.

Treatment. The treatment of chronic pancreatitis consists of three aspects: abstinence from alcohol, support for endocrine and exocrine insufficiency, and palliation of painful symptoms. Management of endocrine insufficiency usually requires administration of insulin, whereas support for exocrine insufficiency can be accomplished by oral administration of pancreatic enzyme preparations. When patient compliance is good, management of endocrine and exocrine disturbances is readily achieved; it is not discussed further here.

Medical Therapy. The mainstays of nonoperative management of pain associated with chronic pancreatitis include absolute abstinence from alcohol; dietary manipulations, including small-volume low-fat meals along with use of oral pancreatic enzymes to decrease pancreatic secretion thereby decreasing pain; and provision of analgesia. For most patients with chronic pancreatitis in whom pain is severe, medical therapy is not successful and surgical intervention becomes necessary. Simple nonoperative measures, such as manipulations of diet, have not been shown to ameliorate pancreatic pain in a controlled clinical trial. Pharmacologic attempts to suppress pancreatic secretion have also been largely unsuccessful. Anticholinergic drugs have been demonstrated experimentally to decrease pancreatic secretion, but administration of atropinelike drugs to patients has not reduced pancreatic pain. Cimetidine, a potent inhibitor of gastric acid secretin, has been used to decrease stimulation of the pancreas by secretin released by intraduodenal acid. Cimetidine, however, does not relieve pancreatic symptoms. Octreotide has recently been used for treatment of pain in chronic pancreatitis with limited success. In most instances, the medical management of chronic pancreatic pain relies on the use of narcotic analgesics. The long-term commitment to such analgesics required by patients with chronic pancreatitis often leads to physical dependence. Data reported by Ammann and coworkers (66) suggest that medically treated patients experience abdominal pain for a mean of greater than 5 years before pancreatic dysfunction becomes so severe that pain is relieved. The nihilistic approach of waiting until the disease “burns out” should not be encouraged.

Various procedures to ablate afferent nerves from the pancreas have been used in attempts to palliate pancreatic pain. Dramatic temporary relief of pain from acute pancreatitis can be obtained by injecting solutions of lidocaine or bupivacaine into the splanchnic nerves or the left celiac ganglion (67). Positive results in patients with acute pancreatitis have encouraged many investigators to extend these techniques to patients with chronic pancreatitis. Neural ablation may be achieved by several operative or nonoperative methods. One nonoperative approach involves the use of celiac plexus block with alcohol after prognostic blocks have produced effective pain relief (see Chapter 104). In patients who are undergoing operative pancreatic procedures, alcohol can be injected into the celiac ganglia directly at the time of laparotomy. Destruction of the celiac ganglia has also been accomplished by resection. The ganglia can be removed by a posterior incision through the twelfth rib below the diaphragm.

A prospective controlled study of splanchnicectomy for relief of chronic pancreatic pain has not been performed. Retrospective clinical series by proponents of the procedure claimed that permanent pain control is achieved in greater than 90% of patients (68). These initial encouraging results, however, have not been reproduced by most other surgical investigators. A definitive statement of the usefulness of neural ablative procedures in treatment of chronic pancreatitis probably cannot be made. Finally, spinal opioids may have use in chronic pancreatic pain (see Chapter 103).

Surgical Therapy. The use of endoscopic retrograde cannulation of the pancreas, ultrasonography, and CT scanning has improved the ability to assess the structural changes associated with chronic pancreatitis and its complications. Two major patterns have been recognized. Some patients, both alcoholic and nonalcoholic, have enlarged major pancreatic ducts alternating with segmental areas of narrowing. The ectatic ducts are often associated with intraductal stones and calcification. This form of structural abnormality has been termed *large duct* or *obstructive* disease. Many physicians have interpreted these changes as resulting from pancreatic ductal hypertension caused by blockage of the flow of pancreatic secretions. An alternative explanation is that the structural changes are a result of atrophy of pancreatic parenchyma and periductal scarring.

A second form of pancreatitis has been termed *small duct disease*. In these patients, pancreatography demonstrates chronic calcifying pancreatitis, in which major

pancreatic ducts are not enlarged. Proteinaceous plugs can be seen in terminal ductules and acini. Atrophy and dilatation of the fine arborizations of the pancreatic ductal system can be present.

The surgical treatment of chronic pancreatitis is based on two assumptions about the functional significance of these structural abnormalities. The first assumption is that pancreatic ductal obstruction is the cause of pain in large duct disease and that decompression of the pancreatic duct by operative manipulations relieves pain. The second assumption is that ductal hypertension is absent in small duct disease. Periductal or perineural inflammation is assumed to cause the chronic abdominal pain in patients with nondilated ducts. For these patients, pancreatic resection has been proposed to remove the source of chronic inflammatory stimuli. The type of operation selected depends, then, largely on pancreatic anatomy. Workup for surgery should include both CT scan and ERCP.

Operative therapy in chronic pancreatitis is effective in reducing pain but should not be undertaken for the purpose of improving endocrine or exocrine function. Glucose intolerance and fat malabsorption are not improved by operations for chronic pancreatitis (69).

Longitudinal pancreaticojejunostomy has become the standard surgical approach for patients in whom pancreatography demonstrates dilated pancreatic ducts or alternating areas of dilatation and stricture. As currently performed, the procedure decompresses the entire pancreatic duct by creating a side-to-side anastomosis between the opened pancreatic duct and a Roux-en-Y limb of jejunum (Fig. 67-6). The pancreatic duct should be at least 7 to 8 mm in diameter or larger for this procedure to be appropriate. A pancreatic duct greater than 1 cm in diameter, the presence of pancreatic calcifications, and an anastomosis between the pancreas and jejunum longer than 6 cm have been found to be determinants of success for the side-to-side pancreaticojejunostomy. The gland is left *in situ*. The main pancreatic duct is filleted along its entire length, nearly to the ampulla of Vater. Splenectomy is unnecessary.

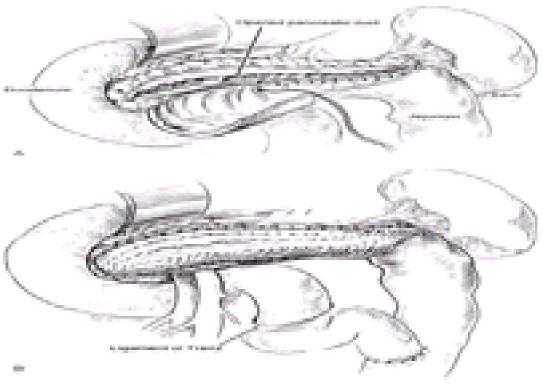

Figure 67-6. Operative performance of pancreaticojejunostomy. **A:** The anterior surface of the pancreas has been exposed by reflecting the stomach cephalad and the transverse colon caudad. The main pancreatic duct has been opened longitudinally, exposing a grossly dilated pancreatic ductal collecting system. A Roux-en-Y limb of jejunum has been constructed. The jejunal limb has been opened longitudinally for a distance equal to that of the longitudinal opening in the pancreatic duct. A side-to-side pancreaticojejunostomy is then performed by suturing the jejunal limb to the thickened fibrotic capsule of the pancreas. **B:** Completion of pancreaticojejunostomy, showing configuration of the Roux-en-Y jejunal limb. A double-layer pancreaticojejunostomy has been constructed. Pancreatic exocrine secretion can drain through the anastomosis through the Roux-en- Y limb of the jejunum.

Preservation of remaining pancreatic function is good because no pancreas is resected. However, even though neither islet cell nor acinar tissue is destroyed in performing pancreaticojejunostomy, the incidence of diabetes and clinically symptomatic exocrine insufficiency is increased in the years after the operation (Table 67-4). This observation suggests that the chronic destruction of pancreatic tissue associated with chronic pancreatitis is not halted by decompression of the duct.

Procedure	Operative mortality rate (%)	Late deaths (%)	Postoperative diabetes (%)	Postoperative steatorrhea (%)	Pain relief (%)
Pancreatic ductal drainage					
Pancreaticojejunostomy	4	[illegible]	[illegible]	[illegible]	[illegible]
Pancreatic resection					
Distal pancreatectomy	4	[illegible]	[illegible]	[illegible]	[illegible]
Pancreaticoduodenectomy	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

TABLE 67-4. Operative therapy for chronic pancreatitis

Many large series have reported the effectiveness of pancreaticojejunostomy in the treatment of pain. Complete relief or significant improvement can be expected in more than 80% of patients. Abstinence from alcohol improves the chance for pain-free survival. Unfortunately, there is an overall recurrence rate of 25% to 50% of patients within 5 years.

When pancreatography demonstrates normal pancreatic ducts or ducts of inadequate caliber for the performance of pancreaticojejunostomy, pancreatic resection has been performed for the treatment of pain of chronic pancreatitis. If the chronic inflammatory process is confined to the tail of the gland, distal pancreatectomy can be performed. Ideally, the extent of resection is determined by the limits of pancreatic disease. Removal of up to 95% of the gland has been reported (70). If the chronic inflammatory process is limited to the head of the pancreas, with relatively normal tissue distally, pancreaticoduodenectomy has been performed. The incidence of postoperative diabetes varies widely, from 30% to 80%, and is highly dependent on the extent of resection. Radical resection of 80% to 95% of pancreatic tissue guarantees the development of diabetes. Symptomatic fat malabsorption occurs in all patients after pancreaticoduodenectomy (71).

Reports of the success of pancreatic resection for relieving pain have varied (see Table 67-4). Pain relief is attained in up to 75% to 80% of patients undergoing 95% distal pancreatectomy, but the combination of the required splenectomy and a high incidence of insulin- dependent diabetes has resulted in infrequent performance of this procedure. Some 60% to 80% of patients treated with standard or pylorus-preserving pancreaticoduodenectomy are reported to have pain relief at 5 to 6 years (72).

The results of operative series must be viewed from the perspective of long-term studies, which suggest that chronic pancreatitis is associated with progressive pancreatic dysfunction and eventual relief of pain in most patients, even without operation. Ammann and coworkers (66) observed that deterioration in pancreatic exocrine function was closely related in timing to the relief of chronic pain. In 85% of alcoholic patients with chronic pancreatitis, spontaneous and long-lasting relief of pain was reported in surviving patients after 5 years. Cessation of pain was noted at the point at which pancreatic function began to decline markedly. These data imply that pain in chronic pancreatitis is related to secretory capacity, and with reduction in secretory capacity below some critical level, the mechanism that initiates the pain disappears. If this supposition is correct, pancreatic resection can be effective because it decreases exocrine function, and pancreaticojejunostomy can be useful because patients with dilated ducts have already lost a critical amount of secretory capacity. Operative therapy thus does not alter the natural history of chronic pancreatitis; rather, it may accelerate the symptomatic evolution of the disease.

Pancreatic Cancer (XXI7)

Pancreatic cancer is a highly lethal disease that currently ranks as the fifth most common cause of cancer-related deaths in the United States, exceeded only by lung, colorectal, breast, and prostate cancers. In the United States, there are approximately 28,000 new cases of cancer of the pancreas diagnosed each year. Since 1960,

the relative 5-year survival rate for all cases of pancreatic cancer has risen from 1% to 3%. Untreated, some 90% of patients die within the first year. Blacks, males, smokers, the aged, and those with diabetes mellitus appear to be at most risk. A history of chronic pancreatitis and ingestion of a diet high in fat may also be of importance. Finally, six specific disease entities carry an increased risk of pancreatic cancer: hereditary nonpolyposis colorectal cancer, familial breast cancer, the Peutz-Jeghers syndrome, ataxia-telangiectasia syndrome, familial atypical multiple mole-melanoma syndrome, and hereditary pancreatitis (73).

Symptoms and Signs. Pain is the hallmark symptom in patients with cancer of the pancreas (see Chapter 35). For nearly all patients with carcinoma of the pancreas, pain becomes a management problem at some time during their illness and is present in 70% of patients initially. Pain associated with cancer of the pancreas usually begins as a dull, nagging discomfort in the epigastrium but becomes rapidly and progressively more severe. The pain is gnawing, relentless, and visceral in character. Radiation to the back is noted in 25% of patients. Pain can be the only symptom associated with tumors of the body or tail of the gland; tumors in these locations can grow to a large size before causing secondary complications that prompt the correct diagnosis. Constant pain usually implies local invasion of surrounding structures and infiltration of the splanchnic nerves.

Anorexia and weight loss, seen in 75% of patients, are frequent but nonspecific accompanying symptoms. Nausea, vomiting, and weakness are each noted in approximately 50% of patients. A palpable abdominal mass is present in 20%. The most common physical finding is jaundice. Jaundice is present initially in 13% of patients with pancreatic cancer, although jaundice develops in 75% of these patients at some time during their illness. The presence of jaundice implies obstruction of the extrahepatic biliary system by direct neoplastic growth. Contrary to a widely held belief, the jaundice is usually not painless. In addition, a gallbladder is palpable in less than 30% of patients. At the initial examination, an enlargement of the liver is present in 33% of patients and ascites is noted in 20%.

The “hidden” retroperitoneal location of the pancreas largely accounts for the lack of specific symptoms, difficulty in physical examination, and problems in diagnosis. Most patients with cancer of the pancreas have locally or systemically disseminated disease at diagnosis. In addition, the anatomic relationship of the pancreas to other structures causes technical difficulties in the extirpation of pancreatic lesions.

Diagnosis. If pancreatic cancer is suspected, the diagnosis can be confirmed by a combination of techniques. CT scanning, endoscopic pancreatography and cholangiography, percutaneous biopsy, and operative exploration have important roles in the management of these patients. Selective celiac and mesenteric angiography along with portal venous evaluation are often used for staging and assessment of resectability. MRI cholangiogram is a newer technique that can be used for assessment of pancreatic and ductal anatomy.

The prognosis of cancer of the exocrine pancreas remains relatively poor and is largely dependent on the anatomic location. If the tumor has spread beyond the confines of the pancreas, surgical resection for cure is essentially not possible, and almost every patient with unresectable cancer of the pancreas dies of the disease. The majority of patients presenting with periampullary cancer are treated surgically. Currently, for all patients explored with a curative intent for a preoperative diagnosis of periampullary cancer, resectability rates of 35% to 40% are reported (12). The overall 5-year survival rate for all patients with resected periampullary cancer is 15% to 25%, depending on the exact site of origin of the tumor. Adenocarcinoma of the body and tail of the pancreas comprise some 30% of pancreatic cancers. The resectability rate of these cancers is less than 7% and the prognosis is dismal, with a mean survival of 5 to 6 months. Five-year survivors are rare.

Treatment. Currently, the only potentially curative therapy for cancer of the pancreas is surgical resection (74,75). Radiation therapy and chemotherapeutic approaches offer palliation to unresectable patients, but long-term survival is only modestly improved. Because of these considerations, symptomatic palliation is the primary goal for many patients with cancer of the pancreas.

Symptomatic palliation should be concerned with three general aspects of care: relief of anatomic complications, attention to nutritional depletion, and treatment of pain. Biliary obstruction and abnormal gastric emptying result from encroachment on the common bile duct and duodenum by tumor growth. Operative decompression of the biliary system is effective in relieving the intense pruritus associated with biliary obstruction. Gastric outlet obstruction usually requires the formation of some type of gastroenteric bypass. The malnutrition that so commonly accompanies pancreatic malignancy should be managed, when feasible, with oral or enteral feeding regimens. Pancreatic exocrine insufficiency, usually subclinical, may occasionally require oral pancreatic enzyme supplementation.

Most patients with carcinoma of the pancreas can be maintained on oral opioids and other analgesics as outpatients for most of the duration of their illness. Oral medications permit continued personal independence, with few intellectual or motor disturbances. For those patients in whom pain is not adequately controlled by oral or parenteral medication, celiac plexus block with alcohol or surgical splanchnicectomy is highly effective and should be considered if personnel skilled in these procedures are available. Newer approaches, including ambulatory epidural opioid analgesia, are discussed in Chapter 102 and Chapter 103.

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CHAPTER 68

Painful Diseases of the Kidney and Ureter

Sandip P. Vasavada, Craig V. Comiter, and Shlomo Raz

Some of the most severe pain one can experience is the pain of acute urinary obstruction. There exist a wide variety of causes for upper urinary tract pain, from infection and obstruction to neoplasm and chronic renal diseases. In this chapter we emphasize those diseases of the kidney and ureter in which pain is the presenting symptom or potentially a major problem in the management of the patient. One must have a solid understanding of the anatomy of the kidney and ureter as well as a detailed knowledge of its innervation before approaching therapeutic decision making. The following discussion encompasses both basic anatomy of the nervous supply to the kidney and ureter as well as a presentation of various clinical upper urinary tract diseases that may present with pain.

BASIC CONSIDERATIONS

Anatomic Aspects

Figure 68-1 and Figure 68-2 depict the gross anatomy and nerve supply of the kidneys and ureters and indicate their relationship to other structures that are important in considering the pathophysiology of renal and ureteral pain. Both structures receive sympathetic, parasympathetic, and sensory (afferent) fibers (1,2,3,4,5 and 6).

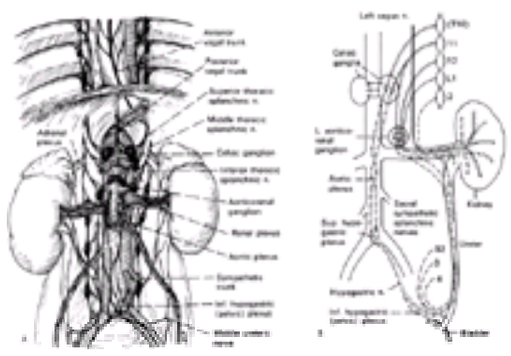

Figure 68-1. **A:** The gross anatomy and innervation of the kidneys. **B:** The autonomic and sensory nerve pathways supplying the kidney and ureters.

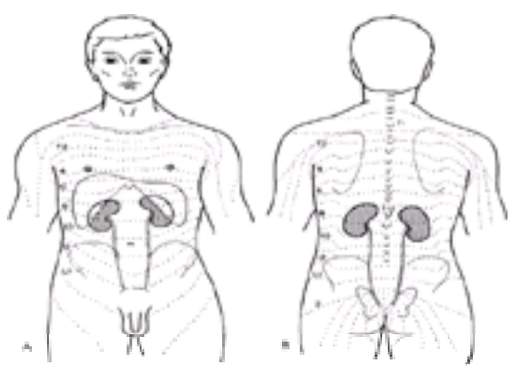

Figure 68-2. The relationship of the kidneys to the liver and the dermatomes (indicated by dotted lines and numbered for identification). **A:** Anterior view showing that the skin overlying the kidneys is supplied by dermatomes T-6 to T-9, with the left kidney higher than the right kidney. **B:** Posterior view showing that the dermatomes in the back overlying the kidneys are one segment lower than in the front because of the migration of the posterior division of the spinal nerves (see Chapter 8 for details).

Innervation of the Kidneys

Sympathetic Nervous System. The sympathetic fibers are derived mainly from the celiac and aorticorenal ganglia and also directly from the upper portion of the lumbar sympathetic trunk. These two collections of ganglia receive preganglionic fibers, which convey afferent (sympathetic) impulses to the kidneys from the T-8 to L-1 spinal cord segments via the corresponding white rami communicantes and paravertebral ganglia. They may also reach the kidney through the middle (lesser) and inferior (least) thoracic splanchnic nerves and the first (and perhaps the second) lumbar splanchnic nerves. The middle (lesser) thoracic splanchnic nerve derives from roots given off by the tenth and eleventh paravertebral ganglia and ends in the ipsilateral celiac or aorticorenal ganglion or both. The inferior (least) thoracic splanchnic nerve derives from the twelfth thoracic paravertebral ganglion and usually ends in the aorticorenal ganglion near the renal plexus. Within these ganglia, preganglionic neurons synapse with postganglionic neurons, which pass directly to form the renal plexus. Not infrequently, the least splanchnic nerve and the first (and perhaps the second) lumbar splanchnic nerve pass directly to the renal plexus to synapse in the posterior renal ganglion or in other smaller renal ganglia incorporated at nodal points in the renal plexus. The renal plexus occasionally also receives small communicating rami from the suprarenal plexus. Sympathetic fibers provide predominantly vasoconstrictor activity to the vessels of the kidney.

Parasympathetic Nervous System. The parasympathetic nerve supply comes from the vagus nerves, consisting of preganglionic neurons. Most of these fibers traverse the celiac plexus, but some fibers, particularly on the right side, pass directly to the renal plexus. Thus, together with the sympathetic innervation, the renal autonomic plexus is formed. Within the plexus the fibers proceed into the substance of the kidney in which parasympathetic fibers produce vasodilation. Interestingly, after renal transplantation, renal function is apparently unaffected despite separation of the kidney from its original autonomic nerve supply (7).

Afferent (Sensory) Fibers. The afferent (sensory) fibers are composed of spinal nerves whose cell bodies are located in dorsal spinal nerve root ganglia and whose central processes pass through the dorsal nerve roots of the tenth, eleventh, and twelfth thoracic spinal nerves to synapse with dorsal horn neurons. The distal branches of these fibers accompany sympathetic nerves and thus pass through the white rami communicantes, the paravertebral sympathetic ganglia (without

synapsing) and thence to the splanchnic nerves to reach the renal plexus.

Renal Plexus and Branches. The renal plexus consists of a fine network of sympathetic, parasympathetic, and sensory fibers surrounding the renal vessels, especially the renal artery. These fibers reach the pelvis and (except for the parasympathetic fibers) the calyces and substance of the kidney by following the branches of the renal artery, some of them traveling within the muscularis of the vessel.

Intrinsic Nerves. The nerves within the kidney form rich perivascular plexuses around the renal artery and its branches, continuing along even the smaller arterial branches, arterioles, and capillaries. The sympathetic postganglionic fibers are distributed to the vascular musculature and to the smooth muscles in the renal pelvis and calyces; from the slender rami associated with the interlobular arteries, strands of these fibers extend along the afferent arterioles to the juxtaglomerular apparatus. The parasympathetic postganglionic fibers supply the muscles of the pelvis and calyces and probably do not extend into the renal parenchyma. Afferent (sensory) nerve fibers terminate in the musculature of the renal pelvis, the adventitia and endothelium of the renal vessels, and the renal capsule.

The parenchyma is supplied mostly by thin unmyelinated fibers, although some small myelinated axons can be found. The renal pelvis and renal calyces also are richly supplied with unmyelinated nerve fibers, which terminate in relation to the musculature, but myelinated fibers are more abundant than in the parenchyma.

Innervation of the Ureters

The ureters receive sympathetic, parasympathetic, and sensory nerves derived from the renal, spermatic (or ovarian), and hypogastric plexuses. The upper half or two-thirds of each ureter receives the same nerve supply as the corresponding kidney. Preganglionic fibers with their cell bodies in T-10 to L-1 (and perhaps L-2) pass along the anterior roots, the white rami communicantes, the paravertebral sympathetic trunk, and thence through the splanchnic nerves, which end in the aforementioned ganglia, where they synapse with postganglionic fibers. The latter pass to and through the renal and spermatic (or ovarian) plexuses to reach and contribute to the upper portion of the ureteral plexus. Parasympathetic fibers to the upper portion of the ureter are derived from vagal fibers that pass through the celiac and renal plexus and then into the wall of the ureter, where they synapse with short, postganglionic fibers. The afferent (sensory) fibers to the upper portion of the ureter are derived from T-11 and T-12 and traverse the same structures as the sympathetic fibers without interruption to end in the muscles of the upper portion of the ureter.

The nerves to the lower portion of the ureter take a slightly different course. Preganglionic sympathetic fibers have their cell body in L-1 and possibly L-2 spinal segments and pass through the anterior roots, white rami communicantes, and paravertebral chain, within which they synapse with postganglionic fibers, some in the upper two ganglia and others in the sacral ganglia. Postganglionic fibers from the upper lumbar chain pass as lumbar splanchnic nerves to reach the aortic plexus and then pass to and through the superior hypogastric plexus and hypogastric nerves to reach the ureter. The postganglionic fibers that derive from the sacral trunk can be considered sacral splanchnic nerves and reach the inferior hypogastric plexus, where they pass to the ureter. The parasympathetic nerve fibers to the lower part of the ureter arise from S-2 to S-4 segments and pass sequentially through the pelvic splanchnic nerves (nervi erigentes) and the inferior hypogastric plexus (some go through the hypogastric nerves) to reach the lower portion of the ureter. The afferent (sensory) nerves to the lower portion of the ureter have their cell body in dorsal root ganglia of T-12 and L-1 (and perhaps L-2); the proximal branch enters the spinal cord and the distal branch passes in the company of the sympathetic fibers to the lower portion of the ureter. Although these various fibers are arranged in three corresponding groups—the superior, middle, and inferior ureteral plexus—they branch freely and intercommunicate with one another.

Despite the extensive network of nerve fibers, the majority of ureteral peristalsis does not require outside autonomic input. Instead, small intramural pacemakers within the intrinsic smooth muscle of the minor calyces help propagate the urine downstream.

Renal and Ureteral Pain

Location and Characteristics. Diseases of the kidneys, ureters, or both, like other visceral diseases, may cause localized (true) visceral pain and referred visceral pain. Moreover, if the disease involves the parietal peritoneum, it may cause either localized or referred parietal pain. Of these, referred visceral pain is the most frequent and most important.

Several investigators have studied the distribution of referred pain caused by diseases of the ureter and kidney. As early as 1900 (4 years after the first use of a practical cystoscope), Lennandier demonstrated that the distension of human kidney pelvis produced pain (8). Some four decades later, McLellan and Goodell carried out the most definitive study to date (9). Figure 68-3A illustrates the ascending location of the cutaneous sites of pain caused by ascending stimulation of the ureter by dilatation with a balloon at the ureterovesical junction and then at 5, 10, 15, 20, and 25 cm above the ureteral orifice. When stimulation of the ureter was at threshold intensity, pain was discretely localized and approximately 5 cm in diameter, the location being approximately on a line drawn along the lateral edge of the rectus muscle. Stimulation of the kidney pelvis at threshold intensity caused a similar type of pain in the back at the level of the costovertebral angle (Fig. 68-3B). Increasing the intensity of the stimulus produced an even larger area of pain. Stimulation in the upper part of the ureter and pelvis often caused splinting and “spasm” of the lateral abdominal and loin muscles, which did not relax when the stimulus was removed. Several hours later some of the subjects began to have “side ache,” which subsequently increased in intensity during the ensuing 12 hours, undoubtedly due to sustained contraction of the skeletal muscles.

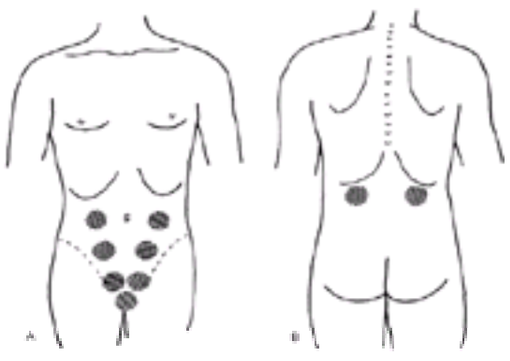

Figure 68-3. **A:** The anterior areas of pain reference to the skin from stimulation of the kidney pelves and of the ureters at the ureteral vesical junction and 5, 10, 15, 20, and 25 cm upward from there. **B:** Schematic representation of posterior area of pain reference produced by either faradic stimulation or local distension in the upper ureter or kidney pelvis, followed by contraction of skeletal muscles. Approximately an hour after the onset of muscle contraction, subject developed aching pain, which persisted from 6 hours to 2 days. (Modified from McLellan AN, Goodell H. Pain from the bladder, the ureter and kidney pelvis. *Pain*. Baltimore: Williams & Wilkins, 1943;23:252–259.)

Other authors also have studied the distribution of pain caused by distension of the pelvis and ureters by inflating distensible catheters in various parts of the upper urinary tract (Fig. 68-4). The following findings have been reported: (a) Distension of the renal pelvis consistently causes pain in the region of the costovertebral angle; (b) distension of the ureteropelvic segment of the ureter produces pain adjacent to the anterior superior iliac spine; and (c) distension of the midureter causes pain to be felt at the middle of Poupart's ligament, whereas distension of the ureterovesical portion of the ureter produces pain in the suprapubic region. Pain of renal pelvic origin is often referred to the ipsilateral testicle or ovary. Pain due to a stone in the terminal ureter may be referred to the scrotal or labial skin, or medial thigh. When the stone is located in the terminal ureter, irritation and edema in the adjacent trigone of the bladder may produce symptoms of frequency of urination as well. In addition to pain, the patient usually experiences hyperalgesia in the dermatomes T-10 to L-1 as well as in the testicle (Fig. 68-5).

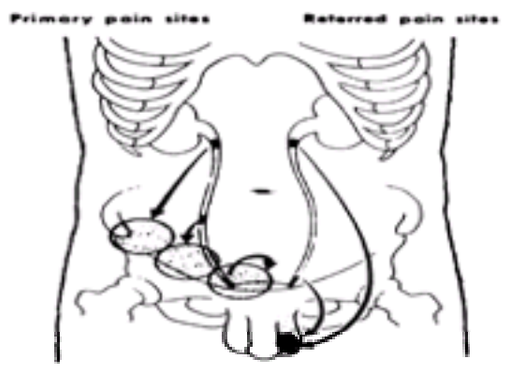

Figure 68-4. Sites of referred pain noted clinically from obstruction and distension of the ureter at the pelvic junction, the midureter, and the ureteropelvic junction. Note that pain of renal pelvic origin may be referred to the ipsilateral testicle (or ovary) and pain due to a stone in the terminal ureter is frequently referred to the scrotal or labial skin. (Modified from Wyker AW, Gillenwater JY. *Method of urology*. Baltimore: Williams & Wilkins, 1975:3.)

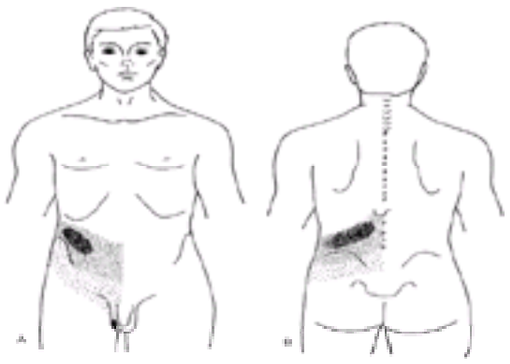

Figure 68-5. The anterior **(A)** and posterior **(B)** sites of pain (*black areas*) and hyperalgesia in the dermatomes (*stippled area*) caused by distension of the kidney, renal pelvis, or ureter.

Several colleagues who have experienced “colic” due to passage of calculi have provided a subtle subjective description of the pain that is worth repeating here. The pain starts as an expanded “bubble” located in the flank and rapidly becomes a feeling of unbearable, expanding pressure that cannot be ignored. The symptom is exacerbated by concern about what might possibly be causing this growing discomfort and the desire for relief. This sensation of something expanding uncontrollably internally may provoke restless attempts to find a comfortable position, but no position is better than any other. The agitated activity of the sufferer seeking relief from pain has even led to mistaken admission to the psychiatric service, from which the patient was transferred when red cells found on routine urinalysis helped in locating the source of the discomfort to the urinary tract.

Mechanisms Producing Pain

Pain related to a urinary organ may be produced by distension of the collecting system or renal capsule, extravasation of urine into the tissues, inflammation, ischemia, or traction and displacement on the pedicle of the organ itself or adjacent organs and structures. Pain related to distension is directly proportional to the rate of the distension (9). Sudden distension usually produces severe discomfort, whereas slow, progressive distension might produce little or no pain (Fig. 68-6).

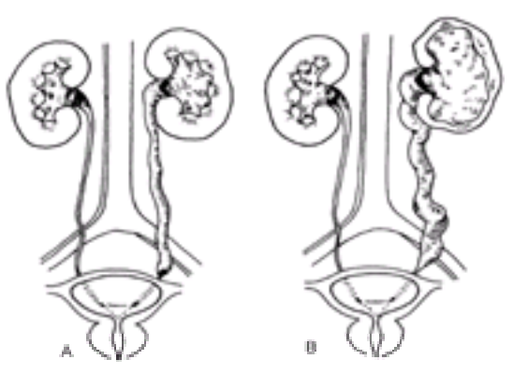

Figure 68-6. **A:** With acute distension of the left ureter and renal pelvis above an obstructing calculus, the patient experienced severe pain requiring narcotics for relief, although the ureter was only slightly dilated. **B:** When the ureter was slowly dilated over many months, the patient experienced no pain despite the fact that the ureter was greatly dilated. (From Wyker AW, Gillenwater JY. *Method of urology*. Baltimore: Williams & Wilkins, 1975.)

The use of contrast agents, which are secreted by the kidney in highly concentrated form, has shown that the acute obstruction associated with passage of urinary calculi is often accompanied by extravasation of significant amounts of the material into the renal parenchyma, surrounding fat, lymphatics, and veins. The severest colic is accompanied by extravasation. Therefore, pain that was formerly attributed solely to distension may also have a component due to extravasation of urine. Mild pain in the flank and costovertebral angle has long been associated with swollen kidneys affected by the inflammatory changes seen in glomerulonephritis and pyelonephritis. Whether such mild pain is due to inflammation of the parenchyma itself or to the distension of the renal capsule as a result of parenchymal swelling is not clear.

Another mechanism that produces pain related to distension of the renal capsule is subcapsular hematoma after accidental trauma. Once the bleeding has stabilized, the pain often remains steady and mild until the hematoma has resolved. Renal ischemia due to arterial embolization can produce severe steady disabling pain followed by abdominal distension. This phenomenon is clearest in individuals whose renal arteries are intentionally embolized to control neoplasia or hemorrhage, but it also occurs in patients with emboli from the left ventricle. Frequently, patients with renal pain will place a hand, with the fingers and thumb spread in opposite directions and palm down, on the affected flank as an aid in describing their pain (10).

The kidneys and ureters share both autonomic and sensory nerves with adjacent viscera; accordingly, diseases that can spread to or from adjacent anatomic structures may mimic pain patterns attributable to these structures and vice versa. Biliary and right renal colic are easily confused if there is no hepatic or bile duct involvement to highlight the difference. Right ureteral colic is occasionally misdiagnosed and treated as appendicitis if the urinalysis showing hematuria or pyuria is missed or ignored. Pain from pancreatitis, pancreatic calculi, or pancreatic pseudocyst can be attributed to the kidneys if these possibilities are not kept in mind and an amylase is not obtained. The duodenum, jejunum, vena cava, and hepatic or splenic colon can be partially obstructed by expanding renal masses.

A number of structures related to the kidneys can contribute to the pain. The anterior aspects of the kidneys are near the peritoneal surfaces, and infection and inflammation of kidneys and ureters can produce a mild peritoneal reaction with accompanying pain and other symptoms. Nausea and vomiting, however, usually *follow* the pain due to diseases of the urinary system, whereas nausea and vomiting usually *precede* the pain generated by disease in gastrointestinal organs.

The posterior superior aspect of each kidney is adjacent to the tendinous portions of each side of the diaphragm. Therefore, penetrating reaction to renal disease

occasionally produces characteristic findings referable to the diaphragm, pleura, and lower lungs, including symptoms of diaphragmatic irritation such as cough, hiccough, shoulder strap pain, pleuritis, pleural effusion, and pneumonitis. Stimulating the inside of the ureter with an electrode (9,11) has reproduced secondary ipsilateral skeletal muscular spasms and pain. The muscles on the affected side along the lateral border of the rectus muscles contracted painfully and ached for more than 24 hours thereafter. Similar spasms and aching occurred in the paraspinous muscles at the level of the costovertebral angle when the renal pelvis was so stimulated. The phenomenon is reproduced clinically by the frequent finding of spinal curvature concave to the affected side during acute obstruction.

Diagnostic Techniques

Sophisticated methods for diagnosing diseases of the upper urinary tract are available. In many cases, the pain history will direct attention to one side or the other, and physical examination may produce signs of mass or tenderness. Because the gonads and kidneys share pain pathways, the physician should carefully examine the ipsilateral testicle or ovary of an individual with occult pain thought to be of renal origin. Response of the kidney to fluid load can be assessed by isotope renography with furosemide-induced diuresis, intravenous pyelography with fluid loading, or urodynamic measurement of pressure during constant flow through a percutaneously inserted nephrostomy catheter (Whitaker test). If diagnostic studies made in the absence of fluid loading appear normal, the occurrence or reproduction of the characteristic pain in response to fluid load is a valuable way of establishing that the upper urinary tract is the source of the patient's pain problem. Diagnostic paravertebral somatic nerve blocks of T-10 to L-2 spinal nerves may also help to establish the nociceptive pathways that are involved. These are discussed briefly later in this chapter.

Computed tomography (CT), ultrasound, and magnetic resonance imaging produce complementary representations of the detailed anatomy and spectra of tissue densities, which are helpful in determining the cause of difficult pain problems affecting the kidneys, ureters, and adjacent structures (12,13,14,15,16 and 17). Moreover, spiral CT is rapidly becoming the procedure of choice for faster and more economical evaluation of acute flank pain (12). Angiography demonstrates arterial and venous anomalies that may obstruct the collecting system directly or secondarily as a result of bleeding. Endoscopic examination of the ureter and renal pelvis and collecting system is now an important addition to the armamentarium of the urologist with newly designed and smaller instruments for diagnostic uses.

In summary, the upper urinary tract can be displayed in intricate detail by current imaging techniques, it can be assessed hydrodynamically and functionally with the aid of pressure measurements and radioisotopes, and the urothelium can be examined almost in its entirety with instruments whose lenses magnify the surface several times. Radiographic imaging by means of ultrasound, plain film, radioisotopes, CT, and magnetic resonance imaging is available to examine the upper urinary tracts in minute detail. One can make arterial and venous angiograms of the vascular supply to these organs. Functional hydrodynamics can be assessed directly and indirectly. No lesion should be missed.

CLINICAL CONSIDERATIONS

Benign Renal Disorders—Inflammation/Infection

Pyelonephritis

Pyelonephritis represents an inflammation and infection of the kidney parenchyma and renal pelvis. The diagnosis is often made on basis of the clinical presentation, as it is quite characteristic. The signs include fever; chills; costovertebral angle tenderness; and occasionally irritative voiding symptoms of urinary urgency, frequency, and dysuria. It can result from hematogenous spread of bacteria or from an ascending infection of the lower urinary tract, yet a host of other causes may be possible (Table 68-1).

Vesicoureteral reflux
Urinary tract obstruction
Renal calculi
Neurogenic bladder
Diabetes mellitus
Immunosuppression
Congenital anomalies
Pregnancy
Catheter drainage

TABLE 68-1. Conditions that predispose to acute pyelonephritis

Laboratory Findings. Urinalysis usually demonstrates white blood cells, WBC casts, and red blood cells. Culture of the urine is usually positive but may be negative in up to 20% of patients with a colony count of less than 10^5 colony-forming units per mL of bacteria (18). Blood tests may reflect the infection, with a resultant elevated WBC count, C-reactive protein level, erythrocyte sedimentation rate, and creatinine level if renal failure is present. Blood cultures may be positive if the infection has entered the bloodstream.

The offending organism is most often *Escherichia coli*; it accounts for greater than 80% of cases. Less often, *Klebsiella, Proteus, Enterobacter, Pseudomonas, Serratia, Enterococcus*, and *Staphylococcus aureus* may be cultured (19).

Diagnosis. The clinical findings as outlined above are usually all that is necessary to diagnose acute pyelonephritis. One must evaluate for potential renal obstruction causing the pyelonephritis, and imaging studies should be performed to rule this out (20). Obstructive uropathy may be secondary to an obstructing calculus, stricture, or mass that precludes adequate drainage of the affected kidney. Also, a focal renal abscess would not respond well to antibiotic therapy alone and may require drainage.

Treatment. Pain-related issues from pyelonephritis tend to improve with appropriate treatment of the underlying infection with antibiotics. Analgesics can often help ease the flank pain while the antibiotics treat the infection; however, more intensive pain therapy is rarely necessary.

Perinephric Abscess

Perinephric abscess represents a focal collection of purulent material usually outside the renal capsule and contained by Gerota's fascia. The etiology may be secondary to hematogenous dissemination or ascending infections from the lower urinary tract. Often, there is a significant delay in making the diagnosis, and therefore there is an associated higher mortality rate (19,20). More recent advancements in diagnostic imaging and antimicrobial agents have improved the outlook dramatically.

Clinical Presentation. Most patients present with a urinary tract infection, which is then followed by severe flank pain, chills, night sweats, malaise, and fever. Of note is that up to one-third of patients may be afebrile (19). Other symptoms referable to the urinary tract infection may include dysuria, urgency, and frequency. In several reported series, there was a higher incidence of renal calculi and diabetes (21).

Laboratory and Radiographic Findings. Urine cultures may be positive in only one-third of cases (19). WBC count elevations and positive blood cultures may be suggestive of perinephric abscess, yet differentiation from acute pyelonephritis may require radiographic imaging. The most specific means for diagnosis of perinephric abscess is either renal ultrasonography or CT scanning (22).

Therapy. Antimicrobial agents are usually first-line therapy for small perinephric abscess; however, on only rare occasions does it result in eradication of larger purulent collections. The mainstay of therapy remains drainage, either percutaneously or by open surgical drainage. Symptoms of pain usually can be managed with

analgesics. Occasionally, reflex skeletal muscle spasms require analgesics and heat before drainage of the lesion (23).

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XGP) is a chronic infection of the renal parenchyma usually associated with renal calculi, urinary tract obstruction, or both. Thus, flank pain may be a presenting symptom of a patient afflicted with this condition and may be present in up to 65% of patients (24). Other common signs include urosepsis, hematuria, and hypertension.

Laboratory and Radiographic Evaluation. More than 50% of patients will have anemia and leukocytosis on hematologic evaluation (24). Abdominal plain films often demonstrate an enlarged renal outline and staghorn calculus in 60% (25). Intravenous pyelography will show an enlarged and nonfunctioning kidney with calculi and mass effect in most cases (25,26). Although renal ultrasonography or plain film modalities help in the diagnosis of XGP, CT scanning is the most useful and accurate means of diagnosis. This will demonstrate renal calculi without pelvic dilation and renal parenchyma replaced with water density masses representing calyces filled with pus. Other changes include thickening of Gerota's fascia and inflammatory changes of the perinephric space (27). The differential diagnosis includes renal tumors including renal cell carcinoma and transitional cell carcinoma (TCC) and other forms of renal cystic disease, tuberculosis, and chronic obstruction.

Therapy. In most instances, XGP is best treated by a complete nephrectomy. As is often the case, the exact diagnosis is not evident until after nephrectomy and pathologic analysis. In rare cases of localized XGP or XGP in a solitary kidney, partial nephrectomy may be performed. The pain associated with XGP usually responds once the chronic infection source (kidney) is removed.

Renal Tuberculosis

Tuberculosis of the kidney is usually secondary to hematogenous spread from another site. The original infection may have occurred years before and becomes reactivated in appropriate circumstances. Once the tubercles set in the renal parenchyma, an inflammatory reaction ensues and lymphocytic infiltration occurs. This tissue eventually becomes replaced by fibrous tissue but may coalesce to form areas of caseous necrosis. When these areas of fibrosis and necrosis occur in the pelvicalyceal system, strictures occur. These narrowings may then cause pain in the kidney due to obstruction and low-grade inflammation. In rare situations, the fibrosis creates squamous metaplasia, which may then degenerate to squamous cell carcinoma (28).

Clinical Presentation. The classic triad of weight loss, anorexia, and malaise is rarely seen in early stages. The diagnosis of renal TB is often very difficult and requires a high index of suspicion. Patients may have recurrent cystitis with its associated symptoms as many have superimposed *E. coli* infections. Of note is that patients may have very advanced genitourinary tuberculosis and have very few symptoms, thus reflecting the insidious nature of this disease process.

Laboratory and Radiographic Evaluation. Urinalysis will de-monstrate microscopic hematuria in approximately 50% of patients and sterile pyuria in almost all patients (28). Urine culture for acid-fast bacteria is paramount to the ultimate diagnosis of genitourinary tuberculosis. The usual cultured organism is *Mycobacterium tuberculosis*; however, it can be difficult to grow. Other laboratory tests, such as erythrocyte sedimentation rate and WBC count, may be elevated. Radiographic evaluation, including intravenous pyelography and retrograde studies, may demonstrate some of the strictured areas; however, CT scanning may help differentiate tuberculosis from other lesions that may be similar in appearance.

Therapy. Renal tuberculosis may have a variety of presentations. Therapy must be based upon the patient's symptoms and signs as well as laboratory data. In well over 90% of cases, renal tuberculosis responds to standard multiantibiotic therapy consisting of isoniazid and rifampin. Occasionally, streptomycin, pyrazinamide, or ethambutol also must be added. The usual course of therapy is 9 months (29). Most often, in cases of significant stricture disease, the offending lesion does not respond well to standard dilation maneuvers performed endourologically. The kidney or ureter often has more extensive disease than may be apparent and partial ureterectomy or nephrectomy may be required (30).

Retroperitoneal Fibrosis

Etiology. Retroperitoneal fibrosis is most commonly idiopathic, yet may be related to leaks from aortic aneurysms or associated with retroperitoneal malignancies or metastatic disease. Methysergide, an effective migraine medication, produced a rash of cases, but its use has now been restricted and carefully controlled. In more than half the cases of retroperitoneal fibrosis, the etiology is undetermined. A dense fibrotic process involves the retroperitoneal structures, surrounds the ureter, and compresses it. The earliest involvement usually occurs at the crossing of the iliac vessels, but later the process can extend to involve the kidneys, the great vessels, and the mediastinum (31).

Symptoms and Signs. The symptoms of retroperitoneal fibrosis are often nonspecific and can include moderate hypertension, vague back or abdominal pain, flank pain, scrotal swelling, and venous engorgement of the lower extremities and abdominal wall. Eventually, uremic symptoms appear after the slowly progressive bilateral renal obstruction interferes with renal function and the outflow of urine (32).

Diagnosis. The uremia secondary to retroperitoneal fibrosis often leads to the evaluation of the ureters and retroperitoneum. Typical findings on urography are hydronephrosis without an obvious point of obstruction and medial deviation of the lumbar course of the ureters. Retrograde passage of ureteral catheters is usually easy in spite of the antegrade obstruction (33). Magnetic resonance imaging and CT scanning demonstrate that the retroperitoneum is replaced by a fibrotic process and simultaneously shows the kidneys and encasement of the vasculature (34).

Treatment. Treatment of retroperitoneal fibrosis involves relief of obstruction. On a temporary or semipermanent basis, ureteral stents are effective. Longer-lasting correction requires surgical lysis of the ureters and replantation to an area less likely to be affected by the disease. An important fact is that retroperitoneal fibrosis or mass, or both, may be secondary to metastatic disease or a primary retroperitoneal tumor, and biopsy is mandatory. The ureters themselves can be replanted laterally or intraperitoneally to remove them from the fibrotic process. The disease process is often progressive, and prognosis is guarded in spite of good initial result (35).

Congenital Lesions Affecting the Kidney and Ureter

Polycystic Kidney Disease

Polycystic kidney disease, a congenital disease with a familial pattern, derives from failure of the junction between the uriniferous tubules and the collecting ducts. This nonunion results in blind secretory tubules connected to glomeruli, producing fluid that is unable to escape and slowly expands into huge cysts compressing the surrounding normal structures. The renal parenchyma is gradually destroyed, and the enlarging cysts swell the kidneys to huge masses, which may reach weights of 5 kg. Pain is produced by the weight of the organ pulling on the renal pedicle, hemorrhage into cysts, cyst rupture, or infection.

Background. Polycystic kidney disease is divided into autosomal recessive and dominant inheritance patterns. The presentation varies between the two inheritance types. In autosomal recessive polycystic kidney disease, infants and children are typically affected, and the cysts tend to be small (less than 2 mm), as compared with autosomal dominant polycystic kidney disease, which affects mostly adults and has larger cysts (36). Furthermore, the associated diseases, such as liver cysts, cerebral artery aneurysms, mitral valve prolapse, and diverticulosis, are more common in autosomal dominant polycystic kidney disease. In autosomal recessive polycystic kidney disease, biliary dysgenesis, hepatic fibrosis, biliary atresia, and portal hypertension predominate (37).

Symptoms and Signs. The presentation pattern in young people is commonly hematuria after athletic activity. Individuals with known family history may request evaluation to rule out the disease and eventually be discovered to have it. Patients who are diagnosed later in life often present with dull, intermittent flank pain. Of these patients, 60% will be hypertensive and 30% will already be uremic (37). In addition to hypertension, large, palpable bilateral lobular abdominal masses may be present. The affected area in patients with infected cysts or recent hemorrhage into a cyst will be tender to palpation.

Diagnosis and Treatment. Renal ultrasound images can differentiate polycystic kidney disease from other types of renal cystic disease, bilateral hydronephrosis, bilateral renal cell carcinoma, and Wilms' tumor. Treatment should include medications to control hypertension, diet modifications, low salt intake, and pain medication during passage of clots and infection. A supporting garment or corset may help with the chronic discomfort caused by the mass of these kidneys tugging on the renal pedicles. Occasionally, nephrectomy is performed on the hypertensive patient with polycystic disease who is about to undergo dialysis or transplantation for renal failure. Additionally, nephrectomy may be necessary before transplantation to allow the donor kidney to reside in the iliac fossa without compression from the

polycystic kidney. Infection of cysts tends to occur late in the disease and is therefore an ominous prognosticator.

Simple (Solitary) Renal Cyst

The cause of solitary renal cyst is unknown. These cysts, in contrast to those seen in polycystic kidneys, do not destroy significant amounts of parenchyma. They do not communicate with the collecting system and, accordingly, rarely cause obstruction of the collecting system by compression.

Symptoms and Signs. The typical patient is older than 40 years of age and complains of intermittent and dull unilateral flank pain that has been present for months or years. When such a cyst becomes infected, symptoms of sepsis will be described. The overwhelming majority of patients have no symptoms whatsoever from the cyst and it is unusual to become symptomatic. Other causes for flank pain must be evaluated before further investigation of renal cysts causing pain (38).

Diagnosis and Treatment. Renal ultrasound or a CT scan provides the best means of establishing the diagnosis of simple renal cyst. In cystic renal lesions of doubtful definition, it might be necessary to puncture the cyst with a fine-gauge needle under ultrasonic or scanning image control, aspirate the contents, and perform cytologic examination. The current radiographic techniques are very sensitive and specific at differentiating simple renal cysts from those more suspicious for neoplasm. Therefore, in most instances, this obviates the use of fine needle aspiration. The work by Bosniak has defined several subclasses of renal cysts based on CT criteria, from grade I to IV (I and II being more likely to be indolent, whereas III and IV are more suspicious for carcinoma) (39). The differential diagnosis includes renal neoplasm, renal carbuncle, hydronephrosis, and hydrocalycosis.

Percutaneous aspiration may temporarily relieve symptoms of simple renal cysts; however, the cystic collections may reaccumulate. It may ultimately be necessary to explore the kidney and unroof the cyst, either by open surgery or laparoscopically, if pain issues persist (40).

Calyceal Diverticulum

Etiology. Calyceal diverticula are outpocketings of the renal collecting system that may be congenital communications or secondary to rupture of a parenchymal abscess cavity into the collecting system. These diverticula become lined with urothelium and continue to communicate with calyces, infundibula, or renal pelves. The communications are often narrowed enough to cause blockage of the outflow of the diverticulum and therefore represent a nidus for infection or stone formation (41).

Symptoms and Signs. Individuals with these lesions are mostly asymptomatic but may complain of chronic, dull, intermittent flank pain. Stones trapped in the diverticula can harbor infection, with symptoms of pyelonephritis occurring from time to time. These lesions may require retrograde pyelography for full delineation and diagnosis. CT scanning may be a useful adjunct, as it can help determine the amount of surrounding parenchyma as well as the rotational direction of the diverticulum. This information assists in surgical planning and operative approach and procedure.

Treatment. Patients who are persistently symptomatic or whose infections cannot be controlled with antibiotics may require some form of definitive therapy for the diverticulum (42). Surgical techniques include percutaneous dilation of the diverticulum with ablation of the tract or percutaneous access with nephrolithotomy if stones are present. In cases in which there is a significant amount of renal parenchyma surrounding the diverticulum, one may choose to perform open diverticulectomy or partial nephrectomy as definitive therapy (43). Additionally, laparoscopic techniques have been applied to treat calyceal diverticula, with reasonable success and minimal morbidity (44).

Horseshoe Kidney

Pathophysiology. Because of its weight, position, and variable blood supply, congenital horseshoe kidney can produce traction on the renal vessels and other adjacent vascular structures, resulting in abdominal pain of a dull, intermittent, and vague nature. Additionally, these kidneys are more likely to have ureteropelvic junction obstruction, reflux, or other congenital urologic abnormalities. Any of the obstructive lesions found in the unfused kidney can occur in the horseshoe kidney and produce similar symptoms.

Treatment. Although successful treatment of obstructive conditions in the upper collecting systems of horseshoe kidneys depends on separation of the isthmus, this is not always feasible or desirable because of the vascular configuration (45,46). Symptoms due to lesions that cannot be corrected may respond to medications or regional analgesia achieved with paravertebral T-10 to L-1 blockade (45,46).

Medullary Sponge Kidney

Etiology. Medullary sponge kidney is a congenital autosomal recessive defect in which the distal collecting tubules are dilated and visible on intravenous pyelography. Associated findings are a high incidence of renal tubular acidosis, hypercalciuria, and hyperparathyroidism.

Symptoms and Signs. Most individuals with this defect are unaffected and asymptomatic (47). Pain is associated with infection and stone formation in the widened (at times cystic) collecting tubules. Because autoelimination of the stones requires erosion through a papilla into the collecting system, the pain is chronic and intermittent as well as difficult to treat.

Treatment. Nerve blocks to relieve the pain might be followed by renal denervation in selected cases. (Nerve blocks are discussed under Renal and Ureteral Calculi and Idiopathic Nephralgia.) Endourologic approaches to this disease may offer relief to the individual who suffers chronically because of pain from trapped intermittently obstructing calculi (48). The mainstay of therapy is modification of the diet and optimization of the patient's metabolic profile to prevent further stone formation. This regimen would include thiazide diuretics, increased fluid intake, and alkalinization of the urine and phosphates to bind the calcium.

Acquired Diseases Affecting the Kidney and Ureter

Renal Vein Thrombosis

Etiology. Dehydration, infection, and coagulopathy are thought to be involved in renal vein thrombosis. Whatever the cause, the obstruction of venous outflow by clot causes renal swelling, capsular distension, and pain.

Symptoms and Signs. Half of the patients present with acute flank pain, hematuria, and persistent proteinuria. The other half experience a gradual onset of chronic flank pain rather than acute pain. In some patients, the first symptom is that of pulmonary emboli.

Diagnosis and Treatment. Intravenous pyelogram will demonstrate a pronounced nephrogram and poor excretion of contrast dye from the affected kidney (49). CT scanning is better at delineating the exact nature of the thrombosis, as it provides some information about the contralateral renal vein and the inferior vena cava. More selective venacavography may be required to determine patency of the renal vein and allow for potential localized thrombolytic therapy.

Anticoagulation therapy often promotes return of full function within 4 to 6 weeks, but acute obstruction may be best treated with thrombolysis (49). Pain is relatively mild and controllable with aspirin and codeine, but the physician should be mindful of the effects of aspirin on the ongoing anticoagulation.

Renal Infarction

Renal infarction is secondary to underlying cardiac or vascular disease in the majority of cases. The most common causes are atrial fibrillation and bacterial endocarditis (50). Other less common etiologies include intimal tear, trauma, contraceptive use, syphilis, cocaine use, and idiopathic thrombocytopenia (51).

Clinical Presentation. Renal infarction can be quite difficult to diagnose, as one may present with a multitude of symptoms. Pain associated with renal infarction usually presents in the flank region; however, not uncommonly it presents as abdominal, chest, or lower back pain. Accordingly, acute abdomen, pyelonephritis, cholecystitis, and even myocardial infarction may mimic the pain of a renal infarct (51,52). Other common clinical features include hematuria, nausea, vomiting, fever, and decreased urine output.

Diagnosis. Several laboratory tests may be abnormal in the face of renal infarction, yet none is exclusively diagnostic. Elevated WBC count is present in up to 70% of patients, whereas elevated lactate dehydrogenase levels are present in almost all patients (53). Also, hematuria is present in varying degrees in up to 80% of patients, with the majority having microhematuria. Several imaging studies are routinely used to accurately diagnose renal infarction.

Intravenous Pyelogram. Imaging of suspected renal infarction usually begins with an intravenous pyelogram, as the diagnosis is often stone disease or obstructive phenomena of the upper urinary tract. The study will show an absent nephrogram, as no contrast penetrates into the kidney. This is in contradistinction to renal calculi, as the obstructive uropathy will often demonstrate a delayed or dense nephrogram. Segmental infarctions may show partial or no evidence of renal involvement (54).

Renal Ultrasound. Sonography again may be used to better define renal obstruction. As the infarcted segments pass through time, sonographic changes occur; however, the main usefulness of renal ultrasound is when it is combined with duplex to study the vasculature, and this aids in the diagnosis of renal infarction.

Nuclear Renal Scan. Nuclear scanning entails use of radioisotope to perfuse the kidney and identify flow through all or part of the kidney. When areas are underperfused, as in renal infarction, this leads to perfusion defects, or so-called cold spots. This study may provide valuable information about the relative function of the kidney as well as the contralateral side. Its usefulness may be limited in the setting of segmental branch occlusion, as renal scans are not as specific as compared with large vessel disease (54).

Computed Tomography. The CT scan is one of the best modalities at differentiating the various diseases that may mimic renal infarction. The finding may be complete absence of perfusion of part or the entire kidney depending on the nature of the infarct. Additionally, the “cortical rim sign” may be suggestive of an infarct. This is described as a high attenuation area on the periphery of the kidney, with the remainder unperfused. The peripheral contrast-enhanced margin is from the presence of preserved capsular and collateral vessels.

Arteriography. Selective renal arteriography is the diagnostic study of choice in the evaluation of infarction. Segmental infarcts appear as wedge-shaped perfusion defects and the arteriogram can demonstrate the exact location of the segmental branch occlusion. When the main renal artery is involved, arteriography shows the extent of collateralization and nature of the occlusion.

Therapy. The treatment of renal infarction is controversial; many options exist. In the setting of acute renal infarction, the options may include surgical revascularization, thrombolysis, or simply observation. The mortality rate has been traditionally high when surgery is performed, as the patients often have significant coexisting morbidities and surgical revascularization may be difficult (55).

Renal and Ureteral Calculi

Etiology. Nephrolithiasis has a multifactorial etiology, including hormonal, anatomic, environmental, genetic, and dietary factors that predispose one to developing stones. Calcium metabolism is intimately related to stone disease and modification of the diet may effect stone formation. Additionally, magnesium, citrate, sodium, uric acid and bicarbonate and others may influence stone formation. Investigation into abnormalities of any of these factors by 24-hour urine analysis is paramount for evaluation of the etiology of nephrolithiasis. The most common types of stones found in North America are calcium oxalate and calcium phosphate stones (70%), followed by infection stones (struvite, magnesium ammonium phosphate; 15%), uric acid stones (5% to 10%), and cystine stones (1% to 5%) (56,57 and 58).

Symptoms and Signs. Currently, metabolic diagnosis is not a cost-effective screening method for identifying stone formers, and the physician's first contact with such individuals usually is during the acute pain caused by the passing of a calculus. Pain of passage is characterized as an “expanding bubble” of severe discomfort unrelieved by position changes. The site of referred pain depends on the position of the stone in the collecting system. The severity of the pain is such that large doses of potent narcotics (e.g., 15 mg of morphine sulfate or 125 mg of meperidine) may not relieve the pain. Renal pelvis and calyceal stone pain is referred to the costovertebral angle, whereas stones obstructing the upper ureter refer pain to the flank and ipsilateral gonad. Midureteral stones cause referred pain in the anterior superior iliac crest and inguinal region, and lower ureteral stones refer pain to the pubic area and scrotal or labial skin. Stones in the terminal ureter may also cause significant urinary urgency and frequency due to irritation of the trigone of the bladder.

Hyperesthesia and tenderness of the kidney region and spasm of the abdominal and flank musculature may accompany the pain of kidney stones. Not infrequently, retraction of the testicle, nausea, vomiting, urgency, “cold sweat,” and, occasionally, signs of shock are present. Often there is a compelling urge to urinate or even defecate, and urination becomes very painful.

The mechanisms of pain are obstruction and distension of the collecting system and renal capsule, extravasation of urine into the tissues, and irritation of the mucosa. In addition to the reflex spasm of the skeletal muscles, reflex spasm of the smooth muscles of the ureteropelvic junction and ureters frequently occurs. This spasm becomes a new source of noxious stimuli that gives rise to pain and other reflex mechanisms, which in turn aggravate the spasm. In this fashion, a vicious circle is initiated, causing aggravation and persistence of the pain. Additionally, reflex vasoconstriction of the renal vascular complex can occur, with potential deterioration of renal function (3).

Diagnosis. Diagnosis of renal calculus disease is based on the history of the pain, which has a characteristic radiation and progression from flank to groin, along with physical findings of costovertebral angle tenderness. Gross or microscopic hematuria is typical, but in a significant percentage of individuals, the symptoms of stone passage vary from none to vague and poorly localized abdominal malaise. The patient may be cool and clammy during episodes of colic. In contrast to the patient with intestinal disease, whose problem is usually heralded by nausea, vomiting, or both, the patient with renal colic usually becomes nauseated after the onset of pain (i.e., the nausea is caused by intense pain). The patient with intraperitoneal lesions that irritate the peritoneum usually tries to lie still, whereas the patient suffering from urinary colic is often restless and seeks different positions in attempts to get relief from the pain.

Plain radiographs of the abdomen and pelvis may show calcific stones of fair size but will fail to demonstrate radiolucent stones or smaller calcific densities in the presence of much gas and fecal matter in the colon. Therefore, an intravenous pyelogram should be done in patients suspected to be passing a stone except for those known to be allergic to contrast agents. More recently, a move toward performing unenhanced helical CT scanning has shown that this modality can quickly and effectively diagnose most cases of stone disease with excellent accuracy. Viewig et al. reviewed 105 patients who presented to Duke University Medical Center with acute flank pain. Unenhanced helical CT yielded a sensitivity of 98%, specificity of 98%, and an overall accuracy of 96% for diagnosing ureteral stones (59). This technique is particularly useful for the patient suspected of being a narcotic abuser who visits emergency facilities feigning renal colic to obtain the analgesics but claims allergy to contrast agents as a means of avoiding discovery.

Treatment. Therapy depends on the size of the stone, its location, presence or absence of sepsis, the amount of pain the individual is experiencing, and occasionally social circumstances. Ureteral stones less than 5 mm in diameter will pass spontaneously in 80% of the cases; stones that are 5 to 10 mm in diameter will pass spontaneously in approximately 20% of patients; and stones larger than 10 mm in diameter are much less likely to pass on their own.

Opioids. In most patients, relief of the severe pain is one of the primary objectives of the treatment of ureteral colic. Morphine, like all other phenanthrene derivatives of opium, tends to cause contraction of all smooth muscles, with the notable exception of those of the blood vessels. Clinical studies have shown that morphine can increase intrabiliary pressure to 15 times the normal value (3). Although large doses of morphine (e.g., 15 mg intravenously, slowly) may relieve the pain through its central effects, it is likely to aggravate the smooth muscle spasm. Meperidine has a slightly less spasmogenic effect than other potent analgesics and can be used in combination with atropine given simultaneously. Dextroamphetamine given in conjunction with an opioid potentiates the latter's analgesic efficacy and thus reduces the narcotic dosage required to achieve pain relief, it also is an effective antiemetic drug (60).

Regional Analgesia. If none of these agents provides good pain relief, serious consideration should be given to use of nerve block techniques, which interrupt the innervation of the kidney and ureter. Of the several regional analgesic techniques available, paravertebral sympathetic block and segmental epidural block are the most practical and effective. Paravertebral block, first used by Mandl to successfully treat renal colic and subsequently used by many European clinicians with very good results, has the disadvantage of requiring insertion of several needles (61). For this reason, continuous segmental epidural analgesia, limited to T-10 to L-1 inclusive, is the more practical procedure; it not only provides complete and persistent relief of pain as long as the analgesia is continued, but also interrupts efferent sympathetic impulses and thus eliminates the reflex spasm and any associated renal vasospasm. This in turn increases the chance of spontaneous passage of stones that are less than 10 mm in diameter.

Bonica reported on the results of either paravertebral sympathetic block or continuous epidural block in 53 patients, including eight physicians, during the past four decades (62,63). In addition to providing complete pain relief, in some patients the treatment resulted in downward movement of stones that had not advanced for 18 to 36 hours before the block. In 23% of these patients, treatment was accompanied by passage of the stone into the bladder; in another 18% of patients with calculi that had not advanced for a number of hours, the stone moved to the ureterovesical junction, where it was extracted through a cystoscope (Fig. 68-7). An important advantage of regional analgesia is that it poses no risk of respiratory depression. In contrast, if the patient is given a narcotic and then suddenly passes the stone, the pain often promptly subsides along with the pain-induced respiratory stimulation; in this situation the patient may incur severe respiratory depression. In addition, epidural analgesia can be extended if it is necessary to treat the stone through percutaneous ultrasonic pyelolithotomy or open surgery.

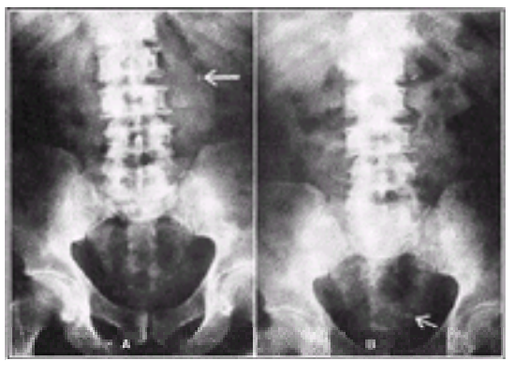

Figure 68-7. **A:** Radiograph of a patient with a stone in the left ureter at the level of the second lumbar interspace (*arrow*), which produced severe colicky pain in the left flank with radiation to the left groin, testicle, and inner aspect of the thigh. The stone did not advance for 48 hours, and the pain persisted despite repeated administration of narcotics. Paravertebral sympathetic block of T-10 to L-2 caused complete relief of pain and permitted the patient to be up and about. The nerve block was repeated in 12 hours. **B:** Radiograph taken after second nerve block showing that the calculus had descended to the ureterovesical junction (*arrow*). From this position, it was extracted with cystoscopic manipulation.

Urologic Therapy. Stones accompanied by sepsis are a truly life-threatening medical emergency. A history of chills and fever and findings of preshock or shock, fever, or elevated WBC count should alert the physician to the probability of concurrent sepsis. Intravenous lines must be established immediately for infusion of antibiotics and fluids, medications, and electrolytes to combat shock. Once the patient is in stable condition, this will be a convenient route for administration of potent opioid analgesics if someone experienced in epidural analgesia is not available.

Some means of drainage of the obstructed organ must be established. It can be drained percutaneously with the aid of local anesthesia or epidural block, or endoscopically via cystoscopic retrograde passage of a ureteral stent to bypass the stone and drain the infected collecting system. Topical anesthesia of the urethra may be achieved with 2% lidocaine (Xylocaine) jelly if the procedure is performed under local anesthesia. Instrumental manipulation within the bladder is made less uncomfortable by epidural block or by instillation through a small catheter of 20 mL lidocaine before cystoscopy. In instances in which sepsis and infection are not present, a wide variety of endourologic techniques are available to treat the stones, depending on their location. Most small upper urinary tract and some lower urinary tract stones are amenable to extracorporeal shock wave lithotripsy. Larger- or medium- sized stones in the kidney may necessitate percutaneous removal through a tract in the flank region to allow larger instruments to remove the stones. Ureteroscopy with a wide variety of baskets, probes, and lasers are also used, with good success rates for treatment of stones (64).

Urine and blood are cultured. Pending identification of the organism and its sensitivities, broad-spectrum antibiotics are administered. Because coliforms are the most likely offenders, although cocci may also be involved, a combination of antibiotics including an aminoglycoside is a good choice (e.g., ampicillin, 1 g every 6 hours, and gentamicin, 1 mg per kg every 8 hours). When the sepsis has been well controlled, removal of the stone by extracorporeal lithotripsy, percutaneous techniques, or endoscopic ureteral manipulation can be safely carried out as indicated.

An example of a socially motivated stone removal is the airline pilot discovered to have a renal calculus as a result of a workup for microhematuria found in an annual examination urinalysis. Such individuals are barred from flying commercial aircraft if they harbor stones. Therefore, otherwise asymptomatic stones in such individuals are often manipulated into a position that will allow them to pass or be broken up by extracorporeal shock wave lithotripsy (48).

Ureteropelvic Junction Obstruction

Etiology. In ureteropelvic junction obstruction, a minimally compensated congenital or acquired constriction of the ureteropelvic junction or adynamic segment decompensates as the result of sudden increase in local edema, angulation, or fluid load, producing acute renal colic. Aberrant vessels may also cause obstruction to the outflow of the kidney.

Diagnosis. When prompted, the patient might remember that past episodes of colic have followed increased intake of fluids, such as bouts of beer drinking, or high intake of salty foods such as smoked ham, pickles, or saltines, which induce a sodium-load diuresis. Diagnosis is made by obtaining an intravenous pyelogram during an episode of colic. Failing this, intravenous pyelography with a diuretic phase induced by furosemide may reproduce the colic and demonstrate the lesion. As a diagnostic maneuver, it may be possible to reproduce the pain during cystoscopy under local anesthesia and retrograde filling and overdistension of the renal pelvis through a ureteral catheter; however, this technique is seldom used today (65).

Treatment. Treatment of intermittent hydronephrosis involves surgical relief of the obstruction. In the period between diagnosis and definitive treatment, the patient is instructed to avoid fluid loading of the kidney; if an episode should occur, analgesics are dispensed as needed (65). Surgical therapy may be performed in a variety of ways, including open (dismembered pyeloplasty), antegrade, and retrograde techniques (66).

Clot Colic

Etiology. Renal bleeding unassociated with glomerulonephritis often produces clots. During passage, the clots can obstruct the ureter, producing colic indistinguishable from that due to passage of calculi as far as symptoms are concerned. Clot passage commonly occurs after blunt renal trauma, after renal surgery, with rupture of renal cysts, and from renal neoplasms.

Treatment. While diagnostic studies are under way, management of the pain is similar to management of pain due to acute obstruction of any kind. Analgesics are given, and if vomiting is a significant problem, intravenous fluids are administered. In the presence of severe bleeding, blood should be cross-matched in case transfusion becomes necessary, and vital signs and hematocrit should be closely monitored. Removal of the offending cause is the treatment of choice; however, angiographic embolization may yield temporary or permanent control (67).

Papillary Necrosis

Etiology. Patients at greatest risk of developing papillary necrosis—a rare, potentially life-threatening condition—are diabetics, chronic phenacetin abusers, alcoholics, persons with the sickle cell trait, and patients with chronic pyelonephritis. These disease processes cause the renal papilla to lose its vascular integrity and it sloughs into the collecting system, thereby obstructing the ureter and producing renal colic. Because infection is a common contributing factor, the danger of an infected, closed space threatens whenever a papilla sloughs and obstructs the collecting system. If this diagnosis is suspected, prompt action to relieve the obstruction is mandatory (68).

Diagnosis and Treatment. If pyelography is carried out in the patient with colic who is passing a papilla, a negative filling defect in the calyx outlining the bed of the slough can be seen. The appearance of this defect has been described as the “signet ring” sign. The location of radiolucent necrotic tissue in the ureter is also seen

as a filling defect.

If the ureter is obstructed, prompt relief by retrograde passage of a catheter or percutaneous nephrostomy is mandatory in the management of sepsis. The urine should be strained, and retrieved necrotic tissue should be sent to a pathologist to confirm the diagnosis (68).

Hydronephrosis of Pregnancy

Etiology. At the beginning of the fourth month of pregnancy, progressive dilation of renal calyces, pelves, and ureters above the pelvic brim starts and continues until the last 2 months, when it usually regresses. At least two factors are involved: mechanical compression by the enlarging uterus and endocrine effects on the smooth muscle of the ureter and renal pelvis. Because the left ureter is cushioned by the sigmoid colon, it is less affected by uterine compression than the right.

Symptoms and Signs. In the absence of infection or other complicating factors (see Ovarian Vein Syndrome), hydronephrosis of pregnancy does not typically cause pain or other symptoms. Complications combined with obstruction may produce persistent pain. One should evaluate for renal or ureteral stones causing the symptoms of flank pain, and microhematuria is often present (69).

Treatment. When persistent pain develops, care must be exercised in the use of narcotics because of the possible depressant effects on the fetus. Combining small doses of narcotics with nonsteroidal antiinflammatory drugs and perhaps even dextroamphetamines can minimize this risk. Because obstruction can be relieved with the aid of indwelling internal stents, which can usually be passed with the aid of topical anesthesia, the problem of long-term analgesics can be bypassed (69).

Ovarian Vein Syndrome

Etiology. Initially known as the *right ovarian vein syndrome*, this condition is most commonly seen in women of child-bearing age after pregnancy (see previous section). Presumably, a process is set in motion during pregnancy in which an aberrant ovarian vein traps the ureter after hormonal changes, and the obstruction caused by the uterine enlargement produces ureteral dilation. The resulting constriction persists postpartum, leaving permanent hydroureteronephrosis above the level of the surrounding vein. Because hydronephrosis of pregnancy is more common (80%) and more severe on the right side, that side is more frequently involved in the ovarian vein syndrome. Symptoms are pain in the involved flank due to obstruction and those of the accompanying infection.

Diagnosis and Treatment. Postpartum pain in the right flank or abdomen, or both, accompanied by chills, fever, malaise, nausea, and vomiting should alert the clinician to the possibility of ovarian vein syndrome. On examination there is flank tenderness. Ultrasound or pyelography helps establish the diagnosis.

Relief of pain with analgesics is required until obstruction is bypassed by ureteral stenting and antibiotic therapy is instituted to control infection. Permanent relief is provided by surgical excision of the obstructing vein (70).

Infundibular Stenosis (Fraley's Syndrome)

Etiology. In Fraley's syndrome, flank pain is caused by obstruction of the superior infundibulum and its calyces. The latter obstruction is produced by intrarenal vessels impinging on the infundibular channel as the secondary vessels wind around it in their course through the renal sinus.

Diagnosis and Treatment. All reported cases of Fraley's syndrome thus far have been adults (71). Patients complain of steady, dull pain in the costovertebral angle and flank, usually for months or years. The key to diagnosis is that lying down relieves the pain. Tenderness may or may not be present on examination. Upon careful review of the pyelogram, which includes oblique views, a linear filling defect caused by vascular compression is seen crossing the infundibulum to the superior calyx. A 30- or 60-minute drainage film shows contrast trapped in the superior calyx. Angiography may be helpful to further delineate the crossing vessel in relation to the collecting system.

Treatment of Fraley's syndrome requires severance and reanastomosis of the infundibulum or the occluding vessel, preferably the former (71).

Conditions Causing Pseudorenal Pain

Etiology. Ilioinguinal neuropathy and genitofemoral nerve entrapment, which cause pseudorenal pain, almost always follow inguinal surgery, most frequently herniorrhaphy. Genitofemoral entrapment is rare, but both conditions can be mistaken for renal pain by the unwary (72,73).

Symptoms and Signs. These conditions are characterized by radicular (segmental) pain in the distribution of dermatomes T-10 to T- 12 that can mimic renal pain. Unlike renal colic, however, pseudorenal pain is usually brought on by a physical strain such as heavy lifting, sleeping in an awkward posture, or occasionally by a blow to the spine. It is relieved by a change of position, which is not the case with most renal pain [for an exception to this see Infundibular Stenosis (Fraley's Syndrome)].

Diagnosis. Conditions causing pseudorenal pain are rare; they are mentioned in this chapter for the sake of completeness in considering the differential diagnosis of renal pain (72,73).

Idiopathic Nephralgia/Loin Pain-Hematuria Syndrome

Etiology. Idiopathic nephralgia and loin pain-hematuria syndrome are extremely rare conditions characterized by intractable flank pain and hematuria and less frequently symptoms of frequency, nocturia, and dysuria, in the absence of demonstrable pathology. In former years, the condition was diagnosed more frequently and was attributed to irregular and incomplete contraction of the calyces and renal pelvis resulting from uncoordinated overactivity of the sympathetic nerve supply so that impulses for peristalsis either did not reach or did not pass beyond the ureteropelvic junction (74).

As knowledge of renal pathophysiology increased and advanced diagnostic methods became available; the number of patients diagnosed with this syndrome steadily declined and now is minuscule. Nonetheless, if after comprehensive urologic, neurologic, orthopedic, psychiatric, and radiologic evaluation, no demonstrable pathology is found for persistent and disabling renal-type pain and other related symptoms, one is faced with the need for treatment. In the rare instances in which this occurs, patients should be submitted to comprehensive psychosocial evaluation, including psychometric testing, to eliminate pain due to psychological problems.

Therapy. If all of the diagnostic procedures discussed so far prove negative and the patient has persistent, disabling pain, diagnostic-prognostic paravertebral nerve block of T-10 to L-2 inclusive with a local anesthetic is carried out. At least three such procedures should be carried out using local anesthetics with different durations of action and the patient's response carefully monitored and compared with the predicted duration of the analgesia. If the patient derives complete pain relief for the duration of the blockade, a series of such blocks might alter the behavioral response to the underlying stimulus, whatever it may be, and provide adequate relief of the pain syndrome. When such procedures provide complete but only temporary relief, renal denervation may be considered.

Denervation. In the early part of the twentieth century, denervation of the kidneys was achieved by periarterial stripping of the nerves. This procedure does not effect complete denervation, however, because some of the nerves run in the wall of the vessel. Moreover, because the fibers removed are postganglionic and only small sections are removed, regeneration occurs within weeks and months. These factors, together with the fact that the operation is tedious and carries an inherent risk of laceration of vessels, caused a number of clinicians to abandon this procedure and replace it with aorticorenal ganglionectomy. Fontaine et al., among others, obtained good results by combining aorticorenal ganglionectomy and splanchnicectomy (75).

The most impressive report on the efficacy of denervation for idiopathic nephralgia is that published by Bauer (7). He noted that in a large series of cases, all but one patient was freed of persistent “idiopathic” renal pain by denervation of the kidney. More recently, White and Sweet (76) reported that four patients, in whom paravertebral block of T-10 to L-1 (or L-2) produced complete temporary relief, derived relief for 1 to 8 years after sympathetic denervation. For reasons previously mentioned, the preganglionic operation of dividing small and lesser splanchnic nerves and removing the three lower thoracic and first and second lumbar sympathetic ganglia, as well as the intervening trunks, is the procedure of choice. We have performed this procedure in one patient with a successful outcome. As has been amply demonstrated after autotransplantation and heterotransplantation of kidneys in many patients, total denervation has little effect on renal function. Accordingly, renal autotransplantation is used often in these cases, as renal denervation shows some promise in terms of therapy for these exceptionally difficult-to-manage patients

(77). Nonetheless, despite surgical denervation with autotransplantation, recurrent graft pain has been demonstrated and overall success rates are less than 70% (78). Although some have proposed a psychological or even factitious etiology of the loin pain-hematuria syndrome, there is some evidence to support the neuropathic basis of this condition. It has been reported that capsaicin irrigation of the renal pelvis will provide long-term relief (79).

Malignant Disorders Affecting the Kidney and Ureter

Renal and Ureteral Tumors

A variety of tumors of the kidney and ureter can cause pain in the flank and various other symptoms and signs. The most important tumors are renal cell carcinoma, TCC of the renal pelvis and ureter, sarcomas, renal oncocytoma, and Wilms' tumor of the kidney (see Chapter 35).

Renal Cell Carcinoma. Renal cell carcinoma represents an adenocarcinoma of the renal parenchyma. Because of the variety and diversity of the presenting symptoms and signs related to secondary effects of this tumor (paraneoplastic syndrome), it has been dubbed *the internist's tumor* (80). The tumor occurs in all age groups, but it is most prevalent in the sixth and seventh decades of life and has a male predominance, with a ratio of 3 to 2 (81). This tumor afflicts all races, but its highest incidence is in Scandinavia. This tumor accounts for 3% of adult malignancies and in 1995 accounted for 28,000 new cases and an associated 11,000 new deaths (82).

Etiology. Although the exact cause of renal cell carcinoma has not been defined, there is evidence for carcinogenic and genetic factors. Smoking increases the risk of renal cancer by approximately 40%. Cadmium exposure also has been associated with an increased risk; the presence of both factors increases the risk of renal cancer even further (81). A genetic propensity for renal carcinoma also has been demonstrated by mutations in chromosome 3p25–26, particularly in patients with Von Hippel- Lindau disease (83). Cohen et al. described an abnormal karyotype caused by reciprocal translocation of chromosomes 3 and 8 in families in which a kidney tumor was prevalent (84). He reported that eight of 10 of the family members with tumors had the chromosomal abnormality, whereas the 22 without cancer did not. These data support a multifactorial basis for renal cell carcinoma, including environmental, genetic, and hormonal factors.

Grawitz (85) originally postulated that these tumors arose from adrenal rests because of their microscopic resemblance to adrenal tissues, which prompted him to name the tumor *hypernephroma*; subsequent studies established that the tumors are of renal tubular origin. Three main cell types can be identified in these malignancies: (a) clear cell carcinoma, (b) granular cell carcinoma, and (c) sarcomatoid cells. Renal cell carcinomas are given a pathologic grade of I, II, or III, based on degree of cellular anaplasia, with grade I being least anaplastic and grade III showing the greatest degree of anaplasia (Furhman grading system). Metastatic spread occurs both by direct extension and through lymphatic and hematogenous routes. The most common sites of metastasis are lungs (55%), lymph nodes (34%), liver (33%), bone (32%), adrenal (19%), contralateral kidney (11%), brain (6%), heart (5%), spleen (5%), bowel (4%), and skin (3%) (86).

Symptoms and Signs. Renal cell carcinoma may present with a wide variety of clinical symptoms and signs, including the classic triad of flank pain, hematuria, and a palpable flank mass. Additionally, nonspecific systemic symptoms and numerous paraneoplastic syndromes may be evident and may imply higher-stage disease (87). In several series, the classic triad occurred in only 4% to 6% of the patients studies (81). The individual features of the triad occurred more frequently than the entire triad. Hematuria, noted in 35% to 59% of the patients reviewed, was most common. Pain directly related to the primary tumor, provoked by stretching of the renal capsule or sudden expansion due to bleeding into it, was found in approximately one-third of the cases (range of 10% to 38%), although in one study of 309 patients, pain was present in 41% of the patients (55). A palpable mass was found in approximately 22% (range of 2% to 35%) (86), although in the study of 309 patients, it was noted in 45% of the patients. In the series of studies cited by Bagley, 30% of the patients had none of the classic triad of symptoms (81). Thus, the disease may remain clinically silent during the early stages, and in more than 50% of patients, metastatic disease is present at the time of diagnosis (86).

Hypertension and weight loss are relatively uncommon presenting signs of renal cell carcinoma except in cases of advanced disease. Tumor obstructing the spermatic vein can cause a varicocele, which fails to disappear when the patient lies down. Furthermore, a right-sided varicocele with similar characteristics may be indicative of vena caval obstruction. Abnormal liver function tests are found in approximately 15% of patients, including some without metastasis, the cause of which is unknown. A similar fraction have hypercalcemia.

The paraneoplastic syndromes associated with renal cell carcinoma may rarely lead to the diagnosis of the tumor. Other secondary symptoms include intermittent fever, weakness, anemia, or erythrocythemia due to overproduction of erythropoietin. Fever is the presenting symptom in one out of eight of the cases. Cardiac failure associated with hypertension may occur because of the arteriovenous shunting within the neovasculature of the tumor.

Diagnosis. The diagnosis of renal cell carcinoma requires thorough history and physical examination as well as radiography and other more sophisticated diagnostic procedures mentioned earlier in this chapter. The presence of a spiking fever in conjunction with regional mass makes differential diagnosis between renal tumor and renal abscess quite difficult, and radiologic findings may not distinguish between these two lesions; final diagnosis must await surgical exploration or fine needle aspiration. Currently, the tumor is likely to be discovered incidentally by ultrasound imaging or CT scanning for other abnormalities. If the cancer is identified within the kidney at the time of screening for other diseases, approximately 85% of the patients survive 5 years (88). However, if one or more of the symptoms of renal cell carcinoma is present, 5-year survival rates diminish (89). Once ultrasound imaging suggests diagnosis of renal carcinoma, further studies of the mass by CT scan and angiography usually confirm the diagnosis and lead to exploration and excision. Tumors picked up incidentally in early stages by these means are much less likely to have developed a neovasculature, which lights up the angiogram in large neoplasms.

Treatment. Surgical removal remains the only effective treatment for renal cell carcinoma. Localized stage I (tumor confined to the kidney) and stage II (tumor locally invasive but confined to Gerota's fascia) and locally advanced renal cell carcinomas are amenable to radical nephrectomy (87). This procedure includes early control of the renovascular pedicles and removal of the kidney and the associated tumor, the adrenal gland and the surrounding perinephric fat, and Gerota's fascia along with the regional lymph nodes. More recently, data suggest that tumors confined to the mid- and lower poles or smaller upper pole tumors do not necessitate ipsilateral adrenalectomy (90). In cases of small (less than 4 cm) tumors, solitary kidney, and presence of conditions that may predispose one to lose renal function in the future (e.g., diabetes, stone disease, renal artery disease), partial nephrectomy is an accepted surgical option (91,92).

Metastatic Renal Cell Carcinoma. Stage III renal carcinoma, which by definition includes regional invasion of the renal vein or vena cava, or both, or metastasis to regional lymph nodes, or a combination of these, is also treated by radical nephrectomy. This procedure results in 42% to 50% 5-year survival (87). Local extension of the tumor into the renal vein appears to have less effect on the prognosis than nodal involvement. Accordingly, tumor thrombus in the renal vein and inferior vena cava still has a 5-year survival rate of greater than 50% when lymph nodes are negative (93).

No uniformly satisfactory treatment exists for stage IV renal cell carcinoma, which by definition includes invasion of surrounding organs and widespread metastatic disease. Because up to 50% of patients have evidence of metastatic disease at the time of diagnosis, therapy remains a major problem. In selected patients who have a proven solitary metastasis, surgical excision of the primary tumor and the metastasis, may provide long-term cure, whereas in patients with widespread metastasis, the prognosis is poor even when radiation, chemotherapy, or hormonal manipulation is added to the surgery. Currently, immunotherapy with a wide variety of agents is used to control metastatic disease (94). These agents may include interferon, various interleukins, and other cytokines.

In patients with metastatic lesions from renal cell carcinoma, pain control is a very critical issue. Pain due to metastatic lytic lesions of the bone or periosteal elevation can often be successfully treated by irradiation of the involved area. Occasionally, long bone lesions may benefit from internal fixation. Pain caused by infiltration of nerves or nerve plexuses or spread to other organs can be severe, intractable, and not relieved by oncologic therapy. Treatment should include the use of nonopioid and narcotic analgesics and various adjuvant agents, such as amitriptyline and other antidepressants, which have proven useful in relieving the lancinating deafferentation pain. Attempts should be made to use a multimodal approach, combining pharmacologic therapy, psychological techniques, neurostimulation techniques, nerve blocks, intraspinal opioids, and neuroablative procedures.

Sarcomas. Sarcomas account for only 3% of the malignancies of the kidney or renal pelvis. The majority of these lesions are leiomyosarcomas, but other histologic varieties have been reported (81). The mean age of patients who develop this type of tumor is approximately 50 years, with a range of 10 to 86 years.

The symptoms and signs depend on the size of the lesion. These tumors have a tendency to be locally infiltrative and may involve local area nerves. Large tumors cause pain by stretching of the renal capsule and perhaps by compression or irritation, or both, of intercostal nerves. No radiologic findings have been considered diagnostic despite use of modern imaging techniques. Treatment generally has consisted of excision by nephrectomy and mass excision. The poor results noted, with frequent local recurrence and metastases, have prompted interest in combining surgery with radiotherapy and chemotherapy, which has been promising with

sarcomas in other sites (81).

Renal Oncocytomas. Oncocytomas are solid tumors of the renal parenchyma that have a benign course. This type of tumor accounts for 3% to 5% of all renal tumors (87). The age of patients with these tumors has ranged from the third to the ninth decade and there is a slightly higher incidence among males than females. However, renal oncocytomas can have coexistent renal cell carcinomas in up to 30% of cases. The management scheme should therefore follow the same course as that for any suspicious renal mass (95).

The signs and symptoms are somewhat similar to those of renal cell carcinoma and include flank pain, hematuria, and a palpable mass. The prognosis of patients with oncocytoma appears to be excellent.

Transitional Cell Carcinoma (TCC) of the Upper Urinary Tract. Upper tract TCC constitutes 5% of all renal tumors (96). These tumors first appear in the fifth and sixth decades of life, with a progressive increase in incidence with advancing age. Carcinoma of the ureter is most common in older age groups, being rare before 30 years of age. The incidence of carcinoma of the pelvis and ureter is greater in males than females by a ratio of 2 to 1. The incidence of bilaterality is 2% to 4% and approximately 30% to 50% of patients with renal pelvic TCC will develop TCC of the bladder.

Etiology and Pathology. Transitional epithelial cells lining the calyces and renal pelvis, as well as the ureter, are subject to environmental carcinogens. A strong relationship between carcinoma of the renal pelvis and a long-standing history of phenacetin ingestion has been established, as has an association between carcinoma of the renal pelvis and Danubian endemic familial nephropathy. Tobacco abuse is also associated with a higher incidence of transitional cell cancers (97).

Malignant lesions of the renal pelvis can be classified into TCCs, squamous cell carcinomas, adenocarcinomas, and connective tissue tumors. Approximately 90% of all tumors of the renal pelvis are transitional cell tumors. In the ureter, more than 70% of TCCs are primary transitional cell malignancies, and only 8% are squamous cell tumors (96). TCC is spread by direct extension and through blood and lymphatic channels. Approximately 85% of TCCs of the renal pelvis are papillary and less often demonstrate muscle invasion at the time of resection. The other 15% are sessile; of these, approximately 80% show muscle invasion at the time of resection.

Symptoms and Signs. Gross or microscopic hematuria appears in 80% to 90% of patients with upper tract TCC (96). Pain is usually precipitated by ureteral or ureteropelvic junction obstruction secondary to the tumor mass. These patients are likely to suffer pain in the psoas, quadratus lumborum, and erector spinae muscles; if there has been extension to the vertebral column, back pain is present. Palpable flank mass in a patient with TCC signifies massive extrarenal extension or hydronephrotic renal destruction secondary to obstruction.

Diagnosis. Diagnosis is helped by the appearance of a defect in the collecting system or renal pelvis on excretory pyelography. In patients with ureteral tumors, approximately 50% will present with urinary frequency or dysuria. Radiographically these patients will have ureteral dilatation, which develops as a result of accommodation of a slowly expanding tumor mass and reflects the absence of ureteral spasm produced by the presence of a calculus. Urine cytology will be atypical in most patients with higher-grade lesions (96).

Treatment. Nephroureterectomy traditionally has been the treatment of choice for TCC of the pelvis, ureter, or both. A stage I tumor of the ureter can be managed by excision of the tumor along with an ureteroureterostomy. In patients with tumor of the renal pelvis, radical nephroureterectomy is advocated; this includes *en bloc* removal of the kidney, ureter with the cuff of the bladder, and the surrounding lymphatic structures. The addition of lymphadenectomy at the time of surgical resection may not provide any improved disease control but does provide information with regard to the stage of the disease, which can be used to select patients for adjunctive chemotherapy when appropriate agents have been identified. The 5-year survival rate is greater than 80% in grade I tumors, approximately 70% in grade II, but less than 30% to 50% in grades III and IV. The prognosis in patients with transitional cell cancer of the ureter is less favorable, with patients rarely living more than 2 years after diagnosis. Other options now include endourologic management of the upper tract TCC in both antegrade and retrograde fashions. Additionally, adjunctive use of Calmette-Guérin bacillus placed in the kidney or ureter may decrease local recurrence rates (98).

Wilms' Tumor. Wilms' tumor, which develops in approximately 500 children each year in the United States, accounts for approximately 95% of primary renal malignancies in childhood (99). Moreover, it is the third most common solid tumor in childhood, following tumors of the central nervous system and neuroblastoma in incidence. During the past three decades, methods of treating this tumor have improved significantly, providing striking increases in survival rates.

Etiology and Pathology. The cause of Wilms' tumor is unknown, but the predilection of patients with certain genetic factors to develop this type of neoplasm suggests a partial genetic basis. Recent chromosomal studies have localized the Wilms' tumor gene (*WT-1*) locus to the 11p13 (99). Children with aniridia, hemihypertrophy, Von Recklinghausen's disease, or genitourinary congenital anomalies have an increased risk of developing Wilms' tumor as well (99).

Grossly, most Wilms' tumors are large, fleshy, soft tumors that grow in extensive fashion within an apparent “capsule.” In advanced stage III of the disease, metastasis to the regional lymph nodes is present, whereas in stage IV of the disease, there is a hematogenous metastasis to the lung, liver, brain, or bone.

Symptoms and Signs. Most children present because of an abdominal mass first noted by a parent (often when bathing the child). Other frequent presenting symptoms and signs include pain, anorexia, fever, or hematuria. The latter symptom is a sign of renal-collecting system involvement and is seen with much less frequency than in renal cell carcinoma. Mild hypertension is noted in many children, and plasma renin levels may be increased. Primary Wilms' tumor often undergoes extremely rapid growth in apparent size.

Diagnosis. In addition to a thorough history and physical examination, roentgenograms of the chest and ultrasonography should be performed in all children (99,100). The evaluation of the inferior vena cava, best also performed by ultrasonography, should be done routinely to provide information about tumor size, site, and extent. CT may assist in delineating any lung lesions as well as determining the exact extent of the kidney tumor and adjacent organ or contralateral kidney involvement. Other diagnostic procedures mentioned in the earlier part of this chapter should also be considered.

Treatment. Treatment of Wilms' tumor consists of surgical removal of the kidney and the entire tumor, a segment of the ureter, and regional lymph nodes (99). Depending on the tumor stage and histopathologic findings, the addition of chemotherapy or radiation therapy, or both, is used adjunctively to prevent relapse. Additionally, in select instances, preoperative chemotherapy is warranted (100). Most recent studies suggest that nearly 80% of all patients with Wilms' tumor are cured with optimal current therapy. Survival is inversely proportional to the stage of the disease. The 5-year survival rate is 97% for those with stage I (favorable histology) and 92% for those with stage II (favorable histology). Stage III disease 5-year survival is 84% with favorable histology and drops to 68% with unfavorable histology, whereas it is only approximately 55% for those who have pulmonary metastasis and even lower for the very few patients who have metastasis to the liver, bone, and brain (stage IV unfavorable histology) (100,101). Metastasis to the lungs accounts for approximately two-thirds of the relapses, but with aggressive treatment, control of metastasis is possible in at least half of the cases.

Effective pain control before and after the surgical operation is an important part of management. Recent studies have provided impressive evidence that the prevalent misconception that children do not experience as much pain as adults is incorrect. Parenteral, oral, or intraspinal narcotics may be useful in the management of this type of pain.

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CHAPTER 69

Abdominal Pain Caused by Other Diseases

Kaj H. Johansen, E. Patchen Dellinger, and John D. Loeser

This chapter discusses disorders that cause abdominal pain not discussed in the preceding four chapters of this section and includes Intraabdominal Vascular Diseases; Diseases of the Peritoneum, Mesentery, and Diaphragm; Other Intraabdominal Diseases, including abscesses, neurogenic ileus, gas entrapment syndrome, and abdominal migraine; Systemic Disorders, including hematologic, biochemical, and biological disorders; and Extraabdominal Diseases, including thoracic visceral disease, gynecologic disease, pain of neuropathic origin, and pain of musculoskeletal and tegumentary origin (Table 69-1). Many disorders discussed in this chapter have been considered in more detail by Sleisenger and Fordtran (1) and Nyhus and colleagues (2).

TABLE 69-1. Abdominal pain caused by other disorders

INTRAABDOMINAL VASCULAR DISEASES

Abdominal pain can arise from multiple different vascular causes but is of special importance because it may presage several different and highly lethal conditions: expansion or rupture of an arterial aneurysm, abdominal implications of aortic dissection, or acute intestinal ischemia leading to infarction, perforation, and peritonitis. Recognition of the underlying cause is thus a crucial aspect of the successful management of such abdominal pain. In this section the pertinent pathophysiologic states are discussed; the symptoms associated with each condition are elucidated; appropriate means of diagnosis and management, both of the pain and the underlying conditions, are presented; and the natural history of these conditions, both in the untreated state and following appropriate management, are discussed. We first consider aortic aneurysm, then aortic dissection, then acute and chronic intestinal ischemia. Finally, intestinal consequences of systemic vasculitis are briefly considered. A more comprehensive discussion of these conditions can be found in several excellent textbooks on vascular surgery (3,4 and 5).

Abdominal Aortic or Iliac Aneurysm

Etiology

The vast majority of intraabdominal aneurysms are found in the infrarenal aorta, starting 1 or 2 cm distal to the renal artery orifices and ending at or just before the aortic bifurcation (Fig. 69-1). Historically, aneurysms were once a common consequence of trauma, bacterial infection, or syphilis, but the overwhelming majority now arises as a consequence of an apparent systemic lathyrism (a collagen-elastin defect) manifested by a weakening and fragmentation of the arterial media. Causes for this collagen-elastin defect are probably multiple, including inheritance of a biochemical defect (6), inadequate nutrition because of sparse arterial vasa vasorum (7), hydraulic stresses (8), and increased lytic enzymes, either primary or secondary to such exogenous stresses as cigarette smoking (9). While aneurysm shares numerous risk factors with atherosclerosis (advanced age, male gender, smoking, hypertension) the two entities are morphologically, anatomically, and histopathologically distinct (10). Because aneurysmal dilatation is a systemic disorder, it is not surprising that other intraabdominal vessels can occasionally (although much less commonly) develop aneurysms as well (11). These are most commonly seen in the renal, hepatic, superior mesenteric, celiac, and pancreaticoduodenal arteries. Aneurysmal dilatation can also occur in a special circumstance in the splenic artery; this is a rare but serious disorder in pregnant women, unfortunately too commonly presenting with hypovolemic shock following rupture (12).

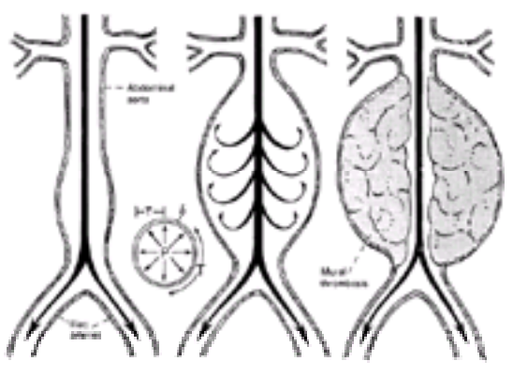

Figure 69-1. Development and progression of an abdominal aortic aneurysm. **A:** Initial phase. The insert shows that tension (*T*) on the wall varies directly with the

product of the intraluminal pressure (*P*) and the radius (g) of the lumen and inversely with the thickness (d) of the wall. T is proportional to Pg/d. Any slight dilatation shown in A increases the radius and decreases the thickness, thereby increasing the tension and progressively enlarging the aneurysm. **B:** As the artery dilates, blood near the wall flows more slowly, creating turbulence. Turbulent flow causes the wall of the vessel to vibrate, further weakening it. **C:** Both turbulence and irregularity on the lining of the damaged wall promote the formation of a mural thrombus, which significantly reduces the diameter of the lumen. (Modified from Johansen K. Aneurysms. *Sci Am* 1982;247:110–111.)

Aneurysms occasionally arise as a consequence of infection, most commonly in the aorta or in one of its branches. Formerly, this was usually related to embolization from subacute bacterial endocarditis, but a more recent report suggests that mycotic aneurysms arise more commonly from vascular trauma, various immunosuppressed states, and concurrent sepsis (13). An aneurysm of special importance, both because it is iatrogenic and because it heralds such potentially lethal conditions as graft infection or aortoenteric fistula, is the anastomotic aneurysm arising at a suture line of a previously placed arterial prosthetic graft, resulting in aorto- or graft-enteric fistula (14).

Pathophysiology

Pain arising from aneurysms within the abdomen results primarily from the stretching of sensory nerves of the retroperitoneum due to aneurysm expansion; such nerves may be stimulated even more significantly with aneurysmal rupture. Because aortic aneurysmal rupture most commonly occurs to the patient's left side into the retroperitoneum beneath the sigmoid colon (Fig. 69-2), stimulation of nerves of the lumbosacral plexus on the left side is usual. Indeed, individuals with slowly leaking aneurysms are sometimes first evaluated by a urologist, neurosurgeon, or orthopedist because of the initial mistaken impression of ureteral colic or lumbar disk disease. Erosion of an expanding aortic aneurysm into the lumbar vertebrae can cause severe back pain, probably a consequence both of irritation of lumbar nerve roots and of the overlying periosteum. On unusual occasions patients with aneurysmal rupture can present with pain in the right upper quadrant so that the initial impression is that of biliary colic, as noted during the terminal illness of Albert Einstein (15).

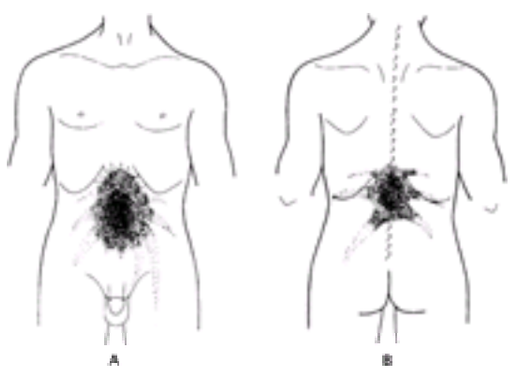

Figure 69-2. **A,B:** Distribution of the pain caused by rupture of the abdominal aorta consequent to aneurysm.

Symptoms and Signs

Most infrarenal abdominal aortic aneurysms are asymptomatic until rupture. Patients occasionally complain of a dull, diffuse, poorly localized midabdominal pain, commonly not significant enough to prompt medical consultation. Rarely, aneurysms can obstruct the gastrointestinal tract or the ureter by extrinsic compression, resulting in intermittent or constant symptoms appropriate to those organs. Erosion of an aneurysm into the lumbar spine can cause symptoms either locally, presenting as chronic back pain, or as a consequence of encroachment on nerve roots, wherein projected pain might be noted in the distribution of these lumbosacral nerve roots (i.e., into the pelvis, groin or scrotum, or lower extremity).

Much more commonly, pain is a cardinal feature of acute aneurysmal expansion or rupture. The patient frequently notes sudden tearing aching pain in the midabdomen and mid-back, most commonly radiating into the left flank or groin for reasons noted previously. Such pain is commonly associated with the symptoms and signs of hypovolemic shock, because what might be a substantial portion of the patient's blood volume exits into the retroperitoneum. Similar tearing aching pain followed by hypovolemic shock results from the rupture of aneurysms of various intraabdominal visceral arteries and their branches as well. The *double rupture* sign has been reported with splenic artery aneurysm rupture, seen primarily in pregnant women (see previous discussion). Severe sharp left upper quadrant pain occurs and then subsides as the initial aneurysm rupture is tamponaded in the lesser sac; further pain and shock supervene when the rupture breaks into the free peritoneal cavity (12).

Diagnosis

Aneurysms are found most commonly in elderly men; the average age for a standard population of patients with abdominal aortic aneurysm is 70 years, and the male to female ratio is 4:1 to 8:1 in most series. A history of aneurysm elsewhere strongly predicts abdominal aortic aneurysm, and hypertension and cigarette smoking are associated with greater frequency in patients with aneurysms. A tendency to aneurysmal deterioration of arteries may be traced in families, suggesting that the elderly relatives of aneurysm patients might be at increased risk of developing aneurysms themselves (16). Risk factors for the development of mycotic or anastomotic aneurysms have been mentioned previously. As noted, the vast majority of intraabdominal aneurysms are asymptomatic and most commonly are discovered by serendipity during physical examination or on roentgenographic or other imaging evaluation performed for other purposes. For example, calcium outlining the wall of an intraabdominal aneurysm can be discovered on plain roentgenograms or computed tomographic (CT) scans of the lumbosacral spine performed for low back pain or on excretory urograms performed for putative ureteral colic. Abdominal ultrasonograms obtained for evaluation of possible biliary colic can demonstrate an occult abdominal aortic aneurysm.

Because the aorta bifurcates at the level of the umbilicus, the physical examination should emphasize careful palpation of the epigastrium. Aneurysm is diagnosed on physical examination by evidence for a pulsatile mass substantially broader than the 2-cm upper limits for the diameter of the normal adult infrarenal aorta. Tortuosity of the abdominal aorta can sometimes mimic aneurysm formation, especially in the elderly, and overlying inflammatory or neoplastic masses can transmit the aortic pulse and cause the mistaken impression of aneurysm (17). Aneurysms of visceral arteries are rarely symptomatic until rupture. A large iliac aneurysm might occasionally be palpable on rectal examination, frequently presenting initially with urologic or gynecologic symptoms; these are sinister lesions with a dismal prognosis following rupture (18).

Current diagnostic procedures most important for demonstrating the presence and size of intraabdominal aneurysms include B-mode ultrasonography (19) and CT scanning (20). With a high sensitivity, specificity, and overall accuracy, these can be used to define the presence of aneurysms as well as to discern their sizes, with a resolution rate of less than 1 mm. Arteriography generally has little to add in the diagnosis of aneurysms and on occasions it can be frankly misleading because aneurysms in general (and infrarenal abdominal aortic aneurysms in particular) fill circumferentially with thrombus so that the angiographic dye column can appear little different from the normal aortic lumen. Arteriography may be useful in the preoperative evaluation of certain aneurysm patients (e.g., those with hypertension or peripheral arterial occlusive symptoms).

Patients whose aneurysms rupture present with signs and symptoms of sudden abdominal, flank, and back pain and circulatory collapse. Thus, the clinician usually can differentiate this condition from several others that might resemble it superficially, including perforating peptic ulcer, visceral artery embolism, and myocardial infarction accompanied by cardiogenic shock. Although the pain patterns and collapse seen with each of these conditions can be similar to those of aneurysm rupture, initially all are usually characterized by relative *normovolemia* (in the case of perforated ulcer or mesenteric embolism) or *hypervolemia* (in the case of myocardial infarction), in contrast to the signs of profound *hypovolemia* that accompany ruptured aneurysm. Subacute rupture of an aneurysm can, as noted previously, lead to confusion with ureteral or biliary colic or with the orthopedic or neurosurgical implications of lumbar spine disease.

Treatment

No effective nonoperative therapy for intraabdominal aneurysms exists. Whereas hypertension and cigarette smoking can play a role in the early genesis of the arterial wall degeneration leading to aneurysm formation, once developed the arterial dilatation proceeds inexorably toward rupture in consonance with Laplace's law (21). Aneurysms of the abdominal aorta exceeding 5 cm in greatest diameter warrant repair in otherwise good-risk patients.

In brief, the operative management of aneurysm involves proximal and distal control of the artery and, in cases of aortic or iliac aneurysms, opening of the artery and intraluminal insertion of an appropriately sized prosthesis (Fig. 69-3). Visceral artery aneurysms can often be treated by simple ligation, although those involving the hepatic or superior mesenteric artery frequently require bypass grafting, usually with autogenous vein. Advances in endovascular techniques and materials make it possible that certain aneurysms (e.g., in patients who are poor operative candidates) may be managed by relatively minimally invasive transcatheter procedures.

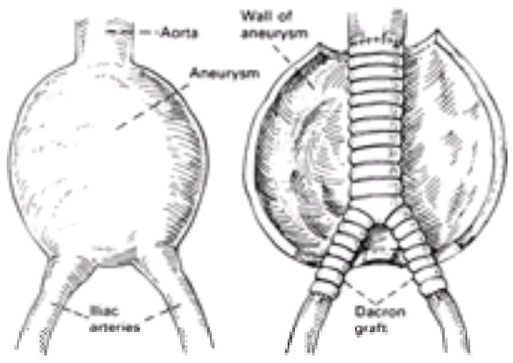

Figure 69-3. **A:** Large aneurysm of the abdominal aorta, extending cephalad from just above the bifurcation of the aorta. The aorta above the aneurysm and the two iliac vessels are clamped, the dilated sack is opened, and a graft is sutured in place from within. **B:** Dacron prosthetic graft in place, resulting in reestablishment of blood flow. (Modified from Johansen K. Aneurysms. *Sci Am* 1982;247:110–111.)

When an aortic or visceral arterial aneurysm ruptures, repair must be performed under emergent circumstances in a patient who frequently is in hypovolemic shock and who requires simultaneous volume resuscitation. Initial control of the proximal aorta, usually at the aortic hiatus of the diaphragm, is crucial; the retroperitoneal hematoma accompanying aneurysm rupture can make dissection around the aneurysm neck difficult. Control of the distal thoracic aorta by left thoracotomy or by direct opening of the aneurysm and passage of a proximal balloon-tipped catheter might be necessary. In addition to their severe hypovolemia, these elderly patients are at markedly increased risk for myocardial infarction, stroke, acute renal failure, and colon ischemia (22).

Outcome. Surgery for intraabdominal aneurysms is highly successful when performed on an elective basis. Despite the advanced age of patients with intraabdominal aneurysms, and the not infrequent concurrence of atherosclerotic involvement of the coronary and cerebrovascular vessels, the operative mortality in several large series is as low as 1% to 3%. Several studies have confirmed that an operative mortality of 5% can be achieved for elective aneurysmorrhaphy, even in octogenarians (23). Equivalent results have been found for the management of other intraabdominal aneurysms approached electively.

The outcome is different for patients who suffer aneurysmal rupture prior to appropriate management. Those who can undergo urgent repair operation before development of hypotension and shock might have an outcome little different from that of patients undergoing elective operations. In those in whom hypotension develops, operative mortality is at least 50%, up to 70% in some series; including those patients who succumb from aneurysmal rupture prior to reaching the hospital, overall mortality may exceed 90% (24). The outcome can be equally dismal for rupture of other intraabdominal aneurysms, frequently because they might be hidden deep in the pelvis, as in the case of iliac aneurysms, or might mimic other intraabdominal problems and therefore delay diagnosis, as in the case of various visceral artery aneurysms. Because the mortality of rupture associated with splenic artery aneurysms in young women exceeds 65%, the presence of such lesions in these patients warrants an aggressive resectional approach (12).

Landmark studies by both DeBakey and colleagues (25) and Szilagyi and associates (26) have demonstrated that successful aneurysm operation restores the patient to a life expectancy not different from that of an age-matched control population. This, and the well-documented low operative mortality for elective surgery, clearly supports adoption of an aggressive posture toward resection of almost all intraabdominal aneurysms. On follow-up these patients must be examined serially for the development of aneurysms elsewhere, as well as for anastomotic or infectious complications of their prosthetic grafts, which occur in 1% to 2% of all patients (14).

Abdominal Pain Associated with Aortic Dissection

Aortic dissection almost always occurs in the ascending or descending thoracic aorta and presents initially with severe tearing upper or mid-back or chest pain; the entity is fully discussed in Chapter 61. On rare occasions, aortic dissection may develop in the abdominal aorta (particularly after blunt trauma) and result in abdominal, flank, or low back pain: More commonly, such symptoms develop as complications resulting from distal extension of a thoracic aortic dissection. Two mechanisms leading to abdominal pain are relevant in this regard. First, the false lumen associated with thoracic aortic dissection may involve and thus occlude somatic branches of the abdominal aorta, leading to ischemia or even infarction of, for example, the gut, spleen, kidney, or spinal cord. Even for type B dissections starting in the descending thoracic aorta, which are otherwise conventionally treated medically (b-blocker drug administration), evidence for visceral or other abdominal aortic tributary involvement is an indication for operative repair of the thoracic aortic dissection, usually by thoracotomy and graft replacement of the damaged aorta. Innovative transcatheter approaches with stenting of branch arteries or fenestration of the dissection flap may be useful alternatives to thoracotomy.

Second, approximately one-third of aortic dissections extending into the abdominal aorta or iliac artery become aneurysmal. The natural history of these lesions is ominous and operative repair is indicated when symptoms occur or (as for standard aortic aneurysms) when the diameter grows to exceed 5.0 cm. Symptoms are similar to those for standard abdominal aortic aneurysms: Operative repair is complicated by the thin friable wall of the dissected, aneurysmal aorta. Operative management involves graft replacement of the aneurysmal dissection, sometimes requiring complex thoracoabdominal aortic reconstruction.

Intestinal Ischemia

Intestinal ischemia can either be acute or chronic, arising from embolic phenomena to the visceral arteries (usually the superior mesenteric artery) or secondary to thrombotic occlusion of atherosclerotic stenosis of one or more of these vessels. A further poorly understood syndrome of bowel ischemia is characterized by peripheral mesenteric vasoconstriction in the absence of proximal arterial disease, the *nonocclusive mesenteric ischemia syndrome* (27). Uncommon causes of pain secondary to visceral ischemia may result from rare vascular disorders involving the splanchnic vessels. These include the *celiac band syndrome*, various forms of vasculitis, fibromuscular dysplasia, and the effects of irradiation. In this subsection we first briefly mention the anatomy and regulation of mesenteric blood flow, then consider the causes, pathophysiology, and symptoms and signs of acute ischemia and chronic ischemia, and finally discuss the diagnosis and therapy for both types of intestinal ischemias. This is followed by a brief discussion of vasculitis.

Basic Considerations

A sound clinical approach to intestinal ischemia is necessarily based on an understanding of the anatomy and physiology of the splanchnic circulation. The gastrointestinal tract is supplied by the celiac axis and its branches and the superior and inferior mesenteric arteries. The blood supply to the intraabdominal portion of the gastrointestinal tract is richly endowed with several anastomotic interconnections that help to protect it against the consequences of occlusive vascular disease (28). In the presence of chronic progressive arterial occlusive disease these anastomotic interconnections, including the pancreaticoduodenal arcades, the arch of Riolan, and the marginal artery of Drummond, usually are robust enough to maintain intestinal viability. On the other hand, in certain sites the collateral supply might be only marginally adequate.

The blood flow to the abdominal viscera, like that in other parts of the body, is regulated by various intrinsic mechanisms, including local response to alterations in

pressure or to an increase in tissue metabolites. In addition, the function of the extrinsic autonomic nervous system is relevant. Intrinsic or local modulation of blood flow occurs in response to changes in arteriolar transmural pressure or to alteration in tissue oxygenation, appearing to involve changes in both arteriolar resistance and precapillary sphincter activity. The extrinsic neurogenic regulation of mesenteric and intestinal flow is mediated by the sympathetic postganglionic fibers supplied by the splanchnic nerves: Increased activity causes vasoconstriction while decrease or inhibition of the sympathetics results in vasodilation. In addition to the intrinsic and neurogenic regulation of mesenteric blood flow, gastrointestinal hormones, as well as various endogenous or exogenous circulating vasoactive substances, can exert an important circulatory effect. Vasodilators include cholinergic stimuli, cholecystokinin, gastrin, prostaglandin E, and other gastrointestinal hormones (see Chapter 66), as well as circulating b-adrenergic stimulants. Operative vasoconstrictors include a-adrenergic stimulants, vasopressin, angiotensin II, and digitalis glycosides (29,30,31 and 32).

Acute Intestinal Ischemic Syndromes

Most patients with acute intestinal ischemic syndromes present with a sudden episode of severe abdominal pain and prostration. The most important syndromes are acute mesenteric arterial occlusion, mesenteric arterial embolization, the nonocclusive mesenteric ischemia syndrome, and mesenteric venous thrombosis. The causes, pathophysiology, and symptoms and signs of these acute ischemic syndromes are discussed, after which the diagnosis and treatment of both types are considered.

Etiology. Arterial embolization occurs most commonly in the superior mesenteric artery because of the caliber of the vessel and the obliquity of its takeoff from the abdominal aorta. Emboli to the celiac axis and the inferior mesenteric artery are less common. Most mesenteric emboli occur in patients who have atrial fibrillation, valvular or atherosclerotic heart disease, or mural thrombi in the heart following myocardial infarction.

Acute mesenteric arterial occlusion and the consequent ischemic necrosis of the gut are most commonly caused by thrombosis of advanced arteriosclerotic disease affecting at least two of the major visceral branches of the aorta, with the lesion usually affecting the most proximal segment of both the celiac and superior mesenteric arteries near their origins from the aorta.

Nonocclusive mesenteric ischemia syndrome is characterized by severe mesenteric malperfusion without apparent organic occlusion in the major splanchnic arterial branches (27). It is most commonly seen in elderly patients with congestive heart failure who frequently are being treated with digitalis. Other precipitating factors are shock, hypoxia, hemoconcentration, or a recent myocardial infarction. Occasionally, however, a precipitating event is not identifiable (33,34). Approximately 50% of patients have angiographic findings considered to be specific for the syndrome; these include a narrowed and irregular superior mesenteric artery, spasm of the mesenteric branch arcades, and impaired filling of intramural vessels (34,35).

Acute mesenteric venous thrombosis occurs much less frequently than arterial occlusion, accounting for much less than 10% of patients with intestinal ischemia (36). The thrombotic process involves the superior mesenteric vein in 95% of patients with this condition. It is caused by (or is associated with) various disorders predisposing to stasis in the mesenteric venous bed, including congestive heart failure, portal hypertension, abdominal neoplasm, intraabdominal inflammation, abdominal surgery or trauma, and hypercoagulable states such as polycythemia vera or deficiencies in protein C, S, or antithrombin III (36).

Pathophysiology. The extent, severity, and possible reversibility of intestinal ischemic processes depend on the rapidity with which the occlusion occurs and, to a lesser extent, on the anatomic characteristics of particular vessels. If occlusion of a large vessel occurs gradually, adequate collateral circulation may develop, so ischemia might be minimized or prevented if the large vessel becomes completely blocked. Thus, chronic arterial occlusive diseases ordinarily do not cause symptoms or signs of ischemia unless two or more major vessels are affected because of the large number of collateral channels that interconnect the major arterial trunks. In contrast, occlusion of a vessel that occurs abruptly or over a period of time too brief to allow the development of adequate collateral circulation is likely to result in ischemic necrosis. A classic example of this is embolization to the superior mesenteric artery in an individual with atrial fibrillation but normal mesenteric arteries (28).

With acute visceral ischemia, ultrastructural changes are evident in the absorptive cells within 5 minutes after occlusion of the mesenteric artery, after which the epithelium becomes detached from the basement membrane, especially at the villus tips, and subepithelial blebs form (28,37). Within 30 to 60 minutes the upper portion of the villi is denuded of epithelium and the mucosa undergoes necrosis and alteration with the appearance of a variable inflammatory infiltrate, probably in response to both tissue necrosis and secondary bacterial invasion (28). Among the phenomena that characterize acute ischemic intestinal necrosis is an increase in capillary permeability followed by loss of capillary integrity, as reflected by submucosal gut edema and hemorrhage (38). Later, the exudation of protein-rich fluid and frank blood into the lumen of the bowel reflects extensive loss of vascular epithelial integrity. Eventually even the relatively resistant muscular layers become necrotic and bowel perforation occurs, usually with consequent development of peritonitis. In those ischemic episodes that do not perforate or require immediate resection, the resolution of the acute inflammatory reaction is followed by development of granulation tissue, fibrosis, and finally the scar and stricture formation that frequently characterizes this process.

Symptoms and Signs. Acute mesenteric occlusion with consequent infarction of the small intestine produces severe, poorly localized abdominal pain that initially can be colicky in nature and periumbilical in location. Early in the clinical presentation the patient's pain often appears to be out of proportion to physical findings or laboratory studies. Generally, this is accompanied by gastrointestinal hyperperistalsis characterized by vomiting and by the passage of loose nonbloody stools.

Development of peritonitis and specific localized pain and tenderness occurs only after transmural gut infarction and perforation has occurred. On the other hand, patients who suffer acute mesenteric artery thrombosis on the basis of prior atherosclerotic stenosis present with steady, aching midabdominal pain with early superimposed spasm or colic, the bowel's initial response to ischemia. Again, peritonitis is a late sign, following infarction, perforation, and peritoneal soiling, at which time the patient commonly manifests symptoms and signs of sepsis including tachycardia, hypotension, fever, acidosis, and marked leukocytosis, often in excess of 30,000 per µL. Other physical signs include severe generalized tenderness to direct palpation, rebound tenderness, and abdominal muscle spasm with rigidity and other signs of peritonitis (see Diseases of the Peritoneum, Mesentery, and Diaphragm, later in this chapter). At this point, severe and unrelenting abdominal pain persists, even if massive doses of narcotic analgesic agents are administered.

Chronic Intestinal Ischemic Syndromes

In contrast to the frequently occurring acute intestinal ischemic syndromes, chronic or, more precisely, recurrent acute ischemia is uncommon and is represented by intestinal angina and celiac compression syndrome.

Etiology and Pathophysiology. Intestinal angina is the symptom complex associated with gradual and progressive mesenteric arterial occlusive disease, usually atherosclerotic, that affects at least two of the three major splanchnic vessels. While nutrients are undergoing digestion and absorption in the small intestine, sufficient vascular perfusion is required to permit increased intestinal blood flow and oxygen consumption; a partially or completely occluded mesenteric arterial system cannot provide ample blood flow and a relative ischemia results. Consequently, the patient experiences postprandial periods of pain that can be considered analogous to those of angina pectoris in the heart.

The *celiac band compression syndrome* is characterized by recurrent abdominal pain associated with a narrowing of the celiac axis alone (39). This disorder is an apparent exception to the general rule that at least two major visceral arteries must be narrowed before symptoms occur. Among patients who have been surgically explored, the celiac artery has been found to be compressed by the median arcuate ligament of the diaphragm or by neurofibrous tissue surrounding the celiac plexus (28).

Symptoms and Signs. Intestinal angina is characterized by stereotypic bouts of intermittent dull or cramping midabdominal pain that characteristically occurs from 15 to 30 minutes after a meal. The relationship to meals, presumably the time when bowel blood supply cannot meet metabolic demands, leads to the descriptive term *intestinal angina*. Rarely, it is colicky in nature. Duration of the pain is usually less than 1 hour in the early part of the natural history of this syndrome, but as the underlying superior mesenteric artery stenosis increases, the pain becomes more severe and longer in duration until it becomes continuous. Other symptoms include weight loss (which may be substantial) and occasionally diarrhea and signs of malabsorption.

Celiac band compression syndrome, found most frequently among women younger than those expected to have significant atherosclerotic disease, is characterized by epigastric pain of variable frequency and duration. The pain might or might not be related to meals and is infrequently associated with nausea and vomiting (28). The only physical finding noted with regularity is an epigastric bruit that does not radiate to the lower abdomen.

In chronic visceral ischemic syndromes, the patient is often initially unaware of the relationship of pain to eating, as well as the fact that weight loss and diminished oral intake have been subconsciously accepted to avoid recurrent abdominal pain.

Management of Intestinal Ischemic Syndromes

Diagnosis. The major predictive factors for developing acute mesenteric ischemia relate to a prior history of rheumatic heart disease or myocardial infarction, intracardiac thrombus, which ultimately leads to mesenteric embolus, or a picture of widespread premature atherosclerosis, as with acute mesenteric artery thrombosis. The clinical picture of patients with nonorganic mesenteric ischemia has been noted previously. Patients with mesenteric embolization sometimes relate a history of prior embolization and might have been on anticoagulant therapy in the past. Prior cardiac disease is noted in 90% to 95% of patients with emboli, most commonly in regard to a past history of myocardial infarction with akinetic or dyskinetic left ventricular segments (40).

The crucial diagnostic procedures in all circumstances, building on a heightened sense of clinical suspicion, are the performance of contrast aortography and selective mesenteric arteriography; these can provide the bases for both diagnosis and possible treatment. Duplex sonography has been a highly accurate screening maneuver, especially to examine the origins of the mesenteric vessels in a noninvasive fashion (41). Other studies, including plain roentgenography, radioisotope or malabsorption studies, and other imaging techniques have yet to prove their value in the diagnosis of the mesenteric ischemic syndromes. It is widely believed that polymorphonuclear leukocytosis, metabolic acidosis, hyperkalemia, and hyperamylasemia can frequently be demonstrated in those with mesenteric ischemic syndromes; they are actually the consequences of bowel infarction and are thus the late manifestations of a clinical situation that, by the time they appear, often represent a clinically unsalvageable situation.

Flush aortography with selective arteriographic injections into the orifices of the celiac axis and the origins of the superior and inferior mesenteric arteries is frequently diagnostic for the various conditions that lead to acute and chronic mesenteric ischemia. Superior mesenteric artery embolization often shows a characteristic *meniscus sign* on arteriography (i.e., dye outlines the crescentic *tail* of the embolus), usually 3 to 10 cm from the origin of the superior mesenteric artery. Because acute superior mesenteric artery thrombosis generally occurs at the site of an ostial atherosclerotic stenosis, in such cases only a stub of artery can be seen. This is best (and sometimes only) seen on lateral aortography.

Aortography can also demonstrate spasm of the large splanchnic arteries, a sign seen most notably with nonocclusive organic mesenteric ischemia. Contrast studies are also useful for demonstrating the celiac band syndrome, in which the crura of the diaphragm are felt to impinge on the celiac axis or superior mesenteric artery (39). Pressure studies to define gradients across the stenosis, before and after the administration of rapid-acting vasodilating agents such as papaverine, can be of further diagnostic use.

Certain features of acute mesenteric ischemia can be confused with those of perforated peptic ulcer, appendicitis, ruptured aneurysm, or occasionally, myocardial infarction. When the condition is chronic it can mimic such conditions as pancreatic or gastric cancer or chronic relapsing pancreatitis; occasionally, the profound weight loss from dietary changes that occurs with chronic mesenteric ischemia can be confused with that of depression or neurosis, and unavailing treatment with pain medications, antidepressants, and tranquilizers may be continued for a substantial period of time.

Treatment. Management of acute and chronic mesenteric ischemic conditions can sometimes be initiated at the time of diagnostic arteriography. The advent of techniques for the administration of low-dose fibrinolytic agents (e.g., streptokinase, urokinase, and specific tissue plasminogen activators) suggests that, in selected cases of intestinal ischemia not accompanied by impending tissue infarction, the embolic or thrombotic occlusion might be relieved nonsurgically. In the case of mesenteric arterial thrombosis, as has been demonstrated in the peripheral arteries, lysis of an acute thrombosis can often reveal a high-grade atherosclerotic stenosis that may then be treatable by percutaneous transluminal angioplasty or stenting (42). The angiographic catheter is probably most effective in treating the syndrome of nonorganic mesenteric ischemia; once relatively normal proximal mesenteric arteries with peripheral splanchnic vasoconstriction have been demonstrated, the administration of intraarterial vasodilators such as papaverine has been shown (27,35) to be a useful therapeutic maneuver in this otherwise lethal condition.

Unfortunately, in many cases of both acute and chronic mesenteric ischemia, the onset of severe abdominal symptoms heralds gut infarction, perforation, and peritonitis; therefore, the diagnosis of significant mesenteric ischemia generally requires laparotomy. Superior mesenteric artery embolus frequently can be treated by a relatively straightforward embolectomy. Generally, the patient should already have been heparinized by the time of operation, and anticoagulation should be continued with heparin and then with warfarin indefinitely. Resection of clearly nonviable bowel is necessary; the presence of marginally viable intestine left *in situ* mandates a formal second-look exploration in 12 to 24 hours (43). Techniques for assessing tissue viability, such as intraoperative Doppler, fluorescein clearance, and tissue oximetry, have been used, but a consensus has not been reached concerning their accuracy. Some have advocated the use of postresection vasodilators administered through a percutaneous catheter in an attempt to salvage such marginal tissue (44).

In the case of atherosclerotic superior mesenteric artery stenosis or thrombosis, or both, general management usually involves bypass grafting from the aorta to the superior mesenteric artery just distal to the site of occlusion (45). Thromboendarterectomy has been used, but can require a more extensive dissection to expose the most proximal part of the superior mesenteric artery (46). As with mesenteric artery embolus, bowel resection might be required, and a second-look operation is prudent.

The celiac band syndrome, when identified by careful lateral aortography and pressure gradient measurements, is approached successfully by a combined complete exposure of the celiac axis, including lysis of the diaphragmatic crura at this level, or bypass grafting using a saphenous vein or prosthetic graft as previously described. Some have argued that the extensive dissection in this area effectively performs a splanchnic neurectomy, thereby resulting in the pain relief noted in most patients so treated.

Outcome. Untreated, acute mesenteric infarction leads to death in almost all circumstances. For acute mesenteric ischemia the mortality is still excessive, primarily because the diagnosis is often delayed and the aggressive therapy required for intestinal salvage frequently cannot be effectively carried out in these desperately ill patients. Nevertheless, some patients can be treated successfully, and their follow-up requires consideration of the basic underlying pathophysiology. Patients who have suffered a mesenteric artery embolus must be indefinitely anticoagulated against the possibility of future emboli; myocardial revascularization and resection of left ventricular aneurysm might be useful to diminish the incidence of recurrent cardiogenic emboli.

In patients who have suffered mesenteric artery thrombosis superimposed on an atherosclerotic stenosis, the systemic nature of this disease, and these patients' markedly elevated risk for coronary and cerebrovascular ischemic events, must be emphasized. Patients who undergo transcatheter stenting or elective surgical reconstruction for atherosclerotic mesenteric vessel stenosis, or who have operative repair of the celiac band syndrome often enjoy a gratifying relief of their chronic pain and weight loss following resumption of normal food intake and body weight.

Mesenteric Vasculitis

A number of systemic collagen diseases associated with vasculitis can cause abdominal pain. These disorders have several common denominators that are of interest to physicians and surgeons. They can involve multiple intraabdominal organs, often producing pain; they can begin suddenly, occasionally evoking a crisis with severe abdominal pain that can mimic that of a surgical lesion; and they may be accompanied by a serositis that can affect the peritoneum (47). These conditions include polyarteritis nodosa, lupus erythematosus, Henoch-Schönlein purpura, dermatomyositis, polyarteritis, and rheumatoid vasculitis.

Symptoms and Signs

Polyarteritis Nodosa. Abdominal pain and other gastrointestinal symptoms have been reported in up to 65% of patients with polyarteritis nodosa (48). This condition occurs most commonly in young men and is characterized by a necrotizing vasculitis of the muscular arteries that can affect not only the gastrointestinal tract but most other organs as well. This condition is particularly confusing because some patients experience such severe abdominal pain, but no lesion can be found at surgery to explain the pain. Clinically apparent ischemic disease of the bowel is more frequent and can range from massive infarction to segmental ischemia with ulceration, hemorrhage, or perforation (28). Although clinically significant liver disease is uncommon in this condition, hepatic artery thrombosis caused by polyarteritis is the leading cause of otherwise unexplained cases of infarction of the liver.

Systemic Lupus Erythematosus. Systemic lupus erythematosus (SLE) involves the gastrointestinal tract in as many as 60% of patients (28). Nonspecific

gastrointestinal symptoms such as anorexia, nausea, mild pain, and diarrhea occur in approximately 30% of patients. Vasculitis of the intestine is the most dangerous manifestation of SLE because it causes acute or subacute cramping pain, vomiting, and diarrhea and results in intestinal perforation and death in almost 50% of affected patients (49). Another gastrointestinal manifestation of SLE is a pseudoobstruction picture in which patients present with acute cramping abdominal pain, and radiographs show dilated loops of small bowel, which might be edematous. Surgery should be avoided unless true obstruction is present. Acute pancreatitis occurs with SLE and can be severe; it can result from glucocorticoid therapy or from active SLE itself (28). Abdominal pain can also be caused by serositis.

Henoch-Schönlein Disease. Henoch-Schönlein disease, also referred to as *anaphylactoid purpura*, is a disorder of unknown cause associated with small vessel vasculitis. Typically it is associated with a clinical triad of palpable purpura, arthritis, and abdominal pain (28). Although the disease is usually seen in children and young adults, individuals of any age can be affected. Gastrointestinal involvement, which is seen in approximately 70% of pediatric patients, is characterized by colicky abdominal pain generally associated with nausea, vomiting, diarrhea, or constipation; these are frequently accompanied by passage of blood and mucus rectally. The symptoms and signs reflect localized or segmental ischemia and ulceration. Intussusception, gross infarction, and perforation rarely occur. Most patients recover completely and some do not require therapy.

Dermatomyositis. Dermatomyositis is important because of an increased incidence of associated gastrointestinal malignancy with this disorder (28). The malignancy can antedate or postdate the onset of myositis by up to 2 years; this is usually classified as group III dermatomyositis. Group IV dermatomyositis is associated with vasculitis in the skin, muscles, gastrointestinal tract, and other organs and can cause ischemic infarction of the gastrointestinal tract.

Diagnosis. The diagnosis of mesenteric vasculitis is greatly aided by systemic features of each of these conditions and less so by abdominal findings, which are nonspecific. One finding that differentiates vasculitis from chronic atherosclerotic mesenteric insufficiency is that these patients can have steatorrhea in the absence of pain (28). Radiographs demonstrate a mucosal ulceration or edema (*thumbprinting*) that can be indistinguishable from Crohn's disease either in appearance or location. Abdominal angiography is useful, especially in demonstrating aneurysms at the bifurcation of the medium-sized arteries, thereby suggesting the diagnosis of polyarteritis nodosa.

Treatment. The prognosis of untreated polyarteritis nodosa is extremely poor, with death often resulting from gastrointestinal or renal complication or other causes. Aggressive therapy using corticosteroids significantly increases the 5-year survival rate (49). A combination of prednisone, 1 mg per kg per day, and cyclophosphamide, 2 mg per day, during the first month of therapy, given thereafter every other day and eventually tapered after approximately 6 months, has been reported to result in a long-term remission rates of up to 90%, even following the discontinuation of therapy (48). Similar results have been obtained with this treatment in patients with Wegener's granulomatosis and other types of vasculitis that involve the upper and lower respiratory tracts.

No cure for SLE is known; complete remissions occur but are rare, so the patient and physician should plan to control acute severe flares and to develop maintenance therapies in which symptoms are suppressed to an acceptable level (49). The patient who is disabled because of pain and fatigue should be managed with nonsteroidal antiinflammatory drugs, including salicylates. Life- threatening and severe disabling manifestations of SLE should be treated with high doses of glucocorticoids (1 to 2 mg per kg per day).

Most patients with Henoch-Schönlein purpura recover completely, and some do not even require therapy. When corticosteroid therapy is required, it is usually administered as 1 mg per kg per day of prednisone and tapered according to the clinical response.

If corticosteroids are not sufficiently effective in providing good pain relief for all these conditions, they should be supplemented with appropriate doses of nonsteroidal antiinflammatory drugs alone or in combination with codeine or other mild narcotics to tide the patient over.

Many vasculitis patients pose a dilemma to surgeons who must make the decision of whether to carry out a surgical exploration for possible infarction or perforation. If clinical signs of an acute abdomen are present, laparotomy should be carried out: Laparoscopic exploration is less invasive but may be less complete. The clinical assessment is made more difficult because many patients with systemic vasculitis are already receiving corticosteroids, and these agents can mask important signs of a serious intraabdominal process.

DISEASES OF THE PERITONEUM, MESENTERY, AND DIAPHRAGM

Anatomically, the surface of the peritoneal membrane is 1.7 m^2 and is similar to the total body surface area, although the functional work surface of this membrane is substantially less (60%) because of changes in vascularity, membrane potential, and diffusion gradient. Both parietal and visceral peritoneum normally secrete small quantities of serous fluid. When exposed to insult, however, their porosity increases, with a rapid outpouring of fluid from both vascular and interstitial spaces (third space) that allows the sequestration of large amounts of fluid. This impaired diffusion also allows the reverse to occur (i.e., the rapid absorption of bacteria and microscopic debris that can lead to bacteremia). This exposes the perfused organs to two specific effects: (a) microscopic bacterial seeding of the offending organism, and (b) the functional organ response to the shower of bacteria and endotoxins. As the process progresses, the damaged membrane leaches fluid from the vascular compartment and provides a pathway for bacteria to reach the vascular tree.

Several intraperitoneal factors mitigate against the sequence of events being constant. Gravity helps to localize all peritoneal collections in dependent locations, consisting of the pelvis and flanks. Moreover, the greater omentum acts as an initial sealer of perforations, and the lymphatic system is important in removing bacteria and other particulate matter. Following peritoneal insult, fibrin deposition also tends to seal visceral leaks and wall off the contaminated region. This inflammatory response, which includes the exudation of lymphocytes, neutrophils, macrophages, and opsins, occurs rapidly so that intraperitoneal bacterial phagocytosis and destruction occur immediately following the initial insult. After this protective action, the fibrin can be removed from the peritoneal cavity through fibrinolysis by regeneration of mesothelial cells that demonstrate increased fibrinolytic activity, but this process is depressed in injured cells. This temporary suppression of fibrinolysis can provide time for fibroblasts to convert fibrins to fibrous adhesions. Normally, however, peritoneal injuries or defects heal without formation of fibrous adhesions unless other factors such as infection, ischemia, or foreign bodies are associated or superimposed.

Diseases of the Peritoneum

Table 69-1 lists the diseases of the peritoneum. The cardinal symptoms of peritoneal disease are abdominal pain and ascites, with fever, distension, nausea, vomiting, and altered bowel habits varying in their occurrence. Direct tenderness, percussion tenderness, and involuntary spasm of the abdominal musculature are the major signs of irritation of the parietal peritoneum. These signs and symptoms can be minimal or absent in the elderly or debilitated patients and vary depending on the location, cause, and acuteness of the underlying process. In addition to a complete history and physical examination, diagnosis of diseases of the peritoneum is helped by plain radiography, barium contrast studies, peritoneography, ultrasonography, CT scanning, and gallium 67 scanning. In addition, all patients with prior ascites and any suspicion of peritoneal disease should undergo paracentesis to permit analysis of the ascitic fluid. Percutaneous peritoneal biopsy can also yield a tissue diagnosis of the cause of the peritoneal disease, but its use is limited to patients with ascites. Peritoneoscopy (laparoscopy) is an excellent diagnostic tool for visualization and direct biopsy of observed lesions of the peritoneum.

Acute Bacterial or Chemical Peritonitis

Bacterial peritonitis most commonly results from perforation of an abdominal viscus, such as perforated ulcer or diverticulum, ruptured appendix, and during abdominal trauma (50,51). Chemical peritonitis is caused by perforation of an ulcer with liberation of sterile acid, enzymatically active pancreatic juice, or other chemicals.

Symptoms and Signs. Regardless of cause, abdominal pain, nausea, vomiting, tachycardia, and fever are the cardinal signs of bacterial peritonitis. The severity of these symptoms and signs is related to the extent of the peritoneal contamination. If the infection is localized, symptoms and signs can be mild, whereas with generalized peritonitis, symptoms and signs are severe; as a significant third-space deficit develops, the blood pressure eventually falls and the pulse becomes weak, rapid, and thready. The fluid volume contained in the abdomen in a case of severe, generalized peritonitis approximates the fluid losses seen with 50% body surface red burns (52). Because motion is painful, patients usually lie still, preferably on their side with their hips slightly flexed, to relax their abdominal muscles.

Early in the course of the disease the abdomen is scaphoid and contracted, particularly across the epigastrium, an appearance produced by spasm of the rectus abdominis muscle in response to motion of the diaphragm. Abdominal distension develops later. Diffuse tenderness is present, with percussion tenderness referred to the point of pressure, and abdominal muscle spasm is felt, the degree of which depends on the site of the peritonitis. In patients in whom the anterior parietal peritoneum is inflamed, the abdominal musculature is often completely unyielding, whereas rigidity is not a prominent sign if the posterior peritoneum is primarily

involved, as seen with retroperitoneal or pelvic abscess. Ileus usually develops rapidly.

Diagnosis. Laboratory findings are not specific. Leukocytosis is present and can be marked. Hemoconcentration results from loss of fluid into the peritoneal cavity, electrolyte concentrations vary, and metabolic acidosis and respiratory alkalosis are often seen. Plain abdominal films show distension of the small and large intestines and demonstrate air–fluid levels. On upright films air may be seen beneath the diaphragm if a viscus is perforated. If the patient cannot stand for upright films, free air can be seen over the liver on a left lateral decubitus film.

Complications of peritonitis can be local, consisting of wound infection, intraperitoneal abscess, and fistula formation, or systemic, consisting of septicemia, shock, and organ dysfunction.

Treatment. Patients with mild cases of diverticulitis in whom the process is well localized should be managed nonoperatively (50,51,53). Treatment should include nasogastric suction, antibiotics, pain control with analgesics or other appropriate methods, administration of fluids, and monitoring of blood volume, acid–base, and electrolyte status, as well as of cardiopulmonary and renal function. Percutaneous drainage of a localized abscess should be given serious consideration.

In patients with generalized, severe peritonitis in whom surgery is indicated, ample preoperative preparation is necessary to restore fluid balance and to stabilize circulatory and pulmonary function. In addition to nasogastric suction, which reduces distension and thus helps pulmonary function, adequate volumes of electrolyte solutions are administered to correct the hypovolemia. Complete blood and other laboratory studies should be carried out.

Because these patients have severe abdominal pain they may be managed with epidural opioid analgesia during the preparation for surgery. As soon as the blood volume has been restored, opioids can be supplemented with low concentrations of local anesthetic to provide more effective relief and also to eliminate the intense vasoconstriction of the splanchnic region that is frequently found in such patients. Moreover, epidural analgesia may decrease the ileus and degree of muscle spasm that invariably decrease chest wall compliance and thus produce hypoxemia. In most patients, the ideal anesthesia is a combined segmental epidural block with tracheal intubation carried out under topical anesthesia, followed by light inhalation or intravenous analgesics and sedatives.

Antibiotic therapy is essential and should be initiated early with an antimicrobial drug or combination possessing activity against a polymicrobial flora consisting of aerobic, facultative, and anaerobic species (50,51). Twenty percent to 30% of patients have bacteremia, usually caused by *Escherichia coli*, *Bacteroides fragilis*, or both.

Other Types of Infectious Peritonitis

Although peritonitis is an unusual form of tuberculosis, it constitutes an important disease of the peritoneum. Its insidious nature and the clinical circumstances in which it occurs often cause it to be mistaken for neoplastic disease or ascites caused by cirrhosis (53,54).

The most common complaints are fever, anorexia, weakness, malaise, and weight loss. Abdominal pain is reported in only 50% of patients, and this is usually described as a vague, dull, diffuse discomfort. Abdominal tenderness is usually diffuse and present in 65% of patients.

With the advent of antituberculosis agents, the mortality of tuberculous peritonitis has been reduced from 60% to almost 0. Symptoms should begin to improve within 1 to 2 weeks of the onset of therapy, and fever should resolve within 4 weeks. The pain is managed with nonopioid systemic analgesics.

Peritoneal inflammation caused by fungi and parasites is uncommon, and pain is not a major symptom; therefore, it is not considered further here.

Familial Paroxysmal Polyserositis (XXII-1)

Etiology and Pathophysiology. Familial paroxysmal polyserositis (FPP), also called familial Mediterranean fever, is a disease characterized by recurring episodes of acute self-limited serositis, especially peritonitis. It is an inherited disease transmitted as an autosomal recessive trait that occurs predominantly in Mediterranean peoples, with Sephardic Jews accounting for 50% of cases, Armenians 22%, Arabs 11%, Turks 7%, and other ethnic groups the remaining 10% (55). The onset of the disease is usually within the first two decades of life, but 20% of patients have their first episode after the age of 20 and 4% after the age of 30. About 60% of patients are boys or men.

Symptoms and Signs. Disease usually appears suddenly with attacks of serositis that include peritonitis in 55% of patients, arthritis in about 25%, and pleuritis in 5%. During the course of FPP 95% of patients eventually develop peritonitis; this is the sole manifestation in 30% (55). The attack consists of a sudden onset of fever, usually 101° to 103°F (38.3° to 39.4°C), with localized or diffuse abdominal pain, exquisite direct abdominal tenderness with marked rebound tenderness, and leukocytosis in almost 90% of patients. The plain film of the abdomen shows air–fluid levels. After 6 to 12 hours these signs and symptoms recede and the patient is usually well within 24 to 48 hours. The attacks occur at irregular and unpredictable intervals and the patient is entirely well between them. Except for the rapid resolution and recurrent nature of the disease, FPP presents all the characteristics of an acute surgical abdomen.

Treatment and Prognosis. The therapy that has proven to be highly effective consists of the administration of colchicine in doses of 0.6 mg twice or three times a day (55,56). Studies have shown that this decreases both the severity and frequency of attacks, and long-term studies report continuous suppression of attacks with little evidence of adverse effects (56).

Prognosis of FPP is excellent, and many patients have been followed for years with persistent good general health despite hundreds of attacks (55). Attacks can increase in frequency with age, perhaps with occasional remissions or periods in which the disease is quite intractable.

Neoplasm of the Peritoneum

Primary Mesothelioma

Primary mesotheliomas are tumors arising from the epithelial and mesenchymal elements of the mesothelium. Approximately 25% of these tumors involve the peritoneum, 65% involve the pleura, and 10% are pericardial (57).

Etiology and Pathology. Asbestos is the only substance that has been shown to have an epidemiologic relationship to mesothelioma, and the apparent increased incidence since the 1950s can be related to expansion of the asbestos industry (57). In addition to historic evidence of asbestos exposure, 50% of patients with mesothelioma have pathologic evidence of pulmonary asbestosis, including pulmonary fibrosis, pleural hyaline plaques, and asbestos bodies in the lungs. Because at least 30% of patients with mesothelioma have no history of asbestos exposure, however, other factors also play a role.

Mesotheliomas, especially peritoneal ones, are more common in male subjects, possibly reflecting occupational factors. The highest incidence is in the sixth decade, but the condition has been reported in young children (57).

Symptoms and Signs. Patients presenting with peritoneal primary tumors usually complain first of abdominal pain and abdominal mass or increased abdominal girth, along with anorexia, nausea, vomiting, constipation, and weight loss (57). Signs of asbestosis are evident in chest radiographs in 50% of patients, and early pleural mesothelioma can be apparent, with chest pain, dyspnea, or cough.

Diagnosis and Treatment. Other than an elevated sedimentation rate, the blood count and blood chemistries are normal. Radiography is not useful. Ultrasonography, CT, and magnetic resonance scanning can demonstrate sheetlike masses and ascites. Paracentesis reveals an exudate that can be hemorrhagic. Peritoneal cytologic studies and biopsy and peritoneoscopy can suggest a diagnosis, but laparoscopy is usually necessary to provide adequate biopsy samples for definitive diagnosis and to rule out a primary neoplasm. The prognosis of mesothelioma is poor, and most patients survive only 1 year after diagnosis (57). Surgical resection and radiation therapy are not curative.

Secondary Carcinomatosis

Peritoneal involvement by spread from a primary neoplasm is one of the most common causes of peritoneal disease. Pathologic studies of selected open peritoneal biopsy specimens in a large general hospital showed that approximately 65% were neoplastic and, of these, 75% were metastatic adenocarcinomas (58). Sarcomas, carcinoids, teratomas, and nervous tissue tumors are rare. Malignancies of lymphoid or myeloid tissue can also infiltrate the peritoneum. The most common lesions involved are malignant lymphoma, Hodgkin's lymphoma, Hodgkin's disease, and myeloid metaplasia (59).

Symptoms and Signs. Patients with peritoneal carcinomatosis present with ascites, diffuse abdominal pain, weight loss, and, less frequently, nausea and vomiting. The pain can be produced by various interactions between the tumor and intraabdominal organs. Barium contrast studies can show nodular indentation of the intestine or angulated fixed or displaced intestinal loops, especially if attention is paid to major areas of intraperitoneal seeding. These areas include the pouch of Douglas at the rectosigmoid, the right lower quadrant at the lower end of the small bowel, the left lower quadrant along the superior border of the sigmoid mesocolon and colon, and the right paracolic gutter lateral to the cecum and ascending colon (58).

Diagnosis. In addition to barium contrast studies, other diagnostic procedures include paracentesis, ultrasonography, and CT scanning. The diagnosis is made most directly by cytology, peritoneal biopsy, laparoscopy, or abdominal exploration.

Treatment. Once the neoplasm has spread to the peritoneum, the prognosis is poor. Paracentesis is useful for removal of a large volume of fluid and is tolerated without hemodynamic problems. Cytotoxic agents, radioisotopes, and sclerosing agents have been used with varying success. Peritoneovenous shunting has become more widely used as a method of palliation for malignant ascites. Surgery is not indicated except in patients with intestinal obstruction that is not responsive to conservative measures.

Diseases of the Mesentery and Omentum

Patients with mesenteric disease usually present with nonspecific symptoms such as abdominal pain, abdominal distension, or intestinal obstruction. The most frequent physical finding is a mass that might be mobile. Associated lymphatic obstruction can cause steatorrhea, chylous ascites, or protein-losing enteropathy, with hypoalbuminemia and edema. Of the various pathologic processes, only mesenteric inflammatory disease and mesenteric and omental tumors produce abdominal pain (59).

Mesenteric inflammatory disease is characterized by recurrent episodes of cramping abdominal pain, either localized or generalized, and weight loss, nausea, vomiting, and low-grade fever. Corticosteroids have been claimed as useful therapy.

Mesenteric tumors are rare and can arise from any of the cellular elements of the mesentery. Metastatic tumors of the mesentery are more common than primary mesenteric tumors and are usually the result of an enlarged lymphomatous or carcinomatous lymph node. In contrast to mesenteric tumors, omental tumors are derived from muscle in 60% of patients and include leiomyomas, leiomyosarcomas, and hemangiopericytomas (58). These are characterized by abdominal pain, abdominal mass, and weight loss.

Torsion of the omentum is an acute condition that mimics appendicitis or cholecystitis and is characterized by abdominal pain in the right lower (80% of patients) or the right upper quadrant (10%). Tenderness, guarding, and ileus are usually present, and nausea, vomiting, abdominal mass, and leukocytosis are present in 50% of patients. Surgical excision of the gangrenous omentum is necessary.

Diseases of the Diaphragm (XVII-8)

Diseases of the diaphragm that can cause pain are diaphragmatic hernias, rupture, and tumors.

Herniation (XIX-2)

Diaphragmatic hernias are caused by congenital abnormalities in the formation of the diaphragm (60). Most commonly the left pleural and peritoneal membrane fails to fuse with the septum transversum, causing a left posterolateral defect without a hernia sac. The fusion may be complete, but a failure of muscularization posterolaterally is present. A hernia with a sac is formed, called the *Bochdalek's hernia*. Approximately 25% of patients with Bochdalek's hernia are asymptomatic, but 50% have vague intermittent abdominal pain and 25% have chest pain, cardiovascular symptoms, and dyspnea (61). Incarceration of the intestine leads to acute sharp retrosternal pain that radiates to the left upper quadrant or back, along with the typical symptoms of intestinal obstruction.

The diagnosis can usually be made on the lateral chest film, which reveals a blunted cardiophrenic angle, a small effusion, and a gas-filled intestinal loop. Surgery is always indicated in patients with incarceration or obstruction because of the danger of strangulation (60).

Rupture

Blunt injury to the abdomen can cause diaphragmatic rupture that is said to occur in about 5% of all patients undergoing surgery for trauma (62). Because the early clinical course can be dominated by signs of other injuries, signs of visceral herniation are often delayed. Patients can present many years later with postprandial fullness, chest pain, nausea, vomiting, cramps, dyspnea, or obvious bowel obstruction and strangulation, with severe epigastric and chest pain (62).

Diaphragmatic rupture should be suspected in any patient who has vague abdominal symptoms and a history of blunt abdominal trauma. Because of the high frequency of later visceral herniation, diaphragmatic laceration should be repaired surgically.

Tumors and Cysts

Diaphragmatic neoplasms usually cause pleuritic chest pain simulating that of intraabdominal disease, with the pain referred primarily to the epigastrium. Chest radiographs reveal irregularity of the diaphragm or a large mass that abuts the diaphragm.

Diaphragmatic cysts can also cause upper abdominal pain, located primarily in the epigastrium. When located on the right side, however, they suggest possible hepatic or subphrenic abnormalities. The cysts are usually bronchogenic, mesothelial, or fibrous. They can be acquired or congenital. If pain is severe and persistent, surgical removal is necessary.

OTHER INTRAABDOMINAL DISEASES

Intraabdominal Abscesses

The three types of intraabdominal abscesses are intraperitoneal, retroperitoneal, and visceral and occur with about equal frequency. Intraperitoneal abscesses (subdiaphragmatic, midabdominal, or pelvic) (50,51) are localized collections of pus that can occur consequent to either generalized peritonitis or a more localized intraabdominal disease process or injury. In the former case the normal barriers that limit the inflammatory process are inadequate and the abscess can occur at some distance from the original source of contamination. In the latter instance the spread of peritonitis is limited by contiguous viscera, omentum, and peritoneum, and the abscess develops closer to the source of contamination. Intraabdominal abscess can be a postoperative complication of the surgical treatment of peritonitis. Retroperitoneal abscesses can be located in the anterior or posterior part of the space. Visceral abscesses can involve the liver, pancreas, spleen, kidney, and gallbladder. Because many of these are discussed elsewhere in this section, the discussion here is limited to subdiaphragmatic, midabdominal, anterior retroperitoneal, and splenic abscesses.

Most intraabdominal abscesses develop from infecting organisms that are a complex mixture of anaerobic, facultative, and aerobic bacteria, which are part of the normal bowel flora. The most important isolates from these abscesses are facultative gram-negative rods, such as *E. coli* and *Klebsiella* spp., and anaerobes, especially *Bacteroides fragilis* (50,51). Antimicrobial therapy requires agents effective against these organisms.

Subdiaphragmatic Abscess (XIX-1)

The subdiaphragmatic space, arbitrarily defined as lying below the diaphragm and above the transverse colon, consists of four subdivisions. On the right side are the suprahepatic and subhepatic spaces, while on the left side the subhepatic and suprahepatic spaces freely communicate and constitute a single combined subphrenic space. The other left-sided space behind the stomach and anterior to the pancreas is the lesser sac. A subhepatic abscess is found on either side of the falciform ligament, between the liver and the transverse colon. Some clues to localization are afforded by a knowledge of the primary disease process. A right-sided abscess is more frequent after appendicitis, whereas perforated duodenal ulcer causes right anterior subhepatic abscess and pancreatic disease is more likely to result in a lesser sac abscess.

Symptoms and Signs. The clinical manifestations of subphrenic abscess usually begin within 1 to 6 weeks following surgery, but occasionally do not appear for several months (50,51). Fever is nearly always present and can be the only evidence of abscess. Nonspecific constitutional symptoms such as anorexia and weight loss are less common. The most frequent findings relate to the thorax and abdomen and include nonproductive cough, chest pain, dyspnea, and shoulder pain caused by the irritation of the diaphragmatic pleura. Rales, rhonchi, or a friction rub can be audible. Dullness to percussion and decreased breath sounds might be present when basilar atelectasis, pneumonia, or pleural effusion occurs. Pain, the most common abdominal complaint, may be poorly localized. Abdominal distension and hypoactive bowel sounds may occur. Physical findings are subtle or absent due to the difficulty of examining the abdominal cavity above the costal margin. A mass, wound drainage, or sinus tract of a previous abdominal incision site is sometimes present. Subhepatic abscess usually presents with symptoms referable to the abdomen and is less likely to cause any pleural or diaphragmatic abnormality. Abdominal pain and tenderness are usually present, and a mass is occasionally found.

Diagnosis. Leukocytosis occurs in most patients with subphrenic abscess, and blood cultures are occasionally positive. Chest radiographs usually demonstrate ipsilateral pleural effusion, an elevated or immobile hemidiaphragm, pneumonitis, and atelectasis. Plain abdominal films can reveal extraintestinal gas in the abscess, displacement of adjacent organs, or a soft tissue density representing the abscess. Ultrasonography is especially useful in right-sided subphrenic abscess. A left-sided subphrenic area is more difficult to examine, however, because of the gas-filled stomach, splenic flexure, and aerated lung and ribs, and also because the spleen varies in size and shape and can produce a few echoes that resemble those of an abscess. CT scanning generally provides the most accurate information about the presence and extent of abscess into these areas.

Treatment. Treatment of these abscesses involves surgical drainage, either by open operation or by percutaneous catheter drainage. The drain remains in place until the abscess cavity is obliterated, usually 2 to 3 weeks or longer. Antibiotics effective against both aerobic, facultative, and anaerobic organisms are a good adjunct but are no substitute for drainage. Adequate nutrition is critical during the often-prolonged hospital course.

Midabdominal Abscess

A midabdominal abscess can form in the peritoneal cavity anywhere between the transverse colon and pelvis. It is frequent in the paracolic gutters but can be located between the loops of the small bowel and mesentery. They are referred to as right lower quadrant, left lower quadrant, or interloop abscesses according to their location.

Etiology, Symptoms, and Signs

Right Lower Quadrant Abscess. Abscess in the right lower quadrant develops most commonly as a complication of acute appendicitis and less frequently from colonic diverticulitis, regional enteritis, or perforated duodenal ulcers, with drainage down the right paracolic gutter. The clinical manifestations include right lower quadrant pain and tenderness and a mass that develops following symptoms suggesting those of acute appendicitis. The mass may be associated with partial or complete small bowel obstruction.

Left Lower Quadrant Abscess. Left lower quadrant abscess usually develops from perforation of a diverticulum in the descending or sigmoid colon and less commonly from a perforated colonic carcinoma. The symptoms are those of acute diverticulitis and include left lower quadrant pain, tenderness, anorexia, and nausea followed by fever, leukocytosis, and development of a palpable mass.

Interloop Abscess. Interloop abscess comprises loculations of pus between the folded surfaces of the small and large intestines and their mesenteries. It is usually a complication of bowel perforation, anastomotic disruption, or Crohn's disease. Clinical manifestations are usually subtle and consist of fever, leukocytosis, and abdominal pain and tenderness. Signs of paralytic ileus that may be difficult to distinguish from obstruction or palpable mass can develop. Plain abdominal films occasionally suggest the diagnosis by the presence of bowel wall edema, separation of bowel loops, localized ileus, and air–fluid levels on upright films.

Treatment. The therapy of midabdominal abscess includes surgical drainage and antibiotics. CT scan often shows the abscess, but if ileus prevents opacification of all bowel loops with contrast, it may be difficult to distinguish an abscess from a fluid-filled bowel loop. Occasionally, in a gravely ill patient with no localizing findings, abdominal exploration might be necessary to find and drain the abscess. At operation the abdomen must be explored thoroughly, because these abscesses are frequently multiple. If the clinical picture does not improve promptly, reexploration might be necessary to find missed or new abscesses.

Anterior Retroperitoneal Abscess

Etiology, Symptoms, and Signs. Abscess in the anterior retroperitoneal space is a complication of acute appendicitis, colonic perforation from diverticulitis or tumor, gastric or duodenal perforation, regional enteritis, or pancreatitis. The major symptoms are abdominal or flank pain, fever, nausea and vomiting, and pain in the hip, thigh, or knee from psoas muscle involvement. Physical examination may reveal a palpable mass in addition to the abdominal or flank tenderness. Extension of the hip may aggravate the pain.

Diagnosis and Treatment. Diagnosis is based on the symptoms and signs, the presence of leukocytosis, and findings on plain radiographs, which show extraintestinal gas in the abscess, displacement of adjacent organs, and loss of the psoas muscle shadow. Barium studies of the intestinal tract can show displacement of adjacent viscera. CT scanning often defines retroperitoneal abscess when other studies are negative or equivocal.

Treatment usually involves surgery or percutaneous catheter drainage and antibiotics effective against enteric aerobic, facultative, and anaerobic organisms. Occasionally, a small diverticular or appendiceal abscess resolves with antimicrobial therapy alone.

Splenic Abscess

Etiology. Most splenic abscesses develop as a result of uncontrolled infection elsewhere. In 75% of patients they are small, multiple, and clinically silent and are found incidentally at autopsy (63). In the remaining 25% of patients the splenic abscess is solitary, and diagnosis is especially important because splenectomy is usually curative. A solitary abscess can arise from the following: systemic bacteremia that originated in another site and is now causing infection in a previously normal spleen; infection, presumably of hematogenous origin; a spleen damaged by blunt or penetrating trauma; bland infarction such as occurs in sickle cell trait or disease or other diseases such as malaria; or extension from contiguous infection, such as subphrenic abscess. The most common infecting organisms are staphylococci, streptococci, anaerobes, and facultative gram-negative rods, including *Salmonella* (63).

Symptoms and Signs. The clinical manifestations include subacute onset of fever and left-sided pain that is often in the flank, upper abdomen, or lower chest and that can radiate to the left shoulder (63). The left upper quadrant is commonly tender to palpation and splenomegaly may be present. Occasionally, a splenic friction rub is audible. Leukocytosis is usual and blood cultures sometimes grow the infecting organisms.

Diagnosis. The signs and symptoms and radiographic findings should lead to a diagnosis. Radiographs show a left upper quadrant mass; extraintestinal gas in the abscess from gas-forming organisms; displacement of other organs, including the kidney, colon, and stomach; elevated left hemidiaphragm; and left pleural effusion. Liver and spleen radionuclide scanning, CT scanning, and ultrasonography should demonstrate intrasplenic defects with abscesses larger than 1 to 2 cm.

Treatment. Untreated abscesses are followed by such complications as hemorrhage into the abscess cavity or rupture into the peritoneum, bowel, bronchus, or

pleural space. Treatment consists of systemic antibiotics and splenectomy, which are curative (see previous discussion).

Other Gastrointestinal Disorders

Two conditions that can cause abdominal pain, distension, and other symptoms and signs of an acute abdomen are briefly discussed here. They are neurogenic intestinal obstruction (adynamic ileus) and abdominal migraine. Although pain is usually not severe and the conditions are self-limited, they are considered here to emphasize simple methods of treatment usually not considered by surgeons or internists.

Neurogenic Intestinal Obstruction

In Chapter 66 it was noted that intestinal obstruction is a common cause of abdominal pain. In most cases the obstruction is caused by mechanical factors that require surgical intervention. A number of cases have been noted, however, in which the obstruction is caused by neurogenic factors that produce adynamic ileus, which often can be corrected by interrupting certain sympathetic pathways. Adynamic ileus is said to be the most common cause of intestinal obstruction. Dynamic ileus, in contrast, which is characterized by prolonged contraction or spasm of a segment of the large bowel, is uncommon.

Etiology. Adynamic ileus occurs to some degree after any intraabdominal operation. Its severity and duration vary directly with the amount of intestinal handling and length of the operation. It usually lasts 2 to 3 days after most operative procedures, but in some cases, it can last for a longer period. The pathophysiology of this condition is discussed in detail in Chapter 41. It is the result of viscerovisceral, cutaneovisceral, and somaticovisceral reflexes that are consequent to tissue injury, marked nociceptive input, and reflex sympathetic hyperactivity. The severity and duration of ileus tend to be less following laparoscopic procedures when compared with similar procedures performed via celiotomy.

Acute adynamic ileus also occurs after any peritoneal insult, and its severity and duration are dependent to some degree on the type of peritoneal injury. Thus, hydrochloric acid, colonic contents, and pancreatic enzymes are the most irritating, whereas blood and urine are less irritating. Patients with severe acute hemorrhagic pancreatitis frequently develop severe ileus that lasts for days and sometimes a week or longer.

Another common cause of severe prolonged adynamic ileus is fracture of one of the lower thoracic vertebrae. This causes severe compression of one or more nerves with consequent radiculalgia and reflex responses, including sympathetic hyperactivity in those segments adjacent to the fracture. Other retroperitoneal conditions that cause adynamic ileus include ureteral calculus, severe pyelonephritis, retroperitoneal infection, and hematoma. Thoracic disorders, including lower lobe pneumonia, fractured ribs, myocardial infarction, and pulmonary embolism, frequently produce adynamic ileus, as do electrolyte disturbances, particularly potassium depletion. Intestinal ischemia, whether it results from vascular occlusion or intestinal distension itself, can perpetuate an adynamic ileus. Dynamic ileus occurs in patients with heavy metal poisoning, porphyria, and extensive intestinal ulceration.

Pathophysiology. The pathophysiologic mechanism is predominantly an autonomic functional imbalance with an increase in sympathetic activity and perhaps a concomitant decrease in the activity of the parasympathetic nerves supplying the gastrointestinal tract. It was formerly thought that in this condition the intestinal musculature is paralyzed. This is not the case, however, because it has been repeatedly demonstrated experimentally and clinically that interruption of sympathetic supply to the gut causes a progressive decrease in the ileus and increases the ability of intestinal musculature to return to normal function. Thus, the term *paralytic ileus* should be discarded and replaced by the term *reflex inhibition ileus* (64). Obviously, adynamic ileus caused by peritonitis, with marked electrolyte imbalance (particularly hypokalemia), is exacerbated by interference with normal ionic movements during smooth muscle contractions. Certain drugs, such as phenothiazines and narcotics, inhibit bowel motility.

Symptoms and Signs. Clinically, acute adynamic ileus is characterized by cramping abdominal pain, distension, vomiting, absence of peristaltic sounds, and other signs and symptoms of intestinal obstruction. An important deleterious effect of severe ileus is a marked increase in intraabdominal pressure with consequent cephalad displacement of the diaphragm, encroachment of the lower lobes of the lungs, and a decrease of lung capacities and pulmonary compliance. If the ileus is a result of postoperative pain or some other painful disorder, reflex responses decrease chest wall compliance; combined with the effects on the lungs, atelectasis is produced, with consequent alveolar-arterial mismatch and hypoxemia that can progress to pneumonitis. As a consequence, the patient develops tachypnea associated with dyspnea that results in inadequate pulmonary ventilation.

Treatment. The standard treatment for adynamic ileus is use of nasogastric suction and intravenous fluid administration to correct electrolyte imbalance, particularly hypokalemia.

Although these procedures are usually effective and certainly reasonable in patients with mild ileus, the most effective therapy for severe ileus is interruption of the sympathetic supply to the bowel using a segmental epidural block with local anesthetics. The use of sympathetic blockade to increase the tone and motility of the gastrointestinal tract and enhance its function was first suggested by Wagner in 1919, who published a more extensive report containing favorable results 3 years later (64). This prompted a number of others to use spinal anesthesia and splanchnic block. In 1928 Ochsner and colleagues (65) reported that physiologic, chemical, and paralytic ileus in dogs could be relieved by injection of the splanchnic nerves, and they suggested that this method be used in the treatment of clinical ileus. Two years later, they reported their extensive experience in humans. In the first edition of this book (64), a large number of favorable reports were cited of the use of this method by many highly respected surgeons, including Ochsner and colleagues, Smithwick, Morton and Scott, J. C. White and associates, and a number of distinguished European clinicians. Continuous segmental epidural blockade is an effective method of decreasing the incidence of postoperative ileus and as an effective treatment for patients who developed it after surgery, following fractures of the thoracic vertebrae, and as a result of other conditions that provoke segmental reflex inhibition of the gastrointestinal tract (see Chapter 102 and Chapter 103). Continuous segmental block using appropriate doses of local anesthetics to block thinly myelinated and unmyelinated sympathetic and nociceptive fibers relieves the ileus and any consequent discomfort.

Sarnoff and associates (66) reported the successful use of differential spinal block to treat patients with dynamic ileus. Under the influence of sympathetic visceromotor block, peristaltic action became coordinated, large amounts of flatus and feces were expelled, and the colicky pain and distension were relieved.

Abdominal Migraine (XXII-2)

Etiology, Symptoms, and Signs. Abdominal migraine is a migraine equivalent that occurs mostly in children, but adult cases have also been recorded (67). Many synonyms exist, including periodic syndrome of children, cyclic vomiting, recurrent abdominal pain and headache, and navel colic. This symptom complex consists of recurrent and identical attacks of periumbilical pain, nausea, vomiting, headache, pallor, perspiration, slowing of the pulse, fever, occasional diarrhea, and limb pains. Attacks usually last less than 6 hours, with most occurring in children between the ages of 3 and 10, particularly in those whose parents have migraine (68,69). No abdominal symptoms are noted between attacks. Gastrointestinal abnormalities have been reported in patients with migraine; their relation to symptoms is unclear (70).

The close relationship between recurrent abdominal crisis and migraine was substantiated by Farquhar (71), who found that one- third of those in a series of 112 children between the ages of 3 and 15 years with this syndrome suffered from associated migraine while one or more relatives of two-thirds of these children had migraine. The combination of migraine and abdominal pain was seen in 20% of 73 children aged 9 to 15 years who had migraine and in 12% of 100 migraineurs aged 50 to 66 years (72). It has also been noted that a significant percentage of children who have recurrent abdominal pain (crises) develop migraine during adult life.

Diagnosis and Treatment. Bruyn (68) emphasized that if the physician takes the trouble to explore the patient's biography in detail, and a history emerges of common or classic migraine attacks, the diagnosis is made whether the abdominal attacks replace migraine attacks or are associated with them. The diagnosis is also more probable when a family member has migraine. If ergotamine is prescribed and the attacks then diminish or even cease altogether, this can be interpreted as confirmation of the diagnosis.

Because the symptoms and signs simulate those of appendicitis, biliary colic, pancreatitis, lead intoxication, and gallbladder disease, these should be excluded. Bruyn (68) cited reports of adult patients with abdominal migraine who had been mistakenly subjected to as many as five futile laparotomies and of one patient who underwent cholecystectomy and thoracic sympathectomy and subsequently became a morphine addict. Obviously, therefore, a thorough physical and laboratory examination is essential to exclude the possibility of an intraabdominal disease.

Bruyn (68) further emphasized that the diagnosis should not be difficult if the following points are borne in mind: (a) migraine in the history of the patient or relatives; (b) repetition of identical abdominal crises; (c) attack-free intervals; (d) absence of systemic signs such as an increase in erythrocyte sedimentation rate, leukocytosis,

and abnormal urinalysis results during and between attacks; (e) unremarkable physical examination during and between attacks; (f) normal electrocardiographic results during and between attacks; (g) positive response to ergotamine; and (h) the occasional presence of other migrainous symptoms, such as nausea, vomiting, perspiration, and body temperature changes. Prevention and treatment are similar to migraine as discussed in Chapter 48.

Abdominal Adhesions

All patients who have undergone prior abdominal operations have at least some intraabdominal adhesions. The adhesions are likely to be more extensive if there were multiple prior operations, if any of the prior intraabdominal events involved significant inflammation such as occurs with peritonitis, or both. Many physicians and patients have the belief that these adhesions can cause abdominal pain. Adhesions can cause bowel obstruction, and bowel obstruction is often painful. However, bowel obstruction is readily diagnosed by its clinical presentation and characteristic radiologic studies. In the absence of bowel obstruction, intraabdominal adhesions do not cause pain, and it is a waste of time to refer such patients to a surgeon for lysis of adhesions. It is also not helpful to put the idea of painful adhesions in the mind of a patient.

SYSTEMIC DISORDERS

A number of systemic disorders cause abdominal pain that simulates that of intraabdominal disease but do not require surgical intervention. Laparotomy is not only unnecessary for such patients but can set the stage for postoperative problems associated with the underlying disease as well as for complications of the operation itself. Among the most important of these systemic problems are hematologic disorders and metabolic or biochemical disorders. Because they are complex, they produce widespread symptoms and signs, but here only those aspects relevant to abdominal pain are considered.

Hematologic Disorders

Various hematologic conditions can produce abdominal pain as part of their symptom complex. Most have pain as a prominent feature only during a *crisis*. In some, however, such as paroxysmal nocturnal hemoglobinuria, pain is a prominent constant feature.

Sickle Cell Anemia

Sickle cell anemia is a chronic hemolytic anemia occurring almost exclusively in blacks. It is characterized by the sickle- shaped red blood cells produced by homozygous inheritance of hemoglobin S (HbS). This condition is a significant cause of morbidity and mortality among blacks. Approximately 0.15% of black children in the United States have the disease (73). The prevalence is lower among adults because patients with sickle cell anemia have a decreased life expectancy.

The protean clinical manifestations of this disorder can all be attributed to a specific molecular lesion, the substitution of valine for glutamic acid in the sixth acid of the beta chain. On exposure to low levels of oxygen, a red blood cell containing HbS changes from a biconcave disk to an elongated crescent-shaped or sickle-shaped cell. In addition, sickling is precipitated by a lowering of pH and by an increase in body temperature (73,74). As a red blood cell sickles, it becomes rigid. The distorted but inflexible red blood cells plug small arterioles and capillaries, leading to occlusion and infarction. Because sickled red blood cells are too fragile to withstand the mechanical trauma of circulation, hemolysis occurs when they are released into the circulation. Almost all the systemic effects of this disease are related to the sickling phenomenon and to the increased fragility of the red cell. Severe disease is incompatible with long life, and 50% of patients with severe sickle cell anemia are dead before the age of 10 years (47). Those in the surviving pool of patients often develop a crisis. Improvements in treatment have increased survival (74).

Symptoms and Signs. With heterozygous inheritance, patients have sickling trait but are healthy and do not experience hemolysis, painful crises, or thrombotic complications. In contrast, the clinical manifestations in homozygotes are caused by anemia and by tissue ischemia and infarction. Anemia is usually severe but varies greatly among patients, with most patients having mild jaundice. Anemia can be exacerbated in children by acute sequestration of sickle cells in the spleen, producing splenomegaly. If the splenomegaly is severe, it can cause abdominal pain because of its capsule stretching and compressing surrounding viscera or impinging on the diaphragm.

Throughout their lives the homozygotes are plagued by recurrent painful crises (74,75). These episodes can appear with explosive suddenness and attack various parts of the body, particularly the abdomen, chest, and joints. Approximately one-third of the painful crises are preceded by a viral or bacterial infection. The frequency of painful crises is highly variable. A given patient might have months or even years without a crisis and then have a cluster of frequent and severe attacks. In some individuals crises occur more frequently in cold weather, perhaps precipitated by reflex vasospasm, while in others crises occur more often in warm weather when patients are likely to become dehydrated.

The episodic abdominal pain is usually severe and associated with vomiting and is a frequent feature of the painful vasoocclusive crisis. The organs most often involved include the liver, gallbladder, and spleen. The severity of the pain and other symptoms simulates that of acute severe intraabdominal disorders, and thus it is often difficult to distinguish between painful sickle crisis and such acute processes as biliary colic, appendicitis, and perforated viscus. Many patients have undergone surgical exploration because they were thought to have an acute surgical problem. The clue that the patient is undergoing a sickle cell crisis rather than an acute abdomen is the presence of increased sickling on the peripheral blood smear and evidence of some degree of hemolysis. Moreover, whereas abdominal tenderness is common, the guarding is of a voluntary nature because the muscles can relax and bowel sounds are usually normal, with no rebound tenderness.

Those who are SS homozygotes frequently develop attacks of acute pleuritic chest pain with fever. Although the initial chest radiograph is usually unremarkable, an infiltrate can evolve. The important differential is between pneumonitis and pulmonary infarction. Culture and Gram's staining of the sputum help in establishing the presence of pneumonia.

Diagnosis. The diagnosis is made through the history, physical examination, and comprehensive laboratory studies of the blood. The homozygous state is determined by electrophoresis, which shows only HbS and a variable amount of HbF. The heterozygote is recognized by the presence of both HbA and HbS, with more HbA than HbS.

Treatment. Therapy is usually symptomatic. Splenectomy and hematinics have proven valueless (73). Transfusions should be given only for an anemia that is more severe than usual. The severe abdominal pain should be managed with vigorous oral intravenous hydration and with nonopioid and opioid analgesics. In those hospitals in which such services are available, patient-controlled analgesia is an excellent method of providing effective pain relief. Prophylactic antibiotics, pneumococcal vaccine, early identification and treatment of serious bacterial infection, and general prophylaxis have reduced the mortality, particularly during childhood (73,74 and 75).

Acute Hemolytic Crisis

In some instances autoimmune hemolytic anemia, thrombotic thrombocytopenia, purpura, or other hemolytic disorders can begin abruptly and cause moderate to severe pain in the abdomen, back, or limbs. The abdominal pain can be severe, and the accompanying muscular spasm and rigidity might simulate the signs of an acute surgical emergency (47). Profound prostration and shock can develop, followed by oliguria or anuria. Pallor, jaundice, tachycardia, and other symptoms of severe anemia can be prominent.

Such patients require careful evaluation and supportive therapy consisting of effective pain control, infusion of appropriate fluids, and other measures to prevent or treat shock.

Chronic Hemolytic Anemia

Other congenital hemolytic anemias can also cause abdominal pain as part of their complex clinical manifestations. The major features relate to anemia, jaundice, the occurrence of crises, splenomegaly, and the development of gallstones. The jaundice of hemolytic disease is acholuric, with the bilirubin being unconjugated and thus not excreted in the urine. The spleen is commonly enlarged in this group of patients, but usually the degree of enlargement is mild to moderate. If the spleen assumes gigantic proportion, as in a few patients, it can produce abdominal pain described as a vague sensation of oppression or weight in the left side of the abdomen or, less commonly, is the site of an attack of acute abdominal pain (47). Crises can result from the transient failure of red cell production, so-called aplastic crises. It is the hemolytic crisis, however, that produces a manifestation of an acute abdominal catastrophe (see Acute Hemolytic Crisis, previously in this chapter). In these patients

the abdominal pain can be severe and accompanied by muscular spasm and rigidity, possibly simulating the signs of an acute surgical emergency.

In some patients symptoms of gallbladder disease might be the initial manifestation of a hemolytic crisis because of one of these congenital hemolytic anemias and can be what brings the patient to the physician (47). The stones are of the pigmented type and are presumed to be the consequence of continuous excessive bilirubin load presented to the liver. Such patients have a progressive increase in the incidence of gallstones with age. In some disorders, particularly in hereditary spherocytosis, as many as 85% of adult patients develop stones.

The therapy of patients with congenital hemolytic anemias is usually supportive. Effective pain control with nonopioid and opioid analgesics in appropriate doses is part of the initial treatment. Fluid replacement and transfusions might be required. In cases of major thalassemia (Cooley's anemia), the obvious benefits of transfusion therapy are partially offset by the risk of iron overload hepatitis and alloimmunization. Despite these problems, children with Cooley's anemia fare better if their hemoglobin is maintained at a level greater than 9 g per dL (47). In view of the increased demand of the hyperplastic marrow, it is reasonable to maintain these patients on a daily supplement of folic acid. Because splenic sequestration contributes to shortened red blood cell survival, many patients derive some benefit from splenectomy because the need for transfusions is decreased. Splenectomy is also indicated if the size of the tumor is so great that it produces severe respiratory problems or is a source of great discomfort because of its encroachment on the diaphragm and other organs.

Biochemical and Biological Disorders

Acute Intermittent Porphyria (XXII-3)

Acute intermittent porphyria is a dominantly transmitted inherited disorder that can exist in latent form indefinitely or be manifested as acute attacks of neurologic dysfunction precipitated by various environmental and endogenous factors (76,77).

Etiology and Pathophysiology. The basic enzyme defect in this disease is a 50% decrease of uroporphyrinogen synthetase. Consequently, d-aminolevulinic acid, porphobilinogen, and uroporphyrinogen are produced in excess by the liver and excreted in the urine. This metabolic abnormality is accompanied by acute attacks of mental or abdominal neurologic symptoms. It is inherited as an autosomal dominant trait with an overall prevalence of 5 to 10 per 100,000 population in the United States. The prevalence, however, is much higher in some countries (76); for example, in Sweden, it is 1 in 13,000 population (47). The frequency and severity of attacks and prevalence are greater in women (60% to 75%) than in men.

The disease exists in latent form until an attack of acute neurologic dysfunction is precipitated by one of four groups of factors: drugs, starvation, sex hormones, and infection. Drugs implicated in precipitating attacks of acute porphyria include barbiturates, sulfonamides, phenytoin, methsuximide, griseofulvin, meprobamate, amidopyrine, antipyrine, dipyrone, imipramine, ergot preparations, methyldopa, pentazocine, danazol, chloramphenicol, and chlorpropamide (76). Starvation and crash dieting precipitate attacks of porphyria. The deleterious effects of diet relate to the ability of glucose and certain other carbohydrates to block the induction of hepatic d-aminolevulinic acid synthetase. Female sex hormones are also implicated in precipitating attacks of porphyria; a small percentage (less than 5%) of women with this disorder have an attack during pregnancy. Acute attacks of porphyria can also follow bacterial and viral infections, but the mechanism is unknown.

Symptoms and Signs. Symptoms of the acute attack result from nervous system damage. Any part of the system can be involved, and the specific clinical findings depend on the areas that are affected. The outcome of the acute attack can vary through a spectrum from death to complete recovery, although some patients who recover can retain varying types of neurologic deficits. Symptoms rarely occur before puberty.

Abdominal pain is frequently the initial and most prominent symptom of the porphyric attack, occurring in approximately 95% of the patients. The pain can be moderate but more frequently is severe in degree and cramping or colicky in nature. It can be localized in one of the lower quadrants or in the periumbilical region, but in some cases it is felt throughout the abdomen. The pain can radiate to the back or loins and is accompanied by vomiting, constipation, and mild abdominal tenderness (76,77). It has been suggested that the pain results from autonomic neuropathy that causes disturbed gastrointestinal motility or alternating areas of spasm and dilation. Low- grade fever and mild leukocytosis along with the pain can suggest other diagnoses. Other autonomic manifestations include labile hypertension, sinus tachycardia, postural hypotension, and sweating. Because these symptoms can be attributed to various conditions requiring emergency surgery, many patients have already been subjected to unnecessary laparotomy when seen with another acute attack.

Patients can also manifest peripheral neuropathy that is predominantly motor, but sensory components can also be present. Deep tendon reflexes are diminished or absent. Neuralgia in the extremities associated with areas of hypesthesia and paresthesia and foot- or wristdrop are typical. Central nervous system involvement can produce an organic brain syndrome, seizures, cerebellar and basal ganglia manifestations, hypothalamic dysfunction, and bulbar paralysis.

Acute attacks can last from days to months and vary in frequency and severity. The characteristic finding of this disease is increased porphyrin precursor excretion in the urine.

Diagnosis. Diagnosis is made by establishing the presence of excessive urinary porphobilinogen. These precursors can be quantitated accurately by chromatographic techniques. Clinically they can be detected by qualitative analysis using the Watson-Schwartz or Hoesch's test (76). If these tests are not available, a useful technique involves collecting a sample of urine and exposing it to light and air. Because porphobilinogen is colorless the initial sample appears normal, but on exposure to light or air the urine darkens. This phenomenon is largely accounted for by the formation of porphobilin, a dark brown nonporphyrin oxidation product of porphobilinogen.

Treatment. Treatment involves prevention of attacks, treatment of symptoms, and attempts to reverse the fundamental disease process. Prevention of attacks entails instructing patients to avoid the known precipitating factors listed previously. Many patients scheduled for surgery should inform both the anesthesiologist and surgeon of their conditions, because physicians know to avoid the use of thiopental or other barbiturates for sedation or induction of anesthesia.

Pain control is the first step in symptom management. Some believe that phenothiazines can be useful for the control of abdominal pain, presumably by their effects on decreasing autonomic outflow. Usually, these patients require large doses of intravenous opioids, either in incremental doses or by continuous infusion. An excellent alternative is patient-controlled analgesia. If these methods do not provide effective relief, serious consideration should be given to the induction of continuous segmental epidural analgesia with a local anesthetic (see Chapter 102). This technique has the advantage of providing complete pain relief because it blocks all nociceptive input from the abdomen and interrupts sympathetic efferent impulses, thus helping to decrease the effects of the pathophysiologic process.

Other Porphyrias

Other rare types of porphyrias cause intermittent acute attacks of abdominal pain, including hereditary coproporphyria (IASP XXII-4) and variegata porphyria (IASP XXII-5). Both can be associated with neurologic and mental disturbances. Variegata porphyria also causes photosensitivity and is accompanied by cutaneous lesions. Photosensitivity occurs with hereditary coproporphyria, but not as frequently as with variegata porphyria.

Other Metabolic and Biochemical Disorders

Other metabolic and biochemical disorders that cause abdominal pain include diabetes, uremia, lead and other heavy metal poisoning, food poisoning, and spider bites. In all these conditions, abdominal pain is only one of many symptoms and signs. In each case the pain is controlled symptomatically with nonopioid or opioid analgesia or with a combination of these, depending on the severity of the pain.

Lead Poisoning. Abdominal pain is an especially frequent symptom of lead poisoning in children. Obviously, analgesics must be given in reduced but appropriate dosages to provide good pain relief. If the pain is expected to persist for several days or weeks, continuous epidural opioid analgesia is highly effective and has advantages over other methods of administration of these drugs (see Chapter 103).

Spider Bite. Spider bite first produces a momentary sharp pain at the site of bite, followed by a cramping pain that begins locally within 15 to 60 minutes and gradually spreads (78). The abdomen becomes boardlike and the waves of pain become excruciating, causing the patient to turn, toss, and cry out (78). Respirations are often labored and grunting. The pain is associated with nausea, vomiting, headache, sweating, salivation, hyperactive reflexes, twitching, tremor, paresthesia of the hands and feet, and occasionally, systolic hypertension. A mild leukocytosis is usual, but many patients have high fever. After several hours the pain subsides, although a mild recurrence for 2 to 3 days is common. It can be a week before well-being is restored. Death caused by cardiac or respiratory failure has ensued mostly in children

and the aged.

Treatment consists of pain relief measures and administration of antivenom. Initial treatment should begin with pain control with opioids, first administered intravenously and subsequently intramuscularly at regular intervals. If the patient is hospitalized, a better alternative would be epidural opioid analgesia or segmental epidural analgesia with local anesthetics. A 10-mL vial of 10% calcium gluconate injected intravenously slowly over 10 to 20 minutes usually produces dramatic but transient cessation of cramps (78,79). A solution of 10% methocarbamol administered intravenously can also be effective in treating the muscle spasm. When the symptoms are severe, or when the patient is a small child or is at special risk because of other associated medical problems, treatment with *Latrodectus* antivenom is indicated. An intravenous injection of one vial (2.5 mL) diluted in 50 mL of saline and administered over a 15-minute period is usually effective; this can be repeated within a few hours if symptoms recur (78).

EXTRAABDOMINAL DISORDERS

Abdominal pain can and often does occur as a referred phenomenon that is part of the symptoms and signs of thoracic or pelvic visceral disease, or as a projected pain from disease of the spine or other musculoskeletal, and, rarely, neuropathic disorders. Most of these are discussed in detail in Chapter 60, Chapter 61, Chapter 62, Chapter 63 and Chapter 64 in Section C) and Chapter 72 (Gynecologic Pain), and only brief comments are made here in regard to the abdominal pain.

Thoracic and Pelvic Visceral Disease

Diseases arising within the thoracic cavity can produce diaphragmatic irritation or referred pain that is often indistinguishable from pain arising from the pancreas, stomach, or biliary tract. Fortunately, certain general guidelines can be used that help to differentiate a thoracic from an abdominal origin (47). Thoracic pain is almost never associated with abdominal tenderness. Bowel sounds are usually present and, with careful questioning, the time sequence reveals that symptoms and signs of a cardiopulmonary or esophageal disorder preceded the development of the abdominal pain.

Acute Myocardial Infarction

Generally, acute myocardial infarction produces characteristic symptoms of retrosternal and anterior chest pain with radiation to one or both arms, neck, and, occasionally, the jaw. A significant percentage of patients, however, also have radiation of pain in the epigastrium. Indeed, in some patients, the epigastric pain is the predominant symptom. It is probably caused by an inferior wall infarction that produces diaphragmatic pleuritis with pain referred to the lower chest and abdomen, associated with belching and occasionally back pain. One or more of these symptoms can mimic the initial symptoms of a penetrating ulcer, cholecystitis, or pancreatitis and can present a difficult differential diagnosis.

In either case it is essential for the patient to be admitted to the hospital, often with a stay in the coronary care unit, while serial electrocardiograms, cardiac monitoring, and cardiac enzyme levels are obtained. The pain of myocardial infarction usually begins to decrease within 12 to 24 hours, whereas if the condition is an acute intraabdominal problem pain continues and is associated with severe abdominal tenderness, reflex muscle spasm that produces rigid abdomen, and the absence of peristalsis.

Acute Pericarditis

Acute pericarditis of the diaphragmatic portion of the pericardium can cause irritation of the diaphragm that involves not only the central portion, supplied by the phrenic nerve, but also the peripheral part, supplied by the lower sixth and seventh thoracic spinal nerves, with consequent pain and muscle spasm in the lower chest and epigastrium. The pericardial source of the pain can be ascertained by the fact that this pain is markedly aggravated by deep breathing, is associated with dyspnea and triphasic pericardial friction rub, and radiates to the neck and trapezius ridge. On the other hand, all symptoms and signs except the pericardial friction rub can be present with a subdiaphragmatic irritation caused by subphrenic abscess, acute cholecystitis, or pancreatitis.

Pulmonary Embolism

Confusion between the pain of pulmonary embolism and that of intraabdominal disease arises primarily with medium-sized emboli that produce a pleuritis with consequent pleuritic pain. If the pleuritis involves the diaphragmatic portion of the pleura, the patient might experience pain in the epigastrium and lower part of the thorax laterally and posteriorly. Again, the pain is markedly aggravated by deep breathing and is associated with friction rub and radiographic evidence that the lesion is in the chest.

With a large central embolus the patient experiences sudden, severe, crushing central pain that can radiate to the upper epigastrium. The preeminence of pain in the retrosternal region, however, associated with a feeling of impending death (*angor animi*) that lasts from a few minutes to several hours, should suggest pulmonary embolism. If massive central pulmonary emboli produce certain cardiovascular collapse and death, symptoms are usually not confused with those of an acute abdomen. Other symptoms and signs that differentiate acute pulmonary embolism from an acute intraabdominal disorder include dyspnea, which is found in most patients with pulmonary embolism, hemoptysis, a history of venous disease, changes in blood viscosity, obesity, and a period of prolonged bed rest or inactivity.

Pneumonia

The clinical symptoms and signs of pneumonia include fever, cough, purulent sputum, mild dyspnea, and usually pain, which can be retrosternal or, most frequently, pleuritic, and is felt in the side and back of the chest. On the other hand, if the pneumonia involves the diaphragmatic pleura, the patient experiences pain in the lower chest and upper abdomen. A differential diagnosis is aided by the fact that the pain is exaggerated by deep breathing and coughing and by the presence of rales and other signs of pneumonic consolidation.

Upper Respiratory Infection

The symptoms and signs of upper respiratory infection in adults are located in the chest and should never cause confusion with those of abdominal disorders. On the other hand, as Kirkpatrick indicated (47), children with an upper respiratory infection can experience nonspecific abdominal pain localized in the right lower quadrant that might be mistaken for that of acute appendicitis. In such cases the lower quadrant pain is caused by a mesenteric adenitis, a relatively uncommon complication that occurs consequent to a respiratory infection and afflicts children 5 to 15 years of age, more commonly in boys than in girls. Characteristically, the child has an acute pharyngitis or otitis media and develops cramping periumbilical pain during the recuperative phase. Leukocytosis ranging from 12,000 to 18,000 per µL and a mild fever of 99°F to 100°F (37.2°C to 37.8°C) suggest either appendicitis or mesenteric adenitis. Kirkpatrick (47) suggested that, if signs of upper respiratory infection are still present, reevaluation as an outpatient in 12 hours should help to avoid an unnecessary operation and minimize the risk of missing appendicitis. If the upper respiratory infection has resolved but the pain persists, however, then hospital admission, repeat blood work, and close observation are necessary to avoid missing an attack of acute appendicitis.

Esophageal Disease

Acute and chronic esophagitis produced by chemical or infectious disorders often cause pain in the sternum that extends down into the epigastrium. The pain is usually constant with periodic increases in intensity produced by esophageal spasm and is markedly aggravated by swallowing (odynophagia). It is rare for the pain to be located only in the epigastrium and therefore the differential diagnosis should not be difficult, especially with a history of ingestion of a chemical or other signs of esophagitis.

Esophageal motor disorders can also cause retrosternal pain with radiation to the epigastrium and back and also to the neck, jaw, teeth, or both arms, thus simulating the pain of acute myocardial infarction (see Chapter 63). The pain, which lasts seconds to many hours, is aggravated by cold liquids, solids, and emotional stress and is partially relieved by nitroglycerin. The differential diagnosis is aided by manometry, scintigraphy, and provocative tests using pharmacologic agents.

Esophageal lacerations and rupture can also cause pain in the lower sternum and epigastrium; if located in the lower part of the esophagus the epigastric pain can be the most prominent. Spontaneous rupture, called *Boerhaave's syndrome*, also causes excruciating, crushing, or tearing pain in the lower retrosternal region and epigastrium. Because the rupture occurs during intense vomiting following a large meal, together with other symptoms and signs, it is easily differentiated from

intraabdominal disorders.

Similarly, carcinoma of the esophagus produces moderate to severe retrosternal pain with radiation to the epigastrium when the lesions are in the lower part of the esophagus. The pain radiates to the back and interscapular region, is continuous, and is aggravated by food ingestion. The differential diagnosis is aided by the history and by radiography, CT scanning, and esophagoscopy.

Retroesophageal reflux caused by incompetent gastroesophageal sphincter also produces a symptom complex characterized by retrosternal epigastric burning pain, dysphagia, and occasional bleeding. When these signs and symptoms are present the diagnosis should be suspected from the history and confirmed by esophagoscopy, acid perfusion test, and pH monitoring.

Gynecologic Disorders

Some gynecologic conditions can mimic those of acute abdomen by producing pain in the right or left lower quadrant or in the suprapubic region, with radiation to the back. These include acute salpingitis, twisted ovarian cyst, ruptured ovarian follicle, and various other disorders (see Chapter 72). To avoid a misdiagnosis, it is mandatory for pelvic and rectal examinations to be carried out; if necessary, a pregnancy test is done. Pelvic examination reveals exquisite cervical tenderness (other differential diagnostic procedures are discussed in Chapter 72 and summarized in Table 70-3).

Pain of Neuropathic Origin

In Chapter 60 it was noted that most pathologic processes of the thoracic portion of the spinal cord and of the thoracic spinal nerve roots or peripheral nerves produce similar pain syndromes in the chest and the abdomen. They have been discussed in detail in Chapter 60. To avoid repetition, only a few comments pertinent to abdominal pain are made here.

Brain Lesions

It is uncommon in the brain or brainstem to cause pain only in the abdomen without causing pain or other sensory disturbances in the extremities. The one exception is a very rare form of epilepsy that can cause pain in the abdomen as an aura or as part of the seizure itself (80). Abdominal epilepsy is more common during childhood and can abate spontaneously in adolescence. The patient usually complains of unpleasant sensations that can vary from paresthesiae to pain. Nausea and vomiting can occur (81). Some of these patients were described as having intussusception in association with their epileptiform disorder. Motor phenomena and a sensory deficit are usually not present (82), but autonomic phenomena are common. Most patients with this type of seizure disorder also report environmental distortions and emotional changes.

Central pain caused by vascular lesions or by tumors of the brain and brainstem usually leads to pain in the contralateral extremities and side of the trunk and other signs and symptoms of brainstem lesions. Although some of the pain can be felt in the abdominal wall on the same side, it is rarely, if ever, localized only to the abdomen.

Lesions of the Spinal Cord, Meninges, and Epidural Space

Intramedullary lesions or diseases of the lower thoracic portion of the spinal cord, including tumors, syringomyelia, trauma, multiple sclerosis, abscess, hemorrhage, and other conditions, can produce pain in the trunk that includes the abdominal wall. The pain can be a spontaneous, burning, diffuse, poorly localized pain that is continuous or explosive in nature or, in some cases, the pain can have a radicular (segmental) distribution involving several segments, depending on the extent of the lesion; this is often associated with hyperalgesia, hyperpathia, and paresthesia.

Extramedullary intrathecal lesions such as primary or metastatic lesions, abscesses, and hemorrhages initially produce low back pain localized around the segments of the lesions. Subsequently, however, the pain becomes radicular and is aggravated by straining and coughing and is associated with paravertebral tenderness and paresthesia. These are followed by sensory loss, muscle weakness, and lower motor neuron signs at the level of the lesion.

Epidural spinal cord compression caused by primary or metastatic tumor, hemorrhage, posterior disk protrusion, abscess, or hemorrhage produces localized low back pain at the level of the site of lesion in 95% of patients and bilateral radicular pain involving the abdominal wall in 55% (83). The pain is aggravated by neck flexion, straight leg raising, coughing, sneezing, and Valsalva's maneuver. Deep palpation and fist pounding produce back tenderness. Early in the course of the disease no other signs are seen but muscle weakness develops later, varying from mild weakness to paraplegia. Numbness and paresthesia are noted in 50% of patients and bladder and bowel dysfunction are frequent (57%) (see Chapter 60 for details).

Arachnoiditis, characterized by inflammation and fibrosis of the arachnoid membrane, is a well-recognized cause of chronic pain. Although the cauda equina is the most common site, arachnoiditis can occur at any spinal level. It can be focal and involve only one root, thereby leading to a segmental pain syndrome with variable loss of sensory and motor function. Arachnoiditis can also affect multiple segments and lead to a more diffuse pain syndrome in the lower trunk and abdomen. The pain of arachnoiditis is constant but is worsened by physical activity. Often a dysesthetic component is present, and paresthesiae are common. Patients often report both a deep aching and a superficial sharp jabbing pain. This type of pain is not often ameliorated by narcotics.

Lesions of Roots and Trunks of the Thoracic Nerves (XX-3)

Lesions of the nerve roots produce radiculopathy and consequent radiculalgia or segmental pain. The pathology can be a result of an acute or chronic infectious process or of mechanical compression.

Herpes Zoster. Herpes zoster is an infection by the varicella-zoster virus that involves the ganglion cells, rootlets, and posterior horn. It produces a continuous aching, itching, or burning pain with superimposed bouts of severe lancinating pain. Hyperalgesia and hyperesthesia are present in the affected segments. These patients usually develop a rash in the involved segments that spreads along the entire nerve or part of the affected nerve, frequently in the upper or lower anterior abdomen. Some patients develop postherpetic neuralgia, which is a chronic condition that produces severe, intractable, continuous, unrelenting, burning pain and itching accompanied by severe spasm with stabbing lancinating pain that persists long after the acute phase. The skin of the posterior and lateral lower thoracic cavity and abdominal wall has dried white or brownish black scars that represent the healing of the vesicles. Patients may experience hyperalgesia, hyperesthesia, and hyperpathia and frequently hypesthesia, depression, sleep disturbance, anorexia, lassitude, and constipation (see Chapter 22 and Chapter 60).

Tabes Dorsalis. Tabes dorsalis is one of the many forms of tertiary syphilis. Formerly a common affliction, the development of serologic testing and effective antibiotic therapy has made this an exceedingly rare disease in most developed nations. The immunosuppression that is part of acquired immunodeficiency syndrome has led to a recrudescence of syphilis. Pains are often the earliest signs of tabes; the vast majority of patients has typical lightning pains during the course of the disease. The electric shock– like stabbing pain might last only a brief moment or be continuous for days. Girdlelike pains about the thorax or abdomen are common, although most patients have pains in the limbs. Paresthesiae and objective sensory changes in the region of the pain occur in about 25% of patients. Most patients with tabes dorsalis have altered position sense, absent deep tendon reflexes, hypotonia, ataxia, and Argyll Robertson pupils (miotic pupils that fail to react to light but contract with accommodation).

Even worse than the intermittent lancinating pains is the pain syndrome known as *gastric crisis*. This has been reported in about 10% of tabetics. The patient has a sudden onset of agonizing epigastric pain associated with nausea and vomiting. Such an attack can last for days, but spontaneous remission always occurs. This pain syndrome is exceedingly difficult to differentiate from renal or biliary colic or penetrating ulcer on the basis of the clinical presentation alone. A similar pain syndrome can affect the lower abdomen and pelvic areas.

Nerve Root Compression. Many factors can cause compression radiculopathy, including tumors, disk protrusions, vertebral fractures, osteophytes, and adhesive arachnoiditis. All of these produce a segmental sharp burning pain, hyperesthesia, hyperalgesia, hypesthesia, and dysesthesia in the segments involved.

Protrusion of the intervertebral disk deserves special note here because, contrary to former teachings, herniation of a thoracic intervertebral disk is now being recognized with increasing frequency. In most cases it involves one of the lower thoracic disks, producing radiculalgia with segmental pain in the lower abdomen.

Initially, the pain is vague and poorly localized and can be referred laterally or bilaterally in the abdomen. Typically, the pain is aggravated by neck flexion and by an increase in intraspinal pressure resulting from coughing, sneezing, or straining. The pain is usually relieved by recumbency. Subjective numbness and paresthesia, such as coldness and a burning sensation, are early and outstanding symptoms. If the disk is posterior, it produces compression of the spinal cord with weakness and heaviness of the leg. Physical signs of upper neuron damage can also be present, including hyperactive deep reflexes, spasticity, and the Babinski's response. Early recognition and removal prevent irretrievable damage to the spinal cord (see Chapter 60).

Other causes of the segmental abdominal pain of neuralgia are vertebral compression resulting from arthritis, metastatic or traumatic fractures, tumors of the vertebrae, osteomyelitis of normal curvature, and paravertebral compression resulting from adenopathy. All these usually produce unilateral segmental neuralgia characterized by continuous burning or sharp pain that affects part or the entire segment of the nerve and is associated with paroxysms of stabbing pain. Patients frequently have paravertebral tenderness and segmental hyperalgesia, hyperesthesia, and hypesthesia, and usually show radiographic evidence of the disease.

Intercostal Neuropathy

One or more of the lower six or seven intercostal nerves can be irritated, infected, or damaged by lesions of the ribs, which can include trauma, fractures, and primary or metastatic tumors. These conditions are characterized by superficial continuous burning pain in the lower part of the posterior and lateral chest and the abdominal wall. Pain is usually unilateral.

Abdominal Cutaneous Nerve Entrapment Syndrome (XX-5)

The cutaneous entrapment syndrome is a special type of intercostal neuropathy that deserves mention because it causes pain in the anterior abdominal wall or can cause segmental neuralgia.

Etiology. The most common type is a result of entrapment of one or more of the anterior cutaneous branches of the thoracoabdominal intercostal nerve(s) in the rectus sheath. Applegate (84) described a small fibromuscular ring near the lateral margin of the rectus abdominis muscle through which the intercostal nerve turns sharply in an anterior direction on its terminal course through the skin in which it is firmly anchored. The nerve enters the ring accompanied by the epigastric artery and vein from which it is separated by a well-defined fatty mass. All these structures continue in a channel between the fibers of the rectus muscle and its anterior sheath, passing subcutaneously and ending at the skin (Fig. 69-4A).

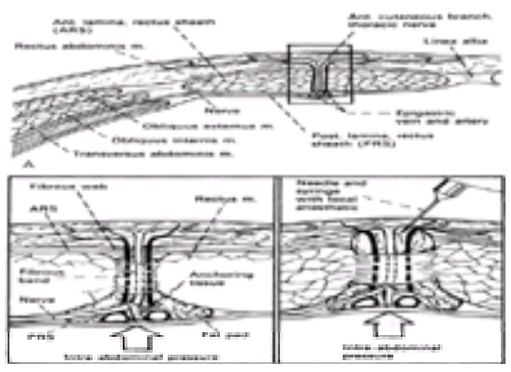

Figure 69-4. Mechanism of abdominal cutaneous nerve entrapment syndromes. **A:** Normal anatomy of the neurovascular bundle as it passes through the fibrous muscular foramen in the rectus muscle, together with increased intraabdominal pressure, cause the nerve, which is anchored by fibrous tissue, to be stretched. **B:** Herniation of the neurovascular bundle and the fat pad surrounding it through the fibromuscular foramen in the rectus muscle and the aponeurotic opening at the rectus margin. **C:** Technique of injecting a local anesthetic to confirm the diagnosis and as part of the treatment. (Modified from Applegate WV. Abdominal cutaneous nerve entrapment syndrome. *Surgery* 1972;71:118–124.)

In some patients the walls of the muscular channels are split or spread apart. This allows the fat and neurovascular bundle to herniate into the subcutaneous tissue, where they are intermittently compressed or become incarcerated as a tender mass that is palpable from the surface (Fig. 69-4B). The weakness of the channel is induced by sustained and increased intraabdominal pressure or by stretching of the abdomen during pregnancy, or is consequent to severe ascites or a large intraabdominal tumor. The weakness can also be caused by a chronic, persistent strong cough.

Contraction of the abdominal muscles causes local compression of the trapped nerve in the muscular channel, which provokes bouts of sharp burning pain. Pain is also produced by sudden twisting or lateral flexion of the spine away from the affected side, causing the nerve to be stretched and pressed tightly against unyielding fibrous tissue in the ring.

Entrapment of the lateral cutaneous branch of the thoracoabdominal intercostal nerves can also occur as each traverses the internal and external intercostal and serratus anterior muscles to reach the subcutaneous tissue, where it divides into anterior and posterior subdivisions (see Chapter 60). Indeed, the cutaneous branch of the posterior primary division can also become trapped as it traverses the paraspinal muscles and their fascia.

Symptoms and Signs. Initially, most patients experience bouts of intermittent dull aching pain that can be associated with sharp piercing pain in the distribution of the dermatome and paresthesia, hyperesthesia, and local tenderness, the characteristics of neuropathy. The distribution of the pain symptoms depends on the site of entrapment and on the number of nerves involved. In most cases one anterior cutaneous nerve is entrapped, causing pain in the medial part of the anterior abdominal wall over the rectus muscle. The pain is reproduced by localized pressure with a fingertip. Entrapment of the lateral cutaneous branch produces pain and sensory disturbance in its distribution and is also reproduced by fingertip pressure at the midaxillary line.

Diagnosis. Pain from cutaneous nerve entrapment can be confused with acute pain caused by intraabdominal visceral disease; the latter must be ruled out to avoid unnecessary surgery. The diagnosis is made by keeping entrapment syndromes in mind, by the characteristics (quality, location, intensity, and duration of pain), and by reproducing the pain with fingertip pressure. The anterior cutaneous syndrome is also reproduced by increasing the tension of the rectus abdominis muscles by having the patient raise the head and shoulders from the examining table. Often the symptoms are also reproduced by strong coughing efforts in the standing position. The diagnosis is confirmed by prompt and complete relief of the pain following injection of the localized tender area with 1 to 2 mL of a local anesthetic solution (Fig. 69-4C).

Treatment. Conservative measures such as heat, cold, massage, and transcutaneous electric nerve stimulation can provide moderate but temporary relief of the pain. Repeated injection with a local anesthetic usually produces only temporary relief, although some patients experience progressively longer intervals of pain relief with a series of injections. In patients who obtained complete but only transient relief of the pain following a series of blocks, Mehta and associates (85,86) recommended injection of a 5% aqueous phenol solution. They reported relief at 2 to 3 weeks postinjection in 60% of 103 patients treated and long-term relief in 70% of 82 patients who could be contacted several months after injection. An alternative method is surgical exploration and relief of the entrapment.

Pain Primarily of Musculoskeletal Origin

Disorders of the lower thoracic spine are likely to produce localized pain in the lower part of the back, with occasional spread to the lateral part of the thorax; rarely do they produce pain in the abdomen unless the lesion causes a radiculopathy or neuropathy. Occasionally, fractures of the anterior part of the lower ribs or fracture or dislocation of the lower costal cartilages can result in upper abdominal pain. The epigastric pain can also be caused by damage, infection, or irritation of the xiphoid process. Finally, myofascial syndromes involving one or more of the abdominal muscles can cause moderate to severe continuous pain. These three conditions are discussed briefly here.

Slipping Rib Syndrome

The slipping rib syndrome, also known as a *rib tip syndrome* or *slipped rib cartilage syndrome*, is characterized by sharp stabbing pain localized to the upper quadrant or to the epigastrium. The pain is present at rest and is aggravated by movement, especially twisting, hyperextension, or raising the arm. Occasionally, the pain is dull aching or burning, located below the costal margin and radiating to the back. The condition is discussed in detail in Chapter 60.

Xiphoidalgia

Xiphoidalgia, or painful tender xiphoid process, is characterized by spontaneous deep aching or sharp pain that varies in intensity from a slight to agonizing discomfort simulating that of myocardial infarction. The pain is felt in the region of the xiphoid process, with radiation to the epigastrium and occasionally to the lower chest. The pain is aggravated by movements that act on xiphoid processes such as bending, stooping, or turning or by an increase in intragastric pressure caused by a large meal. The pain can be constant or recur several times a day and last for minutes to several hours. Pressure on the xiphoid process produces spontaneous pain that is felt most severely in the region of the xiphoid process, with radiation to the epigastrium, retrosternally, and occasionally to the precordium. The condition can persist for weeks or months but usually disappears spontaneously (see Chapter 60). Nonsteroidal antiinflammatory drugs are often helpful for this condition.

Epidemic Myalgia

Epidemic myalgia, also known as *Bornholm's disease*, epidemic pleurodynia, and devil's grip, has already been discussed in Chapter 62 (see Disorders of the Pleura). It is mentioned here because it affects not only the intercostal but also the abdominal muscles in many patients and causes abdominal pain. After a nondescript course of from 1 to 10 days adult patients experience bouts of severe sharp pain in the lateral chest wall, while in children the pain involves the upper abdominal muscles. The involved muscles are usually tender. Bouts of pain are separated by symptom-free intervals. Fever, headache, and pharyngitis are present. The illness usually lasts 3 to 7 days, but relapses can occur. Specific diagnosis is made by isolation of the virus from the throat or feces early in the course of the disease or by demonstration of a rising titer of type-specific neutralizing antibodies.

Treatment is usually conservative, consisting of pain control using systemic analgesics; these also relieve headache and reduce fever.

Myofascial Pain Syndromes

Myofascial pain syndromes are common causes of pain in various parts of the body. Their etiology, pathophysiology, characteristics of the pain, other symptoms, diagnostic procedures, and therapy are discussed in detail in Chapter 29. Here, we briefly mention the characteristics of the syndromes with trigger points (TPs) that can be located in the externus obliquus, transversus abdominis, and rectus abdominis muscles. Painful TPs are frequently found in the muscle of the anterior wall and all major quadrants; in particular, the rectus abdominis muscles usually contain multiple TPs.

These syndromes are important because TPs in these abdominal muscles can initiate somatovisceral reflex phenomena that might induce visceral dysfunction, possibly resulting in as much distress as that induced from the referred pain (87). Symptoms referred from these myofascial TPs commonly confuse the diagnosis by mimicking those of visceral disease. Sola (88) has successfully treated several patients with confirmed cardiospasm by injection of these TPs with dilute solutions of local anesthetics. In these patients the TPs were located in the left upper rectus abdominis muscles. Edegawa and Friedman (89) described a similar treatment for cardiospasm as well as for functional gastrointestinal disturbances, such as bloating, diarrhea, and constipation involving injection of all four major abdominal quadrants.

Pain patterns of TPs in the abdominal muscles, especially the obliques, are less consistent from patient to patient than are the patterns for most other muscles. Abdominal pain referred from TPs on one side frequently causes bilateral pain. In addition to the localized and referred pain, patients can complain of burning, fullness, bloating, and swelling of gas, although objective evidence is frequently missing.

Figure 69-5 and Figure 69-6 depict the location of TPs and the areas of referred pain that they produce. The solid area of referred pain in the figures indicates the essential zone, the site of pain that is experienced by most patients. The area that is stippled indicates the spillover zone, the site of pain that is experienced by some patients. Referred pain from myofascial TPs in the abdominal musculature is likely to appear in the same quadrant and occasionally in any other quadrant of the abdomen, as well as in the back (87,88). These TPs can initiate somatovisceral responses, including projectile vomiting, anorexia, nausea, intestinal colic, diarrhea, urinary bladder and sphincter spasm, and dysmenorrhea (87). When such visceral symptoms occur with abdominal pain and tenderness, the combination can strongly mimic the manifestations of acute visceral disease, especially appendicitis and cholecystitis.

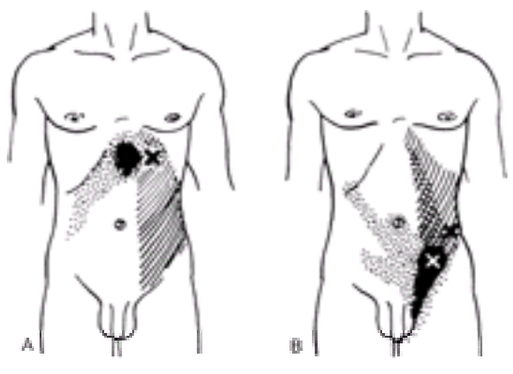

Figure 69-5. Pain patterns produced and sustained by trigger points (*X*) in the abdominal muscles. **A:** Trigger point in the external oblique muscle overlying the lower part of the anterior chest wall. **B:** Pain in the groin and testicle, with radiation to the upper lateral abdominal caused by a trigger point in the lower lateral abdominal wall musculature. The solid black depicts the essential zone and the stippled pattern depicts the spillover zone. See text for details.

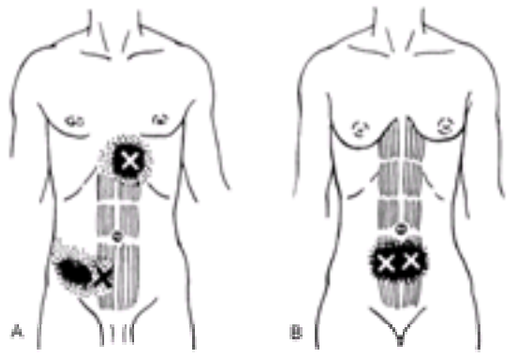

Figure 69-6. Pain patterns produced and sustained by trigger points (*X*) in the rectus abdominis muscle. **A:** Right lower quadrant pain and tenderness in the region of McBurney's point caused by a trigger point in the lateral border of the ipsilateral rectus abdominis muscles and by a trigger point at the upper attachment of the rectus muscle that occasionally causes lower esophageal spasm (*cardiospasm*). **B:** Pain pattern in the hypogastric region produced by trigger points in the lower part of both rectus abdominis muscles. Through somatovisceral reflexes, the trigger point can intensify the pain of dysmenorrhea or can cause other types of visceral dysfunction. The solid black depicts the essential zone and the stippled pattern depicts the spillover zone.

Activation of TPs in the abdominal musculature can be a result of trauma or stress of the muscle or can represent viscerosomatic responses to visceral disease,

including peptic ulcer, intestinal parasites, ulcerative colitis, diverticulosis, and cholecystitis (87). Once activated, TPs can then be perpetuated by emotional stress, occupational strain, faulty posture, and overenthusiasm for fitness exercises.

TPs are located by systemic point pressure of the area in which the TPs are suspected to exist. When the pressure is applied to the TP, patients experience aggravation of pain similar to the spontaneous pain that they have had. Local muscle twitch and other signs can also be felt.

Treatment. Treatment of myofascial syndromes is discussed in detail in Chapter 29. It consists of therapy directed at decreasing the activity of the TP, supportive measures, and corrective actions (Fig. 69-7) as described in detail in Chapter 29. Stretch and spray of the involved abdominal muscles involves hyperextension of the spine, protrusion of the abdomen, and a downward spray pattern. Corrective actions include self-administration of ischemic compression, learning how to breathe with the abdomen (diaphragm), and carrying out various progressive exercises (87).

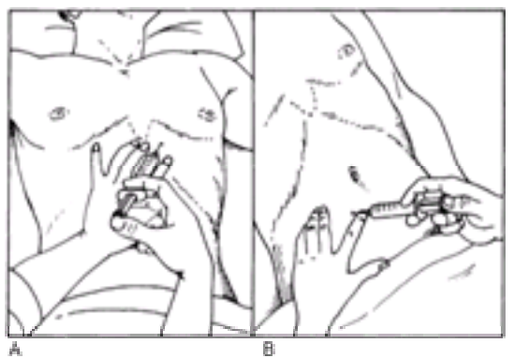

Figure 69-7. Technique of injection in patients with myofascial syndromes caused by trigger points in the abdominal muscles. **A:** Injection of the trigger point in the upper part of the external oblique muscle responsible for the pain pattern shown in Figure 69-5A. **B:** Injection of the lower part of the right rectus muscle to eliminate the pain shown in Figure 69-6A.

Abdominal Pain of Tegumentary Origin

Painful Scars

Pain in the abdominal or flank region can be caused by posttraumatic or postoperative scars that usually contain small neuromata. These painful abdominal disorders are similar to those of postthoracotomy and postmastectomy pain (see Chapter 64). The scars can occur in any part of the abdomen but develop most frequently following a subcostal curved incision for cholecystectomy, a flank incision for operation on the kidney, and incision for appendectomy. They are especially likely to develop into painful scars if the scar drains persistently or is infected.

Patients usually complain of a continuous aching, burning pain in the region of the scar and, around it, occasional bouts of lancinating pain that can develop spontaneously with movement of the trunk, can be provoked by pressure on the neuroma, or result from both. In most patients the pain is mild to moderate and can be managed with nonopioid analgesics and adjuvants. In patients with severe lancinating pain, diagnostic and prognostic blocks consisting of infiltration of small amounts of dilute solutions of a local anesthetic into the scar can be performed. If properly done, these produce complete pain relief that lasts for several hours, usually beyond the duration of the pharmacologic effect of the local anesthetic. Repeated injections provide longer and longer periods of pain relief and can be curative. Injection of alcohol into a neuroma can produce prolonged relief (see Chapter 102, section Local Infiltration). If injection therapy does not produce prolonged pain relief, however, excision of the scar by plastic surgery should be considered.

Acute and Chronic Dermatologic Diseases

Various acute and chronic dermatologic diseases can involve the abdominal wall and flank region and cause pain (see Chapter 32).

Chronic postburn pain can also involve the abdomen and cause persistent aching, burning pain in the site of the postburn scar. These disorders are often difficult to treat, but if the pain is sufficiently severe, intercostal block with a long-lasting local anesthetic should be given a trial. This chronic pain syndrome might also respond to intravenous infusion of local anesthetics (see Chapter 102).

Postoperative Pain

Acute postoperative pain is most severe following upper abdominal and thoracic operations and following renal surgery. The incidence and severity of pain following lower abdominal surgery are lower, but moderate to severe pain occurs in a significant percentage of patients. Postsurgical pain is discussed in detail in Chapter 41.

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CHAPTER 70

General Considerations

John S. McDonald and Andrea J. Rapkin

Pain that arises from the pelvic cavity and the perineum is a common cause of pain that afflicts women. The prevalence of chronic pelvic pain is really undefined, yet studies quote percentages from 12% to 20%, with a lifetime occurrence rate as high as 33% (1). Up to 10% of gynecologic referrals are for chronic pelvic pain and many of these are handled by initial surgical intervention, with statistics revealing 44% undergo laparoscopies (2). In pain clinic referrals, 30% of the women have already had a hysterectomy (2,3). Curiously, though, only 12% of all hysterectomies are performed for the treatment of pelvic pain.

This chapter provides an introduction of general considerations and a basic review of the underlying essentials of pain of pelvic origin. It also addresses how to approach the patient with pain in the pelvic and perineal areas. In doing so, we first address basic considerations including anatomy, neurology, physiology, etiology, and epidemiology. We then address clinical considerations that include physical examination, differential diagnosis, the actual diagnosis, and finally, suggestions on treatment. Much of the anatomic and neurologic data are derived from the last edition of this book.

BASIC CONSIDERATIONS

Anatomy of the Pelvis

The pelvis is the lowest segment of the abdominal cavity and is roughly shaped like a basin, with the top being in a line from the top of the pubis extended to the top of S-1 and the bottom being in a line from the bottom of the pubis extended to the tip of the coccyx. The boundaries anteriorly are the pubic arch, posteriorly the sacrum and coccyx, and laterally the iliac bones (4). The skeletal pelvis is composed of its ligaments and muscles and contains the respective male and female pelvic viscera. The muscles of the pelvis include the obturator internus muscles, piriformis and coccygeus muscles, and the levatores ani muscles, which form the pelvic diaphragm. Additionally, the muscles include the deep transverse perineal muscle and sphincter urethrae, which together constitute the urogenital diaphragm. The pelvis also contains the urinary bladder, terminal part of the ureters, sigmoid colon, rectum and a few coils of small intestine, and internal genitalia, together with blood vessels, lymph vessels, lymph nodes, and nerves.

Skeletal Pelvis

The anatomies of the female and male pelvises are shown in Figure 70-1. The pelvis is massively constructed in line with the primary function of withstanding stresses caused by the entire upper body weight and the powerful body musculature (4,5). The pelvis is composed of two parts, the greater segment and the lesser segment, sometimes called the *false* and *true* pelvis.

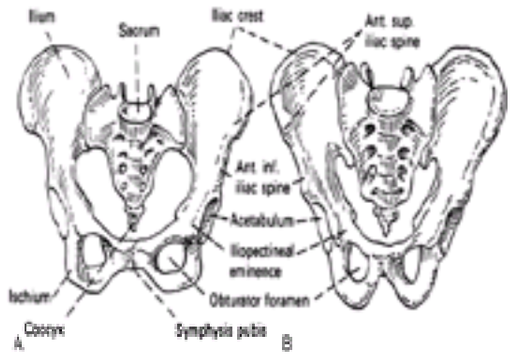

Figure 70-1. Anterior view of the female pelvis **(A)** and male pelvis **(B)**. (Modified from Clemente CD, ed. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:273.)

Greater Pelvis

The greater (false) pelvis consists of the phalangeal parts of the iliac bones above the linea terminalis on each side and the base of the sacrum posteriorly. The bone structure along this junctional zone is particularly massive and forms the main pathway on each side from the acetabular fossae to the vertebral column around the visceral cavity. The cavity of the greater pelvis is part of the abdomen and, because of the inclination of the pelvis as a whole, the cavity has little skeletal wall anteriorly.

Lesser Pelvis

The lesser (true) pelvis encloses a true basin when the soft tissues of the pelvic floor are in place (4,5). From the skeletal point of view it is a narrowed continuation of the greater pelvis with irregular but more complete walls bounding the pelvic cavity or canal. This cavity, which is of special obstetric importance, has an axis that is curved in the median plane. It is limited above by a superior opening, occupied in life by viscera traversing it, and limited below by the inferior opening that is largely closed by the pelvic floor and its sphincter mechanisms. Figure 70-2 depicts the boundaries and diameters of the superior pelvic aperture (see Fig. 70-2A) and of the inferior pelvic aperture. Figure 70-2B and Figure 70-2C show a sagittal section through the female pelvis depicting the planes of the inlet and outlet and their relation

to each other (see Fig. 70-2D). From a standing position, the pelvic canal curves obliquely backward relative to the trunk and abdominal cavity. The whole pelvis is tilted forward so that the plane of the pelvic brim makes an angle of 50 to 60 degrees with the horizontal.

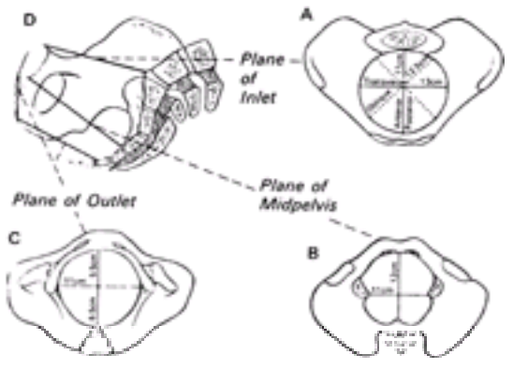

Figure 70-2. Planes and diameters of the pelvis. **A:** Superior plane or obstetric inlet, bounded posteriorly by the promontory of the sacrum, laterally by the iliopectineal line, and anteriorly by the rami of pubic bones and the upper margin of the symphysis pubis. **B:** Midpelvic plane, bounded posteriorly by the sacrum near the junction of the S-3 and S-4 vertebrae, laterally by the ischial spine, and anteriorly by the inferior aspect of the symphysis. **C:** Inferior plane or obstetric outlet, composed of two triangular components. The posterior component is bounded behind by the sacrococcygeal joint, laterally by the sacrotuberous ligament, and anteriorly by the biischial diameter; the anterior component is bounded by the biischial diameter behind, laterally by the inner margin of the pubic arch, and anteriorly by the inferior margin of the symphysis. The floor or the pelvic outlet is composed of the soft tissues of the perineum and the structures making up the urogenital diaphragm. **D:** Sagittal view of the pelvis showing important anteroposterior diameters (*solid lines*). (From Bonica JJ, McDonald JS. *Principles and practice of obstetric analgesia and anesthesia*, 2nd ed. Baltimore: Williams & Wilkins, 1995:763.)

Joints and Ligaments of the Pelvis

The pelvis has a massive complex of joints and ligaments that tie together the ilium with the sacrum and with the fifth lumbar vertebra. The two pubic bones meet in the midline plane, where they form the cartilaginous joints of the pubis symphysis.

Sacroiliac Joint

The sacroiliac articulation is synovial between the articular surfaces of the sacrum and ilium. The articular surfaces exhibit irregular elevations and depressions that are more pronounced in the male and fit into one another. These surfaces restrict movement but contribute to the strength of the joint that transmits weight from the vertebral column to the lower limb. The articular surface is covered by hyaline cartilage and the ilium by fibrocartilage (Fig. 70-3). The articular capsule is attached close to the margin of the articular surfaces of the sacrum and ilium (4,5). The joint is held together by anterior, interosseous, and posterior sacroiliac ligaments (Fig. 70-4; see Fig. 70-3), which are all supplied by the posterior primary divisions of the upper three sacral nerves.

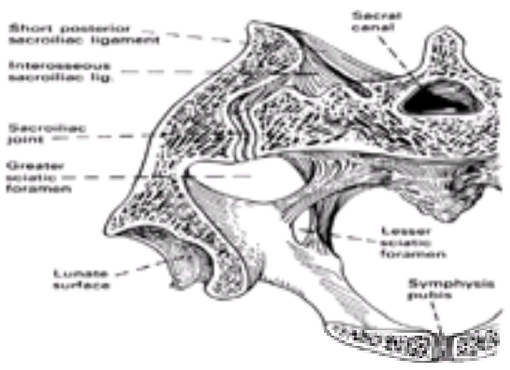

Figure 70-3. Coronal section through the pelvis showing the sacroiliac joint through the anterior sacral segment. The anterior part of the joint is covered by hyaline cartilage on the sacral surface, and fibrocartilage overlies the surface of the ilium. The interosseous sacroiliac ligament fills the cleft above and behind the joint cavity. The joints of the surfaces are irregularly shaped and the interconnecting bones fit snugly, thus restricting movement but buttressing the weight-bearing function of the joint. (Modified from Clemente CD, ed. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:360.)

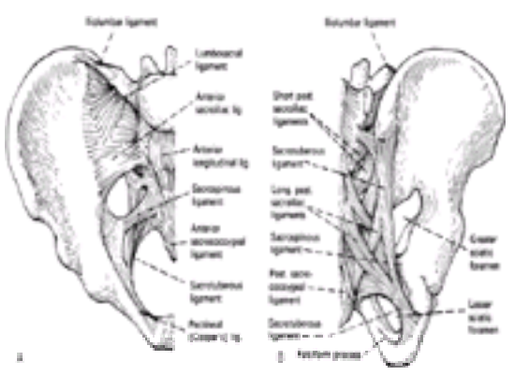

Figure 70-4. Joints and ligaments of the right half of the pelvis. **A:** Anterior view. **B:** Posterior view. See text for details. (Modified from Clemente CD, ed. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:361–362.)

Anterior Sacroiliac Ligament. The anterior sacroiliac ligament is a thickening of the anterior inferior parts of the fibrous capsule. It is well developed at the level of the arcuate line and inferiorly at the level of the posterior inferior iliac spine, where it connects the base and lower part of the sacrum to the auricular surface of the ilium and preauricular sulcus.

Interosseous Sacroiliac Ligament. The interosseous sacroiliac ligament is massive and strong and forms the chief bond between the two bones. It fills the irregular space immediately above and behind the joint and is covered by the posterior sacroiliac ligament. It consists of deeper and more superficial parts, with the deeper parts having cranial and caudal bands that pass from the depression behind the auricular surface of the sacrum to the depression in the iliac tuberosity. These bands are covered by and blend with the more superficial part, which forms a fibrous sheet connecting the cranial and posterior margins of the rough area behind the auricular surface on the sacrum with the corresponding margin of the iliac tuberosity.

Posterior Sacroiliac Ligament. The posterior sacroiliac ligament overlies the interosseous ligament, from which it is separated by the dorsal rami of the sacral spinal nerves and vessels. It consists of several fasciculi that course in various directions. The deeper upper part is called the *short posterior sacroiliac ligament* and passes from the lateral sacral crest with varying degrees of obliquity to the posterior superior iliac spine and inner lip of the posterior part of the iliac crest. The lower fibers, which make up the long posterior sacroiliac ligament, pass from the second, third, and fourth sacral crests to the posterior superior iliac spine. This ligament descends

obliquely and becomes continuous with the sacrotuberous ligament and medially with the posterior layer of the thoracolumbar fascia.

Movement. The sacroiliac joint allows a small amount of anteroposterior rotatory movement around a transverse axis that is usually 5 to 10 cm below the promontory of the sacrum vertically. These movements occur during flexion and extension of the trunk. The range is the same in male and nonpregnant female subjects but is increased considerably during pregnancy. The greatest change in position of the sacrum in relation to the iliac bones occurs when the individual arises from a recumbent to a standing position: The sacral promontory moves forward as much as 5 to 6 mm as the body weight is taken on the sacrum. The backward movement of the lower end of the sacrum is considerably less. In middle age and beyond, fibrous adhesions and a gradual obliteration of the synovial cavity occur in both genders, earlier in men and after menopause in women (4,5). In old age the joints can become completely fibrosed and even ossified.

Vertebropelvic Ligament. The ilium is connected with the L-5 vertebra by the iliolumbar ligament, and the sacrum is connected to the ischium by the sacrotuberous and sacrospinous ligaments (see Fig. 70-4).

Iliolumbar Ligament. The iliolumbar ligament is attached to the tip and to the lower and front part of the transverse process of the L-5 vertebra. Sometimes it has an additional weak attachment to the transverse process of the L-4 vertebra. It radiates as it passes laterally and is attached by two main bands to the pelvis. The inferior band, the lumbosacral ligament, runs from the inferior aspect of the L-5 transverse process to the upper medial aspect of the ilium, blending with the anterior sacroiliac ligament. The superior band passes from the transverse process of the L-5 vertebra to the posterior surface of the medial part of the iliac crest. This band gives partial origin to the quadratus lumborum muscle, which is also attached to the crest of the ilium immediately in front of the sacroiliac joint.

Sacrotuberous Ligament. The sacrotuberous ligament is attached by a broad, flat base to the posterior superior and inferior iliac spines (where it partially blends with the posterior sacroiliac ligament), to the fourth and fifth transverse tubercles of the sacrum, and to the lateral margin of the lower part of the sacrum and upper part of the coccyx (see Fig. 70-4). These fibers run obliquely downward and laterally and converge to form a thick, narrow band that is fixed to the medial margin of the ischial tuberosity and then continues along the ramus of the ischium as the falciform process. The free concave edge of the falciform process blends with the fascial sheath of the internal pudendal vessels and pudendal nerve. The lowest fibers of the gluteus maximus are attached to the posterior surface of the sacrotuberous ligament. The ligament is pierced by the coccygeal branch of the gluteal artery, by the perforating cutaneous nerve, and by minute filaments of the coccygeal plexus.

Sacrospinous Ligament. The sacrospinous ligament is a thin, triangular-shaped structure that attaches to the spine of the ischium. It attaches medially by its broad base to the lateral margin of the sacrum and coccyx in front of the sacrotuberous ligament. The pudendal nerve passes posteriorly to the point at which the ligament attaches to the spine. It is an important landmark in carrying out pudendal nerve block for vaginal delivery or during surgical procedures on the perineum.

Function. The sacrotuberous ligament and, to a lesser extent, the sacrospinous ligament, oppose upward tilting of the lower part of the sacrum under the downward thrust that is imparted to the upper end of the bone by the weight of the trunk. These two ligaments convert the sciatic notches into two foramina. The greater sciatic foramen is bounded in front and above by the greater sciatic notch, behind by the sacrotuberous ligament, and below by the sacrospinous ligament in the spine of the ischium. It is partially filled by the piriformis muscles that emerge from the pelvis through it. Above this muscle the superior gluteal vessels and nerves pass out of the pelvis while below it pass the inferior gluteal vessels and nerves, internal pudendal vessels and pudendal nerves, sciatic nerve, posterior femoral cutaneous nerve, and nerves to the obturator internus and quadratus femoris muscles. The lesser sciatic foramen is bounded in front by the body of the ischium, above by the spine of the ischium and sacrospinous ligament, and behind by the sacrotuberous ligament. It transmits the tendon of the obturator internus muscle, the nerve to this muscle, and the internal pudendal vessels and pudendal nerves.

Pubic Symphysis. The pubic symphysis is the point at which the two pubic bones meet each other in the medial plane to form a cartilaginous ligament and are connected by the superior pubic and arcuate pubic ligaments and by an interpubic disk of fibrocartilage. The superior pubic ligament connects the pubic bone superiorly and extends as far as the pubic tubercles. The arcuate ligament is a thick arch of fibers that connects the lower borders of the symphysis surface of the two pubic bones and forms the upper boundary of the pubic arch. Above, it blends with the interpubic disk and is attached laterally to the inferior rami of the pubic bone. The interpubic disk connects the adjacent surfaces of the pubic bones; each surface is covered with a thin layer of hyaline cartilage and is firmly attached to the bone, an arrangement that resists shearing forces. The opposed surfaces of the hyaline cartilage are connected by a lamina of fibrocartilage that varies in thickness. Some separation between the pubic bones occurs late in pregnancy and during childbirth.

Mechanism of the Pelvis

Although the skeletal pelvis supports and protects the contained pelvic viscera, it is primarily part of the lower limb and affords surfaces for the attachment of the muscles of the trunk and lower limbs (4,5). Its most important mechanical function is transmission of the weight of the head, trunk, and upper limbs to the lower extremities. Movements of the sacrum are regulated by its form and ligamentous attachment. When viewed as a whole, it presents the shape of a wedge, with its base upward and forward. The first component force is therefore acting against the resistance of the wedge, and its tendency to separate the iliac bones is resisted by the sacroiliac and lumbar ligaments posteriorly and by the ligaments of the symphysis pubis anteriorly. During pregnancy hormonal changes cause the pelvic ligaments and joints to become relaxed and capable of more extensive movements. This renders the locking mechanism of the sacroiliac joint less restrictive and permits greater rotation, a change that allows alteration in the diameter of the pelvis during childbirth. The less effective the locking mechanism, the more the strain of weight bearing pulls the ligaments, frequently resulting in sacroiliac strain during and after pregnancy. After childbirth the ligaments tighten up again and the locking mechanism becomes more effective. In some cases, however, the locking occurs in the position of rotation of the hip bones that occurred during pregnancy. This so-called subluxation of the sacroiliac joint causes pain by the unusual tension that is imposed on the ligaments. Reduction by forcible manipulation after the joint is completely anesthetized can be attempted.

Pelvic Muscles and Fascia

The muscles within the pelvis are divided into two groups: (a) the piriformis and obturator internus muscles; and (b) the levator ani and coccygeus muscles that, with the corresponding muscles of the opposite side, form the pelvic diaphragm. All the fascia investing the muscles form a continuum of connective tissue that joins the fascial covering of the pelvic viscera above with the fascia of the perineum below.

Pelvic Fascia

The pelvic fascia consists of the parietal pelvic fascia, which constitutes the fascial sheaths of the pelvic muscles, and the visceral pelvic fascia, the fascial sheaths of the pelvic viscera and of their blood vessels and nerves (see Anatomy of the Perineum and Neurology of the Perineum, later in this chapter). The parietal pelvic fascia covering the pelvic surface of the obturator internus muscle is well differentiated as the obturator fascia. The fascia of the piriformis muscle is thin and fuses with the periosteum of the anterior surface of the sacrum around the margin of the anterior sacral foramina. Its sacral attachment ensheathes the nerves emerging from these foramina. The fascia of the pelvic diaphragm extends over both surfaces of the levator ani muscles. The portion above is called the *superior fascia* of the pelvic diaphragm, and the part below it is called the *inferior fascia* of the pelvic diaphragm, also known as the *anal fascia*. Laterally the superior fascia follows the line of attachment of the muscle and therefore varies somewhat. Anteriorly it is attached to the back of the symphysis pubis about 2 cm above its lower border. It can be traced laterally across the back of the superior ramus of the pubis for a short distance to the obturator fascia, with which it blends along a somewhat irregular line to the spine of the ischium. The inferior fascia of the pelvic diaphragm covers the medial wall of the ischiorectal fossa. Above it is continuous with the fascia of the pudendal canal and with the obturator fascia along the line of attachment of the levator ani muscle. It is continuous below with the fascia on the sphincter urethra and sphincter ani externus muscle.

Levator Ani Muscle

Figure 70-5 depicts a sagittal section of the pelvis with the viscera removed to show the pelvic aspect of the left levator ani and coccygeal muscles. The levator ani muscle is a broad, thin structure attached to the inner surface of the side of the true pelvis. It unites with the opposite muscle to form the greater part of the floor of the pelvic cavity. It is attached anteriorly to the pelvic surface of the body of the pubis, lateral to the symphysis, behind to the medial surface of the spine of the ischium, and between these two points to the obturator fascia. Morphologically the levator ani can be divided into the pubococcygeus and iliococcygeus muscles.

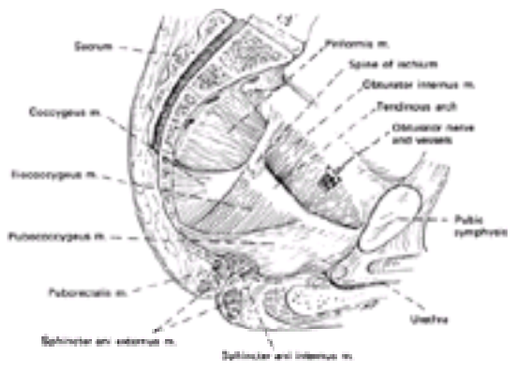

Figure 70-5. Sagittal section of the pelvis showing the muscles of the left lateral wall of the pelvis. The obturator nerve and vessels pass through the obturator muscle, which is normally covered by fascia (not shown). (Modified from Clemente CD, ed. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:499.)

Pubococcygeus Muscle

The pubococcygeus muscle arises from the posterior surface of the pubis and from the anterior part of the obturator fascia. Its fibers are directed backward almost horizontally along the line of the anal canal and become attached to the front of the coccyx by a tendinous plate that is continuous with the anterior sacrococcygeal ligament. The medial coccygeus muscle arises from the ischial spine and from the posterior part of the tendinous arch of the levator ani muscle. Its fibers attach to the sides of the coccyx and to the opposite muscle in the median raphe on the undersurface of the tendinous plates of the pubococcygeus that contribute to the anococcygeal ligament. The superior or pelvic surface of the levator ani is separated by its covering fascia from the bladder, prostate, rectum, and peritoneum, while its inferior or perineal surface forms the medial boundary of the ischiorectal fossa and is covered by the inferior fascia of the pelvic diaphragm. Its posterior border is free and is separated from the coccygeus muscle by areolar tissue, while the medial borders of the two muscles are separated by the visceral outlet, an interval through which the urethra, vagina, and anorectum pass from the pelvis. The nerve supply of the levator ani muscle includes a branch from the S-4 nerve, a branch that arises either from the inferior rectal nerve or from the perineal branch of the pudendal nerve. The function of the levator ani muscle is constriction of the lower end of the rectum and vagina, and probably fixation of the perineal body. The levator ani, together with the coccygei, form a muscular diaphragm that supports the pelvic viscera and opposes itself to the downward thrust produced by any increase in intraabdominal pressure.

Coccygeus Muscle

The coccygeus muscle is posterosuperior in the same tissue plane as the levator ani muscle. It consists of a triangular sheath of muscular and tendinous fibers, arising by its apex from the pelvic surface of the spine of the ischium and sacrospinous ligament. It is attached at its base to the margin of the coccyx and side of the S-5 segment. The muscle receives its nerve supply through branches from the S-4 and S-5 spinal nerves. The coccygeus functions in pulling forward and supporting the coccyx after it has been pressed backward during defecation or parturition. The coccygeus, together with the levator ani and piriformis muscles, closes the posterior part of the pelvic outlet.

Pelvic Viscera and Their Peritoneal Covering

The pelvic viscera consist of the urinary bladder, terminal parts of the ureters, sigmoid colon, rectum and a few coils of small intestine, blood vessels, lymph vessels, nodes, nerves, and internal genitalia. In men the internal genitalia consist of the prostate, seminal vesicles, ejaculatory ducts, and vas deferens; in women the internal genitalia consist of the ovaries, uterine tubes, uterus, and vagina. A description of the anatomy of each of these structures is beyond the scope of this book and is limited to the illustration of these organs (Fig. 70-6 and Fig. 70-7). Painful disorders of female internal genital organs are discussed in Chapter 72, while those that affect the male genital organs and the bladder are described in Chapter 73. Because pain from diseases of these organs usually involves inflammation of the pelvic peritoneum that overlies these structures, it is briefly described here. Following the suggestion by Williams and Warwick (4) to trace the peritoneum from one viscus to another and from the viscus to the parietes, it is helpful to follow its continuity in the vertical and horizontal directions. Here the discussion is limited to its vertical disposition.

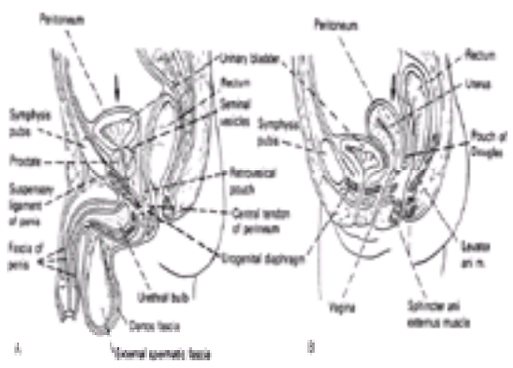

Figure 70-6. Schematic diagram of the pelvis and perineum in the medial sagittal plane showing the fascia and some of the muscles. **A:** Male pelvis and perineum. **B:** Female pelvis and perineum. See text for details. (**A** modified from Clemente CD, ed. *Gray's anatomy of the human body*, 30th ed. Philadelphia: Lea & Febiger, 1985:502; **B** modified from Bonica JJ. *Principles and practices of obstetric analgesia and anesthesia*. Vol 1. Philadelphia: Davis, 1967:502–503.)

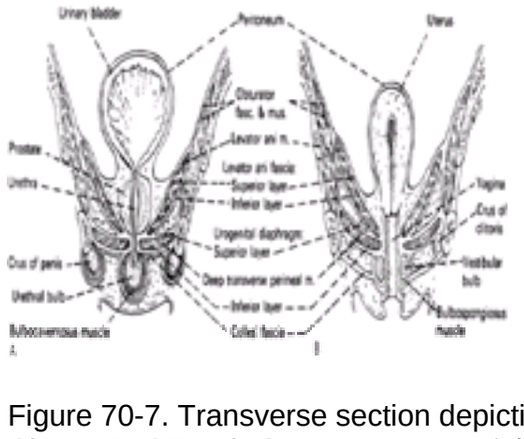

Figure 70-7. Transverse section depicting the fascia and muscles of the male **(A)** and female **(B)** pelvic and anal regions. See text for details. (Modified from Clemente CD, ed. *Gray's anatomy of the human body*, 27th ed. Philadelphia: Lea & Febiger, 1959:476.)

Vertical Disposition of the Pelvic Peritoneum

The peritoneum descends from the abdomen proper over structures in the pelvic cavity. It is reflected from the posterior pelvic wall as the anterior layer of the sigmoid mesocolon, which invests the sigmoid colon and returns to the pelvic wall as the posterior layer of the sigmoid mesocolon. It then descends, covering the front and

sides of the upper third of the rectum and the front of the middle third of the rectum.

In the Male. In the male, the peritoneum leads to the front of the rectum (at the junction of the middle and lower thirds) and passes forward onto the upper end of the seminal vesicles and the upper surface of the urinary bladder. Between the rectum and bladder it dips slightly downward to form a recess, the rectovesical pouch, the bottom of which is a little below the level of the upper ends of the seminal vesicles and approximately 7.5 cm from its anal orifice (4). From the apex of the bladder it is carried along the medial umbilical ligaments to the anterior abdominal wall, up to the level of the umbilicus. When the bladder is distended the peritoneum is stripped away from the lower part of the anterior abdominal wall so that a considerable part of the anterior surface of the bladder lies directly against the abdominal wall, without the intervention of the peritoneum. This permits an instrument to be passed through the abdominal wall into the distended bladder without passing through the peritoneal cavity.

In the Female. In the female, the peritoneum passes from the front of the rectum onto the posterior fornix of the vagina and from there to the back of the cervix and body of the uterus to form the rectouterine fold. This dips downward to form the rectouterine pouch of Douglas, the bottom of which is approximately 5.5 cm above the anal orifice. The peritoneum continues over the fundus of the uterus and descends on its anterior (vesical) surface as far as the body of the uterus and cervix. From here it is reflected anteriorly onto the upper surface of the bladder to form a shallow recess, the vesicouterine pouch. The layers of the peritoneum on the anterior and posterior surfaces of the uterus are reflected laterally from the lateral margins of the uterus to the side walls of the pelvis to form an expanded fold on each side, the broad ligament of the uterus (Fig. 70-8).

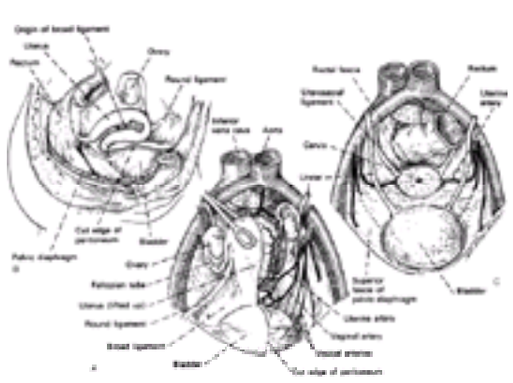

Figure 70-8. Ligaments of the uterus. **A:** Anterior view. **B:** Parasagittal view. **C:** Superior view. (Modified from Netter FH. *The CIBA collection of medical illustrations.* Vol 2, Reproductive system. Summit, NJ: CIBA Pharmaceuticals, 1979:89, 95, and 97.)

Uterine Ligaments

The uterus is connected to the bladder, rectum, and walls of the lesser pelvis by a number of ligaments. Some of these are merely peritoneal folds and have little supporting effect, while others consist of nonstriated muscles and fibrous tissue and function as real ties to provide some measure of dynamic control. These ligaments consist of the anterior, uterosacral (posterior), broad, round, and transverse ligaments (see Fig. 70-8).

Anterior and Posterior Ligaments. The anterior ligament consists of the uterovesical fold of the peritoneum, which is reflected onto the surface of the bladder from the front of the uterus at the junction of the cervix and body of the uterus. The posterior ligament consists of the rectovaginal fold of peritoneum, which is reflected from the back of the posterior fornix of the vagina onto the front of the rectum. It forms the bottom of the deep rectouterine pouch that is bounded anteriorly by the posterior wall of the body of the uterus, supravaginal portion of the cervix, and posterior fornix of the vagina, posteriorly by the rectum, and laterally by two folds of the peritoneum that pass backward from the cervix, one on each side of the rectum, to the posterior wall of the lesser pelvis. These are the rectouterine folds, which contain a considerable amount of fibrous tissue and nonstriated muscular fibers, are attached to the front of the sacrum, and constitute the uterosacral ligament. On rectal examination, the uterosacral ligaments can be palpated as they pass backward on the side of the rectum (4).

Broad Ligaments. Each of two broad ligaments passes from the side of the uterus to the lateral wall of the pelvis (see Fig. 70-8). With the uterus, both form a septum across the cavity of the lesser pelvis, dividing it into an anterior part containing the bladder and a posterior part containing the rectum, terminal coils of the ileum, and part of the sigmoid colon. When the bladder is empty or only slightly distended, the surface of the broad ligaments is directed superiorly and inferiorly, and they have a free anterior (unattached) border. As the bladder fills, the plane of the ligaments alters and their free border becomes superior in position; in this condition the broad ligaments consist of anterior and posterior layers that are continuous with each other at their upper free border and diverge from each other below, where they approach the superior surface of the levator ani muscle. The uterine tube is contained in the free border. The lateral part of the ligament between the tubes and ligament of the ovary and mesovarium is known as the *mesosalpinx*. The infundibulum of the uterine tube projects from the free border near its lateral extremity. The ovary is attached to the posterior layer by the mesovarium. The part of the broad ligament that extends from the infundibulum of the tube and the upper pole of the ovary to the lateral wall of the pelvis contains the ovarian vessels, nerves, and lymph vessels and is known as the *suspensory ligament* of the ovary. The term *mesometrium* is applied to that part of the broad ligament extending from the pelvic floor to the ovary, ligament of the ovary, and body of the uterus. The uterine artery, vein, and nerves pass between the layers of the broad ligaments at their inferior border approximately 1.5 cm lateral to the cervix and then ascend in the medial part of the broad ligament, turning laterally below the uterine tube to anastomose with the ovarian artery.

Round Ligaments. The round ligaments of the uterus are two narrow, flat bands from 10 to 12 cm long that are situated between the layers of the broad ligament in front of and below the uterine tubes. Each ligament begins at the lateral edge of the uterus and is directed anteriorly and laterally across the vesical vessels, obturator vessels and nerves, and obliterated umbilical artery, and over the externus iliac vessels. It then passes through the deep inguinal ring to hook around the beginning of the inferior epigastric artery, traversing the inguinal canal. It finally breaks up into strands that merge with the areolar tissue in the labium majus.

Transverse Cervical Ligaments. Each transverse cervical ligament of Mackenrodt, also called the *cardinal ligament*, is attached to the side of the cervix uteri and to the vault and lateral fornix of the vagina. Both are continuous with the fibrous tissue that surrounds the pelvic blood vessels and help to maintain the position of the uterus.

Function. All these ligaments act as mechanical supports for the uterus, helping to maintain it in its normal position. The levator ani and coccygei muscles, the muscles of the uterogenital diaphragm, and the perineal body appear to be of particular importance in this respect.

Anatomy of the Perineum

The perineum overlies the inferior pelvic aperture, or pelvic outlet. Its deep boundaries are the pubic arch and arcuate pubic ligament anteriorly, the tip of the coccyx posteriorly, and the inferior ramus of the pubis and ramus of the ischium, ischial tuberosity, and sacrotuberous ligament laterally (4,5). The space within these boundaries is somewhat trapezoidal in shape. The surface of the body of the perineum in the man is limited by the scrotum in front, the buttocks behind, and the medial sides of the thighs laterally, whereas in the woman the external genitalia (labia majora and minora) limit the perineum anteriorly. Most anatomists divide the perineum into two parts by drawing a line transversely in front of the ischial tuberosity. The region posterior to this line contains the termination of the anal canal and is thus known as the *anal region* or *anal triangle*, while the anterior part contains the external urogenital organs and is known as the *urogenital region* or *urogenital triangle*. The muscles and fascia of the perineum are also divided into these two groups, anal and urogenital, although these two groups meet in the perineal body and actually constitute a single morphologic unit (4,5).

Muscles and Fascia of the Anal Region

Figure 70-9 depicts the musculature of both the male and female perineum. Each muscle is briefly described.

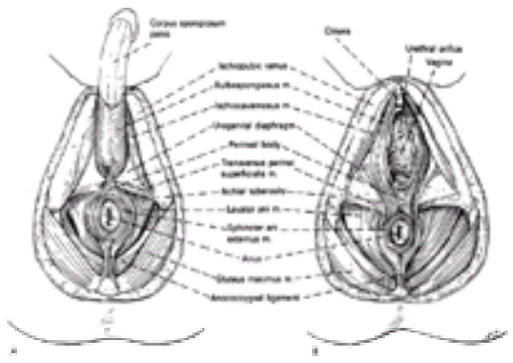

Figure 70-9. Muscles of the perineum. The inferior fascia of the urogenital diaphragm has been removed to depict the muscles. **A:** Muscles of the male perineum. **B:** Muscles of the female perineum.

Sphincter Ani Externus Muscle. The sphincter ani externus muscle surrounds the lower part of the anal canal and is intimately adherent to the skin below, whereas above it overlaps the sphincter ani internus. The muscle is composed of three parts: subcutaneous, superficial, and deep. The subcutaneous lamina is a band of fibers that lies beneath the skin and surrounds the anal orifice. Some fibers are attached anteriorly to the perineal body and posteriorly to the anococcygeal ligament. The superficial lamina lies deep to the subcutaneous lamina and constitutes the main portion of the muscle (5). It also arises from the narrow tendinous anococcygeal ligament that stretches from the tip of the coccyx to the posterior margin of the anus. The muscle fibers then encircle the anus and meet anterior to the anus to be inserted into the perineal body. Here the muscle joins with fibers from the transversus perinei superficialis, levator ani, and bulbospongiosus muscles. The deep lamina forms a complete sphincter to the anal canal with its fibers surrounding the canal closely applied to the internal anal sphincter, while its deep fibers are interlaced with fibers of the puborectalis muscle. In front the deep part of the external anal sphincter blends with other muscles at the perineal body. This muscle is supplied by the perineal branch of the S-4 spinal nerve and by twigs from the inferior rectal branch of the pudendal nerve (S-2 and S-3 spinal nerves).

The sphincter ani internus muscle is a muscular ring that surrounds approximately 2.5 cm of the anal canal. Its inferior border is in contact with, but quite separate from, the external sphincter. It is approximately 5 mm thick and is formed by an aggregation of the involuntary circular fibers of the large intestine. The distal border is approximately 6 mm from the orifice of the anus. This muscle is supplied by fibers from the middle rectal plexus (see previous discussion).

Corrugator Cutis Ani Muscle. The corrugator cutis ani muscle is a thin layer of involuntary muscle and yellow elastic fibers that radiates from the orifice. It is believed that the fibers fade into the submucous tissue, while blending with the true skin laterally. By its contraction this muscle puckers the skin, raising it into ridges around the anal orifice.

Fascia. The superficial fascia of the region is thick and areolar in texture and contains many fat cells in its meshes. On each side a pad of fatty tissue extends deeply into the lateral space between the levator ani and obturator internus muscles called the *ischiorectal fossa*. The deep fascia lines the ischiorectal fossa and makes up the inferior fascia of the pelvic diaphragm and the part of the obturator fascia below the attachment of the levator ani muscles (see Fig. 70-9).

Ischiorectal Fossa. The ischiorectal fossa is somewhat wedge shaped, with its space directed to the surface of the peritoneum and its thin edge at the line of meeting of the obturator internus and levator ani muscles covered by the obturator fascia and by the inferior fascia of the pelvic diaphragm. The internal pudendal vessels and their accompanying nerves are in the lateral wall of the ischiorectal fossa and are enclosed in a special sheath of fascia to form the pudendal canal. This sheath is fused with the lower part of the obturator fascia, extending upward to blend with the inferior fascia of the pelvic diaphragm and downward to become continuous with the falciform process of the sacrotuberous ligament.

Muscles and Fascia of the Male Urogenital Region

Muscles. In both men and women the muscles of the urogenital region consist of the bulbospongiosus, ischiocavernosus, transversus perinei superficialis and profundus, and sphincter urethrae. The muscles are grouped into superficial and deep layers. The superficial urogenital muscles include the midline bulbospongiosus, right and left ischiocavernosus, and right and left transversus perinei superficialis, all of which occupy the superficial perineal space. The deep perineal space is occupied by the sphincter urethra and right and left deep transversus perinei profundus, collectively known as the urogenital diaphragm (see Fig. 70-7). The following review of these muscles is intended to supplement this illustration.

Transversus Perinei Superficialis Muscle. The transversus perinei superficialis muscles consist of a pair, each of which is composed of a narrow strip of muscle fibers that passes more or less transversely across the superficial space in front of the anus. Each arises by tendinous fibers from the medial and anterior parts of the tuberosity of the ischium. Running medially they end in the perineal body, where they join the muscle of the opposite side. At the perineal body they are also joined by the superficial part of the sphincter ani externus muscle posteriorly and by the bulbospongiosus muscle anteriorly.

Bulbospongiosus (Bulbocavernosus) Muscle. The bulbospongiosus (bulbocavernosus) muscle is located in the medial line of the perineum in front of the anus. It consists of two symmetric parts united by a median tendinous raphe. The muscle arises from this median raphe and from the perineal body, and its fibers diverge into two halves (4,5) (see Fig. 70-7A and Fig. 70-9A). The most posterior fibers form a thin layer that is lost on the inferior fascia of the urogenital diaphragm. The middle fibers encircle the bulk and adjacent part of the corpus spongiosum penis and join with fibers of the opposite side on the upper part of the corpus cavernosum penis in a strong aponeurosis. The anterior fibers spread out over the side of the corpus cavernosum penis and are inserted partly in that body, anterior to the ischiocavernosus, and partly in the tendinous expansion that covers the dorsal vessels of the penis (5). This muscle aids in emptying the urethra after the bladder has expelled its contents. Its middle fibers assist in the erection of the corpus spongiosus penis by compressing the erectile tissue of the bulb. The anterior fibers also contribute to the erection of the penis by compressing the deep dorsal vein of the penis because their tendinous expansion is inserted into and is continuous with the deep fascia covering the deep dorsal vessels of the penis.

Ischiocavernous Muscle. The ischiocavernous muscle, also called the *erector penis muscle*, consists of a pair, with each covering the crura of the penis (see Fig. 70-7A and Fig. 70-9A). Each is an elongated muscle, broader in the middle than at either end and situated at the lateral boundary of the perineum. It is erected by tendinous and fleshy fibers from the inner surface of the ischial tuberosity behind the crus penis and from the rami of the pubis and ischium, on both sides of the crus. From these points, fleshy fibers course anteriorly along the crus and end in an aponeurosis that is inserted into the sides and undersurface of the crura as they become the body of the penis. This muscle compresses the crus penis and thus helps to maintain erection of the penis.

Transversus Perinei Profundus Muscle. The transversus perinei profundus muscle arises from the inner surface of the ramus of the ischium and passes to the median line, where it interlaces in a tendinous raphe with its fellow of the opposite side. Lying in the same plane as the sphincter urethra, these two muscles are interposed between the superior and inferior fascial layers of the urogenital diaphragm and form much of the bulk of the structure (see Fig. 70-7). These two muscles were formerly described together as the constrictor urethrae. They are believed to help in steadying the perineal body and therefore are likely to contribute to the general supportive function of the region (4).

Sphincter Urethrae Muscle. The sphincter urethrae muscles, in the man, surround the whole length of the membranous portion of the urethra and are enclosed in the fascia of the urogenital diaphragm. The superficial or external fibers arise in front of the transverse perineal ligament and from the neighboring fascia, and pass backward on each side of the urethra to converge on the perineal body. Their deep fibers arise from the inner surface of the ramus of the pubis and pass medially to form a continuous circular investment of the membranous urethra. The muscles of both sides act together as a sphincter to compress the membranous region of the urethra, particularly if the bladder contains fluid. Like the bulbospongiosus muscle during micturition, they are relaxed and only come into action at the end of the process to eject the last drops of urine. These muscles are also concerned with ejaculation. All the muscles of the urogenital region are supplied by the perineal branch of the pudendal nerve.

Fascia. The fascia of the male urogenital diaphragm consists of a superficial (external, inferior) fascia and deep (internal, superior) fascia. The inferior fascia is a flat, triangular, membranous sheet that bridges the angular interval between the ischiopubic rami. It is attached laterally to the medial border of the rami from the arcuate pubic ligament to the ischial tuberosity. The middle portion of the fascia is pierced by the urethra. The superior fascia of the urogenital diaphragm is also a flat

triangular membrane that stretches across the same interval as the superficial fascia. It lies between the transversus perinei profundus and pubococcygeus portions of the levator ani, representing the fused fascial membranes of both these muscles. It is securely attached to the symphysis pubis anteriorly and joins other perineal layers at the central tendinous point posteriorly. Laterally it is attached to the medial borders of the ischiopubic rami, where it is continuous with the obturator fascia.

Muscles and Fascia of the Female Urogenital Region

Muscles. This group of muscles in the woman is composed of the same five paired muscles as in the man, with some difference in size and disposition because of the presence of the vagina and female external genitalia. They are similarly grouped into superficial and deep layers, with the latter constituting the urogenital diaphragm (see Fig. 70-7B and Fig. 70-9B).

Transversus Perinei Superficialis Muscle. The transversus perinei superficialis muscle in the woman is a narrow muscular slip that differs little from the corresponding muscle in the man.

Bulbospongiosus Muscle. The bulbospongiosus muscle surrounds the orifice of the vagina and has been called the *sphincter vaginae*. Each muscle covers the lateral parts of the vestibular bulbs and is continuous posteriorly with the perineal body, where it blends with the external and sphincter muscles. Its fibers pass forward on each side of the vagina to become attached to the corpora cavernosa clitoridis. A fasciculus crosses over the body of the clitoris and compresses the deep dorsal vein. The anterior fibers contribute to the erection of the clitoris by compression of the deep dorsal vein.

Ischiocavernosus Muscle. The ischiocavernosus muscle in the woman is smaller than in the man. It covers the unattached surface of the crus clitoridis. It is erected by tendinous and fleshy fibers from the inner surface of the tuberosity of the ischium from the surface of the crus clitoridis and from the adjacent surface of the ramus of the ischium. The muscular fibers end in an aponeurosis that is attached to the sides and undersurface of the crus clitoridis. This muscle compresses the crus clitoridis and thus retards the return of blood through the veins that help to erect the clitoris.

Transversus Perinei Profundus Muscle. The transversus perinei profundus muscle in the woman courses from the inferior ramus of the ischium to the side of the vagina, meeting fibers of the muscles from the opposite side. It helps to fix the perineal body.

Sphincter Urethra Muscle. The sphincter urethra muscle, as in the man, consists of superficial and deep fibers. The superficial fibers arise on each side from the margin of the inferior ramus of the pubis and transverse perineal ligament. These fibers are directly across the pubic arch in front of the urethra and pass around it to blend with the muscular fibers of the opposite side between the urethra and vagina. The internal fibers encircle the lower end of the urethra. The actions of these muscles are similar to those of the man. All the muscles of the woman in the genital region are supplied by the perineal branch of the pudendal nerve.

Fascia. The urogenital diaphragm in the woman, as in the man, is formed by two layers of fascia between which are interposed a deep transverse perineal muscle and sphincter urethra (see Fig. 70-7B). The fascial layers are not as strong in the woman as in the man. The fascial layers are attached anteriorly to the pubic arch by connecting to the arcuate pubic ligament and posteriorly the two continuous deep layers of the superficial fascia surround the superficial transverse perineal muscle. In the midline the fascial layers are divided by the aperture of the vagina and blend with its external coat. The urogenital diaphragm is perforated by the urethra anterior to the midline. Between the two fascial layers are the dorsal vein of the clitoris, a portion of the urethra, the deep transverse perineal muscle and sphincter urethrae muscle, the greater vestibular glands and their ducts, the internal pudendal vessels, the dorsal nerves of the clitoris, the arteries and nerves of the vestibular bulbs, and a plexus of veins.

Neurology of the Pelvis

Like other abdominal viscera, the viscera of the pelvis are supplied by sympathetic and parasympathetic nerves that contain both efferent and afferent fibers. Chapter 65 contains a description of the distribution of the celiac plexus and its subsidiary plexuses, which supply viscera in the abdomen proper. It is mentioned in Chapter 65 that the aortic plexus contributes fibers to the formation of the superior and inferior hypogastric plexuses, which totally innervate the pelvic viscera. The inferior mesenteric plexus also supplies the pelvic portion of the large bowel. These and other subsidiary plexuses supplying the pelvic viscera are briefly described here.

Superior Hypogastric Plexus

The plexus is formed above by the union of branches from the aortic plexus, with contributions by the L-3 and L-4 splanchnic nerves (4,5,6,7,8 and 9). The plexus is situated in front of the bifurcation of the abdominal aorta, left common iliac vein, median sacral vessel, body of the last lumbar vertebra, and promontory of the sacrum, and between the two common iliac arteries (Fig. 70-10). Although surgeons in the 1920s and 1930s who resected this nerve for the treatment of severe dysmenorrhea referred to it as the presacral nerve, it is rarely sufficiently condensed to resemble a sacral nerve but rather is a complex structure of intertwining fibers. Moreover, the plexus is prelumbar rather than presacral in position. It lies in the extraperitoneal connective tissue, and the parietal peritoneum can easily be stripped off its anterior surface. The plexus varies in breadth and in degree of condensation of its constituent nerves and often lies a little to one side of the median plane, more often to the left than to the right. The root of the sigmoid mesocolon containing the superior rectal vessels lies to the left side of the lower part of the plexus. Scattered nerve cells are found in the plexus.

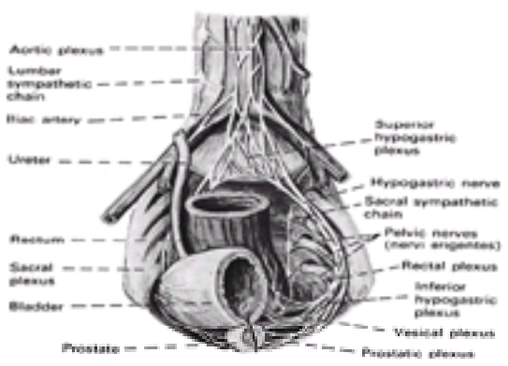

Figure 70-10. Anatomy of the superior and inferior hypogastric plexuses and subsidiary plexuses. See text for details.

At its lower border the plexus divides into right and left hypogastric nerves, often called the *middle hypogastric plexuses*, which descend to contribute to the inferior hypogastric (pelvic) plexuses. The superior hypogastric plexus gives off branches to the ureteric and testicular (or ovarian) plexuses and to those on the common iliac arteries. As emphasized in Chapter 66, the plexus contains sensory fibers that transmit nociceptive impulses from the body of the uterus and cervix that pass cephalad through the lower lumbar splanchnic nerves. In addition to the sympathetic fibers, which descend to form the superior hypogastric plexus, it contains parasympathetic fibers derived from the pelvic splanchnic nerves, which ascend from the inferior hypogastric plexus. Usually, these parasympathetic fibers pass cephalad to the left of the superior hypogastric plexus, across the sigmoid vessels and branches of the left colic vessels, to become distributed partly along the branches of the inferior mesenteric artery. Parasympathetic fibers also arise directly from the pelvic splanchnic nerves and pass as independent retroperitoneal nerves to supply a short portion of the distal left part of the transverse colon, left colic (splenic) flexure, descending colon, and sigmoid colon (Fig. 70-11). The parasympathetic supply to the distal colon is largely through these direct branches of the pelvic splanchnic nerves and not through the hypogastric and inferior mesenteric plexuses (6,7,8,9 and 10).

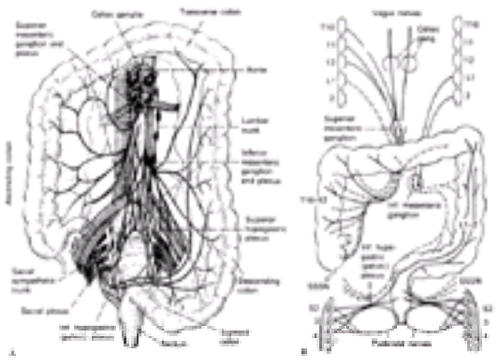

Figure 70-11. Innervation of the large intestine. **A:** Anatomic relationship of the nerves supplying various parts of the colon and rectum. **B:** Schematic depiction of the innervation of the vagus, sympathetic, and sensory fibers. The right and transverse colon up to the splenic flexure is supplied by the preganglionic parasympathetic fibers of the vagus nerves, which synapse in the wall of the viscus with short postganglionic fibers. The sympathetic supply is through preganglionic fibers derived from T-10 to T-12 (*solid lines*), which synapse with postganglionic fibers (*dashed lines*) in the superior mesenteric ganglion. This portion of the gut also receives postganglionic fibers from the L-1 ganglion. This part of the colon is supplied by sensory (nociceptive) fibers that accompany the sympathetic nerves and enter the spinal cord at T-10 and L-1 inclusively. The descending colon receives preganglionic sympathetic fibers from L-1 to L-2, which synapse in the inferior mesenteric ganglion with the postganglionic fibers that supply the viscus as far as the sigmoid colon. Postganglionic sympathetic fibers to the rest of the colon from the rectosigmoid junction and rectum are derived from sacral sympathetic splanchnic nerves (SSSN), which are derived from the sacral portion of the sympathetic chain. The descending colon is supplied with parasympathetic preganglionic fibers, which originate in spinal cord segments S-2, S-3, and S-4 and pass through the inferior hypogastric (pelvic plexus) and from there to the colon and rectum, where they end in the wall of the viscus and synapse with short postganglionic fibers. The sensory fibers that conduct nociceptive impulses accompany the parasympathetic nerves and enter the spinal cord in the S-2, S-3, and S-4 segments. Sensory supply to the rectum is through the pudendal nerve. (See Chapter 65 for a more detailed description of the origin and course of these nerve pathways.) (Modified from Netter FH. Innervation of the small intestine. In: *The CIBA collection of medical illustrations.* Vol 3, Digestive system, lower digestive tract. Summit, NJ: CIBA Pharmaceutical, 1979:76–79; and Bonica JJ. *The management of pain*. Philadelphia: Lea & Febiger, 1953:395–397.)

Hypogastric Nerves (Middle Hypogastric Plexus)

The superior hypogastric plexus divides below into right and left hypogastric *nerves*, each of which runs down in the extraperitoneal connective tissue into the pelvis medial to each internal iliac artery and its branches to contribute to the formation of the inferior hypogastric (pelvic) plexus. Each nerve can be single or can form an elongated narrow plexus that consists of two or three longitudinal nerves connected by anastomosing filaments. Each nerve or plexus can be joined near its beginning by the lowest lumbar splanchnic nerve. From each hypogastric nerve branches pass to the testicular or ovarian plexus, ureteric plexus, the plexus on the internal iliac artery, and sigmoid colon.

Inferior Hypogastric (Pelvic) Plexus

Each of the two inferior hypogastric plexuses is formed by fibers contributed by (a) the hypogastric nerves, which contain mostly sympathetic efferent and afferent fibers; (b) postganglionic sympathetic fibers from the sacral splanchnic nerves; and (c) parasympathetic fibers derived from the pelvic splanchnic nerves (nervi erigentes) that have their cell bodies in the S-2, S-3, and S- 4 segments of the spinal cord (Fig. 70-12; see Fig. 70-10).

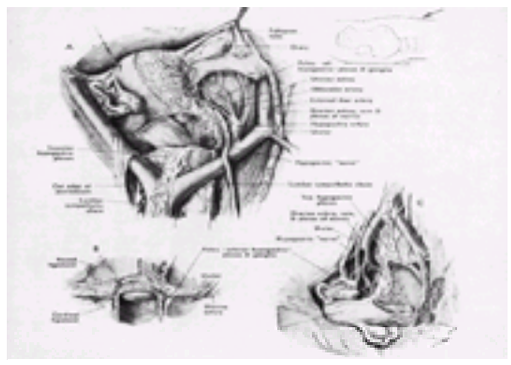

Figure 70-12. Nerve supply of uterus. **A:** Superior view of pelvis (inset: *arrow*). The peritoneum has been removed to show the distribution of the lower portion of the aortic plexus, superior hypogastric plexus, and pelvic (inferior hypogastric) plexus. Note the relation of the nerve supply to the uterus. **B:** Coronal section of cervix and vagina showing distribution of the pelvic plexus in the paracervical region. Note the relation of the plexus to the uterine artery and ureter. **C:** Sagittal section of pelvis with view of its right lateral wall showing course and relation of some of the nerves to the uterus. (From Bonica JJ, McDonald JS. *Principles and practice of obstetric analgesia and anesthesia*, 2nd ed. Baltimore: Williams & Wilkins, 1995:520.)

Each of the two hypogastric plexuses lies in the extraperitoneal connective tissue. In the man each plexus is situated on the rectum, seminal vesicle, prostate, and posterior part of the urinary bladder. In the woman each plexus is placed on the side of the rectum, uterine cervix, vaginal fornix, and posterior part of the urinary bladder and extends into the base of the broad ligaments of the uterus. Lateral to the plexus are the internal iliac vessels and their branches and tributaries and the levator ani, coccygeus, and obturator internus muscles. Behind are the sacral and coccygeal plexuses and above are the superior vesical and obliterated umbilical arteries. The plexus contains numerous small ganglia.

The cell bodies of preganglionic efferent sympathetic fibers originate in the lower three thoracic and upper two lumbar segments of the spinal cord. Some of these lie in the ganglia in the lumbar and sacral parts of the paravertebral sympathetic trunk, while others synapse with cell bodies of postganglionic sympathetic neurons in the lower part of the aortic plexus and in the inferior and superior hypogastric plexuses. The sympathetic afferents follow the course of the sympathetic pathways in a reverse direction, with their cell bodies located in the posterior ganglia and their proximal axons passing into the spinal cord to contact cells of the superficial dorsal horn.

The preganglionic parasympathetic fibers originate in the S-2, S-3, and S-4 sacral segments of the spinal cord, reach the plexus in the pelvic splanchnic nerves, and synapse with cell bodies of postganglionic parasympathetic neurons located in the plexus or, more frequently, in the walls of the viscera supplied by the inferior hypogastric plexus. From the inferior hypogastric plexus many branches are distributed to the pelvic (and some abdominal) viscera directly by accompanying the branches of the internal iliac artery (10). As mentioned previously, parasympathetic fibers pass upward into the superior hypogastric plexus (or as separate filaments accompanying it) to reach the inferior mesenteric plexus through the medium of the aortic plexus and supply the splenic flexure and descending and sigmoid parts of the colon. Afferent fibers associated with parasympathetic fibers convey sensations for reflex action but also convey nociceptive impulses.

Subsidiary Plexuses

The subsidiaries of the inferior hypogastric plexus are the middle rectal plexus, vesical plexus, prostatic plexus, and uterovaginal plexus.

Middle Rectal Plexus. The middle rectal plexus arises from the upper part of the inferior hypogastric plexus, with the fibers passing to the rectum either directly or along the middle rectal artery. The plexus communicates above with branches of the superior rectal plexus (derived from the inferior mesenteric plexus) and extends inferiorly as far as the internal anal sphincter. The nerve supply of the rectum and anal canal is derived from the superior rectal plexus, middle rectal plexus, and inferior rectal (hemorrhoidal) nerves, which are branches of the pudendal nerves. Parasympathetic preganglionic fibers from the superior and middle sacral plexuses

synapse with postganglionic neurons in the myenteric plexus, which is well developed in the wall of the sigmoid colon, rectum, and anal canal (see Fig. 70-11).

The sympathetic afferents and efferents pass through the plexus uninterrupted. The efferent sympathetic fibers in the rectal plexus are concerned with inhibition of expulsive musculature and contraction of the sphincter. Afferent fibers that transmit nociceptive impulses pass along both the sympathetic and parasympathetic nerves, but the parasympathetic afferent and efferent fibers are more active in controlling the defecation process. The inferior rectal nerves supply motor fibers to the external anal sphincter and sensory somatic fibers to the lower (ectodermal) part of the anal canal.

Vesical Plexus. The vesical plexus arises from the anterior part of the inferior hypogastric plexus. It is composed of many nerves that accompany the vesical arteries to the bladder. Branches from the plexus pass to the seminal vesicles and vas deferens. Many small collections of nerve cells are present among the nerve fibers in the muscular wall of the bladder. The sympathetic preganglionic efferent fibers in the plexus have their cell bodies in the lower two thoracic and the upper two lumbar segments of the spinal cord. Their axons pass through the inferior thoracic splanchnic nerve and the upper two lumbar splanchnic nerves, eventually ending to synapse with cell bodies of postganglionic fibers that are scattered in the superior and inferior hypogastric plexuses and in the wall of the bladder (Fig. 70-13).

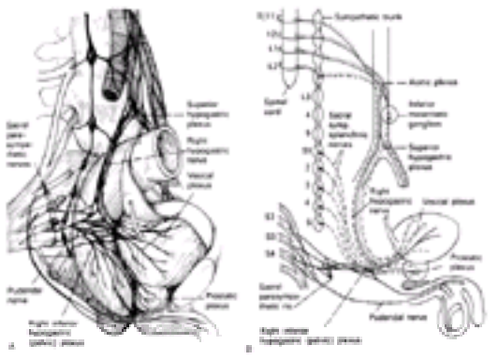

Figure 70-13. **A:** Nerve supply of the urinary bladder and prostate showing the relationship of the various nerve structures to the large intestine and their distribution in the bladder and prostate. **B:** Schematic illustration showing the segmental nerve supply to the bladder, penis, and scrotum. (*Solid lines*, preganglionic fibers; *dashed lines*, postganglionic fibers; *dotted lines*, sensory fibers.)

The parasympathetic preganglionic efferent fibers arise from the S-2, S-3, and S-4 segments of the spinal cord and synapse with cells near to or in the walls of the bladder. These nerves convey motor fibers to the muscular coats of the bladder and inhibitory fibers to the sphincter. The efferent sympathetic nerves convey motor fibers to the sphincter and inhibitory fibers to the muscular coats. Some authorities maintain that the sympathetic fibers are mainly vasomotor in function, and that filling and emptying of the bladder are normally controlled exclusively by the parasympathetic nerves (1) (a further description of the nerve supply to the bladder is given in Chapter 73).

Prostatic Plexus. The prostatic plexus arises from the lower part of the inferior hypogastric plexus and is composed of relatively large nerves that enter the base and sides of the prostate and contain collections of nerve cells. The nerves are distributed to the prostate, seminal vesicles, prostatic urethra, ejaculatory ducts, corpora cavernosa, corpus spongiosum, membranous and penile parts of the urethra, and bulbourethral glands. The nerves that supply the corpora cavernosa form two sets, the lesser and greater cavernous nerves of the penis. These nerves arise from the anterior part of the prostatic plexus and join with branches from the pudendal nerve to pass anteriorly below the pubic arch. Filaments of the lesser cavernous nerves pierce the fibrous covering of the penis near its root and supply the erectile tissue of the corpus spongiosum and penile urethra. The greater cavernous nerves run anteriorly on the dorsum of the penis, communicate with the dorsal nerve of the penis, and are distributed to the erectile tissue. Some of the filaments pass to the erectile tissue of the corpus spongiosum. The sympathetic nerves that supply the male genital organs produce vasoconstriction, while parasympathetic nerves produce vasodilation (6).

The seminal vesicles are supplied by nerves derived from the vesical plexus, prostatic plexus, and lower part of the inferior hypogastric plexus. Nerve filaments pass from these structures to the ejaculatory ducts and vas deferens. It is generally believed that constriction of the seminal vesicles and seminal ejaculation are brought about by the sympathetic nerves (6,8). These nerves also produce inhibition of the bladder musculature and contraction of the sphincter during ejaculation, thus preventing reflux of the seminal fluid into the bladder (a more detailed description of the nerve supply to the prostate is given in Chapter 73).

Uterovaginal Plexus. The uterovaginal plexus arises from the inferior hypogastric plexus, predominantly from that part of the plexus lying in the base of the broad ligament (see Fig. 70-12). Some nerves pass caudad from the plexus down with the vaginal arteries, others pass directly to the cervix uteri, and still others pass cephalad with or near the uterine arteries in the broad ligament. The nerves passing to the cervix form a plexus in which small paracervical ganglia are found. One ganglion is sometimes large and is called the *uterine cervical ganglion*. The uterine nerves pass cephalad, with the uterine artery supplying branches to the body of the uterus. In the upper part of the broad ligament they supply branches to the uterine tube and communicate with the tubal nerves from the inferior hypogastric plexus and with the nerves of the ovarian plexus. Branches of the uterine nerves ramify in the myometrium and endometrium by accompanying blood vessels.

The efferent preganglionic sympathetic fibers supplying the uterus are derived from cell bodies located in the T-10, T-11, T-12 (and sometimes T-5 to T-9), and L-1 (and sometimes L-2) segments of the cord, while the axons pass peripherally and synapse in various ganglia (8). The preganglionic parasympathetic fibers arise from the S-2, S-3, and S-4 sacral segments of the cord and are relayed in the paracervical ganglia. The sympathetic nerves can produce uterine contractions and vasoconstriction and the parasympathetic nerves can produce uterine inhibition and vasodilation. The results of the activity of these two systems are complicated, however, by the pronounced hormonal control of uterine function (4,8).

The vaginal plexus arises from the lower part of the pelvic and uterovaginal plexuses and follows the vaginal arteries and their branches to be distributed to the walls of the vagina, erectile tissue of the vestibular bulbs and clitoris (cavernous nerves of the clitoris), urethra, and greater vestibular glands. These nerves contain numerous parasympathetic fibers, which have a vasodilatory effect on the erectile tissue. (A more detailed description and illustrations of the nerve supply to the pelvic viscera are contained in Chapter 71 and Chapter 73.)

Neurology of the Perineum

The perineum derives its nerve supply primarily from various branches of the pudendal nerve. It also receives some fibers from the anterior labial or scrotal branches of the ilioinguinal, genital branch of the genitofemoral, perforating cutaneous, and muscular branches of the S-2, S-3, and S-4, and anococcygeal nerves. The perineal branches of the ilioinguinal and genitofemoral nerves are discussed in Chapter 75 in connection with the nerve supply to the lower limbs. The anatomy of the pudendal plexus and then the anatomy and distribution of the pudendal nerve are presented first.

Pudendal Plexus

The pudendal plexus is formed by the union of the anterior divisions of the S-2 and S-3 nerves and of the entire S-4 nerve (Fig. 70-14). It lies in the lower part of the posterior wall of the pelvic cavity and the anterior surface of the piriformis muscle, where it divides into the pudendal nerve, perforating cutaneous nerve, and visceral and muscular branches. The visceral branches make up the pelvic nerve, which leaves the pudendal plexus and proceeds anteriorly to join the pelvic plexuses to contribute parasympathetic fibers.

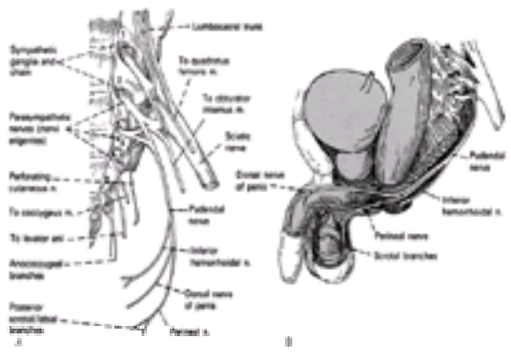

Figure 70-14. **A:** Anatomy of the pudendal plexus and its branches. See text for details. **B:** Parasagittal view depicting the course and branches of the left pudendal nerve in the male subject. (**A** modified from Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia*. Vol 1. Philadelphia: Davis, 1967:490; **B** modified from Netter FH. *The CIBA collection of medical illustrations*. Vol 2, Reproductive system. Summit, NJ: CIBA Pharmaceuticals, 1979:19.)

The muscular branches of the pudendal plexus are provided mainly by the S-4 nerve to supply the levator ani, coccygeus, and sphincter ani externus muscles. The nerves to the levator ani and coccygeus muscles enter these structures on their pelvic surface. The nerve to the sphincter ani externus, generally known as the *perineal branch* of the S-4 nerve, pierces the sacrotuberous ligament and coccygeus muscle and enters the ischiorectal fossa to supply muscular branches to the sphincter and cutaneous branches to the skin between the anus and coccyx.

The perforating cutaneous branches of the S-2 and S-3 nerves descend in front of the coccygeus muscle and pass through it, perforate the sacrotuberous ligament, and turn around at the inferior border of the gluteus maximus to supply the skin of the buttocks. Some of the fibers, however, run anteriorly to the perineum. The anococcygeal nerve, derived from the S-4 and S-5 and coccygeal nerves, also penetrates the sacrotuberous ligaments to supply the skin behind the anus in the anococcygeal area.

Anatomy of the Pudendal Nerve

The anatomy of the pudendal nerve is shown in Figure 70-15 and Figure 70-16. The somatic fibers are derived from the anterior primary division of the S-2, S-3, and S-4 nerves, while the sympathetic fibers are contributed by the sacral portion of the sympathetic chain. All these fibers combine to form a single trunk approximately 1 cm proximal (posterior) to the ischial spine. The formed nerve is directed anteriorly and inferiorly and leaves the pelvic cavity by passing through the greater sciatic foramen inferior to the piriformis muscle, between it and the coccygeal muscle. It then reenters the pelvic cavity through the lesser sciatic foramen and proceeds anteriorly through Alcock's (pudendal) canal.

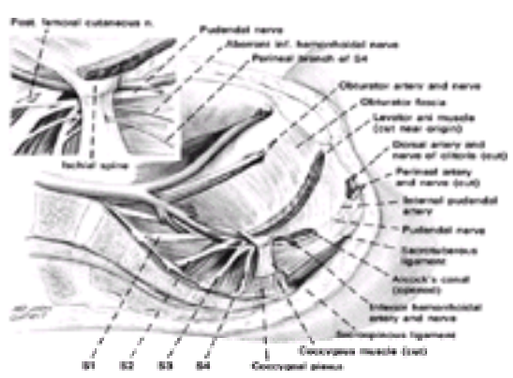

Figure 70-15. Sagittal section of the perineum showing the origin and course of the pudendal nerve. The pudendal nerve passes posterior to the junction of the ischial spine and the sacrospinous ligament and then reenters the pelvis to pass through Alcock's canal. Inset: Aberrant hemorrhoidal nerve (which occurs in 50% of individuals) and perineal branch of S-4. See text for details. (Modified from Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia*. Vol 1 Philadelphia: FA Davis, 1967:490.)

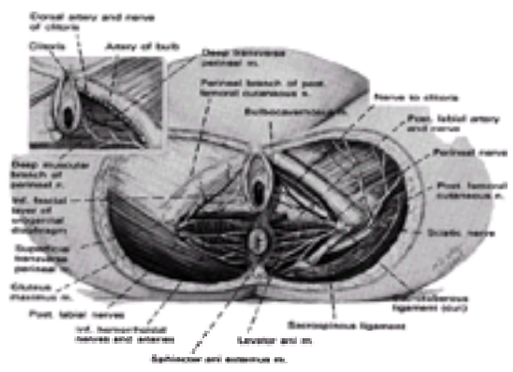

Figure 70-16. Nerve supply of the perineum of a gravida showing the principal branches of the pudendal nerve as well as the posterior femoral cutaneous nerve and other nerves that supply sensory fibers to the skin, subcutaneous tissue, external genitalia, and muscular fibers to the various muscles. The superficial transverse perineal muscles have been cut to show the course of the perineal nerve. Inset: Deeper dissection after inferior (superficial) fascia of the urogenital diaphragm has been removed shows the course of the dorsal nerve of the clitoris. The posterior two-thirds of the nerve passes through the thickness of the muscle. (Modified from Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia*. Vol 1. Philadelphia: Davis, 1967:491.)

The nerve passes posterior to the junction between the ischial spine and sacrospinous ligament and anterior to the sacrotuberous ligament. Except when the ischial spine is long and prominent, the nerve does not pass behind the spine but rather passes diagonally across the posterior surface of the sacrospinous ligament just as it attaches to the spine (11). Here, it is medial to the internal pudendal vessels that separated from the nerve to the obturator internus muscle. The posterior femoral cutaneous nerve lies lateral and posterior to the pudendal nerve, while the sciatic nerve is much more lateral and some distance away from the pudendal nerve.

The pudendal nerve trunk divides into three main branches, the inferior hemorrhoidal, perineal, and dorsal nerve to the clitoris (or to the penis). Each of these makes an important contribution to the nerve supply of the perineum.

Inferior Hemorrhoidal Nerve

In approximately 50% of individuals, the inferior hemorrhoidal nerve arises directly from the S-3 and S-4 nerves, while in the other 50% it arises from the pudendal nerve (11,12). In the latter instance it branches off from the parent nerve just distal to the sacrospinous ligament and then accompanies the pudendal nerve within the posterior part of Alcock's canal. The inferior hemorrhoidal nerve pierces the medial wall of Alcock's canal, crosses the ischiorectal fossa, and proceeds medially and anteriorly across the ischiorectal fossa accompanied by the inferior hemorrhoidal vessels to reach the perianal region. Midway in its course to the anus it divides into muscular branches for the sphincter ani externus, cutaneous filaments that supply the skin around the anus, and branches that communicate with other nerves of the

perineum. When the inferior hemorrhoidal nerve arises separately, it does not pass through Alcock's canal but proceeds anteriorly from its origin, lying significantly more medially than the pudendal nerve.

Perineal Nerve

The perineal nerve is the largest of the three branches of the pudendal nerve. It arises near the base of the urogenital diaphragm, approximately 3 cm above the inferior border of the ischial tuberosity, and divides almost immediately into the superficial cutaneous and deep muscular branches. The superficial part of the perineal nerve is purely cutaneous and consists of two nerves, medial posterior and lateral posterior labial (or scrotal) nerves. These supply the skin of the perineum and the major portion of the ipsilateral labia majora and minora (or the scrotum) (Fig. 70-17). They also communicate with the inferior hemorrhoidal nerves and with the perineal branch of the posterior femoral cutaneous nerve.

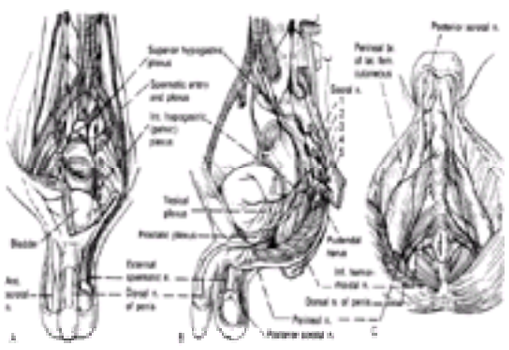

Figure 70-17. Nerve supply of the male genitalia. **A:** Anterior view. **B:** Sagittal view. **C:** Perineal view.

The deep branch of the perineal nerve arises at the anterior end of the ischiorectal fossa and proceeds anteriorly by passing between the superior and inferior layers of the urogenital diaphragm to reach the urethra. Its branches supply the following muscles: transversus perinei superficialis, bulbocavernosus, ischiocavernosus, transversus perinei profundus, sphincter urethrae, and anterior part of the levator ani and sphincter ani externus. It also supplies sensory fibers to the fascia of these muscles. The deep branch of the perineal nerve terminates in the urethra and supplies the erectile tissue of the bulb of the vestibule, urethra, and mucous membrane of the urethra with vasomotor nerves.

Dorsal Nerve of the Clitoris (or Penis)

The third branch of the pudendal nerve, the dorsal nerve of the clitoris in the woman or of the penis in the man, emerges from the anterior end of Alcock's canal, passes through the urogenital diaphragm, and proceeds anteriorly, lying between the two layers of the fascia of the diaphragm. Near the apex of the urogenital diaphragm, it pierces the superficial fascial layer and proceeds anteriorly on the side of the dorsal artery of the clitoris or penis to reach the dorsum of the structure it supplies. This nerve also supplies a small branch to the corpus cavernosum muscle and carries sympathetic fibers that supply the erectile tissue (see Fig. 70-14B).

Physiology of the Pelvis and Perineum

Pelvic pain does not come from cutting, crushing, or burning a visceral structure: Pain, in fact, from visceral structures comes from distension and stretching. Chronic pelvic pain is likely due to the classic visceral stimuli such as stretch, distension, or hypoxia or inflammatory stimuli. Simple examples of this are the distension of the cervix during the first stage of labor that causes the majority of pain during that time period; another is the hypoxia associated with a uterine fibroid that undergoes infarction. Another may be the pain associated with a hemorrhagic corpus luteum cyst as its capsule distends to three to five times its size. Pain transmission from visceral organs (bowel, bladder, rectum, uterus, ovaries, and fallopian tubes) is distinct from somatic structures (skin, ligaments, muscles). Visceral pain is characteristic of deep pain that is difficult to localize and stimulates autonomic reflexes such as nausea, vomiting, and diaphoresis (13). Viscerosomatic convergence characterizes the visceral input to the dorsal horn. This explains the frequent “referred visceral pain to cutaneous areas” phenomena. This and the poorly localizable quality of visceral pelvic pain are due primarily to the fact that there are no second-order neurons receiving only visceral input. Furthermore, there are many more somatic second- order neurons than there are viscerosomatic neurons (14). Somatic structures have nociceptors that are special types of receptors sensitive to tissue damage. Pain from the pelvic reproductive organs may emanate from high-level activity in nonspecific wide dynamic range receptors (15,16).

Visceral pain may be responsible for referred pain. Commonly, referred pain is more or less localized in the same dermatome supplied by the spinal cord segment receiving the visceral stimulus. Examples of gynecologic pains associated with referred pain in certain specified dermatomes are the T-10 to L-2 spinal segments with referral to the anterior abdominal wall and anterior thighs, and the L-1 to L-2 spinal segments with referral to the lower back (17,18 and 19). One animal model of referred pain included uterine inflammation that caused plasma extravasation in skin of the abdomen and groin areas of referral (17).

Etiology and Epidemiology of the Pelvis and Perineum

It is truly difficult to point to a single cause for pain. This section outlines some of the basic underlying mechanisms that set the stage for the development of the final common pathways for recognition of pain. Because etiology and epidemiology are so close in definition we simultaneously consider both of these. Epidemiology is defined as the various factors that determine frequency and distribution of disease and its consideration, as noted, is in conjunction with etiology in this section.

We have organized this section on etiology and epidemiology into categories for the purpose of discussion and logical order (Table 70-1). This order has nothing to do with frequency or severity of the disorders. A detailed description of many of the disorders is found in Chapter 72.

TABLE 70-1. General causes of chronic pelvic pain

Gynecologic Disorders

Ovarian Disorders. The pain associated with this category is largely due to stretch of tissues due to hemorrhage or lost blood supply due to twisted pedicles. Some of the common abnormalities are presented here.

Corpus Luteum Cyst. Corpus luteum cyst consists of a hemorrhagic episode with onset of pain when distension occurs to the point of excessive stretch of the peritoneal covering surrounding the cyst. Diagnosis is made with ultrasound. Laparoscopy can allow for confirmation and a definitive surgical correction; however, pain medication and observation usually suffice unless hemoperitoneum ensues, due to rupture of the cyst. The cyst resolves over 4 to 8 weeks.

Twisted Ovarian Cyst. Some ovarian cysts can twist to the point that local vascular supply is embarrassed and this can elicit pain of varying degrees. This type of pain usually develops rapidly and presents with sharp definition and radiation to the iliac fossa, often with nausea and localized peritoneal signs. Diagnosis here is by laparoscopy, where definitive therapy can be put into place with either aspiration followed by excision or total excision of the entire cyst or ovary without aspiration if there is concern about the possibility of any malignant potential. If the ovary is necrotic, reducing the torsion is inadequate therapy, and oophorectomy is necessary.

Cyclic Pelvic Pain. Cyclic pelvic pain implies pain associated with menstrual cycling. Cyclic pain can include both primary and secondary dysmenorrhea. Atypical cyclic pain is a variation of secondary dysmenorrhea. The diagnosis of cyclic pain is simple and depends on accurate history taking and a review of daily pain with a detailed menstrual record. Up to 50% of menstruating women are said to suffer from primary dysmenorrhea (20). *Primary dysmenorrhea* is defined as menstrual pain without pelvic pathology. Often primary dysmenorrhea appears early on, in the first or second year after menarche. Pain is in the suprapubic area with referral to both thighs or the lumbosacral area. Typical of visceral pain there may be associated nausea, vomiting, and diarrhea. Onset is just prior to or just after the first day of menstruation and lasts for 48 to 72 hours. Dysmenorrhea pain is transmitted via the thoracolumbar spinal segments and pelvic afferents.

The stimulus relevant during the development of such pain is thought to include some of the following components:

- Myometrial contractions leading to intense intrauterine pressure and uterine hypoxia
- Prostaglandins and leukotriene production that sensitizes afferent pelvic nerves
- Altered central receptivity of the afferent input from the pelvis (21)

Secondary dysmenorrhea is menstrual pain associated with pelvic pathology. It may occur years after the beginning of menstruation. The most common causes of secondary dysmenorrhea are endometriosis and adenomyosis. Other causes pathology associated with the uterus, tubes, and ovaries must be considered, such as subacute salpingo-oophoritis. To rule out secondary dysmenorrhea a full gynecologic workup must be carried out including pelvic examination, ultrasound, and magnetic resonance imaging (MRI) if deemed necessary, laboratory studies to rule out specific offending agents such as gonorrhea and chlamydia, and laparoscopy if indicated.

Medical and surgical therapy must be outlined for the benefit of the patient so she can understand her options for obtaining relief from pain. Medical therapy is primarily focused on use of nonsteroidal antiinflammatory drugs, oral contraceptive pills, and other more potent analgesics if necessary. The goal is to restore function. Some have used acupuncture as a treatment adjunct. Surgical approaches to dysmenorrhea are chiefly laparoscopic in nature, with certain ablative neural procedures offered in selected cases of secondary dysmenorrhea; occasionally, there may even be an indication for hysterectomy depending on the level and type of pathology (22). Long-term studies and certainly any controlled studies of neurectomy procedures are grossly lacking.

Ovarian Remnant Syndrome. This syndrome can be associated with a previous total abdominal hysterectomy and bilateral salpingo-oophorectomy. It is thought that a small amount of ovarian tissue is left behind and the resultant ovarian remnants become responsible for the symptoms of pain (23,24). The incidence of small amounts of ovarian remnants left after hysterectomy is really unknown. This diagnosis is considered after a history and an abnormal hormonal evaluation in a patient with pelvic pain are noted, especially if the pain is cyclic (23,25). A pelvic examination may result in the finding of a tender mass in the lateral region of the pelvis. Hormonal levels may not be confirmatory because, occasionally, follicle-stimulating hormone may not be elevated depending on the hormonal activity inherent in the ovarian tissue *in situ*. Often an ultrasound after ovarian stimulation with clomiphene can confirm a mass in the correct location. If the diagnosis is confirmed, a laparotomy and removal of residual ovarian tissue is the usual treatment (26). Surgical management via laparoscopy has been associated with complications including hemorrhage and ureteral, bladder, and bowel injury. Recurrent remnants occur in 15% of cases. An alternative to surgical management is treatment with gonadotropin-releasing hormone agonists and estrogen with progestin supplement (23,27).

Uterine Disorders

Endometriosis. Another major and distressing cause of chronic pelvic pain and secondary dysmenorrhea is endometriosis. Endometriosis is second only to primary dysmenorrhea as a leading cause of pain in women. The incidence is estimated to be 1% to 2% in the general female population, but as high as 15% in infertile women. There is an apparent increase in incidence of endometriosis in the past decade that may reflect better diagnosis and more liberal use of laparoscopy in early diagnosis. One remarkable statistic is that endometriosis is diagnosed in 28% to 74% of the patients who have laparoscopic examination for chronic pelvic pain (28,29,30,31 and 32). The strict definition is the presence of endometrial glands and stroma located outside the uterine cavity. The favored theory of etiology is retrograde menses. The diagnosis is suggested by the presence of dysmenorrhea, dyspareunia, dysfunctional uterine bleeding, and infertility. Confirmation is by laparotomy or laparoscopy. The lesions may be seen on the surface of the pelvic viscera adjacent to the uterus. Nonpigmented lesions progress in time to become pigmented. Removal of these lesions usually causes great improvement of the symptoms. Endometriosis, by itself, is one of the major causes of pelvic pain, and perhaps one of the most confounding problems because this disease can present with widely varying symptoms and signs. It is often confusing because it can mimic many other disease states. Endometrial implants may affect many different abdominal organs and the visceral and parietal peritoneum. Typically, they can be dark red or brown, or they may be colorless. The diagnosis is made on the basis of the history and confirmed by laparoscopy and biopsy. Treatment is surgical, with destruction of many of the implants by laser or electrosurgery. Other effective treatment methods are medical, with suppression of both estrogen and progesterone by use of pituitary inhibitory hormones such as the newly developed gonadotropin-releasing hormone agonist drugs such as Synarel, Lupron, or Zoladex. Surgical exploration via laparoscopy with ablative treatment of the identified endometrial implants and, sometimes, surgical severance of either the uterocervical plexus (LUNA procedure) or the superior hypogastric plexus (presacral neurectomy) may give permanent relief of pain (28). Danazol, a synthetic androgen, and high-dose progesterone (medroxyprogesterone acetate, 100 mg per day) are equally effective for pain.

The most common symptoms of endometriosis include infertility, dysmenorrhea, dyspareunia, and abnormal bleeding. Pelvic pain in women with endometriosis may occur at any time in the menstrual cycle. The pain is varyingly described. There may be pain with intercourse, urination, defecation, or it can be constant. Many patients have surgical removal of all reproductive organs, only to have continued pain that is often discovered to be from other causes. Therefore, a complete workup and the elimination of other causes are prudent.

Adenomyosis. The first description was by Rokitansky in 1860: endometrial glands embedded within hyperplastic uterine muscle tissue. He did not coin the term *adenomyosis*, however; this was done by Cullen, who reported the first series of cases in 1896. The incidence has varied from a low of 5% to a high of nearly 70% from routine hysterectomies. Typical signs and symptoms include heavy menstrual bleeding, dysmenorrhea, and an enlarged, tender, and painful uterus.

Fallopian Tube Disorders

Ectopic Pregnancy. Hemorrhage is the primary problem in this disease process. Pain may be due to peritoneal stretch or irritation due to hemoperitoneum. Ultrasound can now rapidly diagnose ectopic pregnancy; laparoscopy confirms the diagnosis and can be therapeutic at the same time. In earlier days there was no concern about tubal sacrifice, but today tubal conservation via salpingotomy with removal of ectopic gestation is the procedure of choice if this can be accomplished with adequate hemostasis (29).

Salpingo-oophoritis. Salpingo-oophoritis can cause chronic pelvic pain, although patients usually present with symptoms and signs of acute or subacute infection before the pain becomes chronic. In the past, frequent recurrent acute infections were typical; however, with the advent of potent broad-spectrum aerobic and anaerobic antibiotic regimens, this is less of a problem. Sweet and Gibbs proposed criteria for making the clinical diagnosis of acute salpingitis (33). Two of the three must be present: lower abdominal pain as well as lower abdominal tenderness (with or without rebound); cervical motion tenderness; and adnexal tenderness. In addition, one of the following minor criteria must be met: temperature greater than 38°C, leukocytosis (greater than 10,500 white blood cells per mm ^{3}), culdocentesis fluid containing white cells or bacteria on Gram's stain, presence of an inflammatory mass, elevated erythrocyte sedimentation rate, a Gram's stain from the endocervix revealing gram-negative intracellular diplococci, or a monoclonal smear from the endocervical secretions revealing chlamydia or gonorrhea.

Patients may present with a history of having had numerous episodes of pain associated with fever and may have been given the diagnosis of pelvic inflammatory disease. However, the patient may not have salpingitis at all. Clinical diagnosis leads to error in 50% of the cases (33). Laparoscopy with visualization of pelvic organs and peritoneal fluid cultures is diagnostic. Intravenous aerobic and anaerobic antibiotic therapy is the standard treatment for salpingo-oophoritis. Only rarely

are hysterectomy and salpingo-oophorectomy required, generally for tuboovarian abscesses.

Miscellaneous Disorders

Pelvic Congestion. Many believe the primary disorder lies in congestion of the arteries and veins in both the right and left pedicles just under the ovaries and fallopian tubes. Clinically, the syndrome includes abdominal and low back pain, dysmenorrhea, dyspareunia, and menorrhagia. The pain is usually bilateral and lower pelvic in distribution and exacerbated by the menstrual period. Anxiety, chronic fatigue, breast tenderness, symptoms of irritable bowel, and premenstrual syndrome are associated complaints. On examination, there is tenderness over the uterus, broad ligaments, and especially the uterosacral ligaments, and often polycystic ovaries are present (34,35).

The diagnosis of pelvic congestion used to be a clinical diagnosis. Now with use of radiology studies and rapid series pelvic venograms, the diagnosis can be more accurately made. Beard and colleagues have published studies in which the diagnosis was made via transuterine venogram. However, this test was technically not feasible or unreadable in 21% of Beard's sample (35). There are a few small studies concerning the utility of pelvic ultrasound with Doppler or MRI for the diagnosis of pelvic congestion (36). Some advocate standing venograms only to make the diagnosis of pelvic congestion.

Vaginal Disorders

Vaginismus. Causes of vaginismus include congenital, infectious, traumatic, or psychological factors. Because the primary cause by far is psychological, it is important to consult a psychologist early on in the diagnosis of this malady. Some of the underlying issues may stem from childhood problems such as sexual abuse. The treatment regimen is complex and demands intensive therapy targeted at several positive forces that knowledgeable psychologists can institute (18).

Tension Myalgia. Tension myalgia is a loose category of diagnoses that should be treated first by identification of the involved muscles that could involve the levator, the piriformis, or the coccygeus muscle groups. These are best treated by attempts to relieve the spasm by heat and massage or local anesthetic injection of the involved muscles directly. Follow-up with specific oriented muscle stretching and exercises greatly helps this painful condition and assists with recovery and prevention of repeated episodes.

Hymeneal Syndrome. Hymeneal syndrome produces an interesting group of patients. Note that the perineum is richly innervated from nerves from different spinal cord segments so that there is some overlap protection in regard to innervation. Patients are often so distraught and histrionic that the initial practitioner may entirely miss the diagnosis due to preoccupation with the reaction the patient displays during physical and gynecologic examination. The patient may complain so vigorously that a pelvic examination is not even possible (i.e., the examiner cannot get past the introitus). In other instances, the examiner does get past the introitus only to find there is no evidence of pain on examination of the vagina, cervix, uterus, and fallopian tubes and ovaries. The past history of these patients may reveal an infection with *Candida albicans*. It would appear that repeated infections by this agent can cause irritation of the superficial nerves in and around the area of the hymeneal ring (3). Patients usually have a history of normal, healthy sexual patterns before the onset of their vaginal pain, but develop significant dysfunction sexually secondary to their disease process. The patient workup must include at least three successful hymeneal blocks that can be performed prior to consideration for surgery. In our series of patients all had repeated hymeneal local anesthetic blocks with demonstrated complete relief of symptoms. The association of the infectious process and specifically the offending fungal agent is too consistent to be coincidence.

Perineal Disorders

Bartholinitis. Infection is the chief problem involving Bartholin glands. This often requires surgical incision and drainage to reverse the effects of inflammation and sequestration of purulent matter. Complete disruption of all communicating and infected sacs should be carried out along with administration of antibiotics (37).

Skene's Urethritis. This set of glands lying along the urethral orifice can also become infected. Usually, heat and gentle pressure can empty the infected material, but rarely, patients may require incision and drainage and antibiotics, similar to those described in bartholinitis (38).

Herpes. The chief pain problems initially include dysuria, dyspareunia, vesicular eruptions, and groin pain. These can be treated with bella donna and opium suppositories, avoidance of sex, acyclovir cream, acyclovir oral medication, and systemic analgesics. Long-term pain can be due to actual neuropathic changes. These are treated by identification of the involved nerve or nerves and local anesthetic blocks for pain relief trials spaced over several weeks. Some patients who are refractory to these may be considered for other methods of nerve treatment, such as cryotherapy or thermolysis. *Focal vulvitis* is a general term that has been used in the past to describe a syndrome of general vulvar pain without evident cause (39).

Condyloma. In early stages, colposcopy helps make the diagnosis. Treatment is by 5-fluorouracil until all wart activity appears neutralized. The skin recovers over a short period of time and develops normal texture again. In some cases, larger lesions may have to be removed by use of cryotherapy, fulguration, or surgical excision. One of the important differentials is human papilloma virus disease (39).

Gastrointestinal Disorders

It is understandable that some patients referred to gynecologists with chronic pelvic pain may well suffer from gastrointestinal pathology (40,41). The cervix, uterus, adnexa, and the lowest portion of the ileum, sigmoid colon, and rectum have the same visceral innervation. This innervation is via sympathetic nerves to spinal cord segments T-10 to L-1 (42).

Irritable Bowel Syndrome. A common cause of pain in the lower abdomen that can be misinterpreted as pelvic pain is irritable bowel syndrome. It can be responsible for a large number of referrals received by general gynecologists. Prime complaints center about a diffuse tightening pain that is intermittent in nature. Periodic episodes of diarrhea may also be experienced. It has a proclivity for the left inferior aspect of the abdomen (42). Diagnosis is made on history and exclusion of other conditions, such as diverticulitis.

Appendicitis. Appendicitis is included in the differential diagnosis, even though it rarely is confused with pelvic pain. The location and the historic aspects of appendicitis are giveaways most of the time, although there can be instances in which the appendix is atypically located and leads to confusion in the diagnosis. Often a gynecologic condition, such as ectopic pregnancy, may further confuse the issue from the diagnostic viewpoint. Finally, another condition termed *chronic appendicitis* may confound the doctor in an attempt to establish a chronic pelvic pain diagnosis (43).

Diverticulitis. As mentioned previously, a common cause of chronic bowel pain that can be confused with pelvic pain is diverticulitis. Diverticulosis can occur in upward of 40% of the asymptomatic population; fortunately, only a small percentage of patients go on to develop the painful and destructive disease of chronic diverticulitis. Diverticulitis can cause left lower quadrant pain also and it can present as a very severe, even *surgical*, appearance. The diagnosis is made on examination and radiology studies (44).

Tumors. Colon tumors can be a cause of chronic lower abdominal pain in women that can also be confused with pelvic pain. History is important here in noting any changes in bowel habits, signs of bleeding, or weight loss, which may suggest neoplasm. Naturally, the diagnosis can be made on digital or endoscopic examination of the patient with the suspicious history.

Hernia. Hernias located at the round ligament are another important consideration in the differential diagnosis of pelvic pain. Although there is a low incidence of inguinal hernia in women, they can occur (45). Spigelian hernias can also confuse the diagnostic picture. These cause lower abdominal pain located in the lower quadrants and they occur between the transversalis and rectus muscles. The actual protrusion is due to a defect in the transversalis fascia. The successful treatment is surgical repair.

Genitourinary Disorders

Another frequent group of disorders that often are confused as being pelvic pain are the pains of urologic origin. Anatomically, sympathetic and parasympathetic nerve complexes are shared closely and may also be involved in other poorly clarified pathways. Developmentally speaking, the urethra-bladder-vagina and vestibule area are all derived from the embryologic urogenital sinus. Some of the confusing diagnoses include urethral diverticula; interstitial cystitis; bladder tumors; upper and

lower excretory tract etiologies of pain, such as stones in the ureters or urethra; and endometriosis (40,46).

Urethral Syndrome. This lower tract disease process is of an irritative nature. Chief signs and symptoms include dysuria, urinary frequency, and often dyspareunia (46,47). A negative urinalysis, negative or a low colony count (e.g., less than 10^4 colonies per mL) on urine culture, and negative chlamydia study help steer attention away from the urologic system and begin to focus on the pelvis. On the other hand, a negative pelvic workup and normal evaluation for vulvovaginitis steer attention toward the possibility of a urethral syndrome. Etiology of the syndrome is unclear for the most part; yet some suggest that there may be an underlying chronic inflammation of the periurethral glands and periurethral muscular fatigue. Treatment consists of pelvic floor muscle biofeedback and chronic suppression with 3 months of a broad-spectrum antibiotic (46). In this syndrome, one should consider the use of vaginal estrogen for postmenopausal women (47). Last, but not least, consideration should be given to pelvic muscle biofeedback and muscle relaxants.

Interstitial Cystitis. Urinary urgency, frequency, and nocturia that are associated with severe suprapubic pain mean consideration of interstitial cystitis as the prime differential diagnostic problem. There is no laboratory confirmation of bacterial, viral, or other infectious agents being involved in this syndrome (48). The consensus criteria for the diagnosis of interstitial cystitis include at least two of the following conditions:

- Pain on bladder filling relieved by emptying
- Pain in suprapubic, pelvic, urethral, vaginal, or perineal region
- Glomerulations on endoscopy or decreased compliance on cystometrogram

If these criteria are not met, the diagnosis of interstitial cystitis should not be made (48). This disease process is thought of as an inflammatory condition or possibly an autoimmune disease. Pathophysiologically, a deficiency of bladder mucosa glycosaminoglycan and an overactive bladder sensory neuropeptide system are considered (49). Several different therapy considerations have surfaced; some of these are a special bladder diet, hydrodistension of the bladder, dimethylsulfoxide bladder treatments, glycosaminoglycan treatments, and transcutaneous electrical nerve stimulation. Other additional therapies include physical therapy, pelvic floor muscle biofeedback, and a series of local anesthetic nerve blocks. Other medical treatments include anticholinergic, antispasmodic, nonsteroidal, or antiinflammatory oral agents. Tricyclic antidepressants and narcotics are also used in medical therapy.

Musculoskeletal Disorders

Pelvic pain can be associated with pain complaints in the nearby low back area, the lower abdomen, and even radiation to the upper thighs. Low back pain can be caused by vascular, neurologic, muscular, skeletal, or gynecologic pathology (50,51). Even though muscular and skeletal problems may not be the chief cause of a given chronic pelvic pain, they can certainly increase its severity (51). A physical therapist who can evaluate posture, muscle length and strength, and joint range of motion should always improve the general efficacy of the treatment regimen (51).

Myofascial pain can be a cause of pelvic pain and, if not the primary cause, can be a significant contributor to fuel the pain overall. Various practitioners have found varying numbers of patients in whom myofascial pain is a significant factor. Reiter and Gambone (39) found 15% with myofascial pain, whereas Slocumb (18,51) found 89%.

Muscles that receive their innervation from the T-12 to L-4 spinal nerves can elicit visceral referral pain to the lower abdomen and muscles such as the rectus, iliopsoas, quadratus lumborum, piriformis, and obturators. Similarly, the reproductive organs such as the tubes, ovaries, and uterus that are innervated from T-10 to L-2 can refer pain to the abdominal wall, low back, thighs, and pelvic floor (51). Myofascial pain is increased by activity emanating from the deep visceral structures that share similar dermatomal innervation (19,52,53). Pain can be increased dramatically by a head lift maneuver during a pelvic examination where one finger is on the abdomen and the other finger is in the vagina. This is a method by which one can elucidate the primary origin of pain (i.e., suprafascial or subfascial).

Osseous Disorders

Osteitis Pubis. Active women in competitive sports who present with pubic pain and adductor pain should be considered for osteitis pubis as a cause. In one study of 59 patients, recovery was slow, taking up to 7 months in women. There was also an associated finding of pelvic malalignment or sacroiliac dysfunction in these patients (54).

Adductor Tendonitis. Adductor tendonitis is usually associated with marathon walkers or runners who suffer from acute injury to the adductor muscle of the anterior thigh that attaches directly to the pubic ramus. The patient complains of pain in the pubic ramus itself and is convinced the pain is of bony origin. It is often misdiagnosed as pelvic pain due to the complaint by the patient of diffuse ache that radiates into the involved pelvic area laterally. Diagnosis is made by running the examining finger along the medial margin of the adductor muscle up to the point of insertion on the pubic ramus. At this point the patient suffers exquisite pain and pinpoints the pain as being located exactly at the point of insertion. A local anesthetic injection completely eradicates the pain within minutes of injection. It may be necessary to repeat such a treatment a few times for complete eradication of the pain.

Osteoporotic Sacral Fractures. Osteoporotic sacral fractures were found to be associated with pelvic pain complaints in which other pathologic causes had been excluded (55).

Neuropathic Disorders

Exploratory laparotomy or laparoscopy may stretch, avulse, or otherwise damage either the ilioinguinal or iliohypogastric nerves or both nerves. A neuropathy may result and develop after variable intervals. The pain may begin days, weeks, or even months after the injury. It is common that there is a gradual escalation of pain over time. This type of neuropathic pain is usually reported as burning or stabbing. It may develop to a degree that incapacitates the patient. Often the well-meaning doctor misses the diagnosis altogether and does not even examine this area or consider it as part of a differential diagnosis. Yet, abdominal cutaneous nerve entrapment or injury should be considered in the differential diagnosis of chronic lower abdominal pain that follows surgical exploration. Such an injury can also follow trauma, automobile accidents, or exercise. Other commonly involved nerves other than the ilioinguinal (T-12 and L-1) and iliohypogastric (T-12 and L-1) are the genitofemoral (L-1, L-2) and obturator (L-2, L-3, L-4). Nerve entrapment pain is typified by exacerbation by exercise and relieved by inactivity (56,57). Other descriptives include stabbing, crampy, burning, or aching pain. There may or may not be pain radiating to upper thigh, labia, or scrotum.

Examination includes the direct palpation of the local area with the blunt end on a pencil or pen with pressure distributed directly vertically downward. In this manner, the affected nerve or nerves can be identified and marked for later local anesthetic injection if the patient so desires (58). A useful maneuver to differentiate pain coming from affected nerves above the fascia as opposed to pain coming from nerves below the fascia is to instruct the patient to lift her head as if performing a *crunch*. This immediately exacerbates the pain above the fascia in the area where pressure is exerted downward. An examining finger in the vagina will quickly determine the pain is not coming from the intraabdominal compartment (59). The diagnosis is further established by a local anesthetic nerve block with only 2 to 3 mL or 0.025% bupivacaine (60). Immediate relief is the usual reaction. It is important to continue this therapy for several weeks to defeat the already established pain pattern at the spinal cord level. Those patients who do not respond may be candidates for cryoneurolysis; this type of therapy can result in long pain-free intervals. Generally good response results have been reported in as high as 70% of patients (60). Concomitant therapy includes use of medications such as low-dose tricyclic antidepressants and anticonvulsants. Physical therapy, psychology referral, and even some life- style changes may be necessary for optimal long-term results.

Ilioinguinal and Iliohypogastric Nerve Disturbances. Patients with these diagnoses have histories that often include surgical or other types of trauma in the area of the lower abdominal wall. The genesis of the pain is not known, but suspect is the retraction placed on nerves located around the incision line that may result in overstretch and avulsive-type neural injuries. The onset of pain after the initial trauma is variable due to the intensity of the injury and perhaps the fiber size. Many gynecologic patients have exposure to the Pfannenstiel-type incision that cross cuts both the ilioinguinal and iliohypogastric nerves. In addition, the injury may be from retraction in the lower corners of the incision where the nerves are located. Interesting enough, many of the patients in this group of patients have histories of repeated abdominal exploration of one type or another because their original physician was convinced the initial problem of intraabdominal pathology had not been solved or perhaps that recurrent pain might be due to abdominal adhesions or other yet defined “organ-related pathology.” This is becoming less common due to the widespread use of laparoscopy, but the latter procedure in itself may cause abdominal neuropathy due to placement of the scope, obturator, or one or more ancillary percutaneous sites. In this case the patient was seen with initially eight tender points identified. These cases are best managed by repeated local anesthetic nerve blocks spaced over time to take advantage of the maximal signal depression, but not so frequently as to set up a new pain from mechanical stimulation. Most patients fall into the responding category by 4 to 6 weeks. Those who do not can benefit from abdominal catheter placement and continuous local anesthetic irrigation of the nerves between the transversalis and oblique muscle groups (61). Those who do not respond to that therapy can be treated with cryotherapy for destruction of those

few refractory nerves still causing problems (62). For ultimate failures in instances where multiple nests of neuromas may still be active and have been refractory to all the previously mentioned modalities, one can consider surgical intervention and extirpation of the nerves to try to correct the problem (63).

Genitofemoral Nerve Disorders. Genitofemoral nerve disorders are also labeled *genitofemoral neuropathies*. Patients report variable stories of low abdominal pain or even back pain that has migrated to the front of the body and now descends into the scrotal or labial area. The pain may be incapacitating. Nerve blocks and tender point injections usually provide pain relief. It is hoped that patients will exhibit gradual reductions in pain scores over time and that they will have an increase in their function. Sometimes the reasons for failure must be viewed as an invitation to explore further the possibility of an overlooked pathologic condition that may have been missed. For example, one patient we managed had been refractory to repeated therapy over time, and on surgical exploration it was discovered that a suture was found around the genital branch of the genitofemoral nerve just at the site of a former hernia repair. Because the distal portion of the nerve was notably atrophic, it was resected above the area of involvement and the patient follow-up has been gratifying in that the patient is now pain free.

Psychological Disorders

The psychological interview is best performed at the time of the first visit, often prior to the physical examination. This is important because it sets up the framework for recognition by the patient that this is a vital aspect of health and well-being. A psychologist working in concert with a physician with established goals provides a productive working relationship. Ideally, it would be beneficial to have the psychologist be schooled or experienced in the area of sexual function and the problems inherent in this very specialized care continuum. The literature is replete with articles relating association of childhood abuse and later sexual and psychological dysfunction, and many minor and major gynecologic pain problems have also been blamed on such disturbances (63). These problems are often hidden and not immediately apparent in early physician relationships because the patient is waiting for some signs of comfort and trust to appear or because the patient has suppressed the past history to the extent that it is not available for recall until an expert uses his or her skill to extract it later on.

Significant psychological impairment can have devastating effects on the success of a planned program for a patient's recovery, especially when it is not even suspected as being a problem. Hypnosis, biofeedback, and group therapy have all been demonstrated to be useful treatment strategies for women with pelvic pain.

Women with chronic pelvic pain can have a high level of psychological disturbance. One survey of 40 women with pelvic pain revealed the typical Minnesota Multiphasic Personality Inventory profile labeled “conversion V” (64). In another study, Minnesota Multiphasic Personality Inventory profiles of women with chronic pain without obvious pathology were compared with those of women with pain arising from endometriosis and a control group (65). The two pain groups differed from controls but not from each other.

Various studies have attempted to define better and better relational aspects of pelvic pain, depression, and sexual abuse. Some of these are very specific and look at the interaction of depression and pain only (66,67). Others have revealed interesting affective disorder problems in women with pelvic pain without a definite diagnosis of pathology versus women with a diagnosis of pathology (67). Women with pelvic pain who had no definite diagnoses were also found to have a higher prevalence of sexual abuse and major depression with associated dysthymic, panic, and somatization disorders (66,67,68,69 and 70).

A study by Rapkin et al. investigated the relational aspect between physical abuse and sexual abuse (69). Abuse of any sort was a predictor that the patient would go on to suffer “chronic pain” later. The conclusions reached were that abuse increased vulnerability and promoted a sense of helplessness (71) (Table 70-2).

Groups	Percentages
Sexual abuse data	
Pelvic pain group	19
Other pain group	16
Control group	12
Physical abuse data	
Pelvic pain group	39
Other pain group	18
Control group	9

TABLE 70-2. Sexual and physical abuse data

One of the problems in the diagnosis of those patients whose pain is labeled as *psychogenic* or *nonorganic* is that many may have neuropathy of various types that many physicians in practice today are not capable of diagnosing or treating. Most gynecologists, urologists, and surgeons are taught to think in terms of organ pathology, not in terms of nerve pathology. It is only recently that medical schools even are beginning to offer classes and approaches to considering neuropathic causes of pain. Unfortunately, many physicians tell patients that they cannot find a reason for the patient's pain and therefore the patient's pain is most likely in the head. Many patients who have been told this can be found to have a specific pudendal, obturator, or genital branch of the genitofemoral nerve neuropathy. Furthermore, most of these were amenable to simple local anesthetic nerve blockade with excellent results. This treatment was often repeated four to five times until the patient had prolonged or even permanent pain relief.

CLINICAL CONSIDERATIONS

History

All chronic pain patients have had their histories taken multiple times. It may be frustrating for them to repeat the details of their pain history, but it is important to get their attention and to establish a caring, concerned rapport with the patient from the outset. During the history it is important to ascertain the chronologic order of the physicians who have been consulted, the diagnostic tests they instituted, the procedures they used in either diagnosis or therapy, and the medications they prescribed. It is also important to get some idea as to the impact the pain has had on the function of the patient. This part of the pain history is vital because it not only illustrates the degree of difficulty the patient has had in the past, but it can also be used as a reference point for future improvement. In this day of long-term follow-up and outcomes orientation, it is especially important for the pain practitioner to carefully follow patients to be certain of outcome.

Physical Examination

The physical examination should be focused primarily on the area of the patient's complaint and must be detailed in regard to sensory and motor findings and structural changes that are noticeable. One of the important characteristics that differentiates the pain examination from other medical examinations is the hands-on examination by the physician. During this process, the areas of pain and the types of stimulation that reproduce the pain are assessed. An example of the physical examination may be illustrated by assuming a patient has pain in her right pelvic area. In such a case the physical examination should begin with the abdomen and include the lower extremities and, of course, a pelvic examination. In the process of examining these areas, the physician must attempt to elicit pain by superficial and deep pressure exerted by either the examining finger or an elongated cotton-tipped swab in the vagina or by a blunt probe, such as the blunt end of a pen or pencil on the abdomen.

In the past, there was a tendency to encourage pain specialists to perform a complete physical examination on every patient because of the fear of overlooking something that may have been previously missed in a prior workup. In cases where a patient comes to the office as a self-referral and does not have a family physician and has not had a routine physical examination then, of course, a complete physical examination is the best course. However, when the patient is referred by her own physician who requests from you a consultation for a specialized area, such as pelvic pain, then it is expensive, time consuming, and probably unnecessary to repeat a complete examination.

Pelvic Examination

An important step in differentiating an abdominal versus a pelvic origin of pain is the pelvic examination. Individual maximum tender points are identified, and then a comparison of the abdominal versus pelvic digital pressures can be made. With this maneuver it becomes clear which is the primary location of pain. This can be amplified with instructions to the patient to raise her head and contract the abdominus rectus muscles. This latter maneuver results in maximal pain above the rectus sheath and localizes the pain to the abdomen, not pelvis. One of the important skills in identification of pain is how to correctly use the examining hands and fingers during the physical examination. There is a skill that must be learned in regard to discovery of these maximum tender points. Percussion and palpation are the key skills that are required. The use of the hands-on experience to determine painful areas in and around the area of primary pain complaint is a skill that is very important and one that is often not taught in clinical training. Nevertheless, it is this very skill that must be learned and learned well if one is determined to work in the area of pain management. Pelvic pain diagnosis can be a problem for those who are not gynecologically trained. This is a problem that demands an extensive and experienced knowledge of the pelvic area and its anatomy and physiology. It literally takes years to be able to learn to perform a good pelvic examination and to be able to sensitively detect subtle abnormalities that may exist in the pelvis. Furthermore, the patients who are referred with pelvic pain are ones already examined by their gynecologists over and over again. The pelvic examination itself must be modified so as to not stimulate great degrees of pain during the examination, yet the operator must still be able to detect abnormalities. Pelvic pain is an area where pain specialists cannot expect to be effective unless they have had extensive training and subsequent experience in the area of pelvic examination. The pelvic examination is made up of the following parts: observation of the external genitalia, Bartholin's glands, hymen, vagina, cervix; and palpation of the cervix, uterus, vulva and ovaries, and rectal/vaginal septum.

Diagnosis

There are several procedures that must be considered basic diagnostic tools in the practitioner's approach to pelvic pain. These include the following tools as a minimum:

- A careful and considerate pelvic examination is directed to the sites of pelvic pain, not the usual pelvic bimanual examination.
- A pelvic ultrasound examination helps identify difficult to detect abnormalities that are hidden due to a patient's not allowing deep palpation due to pain.
- Pelvic MRI is the ultimate tool for detection of hidden tumors, masses, or even totally obscured endometriomas that may lead to occult neural involvement.
- Abdominal MRI is used to rule out possible pathology in the abdomen that cannot be appreciated or cannot be detected on physical examination.
- Computed tomographic (CT) scan is the ultimate examination tool for problems that interface osseous and soft tissue planes. It may be indicated at times even in the face of a normal MRI if historic and laboratory findings point toward abnormalities along this interface.
- Bone scan is important in picking up fractures and other bony pathology that may involve nerve distributions that are not visible on plain roentgenography.
- CA 125 values may be helpful in certain situations to help confirm a diagnosis that is already highly suspicious because of strong history and physical findings. One example might be a suspicion of endometriosis, for example.

It is important to record and assess all previous studies such as those mentioned previously and to take detailed notes on dates and findings. These can help one to understand the past thought processes of physicians who have cared for the patient. Furthermore, tests should not be unnecessarily repeated.

Differential Diagnosis

The physician confronted with a pelvic pain patient who has already been seen by several other doctors must make a very important decision for the benefit of that patient. This decision is to undertake the workup and treatment or to refer the patient to a known specialist in the area of pelvic pain. The evaluation of all the different gynecologic processes that could be responsible for the patient's pain is difficult. An example of the confusion in diagnosis in this area is typified by one study from 1989 that showed that patients suffering from irritable bowel syndrome had over a 20% incidence of hysterectomy. This reveals the confusion in differentiating abdominal pain and pelvic pain (72). Some of the problems confounding the practitioner who attempts to sort out the cause and treatment of the chronic pain patient with pelvic and abdominal pain are the facts that the etiology can be quite variable, the target organs affected quite disparate, and the intensity of the pain quite different. This can lead to early frustrations from invoking diagnostic tests that repeatedly turn up negative. Patients want to believe in their physicians and thus the pressure is intense on physicians to devise some treatment that may be beneficial. To complicate matters, some of the health care team members, such as the gynecologist, internist, neurologist, or family practitioner, are not trained in the application of various diagnostic and therapeutic local anesthetic blocks, while other members of the health care team, such as the anesthesiologist, neurologist, or internist, are not versed in and have had little experience in pelvic examinations. Both of these skills are important in the workup, diagnosis, and management of pelvic pain patients.

An important aspect of the differentiation is the pelvic examination, in which various tissues and sensitive locations are thoroughly examined with care and sensitivity. It is at this time that maximum tender points often are located and appreciated by the appropriately trained and experienced clinician. With physicians not trained to understand the importance of the neuropathic aspect of pain etiology, there is a tendency to blame pelvic organs that are readily apparent or adhesions that are remnants of past surgeries. The latter, however, are rarely the cause of pelvic pain and should not be just a default excuse when no other etiology for the pain is evident. It is also at this time that the clinician needs to do various diagnostic blocks to rule out neuropathies that may well be the culprit. These must be done with a full understanding and appreciation for the innervation pathways for the pelvis. This can only be accomplished after many years of study of the anatomy and relationships of the muscles, ligaments, bony pelvis, and neuroanatomy. Such a topic cannot be summarized in a chapter, and it is not something that can be taught in one or two or even several sessions during a *learning* visit. In instances in which the initial physician has completed a workup that reveals no obvious organic abnormalities and the patient still complains of pain, the physician in charge should consider referring the patient to someone who specializes in pelvic pain. Furthermore, our experience in a well-based diagnosis and management practice of chronic pelvic pain helps us to develop a successful outcome result profile. Table 70-3 serves as an excellent primary differential diagnosis guide.

TABLE 70-3. Pelvic and perineal pain: summary of etiology and differential diagnoses

Other Examinations

There are several laboratory studies to be completed during a workup for pelvic pain. Some of these include complete blood count; erythrocyte sedimentation rate; urinalysis and culture with sensitivities; cervical and urethral cultures (gonorrhea and chlamydia); wet mount of vaginal secretions; Papanicolaou smear; stool guaiac; and, if diarrhea is present, a stool culture. If the pelvic or abdominal examination is suggestive of a mass, an ultrasound or MRI evaluation is indicated. If symptoms and signs are suggestive of other system involvement, fiberoptic or other appropriate endoscopic imaging studies of other organ systems should be considered.

Psychological assessment is very important in nearly all pelvic pain patients because of the special intimate relational aspects of this type of pain. It really does occupy a special role in regard to complexity. All patients should be evaluated by a psychologist familiar with the special management problems posed by those suffering from chronic pelvic pain. Assessment in the context of chronic pain involves a broad range of measures, reflecting biological, social, and psychological influences and sequelae. As noted previously, pelvic pain may well affect sexual functioning, and therefore may well have additional repercussions on mood, health, and well-being of a relationship, and finally, self esteem. The important area of either physical abuse or sexual abuse must be brought up and evaluated. The impact of the pain and the effect on the patient's daily functioning must be explored. Psychological testing should be used at the outset to determine if affective disturbance is

present and to establish a baseline by which later improvements may be gauged.

Special Studies

There are many special studies that can be used to aid in the diagnosis of the patient who has pelvic pain of obscure origin. MRI is most valuable. This examination is noninvasive; cross-sectional high-resolution images of the body are full of anatomic information. The advantage of using MRI for the evaluation of the pelvis is that the contrasting images of the tissues are superior to the CT scan and ultrasound–so much so as to distinguish normal and abnormal tissues not possible with other methods.

Ultrasound is the best image method currently available for early examination of the pelvis. Its advantage is its lower relative cost and the availability of the technique. It works by reflection of high-frequency sound waves off of anatomic structures; the picture formed is the result of the various acoustic densities presented to the waves. Ultrasound is useful as a determinant of whether pelvic organs are normal or not and whether there is displacement due to other pathologic entities.

The CT scan is also valuable as a diagnostic tool in determining pelvic abnormality, especially in relation to bony anatomy. Because the CT scan does use x-rays, the picture is excellent in regard to the bony relationships and thus serves as an excellent medium for evaluation of pelvic problems associated with tumor growth, tumor invasion, and distortion of pelvic anatomy.

Laparoscopy or peritoneoscopy is the spinoff of the older culdoscopy surgical technique (73,74). Its advantage is considerable compared with that older method, however, in that the positioning of the patient is more reasonable and both diagnostic and considerable therapeutic procedures can be performed via the laparoscopic technique. It is the most widely applied diagnostic technique used today in gynecology, and its application avoids many exploratory operative procedures that would have been done in the past. Its use does require significant experience and expertise. It is a valuable tool in both diagnostic and operative procedures.

There are several procedures that must be considered beyond the basic workup tools in a practitioner's approach to pelvic pain. These include the special studies listed in Table 70-4 that form the foundation in an exhaustive approach to the diagnosis of the patient with pelvic pain.

Special study	Benefit
Pelvic examination	Pelvic pain identification
Pelvic ultrasound	Identification of hidden masses
Pelvic magnetic resonance imaging	Detection of hidden tumors
Abdominal magnetic resonance imaging	Rule out abdominal abnormalities
Computed tomographic scan	Ultimate osseous/tissue plane diagnosis
Bone scan	Hidden fractures not visible by x-ray
CA 125 values	Confirm highly suspicious neoplastic diagnoses

TABLE 70-4. Special studies in the diagnosis of the patient with pelvic pain

The workup of a patient with pelvic pain must be taken as a serious responsibility. It must be realized that these patients have gone to numerous physicians only to be told the etiology of their pain cannot be diagnosed. It is important to the patient to note and consider the previous workups and their findings. Some of these studies may need to be repeated, while others should not be repeated.

Treatment by Surgical Therapy

Management of pelvic pain by surgical means is the most common modality of treatment by the gynecologist. The problem with this most common treatment of pelvic pain is there are no studies that prove its worthiness in spite of thousands upon thousands of hysterectomies being performed for pelvic pain. Rarely has there been a randomized controlled study of this modality of treatment. Another problem with such surgical therapy is that it is often deemed *curative* because of a single postoperative follow- up at 6 weeks. Many times the patients begin to have pain again 4 to 6 months after the conclusion of the surgical treatment.

Laparoscopy

The mainstay of diagnosis is laparoscopy. This has become a first-round standard procedure in the evaluation of patients with intractable pelvic pain. Laparoscopy is very useful on the diagnostic side in regard to pelvic pain. It has also become important in the management of pelvic pain. Studies have revealed that a wide variation of patients (from 14% to 77%) did not have pathology; and furthermore, two-thirds had only findings of adhesions that may not cause pain (32,75). Finally, nonsurgical management of chronic pelvic pain has been rated successful in 65% to 90% of patients regardless of presence of *pathology* (76,77,78 and 79). One of these studies had two randomized groups: one with laparoscopic approach routinely performed (n = 49) and one with medical treatment with attention to somatic, psychological, dietary, and physiotherapeutic factors (n = 57) (79). Of the 49 patients in the standard group, 65% had no abnormality, 5% endometriosis, 18% had adhesions, and the remainder myomata, ovarian cysts, or pelvic varices. The 57 patients in the medical group had more effective reduction of pelvic pain (75% versus 41%; p <.01) (79). It would appear that laparoscopy's primary role is to provide reassurance by direct visualization and in the surgical management of adhesions and laser therapy of endometriosis (32,80).

Hysterectomy

Nearly 20% of all hysterectomies performed in this country are for chronic pelvic pain (2). Upward of 30% of patients who arrive at pelvic pain clinics have previously had hysterectomy without relief of pain (3). One center experienced a remarkable reduction in the performance of hysterectomy for chronic pain once a multidisciplinary approach to chronic pelvic pain was initiated (78). Two completely different types of patients with pelvic pain are excellent candidates for hysterectomy, especially if they have relief of pain with hormonal suppression. These are pelvic pain patients with cyclic pain and pelvic pain patients with associated dysfunctional uterine bleeding. One prospective hysterectomy study revealed 18% of the patients had undergone hysterectomy for pelvic pain. Significant improvement in pain and associated symptoms occurred in 95% of these women (81,82). Another study of hysterectomy was a retrospective one that involved 99 women with chronic pelvic pain said to be of uterine origin. Relief occurred in 77% of these patients, but 25% of the patients went on to experience persistent or worsening of their pain at a 1-year follow-up (83). Another hysterectomy study by Hillis and colleagues noted a 74% good response rate after removal (84). Follow- up of these patients revealed that persistent pain was associated with multiparity, prior history of pelvic inflammatory disease, lack of pathology, and Medicare payer status. Hysterectomy continues to remain an option for appropriately selected patients with pain centrally located and where pain can be traced to uterine origin (84). It certainly is not indicated in cases where clear-cut neuropathic pain is a predominant factor.

Presacral Neurectomy

Cotte first described the procedure called *presacral neurectomy* in 1925. Presacral neurectomy was recommended for the pain of dysmenorrhea (85). The presacral nerve is really made up of a plexus of nerves referred to as the superior hypogastric plexus. This plexus receives major afferent input supply from the cervix, uterus, and fallopian tubes. Afferents traveling with the sympathetic nerve supply from the bladder and rectum also pass through the superior hypogastric plexus. The acts of micturition and defecation are dependent on an intact sacral autonomic nerve supply, yet they are relatively unaffected by resection of the superior hypogastric plexus. Afferents from the lateral abdominal cavity that include the adnexal structures travel with sympathetic fibers that enter the spinal cord much higher at the T-9 to T-10 levels. Thus, lateralizing pain of visceral origin is not relieved by presacral neurectomy.

The use of the presacral neurectomy procedure has also not been studied in a controlled fashion. It has been described, however, for the management of central pelvic pain in the setting of both cyclic (dysmenorrhea) and noncyclic pain (86,87,88 and 89). It is often used in conjunction with other treatments for endometriosis. In one study, laparoscopic laser resection of endometriomas resulted in relief of pain in 26% of the women; additional presacral neurectomy increased the pain relief to

75% of patients (87). The surgery is technically difficult to perform via laparoscopy (90). Complications of hemorrhage and ureteral injury are not uncommon. Resection of the right and left side of the sympathetic complex that sweep upward and centrally from the broad ligaments is similar to the presacral neurectomy procedure. This procedure is referred to as the *LUNA procedure*. Again, there is little objective evidence of its efficacy; it has been subjected to only one randomized controlled trial (91). In that study, 81% of the patients had relief with the LUNA procedure, but continued relief at 1-year follow-up was only 45% of the 10 subjects (91).

Multidisciplinary Pain Management

Multidisciplinary pain management was introduced by Dr. John J. Bonica. It was his dream and conviction that a group of health care givers could solve pain problems better than those who would continue on as individual pain practitioners. A multidisciplinary pelvic pain team usually includes an anesthesiologist or pain medicine physician; a gynecologist; a neurologist; a psychologist; a pharmacologist; a physical therapist; and, many times, a dietitian. Medical therapy is built around a solid design that is individualized for the patient. Therapy may include medications, such as nonsteroidal antiinflammatory medications, narcotics, tricyclic antidepressants and g-aminobutyric acid–(GABA)ergics, local anesthetic nerve blocks, psychological therapy, and physical therapy regimens, as well as alternative medicine approaches.

In the final analysis, many patients relate their frustrations in regard to multiple single physician visits, laboratory studies, diagnostic studies, and surgical explorations. Most frustrating, above all, is that these attempts are made without a definitive diagnosis and without a substantial reduction in pain. Most patients confess they were at the end of their mental and physical tolerances; the last straw was the physician who told them “the pain is in your head.”

Support for such teams come from programs using cognitive behavioral therapy, acupuncture, and tricyclic antidepressants that were successful in pain reduction by 50% in up to 85% of the subjects (77,92). Other studies have suggested that similar results may be obtained with a multidisciplinary team (78,79,93,94 and 95). A prospective, randomized, controlled study that used the multidisciplinary approach in combination with traditional gynecologic treatment, psychological, dietary, and physical therapy input was found to be more effective than traditional gynecologic (medical and surgical) management (79).

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CHAPTER 71

Pain of Childbirth

John S. McDonald

Childbirth pain management is one of the most valued aspects of the entire specialty of anesthesiology. It is most appreciated by the mother who, through the ages, has suffered from hours of painful, torturous labor only to be subjected to the final challenge of a painful delivery. Likewise, it is appreciated by the obstetric nurse staff, the obstetricians, and the neonatologists. The strong pain control movement in labor and delivery in this country has been an outstanding marker for the rest of the world and set an important *human caring* standard. There has been much to overcome in regard to false beliefs associated with the childbirth experience. For example, one false belief promoted by the *natural childbirth* proponents was that labor and vaginal delivery can and should be painless. Now, of course, it is known that labor and delivery are actually painful events for the majority of women. Another false belief in some societies is that labor pain itself has an important biological function and should not be relieved. More common is the false belief that any pharmacologic method of modern pain relief has deleterious effects on the mother and fetus because of depression of the brain and breathing.

Pain does have the important biological function of indicating the initiation of labor. This does not mean, however, that it should go on unbridled once it has served this function. In fact, persistent severe pain can have harmful effects on the mother as well as the fetus. It is true that improperly administered analgesia and anesthesia can cause serious complications. But modern research and training have been increasingly responsible for showing that properly administered anesthesia does not contribute to maternal and perinatal mortality and morbidity. The modern expectant parturient in this country now expects and demands high levels of obstetric anesthesiology that help her through the rigors of labor and delivery with both adequate pain relief and safety.

This chapter reviews modern methods of obstetric anesthesiology. The material is presented in two major sections. The first, Basic Considerations, includes a brief historic review and discusses the magnitude of parturition pain and the physiologic and psychological alterations produced by pregnancy and labor. It also discusses how all these are affected by pain and pain relief methods. The second, Clinical Considerations, includes a review of the basic principles of current pain management for controlling childbirth pain.

BASIC CONSIDERATIONS

Historic Notes

Childbirth and childbirth pain management have always been high-priority items for the lay public and medical specialists. Some authorities (1,2 and 3) have suggested that primitive women, like animals, experience no pain in labor or delivery. Contrary to this, all evidence points to the fact that women have suffered pain in childbirth for as long as humans have existed (4,5,6,7 and 8). It is unlikely that the process of labor and the pain associated with it have changed appreciably from even prehistoric times (9).

The earliest attempts to control pain in childbirth consisted of psychological, physical, and even pharmacologic methods, either by themselves or in combination. Unbelievably crude physical methods in the form of brute force were used. The tribal strongman or heavyweight sometimes resorted to jumping on the abdomen of the pregnant woman to hasten the delivery of the child (7). Other physical measures included having the parturient tied to or suspended from a tree, with her arms tied over her head or with ropes under her armpits (7,8). Our aboriginal forebears also used autosuggestion. Incantations, spells, and words of power were used by the woman in labor to put the pain demons to flight. These methods entailed the use of suggestion, distraction, and other psychological forms of relief. The Egyptians and Chinese used the concentrated form of suggestion, which today we call hypnosis. Ellis (10) suggested that possibly the first recorded instance of hypnotism occurred with the protoobstetric case found in Genesis 2:21: “And the Lord God caused a deep sleep to fall upon Adam, and he slept; and he took one of his ribs, and closed up the flesh instead thereof.”

After many centuries, peoples' idea of the cause of labor pain underwent a change. What had once been a sport of evil spirits became a punishment inflicted by an offended deity. This perhaps explained the prophetic curse in Genesis 3:16: “Unto the woman, I will multiply thy sorrow and thy conception; in sorrow thou shalt bring forth children.” When Christianity fully developed, pain became important as a means of obtaining grace, and the woman in labor was expected to accept pain voluntarily. The same affirmation of physical pain became embraced by Oriental cultures, as well as by the various Western religions.

Despite these teachings, attempts to find methods to relieve childbirth pain continued. Pharmacologic agents, in addition to psychological analgesia, began to be used. Herbal concoctions and extracts of poppy, mandrake, hemp, and henbane plants formed the mainstay of these agents (11,12). Alcohol in many different forms was also used as an analgesic in childbirth. In the Persian literature, wine is mentioned as the agent used for the abdominal delivery of Rustan, a semimythical hero (13). In the Middle Ages, wine, beer, brandy, and other alcoholic beverages were kept by the maternity bed for self-administration (14). These methods continued to be used until the advent of modern anesthesia, which was the famous first public demonstration of ether anesthesia for a surgical operation by William T. G. Morton on October 16, 1846 (15).

The Scottish obstetrician, Sir James Y. Simpson, is credited for the introduction of modern analgesia in obstetrics. He used ether for childbirth on January 19, 1847, and chloroform for childbirth on November 8, 1847 (16). The use of analgesia for childbirth aroused violent opposition from some physicians, the public, and particularly the clergy, who labeled Simpson a heretic, a blasphemer, and an agent of the devil. For support they cited the Biblical admonition, “In sorrow thou shalt bring forth children” (Genesis 3:16). In rebuttal, Simpson, who himself was an astute student of the Bible, cited the passage quoted previously (Genesis 2:21). Simpson further added “What God, Himself, did cannot be sinful” (16).

In 1853, the successful administration of chloroform analgesia to Queen Victoria for the birth of her eighth child, Prince Leopold, was a remarkable event. Her positive expression of pleasure with its effect is considered to be one of the most important milestones in the history of obstetric anesthesia. The analgesia was administered by Dr. John Snow, whose precocious concepts, painstaking research, and perspicuous writings did so much for the forward development of the field of anesthesia. He gave Queen Victoria 15- minim doses intermittently on a handkerchief and thus established the method of *chloroforme à la reine*. This event was not published in *The Lancet* until April 18, 1857, because of the opposition of Thomas Wakley, editor of *The Lancet* (17). It was published in the form of a report that Snow had safely administered chloroform to Queen Victoria for the delivery of a new princess, Beatrice. This announcement, late as it was, signaled a moral, medical, and even religious sanction for the alleviation of childbirth pain.

Despite this auspicious beginning, obstetric analgesia and anesthesia remained a field neglected by medicine and medical practitioners for the ensuing 12 decades. Fortunately, during the 1940s and 1950s, a few pioneers in anesthesia became interested in the issue and made Herculean efforts to promote development of this subspecialty. This came about as a result of these efforts and the following factors:

- The increasing number of in-hospital births
- The appreciation by obstetricians of obstetric anesthesia
- The increasing interest among women in obtaining labor pain relief

- The sanctioning of pain relief during childbirth by religious leaders

Fortunately, at the beginning of the twenty-first century many anesthesiologists are interested and involved in research and the teaching of obstetric anesthesia. It is fair to state that in the understanding and usage of the principles of safe obstetric analgesia and anesthesia, more has been accomplished in the past 30 years than in the previous 100 years.

Magnitude of the Problem

The perpetration of the false information about childbirth helped to set back and repress advances in obstetric anesthesiology for decades. This has been and continues to be a result of inadequate dissemination of information to the public about advances in knowledge and current therapeutic procedures. In the past, many proponents of natural childbirth compounded the problem by insisting that pain need not occur during normal labor and that when it occurs it is the product of modern cultural and environmental factors. The origin of this notion is not known, but Behan (18) was among the first to mention it, stating in 1914 that “like menstruation, childbirth naturally should be a painless process. It is only as culture advances that the labor becomes painful, for in women of primitive races pain is absent. Savages of a low degree of civilization are generally little troubled by parturiency.” Nineteen years later the same argument was put forth by Dick-Read (1), who for the next 25 years, traveled worldwide espousing this thesis, strongly condemning pharmacologic analgesia and encouraging the use of his method of natural childbirth (2). In 1950, in the former Union of Soviet Socialist Republics, Velvovski and associates (3) began to use the technique of *psychoprophylaxis*, which was a modification of the Dick-Read method. Prophylaxis was subsequently embraced by Lamaze (19) of France, who did much to popularize it in Europe and the western hemisphere.

The claim by these clinicians and their followers that childbirth among primitive peoples is painless has been disputed. Ford (4), who studied this and other problems of reproduction in 64 primitive societies, wrote that “the popular impression of childbirth in primitive society as painless and easy is definitely contradicted by our cases. As a matter of fact, it is often prolonged and painful.” After studying 80 primitive groups, Freedman and Ferguson (5) reported that the pain response in these groups during childbirth was similar to that observed in American and European parturients. Similar views have been expressed by others who studied the problem of labor pain in primitive societies (6,7). Bonica (*unpublished data*, 1965) observed more than 24 parturients from primitive societies in Australia and Africa, most of whom manifested severe pain behavior. Finally, mention of the prevalence of pain during childbirth and its importance is found in the writings of the ancient Babylonians, Egyptians, Chinese, Hebrews, Greeks, and in the writings of many subsequent cultures and civilizations (20).

Incidence and Intensity of Labor Pain

Although it is a common observation in obstetrics that parturients vary in the amount of suffering associated with labor and vaginal delivery, few well-designed studies on the prevalence, intensity, and quality of labor pain have been performed.

Lundh (21) published a survey of several Swedish investigations, which included both primiparas and multiparas; these revealed that the incidence of intolerable severe pain ranged from 35% to 58%, with the remainder having moderate pain. Bundsen (22) found that 77% of primiparas reported that their pain during childbirth was severe or intolerable. Nettelbladt and colleagues (23) found that 35% reported intolerable pain, 37% had severe pain, and 28% had moderate pain during labor and delivery. Records on 2,700 parturients observed (and many interviewed) by Bonica while visiting or working (demonstrating obstetric anesthetic techniques) in 121 obstetric centers (with some having 100 to 150 deliveries daily) in 35 countries on six continents indicated that the frequency and intensity of labor pain were as follows: 15% had little or no pain, 35% had moderate pain, 30% had severe pain, and 20% had extremely severe pain. The data are similar to those noted among over 8,000 American parturients to whom Bonica administered or supervised anesthetic care during the past 40 years (Bonica, *unpublished data*, 1969) (24,25).

Obviously, the drawbacks of these surveys and observations were that they were based on simple numeric or verbal descriptions of pain and thus lack quantification. One of the first attempts to quantify the intensity of labor pain was made by Javert and Hardy (26), who used the Hardy-Wolff-Goodell dolorimeter to induce experimental pain and asked the parturients to compare it to the pain of their labor. The method entails the application of thermal heat, measured in millicalories (mc), to 3.5 cm^2 of skin for 3 seconds. The stimulus is increased in intensity stepwise until perceptible pain (pain threshold) and eventually the greatest perceivable pain (ceiling or maximum pain) are induced. They used a pain scale that ranged from 1 dol (pain unit), assigned to pain threshold, to 12.5 dol, denoting maximum pain, which was produced by a stimulus of sufficient intensity to produce a third-degree burn. Javert and Hardy (26) studied 26 primiparas and 6 multiparas during the course of normal labor and delivery and found (a) the intensity of pain in the early part (latent phase) of the first stage was 2 to 3 dol; (b) an increase to 3 to 4 dol at approximately 4-cm cervical dilatation; (c) an increase to 5 to 7 dol at 6 to 8 cm; (d) an increase to 8 to 9 dol at full dilatation; and (e) an increase to 9.0 to 10.5 dol as the head dilated and stretched the perineum.

Melzack and associates (27,28) used the McGill Pain Questionnaire to measure pain during labor and delivery in 87 primiparas and 54 multiparas. They found that the mean total pain rating index (PRI) was 34 for primiparas and 30 for multiparas, thus confirming the widely held view that labor is significantly more painful for the first birth than for later births. Significant differences were also found between primiparas and multiparas for each of the four classes of words describing their pain. The sensory qualities of the pain were described as sharp, cramping, aching, throbbing, stabbing, hot, shooting, or heavy; the affective qualities were described as tiring by half and exhausting by more than a third. Subsequently, Melzack (27) compared the mean total PRI scores for several pain syndromes obtained in an earlier study (28) with those of labor and noted that the scores for labor pain were some 8 to 10 points higher than those associated with back pain, cancer pain, phantom limb pain, or postherpetic neuralgia (Fig. 71-1A). As might be expected, although the average intensity of labor pain was extremely high, a wide range in pain scores was observed, which Melzack (27) divided into six groups within the range of the PRI scores recorded (ranging from 2 to 62) (Fig. 71-1B).

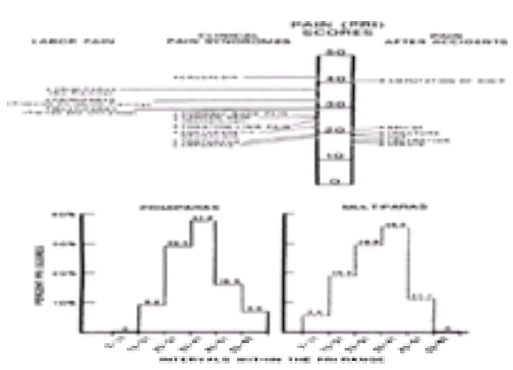

Figure 71-1. **A:** Comparison of pain scores using the McGill Pain Questionnaire obtained from women during labor and from patients in general hospital clinics and an emergency department. The pain rating index (PRI) represents the sum of the rank values for all words chosen from 20 sets of pain descriptions. **B:** Distribution of PRI scores for primiparas and multiparas in six intervals of the total PRI range. [Reprinted from Melzack R. The myth of painless childbirth (the John J. Bonica Lecture). *Pain* 1984;191:321–337, with permission.]

Assigning verbal descriptors of pain intensity to these data suggests that approximately 10% of primiparas and approximately 24% of multiparas experienced mild to moderate pain, approximately 30% of both groups rated their pain as severe, approximately 38% of primiparas and 35% of multiparas felt very severe pain, and 23% of primiparas and 11% of multiparas experienced horrible or excruciating pain. The mean PRI score of 61 primiparas who received prepared childbirth training was 33; and, for the 26 primiparas who received no training, the mean PRI score was 37. On the other hand, no significant difference was noted in any of the PRI measures of the 30 multiparas who had received training and 24 who received no training. Of the 28 parturients who were given successful epidural analgesia, the PRI score decreased from a mean of 28 before the block to a mean of 8.0 and 7.6 at 30 and 60 minutes, respectively, after induction of analgesia. These scores were based on the use of such words as numbness, pressing, and tingling.

Physiologic Alterations during Pregnancy and Labor

To provide optimal pain relief to the parturient using current techniques, it is essential for the anesthesiologist to have (a) a thorough understanding of the maternal physiologic alterations produced by pregnancy, labor, and parturition; (b) a thorough understanding of the physiology and pharmacology of the fetal-placental complex; (c) a thorough understanding of the forces of labor; and (d) a thorough understanding of how these are altered by the administration of analgesics and

anesthetics.

From the viewpoint of anesthetic care, the changes in the mother involving circulation; respiration; acid–base and electrolyte balance; and gastrointestinal, renal, and hepatic functions are the most important. These changes, produced by placental hormones, by the mechanical effects of the growing uterus, or by both, occur because of the increasing metabolic needs of the maternal-fetal- placental complex (9). They also prepare the gravida for the stresses of parturition and for the subsequent occlusion of the placental circulation.

Circulatory Alterations

Antepartum Hematologic Changes. Beginning at 6 to 8 weeks of pregnancy, the total blood, plasma, and red cell volumes progressively increase, reaching a maximum at 28 to 32 weeks and thereafter remaining constant until parturition (Fig. 71-2). This hypervolemia of pregnancy is accommodated by enlargement of the uterus and breasts and by increased blood flow to the kidneys, skeletal muscles, and skin and parallels the increased cardiac output and ventilation. These changes facilitate the maternal-fetal exchange of blood gases, nutrients, and metabolites and enable the gravida to tolerate blood loss during parturition, which is 300 to 500 mL with vaginal delivery and 600 to 1,000 mL with cesarean section (20,29). The increase in plasma volume (50%) is greater than the increase in red cell mass (30%), resulting in hemodilution and a consequent decrease in red cell count, hemoglobin, and hematocrit, the so-called physiologic anemia of pregnancy.

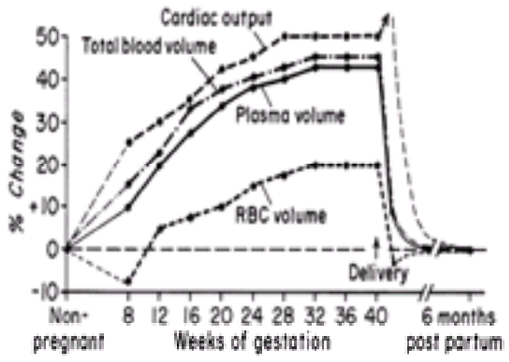

Figure 71-2. Changes in blood volume, plasma volume, red cell volume, and cardiac output during pregnancy and in the puerperium. The curves were constructed from data in the literature and illustrate trends in terms of percentage change rather than in absolute values. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:2, with permission.)

Antepartum Hemodynamic Changes. Figure 71-3 depicts the changes in heart rate and stroke volume and consequently in cardiac output. These three variables differ markedly in the lateral and supine positions, especially during the last trimester, when the enlarged uterus compresses the inferior vena cava and other veins at the pelvic brim. This vein-compressing effect is greatest in the supine position, significantly less in the lateral position, and least in the knee-chest position. Figure 71-4 depicts the effect of the compression by the gravid uterus on the inferior vena cava and the aorta in the supine and lateral positions.

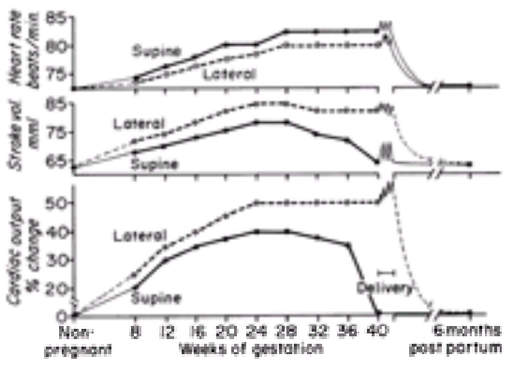

Figure 71-3. Changes in heart rate, stroke volume, and cardiac output during pregnancy and in the puerperium. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:5, with permission.)

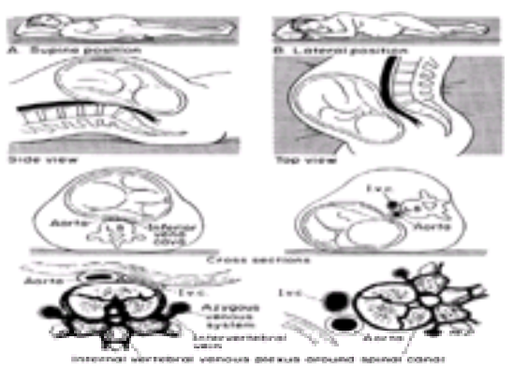

Figure 71-4. Effects of the pregnant uterus on the inferior vena cava and the aorta in the supine position (*left*) and lateral position (*right*) The marked aortocaval compression in the supine position causes venous blood to be diverted to and through vertebral venous plexus, which becomes engorged and thus reduces the size of the epidural and subarachnoid spaces. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:8, with permission.)

The obstruction of the inferior vena cava reduces the venous return to the heart and thus reduces cardiac output. This effect is offset by two compensatory mechanisms: (a) an increase in sympathetic tone with generalized vasoconstriction, and an increase in total peripheral resistance and heart rate; and (b) diversion of some of the blood coming back to the heart from the lower one-half of the body by a detour through the internal vertebral venous plexus. Consequently, in 90% of gravidas, these compensatory mechanisms are sufficiently effective to maintain arterial blood pressure at near normal levels. However, in the remaining 10% the obstruction is so great and the amount of blood returned to the heart and the consequent cardiac output are so low that, despite the intense vasoconstriction and tachycardia, blood pressure falls sufficiently to cause supine hypotensive syndrome (30,31).

Figure 71-5 depicts the changes in arterial blood pressure, venous pressure, and total peripheral resistance during pregnancy. The latter is reduced some 20% (32,33).

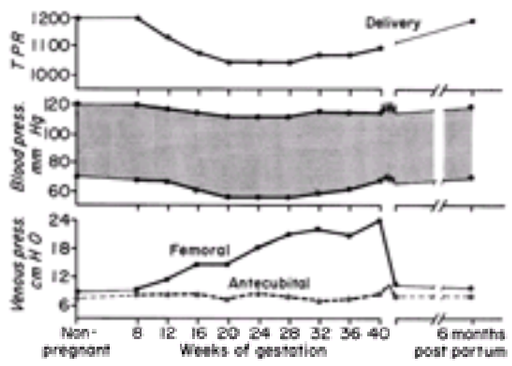

Figure 71-5. Changes in total peripheral resistance (TPR) (*top*), systolic and diastolic blood pressures (*middle*), and venous pressure (*bottom*). Pressure in the antecubital vein remains normal but pressure in the femoral vein steadily increases because of the progressive compression of the inferior vena cava by the gravid uterus. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:5, with permission.)

Parturition Hemodynamic Changes

Cardiac Output. During labor cardiac output increases above prelabor levels (Fig. 71-6). Between contractions, cardiac output during the early first stage is approximately 15% above that of prelabor, during the late first stage it is approximately 30%, during the second stage approximately 45%, immediately after delivery approximately 65%, and 1 hour after delivery it is 30% to 50% above prelabor levels (31,32 and 33). With each uterine contraction the uterus is raised by action of the uterine ligaments, and 250 to 300 mL of blood is also squeezed out of the uterus into the central circulation. Moreover, increased venous return from the pelvis and lower limbs is made possible by a decrease in the degree of obstruction as the uterus is lifted away from the spinal column (34). Consequently, stroke volume, cardiac output, and left ventricular work increase (34,35 and 36). Each contraction consistently increases cardiac output 15% to 25% above that between the contractions.

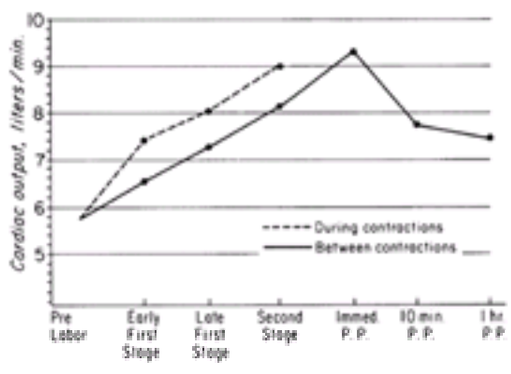

Figure 71-6. Cardiac output during various phases of labor, between contractions, and during contractions. The cardiac output progressively increases between contractions and increases 15% to 20% more during contractions. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:6, with permission.)

Blood Pressure. Figure 71-7 depicts the changes in arterial blood pressure caused by uterine contractions. The magnitude of these changes varies and depends on the intensity of the contraction and the position of the parturient, with these parameters being greater in the supine than in the lateral position. As emphasized later, pain, anxiety, and apprehension produce a significant further increase because of the release of catecholamines. During the second stage the bearing-down efforts often alter blood pressure in a way similar to that produced by the Valsalva's maneuver (34). The changes in venous pressure are rapidly transmitted to the internal vertebral venous plexus and thus cause a transient rise in the epidural and cerebrospinal fluid pressures, which have some influence on the spread of local anesthetic injection into these spaces (37).

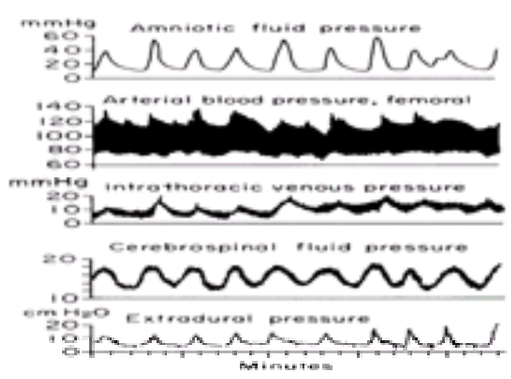

Figure 71-7. Hemodynamic effects of uterine contractions. The increases in arterial blood pressure and central venous pressure are reflected in cerebrospinal fluid and epidural pressures. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:7, with permission.)

During labor, the compression of the large veins is exaggerated by uterine contractions. As the uterus tenses and hardens and increases its pressure on the major veins and arteries across the pelvic brim, often the mother's circulation apparently improves, but with a hidden deterioration of the placental blood pressure. Each contraction tips the uterus around a fulcrum formed by the lumbosacral vertebral prominence, and aortic compression is increased, leading to a hyperdynamic circulation above the compression but a further deterioration below it. Consequently, the maternal cardiac output increases sharply, accompanied by a hypertensive rise of blood pressure above the obstruction but a marked decrease below it.

Clinical Implications. These changes in blood volume and hemodynamics produced by pregnancy, parturition, and puerperium are of significant relevance to anesthetic care. Whereas the increase in cardiac workload is tolerated by healthy gravidas, the increase in the work of the heart in those with heart disease and consequent low myocardial reserve can constitute too great a strain and can precipitate pulmonary congestion. In such patients it is especially important to obviate any further increase in the work of the heart caused by pain during labor by providing effective analgesia, preferably with regional techniques. Moreover, the engorgement of the epidural space reduces its size and therefore less local anesthetic is needed to achieve epidural analgesia. Fluctuations in the cerebrospinal fluid pressure can also influence the extent of subarachnoid block. Finally, and most important, postural hemodynamic changes make it mandatory for gravidas to avoid the supine position during the latter phases of pregnancy and during labor. Because the induction of spinal or epidural anesthesia or other procedures that entail vasomotor blockade deprive gravidas of a compensatory vasoconstriction, they are likely to incur much greater decreases in arterial blood pressure than nonpregnant women. Unless prophylactic measures are carried out, such severe hypotension can develop that the lives of the mother and fetus are threatened (38,39 and 40).

Changes in Respiration

Pregnancy produces impressive anatomic and physiologic changes involving the airway, lung volumes, ventilation, and dynamics of breathing. In most gravidas, capillary engorgement takes place throughout the respiratory tract and the growing uterus causes the diaphragm to rise 4 cm. This rise is counterbalanced by an

increase of 2 cm in the anteroposterior and transverse diameters of the thoracic cage and flaring of the ribs, producing a 5- to 7-cm increase in the circumference of the thoracic cage.

Lung Volumes. Lung volumes begin to change during the fifth month of gestation, with a consequent progressive decrease in expiratory reserve volume (ERV), residual volume (RV), and functional residual capacity (41) (Fig. 71-8). The reduction in functional residual capacity is sufficient to cause some degree of airway closure in 50% of parturients at term during normal tidal ventilation (42). Obesity, recumbency, and the lithotomy position aggravate this effect further. This can result in lowered ventilation- perfusion ratios in the dependent portions of the lung and might account for the lowered arterial oxygen pressure seen in some parturients at term.

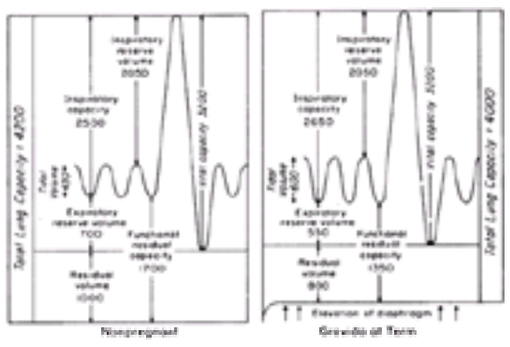

Figure 71-8. Pulmonary volumes and capacity in the nonpregnant state **(A)** and in the gravida at term **(B)**. The changes in the functional residual capacity, expiratory reserve volume, and residual volume begin after the fifth month of pregnancy and increase progressively until term. (Reprinted from Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia*. Vol 1. Philadelphia: FA Davis, 1967:24, with permission.)

Ventilation

Antepartum Changes. Ventilation increases significantly during pregnancy (Fig. 71-9). The changes in lung volumes and ventilation lead to a reduction of arterial and alveolar carbon dioxide pressure, which averages 32 mm Hg at term, and an increase in the oxygen tension to approximately 105 mm Hg. These are accompanied by a decrease in arterial oxygen pressure and by changes in other acid–base parameters (see Acid–Base Balance, later in this chapter).

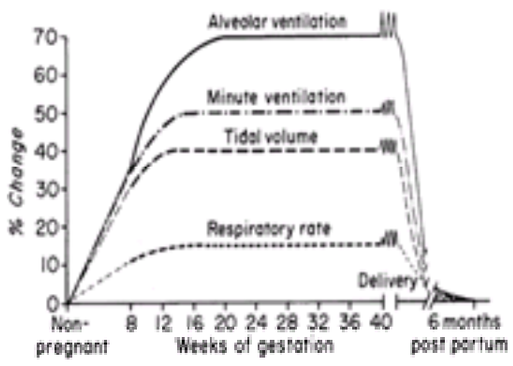

Figure 71-9. Changes in ventilatory parameters during pregnancy. Almost maximum hyperventilation occurs as early as the second or third month of gestation. Because the respiratory rate increases to a much lesser extent than tidal volume and dead space remains normal, the percentage increase in alveolar ventilation is greater than the percentage increase in minute ventilation. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:17, with permission.)

Parturition Changes. Ventilation is further increased by the pain of labor, anxiety, and apprehension or voluntarily in patients trained in natural childbirth. The magnitude of hyperventilation varies greatly, with respiratory rates as high as 60 to 70 per minute and tidal volumes of up to 2,250 mL, and maximum peak inspiratory flow rates of up to 340 L per minute have been reported (43,44). The effects of labor pain on ventilation as well as on circulation are discussed in more detail later in this chapter.

Clinical Implications. These changes in ventilation also have important clinical implications. The anatomic changes are conducive to respiratory obstruction of the nasal passages, to an increased hazard of tracheal intubation, and to misinterpretation of physical findings. Changes in lung volumes and ventilation increase the efficiency of gaseous transfer between maternal blood and the alveolar air so that the carbon dioxide tension is decreased and that of oxygen is increased. Such changes, in turn, enhance the transfer of these gases between the mother and the fetus. On the other hand, these changes make gravidas more susceptible to the effects of more rapid changes in respiratory blood gas levels during respiratory complications than nonpregnant women. Hypoventilation, breath holding, or respiratory obstruction produces hypoxia, hypercapnia, and respiratory acidosis more readily in the gravidas than in nonpregnant women. Conversely, moderate to severe hyperventilation achieved spontaneously by awake gravidas or produced by the anesthesiologist with excessive positive pressure ventilation during general anesthesia can quickly lead to severe respiratory alkalosis. The respiratory alkalosis is associated with a decrease in cerebral blood flow, and possible decreased uterine blood flow, and a shift of the maternal oxygen dissociation curve to the left. Prolonged acute hypocarbia also results in diminished bicarbonate and buffer base levels that contribute to the development of metabolic acidosis during painful labor (45,46).

Other Physiologic Changes

Acid–Base Balance. The acid–base balance changes during pregnancy and labor. The total base level decreases from the normal nonpregnant level of approximately 155 to approximately 148 mEq per L, with a corresponding decrease in potassium, calcium, and magnesium concentrations. The plasma bicarbonate level decreases from an average of 25 to 21 mEq per L (Fig. 71-10). The plasma buffer base concentration, which refers to the total buffer available and includes bicarbonate, protein, and hemoglobin, decreases from a normal adult mean level of 47 to 42 mEq per L and base excess decreases to 3.0 mEq per L. In normal gravidas the pH of the blood remains at 7.4, suggesting that normal pregnant women have a compensatory alkali deficit.

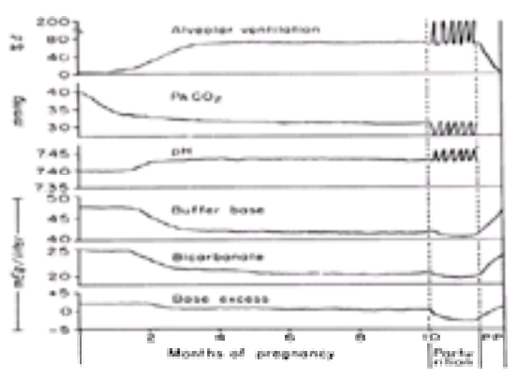

Figure 71-10. Changes in alveolar ventilation, arterial carbon dioxide pressure, pH, and acid–base concentrations during pregnancy, parturition, and postpartum. With

the nearly 80% increase in alveolar ventilation the Paco $_2$ decreases to levels of 32 mm Hg at term, with concomitant changes in the acid–base balance. During parturition further changes occur, especially during uterine contractions, which increase ventilation and decrease the Paco $_2$. All these variables return to normal 1 to 3 weeks after delivery. (Reprinted from Bonica JJ. Maternal respiratory changes during pregnancy and parturition. In: Marx GF, ed. *Parturition and perinatology*. Clinical anesthesia series. Vol 10, No. 2. Philadelphia: FA Davis, 1973:9, with permission.)

Gastrointestinal Function. During pregnancy the stomach and intestines are progressively displaced cephalad by the enlarging uterus, with consequent increases in intraabdominal and intragastric pressures. Together with a decreased gastric emptying time and increased gastric acidity, the tendency to esophageal reflux is increased (20).

Renal and Hepatic Function. During pregnancy the muscular tone and rhythmicity of the urinary tract decrease. This results in an increase in urinary tract dead space and a progressive increase in the glomerular filtration rate that affects the renal plasma flow, filtration fraction, and tubular reabsorption. These changes cause a decrease in the urea nitrogen concentration. Several liver function tests show abnormal values during normal pregnancy, but nonetheless the liver functions without difficulty.

Metabolic Rate and Oxygen Consumption. During pregnancy the basal metabolic rate and oxygen consumption progressively increase; at term their values are 20% above normal. In addition, water, protein, and minerals are retained and stored, along with retention of salts and the acquisition of fat. During parturition the metabolism and oxygen consumption increase further to satisfy the increased requirements of the uterus and, during the second stage of labor, to meet additional needs consequent to the bearing- down efforts. Parturients who have inadequate pain relief have greater oxygen consumption than those who have complete pain relief. Most of the former develop a progressive metabolic acidosis and a steady rise in the free fatty acid level, as well as showing other endocrine responses to pain.

Effects of the Pain of Childbirth

Labor and vaginal delivery produce tissue damage and, like tissue injury from other causes, result in pain and local segmental, suprasegmental, and cortical responses (see Chapter 9). These responses include marked stimulation of respiration, circulation, hypothalamic autonomic centers of neuroendocrine function, limbic structures, and psychodynamic mechanisms of anxiety and apprehension, resulting in what has come to be known as the *stress response* to injury. As a result, the parturient incurs marked increases in respiration, circulation, and metabolism, and other body functions are altered (Fig. 71-11,Fig. 71-12 and Fig. 71-13). These maternal changes can have a deleterious impact on the fetus and newborn. Pain and reflex responses have a predominant role in these alterations of maternal function, because blockade of the nociceptive pathways by regional analgesia with a local anesthetic greatly diminishes or eliminates them. We now summarize the impact of the pain of childbirth on the mother, uterus, and fetus and newborn, and then present data on the effects of analgesia and sedation on these changes.

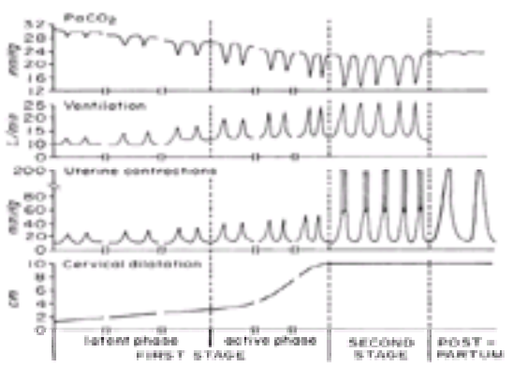

Figure 71-11. Schematic representation of ventilatory changes during labor in an unpremedicated gravida. Note the correlation of the stages of labor as reflected by the Friedman's curve (*bottom tracing*), the frequency and intensity of uterine contractions, minute ventilation, and arterial carbon dioxide tension (*top tracing*). Early in labor uterine contractions are slight and are associated with mild pain, causing only small increases in minute ventilation and decreases in the Paco $_2$. As labor progresses, however, the greater intensity of contractions causes greater changes in ventilation and Paco $_2$. During the active phase, contractions with an increased intrauterine pressure of 40 to 60 mm Hg cause severe pain, which acts as an intense stimulus to ventilation with a consequent reduction of the Paco $_2$ to 18 to 20 mm Hg. During the second stage the reflex bearing-down efforts further increase intrauterine pressure and distend the perineum, producing consequent additional pain that prompts the parturient to ventilate at a rate almost twice that of early labor and causing a commensurate reduction in the Paco $_2$. (Modified from Bonica JJ. Maternal respiratory changes during pregnancy and parturition. In: Marx GF, ed. *Parturition and perinatology*. Clinical anesthesia series. Vol 10, No. 2. Philadelphia: FA Davis, 1973.)

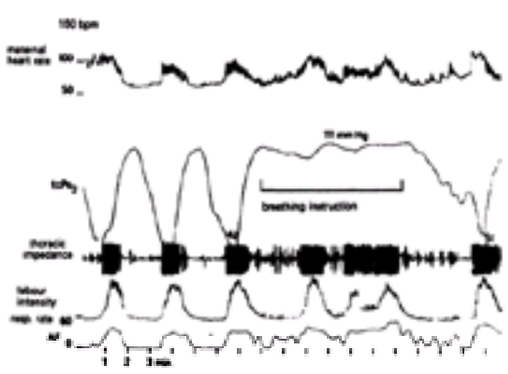

Figure 71-12. Continuous recording of maternal heart rate, transcutaneous (tc)Po $_2$ thoracic impedance, uterine pressure (labor intensity), and respiratory rate after the parturient was given 100 mg of meperidine intramuscularly. With each uterine contraction marked hyperventilation caused the tcPo $_2$ to increase to 110 mm Hg but then to fall to low levels as a result of the marked respiratory alkalosis and of the respiratory depressant effect of the meperidine. The large decreases in tcPo $_2$ were avoided by giving the parturient breathing instructions during the relaxation period. (Reprinted from Peabody JL. Transcutaneous oxygen measurement to evaluate drug effect. *Clin Perinatol* 1979;6:109–121, with permission.)

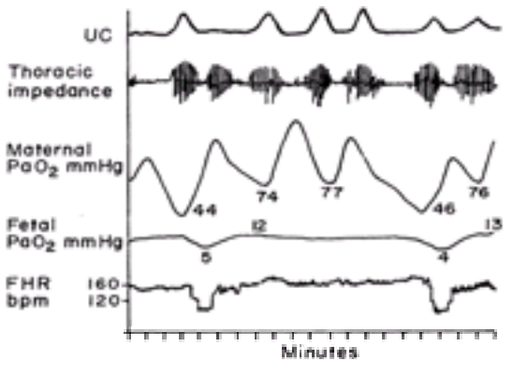

Figure 71-13. Continuous recording of uterine contractions (UC), maternal thoracic impedance, maternal transcutaneous oxygen tension (Pao $_2$), fetal oxygen tension,

and fetal heart rate (FHR) in a primipara 120 minutes before spontaneous delivery of an infant with an Apgar of 7. Marked hyperventilation during uterine contractions was followed by hypoventilation or apnea between contractions. With the parturient breathing air during and after the first and fourth periods of hyperventilation, the maternal Pao_2 fell to 44 and 46 mm Hg, with a consequent decrease in fetal Pao_2 and variable decelerations, which reflected fetal hypoxia. [Modified from Huch A, Huch R, Schneider H, Rooth G. Continuous transcutaneous monitoring of foetal oxygen tension during labour. *Br J Obstet Gynecol* 1977;84(Suppl 1):1–39.]

Changes in Ventilation. The pain of childbirth is a powerful respiratory stimulus, causing marked increases in tidal volume and minute ventilation. In a study by Bonica and Caldeyro-Barcia of a group of unpremedicated, unprepared primiparas, the minute ventilation increased from a normal mean of approximately 10 L per minute between contractions to a mean of 23 L per minute to 35 L per minute during contractions (44). Consequent to the hyperventilation was a fall of the arterial carbon dioxide pressure ($Paco_2$) from a normal pregnant level of 32 mm Hg to a value of 16 to 20 mm Hg, with some as low as 10 to 15 mm Hg, and a concomitant increase in pH to 7.55 to 7.60 (see Fig. 71-11). Hyperventilation consequent to the pain of uterine contraction has also been reported by Brownridge (47), Peabody (41), and Roemer and Vogel (48).

Endocrine Effects. Animal studies have shown that acute pain caused by noxious stimulation produces a significant (20% to 40%) increase in catecholamine levels, particularly norepinephrine (NE), with a consequent 35% to 70% decrease in uterine blood flow (49,50) (Fig. 71-14). Human studies have shown that severe pain and anxiety during active labor cause a 300% to 600% increase in the epinephrine level, a 200% to 400% increase in the NE level, a 200% to 300% increase in the cortisol level, and significant increases in corticosteroid and adrenocorticotropic hormone levels during the course of labor; these reach peak values at or after delivery (51,52,53 and 54). Lederman and associates (52,53) noted that, during the period of active labor, the epinephrine level increased by nearly 300%, the NE level by 150%, and the cortisol level by 200%. They noted that the higher epinephrine levels were significantly associated with uterine contractile activity at the onset of active labor (3-cm cervical dilatation) and with longer labor during the active phase (3- to 10-cm cervical dilatation). Increased epinephrine and cortisol levels were correlated significantly with anxiety and pain.

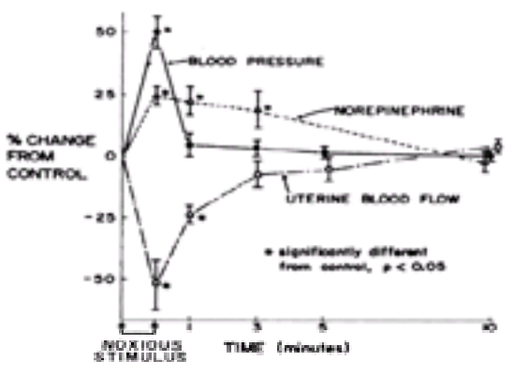

Figure 71-14. Effects of noxious stimulus on maternal arterial blood pressure, norepinephrine blood level, and uterine blood flow. The stress was induced by application of an electric current onto the skin of an ewe at term. The increase in arterial pressure is transient but the decay in norepinephrine level is more protracted and is reflected by a mirror image decrease in uterine blood flow. (Reprinted from Shnider SM, Wright RG, Levinson G, et al. Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. *Anesthesiology* 1979;50:524–527, with permission.)

In a later study, Ohno and associates (55) carried out a comprehensive study of catecholamines and cyclic nucleotides during labor and following delivery and noted a nearly twofold increase in the dopamine level, a threefold increase in the epinephrine level, and a twofold increase in the NE as well as a small increase in the cyclic adenosine monophosphate level. They noted a positive correlation between epinephrine on the one hand and heart rate and systolic blood pressure on the other, as well as a correlation between NE and cyclic adenosine monophosphate during labor. The greater increase in epinephrine than in NE was contrasted with the findings of a previous study, which showed that NE was much greater than epinephrine during physical exercise. This led to the conclusion that elevated sympathoadrenal activity during labor is a result of pain and anxiety rather than of physical effort. Other data, however, show that although pain is a major factor in the elevation of catecholamine levels, physical effort during the second stage does contribute to the increase in catecholamine levels.

Other studies have demonstrated a progressive increase in plasma b-endorphin, b-lipotropin, and adrenocorticotropic hormone levels, all of which are derived from a common precursor (56,57,58,59,60 and 61). These values have been found to peak at delivery or in the immediate postpartum period at 4 to 10 times the prelabor and nonpregnant values. These findings have led to the speculation that plasma b-endorphin might have an intrinsic analgesic role during parturition (62). Against this is the fact that plasma b-endorphin levels that are considerably higher than those observed in these studies do not appear to cross the blood–brain barrier or have analgesic effects in humans (63). In addition, no change in pain threshold has been demonstrated in parturients (64).

Cardiovascular Changes. During labor, the progressive increase in cardiac output is 40% to 50% higher than the prelabor value during the late first and second stages. Some parturients have an increase of nearly 100% with a further increase of 20% to 30% during each painful uterine contraction. Available data suggest that 40% to 50% of the increase during the contraction is caused by the extrusion of 250 to 300 mL of blood from the uterus and by increased venous return from the pelvis and lower limbs into the maternal central circulation. The rest is caused by an increase in sympathetic activity provoked by pain, anxiety, apprehension, and the physical effort of labor, which contribute to the progressive rise in cardiac output as labor advances (34,35). Uterine contractions in the absence of analgesia also cause increases of 20 to 30 mm Hg in the systolic and diastolic blood pressures. The increases in cardiac output and systolic blood pressure lead to a significant increase in left ventricular work that is tolerated by healthy parturients, but can prove deleterious if the parturients have heart disease, pregnancy-induced hypertension (preeclampsia), essential hypertension, pulmonary hypertension, or severe anemia.

Metabolic and Other Effects. During the first and second stages of labor-free fatty acids and lactate levels increase significantly, apparently as a result of the pain-induced release of catecholamines and the consequent sympathetic-induced lipolytic metabolism (65). This assumption is based on the fact that, with complete blockade of nociceptive (afferent) and efferent pathways achieved with epidural or other forms of regional analgesia, only slight increases in maternal free fatty acid and lactate levels and acidosis are seen. During the second stage of labor maternal acidosis is a result of the pain and physical exertion inherent in the active bearing-down (pushing) effort during contractions.

Increased sympathetic activity caused by labor pain and anxiety also increases metabolism and oxygen consumption and decreases gastrointestinal and urinary bladder motility. The increased oxygen consumption, plus that inherent in the work of labor, together with the loss of bicarbonate from the kidney as compensation for the pain-induced respiratory alkalosis and often reduced carbohydrate intake, produce a progressive metabolic acidosis that is transferred to the fetus. The maternal pyruvate level increases, along with an even greater increase in the lactate level and a progressive accumulation of excess lactate, which is reflected by a progressive increase in base excess (45,46,66).

The pain of labor also affects the function of the gastrointestinal tract. Gastrin release is stimulated during painful labor and results in an increase in gastric acid secretion (67). Moreover, the pain and associated anxiety and emotional stress produce segmental and suprasegmental reflex inhibition of gastrointestinal motility and function, and consequently a significant delay in gastric emptying. These reflex effects of nociception are aggravated by the recumbent position and by the use of opioids and other depressant drugs (9,20,68,69). The combined effect of pain and depressant drugs can cause food and fluids other than water to be retained for as long as 36 hours or more. During this period of time swallowed air and gastric juices accumulate progressively, with the pH of the stomach contents decreasing below the critical value of 2.5 in most parturients. These two events, plus the delayed gastric emptying of acidic gastric contents, increases the risk of regurgitation and pulmonary aspiration during the induction of general anesthesia.

Psychological Effects. Severe labor pain can produce serious long-term emotional disturbances that might impair the parturient's mental health, negatively influence her relationship with her baby during the first few crucial days, and cause fears of future pregnancies that could affect her sexual relationship with her husband (23,24,70,71,72 and 73). Kartchner (70), Rogers (71), Melzack (27), and others (72,73) reported a significant number of women who had participated in natural childbirth developed or had aggravation of prelabor depression and other deleterious emotional reactions in the postpartum period, consequent to the pain

experienced during their childbirth without analgesia. Cheetham and Rzadkowolski (72) reported that nearly two-thirds of parturients experienced some type of emotional upset characterized predominantly by a decrease in mental acuity and in social interests, and an increase in their feelings of dysphoria, depression, and anxiety. They pointed out that psychological aspects of labor are accentuated by the well-cited triad of fear, tension, and pain, which might in turn decrease uterine activity and thus prolong labor. In addition, Melzack (27) noted that some women might experience an added burden of guilt, anger, and failure when they anticipate natural, painless childbirth and are then confronted with such severe pain that they require epidural analgesia. Stewart (73) reported that some women who failed to achieve painless childbirth and experienced such severe pain as to require epidural analgesia subsequently became miserable, depressed, and even suicidal, and lost interest in sex. In some cases, the husbands of women who anticipated natural childbirth had to undergo psychotherapy for serious reactions after seeing their wives experience such severe pain that they developed feelings of guilt and subsequent impotence and phobias.

Effects on Uterine Activity and Labor. Through increased secretion of catecholamines and cortisol, pain and emotional stress can either increase or decrease uterine contractility and thus influence the duration of labor. NE increases uterine activity, whereas epinephrine and cortisol decrease it (9,53). Morishima and colleagues (49,74) reported that, in pregnant baboons and Rhesus monkeys, nociceptive stimulation increased uterine activity about 60% to 65% and was associated with a decrease in fetal heart rate and oxygenation. In contrast, severe pain and anxiety in some parturients caused such an increase in epinephrine and cortisol levels that uterine activity was consequently decreased and labor was prolonged (52,53). In a small number of parturients, pain and anxiety produce *incoordinate uterine contractions* manifested by a decrease in intensity coupled with an increase in frequency and uterine tonus (75).

Effects on the Fetus. During labor the intermittent reduction of intervillous blood flow during the peak of a contraction leads to a temporary decrease in placental gas exchange. This impairment is often further increased by pain-induced severe hyperventilation, which causes severe respiratory alkalosis and results in the following: (a) a shift (to the left) in the maternal oxygen dissociation curve, which diminishes the transfer of oxygen from mother to fetus; (b) maternal hypoxemia during uterine relaxation; (c) umbilical vasoconstriction with a consequent decrease in umbilical blood flow (76); and (d) a reduction in uterine blood flow, which is provoked by an increase in NE and cortisol release (see Fig. 71-14).

These deleterious effects on the fetus have been demonstrated in several species of animals and in humans (49,53,74,75). Figure 71-13 depicts the deleterious effects on fetal heart rate that are caused by marked hyperventilation during a contraction and by hypoventilation between contractions. Lederman (53) also noted that parturients who were anxious and had pain had a higher incidence of abnormal fetal heart rate patterns, and that their infants had lower 1- and 5-minute Apgar scores.

Under the conditions of normal labor, such series of transient and intermittent impairments of blood gas exchange are tolerated by the normal fetus because oxygen is stored in the fetal circulation and intervillous space and is sufficient to maintain adequate fetal oxygenation during the brief period of placental hypoperfusion. Moreover, the fetus can compensate by increasing the proportion of cardiac output that is distributed to the myocardium and brain (77,78). If the previously mentioned factors are combined with an excessive increase in uterine activity, however, fetal hypoxia, hypercapnia, and acidosis develop that might still be tolerated by the normal fetus, although its ability to withstand oxygen deprivation is limited. If the fetus is already at risk because of obstetric or maternal complications (e.g., preeclampsia, heart disease, diabetes), the pain-induced reductions of oxygen and carbon dioxide transfer can be the critical factors that produce perinatal morbidity and could even contribute to mortality (9,20,49,74). The maternal metabolic acidosis is transferred to the fetus, making it more vulnerable to the effects of intrauterine asphyxia caused by cord compression, prolapse, or other obstetric complications (9,77,79).

Effects of Sedation and Analgesia

There are many clinical studies, backed up by laboratory studies, that have shown that relief of pain can decrease or virtually eliminate most of the untoward maternal and fetal alterations that were just summarized. We summarize some of these in the next few paragraphs.

Ventilation. Partial relief of pain with opioids decreases hyperventilation to the point that the Paco $_2$ is in the 22 to 25 mm Hg range and oxygenation improves (44,45,46 and 47). Complete pain relief achieved with epidural analgesia prevents the transient period of hyperventilation during a contraction and prevents hypoventilation during relaxation, so that the Paco$_2$ remains normal in the range of 28 to 32 mm Hg and the Pao$_2$ increases to approximately 100 mm Hg (Fig. 71-15 and Fig. 71-16).

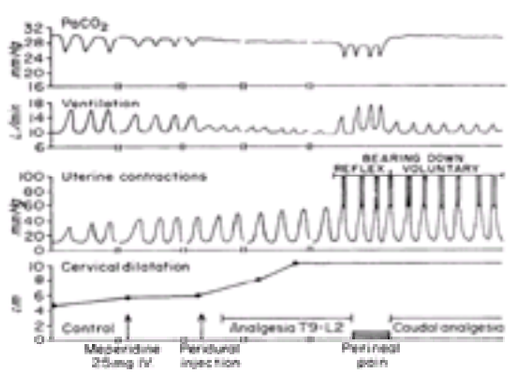

Figure 71-15. Schematic representation of the effects of analgesia on ventilation based on measurements in a primipara. At 5-cm cervical dilatation 25 mg of meperidine intravenously resulted in partial relief of pain and consequently produced smaller changes in ventilation and Paco $_2$. Subsequent induction of segmental epidural analgesia produced complete pain relief, which eliminated maternal hyperventilation and Paco $_2$ changes without affecting uterine contractions. During the second stage the onset of perineal pain and initiation of reflex bearing-down efforts caused a concomitant increase in ventilation and a slight decrease in the Paco $_2$ which were eliminated with the induction of low caudal (S-1 to S-5) analgesia. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:114, with permission.)

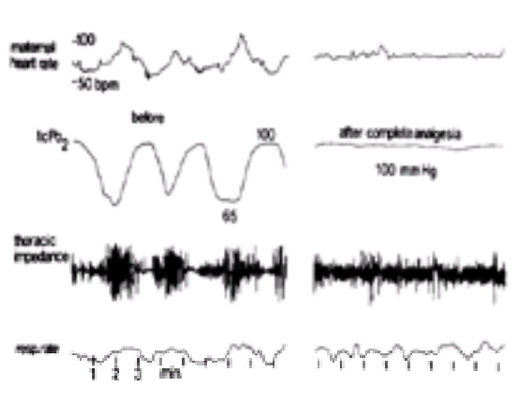

Figure 71-16. Polygraph recording of maternal heart rate, transcutaneous oxygen tension (tcPo $_2$), thoracic impedance, and respiratory rate during labor. Before the induction of epidural analgesia the pain of uterine contractions caused marked hyperventilation and a consequent increase in tcPo $_2$ to 100 mm Hg, which fell to 65 to 70 mm Hg between contractions. After complete epidural analgesia all curves were more regular, and the tcPo $_2$ was maintained at a stable 100 mm Hg. (Reprinted from Peabody JL. Transcutaneous oxygen measurement to evaluate drug effect. *Clin Perinatol* 1979;6:109–121, with permission.)

Neuroendocrine Effects. Studies have provided impressive evidence that epidural analgesia, by blocking nociceptive input and sympathetic efferents, reduces the release of catecholamines, b-endorphins, adrenocorticotropic hormone, and cortisol (51,58,59,65,80,81,82 and 83). This neuroendocrine-lowering effect is primarily the result of the relief of pain during labor (84). This study revealed that spinal anesthesia at the T-4 dermatomal level decreased catecholamine levels in women in labor, but did not do so in women who were not in labor. These results suggest that the mechanism by which catecholamine release is decreased is relief of maternal

pain.

Epidural analgesia during labor and delivery does not decrease catecholamine and b-endorphin release in the fetus and newborn (59,61,81,82,83 and 84). This response indicates that, even during uncomplicated deliveries with adequate maternal analgesia, the newborn can be distressed by the process of birth by vaginal delivery. One study (84) suggested catecholamines have important roles in regard to neonatal adaptation including surfactant synthesis and release, lung liquid resorption, nonshivering thermogenesis, glucose homeostasis, cardiovascular changes, and water metabolism.

Cardiovascular Effects. By decreasing the pain-induced sympathetic hyperactivity and neuroendocrine response, epidural analgesia eliminates that portion of the increase in cardiac output and blood pressure caused by pain. Figure 71-17 and Figure 71-18 show that epidural analgesia decreases the progressive increase in cardiac output and its further increase during uterine contractions to approximately 50% of that before analgesia. A similar decrease in periodic increase in blood pressure is depicted in Figure 71-19. Several studies have proven the value of epidural analgesia in lessening the increase in cardiac output, cardiac work, and blood pressure in laboring parturients. These become important with heart disease, pregnancy-induced hypertension (preeclampsia), and pulmonary hypertension, provided of course that maternal hypotension is avoided (85,86).

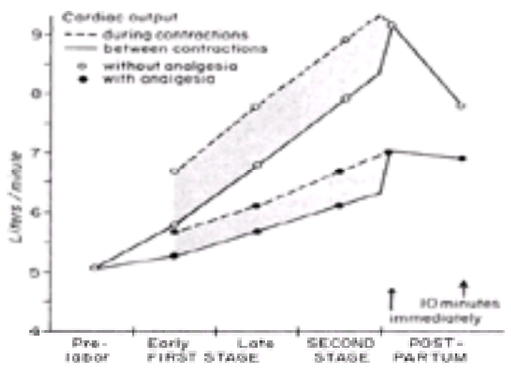

Figure 71-17. Cardiac output during various phases of labor between contractions and during contractions. In a group of patients laboring without analgesia, the progressive increases between contractions and the further increases during each contraction were much greater than corresponding changes in a group of patients who received continuous epidural analgesia. (Data from Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia*. Vol 1. Philadelphia: FA Davis, 1967.)

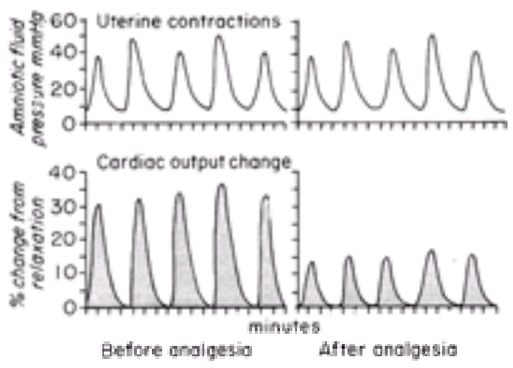

Figure 71-18. Increases in cardiac output during each uterine contraction before and after induction of continuous epidural analgesia in a primipara. With pain relief the increases in cardiac output during contractions were approximately 50% of those before induction of analgesia. (Reprinted from Bonica JJ. Labour pain. In: Wall PD, Melzack R, eds. *Textbook of pain*, 2nd ed. Edinburgh, UK: Churchill Livingstone, 1989:491, with permission.)

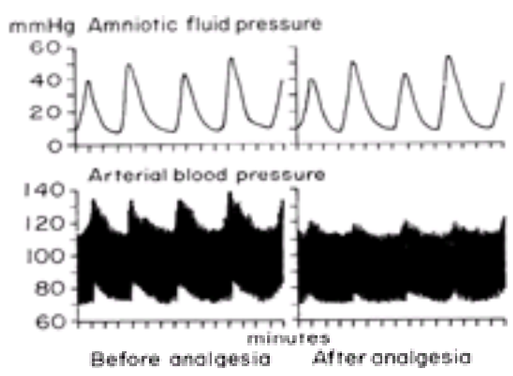

Figure 71-19. Fluctuations in blood pressure produced by uterine contractions before and after induction of continuous epidural analgesia. Like the cardiac output changes (see Fig. 71-18), complete relief of pain resulted in decreasing the contraction-induced fluctuations to nearly 60% of the values measured before analgesia. (Reprinted from Bonica JJ. Labour pain. In: Wall PD, Melzack R, eds. *Textbook of pain*, 2nd ed. Edinburgh, UK: Churchill Livingstone, 1989:491, with permission.)

Metabolic Effects. The relief of pain and associated anxiety with continuous epidural analgesia decreases the total work of labor, maternal metabolism, and oxygen consumption. Buchan (65) showed that during labor, epidural analgesia reduced internal stress by abolishing pain, thus eliminating the progressive increase in the 11-hydroxycorticosteroid levels normally seen throughout labor. Consequently, epidural analgesia significantly reduces maternal and fetal metabolic acidosis. The superiority of epidural analgesia over systemic opioids and other systemic drugs in decreasing maternal work, oxygen consumption, and maternal and fetal metabolic acidosis has been impressively demonstrated by a number of investigators (45,46,51,87,88,89,90 and 91) (Fig. 71-20). Because active pushing during the second stage of labor contributes to metabolic acidosis, epidural analgesia does not completely eliminate metabolic and fetal acidosis. Figure 71-20 demonstrates that epidural analgesia and elimination of the bearing-down effort (pushing) during the second stage almost eliminate maternal metabolic acidosis. Moreover, under these conditions it decreases but does not eliminate the degree of fetal acidosis; the latter may well be a result of the physical stress on the fetus during the process of birth.

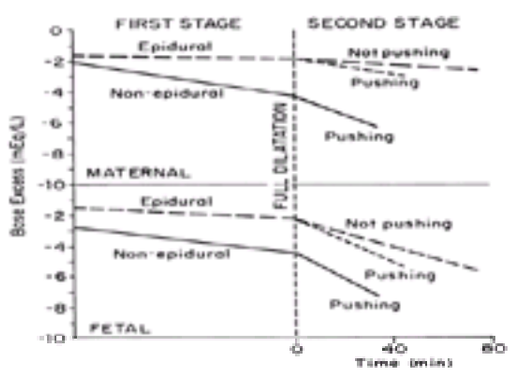

Figure 71-20. Mean changes in extent of maternal (*above*) and fetal (*below*) metabolic acidosis during the first and second stages of labor in a group of parturients

managed without lumbar epidural analgesia and in two similar groups managed with epidural analgesia, one of which retained the bearing-down reflex and the other did not. The parturients were delivered by outlet forceps. Significant metabolic acidosis was experienced by those in the nonepidural group of parturients whereas those given epidural analgesia experienced few or no changes in their acid–base status. Fetuses born of mothers managed without epidural also developed metabolic acidosis during the first stage, and to an even greater degree during the second stage. In contrast, fetuses of mothers given epidural had no change in acid–base status during the first stage but showed a time-dependent increase in metabolic acidosis during the second stage. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:115, with permission.)

Effects on Uterine Activity. By decreasing the sympathetic-induced hyperactivity, sedation and complete analgesia can reduce or eliminate uterine hyperactivity or remedy hypoactivity, and it can convert incoordinate uterine contractions to normal contractions (9,75,91) (Fig. 71-21). Equally important is the efficacy of analgesia in reducing placental hypoperfusion and any existing deterioration in uterine blood flow. Such treatment can thus decrease or even eliminate impairment of blood gas transfer that might be a result of increased catecholamines or uterine hyperactivity (9).

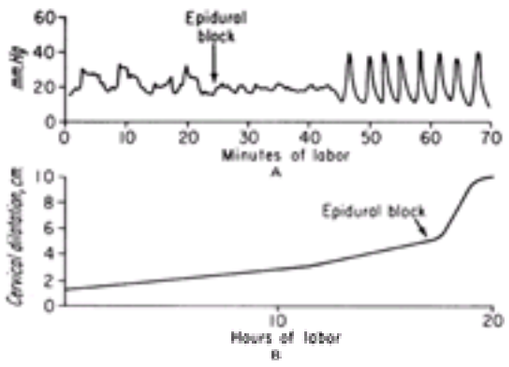

Figure 71-21. Effect of epidural block on incoordinate uterine contractile pattern. **A:** Intrauterine pressure tracings. Note the temporary decrease in uterine contractions and the subsequent normalization of the previously irregular contractions. **B:** Cervimetric curve showing the rapid cervical dilation that followed start of the epidural block. (Reprinted from Bonica JJ, McDonald JS. *Principles and practice of obstetric analgesia and anesthesia*, 2nd ed. Baltimore: Williams & Wilkins, 1995:381, with permission.)

Effects on the Fetus. These benefits of pain relief, best achieved with regional analgesia, are likely to be of value in general for most infants, but they are especially important for the fetus at risk. Regional techniques have been found to be the best method of analgesia for breech delivery and for multiple pregnancies (9,92,93). It has been shown that epidural analgesia, through its vasomotor-blocking effect, increases intervillous blood flow in parturients with severe preeclampsia and probably also in those with hypertension, diabetes, and other conditions that decrease placental blood flow and function (9,92,93,94 and 95). Janisch and coworkers (96) found that continuous epidural analgesia administered to preeclamptic patients during their last few weeks of gestation produced a 100% increase in placental blood flow. Jouppila and colleagues (97) studied the influence of lumbar epidural analgesia that was limited to a few segments and the effect of a more extensive type of lumbar epidural block on parturients with severe preeclampsia. They found that the limited block increased intervillous blood flow by 34%, whereas the more extensive block increased it by a mean of 77%. They attributed this effect to the relief of severe vasoconstriction by the vasomotor block. However, maternal hypotension associated with the epidural must be strictly avoided by appropriate prophylactic measures such as intravenous infusion of fluids and lateral displacement of the uterus to maintain maternal systemic pressure.

Mechanisms, Pathways, and Characteristics of the Pain of Parturition

To provide optimal pain relief with regional analgesia, it is essential for the obstetric team to understand the peripheral mechanisms and pathways of the pain of parturition and the factors that influence its intensity, duration, and quality. Most of these factors vary during the different phases and stages of labor and are therapeutically significant, so they are considered separately over the next few paragraphs.

Pain of the First Stage of Labor

Intrinsic Mechanisms. During the first stage, labor pain initially is entirely in the uterus and its adnexa during contractions. Recall that labor pain may be caused by the following conditions:

- Pressure on nerve endings between the muscle fibers of the body and fundus of the uterus (98)
- Contraction of the ischemic myometrium and cervix consequent to expulsion of blood from the uterus during the contraction (99) or as a result of vasoconstriction consequent to sympathetic hyperactivity (2)
- Inflammatory changes of uterine muscles (98)
- Contraction of the cervix and lower uterine segment consequent to fear-induced hyperactivity of the sympathetic nervous system (2)
- Dilatation of the cervix and lower uterine segment (24,99)

Most data support the concept that the pain of the first stage of labor is predominantly a result of dilatation of the cervix and lower uterine segment and of the consequent distension, stretching, and tearing of these structures during progressive contractions. Contractions of the uterus under isometric conditions (i.e., against the obstruction presented by the cervix and perineum) also probably contribute to the pain of uterine contractions.

These hypotheses are based on the following considerations:

- Stretching of smooth muscle of a hollow viscus is an adequate stimulus for visceral pain (100).
- The degree of cervical and lower uterine segment dilatation is correlated with the rapidity with which it occurs on the one hand and with the intensity of the pain on the other (20).
- The time of onset of uterine contractions is related to the time of onset of the pain. This lag, which is longest in the early stages of labor and lessens as labor progresses, occurs because uterine contractions need time to increase the amniotic fluid pressure to 15 mm Hg above tonus. This has been determined to be the minimum pressure required to initiate distension of the cervix and lower uterine segment (101).
- In the parturient undergoing cesarean section with abdominal field block, the exposed but unanesthetized uterus can be incised and gently palpated without discomfort to the conscious parturient (24,99). On the other hand, forceful palpation and stretching of the cervix and lower uterine segment produced pain similar in quality and location to that experienced during labor (24,99).
- When the cervix is suddenly and widely dilated in parturients or in gynecologic patients, they feel pain similar in quality, distribution, and intensity to that experienced during uterine contractions (24,99,102).

The evidence that contractions of the body of the uterus contribute to the pain of labor is, to some degree, puzzling. Braxton-Hicks contractions of prelabor are frequently painless, even though they can attain the intensity of labor contractions. During the immediate postpartum period, the intensity of uterine contractions of the empty uterus might be two to three times stronger than the contractions of active labor; yet, they are associated either with much less intense pain or with no pain at all. On the other hand, strong contractions are associated with severe pain in most parturients with mechanical distortion caused by abnormal fetal positions and in those in whom the cervix dilates slowly.

Peripheral Pathways. Based on studies of the segments of hyperalgesia associated with various uterine disorders, as well as of hyperalgesia during the second stage of labor, Head (103) concluded the sensory nerve supply of the uterus involved the T-11, T-12, and frequently T-10 and L-1 to L-2 segments. The cervix was supplied by the S-2, S-3, and S-4 segments. Some 40 years later, based on animal experiments and studies of parturients, Cleland (104) concluded that in humans the

sensory supply of the uterus was by T-11 and T- 12, and pain caused by stretch of the birth canal was transmitted through undetermined sacral segments. This latter finding was interpreted to mean that the cervix and vagina are supplied by the sacral segments. As a result of these two studies it became widely taught that nociceptive impulses from the body of the uterus are transmitted through the T-11 and T-12 nerves, and that pain from the cervix and lower uterine segment is transmitted through the pelvic nerve to the S-2, S-3, and S-4 spinal segments.

Bonica's observations were at variance with this concept; he and associates carried out a study that involved 240 parturients and 35 gynecologic patients investigated over a period of 22 years (105). That study entailed the use of discrete blocks of various nociceptive pathways by paravertebral block, segmental epidural block, caudal block, and transsacral block of various segments (105). This extensive study demonstrated conclusively that the upper part of the cervix and the lower uterine segment are not supplied by sensory fibers that accompany the pelvic nerves (nervi erigentes), as stated in almost every modern anatomy and obstetric textbook (106,107,108 and 109). Rather, these structures are supplied by afferents that accompany the sympathetic nerves in the following sequence: the uterine and cervical plexus; the pelvic (inferior hypogastric) plexus; the middle hypogastric plexus or nerve; and the superior hypogastric and aortic plexuses.

The nociceptive afferents then pass to the lumbar sympathetic chain and course cephalad through the lower thoracic sympathetic chain via the rami communicantes of the T-10, T-11, T-12, and L-1 spinal segments. Finally, they pass through the posterior roots of these nerves to make synaptic contact with interneurons in the dorsal horn (Fig. 71-22 and Fig. 71-23).

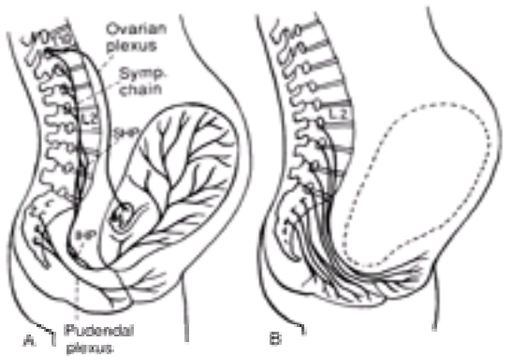

Figure 71-22. Schematic depiction of the peripheral nociceptive pathways involved in the pain of childbirth. **A:** The uterus, including the cervix and lower uterine segments, is supplied by afferents that pass from the uterus to the spinal cord by accompanying sympathetic nerves through the inferior hypogastric plexus (IHP), the hypogastric nerve, the superior hypogastric plexus (SHP), the lumbar and lower thoracic sympathetic chain, and the nerves at T-10, T-11, T-12, and L-1. **B:** The nerves involved in transmission of nociceptive impulses are provoked by noxious stimulation of pelvic structures. See text for details.

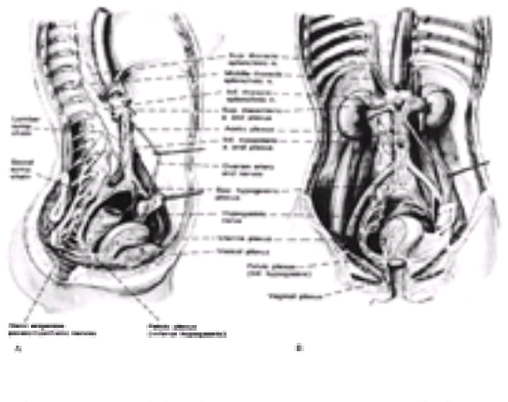

Figure 71-23. Gross anatomy of the nerve supply to the uterus. **A:** Lateral view. **B:** Anterior view. The uterus is shown in the nonpregnant state to permit the various nerves that supply it to be depicted. Note that the uterine and cervical plexuses are derived from the pelvic plexus, which contains parasympathetic and sympathetic efferents. The parasympathetic efferents have their cell bodies in the middle three sacral segments, and the parasympathetic afferents pass through these segments and progress cephalad through the neuraxis. The sympathetic efferents and afferents pass through the hypogastric nerve, which in turn is a continuation of the superior hypogastric and aortic plexuses. Note that fibers from the latter two plexuses pass on to the lumbar sympathetic chain, the afferents of which mediate nociceptive impulses and accompany the sympathetic fibers through these structures. From the lumbar and lower thoracic sympathetic chain the nociceptive afferents pass to the T-10, T-11, T-12, and L-1 spinal nerves and reach the spinal cord via their posterior roots and rootlets. (Modified from Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia*. Philadelphia: FA Davis, 1967:110–111.)

Typical of the pain arising from viscera, the pain of the first stage of labor is referred to the dermatomes supplied by the same spinal cord segments that receive input from the uterus and cervix. During the early phase of the first stage the pain is felt as an ache and is limited to the T-11 and T-12 dermatomes (Fig. 71-24A). As labor progresses to the active phase of the first stage, 3- to 4-cm cervical dilatation, the pain in the T-11 and T-12 dermatomes becomes more severe and is described as sharp and cramping and spreads to the two adjacent (T-10 and L-1) dermatomes (Fig. 71-24B).

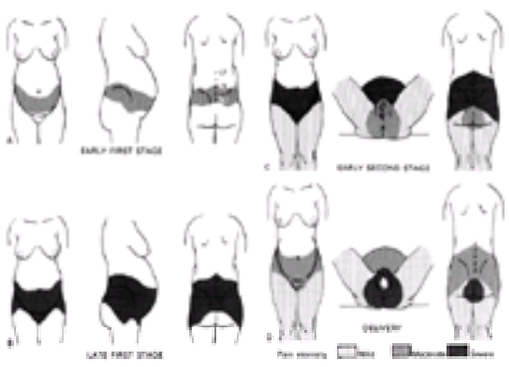

Figure 71-24. The intensity and distribution of parturition pain during the various phases of labor and delivery. **A:** In the early first stage the pain is referred to the T-11 and T-12 dermatomes. **B:** In the late first stage, however, the severe pain is also referred to the T-10 to L-1 dermatomes. **C:** In the early second stage uterine contractions remain intense and produce severe pain in the T-10 to L-1 dermatomes. At the same time the presenting part exerts pressure on pelvic structures and thus causes moderate pain in the very low back and perineum and often produces mild pain in the thighs and legs. **D:** Intensity and distribution of pain during the latter phase of the second stage and during actual delivery. The perineal component is the primary cause of pain whereas uterine contractions produce moderate pain. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:46–47, with permission.)

The distribution of the T-10, T-11, T-12, and L-1 dermatomes in the back overlies the lower three lumbar vertebrae and the upper half of the sacrum (see Fig. 71-9). Often, the pain is not referred to the entire dermatome but can be more severe in one or more patches of varying sizes within the territory of one or more of the individual dermatomes (20,26,27).

Second and Third Stages of Labor

Once the cervix is fully dilated, the amount of nociceptive stimulation arising in this structure decreases, but the contractions of the body of the uterus and distension of the lower uterine segment continue to cause pain in the same areas of reference as in the first stage of labor. In addition, the progressively greater pressure of the presenting part on pain-sensitive structures in the pelvis and distension of the outlet and perineum become new sources of pain. Progressively greater distension causes intense stretching and actual tearing of fascia and subcutaneous tissues and pressure on the skeletal muscles of the perineum. Like other pain caused by stimulation of superficial somatic structures, the perineal pain is sharp and well localized, predominantly to the regions supplied by the pudendal nerves, and can be eliminated by block of these nerves (9,110) (Fig. 71-25A and Fig. 71-25C).

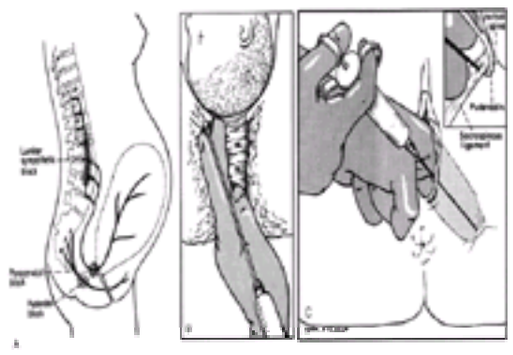

Figure 71-25. **A:** Sites of three regional techniques for obstetric analgesia. Lumbar sympathetic block is rarely used but is highly effective in relieving pain of the first stage and can be preferable to the use of paracervical block, especially in high-risk pregnancies. **B:** Technique of paracervical block. The coronal section of the vagina and the lower part of the uterus containing the fetal head are shown. The 22-gauge needle is contained within a guide, with its point protruding only 5 to 7 mm beyond the end of the guide. This prevents the needle being inserted more than 5 to 7 mm beyond the surface of the mucosa. After negative aspiration an injection of 8 to 10 mL of 0.25% bupivacaine at 4 and 8 o'clock of the cervical fornix produces relief of uterine pain for several hours. **C:** Transvaginal technique of blocking the pudendal nerve. The two fingers of the left hand are inserted into the vagina to guide the needle point into the sacrospinous ligament. As long as the bevel of the needle is in the ligament there is some resistance to the injection of local anesthetic, but as soon as the bevel passes through the ligament there is a sudden lack of resistance, indicating that the needle point is next to the nerve. (Modified from Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia*. Vol 1. Philadelphia: FA Davis, 1967:493, 514–515.)

In the late part of the first stage and during the second stage, a number of parturients develop aching, burning, or cramping discomfort in the thigh and, less frequently, in the legs (Fig. 71-24C and Fig. 71-24D). This is a result of stimulation of pain-sensitive structures within the pelvic cavity, including traction on pelvic parietal peritoneum and the uterine ligaments; stretching and tension of the bladder, urethra, and rectum; stretching and tension of ligaments, fascia, and muscles in the pelvic cavity; and undue pressure on one or more roots of the lumbosacral plexus.

These factors usually produce mild pain referred to the lower lumbar and sacral segments (see Fig. 71-22B), but if the fetus is in an abnormal position, with undue pressure by the presenting part, the referred pain can become moderate or severe (see Fig. 71-24C and Fig. 71-24D).

The transmission of the nociceptive information that arises from these various structures to the dorsal horn and then to other parts of the spinal cord and to the ascending systems to the brain is presumably similar to that of other types of acute pain. The pain is provoked by tissue damage in the cervix and perineum and is thought to be passed to the dorsal horn through A-d and C nociceptive fibers.

Factors That Affect the Pain of Childbirth

In addition to the role played by such intrinsic factors as the intensity, duration, and pattern of contractions and related physiologic and biochemical mechanisms, the amount or degree of pain and suffering associated with childbirth is influenced by physical, psychological, emotional, and motivational factors (9,24,27,94,98,108,109).

Physical Factors. Physical factors that influence the incidence, severity, and duration of the pain of childbirth include the age, parity, and condition of the parturient, the condition of the cervix at the onset of labor, and the relationship of the size of the infant to the size of the birth canal. Many of these factors are interrelated. Generally, an older primipara experiences a longer and more painful labor than a younger primipara. The cervix of the multipara begins to soften even before the onset of labor and is less sensitive than that of the primipara. The intensity of uterine contractions in early labor tends to be higher in primiparas than in multiparas, whereas in the latter phase of labor the reverse is true. In the presence of dystocia caused by a contracted pelvis, a large baby, or abnormal presentation, the parturient experiences more pain than under normal conditions. Melzack and associates (27,28) found that high pain levels were associated with a history of menstrual difficulties. Fatigue, loss of sleep, and general debility influence a parturient's tolerance of the painful experience and increase the pain behavior. This is particularly significant in parturients with prolonged labor.

Psychological Factors. Psychological factors that can and frequently do affect the incidence and intensity of parturition pain include the mentation, attitude, and mood of the parturient at the time of labor, as well as other emotional factors. Fear, apprehension, and anxiety probably enhance pain perception and pain behavior (9,20,23). One of the most frequent causes of fear and anxiety is ignorance of or misinformation about the processes of pregnancy and parturition, and what the onset of labor signifies. An uninformed parturient, especially a primipara, can be disturbed by fear of the unknown, death, suffering, mutilation, possible complications, and concern for her condition or that of her fetus (20). Parturients who have had an unplanned or illegitimate pregnancy or have an ambivalent or negative reaction to gestation report more pain than those who do not (20,23,111). In contrast, other emotional factors, such as intense motivation and cultural influences, can affect modulation of sensory transmissions and certainly can influence the affective and behavioral dimensions of pain. Moreover, cognitive intervention such as giving the parturient preparatory information about labor, thus reducing uncertainty while focusing attention or producing distraction and dissociation from pain (all parts of an *educated* childbirth program), reduces pain behavior.

The influence of education and psychological conditioning inherent in psychoprophylaxis and natural childbirth in modifying pain behavior without significantly affecting pain sensation is now widely appreciated. During 5- to 10-day visits to obstetric centers that practiced psychoprophylaxis or natural childbirth in the Soviet Union, France, Germany, Italy, the Netherlands, Sweden, and the United States, made over a 5-month period in 1959, Bonica observed approximately 700 parturients (and interviewed many) who had received training in one of these methods, and more than 85% of them manifested little or no pain behavior during labor and delivery. When questioned the next day, however, most of them indicated that the process had been painful but many quickly added that they were pleased to cooperate with their instructor and obstetric team (9). Especially impressive was the marked change in behavior of Italian parturients in a large obstetric center in Turin noted during two visits made 5 years apart. During the first visit, in 1954, the labor ward was a scene of cacophony caused by the screaming, pleading, and praying of the nearly 50 laboring women in the same ward. In contrast, 5 years later, one heard only an occasional moan from a similar number of parturients who had undergone an intensive course of psychoprophylaxis. Most went through the entire labor and delivery with minimal pain behavior but later stated that they had had moderate to severe pain.

Summary

It is obvious that the pain-associated responses to noxious stimulation provoked by uterine contractions and other tissue-damaging factors during labor and vaginal delivery are the net effects of highly complex interactions of various neural systems, modulating influences, and psychological factors. Through the interaction of the afferent system and neocortical processes, the parturient receives perceptual and discriminate information that is analyzed and that usually activates motivational cognitive processes. These, in turn, act on the motor system and initiate psychodynamic mechanisms of anxiety and apprehension that produce the complex physiologic, behavioral, and affective responses that characterize acute pain.

CLINICAL CONSIDERATIONS: MANAGEMENT OF THE PAIN OF CHILDBIRTH

The pain as previously described in detail for the first and second stages of labor and that associated with actual delivery not only produces suffering and emotional disturbances, but also induces segmental and suprasegmental reflex responses that further magnify the pain experience. It is the challenge and task of the obstetric team to provide optimal relief of pain to parturients with the resources available.

Many drugs and techniques are currently available for providing analgesia during childbirth. The methods vary according to geographic region or country and depend on the culture, medical personnel, facilities, and other sociologic and professional factors. To be used properly, each drug and technique must be evaluated from four interrelated viewpoints: (a) analgesic potency and other therapeutic efficacy; (b) side effects on the mother; (c) effects on the fetus and newborn; and (d) effects on the forces of labor.

Table 71-1 contains a critical evaluation of the various drugs and techniques in current use from these perspectives. The effects on the mother, fetus, and newborn, and the forces of labor discussed in the table are based on the use of optimal doses and routes of administration of systemic drugs and on the use of optimal concentrations and volumes of local and regional anesthetics.

TABLE 71-1. Pharmacology and applications of obstetric analgesia and anesthesia

General Considerations

Basic Principles

To obtain the most effective results with obstetric analgesia and anesthesia, those on the obstetric team must adhere to certain basic principles. The objective is to provide optimal relief of pain to the mother with little or no risk to her and her infant. The type of analgesia or anesthesia must be tailored to the needs of each mother and infant within the framework of the personnel and resources available. Each member of the obstetric team must be fully informed of the plans and possible problems of other members, with excellent communication, coordination, and cooperation among those on the team. The anesthetist must have a thorough understanding of the physiologic and pathophysiologic alterations caused by pregnancy and labor, and how these are affected by each type of analgesia.

Antepartal and Preanesthetic Care. The proper preparation of the gravida and her spouse during the antepartum period is one of the most important responsibilities of the obstetric team (94). She and her husband should be informed about the physiology and psychology of pregnancy and labor and about the psychological and emotional effects these might produce. Understanding the changes in her circulation, respiration, endocrine function, and other systems helps the gravida to understand and accept the inconveniences, discomforts, and awkwardness of the lopsided silhouette she develops during pregnancy (20,94). Similarly, a discussion of the physiology and clinical course of labor provides her with useful information and helps her to cooperate and participate actively during labor as well as in the many other aspects of educated childbirth. During one of the antepartum visits the obstetrician should bring up the matter of analgesia and anesthesia and, if the gravida indicates that she is interested, the advantages, disadvantages, and limitations of each technique should be clearly explained by a responsible member of the anesthesiology team. If the gravida delivers in the hospital, it is essential that everyone who comes in contact with the patient (from the admission clerk to members of the house staff) thoroughly appreciate the importance of a friendly and reassuring attitude.

Those gravidas who indicate a desire for some form of pain relief should be seen by an anesthesiologist either prior to or soon after admission to the hospital. Proper preanesthetic care requires a thorough evaluation of the parturient, including a medical and anesthesia history, physical examination, assessment of the physiologic and emotional status of the parturient, and discussion of the various forms of analgesia and anesthesia available. Selection of the method of analgesia to be used is made in consultation with the parturient and obstetrician.

Intrapartal and Intraanesthetic Care. During labor, the uterine contractions, cervical dilatation, and advance of the presenting part should be monitored. The cervicographic method of following the progress of labor is recommended. During a home or hospital delivery in which modern equipment is not available, the fetal heart rate is monitored by auscultation. The limitations of this method and of palpating uterine contractions are generally recognized and emphasize the need for the clinical use of more sophisticated techniques, especially in monitoring the labor of women with high-risk pregnancies. Currently, a number of systems permit the continuous and simultaneous measurements of fetal heart rate and myometrial activity; these are simple to operate, easy to maintain, and of reasonable cost. During labor the parturient is made to lie on her side and should only assume the supine position for brief periods (seconds), during which left lateral tilt or left uterine displacement is used. The induction and maintenance of regional analgesia are also carried out with the parturient on her side.

Current Methods of Obstetric Analgesia and Anesthesia

All the drugs and techniques that are currently available to provide pain relief during childbirth can be arbitrarily classified into four categories: (a) nonpharmacologic analgesia, primarily in the form of psychological and physiologic techniques; (b) simple methods of pharmacologic analgesia; (c) inhalation analgesia and anesthesia; and (d) regional analgesia. Detailed consideration of these methods is precluded here, but the pharmacologic methods are summarized in Table 71-1.

Nonpharmacologic Techniques

The past 40 years have seen a progressive increase in the application of several methods that do not entail the use of pharmacologic agents to relieve the pain of childbirth. These include the following methods: (a) natural childbirth, originally proposed and practiced by the late Dick-Read (1,2); (b) the method of psychoprophylaxis originated by Velvovski and associates in the Soviet Union (3) in the late 1940s and practiced thereafter and advocated by Lamaze (19) in Paris and worldwide since then; (c) hypnosis, which has been used sporadically in a few obstetric clinics; and (d) acupuncture and transcutaneous electrical nerve stimulation, both of which have been given clinical trials during the past 15 years.

Psychological Analgesia. The term *psychological analgesia* applies to both educated (natural) childbirth and psychoprophylaxis because, despite claims to the contrary by the proponents of each method, these have similar physiotherapeutic and psychophysiologic bases (9,20). Early proponents of these techniques claimed that most patients can achieve *painless* childbirth, but most current workers in the field acknowledge the fact that pain is not completely eliminated in most parturients but can be somewhat ameliorated. The major benefits of these methods are a decrease in anxiety and apprehension and enhancement of the parturient's ability to cope with the entire process and to control her behavior. In addition, the patients experience a personal sense of achievement and enhancement of the early bonding process by immediate visual, auditory, and tactile contact between the mother and her newborn.

Analysis of published data and observations in various countries suggests that, if psychoprophylactic or natural childbirth methods are properly used by both primiparas and multiparas, the following results can be expected: (a) little or no pain is experienced by 15% to 20%, and no analgesia or anesthesia is required during the entire process; (b) the pain is decreased in an additional 15% to 20% to a moderate degree, and parturients require less pharmacologic analgesia and anesthesia; and (c) the pain is not affected in the remainder of patients but fear and anxiety are less, and parturients manifest less pain behavior (9,94).

One report (112) indicates that women who are trained in prepared childbirth methods have shorter labor, fewer operative deliveries, fewer intrapartum and

postpartum complications, less blood loss, and better and happier babies than those given drug- induced analgesia or anesthesia. Other studies with proper controls indicate no significant differences regarding these variables between those in prepared and unprepared (analgesia) groups (25,26 and 27,113,114). Observations by Bonica that were made in hospitals in the Soviet Union, eastern and western Europe, and North and South America help to explain these discrepancies. He believed the differences in opinion were the result of differences in motivation, attitude, and personality of parturients and their instructors, the practices of the obstetrician, and the skill with which analgesia and anesthesia were given. These observations and extensive obstetric anesthesia experience lead to the conclusion that the logical approach to pain control during the birth process is best when prepared childbirth training is combined with regional analgesia. This viewpoint is supported by Melzack's work in this field (27).

Hypnosis. Most practitioners of hypnosis for pregnant women begin with early preparation at approximately the fifth or sixth month of pregnancy and subsequently thereafter every 2 to 4 weeks. Various techniques have been used. The word *hypnosis* is not used; rather, the term *medical relaxation* is used instead to suggest to parturients what is expected of them during preparatory sessions and at delivery. Although most women derive some benefit, only a small percentage (15% to 20%) of parturients are sufficiently susceptible to hypnotic suggestion to be able to obtain complete pain relief.

Acupuncture and Transcutaneous Electric Nerve Stimulation. Despite the great interest in China in the use of acupuncture analgesia for surgery, the use of this method in obstetrics has been limited to cesarean section (115,116 and 117). The Chinese have not used it for vaginal delivery because of their cultural premise that parturition is a physiologic function and does not require analgesia. This technique has been tried in Europe, North America, and other parts of Asia, with conflicting results. Several obstetric anesthesiologists have given acupuncture an adequate trial but did not obtain satisfactory results and discontinued its use (118,119,120 and 121).

Transcutaneous electric nerve stimulation is another nonpharmacologic technique that has been given a limited clinical trial. The first pair of electrodes is usually applied to the skin overlying the T-10 to L-1 vertebrae, with one electrode just lateral of the midline, while the second pair is applied bilaterally on the skin overlying the S-2 to S-4 vertebrae. Low-intensity high-frequency (60- to 80-Hz) stimulation is applied continuously through the upper electrodes and, as soon as more intense pain caused by the onset of uterine contractions is felt, parturients themselves increase the stimulation until tingling sensations are felt. Uncontrolled clinical trials suggest that 40% to 60% of parturients obtain good or partial relief of pain during the first stage, but two-thirds of these require regional analgesia during the second stage and for delivery.

Simple Techniques of Pharmacologic Analgesia

In many parts of the world in which anesthetists are not available, the midwife or obstetrician must rely on the use of prepared childbirth and on simple methods of drug analgesia. In this context, it must be recalled that mild pain during the early first stage can be relieved by using suggestion combined with sedatives and tranquilizers. With the onset of moderate pain during the active phase of labor, however, opioids are usually required, and these are given either intramuscularly or intravenously in small increments. Properly administered opioids produce adequate but not complete relief of moderate pain in 70% to 80% of parturients and relief of severe pain in 35% to 60% of parturients (9,20,94). Opioids do not produce significant maternal respiratory depression in optimal doses, but can produce neonatal depression that can be minimized. Inhalation analgesia, bilateral pudendal block, or infiltration of the perineum is used for the actual pain of delivery.

Inhalation Analgesia and Anesthesia

Inhalation *analgesia* is a widely used method of relieving childbirth pain because it produces moderately effective pain relief without causing loss of consciousness or significant maternal or neonatal depression. The agents most commonly used are 40% to 50% nitrous oxide in oxygen. This agent can be administered intermittently during uterine contractions, by the parturient, or administered by a midwife or anesthetist. In some parts of the world, one can still obtain premixed cylinders of 50% nitrous oxide and 50% oxygen that are termed Entonox. For optimal results, inhalation of the drug should begin some 10 to 15 seconds before the painful period of each contraction. Properly used, inhalation analgesia produces good pain relief in approximately 60% and partial relief in another 30% of parturients (9,20,92,93,94 and 95).

Inhalation anesthesia in analgesic concentrations only is still used for vaginal delivery because it affords maximum control of depth and duration of action and is rapidly eliminated at the end of the procedure. On the other hand, deep general anesthesia carries the risk of provoking regurgitation or vomiting and consequent pulmonary aspiration (92,95). General anesthesia should therefore only be given by a properly trained specialist who has secured the airway by tracheal intubation (Table 71-2).

Intubation hazards
Visualization impaired due to edema
Increased bleeding caused by trauma
Nasotracheal route contraindicated due to bleeding potential
Desaturation time decreased due to diminished functional residual capacity
Oxygenation hazards
Desaturation time decreased due to diminished functional residual capacity
Increased tidal volume and minute ventilation
Metabolic rate changes and oxygen extraction problems
Cardiovascular hazards
Increased blood volume
Increased cardiac output
Increased cardiac size and position change
Reduced peripheral vascular resistance
Instability due to uterine compression

[See references 106–108.]

TABLE 71-2. Impact of physiologic changes of pregnancy on general anesthesia [a]

Regional Analgesia and Anesthesia

The use of regional analgesia and anesthesia during labor and for delivery has increased dramatically over the past 30 years in the United States and Great Britain; and, more recently, it has increased significantly in many European countries in which the use of pharmacologic obstetric anesthesia has been limited. The most common techniques are continuous lumbar epidural block, subarachnoid (saddle) block, bilateral paracervical or bilateral pudendal block, or both, continuous caudal block, and double-catheter epidural block, which consists of combining segmental epidural and low caudal blocks (Table 71-3).

Technique	Comparison
Needle puncture L-3 to L-4	Less drug required
Test dose for safety	Continuous analgesia
Bolus 5 mL of drug	Maternal movement possible
Begin infusion at 10 mL/hr	Maternal sensation intact
Peripheral analgesia by site of dosage of 8 mL of 5% ropivacaine	Less blood pressure fluctuation

TABLE 71-3. Continuous lumbar epidural infusion technique

Advantages, Disadvantages, and Contraindications. The popularity of regional analgesia and anesthesia is that it provides the following advantages over other

methods:

- In contrast to narcotics and inhalation analgesia, regional analgesia and anesthesia produce complete relief of pain in most parturients.
- The hazard of pulmonary aspiration of gastric contents inherent in general anesthesia is greatly reduced or eliminated.
- By blocking all nociceptive and efferent pathways, it obviates the pain-induced deleterious reflex responses noted in the previous section.
- With most techniques, the use of a dilute solution of local anesthetic produces block of nociceptive (A-d and C) fibers, with minimal or no effect on the larger somatomotor and tactile fibers.
- Provided it is properly administered and complications are avoided, regional analgesia and anesthesia cause no maternal or neonatal depression.
- Administered properly, regional analgesia and anesthesia have no clinically significant effect on the progress of labor.
- *Continuous* epidural analgesia can be extended for delivery and can even be modified for cesarean section, if necessary.
- Regional analgesia permits the mother to remain awake and alert during labor and delivery so that she can experience the pleasure of actively participating in the birth process (by bearing down voluntarily) and of promptly bonding with her child.

On the other hand, the various techniques have certain disadvantages:

- The use of regional analgesia and anesthesia requires greater knowledge of anatomy and greater technical skill for administration than the use of systemic drugs, inhalation agents, or general anesthesia.
- Technical failures occur, although the incidence is small in experienced hands.
- The vasomotor block inherent in spinal, epidural, and caudal block can cause significant maternal hypotension if prophylactic measures are not carried out.
- Techniques that produce premature perineal muscle relaxation can interfere with the mechanism of internal rotation and might increase the incidence of occipitoposterior or occipitotransverse positions.
- Techniques that produce perineal analgesia cause loss of the afferent limb of the reflex urge to bear down and, unless the parturient is instructed how to bear down effectively, it can prolong the second stage, require the use of outlet forceps, or both.
- Spinal, caudal, or lumbar epidural and double-catheter techniques are relatively contraindicated in parturients with coagulopathy because of the risk of hemorrhage within the spinal canal.
- Regional analgesia and anesthesia procedures can only be carried out in a hospital.

In addition to the relative contraindications of the use of regional analgesia and anesthesia in parturients with coagulation defects, other contraindications to this procedure have been noted:

- The use of regional analgesia and anesthesia is contraindicated if the anesthesiologist lacks skill and experience in the technique, lacks knowledge of obstetric physiology and pathophysiology, or lacks knowledge about the prevention and treatment of complications.
- Infection of the puncture site, preexisting coagulation defects, or hemorrhagic hypovolemia or shock are contraindications, especially for subarachnoid and epidural techniques.
- The parturient's refusal or intense fear of regional anesthesia is a contraindication.
- A lack of experience or appreciation by the obstetrician of how regional analgesia and anesthesia influence the management of labor negates the use of these techniques.

To achieve the stated objectives of obstetric analgesia (i.e., good maternal pain relief with little or no risk to the parturient or her infant), it is essential for the anesthesiologist to fulfill the following criteria:

- The anesthesiologist must have a thorough understanding of parturition pain pathways and the pharmacology of local anesthetics, must have acquired sufficient skill and experience with the various techniques, and must know how to manage the parturient during and after regional analgesia has been administered.
- The anesthesiologist must know the possible complications, their prevention, and prompt treatment.
- The anesthesiologist must ensure that none of the regional procedures be started without an *intravenous infusion running and without having equipment for treatment of complications and for resuscitation available for immediate use*.
- The anesthesiologist should avoid using a regional technique if it is contraindicated.
- Except in circumstances in which the use of regional analgesia is particularly indicated and has significant advantages over other methods, it should not be used against the wishes of the parturient.
- Regional analgesia should not be started until the contractions are strong, last 35 to 40 seconds or more, and occur at intervals of 3 minutes or less (9,94). The only exceptions to this rule are the parturients who experience extreme pain during the latent phase of labor and those in whom labor has been induced and maintained with oxytocin.
- The parturient should be continuously monitored during and after administration of the analgesia and her blood pressure, pulse, and respiration measured every 30 seconds during the first 15 minutes and every 5 minutes thereafter.
- Frequently, it is necessary to complement regional analgesia with psychological support and, if necessary, a sedative and small doses of a narcotic.
- Nursing personnel who are skilled and willing to supervise the parturient properly must be available.

Prevention of Complications. Care must be exercised to avoid three serious, life-threatening complications:

- Maternal hypotension can be avoided or minimized by infusing 1 L of fluid 10 minutes before inducing spinal, epidural, or caudal block to compensate for the increased vasodilation consequent to the vasomotor blockade. It is also essential to have the parturient labor on her side to avoid aortocaval compression inherent in the supine position.
- Systemic toxic reactions must be prevented by avoiding excessive doses or accidental intravenous injection of therapeutic doses.
- High or total spinal anesthesia may result from accidental subarachnoid injection of a local anesthetic dose intended for epidural block.

The latter two complications can almost always be prevented by attempting to aspirate blood or cerebrospinal fluid and by injecting a test dose of 2 to 3 mL of a solution containing 5 to 7.5 mg of bupivacaine and 15 mg of epinephrine. If the injection is accidentally subarachnoid, the parturient develops a low T-10 to S-5 spinal anesthesia, which can be used instead of the epidural block. If the injection is intravenous, the epinephrine should produce moderate tachycardia and hypertension within 20 to 30 seconds of the injection that lasts for 30 to 60 seconds. This, of course, means the patient's heart rate must be monitored during the phase of the test dose. A large therapeutic dose should be injected only when neither occurs.

Paracervical and Pudendal Block. The techniques of paracervical block (PCB) combined with pudendal block are shown in Figure 71-25. These procedures can be performed by the obstetrician or the physician managing the parturient. They offer advantages and certain disadvantages.

The primary advantages from their use include (a) the procedures are especially useful in cases in which anesthetists are not available; (b) both procedures can be done easily, provided the physician knows the anatomy well; and (c) PCB provides good relief of uterine pain during the first and second stages of labor, while pudendal block provides good relief of perineal pain during the second stage and delivery.

The primary disadvantages from their usage include (a) PCB produces transient fetal bradycardia in 5% to 20% of cases; (b) pudendal block can impair the bearing-down reflex; (c) both PCB and pudendal block entail the risk of systemic toxicity from overdose or accidental intravenous injection; and (d) the degree of pain relief is less than with other regional techniques.

Subarachnoid Block. Subarachnoid block, also frequently referred to as *spinal anesthesia* and *modified saddle block*, usually produces analgesia and anesthesia extending from the T-10 to the S-5 spinal segments.

The following are advantages of the use of subarachnoid block:

- It is relatively simple to perform and is rapid and certain in its action.
- It entails the use of small amounts of local anesthetic (e.g., 5 mg of bupivacaine), thus eliminating the risk of systemic toxicity.
- It can be initiated in the first stage of labor and carried out until delivery.

- It produces the most profound perineal relaxation, thus facilitating the use of forceps or other maneuvers that require perineal relaxation.

The following are the disadvantages of the use of subarachnoid block:

- It produces a higher incidence and degree of hypotension than epidural block, although these could be reduced with the infusion of fluids prior to induction of the procedure.
- It produces premature perineal paralysis and thus interferes with flexion and internal rotation of the presenting part.
- It eliminates the bearing-down reflex although the parturient can voluntarily bear down effectively, provided the abdominal muscles are not paralyzed.
- It produces not only numbness but also paralysis of the lower limbs, making it impossible for the parturient to move them.
- It carries the risk of postpuncture headache, the incidence of which depends on the size of the needle used and on the number of punctures done. The incidence of headache should be between 1% and 5% if a 25-gauge spinal needle is used (9,92,94,95) (Table 71-4).

Technique	Comparison
Needle puncture L-3 to L-4	Advantage of pure opioid analgesia in SAS for early labor
Single puncture through needle technique	No effect on blood pressure or motor system
Use of opioid early in labor in SAS, use of lumbar epidural later in first and second stage	Decreased risk to fetus due to reduced amount of drug used

SAS, subarachnoid space.

TABLE 71-4. Combined spinal-lumbar epidural technique

Continuous Caudal Analgesia and Anesthesia. Continuous caudal analgesia and anesthesia is a form of epidural blockade that provides good pain relief during labor and produces anesthesia for vaginal delivery (Fig. 71-26).

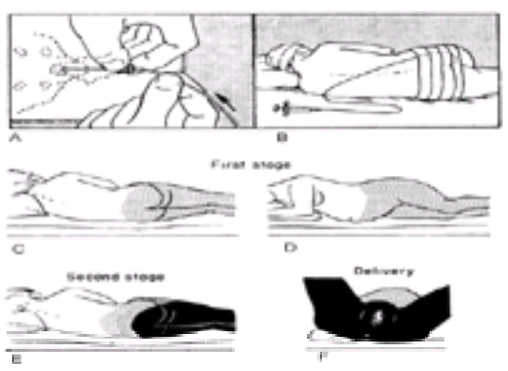

Figure 71-26. Technique of continuous caudal analgesia. **A:** A special 18-gauge, thin-walled, 7-cm needle is inserted and advanced 2 cm and its shaft turned 180 degrees so that its bevel faces the roof of the sacral canal. **B:** A plastic epidural catheter is introduced and advanced 8 to 10 cm to place its tip at the level of the S-1 to L-5 vertebrae. **C,D:** For the first stage and early second stage low concentrations of anesthetics are used to produce only analgesia (*light stippling*). **E,F:** After internal rotation of the presenting part, a higher concentration is injected to achieve motor block and perineal relaxation (*black*) and differential block of the T-10 to T-12 segments (*light stippling*) and of the lumbar segments (*heavy stippling*). (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:110, with permission.)

The advantages of the use of continuous caudal analgesia and anesthesia include that (a) it has a slower onset of vasomotor blockade than subarachnoid block and consequently produces less hypotension; (b) by using an analgesic concentration of local anesthetic (e.g., 0.25% bupivacaine) it produces less perineal and lower limb paralysis than subarachnoid block; and (c) it has no risk of postpuncture headache.

The disadvantages of the use of continuous caudal analgesia and anesthesia include the following: (a) it requires larger amounts of local anesthetic than other regional techniques; (b) more anatomic anomalies occur in the sacrum than in the lumbar region and consequently it is more difficult to execute this procedure, thus entailing a greater risk of failure; and (c) if the procedure is carried out by inexperienced personnel during late labor there is a risk of puncturing the rectum and fetal head.

Continuous Epidural Block. In medical centers in the United States, Great Britain, and other countries that have specialized obstetric anesthesia services, epidural blockade is the procedure of choice for most parturients because it provides effective pain relief in 85% to 95% of women in labor (9,20,92,94,95,122) (Fig. 71-27). Inadequate perineal analgesia for delivery is a frequent occurrence, but this can be avoided by administering a large dose of local anesthetic when delivery is imminent or by having parturients receive a top-up dose (reinjection of local anesthetic) in the sitting position 10 to 15 minutes before delivery.

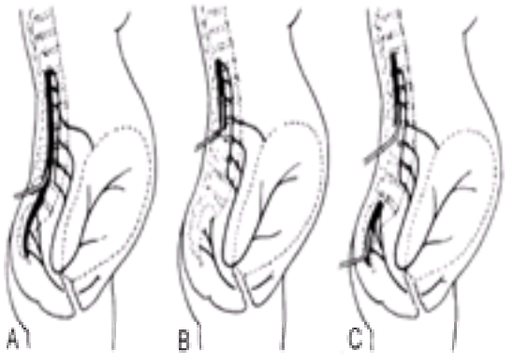

Figure 71-27. Technique of continuous spinal epidural block. **A:** Standard technique for vaginal delivery (analgesia of T-1 to S-5). **B:** Segmental (T- 1 to L-1) block for analgesia during first stage of labor. **C:** Double-catheter technique. White tube, level of catheter; black area in spinal canal, diffusion of local anesthetic. (Reprinted from Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia*. Vol 1. Philadelphia: FA Davis, 1967:614, with permission.)

It is now generally accepted that epidural analgesia does not prolong, and might even shorten, the duration of the first stage of labor (9,92,94,95,116). Although a transitory decrease in uterine activity has been described, this is of little clinical importance. The most recent literature debate on this issue was begun by a well-meaning obstetrician. During a study of epidurals and their effects, the study had to be discontinued due to a flagrant increase in the cesarean section rate. Unless the technique is carried out precisely and the parturient is coached to bear down effectively, the duration of the second stage of labor might be prolonged and instruments might be needed for delivery. Figure 71-28 and Table 71-3 summarize the technique of standard epidural analgesia and its advantages and

disadvantages as compared with other forms of epidural blockade. Figure 71-29 and Table 71-4 summarize the technique of segmental epidural analgesia for the first stage of labor and the extension of this procedure to involve the perineum for the second stage of labor.

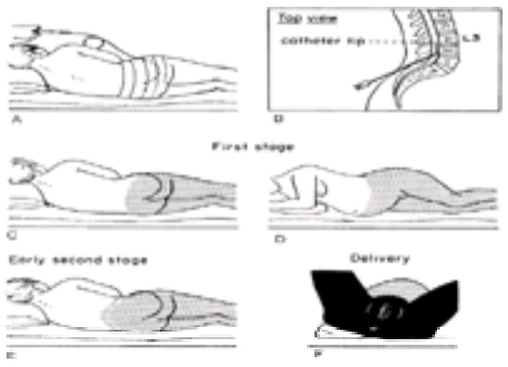

Figure 71-28. The technique of standard continuous lumbar epidural block. A preload infusion of fluid is started. **A,B:** A continuous catheter is then inserted through a needle placed in the L-4 interlaminar space and advanced until its tip is at the L-3 vertebra. **C:** With the onset of moderate pain a test dose is injected and, if negative, 10 to 12 mL of analgesic concentrations of local anesthetic (e.g., 0.25 bupivacaine) are injected to produce analgesia extending from T-10 to S-5. **C–E:** The patient is then made to lie on her side and given oxygen and frequent monitoring, top-up analgesia doses are injected as soon as pain returns to produce continuous pain relief. **F:** After flexion and internal rotation of the presenting part has occurred, a higher concentration of local anesthetic (0.5% bupivacaine) is injected with the patient in the semirecumbent position to produce perineal relaxation and anesthesia (*black*). A wedge is placed under the right buttock for delivery to displace the uterus toward the left, away from the inferior vena cava. (Table 71-5 summarizes the techniques, advantages, and disadvantages of the procedure.) (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:105, with permission.)

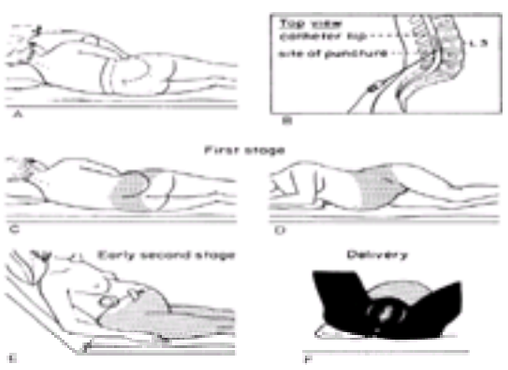

Figure 71-29. Technique of continuous segmental epidural analgesia and anesthesia. After a preload infusion of fluid is started, a continuous catheter is inserted through a needle placed in the L-3 interspace and advanced so that its tip is at L-2. **A,B:** With the onset of moderate pain a test dose is injected and, if negative, 4 to 6 mL of local analgesic solution is injected to produce segmental analgesia **(C,D)**. **E:** For the second stage the analgesia is extended to the sacral segments by injecting a larger volume of the same concentration of local anesthetic, with the patient in the semirecumbent position. **F:** After internal rotation an injection is made of a higher concentration of local anesthetic to produce motor block of the sacral segments and thus achieve perineal relaxation and anesthesia (*black*). The wedge under the right buttock causes the uterus to displace to the left. (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:107, with permission.)

Double-Catheter Technique. The double-catheter technique involves the insertion of one catheter into the lumbar epidural space, with its tip at the level of the T-12 vertebra, and another catheter placed into the sacral canal, with its tip at the level of the S-3 vertebra (Fig. 71-30 and Table 71-5). This technique was first used and advocated by the late John Cleland (123), whose monumental studies of the pathways of uterine pain have already been mentioned. Having had extensive experience with this technique, Dr. Bonica also believed it to be the ultimate in analgesia and anesthesia for labor and vaginal delivery because it provided all the advantages of regional block with few of its disadvantages. The technique permits exquisitely specific analgesia for the first and second stages of labor and produces anesthesia for the delivery. This author has used this technique for delivery of several obstetric patients with valvular heart disease during vaginal delivery. In every case, the patient's blood pressure was maintained within the normal range even during delivery of the baby's head with forceps. The reason for this was activation of the caudal catheter with a small amount of local anesthetic that selectively blocks S-2 to S-4 while the upper T-10 to T-12 analgesia was wearing off. This effectively reduced the spread of the sympathetic blockade to the point that there was just no negative physiologic impact on blood pressure.

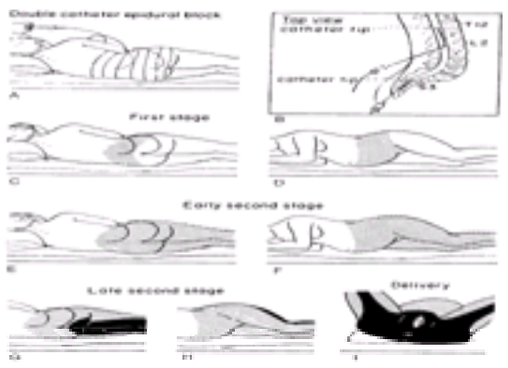

Figure 71-30. Double-catheter technique for epidural analgesia and anesthesia. **A,B:** The two catheters are inserted: The upper catheter is inserted through the L-2 interspace and advanced so that its tip is at T-12; the second catheter is inserted into the sacral canal and advanced so that its tip is at S- 3. **C,D:** As soon as contractions produce moderate pain, small volumes (4 to 5 mL) of analgesic concentrations of local anesthetic are injected through the upper catheter to relieve the pain. Similar injections are repeated throughout labor. **E,F:** When the presenting part exerts pressure on the pelvic structures and perineum, causing pain in the lower lumbar and sacral segments, 5- to 7-mL volumes of analgesic concentrations of local anesthetic are injected through the lower catheter. **G–I:** After flexion and internal rotation are completed a high concentration of the local anesthetic is injected through the lower catheter to produce perineal muscle relaxation and anesthesia of the sacral segments (*black*). (Reprinted from Bonica JJ. *Obstetric analgesia and anesthesia*, 2nd ed. Seattle: University of Washington Press, 1980:113, with permission.)

Technique	Comparison
Needle puncture at L-2 to L-3; catheter advanced 3 cm (T-12)	Requires less drug than standard or single-catheter techniques
Needle puncture in sacrum at S-4; advance catheter to S-3	Most specific technique for labor and delivery
Aspiration test and injection of test dose	Least effect on mother and fetus
If negative at 5 minutes, inject 4 mL of analgesic solution of 0.25%	No effects on newborn
Bupivacaine in upper catheter: analgesia T-10 to L-1	No premature numbness or weakness of limbs
Continuous pump delivery	No premature perineal relaxation; no interference with flexion and internal rotation
With onset of pain in limbs and perineum, inject 5 to 7 mL of 3% rapivacaine	
Continue analgesia until after internal rotation; 5 to 7 mL 0.5% rapivacaine through the lower catheter	Two catheters are required; greater risk of complication and failure

TABLE 71-5. Double-catheter epidural block

The double-catheter technique accomplishes analgesia with smaller individual doses with the following advantages (see Table 71-5):

- Hypotension and other side effects and the risk of systemic toxic reactions in the mother are minimized.
- It causes little or no effect on uterine contractions (because of the smaller doses of local anesthetic).
- It permits the voluntary use of the abdominal muscles because the analgesic concentrations do not produce motor blockade.
- Although the caudal analgesia interrupts the afferent limb of the reflex urge to bear down, the parturient can voluntarily exert as much increase in intraabdominal pressure as she does reflexively and, indeed, in some instances, she can bear down more effectively because she has pain relief.
- The fetus receives less local anesthetic than with any other epidural technique, and therefore incurs no drug-induced cardiovascular or central nervous system depression. With this or any other epidural technique it is best to insert the catheters once it has been decided that active labor has been established, but before the parturient has experienced severe pain, so that she obtains the full benefits of the analgesia.

Intraspinal Opioids for Labor Pain

Both intrathecal and epidural opioids have been used during the first stage of labor to relieve the pain of uterine contractions. The logic of the use of opioids dates back to the original work of Yaksh, who in 1979 published the first article on the use of opioids in the central nervous system (124,125). Most of these studies began in the mid- to late 1980s. Fortunately, now, the use of opioids is firmly established and has paved the way for better and even safer methods of pain relief for obstetric anesthesiology.

Intrathecal Opioids. Morphine in doses ranging from 0.5 to 2.0 mg injected intrathecally has apparently provided fairly good relief from uterine contraction pain, lasting for several hours (126). The onset of analgesia was slow, however, and analgesia during the delivery was poor, requiring supplementary pain relief. The serious disadvantages of the use of intrathecal morphine in labor is the high incidence of adverse side effects, including pruritus, nausea, urinary retention, and rarely, but potentially tragic, respiratory depression.

Epidural Opioids. Epidural morphine has been used in doses ranging from 2 to 10 mg (127,128). Most reports suggest that analgesia was poor, even in the high-dose range, and in many cases, was ineffective in relieving the pain of uterine contractions (129). Like intrathecal morphine, the onset of analgesia was slow, and supplementary analgesia was needed during delivery. Moreover, side effects similar to those seen with intrathecal morphine have been encountered.

Epidural meperidine has been found to produce analgesia within 10 minutes and has been more consistent and reliable than morphine. Both the efficacy and duration of analgesia are dose dependent: With an injection of 25 mg, analgesia was less reliable than that produced by 0.125% bupivacaine (130) and lasted less than 1 hour (131). Increasing the dose to 50 or 100 mg provided analgesia that was almost equivalent to that obtained with 0.25% bupivacaine for approximately 2 hours, but these higher doses were associated with a higher incidence of side effects (132).

Epidural fentanyl in doses ranging from 0.15 to 0.20 mg also provided effective analgesia for the pain caused by uterine contractions within 10 minutes, and lasted for 90 to 130 minutes during labor (112). Perineal analgesia was poor and side effects also occurred. The addition of 0.8 mg of fentanyl to a test dose of bupivacaine provided a more rapid and complete onset of analgesia and significantly prolonged the duration of the effect of the local anesthetic (112).

Epidural Local Anesthetic and Opioid Combinations. A number of obstetric anesthesiologists have used a combination of opioids and dilute solutions of local anesthetics (e.g., 0.125% bupivacaine) with significant success. There are advantages and limitations to all drugs. It is interesting to note that the limitation of opioids is ineffective second-stage analgesia and the advantage of local anesthetics is effective second-stage analgesia. It is similarly interesting to note that the limitation of local anesthetics is selective visceral analgesia and the advantage of opioids is intense visceral analgesia. Thus, we can see the advantage of combining these two for a potent effect on labor pain.

Several opioids have been combined with popular local anesthetics, such as bupivacaine and lidocaine. These have been fentanyl, sufentanil, meperidine, alfentanil, and butorphanol. By far the most frequently used opioid combined with local anesthetic for labor and delivery is fentanyl (133). Sufentanil may well prove to be the preferred opioid of choice because of its advantageous chemical properties. It is twice as lipid soluble as its closest competitor, fentanyl. Furthermore, it has high affinity for the mu receptors themselves. And, finally, there is no evidence of neonatal depression (134).

The main advantage of using such an opioid is to reduce the total amount of local anesthetic and thus enjoy a decreased risk of the untoward effects of these agents (135,136). These, of course, include nuisance complications such as minor hypotension, inability to move the lower extremities, a reduction in the force of uterine contractions, and a slowing of the labor process. They also include major catastrophic complications, such as full-blown central nervous system convulsions and cardiac arrest and death. Thus, the stage is set for more frequent use of such agents if only to avoid these complications.

A newcomer to the local anesthetic stable is ropivacaine. Ropivacaine is the newest member of the amide local anesthetics. Its pharmacologic properties are between mepivacaine and bupivacaine. This local anesthetic stands out among others because of its high potency and low toxicity. Another clinical advantage appears to be some vasoconstriction, thus making it appealing for local anesthetic nerve blocks and field blocks (137). This latter attribute does not carry over to vasoconstriction of the placental circulation, so its usefulness in obstetrics is not impaired (138).

The use of such combinations in dilute dosages mandates the use of a pump and a continuous delivery of the agents on a minute- to-minute basis. There are many different pump systems now available that reliably deliver preset dosages of these combinations. In instances in which adequate analgesia is not obtained with the more dilute solutions, bolus injections of regular strength medications can be administered to push past areas of skipped analgesia; this is particularly applicable in the late second stage and near delivery. The continuous infusion method has been used and reported by several investigators over the past decade; this work substantiates the fact that this method of delivery is safe and effective and indeed the preferable method for delivery of analgesia to the mother in labor (139,140).

The mechanism of action of the opioids is still questionable. Whether they act on the spinal cord itself or act via a circuitous route by systemic uptake is not known. Similarly, it has not been shown whether they act in an additive fashion or a synergistic fashion (141,142).

Episiotomy Pain

Many obstetricians and midwives perform an episiotomy to facilitate delivery, especially in primiparas, although it is also frequently performed in multiparas. Prophylactic episiotomy is done to decrease the duration of the second stage of labor, to protect against tears, and to facilitate the introduction of forceps if their use becomes necessary. The pain caused by this procedure is also transmitted by branches of the pudendal nerve and can be obviated with local infiltration or pudendal block or with other types of regional anesthesia.

In a comprehensive review, Thacker and Banta (143) discussed the benefits and risks of episiotomy in labor and delivery as recorded in the English language literature (350 books and articles published between 1860 and 1980). They cited the fact that, in 1979, an episiotomy was performed in nearly 63% of vaginal deliveries in the United States. It was determined, however, that episiotomy did not offer a clear benefit to women in terms of decreased number of lacerations. Moreover, in reviewing the extensive literature, it was noted that the role of episiotomy in preventing serious pelvic relaxation has not been adequately studied. In fact, women who did not have an episiotomy had little risk of pelvic relaxation. In regard to the issue of doing an episiotomy to protect the brain of infants, it was noted that it is beneficial in extreme cases, such as when the fetus is large and labor is prolonged (143). The probable benefit, however, does not necessarily mean that most routine episiotomies can be justified.

The risks of episiotomy include extension of the episiotomy by tear of tissues, unsatisfactory anatomic results, blood loss, pain, edema, and infection (143).

It was concluded that risks of episiotomy are more severe than many obstetricians appreciate. Although rarely associated with a life-threatening problem,

complications of this procedure can be a source of serious morbidity to young mothers, who already have major personal and social adjustments to undergo.

One study in Great Britain by Kitzinger and Walters (144) revealed that, among 717 women who had had an episiotomy, 45% stated that the perineum was moderately uncomfortable at the end of the first week, 19% thought it was painful, and 9% thought it was very painful. The figures among 341 women who had had perineal tears (no episiotomy) were 39%, 11%, and 4%, respectively. Moreover, in 17% of those who had had an episiotomy the pain often distracted them when breast-feeding and 22% could not sit comfortably when holding the baby. Many of the women who had had an episiotomy experienced pain during sexual intercourse that persisted for more than 3 months in some. It was also concluded (144) that, although episiotomy might be necessary in special cases (e.g., when it is necessary to hasten delivery), it is not necessary in most women and, when done, causes unnecessary pain for varying periods following delivery.

In one report it was suggested that local infiltration with saline solution before the episiotomy repair decreases the severity of postepisiotomy pain (145). It was postulated that the pain is a result of tight enclosure caused by the edema and inflammation that can be accommodated under less pressure if slack is created by prior distension of the tissues. Postepisiotomy pain is treated with cold or hot sitz baths. In women who have moderate to severe pain, nonopioid analgesics, given alone or combined with weak opioids, can be used, but care must be exercised in prescribing these or any other drugs in women who are breast-feeding their infants.

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CHAPTER 72

Gynecologic Pain Syndromes

John S. McDonald and Mark L. Elliott

Pain that emanates from the structures that form the pelvis and pelvic cavity is one of the major catastrophic threats to the health and well-being of both female and male patients. This chapter highlights many of the different gynecologic pain syndromes mentioned in Chapter 70. It is hoped that awareness of these will help the practitioner to think in more global terms and to help develop a rich differential diagnosis when confronted with the patient who has pelvic pain. The material is presented in two discrete sections: one devoted to medical or clinical considerations and a second devoted to psychological considerations. It is fitting that psychology play a major role in this chapter, because it is very rare that women who suffer from chronic pelvic pain do not have either primary or secondary psychological involvement.

The medical section of this chapter is organized into basic considerations, with an introductory discussion of etiology and epidemiology, and clinical considerations, with discussions on physical examination, differential diagnosis, diagnosis, and, finally, treatment. The psychology section of this chapter deals wholly with the psychology of gynecologic pain syndromes. Psychology is the most pivotal and closely related science to pain and the suffering caused by pain.

MEDICAL SECTION

Basic Considerations

Etiology and Epidemiology

Pelvic pain has long confused the physician and patient alike. It is without a doubt one of the most difficult diagnostic and management challenges in medicine. Patients with pelvic pain are often seen by family physicians, internists, gynecologists, urologists, neurologists, and general pain specialists. Gynecologists manage the largest fraction of pelvic pain patients. The confusing and confounding aspects of pelvic pain diagnosis and management come from physicians being locked into the myth that most all pelvic pain is due to organopathologic causes or the complex relational aspect of sexual abuse.

If a health care system can be improved, one aspect of that improvement will be some method of early referral of pelvic pain patients to knowledgeable practitioners such as chronic pain specialists so as to avoid two very important mistakes: (a) the languishing of patients in a diagnostic limbo by family doctors, internists, neurologists, gynecologists, and surgeons and (b) a reduction in the unnecessary surgical procedures performed on the basis of “pelvic pain symptomatology.” One of the goals of this chapter is a modification of referral practice so that patients will not suffer from either of these problems. A new, fresh approach must then also include at the outset the very important and often overlooked psychological aspects of pelvic disease processes and the problems created by them. Psychology now serves as a pivotal focus for understanding the management plans that will or will not make sense with regard to helping the patient get well. The incredible sea of experience in sexual abuse and the manner in which that can make or break a carefully conceived plan of treatment is indispensable. The last section of this chapter is entirely dedicated to psychology and its overall impact with regard to pelvic pain.

Acute Gynecologic Pain Syndromes

Ectopic Pregnancy. One important cause of pain in early pregnancy is abnormal or ectopic pregnancy. In ectopic pregnancy, the conceptus implants itself outside the uterine cavity—for example, in the uterine cornu, along the uterine tube, on the ovary, or on various portions of the abdominal and pelvic peritoneum. In 98% of cases, the ectopic pregnancy is an actual “tubal pregnancy” and occurs whenever the migration of the fertilized ovum toward the uterine cavity is unduly delayed by tubal factors. The incidence is near 1 in 200 pregnancies, but frequency may be influenced by an increasing incidence of acute salpingitis (1).

Ectopic pregnancy presents with two classic clinical scenarios: (a) the threat of massive hemorrhage and (b) severe pain driven by peritoneal distension and stretch. Later, pain may be caused by extrusion of the ectopic pregnancy and by further hemorrhage that causes accumulation of peritoneal blood. As a result, when an ectopic pregnancy causes severe pain in the first trimester, it often indicates an acute abdomen and anemia, which may necessitate surgery. Laparoscopy will confirm an ectopic pregnancy with implantation outside the uterine cavity.

Symptoms and Signs. Pelvic pain is the most common symptom of ectopic pregnancy (2). Pain is limited to the site of implantation and probably represents stretching of the visceral peritoneum over the organ involved. If hemorrhage occurs and is contained within the ectopic site, pain increases. Once the trophoblast breaks through the fallopian tube, massive hemorrhage may occur into the peritoneal cavity. The accompanying pain is initially localized deep in the pelvis as blood collects in the cul-de-sac. In the supine position, blood runs upward along the lateral border of the peritoneal cavity, with resultant diaphragm irritation and shoulder pain. The patient may feel faint, and physical examination may reveal that the patient is pale and has other signs of hypovolemia. Evidence of abdominal distension and tenderness on palpation is also found, especially over the iliac fossa, where the pain starts. Pelvic examination is difficult because of the tenderness of the abdomen. Often, a bulging cul-de-sac can be appreciated on careful palpation.

Diagnosis. Early recognition of ectopic pregnancy is imperative because it is a significant cause of maternal mortality (3). The diagnosis is not difficult and is made on the basis of history, physical examination, and laboratory studies. Aspiration of a bulging posterior cul-de-sac through a large needle yields nonclotting blood—that is, blood that has already clotted and lysed. Decreased and increased human chorionic gonadotropin levels suggest an abnormal gestation, such as ectopic pregnancy. Ultrasonography in the hands of an experienced sonographer can provide helpful information about ectopic pregnancy.

Because pain in early pregnancy can be caused by either a normal or abnormal gestation, the clinician should attempt to make this distinction based on history, physical findings, and appropriate laboratory findings. Signs of shock can occur and may be manifest in public places far removed from hospitals. Such an episode naturally indicates significant intraperitoneal or vaginal blood loss that must be attended to immediately.

Treatment. Treatment of ectopic pregnancy pain involves a correct diagnosis and a surgical procedure appropriate to the individual patient and the operative findings. Current conservative surgical therapy includes opening the tube and removing the conceptus or simply excising the conceptus and rejoining the tube to retain the reproductive abilities of the patient (1). The surgeon must be fully aware of the patient's desires regarding this matter before operating because, even in a patient with a ruptured uterine tube, some portion of the organ might be salvageable. Removal of the conceptus, regardless of its location, usually eliminates the pain. Postoperative pain can be controlled with administration of narcotics (e.g., intermittent injection, patient-controlled anesthesia, or lumbar epidural opioid analgesia).

Abortion. Spontaneous abortion is associated with pain caused by uterine muscle contractions and by attempts to expel the conceptus from the endometrial cavity.

Symptoms and Signs. Spontaneous abortion usually produces intermittent menstrual-like cramping pain that is mild initially but gradually increases in intensity. Later, vaginal bleeding, which can be profuse, and passage of placental tissue from the vagina accompany the cramps.

In septic abortion, signs of infection are also present, such as fever, occasional chills, a purulent discharge, and tenderness of the uterus. When the infection spreads to the adnexa and pelvic peritoneum, signs of peritoneal inflammation appear, including nausea, constipation, reflex muscle spasm, and even signs of septicemia.

Diagnosis. Diagnosis is made by the history and physical findings. A patient with septic abortion reveals laboratory signs of infection. Ultrasonography can be used to reveal a fragmental gestational sac, a low implantation of the sac, and absence of fetal heart movements. Radioimmunoassay for human chorionic gonadotropin is positive, denoting the presence of functional placental tissue.

Treatment. A patient with a threatened abortion, a closed os, no passage of tissue, and vaginal bleeding needs close observation but no immediate intervention. Pain usually stops once the threat of abortion passes, the abortus is passed, or pregnancy is terminated surgically (usually by dilatation and curettage). In the instance of a threatened abortion, the patient's pain and bleeding increase until she completely passes all tissue, which terminates the gestation, or until dilatation and curettage. The pain subsides once this process is complete, although uterine cramps can persist if an oxytocic agent is administered after the procedure to keep the uterus well contracted.

Fibroid Degeneration. During pregnancy, estrogen secretion by the placenta causes uterine myomata, or “fibroids,” to enlarge, often without a concomitant increase in blood supply. Consequently an aseptic degeneration within the tumor can occur.

Symptoms and Signs. Aseptic degeneration of a myoma causes pain that is localized at the site of the tumor. Initially the discomfort is a dull, constant ache, but it usually progresses to an intense unremitting pain that prevents the patient from all activity, including sleep. The location of the pain depends on the location of the fibroid. The tumor is usually tender on palpation, possibly accompanied by slight fever and a moderate leukocytosis.

Diagnosis and Treatment. The diagnosis is usually made through careful evaluation of the pain and its location and by physical examination. Because the pain is usually unremitting until degeneration is complete, administration of narcotics such as morphine might be necessary to relieve the pain. Analgesia and bed rest are continued until the pain ceases.

Endometritis

Etiology and Pathophysiology. Acute endometritis is distinguished from pelvic inflammatory disease (PID) because the former involves only the uterus. Endometritis (infection of the uterus) results when bacteria invade the uterus and multiply. The pain of acute endometritis is caused by multiplication of infecting organisms and accumulation of the products of infection.

Ordinarily, the cervix presents an impenetrable barrier to invasive organisms. When the cervix has been breached by surgical instrumentation (e.g., as in dilatation and curettage) or the passage of a pregnancy (spontaneous abortion or a term pregnancy), however, the uterus is open to colonization by organisms. The offending organism can be one of the normal vaginal flora or can be a more virulent organism introduced by sexual activity, such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Bacteroides*. A pregnant uterus most often becomes infected after attempted evacuation of a failed pregnancy.

Symptoms and Signs. The initial symptoms are lower abdominal pain centrally located over the pubic symphysis. The pain can become crampy in nature, accompanied by foul-smelling vaginal discharge or vaginal bleeding. Urinary frequency can occur as the bladder becomes irritated, and a low-grade fever might be present.

In endometritis, pain occurs on manipulation of the uterus during the vaginal examination and is confined to the uterus; the adnexal areas are relatively free of pain.

Diagnosis. A recent pregnancy or uterine instrumentation combined with the appropriate symptoms and signs is the basis for the diagnosis of endometritis. Visualization of the cervix with culture of the exudate, particularly for organisms causing sexually transmitted diseases, should be performed.

Endometritis must be differentiated from uterine cramping without infection and from cystitis. The patient experiencing uterine pain without infection usually is afebrile, and the white blood cell count is elevated only slightly. Such elevation can be confusing, however, because pregnancy itself causes a leukocytosis. In endometritis, however, the purulent and foul-smelling cervical discharge can show growth when culture and sensitivity tests are performed or can reveal organisms with Gram's stain.

Cystitis is distinguished by the presence of red and white blood cells and bacteria in the urine. These organisms can usually be cultured.

Treatment. Mild endometritis is usually treated on an outpatient basis with oral medication to eliminate the organisms typically found in gynecologic infections. Such medication generally includes an immediate dose of penicillin or cephalosporin followed by doxycycline or tetracycline for 10 days (see the treatment section in Acute Pelvic Inflammatory Disease). Septic abortion requires hospitalization and parenteral antibiotics along with appropriate support if gram-negative sepsis develops.

Pelvic Inflammatory Disease. Acute PID involves infection of the intraabdominal pelvic organs and nearby structures. PID poses a serious threat to the health and welfare of women because an estimated 1 million cases occur annually in the United States and are a major cause of ectopic pregnancies and infertility (4).

Etiology and Pathophysiology. Aerobic or anaerobic bacteria can be the responsible infectious agents that are normally found in the cervical or vaginal flora. Lower genital tract cultures reveal the organisms *N. gonorrhoeae* and *C. trachomatis*. Recently, *Haemophilus influenzae* has been increasingly associated with salpingitis (5). Other microbes include both aerobes—for example, *Escherichia coli* and group B streptococci—and anaerobes—for example, *Bacteroides bivius* and *Bacteroides* species (6,7). These organisms ascend to the upper genital tract through the cervix by cervical instrumentation or through loss of the cervical mucous plug during menstruation.

Sexual activity is the most common denominator for women who have PID (8). In fact, women who have multiple sex partners are more likely to have PID than those who have one partner. A previous episode of PID also predisposes a person to a subsequent episode (4). In the 1960s and 1970s, the use of an intrauterine device called the Dalkon shield was associated with a large risk of PID. Other intrauterine devices have produced an increased risk of subsequent PID; interestingly enough, the incidence is greater in nulliparous women than in multiparous women (9). One published survey showed only a slight risk of infection in the first 4 months after insertion of an intrauterine device (IUD) (10). The use of oral contraceptive tablets instead of an IUD seems to decrease the incidence of PID. This decrease in incidence may be because of changes in the cervical mucus (11). The most common factor in causation of PID is sexual contact with a partner who has gonorrhea (12). Another common cause is surgical instrumentation of the uterus for either diagnostic purposes or termination of pregnancy. This invasive action can spread an infection of the lower genital tract upward.

The pain of PID is caused by multiplication of the infecting agent within the pelvic organs. This causes tissue destruction and accumulation of products of infection that irritate peritoneal surfaces. The edema occurring in response to infection causes further tissue damage and distortion. Some believe patients have pain from adhesions that develop secondarily between damaged intraabdominal organs or between these organs and the abdominal wall. Adhesions often occur in the lower abdomen and pelvic cavity, and perihepatic lesions have been reported, as in the Fitz-Hugh-Curtis syndrome. This is a perihepatitis that occurs as a complication of gonorrhea in some women. It is postulated that when movement occurs between tissues fixed by these adhesions, pain may result. These adhesions are more friable in acute infection and increase with the severity and number of infections. As mentioned, there are those who believe that adhesions can be responsible for pain. On the other hand, there are those whose work have demonstrated no clear relationship between adhesions and pain (13).

Symptoms and Signs. Typical pain in patients with acute PID usually occurs in the abdominal and pelvic areas and is manifest by tenderness of the adnexa, general abdominal rebound tenderness, and extreme discomfort on any movement of the cervix. Some patients with severe cases can have very severe abdominal pain, compounded by intractable nausea and diarrhea.

A gonorrheal infection usually produces severe pain soon after the first menses. In contrast, chlamydial infection usually produces no symptoms at all; sometimes mild pain lasts several weeks. Patients with mixed flora, particularly an anaerobic infection, are often febrile and appear seriously ill as well as in pain. Dysuria and dyspareunia are also common in patients with PID. Among the possible complications of acute PID are the following:

Abscess in the pouch of Douglas
Tuboovarian abscess
Recurrent episodes of PID
Infertility
Ectopic pregnancy
hronic lower abdominal pain

Diagnosis. The diagnosis of PID depends on by far the most common symptom: the presence of abdominal pain. Closely associated are rebound abdominal tenderness, discomfort on motion of the cervix, and tenderness of the adnexa. Diagnosis is aided also by the presence of at least one of the following laboratory findings:

Gram-negative intracellular diplococci found on culture of cervical discharge

Bacteria and white blood cells found in the fluid obtained by culdocentesis

A pelvic or adnexal mass or leukocytosis (white blood cell count >10,500 per µL)

Fever of 38°C (100.4°F)

An erythrocyte sedimentation rate higher than 15 mm per hour.

PID must be differentiated from several other conditions that can cause pelvic pain and/or masses. These include early pregnancy, endometriosis, ovarian neoplasia, appendicitis, diverticulitis, bowel disease, cystitis, and pyelonephritis.

Some delineation of these may be aided by use of ultrasound and pregnancy tests to rule out ectopic pregnancy. Naturally, if culdocentesis produces blood instead of purulent material, an accident of pregnancy or a ruptured ovarian cyst must be suspected as the primary cause. A significant history of prior severe dysmenorrhea, tenesmus, and dyspareunia suggests the possibility of endometriosis. Nongynecologic disease such as appendicitis can present with signs and symptoms that closely resemble those of PID. However, the pain of appendicitis is usually unilateral, and periumbilical and gastrointestinal symptoms such as nausea and vomiting often occur early in the course of the disease. Another bowel disease process—regional ileitis, or Crohn's disease—is a chronic disease process, and thus patients with pain from this disease entity often have a clear history that helps point toward that diagnosis.

Other nongynecologic disease processes involve the urinary system. Infections, particularly acute cystitis and severe pyelonephritis, can often be confused with PID. The discovery of significant amounts of bacteria, white and red blood cells, or casts, or a combination of these in an aseptically collected urine specimen, strongly suggests the presence of a urinary tract infection. In addition, the pain of cystitis is located in a low and central position on the lower abdomen, whereas the pain of severe pyelonephritis can be bilateral and low in the groin and costovertebral angles. The point to make here is that the urogenital system should always be considered and a centrifuged urine sample analyzed to rule out urinary tract disorders when confronted with generalized abdominal pain. When the diagnosis of PID is uncertain, further diagnostic study, such as laparoscopy, is necessary.

Treatment. The current treatment of PID concentrates on coverage of the major bacterial pathogens. The chief antibiotic regimens are noted in Table 72-1. These medications are as noted from the Centers for Disease Control guidelines. After adequate treatment time the pain will begin to subside. Treatment usually needs to be carried out for upwards of 48 to 72 hours. The pain can be managed with a nonsteroidal antiinflammatory drug (NSAID) or a potent opioid, if necessary. Many patients can be treated on an outpatient basis, such as those with a first episode of PID who have a temperature lower than 38°C. These patients must be able to walk and eat and must have no pelvic mass suggestive of abscess.

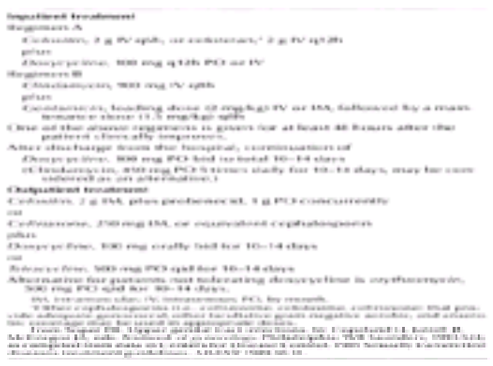

TABLE 72-1. 1989 Centers for Disease Control treatment guidelines for pelvic inflammatory disease

If a patient has any of the following conditions, she should be admitted to a hospital for parenteral antibiotic therapy:

Failure to respond to oral medication

Inability to take oral medication or walk because of severe infection

A greatly elevated temperature

Upper abdominal signs

A suspected or diagnosed abscess

Pregnancy

Ongoing use of an IUD

Most patients improve within 48 hours with parenteral antibiotic therapy. Some patients, however, require surgical intervention because they are seriously ill and have failed to respond to antibiotics or because they have become even more ill in spite of 48 hours of antibiotic therapy. Surgery is almost always indicated for patients who are admitted with a pelvic mass that has disappeared or who are moribund on admission; both conditions suggest a ruptured pelvic abscess. Other patients might require exploratory surgery to establish a diagnosis of PID if the pelvic examination shows no abnormalities and if pain fails to resolve after antibiotic therapy.

Surgery for PID should be tailored to the patient's condition and the patient's desire for conservation of reproductive capability. The use of new and more potent antibiotics has decreased the incidence of life-threatening ruptured abscesses. The advent of more advanced techniques for treating infertility, such as tubal microsurgery and *in vitro* fertilization, has decreased the number of surgical procedures that remove all pelvic organs if a conservative approach is requested by the patient (14,15).

Adnexal Torsion

Etiology and Pathophysiology. Adnexal structures are made up of the uterine tubes, the ovaries, the peritoneum, and the accompanying blood vessels. These structures are anchored proximally at the isthmus of the tubes; the distal ends of the tubes adjacent to the ovaries are free and suspended in the pelvic cavity. Thus, it is easy to see that enlargement of an ovary by an ovarian tumor could rotate the entire fallopian tube and cause ischemia in all of the aforementioned structures. This could lead to necrosis, and severe pain is the end result.

Torsion by itself can also produce intermittent pain if the tube rotates to and fro, or acute progressive pain can result if necrosis occurs. It needs to be stressed that normal adnexal organs only very rarely undergo torsion.

Symptoms and Signs. Adnexal torsion often elicits a dull ache on the involved side that has a sinusoidal pain pattern. Nausea and fever can accompany the pain.

Diagnosis. The diagnosis is made during pelvic examination by noting the presence of an extremely tender mass usually on one side. This certainly suggests that the diagnosis of torsion of the adnexa be considered. Ultrasonic imaging of the pelvis can be useful when tenderness makes delineation of a mass during pelvic examination difficult or impossible. The diagnosis of adnexal torsion is more likely if there is a finding of mild elevation of the white blood cell count in the presence of fever and nausea. The differential diagnosis must include ectopic pregnancy, functional ovarian cysts, endometriomas, ovarian neoplasia, and pelvic inflammation.

Treatment. Once torsion has been diagnosed, surgical confirmation and treatment should be undertaken with laparoscopy as quickly as possible. In the presence of a discrete, painful adnexal mass sufficiently large to warrant operation, laparoscopy is now clearly the choice over laparotomy.

If the adnexa have twisted and the structures involved are gangrenous, the mass should be excised completely without untwisting it. This practice prevents clots from being squeezed from the venous complex involved into the general circulation. When operating on a woman's pelvic organs, the nature and extent of the surgical process must be in accordance with the patient's wishes for future pregnancy.

Bleeding of Functional Ovarian Cysts

Etiology and Pathophysiology. A functioning ovary produces two cysts per month: a follicle cyst and a corpus luteum cyst. The follicle cyst ruptures and releases an egg, while the remaining cells unite and convert to a corpus luteum. With development of pregnancy, the corpus luteum remains and grows; without pregnancy, the corpus luteum withers away usually within 14 days.

Symptoms and Signs. When ovulation occurs, the patient can experience acute unilateral pelvic pain. This has been referred to as *mittelschmerz*, which refers to ovulation pain (16). The pain is often sharp in quality with no radiation. The pain may subside gradually until it disappears, or it may decrease in intensity but convert to a generalized lower abdominal pain. It is not unusual to have pain in the shoulder. Initially, the pain may be due to follicle rupture, whereas subsequent pain may arise from blood collecting in the pelvis. The etiology of the shoulder pain is the diaphragm, which becomes irritated by blood collecting under it. If bleeding continues, a hemoperitoneum can develop and the patient can experience syncope.

Diagnosis. The suspicion of a leaking ovarian cyst must be considered when symptomatology occurs late in the menstrual cycle in conjunction with an adnexal mass. A rupture of such an ovarian cyst should be suspected when a subsequent examination of an adnexal mass reported to be present “disappears.” The presence of intraperitoneal fluid can be detected by ultrasonic imaging. If signs of hypovolemia are present, a hemoperitoneum should be suspected and an immediate peritoneal puncture, culdocentesis, or laparoscopy should be carried out. If blood is obtained on aspiration, however, the source of the bleeding must be located by direct visualization. Although laparoscopy can be used, the presence of a significant amount of blood can make visualization of pelvic organs difficult. Under these circumstances laparotomy may be substituted. Bleeding ovarian cysts may be difficult to distinguish from other causes of intraperitoneal bleeding, adnexal masses, and pain due to pregnancy and endometriosis. Although endometriosis is a possible cause, pain from this condition usually occurs closer to the onset of menses.

Treatment. A ruptured cyst accompanied by severe pain may subside without evidence of a progressive hemoperitoneum. This scenario needs no further treatment except pain control. If recurring monthly pain of this nature is severe enough to warrant suppression of ovulation, then ovulation may be suspended by use of birth control medication. Hemoperitoneum, on the other hand, requires evacuation, drainage, and surgical removal or repair at the site of bleeding.

Dysmenorrhea. Dysmenorrhea is pelvic or low abdominal pain that causes misery and dysfunctional lifestyles for millions of women. It is cyclic pain directly related to menstrual periods. Dysmenorrhea is a common disorder, affecting as many as 5 million young women in this country. The majority of sufferers have severe pain; up to 10% are unable to function normally for some time each month (17). The pain associated with menses can begin a few hours or days before the onset of the menstrual period and last a few days or even throughout the entire period. The pain is often relegated to an unimportant status or “something that will quickly go away.” Thus, often it is not treated adequately and the patients have to find over-the-counter medications for most of their pain relief.

Primary Dysmenorrhea

ETIOLOGY AND PATHOPHYSIOLOGY. Primary dysmenorrhea is pain located in the lower abdomen that has no obvious cause such as endometriosis or other common pathology. The pain of dysmenorrhea is not associated with pelvic structural abnormalities, and the exact cause of the pain is not yet determined for certain. There is evidence that such pain can be caused by relative uterine ischemia from hypercontractility of the myometrium (18,19). Such a hypercontractile state can be the result of excess prostaglandins or vasopressin; the prostaglandin's action could increase uterine contractility and then sensitize nerve endings to the pain-producing effects of other compounds, such as bradykinins. This theory has received support in the laboratory experimentation and because use of prostaglandin inhibitors does result in significant pain relief in dysmenorrhea (20).

SYMPTOMS AND SIGNS. The pain of dysmenorrhea often begins just before menstruation and increases in severity as flow begins. It is cramping in nature and localized in the midportion of the lower abdomen. The pain can involve the lower back and, on rare occasion, the upper thighs. Prodromal symptoms, characteristic of the prostaglandin effect seen commonly with other systems, include the following

Diarrhea
Nausea
Headache
Light-headedness
Palpitations, diaphoresis, and tremulousness
Anxiety

DIAGNOSIS. Patients who fit the picture of menstrual pain beginning shortly after menarche and who report subsequent dysmenorrhea with the symptoms as described may be diagnosed as having primary dysmenorrhea. The pelvic examination is normal, and there are no suspicions of any pathologic problems, but some conditions that cause secondary dysmenorrhea such as uterine polyps and endometriosis can be present despite a normal pelvic examination. It is only after time and exhaustive tests that these conditions may be discovered.

TREATMENT. The pain of dysmenorrhea incriminates uterine ischemia and sensitization of uterine pain fibers resulting from excessive myometrial contractility due to prostaglandin stimulation. Therefore, it is logical that prostaglandin synthetase inhibitors (NSAIDs) that block enzymes of the arachidonic acid pathway are effective therapy for primary dysmenorrhea (21). Some of the commonly used current drugs in the treatment of primary dysmenorrhea are shown in Table 72-2. The action of these agents is somewhat similar except for mefenamic acid, which, in addition to inhibiting prostaglandin synthetase, aids in the breakdown of prostaglandins. All these drugs can cause gastrointestinal irritation as a side effect. Although aspirin inhibits prostaglandin synthetase, it acts primarily as a prostaglandin synthesizer in platelets and is not particularly effective in the uterus (22).

Drug (brand name)	Dose
Carbamazepine (Tegretol)	100 mg bid
Celecoxib (Celebrex)	100 mg bid
Diclofenac (Arthrotec)	50 mg bid
Gabapentin (Neurontin)	300–2,700 mg qd
Ibuprofen (Motrin)	300 or 600 mg tid PO, tailored to individual symptoms and response
Mefenamic acid (Ponstel)	Initial dose of two 250 mg tablets PO, followed by 250 mg q6h (for not more than 1 wk)
Naproxen sodium (Anaprox)	Initial dose 2 tablets 250 mg PO, then one tablet q6–8h
Naproxen (Naprosyn)	250 mg PO bid
Phenylbutazone (Lartical)	100–1,800 mg qd
Propionic acid (Actron)	12.5–25 mg q6h
Orudis	25–50 mg q8h
Tramadol (Ultram)	50 mg tid
Zafirlukast (Accolate)	20 mg bid

PO, by mouth.

TABLE 72-2. Nonopioid analgesics for primary dysmenorrhea

Oral contraceptives sometimes relieve dysmenorrhea through a decrease in the amount of prostaglandin F_2 stored in the endometrium and released into the menstrual blood (23). Oral contraceptives also make the myometrium less sensitive to prostaglandins, as shown by one study that demonstrated decreased motility in response to exogenously administered prostaglandins (24). Although suppression of ovulation can be beneficial in relieving dysmenorrhea, the patient must be willing to accept the risks, however minimal, of oral contraceptives.

Inhalation of terbutaline has also been used for alleviation of the pain of dysmenorrhea. In one double-blind crossover study, significant pain relief was experienced in the 14 women tested (25). One study, which used meclofenamate therapy and found it to be effective, differentiated patient response to placebo versus drug by using a discriminatory test for pain relief as opposed to objective uterine activity (26). Table 72-3 and Figure 72-1 list treatment regimens that may be considered for dysmenorrhea.

1. Nonsteroidal antiinflammatory drugs
2. Oral contraceptives
3. Antidiuretics therapy
4. Gonadotropin-releasing hormone agonist[a]
5. Presacral neurectomy
6. Ovariectomy

[a]Plus add back of estrogen to prevent hypoestrogenism.

TABLE 72-3. Treatment regimen for dysmenorrhea

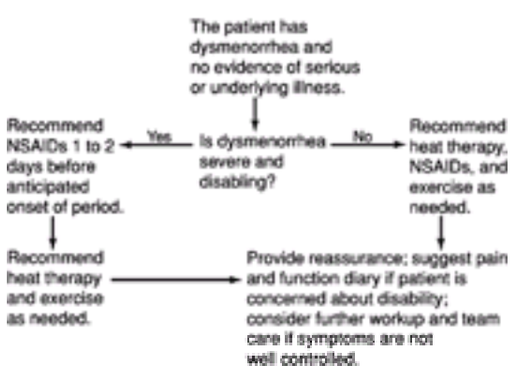

Figure 72-1. Treatment regimen for dysmenorrhea. (NSAIDs, nonsteroidal antiinflammatory drugs.) (From *Paradigm, a practical guide: applying the principles of pain management to common problems*; as adapted from Loeser JD, ed. *Common pain problems: guide to practical management*. Darien, CT: Health Communications Inc., 1998:17, with permission.)

Secondary Dysmenorrhea

ETIOLOGY AND PATHOPHYSIOLOGY. Secondary dysmenorrhea is related to organic pelvic pathology. Pain can be intrauterine in origin, such as that occurring with submucosal fibroids, polyps of the endometrium, or use of an intrauterine device. In these cases pain is thought to be caused by contractions generated by the uterus trying to expel its contents. Although narrowing of the cervical canal was once thought to be a significant factor, studies of canal width in dysmenorrheic and normal women showed no difference (27). Relative stenosis can occur, however, if the endometrial lining sloughs off in large chunks, a condition called “membranous dysmenorrhea.” Other pathologic intrauterine possibilities for acute abdominal pain include deterioration of a myoma that is either subserosal or intramuscular. Such an infarction can cause significant distress and even simulate an acute abdomen as a result of the intensity of pain. Other differential diagnoses must be entertained, however, because infarction of other intraabdominal organs can also simulate uterine fibroid infarction (28).

Secondary dysmenorrhea can also be related to adenomyosis, the presence of endometrial glands deep within the myometrial tissue. When menstruation occurs, menstrual blood is released directly into myometrial tissue, thereby increasing cramping and irritation of the fibers themselves.

Endometriosis, the presence of endometrial tissue in abnormal locations in the pelvis, is a common cause of secondary dysmenorrhea. The mechanism of pain in this condition is not well understood but probably includes a combination of excess prostaglandin production, increased peritoneal sensitivity, chemical irritation of the peritoneum, and bleeding in sites of endometriosis, such as the rectovaginal septum or ovary.

SYMPTOMS AND SIGNS. In some cases secondary dysmenorrhea resembles primary dysmenorrhea and is accompanied by symptoms and signs suggestive of prostaglandin excess. In other cases, the pain of endometriosis can be considered because the pain begins several days before menstrual flow. The pain can be located in the low back and rectum and tends to be more dull and constant rather than cramping in nature. Pain can also occur with intercourse or on urination or defecation. This pain can last longer than the menstrual period, and the pain level can progressively increase over time.

DIAGNOSIS. Pelvic examination often reveals abnormalities that indicate the cause of secondary dysmenorrhea. An enlarged and irregular uterus suggests the presence of fibroids, whereas a visible string from the cervical os corroborates the presence of an intrauterine device. A large, boggy, tender uterus suggests adenomyosis, whereas a fixed retroverted uterus, nodules in the cul-de- sac or on the uterosacral ligaments, and tender masses in the adnexa indicate endometriosis. A study of endometriosis, which used the cell surface antigen CA-125 as measured by serum radioimmunoassay, revealed a most remarkable correlation to women with mild (13.6 U per mL), moderate (22.8 U per mL), severe (27 U per mL), and very severe (50 U per mL) (29). In comparison, women with normal laparoscopic examinations had CA-125 levels of only 7.8 U per mL. It appears that this might be a valuable assay for the diagnosis and management of endometriosis.

Special studies examining the uterine cavity, such as hysterosalpingography, direct visualization with the hysteroscope, or cervical dilatation and uterine curettage, all

help to delineate pathologic conditions such as submucosal fibroids or endometrial polyps. Laparoscopy is a most valuable tool needed to visualize the pelvis and to determine if endometriosis is present.

TREATMENT. Treatment of secondary dysmenorrhea centers around discovery of the cause of the problem causing the pathologic pelvic condition and then elimination of the cause, if possible. Intrauterine devices, fibroids, and polyps can all be removed. Endometriosis requires special treatment. Although adenomyosis can be managed by making the endometrial tissue quiescent in the same ways as those described for endometriosis, definitive management requires hysterectomy.

Chronic Gynecologic Pain Syndromes

Chronic Endometriosis. Endometriosis is defined as functioning endometrial tissue located at extrinsic sites outside the uterus. Most common of such sites are the ovaries, the cul-de-sac, the uterine tubes, the supporting ligaments of the uterus, the pelvic peritoneum, the rectovaginal septum, the cervix, and the surface of the bowel (30). Several theories have been proposed for the etiology of endometriosis. The most likely theory is that of retrograde menstruation, with implantation of endometrial tissue onto peritoneal surfaces (31). Spread of endometrial implants by the lymphatic system has been postulated and reported (32). Hematogenous spread of viable endometrial tissue has also been hypothesized (33).

Endometriosis itself is one of the major causes of pelvic pain and perhaps one of the most confounding problems because this disease can present clinically almost as anything. It can mimic many other disease states. Endometrial implants may attach to many different abdominal organs and tissues. They can be in the typical form of a dark red or brown color, or they may be even colorless. The diagnosis is made on the basis of the history and definitively by laparoscopy. Some of the most popular treatment methods today consist of medical treatment with suppression of both estrogen and progesterone by use of pituitary inhibitory hormones such as the newly developed gonadotropin-releasing hormone inhibitor drugs. Surgical exploration via laparoscopy with laser treatment of the identified endometrial implants and sometimes surgical severance of either the uterocervical plexus (lateral uterosacral nerve ablation procedure) or the superior hypogastric plexus (presacral neurectomy) may give relief of pain (34). Other surgical treatment includes the previously discussed plus the addition of immune therapy management that involves identifying certain immune responsive elements that are treated to elicit a favorable patient response.

The pain of endometriosis can occur at any time and can mimic any known pelvic pathology. The pain can occur with menses or sexual intercourse or can always be present. The mechanisms causing pain are not well established but probably involve release of prostaglandins into the peritoneal fluid from the ectopic endometrium. In addition, chemical irritation of the peritoneal surfaces by the products of menstruation or swelling and stretching of the tissue invaded by an endometrioma could lead to pain. Scarring can also occur at the site of or around the endometrial implants.

Symptoms and Signs. The patient with endometriosis can have dysmenorrhea, dyspareunia, chronic pelvic pain, or all three. In addition, she can be infertile. Other symptoms include hematuria, hematochezia, bowel obstruction, or bleeding from unusual sites such as the pleural cavity or an abdominal scar; all are related to the location of the lesions.

Diagnosis. Occurrence of the pain symptoms described, coupled with infertility, should suggest the possibility of endometriosis. Definitive diagnosis of endometriosis is made by visualization of the lesions. Histologic confirmation is not necessary and is often difficult to obtain because the endometriotic implants might not contain active glandular tissue. Although implants can be present on the cervix and visible on vaginal examination, they more commonly occur on the ovary and peritoneal surface and thus require an operative procedure for diagnosis.

To confirm diagnosis, endometriotic implants—and not just adhesions, which can be caused by pelvic inflammatory disease or previous surgery—must be seen. The classification system described by the American Fertility Society should be used to determine the stage of the disease (Fig. 72-2).

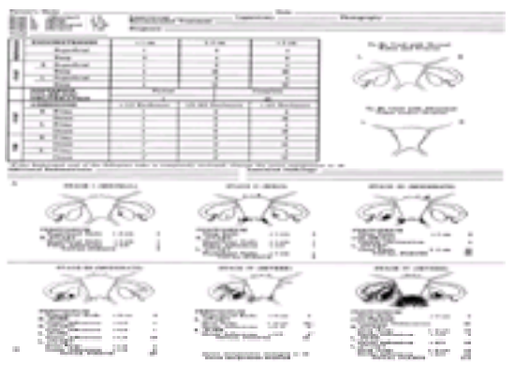

Figure 72-2. Classification of endometriosis. **A:** Suggested questionnaire and sketches of pelvic organs to aid in determination of stage of endometriosis. **B:** Examples and guidelines for use of point system. Determination of the stage or degree of endometrial involvement is based on a weighted point system. Distribution of points has been arbitrarily determined and may require further revision or refinement as knowledge of the disease increases. To ensure complete evaluation, inspection of the pelvis in a clockwise or counterclockwise fashion is encouraged. Number, size, and location of endometrial implants, plaques, endometriomas, and/or adhesions are noted. For example, five separate 0.5-cm superficial implants on the peritoneum (2.5 cm total) would be assigned 2 points. (The surface of the uterus should be considered peritoneum.) The severity of the endometriosis of adhesions should be assigned only the highest score for peritoneum, ovary, tube, or cul-de-sac. For example, a 4-cm superficial and a 2-cm deep implant of the peritoneum should be given a score of 6 (not 7). A 4-cm-deep endometrioma of the ovary associated with more than 3 cm of superficial disease should be scored 20 (not 24). In patients with only one adnexum, points applied to disease of the remaining tube and ovary should be multiplied by 2 (**). Points assigned may be circled and totaled. Aggregation of points indicates stage of disease (minimal, mild, moderate, or severe). The presence of endometriosis of the bowel, urinary tract, fallopian tube, vagina, cervix, skin, and so forth should be documented under “additional endometriosis.” Other pathology, such as tubal occlusion, leiomyomata, uterine anomaly, and so forth should be documented under “associated pathology.” All pathology should be depicted as specifically as possible on the sketch of pelvic organs, and means of observation should be noted. (Modified from The American Fertility Society. Revised American Fertility Society classification of endometriosis. *Fertil Steril* 1985:43:351.)

Treatment. Therapy must be highly individualized and depends on the extent of the disease and on the patient's desire to have children. If avoiding infertility is the prime consideration, measures should be undertaken to preserve and enhance the ability to conceive. If childbearing is to be delayed and relief of pain is the main concern, medical measures are appropriate for mild and moderate stages of the disease.

The object of medical treatment is to render the endometrial tissue quiescent. Early on, the mainstay of current therapy was danazol, a mildly androgenic compound that stops menstruation by inhibiting ovulation. Danazol is given orally in doses of 200 mg qid for 6 to 12 months. The major side effects are some increase in acne and weight, nausea, and irregular vaginal bleeding. A less common side effect is an increase in androgenic effects such as hirsutism, increase in libido, and decrease in breast size. Menstruation usually returns spontaneously within 1 or 2 months of cessation of therapy. Pregnancy rates after danazol therapy are reported to be higher than after other medical regimens for management of endometriosis. One disadvantage is that the drug is expensive. Danazol has largely been replaced now with leuprolide acetate (Lupron) therapy. Lupron is a gonadotropin-releasing hormone inhibitor that effectively switches off both estrogen and progesterone endogenous production. Lupron plus an add-back therapy that contains estrogen is now used to prevent the signs and symptoms of inadequate estrogen.

Another method of treating endometriosis is keeping the patient on a continuous regimen of oral contraceptives of the combination type—that is, a synthetic estrogen and a synthetic progestogen. This treatment suppresses ovulation and endogenous estrogen production and decidualizes the endometrium. The patient on oral contraceptives might experience nausea, fluid retention, and an initial increase in pelvic pain; these conditions subside after the first 2 months of treatment. Although the use of progestogens alone had been recommended, this practice was found to be associated with a higher rate of irregular vaginal bleeding, sometimes necessitating treatment with estrogen. Administration of androgens alone, once a recommended treatment, is no longer popular because of the significant incidence of adverse side effects and the effectiveness of newer regimens. The treatment regimen selected usually continues for 9 to 10 months. Pregnancy rates are somewhat lower after therapy with oral contraceptives than after therapy with danazol.

Surgical removal of implants is usually indicated for moderate endometriosis. This process is generally accomplished using laparoscopy or laparotomy, and the

patient can be placed on danazol postoperatively if she does not wish to conceive. Presacral neurectomy produces variable results and should only be considered in the young woman with disabling dysmenorrhea who has not responded to other measures (35). More severe degrees of endometriosis need more aggressive surgical treatment. In some patients pain relief can be achieved only by total abdominal hysterectomy and bilateral salpingo-oophorectomy to eliminate the cyclic production of ovarian hormones. One fresh approach to endometriosis is the combined surgical and immune therapy method. The latter uses skin testing and then desensitization. This method is being touted as a method to significantly reduce the symptoms of endometriosis, but there are no peer review journal reports yet available for examination. Unfortunately, some women even with hysterectomy still have pain because their pain was of a neuropathic origin. This is why it is absolutely imperative to work with a specialist in pelvic pain who can identify and treat this other major cause of pelvic pain. It makes good sense to have these patients evaluated first by such a pelvic pain specialist, then decide after a regimen of therapy is outlined whether hysterectomy is also indicated.

Chronic Pelvic Inflammatory Disease

Etiology and Pathophysiology. Scarring, tissue damage, and adhesions due to chronic PID can also cause chronic pelvic pain. The nerves to the intraabdominal pelvic organs and contiguous structures can be damaged, or the structures can adhere in such a way that painful stretching is produced by activities such as exercise, sexual intercourse, or passage of digested food along the bowel. Even if there is no damage evident on any diagnostic modality that we currently have, there may well be ischemia to nerves that set up pain patterns that develop a signal to the dorsal root ganglia that evokes pain.

Symptoms and Signs. Patients with damage from chronic pelvic infections can have pain with intercourse or increased physical activity. The pain may also be related to food consumption, bowel functions, or both. During an acute exacerbation they have classic signs and symptoms of an acute infection, such as fever, chills, elevated white cell count, and abdominal pain.

Diagnosis. The diagnosis of chronic PID is based on a documented history of prior episodes of the disease and sometimes by visualization of current damage sufficient to account for the pain. In many instances, however, the actual pathology may be invisible—that is, nerve damage is usually invisible to the examining eye.

Treatment. Major structural damage secondary to infection, such as hydrosalpinx, dense adhesions of the adnexa to the cul- de-sac and posterior aspect of the uterus, or adhesions of bowel and bladder to grossly abnormal adnexal structures, requires surgical treatment. Although the damage is surgically removable or at least partially correctable, all healing involves some scar tissue and any intraabdominal manipulation can lead to further damage. Moreover, no direct correlation between visible pathology and pain has been found. Therefore great care should be exercised not to promise complete pain relief from any surgical procedure. In other words, the general anatomy can be restored to a normal state, but the function is still impaired and the pain persists. It is questionable whether filmy adhesions in the pelvis even require surgery for treatment. Again, pain relief is not guaranteed. If the pelvic organs are visibly normal, surgery is not indicated for pain relief.

Uterine Prolapse

Etiology and Pathophysiology. Past literature supports the testimonial that tearing or stretching of the ligaments supporting the uterus can allow this organ to become displaced and result in pain. The Allen-Masters syndrome was one such literature reference. In addition, tension on nerves and blood vessels in these stretched or torn ligaments is thought to produce pain, but hard evidence is lacking, and it is entirely possible that disruptions of the uterine supports may not contribute significantly to pelvic pain. What this author has been impressed with is the instances in which pelvic support surgery has antedated the onset of pelvic pain. The question arises as to whether there was reduction in blood supply during dissection or actual suture placement in areas that restrict blood supply to nearby nerves.

Symptoms and Signs. Uterine prolapse can occur without symptoms, but symptoms can include a sensation of pressure or a sensation of “something falling.” Severe pain is rare, even in lieu of complete descensus or when the uterus is outside the vaginal introitus. A dull ache and feeling of pelvic heaviness is not atypical.

Diagnosis. In some instances the prolapsed uterus can be replaced by a pessary that can relieve symptoms. If the symptoms are significantly changed by this maneuver, permanent relief by surgery can be considered.

Treatment. Uterine prolapse is usually treated by hysterectomy if patients have finished bearing children. Suspension from above might be considered if the patients have many symptoms and signs and wish to retain their childbearing potential. In earlier days elevation of the uterus with obliteration of the vagina below was promoted by LaForte (36) in elderly patients who did not need a functional vagina and who had total uterine prolapse.

Chronic Pain of External Genital Organs: Vulvodynia

Etiology and Pathophysiology. Vulvovaginal pain can have a variety of etiologies. Some of the causes are obvious; however, a great number of cases of vulvodynia will be labeled unknown because the etiology is just not clear. Some of the most severe vulvodynia sufferers are victims of misdirected medical therapy and others the result of laser or chemical damage. These patients are very difficult to treat. It is important to reduce pain and suffering so that the pain scale does not continue to ascend week by week and month by month. Maceration of the fragile and damaged perineal tissues by improper garments or use of over-the-counter medications should be avoided. Loss of the epithelium can expose nerve endings to chronic stimulation by clothing; this stimulation can be compounded by scratching, which releases irritating algogenic agents such as bradykinin and histamine.

The role of allergy is unclear, but the suspicion is that certain foods, such as coffee, tea, cola, chocolate, citrus fruit, tomatoes, alcohol, and milk, produce perirectal and perineal sensitization with resultant itching in susceptible individuals. Pinworm infestation can also be a cause of perianal itching, particularly at night. Spasms of the levator muscle can cause perirectal and vulvar pain. Hidradenitis, a suppurative, purulent infection of the apocrine glands, can eventually result in chronic abscess, sinus tract formation, and chronic pain.

Symptoms and Signs. The patient with chronic vulvar pain might complain that clothing irritates her or that the vulva is always excessively sensitive. The pain can be localized to one area or generalized to the entire vulva. Draining sinuses or painful abscesses can be present on examination.

Diagnosis. The essential diagnostic element is visualization of the external genitalia and determination of whether a discrete lesion is present. In some cases the diagnosis will be readily apparent, such as a yeast infection. Infectious agents such as ringworm produce a classic red lesion with a serpiginous border of flaking skin. These flakes of skin can be examined for fungus by suspending them in a drop of potassium hydroxide or by examining the skin directly under a Wood's light; fluorescence indicates infection. The most common vulvovaginal fungus, *Candida albicans*, can also be seen on a potassium hydroxide preparation. Generalized maceration can be seen on visual inspection of the vulva. Bacterial cultures should be taken if a purulent exudate is present or if abscesses are noted. A history of pruritus ani suggests that a stool sample be examined for ova and parasites to detect pinworm.

Treatment. Specific infections should be treated with appropriate antibiotics or antifungal agents. General vulvar maceration requires mild cleansing with oil and less frequent immersion of tissues in water. Use of loose absorbent clothing is encouraged, as is dusting the area with cornstarch to absorb moisture. Products containing scents or deodorants should be avoided.

A thorough history of dietary habits should be obtained and offending items omitted in an attempt to reduce pruritus. It might be necessary to eliminate all questionable items and then add them gradually one by one to determine which, if any, are causing the problem. If this is not effective, one should consider skin testing with identification of any obvious allergens. There may be times when chronic abscess of the apocrine glands requires surgical drainage and administration of systemic antibiotics.

Chronic Pelvic Pain Due to Neuropathy. We believe that the majority of patients who present with chronic pelvic pain have neuropathy as the chief cause and not organ disorders. In a significant number of patients who present with pelvic pain with characteristics of pain of gynecologic origin, no obvious organic pathology can be found, even with comprehensive clinical and laboratory examination. When this occurs, the family physician or gynecologist should consider the possibility of a neuropathy that is difficult to diagnose and refer the patient to a chronic pelvic pain specialist. This will be appreciated by the patient who is in search of pain diagnosis and relief, and it certainly is preferable to the physician saying “I cannot find the origin of your pain, and I am afraid the pain may be in your head.” The latter statement should never be made to a patient under any circumstances.

In the late 1940s and early 1950s, several authorities proposed hypotheses to explain pelvic pain without obvious pathology. Taylor (37), one of the most prominent, suggested dysfunction of the autonomic and sensory nervous systems. He studied 10 patients who presented with the syndrome; blood flow probes were placed in the vagina, and an increased blood flow was noted during emotionally stressful situations. Although significant psychopathology was seen, the pain was attributed to

two types of pelvic autonomic disorders— one that Taylor called “vascular dysfunction of pelvic congestion” and the other “sensory change,” otherwise known as hypogastric plexalgia (38). In the former, the mechanism of pain was thought to be a combination of venous distension with interstitial edema, followed possibly by fibrosis of the uterus. In the latter type, the patient could have ultrasensitivity of the pelvic organs and tissues on a hereditary basis.

Theobald (39) called this syndrome “the pelvic sympathetic syndrome,” suggesting that abnormal sympathetic dysfunction might produce ischemia, dilatation of the hollow viscus, chemical irritation in the pelvis, or a combination of these, which in themselves cause pain. Others have suggested that nerve endings from previously damaged structures that were removed can still produce nociceptive impulses, and “phantom organ sensation” and “phantom pain” might ensue (40).

Allen and Masters (41) suggested that the syndrome is caused by small traumatic lacerations of the sacral uterine ligament or of a posterior leaf of the broad ligament. Subsequently, DeBrux and associates (42) examined 25 patients with chronic pelvic pain without obvious pathology in whom large biopsies were taken from the broad ligament, the uterosacral ligaments, and the peritoneum of the pouch of Douglas. They found microscopic lesions indicative of recurrent pelvic peritonitis in several patients. Microscopic findings of endometriosis were found in half of these patients, a hemangioma in two, and a neuroma in one. Renaer et al. (43,44,45 and 46) disputed this hypothesis because real tears in the supporting structure of the uterus are rare; when they do occur their role in chronic pain without pelvic pathology syndrome is negligible.

Ample evidence now exists that the pain of most patients with chronic pelvic pain is due to a neuropathy that has gone undetected by family physicians, gynecologists, urologists, internists, and neurologists. The neuropathology may be associated with the pelvis and include the pudendal nerves, the inferior hypogastric nerves, and the superior hypogastric nerve or even a combination of these. Other causes are also possible and are discussed below.

Symptoms and Signs. The most important symptom of this syndrome is lower abdominal pain and, less frequently, low back pain. Low abdominal pain can be felt either in the whole lower abdomen, in both iliac fossae, or unilaterally (Fig. 72-3). The pain is usually described as a vague discomfort that is continuously present at low levels, but exacerbation and remissions occur unrelated to anything the patient can identify. The pain can be brought on with intercourse or made worse by it (dyspareunia), but this does not prevent the patient from being sexually active. Various other gynecologic problems might be present such as dysmenorrhea, ovarian cysts, past infections, or infertility.

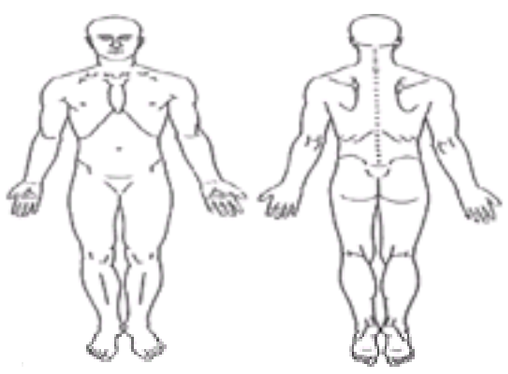

Figure 72-3. Unisex diagram of where a patient denotes painful areas front and back, used to direct the clinician to the chief areas of pain.

Patients can exhibit classic signs and symptoms of depression, such as loss of appetite, fatigue, insomnia, and loss of libido, or might only have a lack of ability to enjoy anything. Some patients can have a high energy level and poor impulse control, acting out anger in sociopathic ways, sometimes directed against the physician. Others can somatize all emotions, dealing with stress by denial and repression and presenting a bland, contented face to the world. As previously mentioned, a significant portion of these patients have experienced sexual abuse as children and as adults (47).

Some patients manifest abnormal illness behavior (48,49 and 50). They have a bodily preoccupation and conviction that they suffer from illness or disease, and they do not respond to reassurance by the physician. They maintain their symptoms—in this case, pain—to meet their psychological needs to be dependent yet in control of the situation. Although they seek cure, they continue to have their presenting complaint of pain in spite of all efforts to diagnose and treat it.

Some patients with chronic pelvic pain without obvious pathology have persistent pain as a result of positive or negative environmental factors (see Chapter 26). In our social system, physical illness elicits noncritical sympathy and support in which patients are cared for and absolved of all responsibility for their condition. In gynecologic patients (as in patients with other disease states), strong positive or negative reinforcing influences in the environment can cause the patient to develop “chronic pain behavior” or “learned pain,” which persists beyond the time of cure of the gynecologic disorder.

Diagnosis. Patients who present with chronic pelvic pain without obvious pathology are a diagnostic challenge. Because all chronic pain patients have significant behavioral components to their illness, these aspects of pain should be routinely evaluated. Serious psychopathology can be found equally in patients with and without organic pathology, so a psychological and behavioral evaluation should be done on all chronic pelvic pain patients by a clinical psychologist with experience and expertise in managing patients with chronic pain. Diagnostic measures to rule out all previously described organic problems should be used appropriately in selective fashion and concurrently with the psychologic and psychosocial evaluation. Because many patients consider the suggestion that psychological factors might be present as demeaning, criticizing, and threatening, it is important at the outset of the evaluation to make clear to patients that psychosocial evaluations are standard and routine in the evaluation of all patients. This often overlooked procedure, in addition to the psychological focusing during the evaluation process, helps to prepare the patient for biological, psychological, and social impressions of the pelvic pain.

The findings of physical and psychological evaluations should be presented by the gynecologist and a psychologist to the patient and the session should include the patient's husband or partner to make the problem of pelvic pain overtly a family problem or joint concern.

If the pelvic examination is normal, these findings should be presented to the patient, and the benefits and risks of visualizing the pelvic organs by laparoscopy should be discussed. Some authors have advocated not doing so (51), but others have shown that pathology can be present even when a comprehensive pelvic examination reveals no abnormality. Moreover, most patients are unwilling to accept the diagnosis that nothing serious is wrong with their pelvic organs unless a gynecologist has verified this by carefully visualizing the pelvis. This information is also useful to the multiple health care providers usually involved with these patients because it allows effective treatment programs to be proposed on a more rational basis.

It is difficult for gynecologists and other health care givers to be aware of the importance of neuropathic disease processes for the chief underlying cause of pelvic pain without evident pathology. In fact, this author believes that more than 60% of pelvic pain is really caused by injury to nerves and not to organs. In the next few paragraphs, various neuropathic causes of pelvic pain are outlined for the benefit of those who are unaware of this important category.

Pudendal Neuropathy. The pudendal nerve takes origin from sacral 2, 3, and 4 roots bilaterally. It winds around the sacral spinous process and then enters the pelvis via Alcock's canal as a single nerve. It divides into four distinct branches that include the clitoral, the superficial perineal, the deep perineal, and the posterior rectal branches. These nerves have a tenuous course that can be threatened by childbirth trauma, surgical trauma, and infectious episodes. The blood supply can also be compromised during various exploratory surgical procedures.

Inferior Hypogastric Neuropathy. The inferior hypogastric nerves are aligned on each side of the cervix and closely adjacent to the ureter. These nerves are the chief parasympathetic input to the pelvis. Bilateral denervation is as effective as a lumbar epidural with respect to sensory input from the uterus and cervix. Thus, they have a powerful sensory role to play in pelvic pain. Examination of this area is not easy, and local anesthetic nerve blocks are difficult to perform, extremely painful, and shadowed by the threat of central nervous system toxic complications due to the fact that the area is very vascular with both arterioles and venules that supply and drain the area (Fig. 72-4).

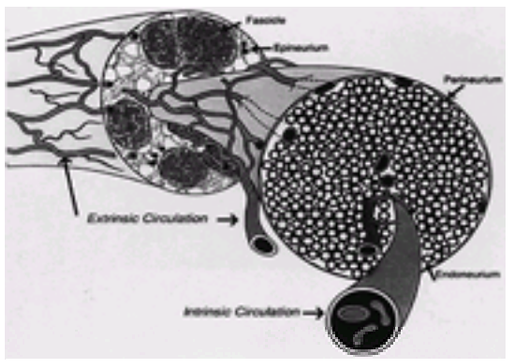

Figure 72-4. Circulation in peripheral nerve. The relationship between the extrinsic epineurial vessels and the intrinsic endoneurial vessels is emphasized. Numerous branching vessels form a rich anastomotic network on the surface of the fascicles. These vessels are connected to the intrinsic vasculature by transperineurial vessels, which are vulnerable to compressive forces acting from within or on the external surface of the nerve sheath. (From Myers RR, Heckman HM, Galbraith JA, et al. Subperineurial demyelination associated with reduced nerve blood flow and oxygen tension after epineurial vascular stripping. *Lab Invest* 1991:65:41–50, with permission.)

Ilioinguinal and Iliohypogastric Neuropathy. The patients with ilioinguinal and iliohypogastric neuropathy have past histories that often include surgical or other types of trauma in the area of the lower abdominal wall. Figure 72-7 shows the area involved in pain usually associated with these nerves. The genesis of the pain is not known, but suspect is the retraction placed on nerves located around the incision line that may result in stretch and avulsive-type neural injuries. The onset of pain after the initial trauma will be variable, due to the intensity of the injury and perhaps the fiber size. Many of the gynecologic patients have exposure to the Pfannenstiel-type incision, which cross-cuts both the ilioinguinal and iliohypogastric nerves. In addition, the injury may be from retraction in the lower corners of the incision, where the nerves are located. This can be seen in Figure 72-6. Interestingly enough, many of the patients in this group have histories of repeated abdominal exploration of one type or another because their original physician was convinced that the initial problem of intraabdominal pathology had not been solved or perhaps that recurrent pain might be due to abdominal adhesions or other yet defined “organ-related pathology.” This is becoming less so nowadays due to the widespread use of laparoscopy, but this procedure in itself may cause abdominal neuropathy due to placement of the scope, obturator, or one or more ancillary sites made percutaneously. A classic example of this patient type can be seen in Figure 72-7, in whom the obvious incisions can be seen and the maximal tender points are noted via the skin markers. In this case the patient was seen and eight tender points identified. These cases are managed by repeated local anesthetic nerve blocks spaced over time to take advantage of the effects of nerve blockade, but not so frequently as to set up a peripheral pain-generated signal from mechanical stimulation. Most patients will fall into the responding category by 4 to 6 weeks (52). Those who do not might benefit from abdominal catheter placement and continuous local anesthetic irrigation of the nerves between the transversalis and oblique muscle groups (53). Those who do not respond to prolonged block can be treated with cryotherapy for destruction of those nerves still causing problems (54). For ultimate failures in instances in which multiple nests of neuromas may still be active and have been refractory to all the modalities discussed previously, one can consider surgical intervention and extirpation of the local neuromata to try to correct the problem (55). This is often not a successful operation, however.

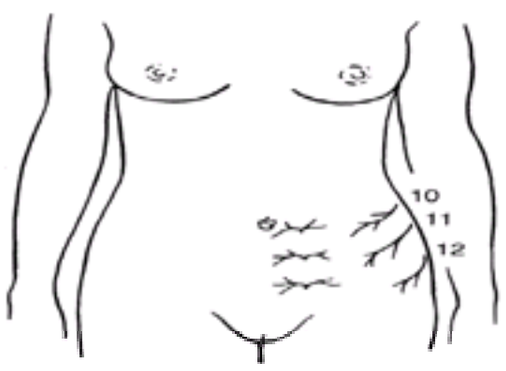

Figure 72-7. Distribution of pain in midabdominal area from T-10, T-11, and T-12. Treatment can be directed at local infiltration in skin area. (From McDonald JS. Associated pain management problems of parturition. In: Bonica JJ, McDonald JS, eds. *Principles and practice of obstetric analgesia and anesthesia*, 2nd ed. Baltimore: Williams & Wilkins, 1995:290, with permission.)

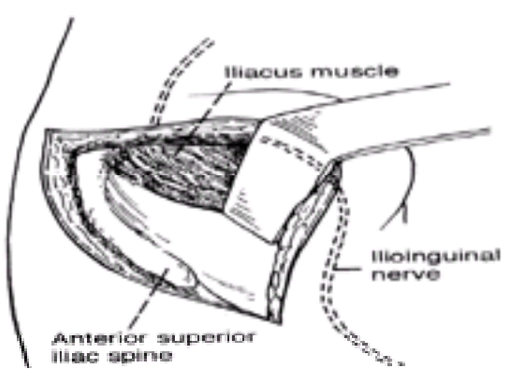

Figure 72-6. Demonstration of neuropathy generated by pressure exerted by the retractor on the ilioinguinal nerve. (From McDonald JS. Associated pain management problems of parturition. In: Bonica JJ, McDonald JS, eds. *Principles and practice of obstetric analgesia and anesthesia*, 2nd ed. Baltimore: Williams & Wilkins, 1995:290, with permission.)

Genitofemoral Neuropathy. Patients with genitofemoral neuropathy present with variable stories of low abdominal pain, or even back pain, that has migrated to the front of their body and now descends into the vulvar area. The pain is often incapacitating when it occurs in sharp, repeated attacks. There is a distinct message to be understood with regard to successes on an immediate basis. On the one hand, it is tremendously reassuring to note the significant reductions in pain after the individual nerve blocks and maximum tender point injections. Almost all patients will have pain reduction within minutes of office therapy. It is hoped that patients will exhibit gradual reductions in pain scores over time and that they will have an increase in their function at the same time. Some failures are to be expected in every type of pain management problem, and this disorder is no different. Sometimes the reasons for failure must be viewed as an open invitation to explore further the possibility of an overlooked pathologic condition. For example, one patient we managed had been refractory to repeated therapy over time, and on surgical exploration it was discovered that a suture was found around the genital branch of the genitofemoral nerve just at the site of a former hernia repair. Because the distal portion of the nerve was notably atrophic, it was resected above the area of involvement, and the patient is now pain free.

Hymenal Neuropathy. Patients with hymenal neuropathy are a most interesting group. Figure 72-8 shows the area of involvement with regard to this syndrome. Note that the perineum is richly innervated by nerves from different spinal cord segments so that there is some overlap protection with regard to innervation. Patients may be so distraught and histrionic that the initial practitioner may entirely miss the diagnosis due to preoccupation with the reaction the patient displays during physical and gynecologic examination. Often the patient complains so violently that a pelvic examination is not even possible— that is, the examiner cannot get past the introitus. In other instances, the examiner does get past the introitus, only to find there is no evidence of pain on examination of the vagina, cervix, uterus, fallopian tubes, and ovaries. The past history of such patients can often reveal a problem with *C. albicans* infection. It would appear that repeated infections to this agent can cause irritation of the superficial nerves in and around the area of the hymenal ring. Patients usually have a history of normal, healthy sexual patterns before the onset

of their vaginal pain but develop significant dysfunction sexually secondary to their disease process. This is usually manifest by symptoms of severe dyspareunia totally focused in the area of the vaginal outlet. In a group of patients we treated, four of five patients experienced complete relief of pain and a return to normal sexual function within 8 weeks of definitive therapy—surgical extirpation of the hymenal ring. In the one patient who did not have complete relief of pain, there was also a problem of significant psychological degree. This patient had a previous hysterectomy and oophorectomy and had problems adjusting to exogenous estrogen and thus had a thin vaginal mucosa with other associated problems.

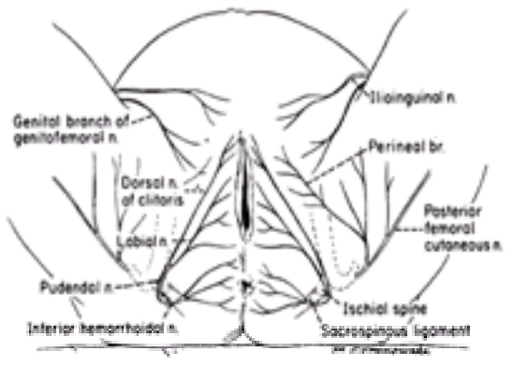

Figure 72-8. The cutaneous nerve supply of the perineum. The major supply is provided by branches of the pudendal nerve, including the inferior hemorrhoidal nerve, which supplies the posterior portion; the superficial branch of the perineal nerve, which divides into medial and lateral parts known as the posterior labial nerves; and the dorsal nerve of the clitoris. (From Bonica JJ, McDonald JS. Other regional analgesic/anesthetic techniques. In: Bonica JJ, McDonald JS, eds. *Principles and practice of obstetric analgesia and anesthesia*, 2nd ed. Baltimore: Williams & Wilkins, 1995:501, with permission.)

Figure 72-5. Pelvic pain assessment sheet. (CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CX, cervix; EXT GEN, external genitalia; GERD, gastroesophageal reflux disease; HTN, hypertension; IHN, inferior hypogastric neuropathy; LSD, lysergic acid diethylamide; MI, myocardial infarction; PCP, phencyclidine hydrochloride; PND, postural nocturnal dyspnea; PROM, promontory; RA, rheumatoid arthritis; TENS, transcutaneous electrical nerve stimulation; THC, tetrahydrocannabinol; TIA, transient ischemic attack; UTI, urinary tract infection.)

The patient workup should include at least two or three successful hymenal blocks performed before consideration for surgery. In our series of patients, all had repeated hymenal local anesthetic blocks, with demonstrated complete relief of symptoms. The association of the *Candida* infection is too consistent to be coincidence. As noted before, one might speculate that the fungus may gain deep mucous membrane penetrance and result in a damaging effect on the nerve endings, perhaps even causing neuromalike formation to occur.

Sympathetic Pelvic Neuropathy. Patients with sympathetic pelvic neuropathy have a historical vignette that is not typical from the standpoint of identification of any single source of causation. The area of innervation is shown in Figure 72-9 and includes the vagina and cervix, with innervation from the pudendal nerves with derivation from S-2 to S-4, and the uterus, tubes, and ovaries, with innervation from the sympathetic pelvic branches of T-10 to T-12. Many of the patients who complain of gynecologic pain have a deep pain in the pelvis not associated with physically detectable abdominal wall tenderness or myofascial disease of the abdominal musculature. This disease entity has been classified as a “sympathetic pelvis syndrome.” It must be recalled that visceral disease often results in pain transmitted to cutaneous areas—that is, referred pain—and often it may be interpreted as a primary disorder located in that specific area of the body. It is possible to have visceral etiology of cutaneous pain in such instances. Some patients will obtain relief from repeated local anesthetic nerve blocks if the physician is patient enough and if he or she is detailed enough to check the progress of improvement every time and note if it is specifically the same area of pain previously identified. In the remaining patients, who obtained relief of their pain for a short time, eventual surgical therapy may be necessary. It is often via a laparoscope, with which one of two nerve ablation techniques can be used—namely, uterosacral nerve ablation or superior hypogastric ganglion resection. Patients who were refractory to the local anesthetic block therapy are usually rendered pain free after the surgical resection; these patients will have a return to normal function and will be quite pleased with their therapy. It is difficult to instill in the reader the emotions felt by the patients who suffer from these pelvic pain disorders and who have been buffeted from physician to physician for years of management without success; their emotional state often is one of hopelessness and dejection due to loss of confidence that anything ever can be done to improve their status. Thus, when they begin to experience the small sense of pain relief and then the definitive procedure that relieves their pain so that they can begin to resume a relatively normal lifestyle, they are forever thankful and grateful.

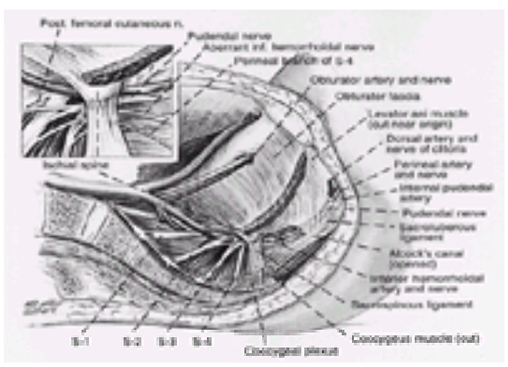

Figure 72-9. Sagittal section of the perineum showing the origin and course of the pudendal nerve. Its three roots derive from the second, third, and fourth sacral nerves, unite approximately 1 cm proximal (cephalad) to the ischial spine, then leave the pelvic cavity by passing through the greater sciatic foramen. The formed nerve then passes posterior to the junction between the ischial spine and the sacrospinous ligament, then reenters the pelvic cavity through the lesser sciatic foramen and proceeds anteriorly through Alcock's (pudendal) canal. (From Bonica JJ, McDonald JS. Other regional analgesic/anesthetic techniques. In: Bonica JJ, McDonald JS, eds. *Principles and practice of obstetric analgesia and anesthesia*, 2nd ed. Baltimore: Williams & Wilkins, 1995:503, with permission.)

Pelvic Joint Instability. Persistent pelvic pain and pelvic joint instability in some females have been associated with precocious puberty and use of oral contraceptives before reproduction. Thus, patients who complain of pelvic pain in which all diagnostic workups have been normal and who have histories of early onset of menarche associated with oral contraceptive use should be considered for possibilities of pelvic joint instability. Physical examination should establish this diagnosis (see Chapter 75).

Pyramidal Muscle Hematoma. Hematoma of the pyramidal muscle is a rare but possible complication that may cause impingement of the sciatic, inferior gluteal, and pudendal nerves. This may result from compression between the muscle and the iliac spine. In these cases a computed tomography (CT) scan should help to confirm the diagnosis (56).

Osteitis Pubis. In active females in competitive sports who present with pubic pain and adductor pain, osteitis pubis should be considered as a cause. In one study of 59 patients, recovery was slow, taking up to 7 months in women. There was also an associated finding of pelvic malalignment or sacroiliac dysfunction in these patients (57).

Adductor Tendinitis. Adductor tendinitis is usually associated with marathon walkers or runners who suffer from acute injury to the adductor muscle of the anterior thigh that attaches directly to the pubic ramus (57). It is often misdiagnosed as pelvic pain due to the complaint by the patient of diffuse ache that radiates into the involved pelvic area laterally. Diagnosis is made by running the examining finger along the medial margin of the adductor muscle up to the point of insertion on the pubic ramus. At this point, the patient will suffer exquisite pain and pinpoint the pain as being located exactly at the point of insertion. A local anesthetic injection will completely eradicate the pain within minutes of injection. It may be necessary to repeat such a treatment a few times for complete eradication of the pain.

Osteoporotic Sacral Fractures. Osteoporotic sacral fractures were found to be associated with pelvic pain complaints in which other pathologic causes had been excluded (57).

Focal Vulvitis. Focal vulvitis is a unique clinical syndrome of superficial dyspareunia and focal areas of inflammation and/or ulceration of the mucosa. This syndrome was described by Keetel in 1971 and later by Peckham in 1986 (58). Patients may disclose a history of many treatment failures. Typical symptoms are extreme pain with intercourse so severe as to cause abstinence. The characteristic signs are 3- to 10-mm areas of inflammation focused in the area of the vestibule that may or may not be detected as actual superficial ulcers. Most of the lesions are located in and around the Bartholin's ducts. Treatment successes include nonspecific therapy with various creams with or without antibiotics, cryotherapy to destroy the local ulcerative lesions, or surgery with actual extirpation of the hymenal ring with a surgical perineoplasty.

Clinical Considerations

Workup and Physical Examination

It is important to discuss some general steps to be invoked in approaching the patient who has acute or chronic pelvic pain problems. The first step, naturally, is careful and complete evaluation of the problem that the patient complains of in his or her first visit and in her own words. In-between steps involve development of a diagnostic pathway and organization of a management pathway. The last step is a follow-up evaluation of the improving patient who, it is hoped, is no longer in severe pain. This last step is one in which you must determine the effectiveness of your therapy plan and, in common terms, is the outcome of your treatment. It is very important in today's level of expectancy with regard to medical care. If therapy is a failure, referral must be considered without delay.

The essential steps in the initial evaluation of chronic pelvic pain patients include the following:

1. **Pain scale.** A pain scale must be established at the very first visit. We use a 0 to 10 scale, with 10 being the worst pain the patient has ever experienced. Some history is necessary to make sure the patient has indeed experienced a severe enough pain to be able to quantify it in a relative sense.
2. **History.** A careful history must be taken; it is important to listen to the patient explain the aspects of her problem herself. A thorough history should include the salient points the patient wants to bring out, yet a certain art form must be developed with regard to leading the patient and making sure the patient stays focused on the important facts and features of her pain. Salient features include circumstances that were operative at the time the pain began, the location and migration of the pain, the motion that makes the pain worse, and circumstances that make the pain worse or better.
3. **Physical examination.** A general physical examination is focused on the area of the patient's complaint. Often a referred patient may well have had recently a complete physical examination by her own local medical doctor. If so, the physical examination may be limited to the area of the pain. There are some instances in which “restricted area” examinations may result in missed diagnoses, but this can be kept to a minimum by making sure all potential diagnoses are considered.
4. **Diagnosis.** The diagnosis can only be reached by careful and detailed history and physical examinations that are repeated when indicated. Furthermore, differential diagnoses must be inclusive enough to include that which is most likely the cause of the problem.
5. **Identified goals.** Just after the development of the differential diagnosis list and even before definitive diagnosis, the physician may talk to the patient about goals in therapy. There are at least two immediate end point goals: improvement in personal and professional function and reduction in pain levels. Patients who are included in such goal-setting discussions will sense involvement in the decision-making loop and will sense that they are an important member of the team. Most important here is the empowerment given to the patient. All patients appreciate being given knowledge of their disease process and being empowered with the logical medical knowledge. Last, and very important, she will be empowered by the understanding that she has the attention of a concerned and sincerely interested physician. Further components of effective treatment include the following.
6. **Therapy.** An extensive treatment or therapy plan should be discussed with the patient, with treatment possibilities laid out so that the patient can see her options. This is valuable for the purpose of letting the patient know there are several therapeutic possibilities, not just a single one. This approach also enhances cooperation with the various therapy modalities.
7. **Follow-up.** Follow-up should begin just 1 week after the initial visit, either at the time of return to the clinic or at the time of a follow-up telephone call. This is an excellent time to review the treatment hierarchy in order to allay any disquietude the patient may have toward her treatment so far or even toward the eventual goals of therapy.
8. **Adjustment.** If progress is not being made, as evidenced by a repeat visit and examination, the physician must be prepared to invoke therapeutic adjustments to redirect effectiveness of medication.
9. **Long-term follow-up.** Times for follow-up can be scheduled on a predetermined basis and those times discussed during the setting of the goals or during the discussion of the therapy at the initial visit. A reasonable follow-up might be 1 week, 2 weeks, or even 4 weeks. By definition, 3 months separate acute pain from chronic pain; therefore, some of the supposed acute pain patients will be moved over to a chronic pain category as the length of time for pain increases and the therapy does not achieve its goal of pain relief and improved function within a 3-month window. Every time a patient is seen for follow-up in clinic or called for response to questions about her therapy, the physician should be made aware of untoward events, responses, or deterioration of patient wellness so that readjustments in therapy can be instituted immediately instead of waiting for a period of time when the patient can come back for a personal clinic appearance.
10. **Outcome.** Outcome is the “graduation” of the patient from the designed therapy regimen that was specifically developed for her. It is the gold standard for measurement of success or failure. It is the single most important focus from the patient's viewpoint because she originally comes to her physician with pain and a need to reduce that pain and improve her functional ability so that she can work and enjoy life again. It is suggested that outcome results be obtained and recorded in the patient's chart or a book of results the physician keeps personally.

Diagnostic Procedures

Several procedures must be considered basic diagnostic tools in a practitioner's approach to pelvic pain. These include as a minimum the following list that forms the basic foundation in the beginning approach to understanding the patient with pelvic pain:

1. **A careful and considerate pelvic examination directed to the sites of pelvic pain**, not the usual pelvic bimanual examination.
2. **Pelvic ultrasound examination** to help identify difficult-to-detect abnormalities that are “hidden” due to a patient's not allowing deep palpation because of pain.
3. **Pelvic magnetic resonance imaging (MRI)**, the ultimate examination for detection of hidden tumors, masses, or even totally obscured endometriomas that may include occult neural involvement.
4. **Abdominal MRI** to rule out possible pathology in the abdomen that cannot be appreciated or cannot be detected on physical examination.
5. **CT scan**, the ultimate examination for problems that interface the osseous and tissue planes (it may be indicated at times even in the face of a normal MRI if historical and laboratory findings point toward suspicion of abnormalities along this interface).
6. **Bone scan** to detect fractures that may involve nerve distributions and cause long-term pain and disability in instances when fractures are not visible on plain x-ray.
7. **CA-125 values**, which may be helpful in certain situations to help confirm a diagnosis that is already highly likely because of strong history and physical findings (e.g., for suspicion of endometriosis).

It is important to record and assess all previous studies such as those mentioned previously and to take detailed notes on dates and findings. These can help one to understand the past thought processes of physicians who have cared for the patient. They should not be repeated unnecessarily because of the delay in time, the added expense, and the implication for the patient that she harbors occult pathology.

Operative Procedures

Two operative procedures must be considered basic workup tools in the approach to pelvic pain:

1. **Laparoscopy** is perhaps the most frequently used gynecologic operative procedure. Its value is unquestioned; however, there may be situations in which strategically planned diagnostic pathways could make this procedure unnecessary.
2. **Laparotomy** is performed after laparoscopy indicates extensive disease and usually is performed for therapeutic reasons. Most of the time it is used in cases in which adhesions are so dense that laparoscopy is not possible. Other times, it may be used when a mass is located in an area difficult to observe.

Once again, it is important to carefully record all previous operative procedures, dates, and outcomes so that some sense can be made out of the complete history of the patient's pain and her therapy.

Initial Therapy

There are five cornerstones of therapy for pelvic pain: medical therapy, local anesthetic nerve block, psychological therapy, physical therapy, and alternative medicine. They can be viewed as a therapy hierarchy and can be used to reassure the patient that she and her pain are paramount in your mind and that her healing is your major goal.

Some type of therapy should begin at the first visit; usually it is a medication to rescue the patient from the severity and constancy of pain. Showing the patient that you are concerned about her welfare and are attempting to help with medication to improve her sleep and to help reduce some of the severity of the pain will go a long way in reassuring the patient she has met someone who has genuine concern about her well-being.

Patient Medical Log. The medical log records pain levels and medications on a daily basis. This is important because patients often are given medication, and very little, if any, feedback is determined. Thus, the patient remains on the same dosage, which may be too great, too little, or appropriate. A long-term goal is to reduce the dependency on medication regardless of the type of medication. This can be done only if the physician notes the progress that is being made on a return visit. Accurate data are required regarding drug dosage, when it was taken, and the effect.

The activity log is another important database that relates to patient function; it is a variation of the medical log and is really vital with regard to the progress that is being made. It can be kept along with the medical log or separately. It is best to begin the log with an activity notation about what the patient used to do or be capable of doing before the onset of the pain disorder. The log can be sheets of paper that the patient records on daily, or it can be regimented. This instrument can be the most valuable index of the functional status of the patient and a good indicator of the progress being made with various therapeutic trials. The activity log focuses the patient's attention on function rather than pain and serves as a key in the doctor-patient relationship.

Follow-Up Visits

Therapeutic Hierarchy

Medication. It is important to begin some therapy on the first visit. This can be by administration of various systemic medications or rest or exercise programs, but this should only be done after careful analysis of the currently used medications and after recording the successes and failures of the medications and therapies tried in the past. This is a time-consuming event, but it is really necessary to make a breakthrough in understanding the complete medical background of the patient. At this time it is also necessary to have an in-depth conversation with the patient about her sleep habits and to consider the addition of one of the low- dose antidepressant medications such as amitriptyline (10 to 25 mg taken at bedtime). The use of this regimen can aid in both decreasing the pain and in providing the patient with some badly needed sleep. Another approach to beginning therapy is emphasis on rapport by carefully outlining to the patient what the various problems are, what the possible etiologies may be, what the possible therapies might be, and how you and your staff will stand by the patient throughout the workup phase and be supportive into the therapy phase. Some may not look on this as therapy, but the concern and consideration of the physician, the eye contact, and the reaching out to touch the patient and display of sincere concern are not to be underestimated.

The basic foundation for treatment of noncancer pain patients of course begins with the use of over-the-counter, readily available drugs such as salicylates. The next step is usually NSAIDs, followed by tricyclic antidepressants. Next come anticonvulsant drugs, which have also been found to be effective in a variety of pain syndromes. Last is the use of the opioids. Yet, it is possible to have the patient continue for a short time on the opioid drugs he or she has been used to taking for pain relief by contacting the referral physician and establishing a good relationship with him or her. The message should be that you would appreciate the continuance of whatever medication the patient has been taking the past few months and that your aim will be to gradually reduce that over time and substitute other drugs such as the NSAIDs. This is done by having the referring physician continue to prescribe opioids for a short period of time that you identify with him or her. This can work out nicely if there is good communication between the two of you. There are some patients and some instances when use of opioid analgesics may have fewer side effects than tricyclic antidepressants and anticonvulsant drugs. There is also a wide difference in the incidence of side effects among opioids such as morphine sulfate, codeine, and pentazocine, which have side effects in the range of 20%, whereas oxycodone has a percentage one-half of that. The adverse effects usually associated with the opioids are pruritus, drowsiness, nausea, vomiting, dizziness, headache, euphoria, dry mouth, and swelling.

Neural Therapy. Early on the patient has had the treatment hierarchy explained so that by now she understands fully what is going on and has some grasp of the plan for her improvement. In this way she can become an informed patient who takes interest in herself and the therapy that is being offered. The following treatment modalities with respect to neural therapy are explained in detail and usually in the order listed so that the patient realizes there are, indeed, other pathways that can be explored if one of the types currently to be tried is a failure. Most important it is necessary to assure the patient that there are many different ways of approaching therapy and some methods work well in some patients and other methods work well in other patients.

One type of therapy is the local anesthetic nerve block. It is used early on for diagnostic purposes but it also serves as a beginning step of therapy. A dilute solution of some type of local anesthetic can be used to infiltrate the affected area with 3 to 5 mL of solution. It is best delivered with a 25-gauge needle or even a 27-gauge needle to minimize patient discomfort on repeated injections. These can be repeated at intervals to effect a decrease in the input signal to the central nervous system.

The transcutaneous electrical nerve stimulation unit is a battery-powered electrical stimulator that delivers intermittent shock waves to the skin (see Chapter 98). This stimulator can be used at the same time other therapies are used, such as local anesthetic nerve blocks. This parallel therapy can sometimes speed up the time for the patient to reach a comfortable level (59).

Another neural therapy is cryotherapy, which essentially consists of freezing of portions of the involved nerve so that it dies. The machines available for such treatments include sophisticated circuitry to provide for identification of involved nerves by electrical stimuli and then freeze therapy to effect destruction at a chosen local point immediately proximal to the involved nerve (60).

Another type of neural therapy is an insertion of a continuous abdominal catheter for the purpose of continuous irrigation of the involved nerves. This method should be considered only when patients are refractory to the local anesthetic block therapy mentioned previously. Its advantages are that it minimizes repeated painful injections, which are a necessary part of the repeat treatments, it reduces the visits necessary for repeated injections, and in some isolated cases it has given continuous pain relief instead of cyclic on and off pain relief (53).

The last method of neural therapy is mentioned here only for completeness and is not recommended by the authors for lasting pain relief. The method is surgical excision of a so-called neural bed in an area that has been repeatedly refractory to nerve block and other methods of pain relief. Surgical entry into the area where repeated therapeutic measures as mentioned previously have been ineffective has sometimes been carried out due to a neuroma persistence or due to ineffective or misdirected local anesthetic nerve blocks. It usually consists of opening of the incision and careful visualization of the incision line and wound bed to denote any

obvious pathology such as suture placement around a nerve or an obvious collection of neuromas due to old nerve damage (55).

Psychology. Psychological strategies are only briefly mentioned here, as they are the major topic of consideration in the next section of this chapter. The psychological interview is performed at the time of the first visit, often before the physical examination. This interview is important because it sets the framework for recognition by the patient that this is a vital aspect of her health and well- being and that its emphasis is noted because of its early inclusion. A psychologist who collaborates with the physician strengthens the message to the patient that there is indeed an intricate relationship between good general medical health and psychological well-being. Ideally, it would be beneficial to have the psychologist be schooled or experienced in the area of sexual function and the problems inherent in this very specialized aspect of health care. The literature is replete with articles relating association of childhood abuse and later sexual and psychological dysfunction; many minor and major gynecologic pain problems have also been blamed on such disturbances (61). These problems are often hidden and not immediately apparent in early physician relationships because the patient is waiting for some signs of comfort and trust to appear or because the patient has suppressed her past history to the extent that it is not readily available for recall.

Significant psychological impairment can have devastating effects on the success of a planned program for a patient's recovery, especially in instances in which it is not even suspected as being a problem. We have developed a “dyssexualis” history that helps us to identify those patients with significant sexual dysfunction early on in the workup (Fig. 72-10).

Figure 72-10. Dyssexualis questionnaire.

Psychological treatment strategies include not only individual psychotherapy but also hypnosis, biofeedback, and group psychotherapy.

Physical Therapy. After completion of the initial workup and consideration of the possible pathology, it is wise to go over the possibilities with the patient and to discuss how the pathology can be related to the anatomy. To facilitate this the physician may want to use anatomy book pictures to demonstrate that relationship. This aspect of the treatment regimen is often overlooked, but it is vital to good recovery and adds substantially to the overall therapy regimen that one needs to put together for the patient. In addition, the patient will realize from the outset that she will not be relying on one treatment method. The latter philosophy is commonly understood by patients, but we cannot emphasize too much how confidence in the physician is eroded when only one method of treatment is suggested and it begins to fail the patient once again. At such a point the patient may become demoralized and depressed because she has experienced such feeling before in her interaction with many prior physicians. The prime physical therapy methods include heat, electrical stimulation, deep ultrasound, and massage. It is important to work with a professional physical therapist so that he or she can devise treatments specifically designed for the patient. The physical therapist should examine the patient, design a special mode of therapy for the patient, and follow the patient over time, with feedback to you for follow-up purposes.

Alternative Medicine. Alternative medicine would not even have been considered 5 years ago during a discussion of pelvic pain. Today it is politically correct, widely used, and often funded by third-party payors. Alternative-care strategies also help to make the patient feel included in her healing process and help her to hold onto some of the “remedy”-oriented methods of treatment that many patients already use. Yoga, meditation, chiropractic, nutrient therapy, and acupuncture are common forms of alternative care.

Patient Goal Setting

It is possible to identify the mutually nonexclusive goals of improved function and decreased pain. Of course, any early discussions regarding pain treatment results must be guarded with respect to any promises of certain definite endpoints. It is unwise to tell a patient who presents with a pain score of 8 out of 10 that by the end of therapy she can expect a reduction to a 2 or 1 out of 10. It makes more sense to say that the general goal over time will be to reduce the beginning pain score from a severe range of 7 to 10 to a moderate pain score of 4 to 6 to a mild range of 1 to 3. In this way, one can avoid fixating on a numerical score. In addition, it is very important to stress function improvement by noting the patient's function percentage from the professional standpoint and the personal standpoint. With regard to the former, it is necessary to identify what the patient's level of professional function was at a full 100% and then identify what it is now at the pain score recorded. With regard to the latter, it is necessary to identify what the patient's level of personal function was at a full 100% and then, similarly, identify what it is now at the current pain level.

Treatment Trials Outcome: Criteria and Results

An attitude of futility develops after a period of time when treatment trial after trial fails to alleviate the pain. Because physical causes are much more socially acceptable than mental or psychological ones, both physician and patient continually seek to find organic pathology. The problem is that the physical causes of chronic pelvic pain are difficult to identify and prove. Special techniques of physical examination are called for, and the physician must have a high index of suspicion for neuropathic conditions such as nerve compression and neurapraxias, which result in problems such as hyperalgesia and allodynia, myofascial pain syndromes, pressure neuropathy of the pudendal nerve, obturator nerve, and the inferior hypogastric ganglion.

This is a time-consuming activity, but it is really necessary to make a breakthrough in understanding the complete medical background of the patient.

Enhancement of the Patient-Doctor Relationship

Enhancing the patient-doctor relationship is difficult to teach. In many ways, the adage “you either have it or not, you cannot develop it” has validity. However, it is possible for any physician to enhance his or her patient-doctor relationship. This is done by simply working on developing the philosophy of caring. Physicians do care; if they did not they would not have gone into medicine. A caring physician is the first requirement. Next, it is important to develop and work on listening skills. Patients have an important story to tell and they want to tell it. You want to listen. All that stands in the way is a busy or overloaded schedule and the physician's patience, which is not an easy item to work on and perfect. Certainly, all of us have harried schedules and often not enough time in a workday. Nevertheless, we can begin by listening to patients' stories without interrupting them over and over, guiding them, and distracting them from their natural “storybook” line. Finally, it is important to let the patient know you sincerely care about her, that you do want her to get better, and that she and her problem are priorities in your life. It is possible to transmit sincerity, but it must be done naturally and freely. This is not something you can “construct” for the moment. Patients will immediately discern whether you are being truly sincere or not.

Avoiding Adversarial Relationships. There will be instances when patients do not “heal” or “perform” as you would like them to or even as you both had agreed they would. This is not a time to be condescending because the patient is well aware of the fact that she has not complied with therapy. She is dreading the next visit, when you will discover she has not kept on track. The last thing she needs at a time like that is to be scolded or embarrassed or demeaned. She needs understanding, support, and to ventilate and explain why she acted in the manner she did. Use such instances as times to grow the patient-doctor relationship closer together, not farther apart.

The Interdisciplinary Pain Approach. The interdisciplinary management approach was championed by Dr. John J. Bonica in the middle 1950s, long before most even understood the concept of pain, pain diagnosis, pain management, or the difference between acute and chronic pain syndromes. He was dedicated to the belief that

patients could be best managed by groups of practitioners from different specialties working together to obtain the most positive results for pain patients. He also was cognizant of the fact that most pain patients have more than one problem at the root of their pain condition.

Interdisciplinary management of pelvic pain problems involve the interaction of several specialties. These include gynecology, anesthesiology, urology, orthopedics, neurology, neurosurgery, psychology, psychiatry, and general surgery. Pelvic pain, more than most pain syndromes, has eluded proper diagnosis and treatment time after time. Patients often become trapped in a web of endless physician shopping for someone who believes their pain is real and for someone who will stick with them until some reasonable relief is obtained. Most physicians resort to the first and most common therapy management tool—surgery. This results in removal of one or more organs in surgery after surgery until no pelvic organs remain; even the bladder is taken in some instances (63)! Because the treatment of chronic pelvic pain is quite controversial and far from being established as a routine or classic therapy model, it makes perfect sense that patients who do suffer from chronic pelvic pain be seen in some type of interdisciplinary complex. This can consist of a clinic where one, two, or even three pain practitioners interact and collectively work on common difficult-to-manage patient problems on a routine basis. Referrals to ancillary specialties can be organized and development of good collegial relationships established. A 1990 study of this model tested against a comparison group that did not use the interdisciplinary model revealed that the former group of patients had more success with pain reduction, anxiety reduction, and depression reduction and had an improved participation in daily psychosocial activities such as return to work, social activities, and sexual activity when compared with the traditionally managed group (64).

PSYCHOLOGICAL FACTORS IN GYNECOLOGIC PAIN SYNDROMES

The medical information presented in this chapter illuminates the spectrum of diagnostic and treatment conundrums that can confound the practitioner who works with chronic pelvic pain and significantly impair the woman's capacity to lead a productive life. Patients with chronic pelvic pain often experience progressively limited professional, social, and/or personal pursuits, if not pleasures. Providing treatment for these women is complicated by a plethora of etiologic factors and numerous diagnostic considerations that cross medical and psychological specialties. Furthermore, they often describe increasing frustration with being transferred between and within medical specialties. Multiple physician visits, multiple diagnostic tests, multiple drug trials, and multiple treatment regimens, including multiple surgeries, often produce little relief from their pain while significantly increasing stress and psychosocial symptoms, such as depression and sexual dysfunction. Unfortunately when medical treatment is not conclusive or successful, women with chronic pelvic pain, more than any other pain condition, are often labeled as “crazy” or told that the pain is “in their head.” Practitioners and partners frequently become quite nihilistic and often manage their frustration in ways that are psychologically detrimental to the patient. Practitioners need to be aware of the potent psychophysiologic impact of the patient's stress and psychosocial environment on medical efficacy and the patient's recovery.

Most studies (e.g., see references 61,65) find that the average woman with chronic pelvic pain is in her early 30s and has an average pain of 7 on a visual analog scale of 10. This pain has often lasted for 3 to 4 years and resulted in an average of three to four gynecologic surgeries before she is seen by a specialist or at a pelvic pain clinic. Frequent use of hysterectomy, much too often without relief of pain, is a further misfortune from which many of these women suffer (65).

It is our belief that psychological evaluation and treatment are critical components when working with a woman suffering from chronic pelvic pain. The complexity of this condition has prompted a more specific focus on the collaboration of medical and psychosocial professionals. We strongly encourage an interdisciplinary approach that includes at least mental health and medical professionals. The physician who is presented with chronic pelvic pain must have a broad-based understanding of the problem in order to facilitate effective triage and referral, if not treatment. This portion of our chapter makes it clear that psychological factors are critical to this process.

Historical Considerations

Psychological trauma, such as sexual and physical abuse, in the history of patients who develop chronic pelvic pain is important to understanding this complex problem (61,65,66,67 and 68). The impact of these historical factors in “causing” pelvic pain remains controversial; however, we believe that they may exacerbate a woman's experience of pain in the pelvis and consequently reduce medical efficacy.

Trauma

History of sexual and physical abuse has become a frequent topic of discussion and debate regarding the etiologic impact on patients with chronic pelvic pain (61,65,66 and 67,69,70). Most studies indicate that an average of 20% to 30% of women with pelvic pain have experienced childhood sexual trauma or abuse (61,65,66,69,71). When the pain is “nonsomatic” or “of unknown etiology,” the frequency of abuse is found to be much higher. For example, Harrop Griffiths et al. (67) found that of 25 women who had undergone a laparoscopy, 64% reported child sexual abuse (48% mild and 16% severe) as compared with 23.3% of women who received a laparoscopy for infertility (23.3% mild and 0% severe). Furthermore, 48% of those with chronic pain also reported adult sexual abuse (20% mild and 28% severe) compared with 13.3% of infertility controls (3.3% mild and 1% severe). Interestingly, when they compared the pelvic pain patients with positive and negative findings during laparoscopy, there was no significant difference in the frequency of sexual abuse.

Reiter et al. (65) found that 64% of patients with “nonsomatic” pain reported childhood sexual abuse. These authors also found that the sexual histories of these patients were different than those of the “organic” patients. The nonsomatic patients had sex at an earlier age and also had a greater number of sexual partners.

Physical abuse history has also been found to be an important diagnostic consideration for women with chronic pelvic pain. In fact, one group of researchers (72) found that childhood physical abuse, not childhood sexual abuse, was directly associated with the symptoms of depression, anxiety, and somatization found in this group of patients. These authors reported that childhood sexual abuse and childhood physical abuse are highly correlated. However, physical abuse has the strongest correlation with psychological symptoms associated with chronic pelvic pain and the greater probability of resulting in adult posttraumatic stress disorder (PTSD) symptoms. Another study in Scandinavia (73) found that women living in a physically abusive relationship were more likely to have experienced chronic pelvic pain. Of those in the abusive relationship, 15% reported pain at the time of the interview, compared with 2% of the control group. In addition, more of the abuse group reported a higher number of psychological problems (82%) compared with the controls (14%).

Toomey et al. (68) studied the differences between patients who had been physically or sexually abused and those who had not. These authors found that the two groups did not differ in their pain descriptions or the functional impact of their pain. However, the abused patients with chronic pelvic pain did differ in the following ways: (a) They had greater perceived “punishing responses” from those around them; (b) they reported less life control; (c) they had a greater somatic focus; and (d) they reported more generalized psychological distress.

Sexual, physical, and other types of traumas warrant special attention because they often result in PTSD (74). These traumas and consequent disorders can cause a variety of psychological and medical symptoms, many of which manifest themselves somatically. It is also interesting to speculate why there is a tendency for individuals to be affected by stress in different, but consistent, body parts (e.g., ulcers, headaches, back spasm). Therefore, stress characteristics and psychological factors may predicate which body parts may be more susceptible to pain by altering peripheral and central nervous system pain receptors. In fact, Bremer et al. (75) found that chronic stress in adulthood resulted in a significant volume change in the right hippocampus for Vietnam veterans in the study. The role of trauma/stress psychophysiology and neurochemistry (e.g., cortisol, prolactin) is becoming a more central area of investigation for understanding pain and interventional efficacy.

Seminal psychophysiologic research by Heim et al. (76) investigated whether stress markers in the hypothalamic-pituitary-adrenal (HPA) axis were altered in 16 women with chronic pelvic pain without organic pathology compared with 14 infertile controls. All subjects received a thorough gynecologic evaluation, including a laparoscopy. Sexual abuse (child or adult) was reported in 66.7% of the subjects with chronic pelvic pain without organic pathology (46.6% experienced “traumatic” abuse), compared with 21.4% of the infertile controls (7.1% “traumatic” abuse). It is important to note that 60% of women with chronic pelvic pain without organic pathology also reported a history of physical abuse, compared with 21.4% of controls. Therefore, it is not surprising that 40% of the chronic pelvic pain subjects met the DSM-IV diagnostic criteria for PTSD (74). Nevertheless, it was interesting that there was no significant difference between the two groups with regard to depression. The neuroendocrine results were equivocal when compared with other PTSD studies. However, the pattern of HPA dysregulation was very similar to findings for patients with chronic fatigue syndrome and fibromyalgia. Patients with chronic pelvic pain without organic pathology in this study were found to have decreased salivary cortisol levels (or adrenocortical hyporesponsiveness) in response to corticotropin-releasing hormone stimulation testing. It is hypothesized that hypercortisolism may be a significant etiological factor in the development of chronic pelvic pain because normal cortisol levels may be protective and low levels might cause an autoimmune insufficiency and therefore hypersusceptibility for a disease or illness process. The ultimate disinhibition of prostaglandin synthesis due to these neuroendocrine changes may also help explain the development and persistence of the pelvic pain. Furthermore, it is unclear how chronic stress might increase prolactin levels due to HPA axis disruption and therefore affect hormone sensitivities (e.g., estrogen, testosterone) and consequently disease or pain symptoms in the

pelvis.

Stress and trauma have also been found to have a serious impact on treatment efficacy for some pain conditions. For instance, Schofferman et al. (77) studied the impact of childhood trauma factors on surgical outcome for 86 post–lumbar surgery patients. The childhood trauma factors included (a) physical abuse, (b) sexual abuse, (c) alcohol/drug use in the primary caregiver, (d) “abandonment,” and (e) “emotional neglect.” The authors found that when patients reported 3 to 5 of these factors there was only a 27% chance of a successful surgical outcome, but a 95% chance of success occurred if none of these factors was endorsed.

The stress or trauma may include more than physical or sexual abuse. Pearce et al. (78) found that women with chronic pelvic pain without organic pathology reported significantly more stressful and traumatic life events (especially death and illness in family members/friends) compared with patients with identifiable pathology and non–chronic pelvic pain controls. Another study (76) found that patients with chronic pelvic pain without organic pathology also reported a significantly higher total number of major stressful life events compared with infertile women. Patients with chronic pelvic pain and traumatic or stressful histories also show a higher propensity for somatization disorders and hypochondriasis than controls (65,78,79). It was concluded that this exposure to illness and death causes a substantial increase in somatic awareness and possibly develops into a preoccupation.

This section on historical considerations is intended to imply neither a psychogenic origin to most chronic pelvic pain nor that psychological intervention is the primary solution. The sole purpose is to educate practitioners about the need for an appreciation of historical factors in the triage and referral process.

Common Psychological Problems

Global Psychological Symptoms

Women with chronic pelvic pain frequently develop a constellation of psychological symptoms, such as depression, anxiety disorders, substance abuse, and sexual dysfunction, that is directly related to the ineffective process of seeking help for their pain or the progression of their pain. A number of studies have found that women with chronic pelvic pain experience of a variety of psychological problems that can cross numerous diagnostic categories. For example, a small study found that of 20 women with pelvic pain, six met DSM-III criteria for major depressive disorder, six met criteria for generalized anxiety disorder, and one met criteria for panic disorder (80). More strikingly, Gross et al. (66) found that in a group of 25 patients with pelvic pain, nine were diagnosed with borderline personality disorders, nine with hysterical personality disorders, four with adolescent adjustment reactions, two with passive-aggressive character disorder, and one with narcissistic character disorder. Slocumb et al. (81) found that pelvic pain patients (n = 41) had higher levels of anxiety, depression, anger, and somatization compared with gynecologic controls (n = 41). The women with chronic pelvic pain were also less relaxed and content than controls, but showed no difference with regard to being friendly.

It is important to insert a qualifier while reading this section. It is very difficult, if not impossible, to differentiate the psychological sequelae associated with having a significant, psychosocially debilitating pain condition and any psychological psychiatric predisposition. In fact, Sternback and Timmermans (82) found that the abnormal Minnesota Multiphasic Personality Inventory (MMPI) profiles of patients with a pain condition (not chronic pelvic pain) returned to normal when the pain subsided.

Fry et al. (69) investigated the psychological symptoms in three groups: (a) normal subjects without pelvic pain or seeking psychiatric treatment, (b) women with chronic pelvic pain, and (c) patients in outpatient psychotherapy (Table 72-4).

Normal	Chronic pelvic pain patients	Outpatient psychiatric patients
Phobia	=	<
Obsessive	=	<
Hysterical	=	<
Anxiety	<	<
Depression	<	<
Somatic anxiety	<	<

=, same as; <, less than; >, more than normal controls.

From Fry RP, Crisp AH, Beard RW, et al. Psychosocial aspects of chronic pelvic pain, with special reference to sexual abuse. A study of 164 women. Postgrad Med J 1991;67:566–574.

TABLE 72-4. Psychological diagnosis in different types of patients

A common debate in the area of psychosocial etiology of chronic pelvic pain is whether patients with diagnosed organic etiology are different from those without a specific organic finding. A study using the MMPI (83) compared 25 women with organic pathology, 15 women without “obvious” pathology, and a pain-free control group. Chronic pelvic pain patients were found to have elevated scores on hypochondriasis, depression, and hysteria independent of organic pathology, but a similar elevation was not found for control group patients. Renaer et al. (84) also found no difference between the MMPI profiles of patients with chronic pelvic pain without organic etiology and those of patients with endometriosis.

Depression is common in a chronic pelvic pain patient population. Patients present with symptoms of dysphoria, anhedonia, sleep and appetite disturbances, pessimism, inertia, irritability, and despair. A small but significant number of patients describe increasing suicidal ideation if nothing can be done to alleviate their pain or help them return to a modicum of daily functioning. Harrop Griffiths et al. (67) found that women with chronic pelvic pain have a higher incidence of lifetime major depression and current major depression. Depression may significantly impede recovery, as Gil et al. (85) found that a negative cognitive style, common to depression, increases pain severity and psychological distress. Fry et al. (69) found that these patients also had a significantly higher level of hostility than gynecologic controls. It is very important to consider depression when the patient presents bitter, hostile symptoms.

The anxiety and fear described by chronic pelvic pain patients take on a ruminative, if not obsessive, style. Patients tend to catastrophize and develop superstitions regarding pain and certain behaviors. This cycle of superstition and disuse often exacerbates pain and perpetuates the problems. More often, however, the anxiety and fear of disuse cause them to overcompensate with excessive activities, especially when they are feeling better. Harrop Griffiths et al. (67) found that patients with chronic pelvic pain were more likely to have current phobias but not panic disorders. Some of our patients experience profound guilt and sometimes shame at not being able to do their perceived “wifely duties.” They may also experience shame and embarrassment because of the location of their pain or the symptoms of their pain. Low et al. (86) found that a positive laparoscopy group (n = 40) was significantly higher on extroversion, psychoticism, state anxiety, and trait anxiety than the group in whom endometriosis was not found (n = 41). The groups did not differ regarding levels of depression or of reported pain. The authors hypothesize that the endometriosis group may be predisposed to this disease by having an overanxious, perfectionistic personality style.

Somatization deserves special attention as an important version of rumination. Patients with chronic pelvic pain can become excessively focused on somatic symptoms and, with time, may have a tendency to overinterpret or misinterpret even the most benign symptoms. For instance, Kellner et al. (87) found that women with chronic pelvic pain had a much higher level of body preoccupation and disease conviction than did gynecologic controls. Also, 44% believed they had been misdiagnosed. Harrop Griffiths et al. (67) also found that these patients complained of significantly more somatic symptoms than infertility controls.

In our clinical experience, character disorders such as the borderline personality are less frequent than reported by some authors (e.g., see reference 88). Nevertheless, borderline patients with chronic pelvic pain warrant special attention in this chapter. These patients demand disproportionate clinical time and can become quite belligerent and act out when their attention needs are not “adequately” met. They may use rage and externalization of blame as manipulative tools to acquire prescriptions or specific, sometimes self-sabotaging, treatments. The physician must be critically aware of the potential for these patients to sexually misinterpret the physical examination. It is highly recommended that a chaperone be present during all physical examinations, especially gynecologic, when working with a borderline patient or a patient who presents with similar psychiatry symptoms.

Substance abuse can become a problem for patients with chronic pelvic pain when analgesics are the only perceived alternative to pain “management.” Harrop Griffiths et al. (67) found that patients had a higher lifetime drug abuse/dependence compared with controls, but no difference in alcohol abuse/dependence. The

problem of abuse is exacerbated when prescriptions for narcotics or anxiolytics are given to keep the “annoying” chronic pelvic pain patient “satisfied” and out of the office. Some of our patients use analgesics and/or alcohol as a psychotropic to numb not only the physical pain but also the emotional/psychological pain or symptoms common to their condition. Narcotics are an important part of the pain management regimen; however, patients should be consistently reevaluated for nonanalgesic use.

Psychological factors are critical to the treatment of women with chronic pelvic pain because the physiologic changes associated with emotional states can alter the recovery process. Bonica et al. (89) believed that perception of pain was influenced by an array of factors along the ascending fibers to the central nervous system. They postulated that stress or other emotional states and the corresponding neurochemical changes could augment nerve transmission at the dorsal horn, spinothalamic tract, or descending inhibitory nerves causing increased pain. For instance, depression can lower lymphocyte levels and increase cortisol levels, whereas anxiety can increase adrenocorticotropic hormone and growth hormone levels. Unmanaged stress associated with the chronic pelvic pain experience can also increase epinephrine, norepinephrine, adrenocorticotropic hormone, prolactin, cortisol, and growth hormone levels, as well as decrease bladder and gastrointestinal motility and increase cardiovascular output, with increases in blood pressure (systolic and diastolic). Emotional topics or increased stress can also significantly increase vaginal wall blood flow. Furthermore, a common physical sequela to psychological stress is muscle tension, which can create and/or significantly exacerbate the pelvic pain experience. This is noteworthy, as many of our patients are being treated for abdominal myofascial trigger points or posttraumatic neuromas, which are obviously sensitive to muscle tension. Any of these psychophysiologic changes could affect treatment efficacy and the recovery process for patients with chronic pelvic pain.

Common Psychosexual Problems

Sexual problems receive little focus in the literature (70). In fact, Van Lankveld et al. (90) stated that “the assessment and management of psychological and psychosexual dysfunction in these patients is rarely addressed.” Patients with chronic pelvic pain, independent of diagnosis, have some constellation of sexual problems. Problems include decreased libido (psychosocial and hormonal), dyspareunia including vaginismus, decreased physical arousal (e.g., decreased lubrication), disrupted orgasmic capacity, and postcoital pain.

The prevalence of dyspareunia in a general gynecologic population is surprising. Glatt et al. (91) found that of 313 consecutive patients attending a routine gynecologic visit, 33.5% reported ongoing dyspareunia. Of these patients, 23.8% reported that they “always” had pain during sex and 55% reported occasional pain.

A number of studies have examined the frequency of sexual problems in the general chronic pelvic pain population. Peters et al. (70) found that 71% of their patients experienced dyspareunia, 42% anorgasmia, and 27% postcoital pain. We (61) found that in our first 76 consecutive patients with chronic pelvic pain, 67.1% were uncomfortable with their sexual frequency and 70.2% reported a decrease in desire. Our patients reported pain during foreplay (38.8%), orgasm (36.5%), and postsexually (80.3%). Lubrication insufficiency was a problem most times or always for 25.6% of subjects. Dyspareunia was common (84.3%) and exacerbated by thrusting (80.3%) and different sexual positions (60.0%). The intercourse pain was described as deeper in the vagina (48.1%) or abdominal (35.0%) versus introital (14.8%). Harrop Griffiths et al. (67) compared the sexual dysfunction frequency of women with chronic pelvic pain (n = 25) and infertility controls (n = 30). They found that 52% of the women had dyspareunia (versus 6.7% of controls), 28% reported inhibited sexual desire (versus 6.7%), 16% reported inhibited orgasm (versus 3.3%), and 28% reported inhibited sexual excitement (versus 16.7%).

A Dutch study (90) investigated the psychological and sexual problems of women with vulvar vestibulitis and found problems with genital pain, lubrication, sexual arousal, and negative emotional interaction with their partner during sex. Interestingly, this study found a significant decrease in the frequency of sexual problems and distress during masturbation. The research found no difference regarding orgasm when with their partner or during masturbation. Nunns and Mandal (92) found very similar results during an investigation of 30 patients with vulvar vestibulitis and age-matched non–chronic pelvic pain controls. These authors found no difference regarding desire, frequency, or orgasm but did find a decrease in lubrication and arousal, in addition to increased negative feelings about making love with their partner. Webster and Brennan (93) found that 58% of patients with interstitial cystitis reported a lack of sexual interest, whereas 48.6% suffered dyspareunia and 68.1% experienced postcoital pain.

The inevitable pelvic changes associated with the aging process can cause sexual problems and result in episodic or chronic pain (94). The menopausal woman, for example, may report vaginal pain caused by vaginal barrel foreshortening and decreased or delayed vaginal expansion. Vaginal lubrication can be significantly delayed or eliminated by vaginal wall thinning, resulting in introital and vaginal barrel discomfort. Menopausal women also report occasional painful uterine spasms with orgasm. They may also report postsexual pain that is described as feeling “bruised” or “sore,” caused by the significant loss of fatty padding in the labia and mons pubis due to hormone changes. The menopausal female may also report a variant of “honeymoon cystitis”–associated intercourse. The changes in the vaginal barrel with menopause allow more direct insult to the urethral passage during intercourse and consequently can cause episodic or persistent postsexual urinary symptoms. It is very important for the practitioner to take seriously any sexual pain concerns reported by aging and menopausal women.

Chronic sexual problems can have a deleterious effect on the relationships of women with chronic pelvic pain. Many couples draw on sexual interaction as their primary, if not sole, means of experiencing or expressing love and closeness. Disruption of this process can be devastating for women with pelvic pain, who are often pressured to be sexual, independent of their pain intensity. Partners often become more irritable, distant, and accusatory, especially when multiple physicians and treatment do not increase the sexual frequency. They may begin to accuse the patient of faking pelvic pain to avoid their “duties,” especially sex. These relationships often become hostile environments that further diminish the libido and sexual function for these patients. Furthermore, they frequently report feeling further ostracized from family and friends due to the social and physical limitations associated with their pain, coupled with the absence of a visual or diagnosable illness or “defect.”

In contrast to our experience, Fry et al. (69) found no difference in relationship satisfaction between chronic pelvic pain couples and controls, even though chronic pelvic pain couples reported increased sexual problems. In fact, a sexual dysfunction clinic couple control group reported significantly more relationship problems than chronic pelvic pain couples, even though both reported similar sexual problems. Low et al. (86) also found marital satisfaction in 81 patients before receiving an exploratory laparoscopy, independent of laparoscopy diagnosis.

Considering the PTSD model, sexual dysfunctions in the patient with chronic pelvic pain may have a self-protective component. Avoidance of sexual activity may help these women manage the possibly conscious or preconscious memories of sexual abuse or trauma. Some of these women have developed a strong fear of “letting go” or “losing control” that they associate with sexual arousal or orgasm. They may also have significantly conflicted feelings about the pleasure associated with sexual activity in light of their possible pleasurable feelings during the abuse.

Chronic pelvic pain and the related sexual problems can also produce significant issues related to identity and femininity. Some of our patients describe decreased feelings of femininity caused by the inability to have sex. This is exacerbated if their partners no longer find them sexually attractive or do not initiate sexual activity because of changes associated with hormone therapy (e.g., hot flashes, bleeding) or surgeries (e.g., disfigurement of genitals with vulvectomy). Even very supportive, concerned partners may back away from sex out of fear of causing or exacerbating their partner's pelvic pain. Furthermore, pregnancy or infertility issues associated medical interventions for pain are often overlooked in working with these patients. When reproductive changes are permanent, as with hysterectomy, the psychological impact should be considered and discussed. Some of our younger patients have been positioned to make a choice between having a family or ameliorating (possibly) their pain.

Gynecologic pain syndromes and the consequent psychological sequelae can have a deleterious effect on psychosocial function. This section has attempted to illuminate the depth and breadth of these problems. We hope that practitioners will use this information to explore psychological problems that may be exacerbating the patient's pain or reducing medical efficacy and not to imply a psychogenic cause of their gynecologic pain. The next section presents general information regarding the psychological evaluation and treatment of women with chronic pelvic pain.

Psychological Evaluation and Treatment

This section is designed to give the nonpsychological practitioner an overview of how psychology can augment treatment efficacy for women with gynecologic pain syndromes. It is not designed to be a comprehensive presentation of all psychological modalities available. We have attempted to present psychological information that directly applies to the patient with chronic pelvic pain and how problems unique to this group of patients can be addressed with psychological evaluation and intervention. Readers are directed to Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92, Chapter 93 and Chapter 94 for more detailed information on psychological testing and treatment options for patients in pain. A more comprehensive presentation of evaluation and treatment procedures for gynecologic pain patients can be found in Elliott (62).

Evaluation

In our experience, treatment plans for patients with chronic pelvic pain rarely involve psychological intervention until all medical diagnostic or intervention options have been exhausted. Consequently, the patient is often transferred (“dumped”) to a psychologist or psychiatrist to treat the problem that is “all in her head.” There is often limited or ineffective communication between the mental health professional, physician, and patient. This causes many of these patients to ignore psychological help and pursue medical treatment from a new physician with a new specialty that can “help” her with her pain. Because of this process, psychology is usually a last resort and attended begrudgingly and sometimes belligerently.

The psychological evaluation of a patient with chronic pelvic pain is critical for the development of an effective treatment plan. Evaluation options are obviously related to the resources available. Some clinics do not have the luxury of a mental health professional or psychometric testing. The increase in health maintenance organization and capitated health care has also tragically decreased reimbursement and thus decreased availability of psychological evaluation and treatment. It is highly recommended that solo medical practitioners find a mental health colleague in the community to involve in the treatment whenever possible. It is most helpful when this collaboration is implemented from the onset of treatment, if not from the onset of the diagnostic process, and not after all other options are depleted.

Initial Consultation. In our clinic, after review of available records, a psychological consult or interview is implemented to collect information about psychological status and coping mechanisms. The patient's fear that the problem is “all in her head” should also be addressed and reassured immediately. Most patients with chronic pelvic pain are very relieved to hear this explanation of our work-up strategy. We then proceed to explain what they can expect during their first visit. Questions and concerns regarding psychological or medical procedures are addressed. We then review the development and characteristics of their pain. It is important to understand the activities or situations that make the pelvic pain worse and under what conditions the pain is better. Previous intervention attempts (i.e., surgical, pharmacologic, and psychological) and the patient's psychological experience with them are also reviewed. Psychosocial, relationship and sexual problems and stressors are discussed, as well as current coping skills and resources. Special awareness is directed to evidence of intense somatic focus and history of physical, sexual, or environmental abuse. Normalization of the psychosocial sequelae associated with chronic pelvic pain is important during this first meeting. Every patient also receives a brief didactic regarding the psychophysiology of emotions such as stress, depression, and anger and the impact on nerves and muscles. The vicious circle involving stress and emotions, muscle tension, and nerve changes is illuminated.

When a psychologist is not on staff and a referral for evaluation or treatment is recommended, the physician must be sensitive to the patient's likely perception of being dumped or seen as having pain caused by psychopathology. The physician needs to take time to quell the patient's fears and explain the psychophysiology of stress as mentioned previously. The physician can greatly enhance this interdisciplinary referral process by providing confident remarks about other patients sent to this psychologist and about how referrals are common.

In our clinic, the information provided during this initial consult is then presented in a team meeting with the physician. Special circumstances are outlined. This might include fear of the pelvic examination due to previous negative or punitive experiences or a phobia regarding needles. This may also include the need to additionally educate an unsupportive or sexually pressuring partner.

The process of listening to and talking with chronic pelvic pain patients is a critical part of treatment. Unfortunately, Grace (95) found in a New Zealand population of patients that a significant portion of these women did not think that their doctor “really understood their concerns,” and they frequently left their practitioner's office without discussing important aspects of the disorder. In fact, only 52% of women being seen by a general practitioner and 62% being seen by a gynecologist felt that their diagnosis was adequately explained. Furthermore, 58% of these women did not feel that their physician took their pain symptoms seriously and they felt that their general practitioner (43%) and gynecologist (24%) presented that nothing was wrong with them. General practitioners (25%) and gynecologists (12%) were perceived to present that the patient's pain was a result of psychopathology. Lastly, 67% of the women reported that they felt their physician expected them to simply put up with their pain.

It is critical that the patient with chronic pelvic pain receive a psychological evaluation with psychometric testing when any of the following are observed: (a) The patient has been referred using narcotics for nonmalignant pain or is being considered for long-term use of opioids; (b) the patient is being considered for an invasive procedure (e.g., implantable epidural pump, spinal cord stimulator); (c) there is a history of medical or pharmacologic noncompliance; (d) there is a history of physical or sexual abuse or trauma; and (e) pain disability seems greatly disproportionate to pathology or there is “excessive pain behavior.”

Evaluation and Diagnostic Tools. The psychometric tools available to evaluate patients with pain are numerous. Each clinical setting has different needs, resources, and psychological expertise in working with chronic pelvic pain patients. Clinicians new to the treatment of this type of pain may consider a more comprehensive evaluation process until more familiarity is achieved. Psychological testing options are not reviewed because evaluation tools are similar to other pain conditions and are presented in Chapter 16. For additional reviews see Turner and Romano (96) and Steege et al. (97). Our clinic uses psychological testing sparingly. We most frequently administer the MMPI-2, a common tool used in the evaluation of pain patients and more recently described for patients with chronic pelvic pain (97,98 and 99).

A special note about the MMPI is especially warranted when interpreting the profiles of patients with chronic pelvic pain. It is common for the pelvic pain patients in our clinic to have significant elevation on scales 1 (hypochondriasis) and 3 (hysteria) and less elevation on scale 2 (depression) (99). This is commonly described as the “conversion V” and sometimes interpreted in reports as evidence of a “conversion reaction.” We recommend against using this specific interpretation or diagnosis without substantial collaborating medical evidence. Remember that these patients are already very sensitive to a psychogenic diagnosis. This configuration in our experience is rarely (if ever) consistent with a hysterical or conversion pain disorder. We believe that this configuration represents hypersensitivity to body function and pain and tendency to overinterpret or misinterpret even benign symptoms. We often use the fairy tale of the “Princess and the Pea” to describe the phenomenon of somatization to the patient.

Another reason for a psychological consultation and testing is to facilitate pharmacologic treatment planning with both analgesic and psychotropic medications. Psychological profiles can help differentiate effective medications or regimens by delineating specific pain and psychological symptoms. For example, we often use a selective serotonin reuptake inhibitor (e.g., sertraline) when there is a combination of dysphoria, irritability, and rumination symptoms. The use of a minimally euphoric analgesic (e.g., methadone) is warranted when there is a history of noncompliance or when there is significant psychological turmoil. Interviews and psychometric testing can also help measure the efficacy of pharmacologic trials with interviews and routine testing (e.g., Beck Depression Inventory).

Treatment Approaches

Pelvic pain research has shown that an integrated interdisciplinary or multidisciplinary approach can significantly enhance pain reduction and recovery. As early as 1977, Beard et al. (100) recognized the importance of an interdisciplinary approach for successful treatment of chronic pelvic pain. He found that for patients with a negative laparoscopy, 11 of 18 showed marked improvement or were pain free with a combination of reassurance or therapy. Later, Beard et al. (101) reported that women (sample size not given) receiving “stress analysis” or “pain analysis” therapies were significantly improved at the end of treatment compared with a minimal intervention control group. Interestingly, at a 3-month follow-up, differences were not maintained, but at 6 months, improvement differences over controls returned.

Kames et al. (64) studied 16 patients who were inappropriate for standard gynecologic methods or who had not been successfully treated with these procedures. Patients received an extensive medical and psychological evaluation. The latter included a broad range of psychometric testing. All patients received psychological therapy once per week that included stress management, self-control procedures (e.g., relaxation and hypnosis), anxiety and depression control, activity management, sex education, and cognitive behavioral therapy. The treatment was reported to be structured but not uniform. The initial phase of psychological treatment involved pain management skills, relaxation tools, and increased awareness of pain or stress triggers. The middle phase focused on goal setting and involvement in appropriate activities, reduction of negative thoughts, and a discussion of sexual concerns common to pelvic pain. The latter sessions involved intervention strategies for individual issues. It is important to note that 50% also received tricyclic antidepressants. This 6- to 8-week program resulted in 67% reporting pain improvement at the end of treatment and 65% at 6-month follow-up. Social activity and sexual activity were reported improved by 44% and 27%, respectively, at the end of treatment and 65% and 79%, respectively, at the 6-month follow-up. At the 6-month follow-up, 92% reported that they were improved and that they were satisfied or highly satisfied with the treatment program.

Peters et al. (70) randomly assigned 106 patients with chronic pelvic pain to one of two treatment groups. In the first group, psychological intervention was implemented only after organic etiology was ruled out via laparoscopy. In the second “integrated” treatment group, medical, psychological, dietary, environmental, and physiotherapy interventions were given equal attention from the onset of treatment. It was reported that 75% of the second group received “psychosocial” treatment,

but no description is given for the therapy modality used. At a 1-year follow-up, the integrated approach provided significant improvement in pain experience, daily activity, and “associated symptoms” compared with the “standard” approach.

Psychological treatment modalities should be chosen based on the individual needs of the patient, which can vary dramatically among patients. Our clinic uses an integrated hierarchical psychological approach. This involves starting with the most basic interventions (i.e., behavior therapy and psychophysiologic interventions) and moving to the next level (i.e., cognitive therapy) only if the previous level intervention attempts were consistently insufficient to manage the pain or psychological issue. Some patients with chronic pelvic pain eventually need intensive psychodynamic therapy to help resolve problems and issues impeding pain treatment efficacy. It is our experience that the most effective treatment approach is a combination of education and didactics and specific structured homework assignments. Patients are often more motivated, compliant participants in treatment when they understand the theory and concepts behind medical and psychological intervention (e.g., nerve, muscle, and emotional interaction). Furthermore, homework is both diagnostic and therapeutic. The homework brings to the surface problem areas along with teaching more adaptive skills. Some authors (98) advocate the use of a 10-session method. This program involves a systematic use of cognitive behavioral therapy, sex therapy, and relaxation training and self-hypnosis techniques. Readers are directed to this helpful article.

Behavioral Therapy. There are numerous articles and books written on the topic of behavioral therapy for pain (102,103), and for more detailed presentations see Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92, Chapter 93 and Chapter 94. There are no known articles recommending interventions specifically designed for chronic pelvic pain. A few areas of note include the use of an activity diary to facilitate a structured behavioral plan to increasingly incorporate realistic activities of daily living as medical treatment unfolds. Many of our patients with chronic pelvic pain feel guilty that they cannot pursue employment and domestic “duties.” They often describe a pattern wherein they have reduced pain and then attempt to “catch up.” They overcompensate and consequently end up being unable to function for the next 1 to 3 days, which causes them to get behind again and perpetuate this pattern. It is very common for patients to underestimate the extent to which abdominal and pelvic muscles are used in even the most basic activities of daily living. Women are often surprised that “limited” activities, such as pushing the vacuum, can reignite their pain. Therefore, we, like other pain clinicians, implement an hourly activity log. This log gives important information for treatment planning and developing more realistic goals between undercompensating when in pain and overcompensating when feeling better. Some form of activity is encouraged to ward off atrophy and to increase endorphin levels. Patients with chronic pelvic pain frequently need a moderated and guided return, both in the case of superstitiously decreased activity caused by the pain and when there is compensatory increased activity due to guilt. The diary helps as a reminder of the maximum or minimum hourly levels set in the therapy session. Behavioral therapy can also help family members develop reinforcement patterns that decrease pain behaviors or secondary gain behaviors. This could be in the form of problem solving and then executing brief but increasing social visits from friends, or it could be in the form of designing trips to locations with easily accessible rest rooms along the way.

We also implement the use of a feeling/stress and pain log. Patients are asked to record her pain and three to five different emotions on a 0 to 5 scale twice daily. The various emotions chosen are individually determined (e.g., irritability, stress, loneliness, rumination, anxiety). This tool is very helpful because many of our patients are extensively focused on somatic sensations and pain and do not see correlations with affective states. Psychophysiology concepts and their usefulness are often reinforced by diary correlation. The chronic pelvic pain patient must be informed that the correlation between emotions and pain is not contiguous and may take 24 to 48 hours to manifest as increased tension and then increased pain.

Psychophysiologic Interventions. The use of progressive relaxation training (PRT), guided imagery, self-hypnosis, breathing exercises, biofeedback techniques, and so forth is well known for treating patients with pain (104). We use combinations of each. Patients are given a handout of scripts for PRT, guided imagery, and breathing exercises and/or a prerecorded audio tape of a staff member reading different scripts. These techniques are especially helpful for patients who are terrified of the pelvic examination or phobic of receiving vulvar or vaginal trigger point injections. We saw a woman who would gag and then vomit at the sight of the needle. Her condition was diagnosed as postsurgical ilioinguinal neuroma and would best respond to local anesthetic injections. We spent a number of sessions teaching this patient breathing exercises and PRT, after which she was able to manage her phobic reaction to the needle and receive the necessary medical treatment. We are using psychophysiologic techniques to help patients when abdominal and pelvic muscle tension increases their pain. Biofeedback is especially helpful when patients have significant problems with somatization. This technique does not cause patients to “stop thinking” about their body but gets them to think differently. Biofeedback and PRT can also be very helpful when provided in conjunction with local anesthetic trigger point injections for mutual enhancement of muscle tension reduction. Furthermore, these techniques can also “force” the patient to take time out during the day and rest. Many of our patients do not give themselves permission for down time that is not “productive.”

Cognitive-Behavioral Therapy. Resources for developing cognitive-behavioral techniques with pain patients are numerous (105,106 and 107), but none has been applied specifically to pelvic pain. These techniques are designed, for example, to teach patients skills that help them more adaptively manage beliefs, thoughts, feelings, and stress that mutually exacerbate their experience of pain (see Chapter 89, Chapter 90, Chapter 91, Chapter 92, Chapter 93 and Chapter 94). Homework is a critical component of cognitive-behavioral approaches. The homework is both diagnostic and therapeutic. The response to homework can give important information regarding personality styles, defenses, and limits of coping skills while at the same time providing more adaptive alternatives.

Many patients with chronic pelvic pain describe a spectrum of negative, pessimistic beliefs that often lead to catastrophizing. This problem is exacerbated by the tendency for these patients to also ruminate. Research suggests that these beliefs are nonadaptive and increase pain (85). Nevertheless, the beliefs need to be initially discussed as understandable, considering the patients' frustrating, disappointing experience during the pursuit of treatment. The patient with chronic pelvic pain needs information regarding the impact of these beliefs on exacerbating her pain and reducing the efficacy of treatment. The specific techniques will not be addressed here; readers are directed to Elliott (62). We also need to discuss realistic “data” with the patient and help her develop a more adaptive data collection system. Our younger patients with chronic pelvic pain are a good example. They develop strong pessimistic beliefs about pregnancy after one physician recommends a hysterectomy. This often leads to depression. It is critical that we discuss the patient's belief system and what “data” she is using to create this assumption. We may need to facilitate a second opinion or correct entrenched misconceptions. Hysterectomy is not always the only option to alleviate pelvic pain.

Patients with chronic pelvic pain have been shown to present with a vast array of psychological or emotional states. These patients often develop symptoms characteristic of learned helplessness (the perceived or real inability to affect or terminate noxious stimuli), which include dysphoria, anhedonia, pessimism, and irritability. Patients need techniques to help them manage, not “control,” their feeling responses to the pelvic pain and to ineffective treatment approaches. Management of feeling techniques can help the patient act as less of a victim to their feelings and to develop a greater sense of self-efficacy. This in turn creates psychological and physiologic changes that can enhance treatment and positively affect the pain experience.

A special note is important regarding management of the hostility common to patients with chronic pelvic pain (69,81). We attempt to teach patients that anger is not a primary emotion and to look for and manage the common antecedents of disappointment, embarrassment, sadness, and so forth. For example, a patient with vulvar vestibulitis came to be very hostile and belligerent. Within a few weeks, staff members were offended by her behavior and refused to work with her. The history revealed a similar pattern in other clinics. We confronted the patient and her husband with this behavior and slowly began to help her see the sadness and emotional pain that caused this “barbed wire defense.”

Treatment should help patients increase awareness of dysfunctional patterns, develop pattern-specific problem solving, and then practice or rehearse the “antidote” plan(s). For example, we saw a patient with chronic pelvic pain and endometriosis who was able to connect the visit of her intrusive mother-in-law with a significant increase in her pain. She described increasing tension in her abdomen and consequent pain as the visit approached. Escalation of pain was common during these visits. We were able to dissect both her belief system and previous lack of coping skill options. We helped her develop a series of “if-then” options. She created “signals” to be used with her husband that indicated different parts of the plan. For instance, if she rubbed her nose, she and her husband were to convene in the kitchen and discuss how to manage her increasing frustration and stress. The patient was then able to rehearse and role-play these signals and other coping mechanisms with a female staff member. The increased sense of self-efficacy and closeness in the marriage was able to ward off the usual negative, pain-escalating effects of the mother-in-law's visit.

Psychodynamic Therapy. The use of psychodynamic techniques for the treatment of pain disorders (108) has been controversial at best. However, with the continued awareness of childhood trauma and neglect in the history of pelvic pain patients, a more psychodynamic approach may become necessary for some patients (see Chapter 93).

A comprehensive psychodynamic history can help with treatment planning for the patient who has not responded to common medical treatments or basic psychological interventions. Traumas, for instance, need to be discussed in a supportive, open environment and not easily mistaken for “false memories.” The historical information can help the therapist and patient make important connections with present defenses or maladaptive behaviors that exacerbate pelvic pain or make intervention ineffective. The psychologist helps the patient see that the past traumas can be triggered by events in the present and consequently affect her pain condition. For example, patients with sexual abuse may have strong trepidation regarding the resolution of their pelvic pain because of the fear that their husbands will try to “catch up for lost time” and treat them in an objectifying, pressuring way similar to their abuse. Therefore, they may have a reflexive contraction due to

anxiety or fear that exacerbates their pain.

A good example involves a patient with lower left quadrant pain and severe dyspareunia who was finally referred to our clinic because a number of gynecologists and a neurologist had not been successful in ameliorating her pain. She had received numerous diagnostic, pharmacologic, and surgical trials. Our team diagnosed her with iliohypogastric neuropathy of unknown etiology and myofascial trigger points exacerbated by a stressful job and poor coping skills. The patient was an active and motivated participant in our program but she did not respond to medical treatments with any continuity; decreasing her overwhelming “work stress” with classic cognitive- behavioral techniques did not help. During a secondary, more intensive history, the patient revealed sexual abuse by her father. The patient did not tell us initially because she was afraid we would diagnose her pain as “all in her head,” as she was told by her last physician. Further discussion revealed that most of the “job stress” was a new boss who looked like her father and who had a similar personality. With this disclosure, the patient was able to observe her abdominal/pelvic “clenching” response every time her boss communicated with her. Luckily, the patient was able to change her job within her company. This change did not cure her pain condition, but it allowed our treatments to be more effective and reduce her pain over a normal, more typical course.

Group Therapy. Group therapy has proved to be a productive, cost-effective modality for pain patients (108). Groups for patients with chronic pelvic pain can be peer-led or facilitated by a professional. These patients can truly benefit from the understanding and discussion of other patients suffering from the same problems and treatment experiences. It is important to note, however, that clinicians should be prepared and available to address the collective questions and frustration, and sometimes hostility, developed during a peer group meeting.

Couples Therapy. The relationship problems (e.g., animosity, abandonment, hurt feelings, limited communication) that develop often require a structured set of skills that facilitate relationship reacquaintance (62). We use a converted version of the skills described under the cognitive-behavioral section to help couples manage accumulated negative feelings and to increase communication efficacy. Of special note is the couple conference. Partners of patients with chronic pelvic pain often need information from a professional that explains the physical, sexual, and psychological aspects of this type of pain. This meeting can sometimes reduce the perpetual distrust, anger, and distance caused by the absence of a specific diagnosis and the prior ineffectiveness of numerous intervention attempts.

Sex Therapy. Sexual problems have been shown to be quite common for women with chronic pelvic pain and consequently can be devastating to their self-esteem and relationship satisfaction. Many of the sexual problems experienced by women with chronic pelvic pain can be successfully treated with sex therapy techniques (62,64). In fact, the treatment of vaginismus (see below) has a 100% success rate when the woman is willing to complete the program. Organic dyspareunia (e.g., that resulting from labial burns secondary to radiation therapy for cancer), on the other hand, can be an exception. Nevertheless, even this problem can be greatly helped by sex therapy using creative problem solving that incorporates the realistic physical limitations and expands the sexual repertoire. It is important that the woman and her partner be given hope and a good referral.

Many psychogenic sexual dysfunctions and disorders have been attributed to an increase in performance anxiety and spectatoring among healthy individuals (109). An increase in maladaptive cognitions (e.g., “Is this going to hurt again?” “Is my partner going to get mad or disappointed?” “Am I ever going to have an orgasm again?”) regarding the capacity for sexual involvement or response is quite disruptive. The woman with chronic pelvic pain also looks for cues and responses that can provide a status report comparing current responses with premorbid responses. Limited information regarding common and normal sexual sequelae associated with this disorder can also confuse, if not thwart, her attempts to cope with these sexual changes. Furthermore, an increase in sensitivity to her partner's reactions and responses is common but exacerbates expectations and increases performance fears. The cumulative result is a significant increase in distractions from bodily sensations and decreased physiologic capacity to respond. Performance vigilance escalates and results in diminished sexual interaction with her partner. Women with chronic pelvic pain may begin to feel a “duty” to provide their partners with sexual interaction independent of their own sexual interest or consequence of increased pelvic pain. It is common for these women to be present in “body only.” During sexual activity done out of “duty,” thoughts are often nonsexual, such as making a shopping list or reviewing work projects, or countersexual, such as thinking about negative aspects of the partner or monitoring body changes. Therefore, women with pelvic pain may pass the time with distracting thoughts until the partner can “get it over with.”

The treatment process must encourage an exploration of “what is available” versus what is missing or unavailable. The realistic limitations provide direction for creative problem solving. Women with chronic pelvic pain (and their partners) may need to redefine their views of sexuality. This may include greater exploration of unaffected body parts. For example, many couples (especially men) use intercourse as a primary source of expressing love in the relationship. The clinician, through the sex therapy, can help the couple expand their sensual and sexual repertoire while broadening their resources for expressing love (e.g., communication skills).

Masters and Johnson (108) described sensate focus as a strategy to decrease performance anxiety and spectatoring. Sensate focus is most effective when prescribed as touching for one's own interest. This means that the patient is to touch her partner (self) in ways that are interesting to the patient. The patient is encouraged to focus on the sensations of temperature, texture, and pressure. Concerns of doing it “right” or for the other person are discouraged. Pleasuring the partner (self), let alone trying to create arousal, is not the goal. However, over time, there is a progression from interest to pleasure to arousal. Lastly, valuable diagnostic information is gleaned from the couple's reactions and difficulties in completing the sensate focus assignments. This information can then be incorporated into developing specialized intervention before proceeding to the next level of sensate focus.

A sex therapy treatment program includes the presentation of pertinent information. This includes the rationale for prescribing the different sexuality exercises. The woman with chronic pelvic pain is also presented with comprehensive information about female sexual anatomy and physiology. In fact, the clinician must be available to discuss any aspect of sexuality that the patient needs to address.

Sensate focus was originally designed for work with couples; however, it can also be very effective for working with women alone. Sexual therapy for women with pelvic pain typically begins with solo assignments in the shower—at first not including breasts and genitals and then including them. With increased focus capacity and comfort, exercises move to the bedroom, where self-examination of her genitals is prescribed. Many women do not have information about the location and sensation of specific parts of their genitals. This continues with a series of self-touching assignments that gradually move toward exploration of maximizing pleasurable sensations without performance pressures. The woman with chronic pelvic pain may need to exert more (or less) direct pressure and experiment with different rates of stimulation (e.g., fast, slow) to determine what types of stimulation are pleasurable and what types result in increased pain. For instance, a vibrator may be included if the patient has decreased capacity for genital sensations due to medical treatments or fear/spectatoring. The woman also continues to refocus from intrusive thoughts that include performance distractions or negative cognitions about her body. Lastly, Kegel exercises are typically assigned to facilitate pubococcygeus muscle tone and, more important, to increase genital awareness and psychological comfort.

Lack of sexual desire is a very common problem of a woman with chronic pelvic pain. It is important to note that this problem is rarely caused by physical or organic etiology, with the exception of pharmacology-induced castration. These problems are almost always a result of fear of pain, psychosocial distress, or conflict in the relationship. It is often the case that decreased libido is a protective measure and should be addressed in an open and supportive way. It is critical to educate partners on how pressure and even supportive attempts to get her “in the mood” are not helpful or effective and cause her to become even more sexually withdrawn. Sex therapy techniques can be very helpful in creating a more conducive environment for the woman to experience and act on her sexual feelings. Fatigue, a common factor in desire changes, needs special problem-solving attention. There is a tendency for women with chronic pelvic pain to feel too tired to “waste” energy on sexuality. Therefore, time management suggestions may be helpful, such as taking a nap before a sexual encounter or dividing more evenly the various household tasks. The touching homework assignments can be redesigned to involve limited physical effort but still provide an opportunity for sensual and sexual expression for the couple.

Treatment exercises for couples (108) provide a structured, boundary-inclusive environment. Neither partner is left with the task of attempting to figure out the intention or lack of intention of the other. This tends to greatly reduce the anxiety and fear associated with a return to sexual expression common to women with chronic pelvic pain. It also decreases the pressure felt by both partners to quickly return to pre-pain patterns of sexual interaction. In addition, we always pace the assignments using the woman's progress and comfort as our guide. This offers her a sense of empowerment and safety concerning her body and sexuality.

A common secondary problem for women with chronic pelvic pain—vaginismus, defined as the involuntary, reflexive spasm of the pubococcygeus muscle resulting from real or perceived threats of penetration—deserves a special treatment note (61,62,109). Treatment of vaginismus typically requires the use of progressive dilators. We use a box of Young's adult dilators starting with the smallest (1½). Pediatric dilators for women with vaginismus are rarely needed. The patient is first taught to redefine her description from “pain” to other words such as “stretching,” “pinching,” “stinging,” “burning,” and so forth. She is also instructed to do Kegel exercises two to three times per day. The first dilator is inserted with the help of an artificial lubricant twice per day for 15 minutes. Over the next days to weeks, she progresses from 30 minutes, to 1 hour, to 2 hours, and finally she sleeps overnight with the dilator. After the second overnight insertion she moves on to the second dilator and repeats the same process. Each subsequent dilator follows exactly the same pattern. When the final dilator is started (usually #4), a decision is made whether the partner will come into treatment to help the transition from the dilator to the penis. In approximately 50% of our cases the partner becomes involved in

specific exercises to help with intercourse.

CONCLUSION

Careful attention to both psychological and medical factors in the woman with chronic pelvic pain can lead to significant improvements in function as well as relief of pain. Very few resources for pelvic pain diagnosis and treatment exist at the present time. This type of pain is common and leads to suffering for patients and their partners. They deserve a higher standard of care than exists in most communities today.

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CHAPTER 73

Pelvic and Perineal Pain of Urologic Origin

John S. McDonald and Kenneth M. Alo'

The pain that arises from the female urinary tract and from male urogenital organs is discussed in this chapter. In addition, problems in adjacent structures located within the bony pelvis are also presented. Nearly 75% of patients seeking treatment for urinary symptoms suffer primarily or secondarily from infection (1). There is a tenfold difference between female and male infection rates: 3% of all women have positive urine cultures, while less than 0.3% of men have positive cultures. Approximately half of men with positive cultures have underlying urinary tract pathology (2,3).

Painful conditions in the pelvis and perineum can occur as a result of infection or distension of the bladder or perineum. Expanding neoplasms or extravasation of urine or seminal products into adjoining tissues can elicit severe pain. In the man, for example, extravasation of seminal fluid after vasectomy can produce disabling lancinating localized pain. Some patients undergoing transurethral surgery who are anesthetized below the ninth thoracic nerve dermatome by subarachnoid block can still experience severe pain due to extravasation of fluid into perivesical structures. This fact should serve as a useful admonition to the anesthesiologist and surgeon of the presence of extravasation and their need to consider early termination of the procedure to prevent the occurrence of the transurethral resection syndrome of fluid overload and hyponatremia (4). Such pain is presumably mediated through the somatic nerves supplying the parietal peritoneum over the dome of the bladder and perhaps through the afferent sympathetic nerves that enter the spinal cord far above the tenth thoracic segment. Unfortunately, some of the gravest chronic urinary tract diseases, such as massive dilation due to prolonged obstruction or advanced tuberculosis, may be accompanied by very little urologic pain, possibly because the nerves mediating painful sensations have been altered or destroyed by the disease process.

The first part of this chapter includes a discussion of the innervation of the pelvic urologic organs and male genitalia and some general comments about the pathology and symptoms of pain related to disorders of these structures. The second part of the chapter includes discussion on important aspects of female urologic disease processes. In addition, we discuss the pathophysiology, symptoms and signs, diagnosis, and treatment of certain painful states of the bladder and urethra in both men and women and of the prostate, seminal vesicles, epididymis and funiculus, testicle and appendages, and penis in the man. No attempt is made to provide a complete catalogue of diseases of the male and female urinary system and male generative tract; nevertheless, we include diverse pathologic states and problems likely to confront a pain management physician.

BASIC CONSIDERATIONS

Anatomic and Physiologic Aspects

Innervation of the Bladder and Urethra

Figure 73-1 depicts the nerve supply to the bladder, prostate, seminal vesicles, testicles, and penis, which constitutes a complex network involving many nerve pathways. The following discussion was originally written by John Bonica (5). It is based on descriptions that he summarized by Kuntz (6), Mitchell (7), Netter (8), and Ruch (9) and is a complete review of the study of the nerve supply to the pelvis.

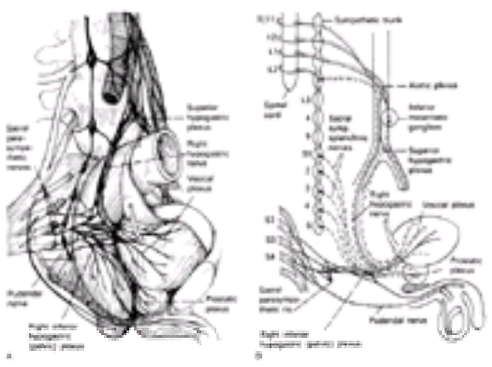

Figure 73-1. **A:** Nerve supply of the urinary bladder and prostate showing the relationship of the various nerve structures to the large intestine and their distribution in the bladder and prostate. **B:** Schematic illustration showing the segmental nerve supply to the bladder, penis, and scrotum. (*Solid lines*, preganglionic fibers; *dashed lines*, postganglionic fibers; *dotted lines*, sensory fibers.)

Bladder

Sympathetic Nerves. The peripheral sympathetic fibers to the bladder originate in the anterolateral cell column of the spinal cord segments at T-12, L-1, and L-2 and sometimes T-11 (see Fig. 73-1B). They then pass sequentially through the anterior roots, the formed nerves, the white rami communicantes, the lowest thoracic and upper two lumbar paravertebral sympathetic ganglia, and thence either through the lower thoracic and upper two lumbar splanchnic nerves to the aortic plexus or caudal to the sacral sympathetic trunk. Those fibers that pass to the aortic plexus proceed caudally to the superior hypogastric plexus, the left and right hypogastric nerves, and the inferior hypogastric (pelvic) plexus to end in the vesical plexus. Some preganglionic fibers synapse in the inferior mesenteric ganglion and some in the superior hypogastric plexus, but the majority synapse in the extrinsic or intrinsic vesical plexuses. Those that pass to the sacral sympathetic trunk synapse therein with postganglionic fibers that proceed through the sacral sympathetic splanchnic nerves to also join the inferior hypogastric plexus.

Parasympathetic Nerves. The preganglionic parasympathetic neurons have their cell bodies in the second, third, and fourth sacral spinal cord segments. Their axons pass through the right and left pelvic splanchnic nerves, known also as *nervi erigentes*, to end in the extrinsic and intrinsic vesical plexus, where they synapse with short postganglionic fibers.

Afferent Nerves. Afferent sensory nerves accompany both the sympathetic and parasympathetic efferent pathways. Many parasympathetic afferent fibers pass to the spinal cord via the ventral roots, and the rest pass through the usual course via the dorsal roots. In addition, the pudendal nerve supplies afferent fibers to the external and internal vesical sphincters and adjacent parts of the bladder. The peritoneum of the dome of the bladder is supplied by afferent fibers of T-11 to L-1

spinal nerves.

Intrinsic Nerves. The external vesical plexus containing sympathetic, parasympathetic, and afferent fibers penetrates the wall of the bladder to join the intrinsic plexus, which includes numerous ganglia. The intramural ganglia are most abundant in the trigone; they become less frequent as the distance from the trigone increases and are probably absent in the fundus. The larger intramural ganglia and some of the smaller ones are situated just below the serosa; other small ganglia are located between muscle bundles. These ganglia constitute relay stations between preganglionic and postganglionic fibers for both parasympathetic and sympathetic pathways. Most of the nerve fibers in the bladder wall are small and unmyelinated, although some are myelinated. Nerve endings with receptors are widely distributed in the mucosa and the submucosa; most of those in the trigone and adjacent areas are connected with afferent fibers that pass to the spinal cord with sympathetic nerves, whereas most of those farther removed from the base of the bladder are connected with afferent components of the pelvic nerves. The parasympathetic fibers supply the detrusor muscle and the sympathetic fibers supply blood vessels, the muscle of the ureters, and the crista of the urethra.

Nerve Function. Animal and human studies (7) have revealed that stimulation of the entire sympathetic supply to the bladder results in powerful contraction of the orifices of the ureters, increased tonus in the trigone and contraction of the internal sphincter, and inhibition of the detrusor muscle. On the opposite side, temporary interruption of the sympathetic supply produces relaxation of the orifices, entire trigone, and internal sphincter and some increase in detrusor muscle activity. In contrast, parasympathetic stimulation elicits contraction of the detrusor muscle and relaxation of the trigone and sphincters.

The nociceptive (pain) pathways from the bladder and urethra are composed predominantly of the afferent fibers contained in the pelvic nerves with their cell body in the dorsal root ganglion of S-2, S-3, and S-4. Numerous human studies detailed in the first edition of this book (5) demonstrated that following resection of the superior hypogastric plexus, there is no diminution of pain caused by distension of the bladder or application of tactile, thermal, or nociceptive stimuli to the bladder mucosa. In contrast, section of the posterior roots of S-2, S-3, and S-4 or injuries of the conus medullaris or the pelvic nerves produce loss of all painful sensation. Langworthy et al. (10) reported vague sensation due to filling of the bladder in cases of paralysis or resection of the sacral nerves, but they regarded conduction of nociceptive impulses from the bladder through the superior hypogastric plexus as highly improbable. Although early clinical evidence seemed to indicate that resection of the superior hypogastric plexus produces relief of severe pain of vesical origin (11), the procedure eliminated spasm of the internal vesical sphincter and produced vasodilation.

Male Urethra. The male urethra is innervated through the prostatic and cavernous plexuses, both of which are part of the pelvic plexus and include parasympathetic, sympathetic, and afferent fibers (see Fig. 73-1). All of these have a similar course as the nerve supply to the bladder. The prostatic plexus is contiguous with the vesical plexus, lies in intimate contact with the prostate gland, and supplies fibers to the neck of the bladder, the prostate, and the prostatic urethra. The cavernous plexus, which may be regarded as an extension of the prostatic plexus along the urethra, gives off branches that communicate with branches of the pudendal nerves to supply the membranous and cavernous portion of the urethra.

Female Urethra. The female urethra is innervated through the vaginal plexus, which is derived from the pelvic plexus, and contains sympathetic, parasympathetic, and afferent fibers. The female urethra is quite short compared with the male urethra, and thus bladder exposure to bacteria and other infectious agents are more a problem for the female compared with the male urethra.

Innervation of the Male Genitalia

Figure 73-2 shows the nerve supply to the male genitalia. The innervation of specific organs is described in following sections.

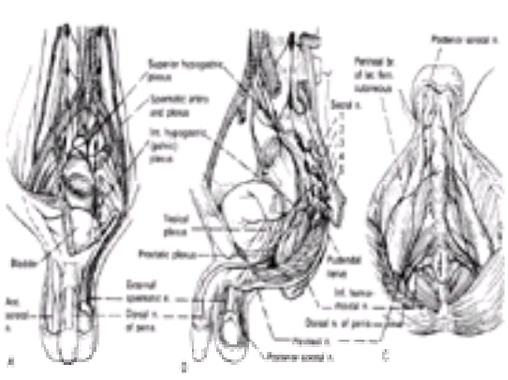

Figure 73-2. Nerve supply of the male genitalia. **A:** Anterior view. **B:** Sagittal view. **C:** Perineal view.

Testis and Spermatic Cord. The testis and the contents of the spermatic cord, which includes the ductus deferens, are supplied by branches of the spermatic plexus, which is derived primarily from the aortic plexus but also from the renal and superior hypogastric plexuses. The spermatic plexus invests the spermatic artery throughout its course and includes chiefly sympathetic postganglionic and afferent fibers. Three groups of nerves contribute to the spermatic plexus: the rostral, intermediate, and caudal groups. Fibers in the rostral group are derived from the aortic and renal plexuses, extend along the spermatic artery, and terminate in the testis. Fibers of the intermediate group arise from the proximal portion of the superior hypogastric plexus, reach and enter the internal inguinal ring to course along the spermatic cord, and finally terminate by supplying the epididymis and the proximal portion of the vas deferens. Fibers in the caudal group are derived in part from a neural complex around the distal portion of the ureter and in part from fibers of the vesical plexus; they supply the distal portion of the vas deferens and epididymis and the seminal vesicles.

The nerves derived from the spermatic plexus are predominantly sympathetic and afferent fibers and transmit nociceptive impulses, whereas those that are derived from the vesical plexus contain parasympathetic fibers and contribute importantly to the supply of the vas deferens and also of the seminal vesicles. Preganglionic sympathetic neurons, which convey efferent impulses to these structures, have their cell bodies in the T-10 to L-1 and sometimes L-2 segments.

Prostate. The prostate is supplied by the prostatic plexus, which is derived from the pelvic plexus and contains sympathetic, parasympathetic, and afferent sensory fibers. Most of the afferent fibers of the testes are components of the tenth thoracic spinal nerve; those that supply the epididymis reach the spinal cord at the T-11 and T-12 segments, while those that supply the vas deferens enter the spinal cord at T-10 to L-1. The course of these nerves to and from the spinal cord is similar to that described for the urinary bladder. Some of the fibers also supply the seminal vesicles and constitute an important supply to the penis.

Scrotum. The skin and subcutaneous tissue and fascia of the scrotum are supplied by (a) small branches of the ilioinguinal nerve; (b) the genital branch of the genitofemoral nerve; (c) the lateral posterior and medial posterior scrotal branches of the perineal nerve, which is a major branch of the pudendal nerve; and (d) the inferior pudendal branch of the posterior femoral cutaneous nerve.

Penis. The sensory nerves of the glans and the skin covering the penis are contributed primarily by branches of the left and right dorsal nerves of the penis, which in turn are branches of the pudendal nerves and consist of fibers derived from the third and fourth sacral nerves. The root of the penis also is supplied by filaments from the ilioinguinal nerves. The compressor urethrae, the ischiocavernous, and the bulbocavernous muscles, which are the voluntary muscles used in the act of ejaculation, are also innervated through branches of the pudendal nerve. The corpora are supplied by two sets of nerves, the greater and lesser cavernous nerves, which constitute the cavernous plexus and arise from the anterior part of the prostatic plexus; these are the nerves involved in penile erection. The greater cavernous nerve passes forward along the dorsum of the penis, joins the dorsal nerves of the penis, and is distributed to the corpus cavernosum of the penis; the lesser cavernous nerves perforate the fibrous covering of the penis and its root and are distributed to the corpora cavernosa and the corpus spongiosum of the urethra and the penile urethra. Vasoconstrictive fibers derived from the hypogastric plexuses join the pudendal nerves to be distributed through its branches to the blood vessels of the penis.

Physiologic Aspects

Micturition. Normal micturition is a complex, unappreciated task that is largely taken for granted until something goes awry. Micturition is part reflex and part voluntary

from a strict definition viewpoint. The reflex is generated from the middle three sacral segments where the reflex center is located in the conus medullaris of the spinal cord; anatomically this is located at the level of the first lumbar vertebral body (12). The reflex center involves afferent and efferent fibers that both send and receive impulses. These centers in turn are under cortical control, with the dual responsibility of facilitation or inhibition of voiding. Habib (13), in stimulation studies, demonstrated that the second sacral nerve played little voiding function; whereas stimulation of the third and fourth sacral nerves played major roles with detrusor contraction and concomitant decreased sphincter resistance. Stimulation of the fourth sacral nerve enhanced voiding due to a decrease in sphincter resistance. Remarkably enough, the sympathetic nerves play no role in voiding. On the other hand, the pudendal nerves, via sphincter control, allow voluntary start and stop of the urinary stream.

Ejaculation. Stimulation of the sympathetic nerves in men and boys causes expulsion of semen by musculature contraction of the seminal vesicles and expulsion of secretions from the prostatic duct due to prostatic smooth muscle contraction.

Erection. Penile erection can occur due to psychic stimulation. Such a process is made possible by transmission via parasympathetic nerves, which reach the cavernous tissue via the prostatic plexus. Although the cavernous tissue also is supplied by sympathetic fibers, these are not essential for erection. More important, sympathetic stimulation generally tends to inhibit erection by producing arteriolar constriction and thus a decrease in blood flow runoff to the cavernous tissue. Erection is characterized by dilatation of the arterioles, which coincides with inhibition of the smooth muscles in the walls of the venous sinuses and partial closure of their outlets through the small smooth channels. Afferent fibers in the pudendal nerves are also important for erection, and their severance causes loss of erection and ejaculation due to paralysis of the urethra, ischiocavernosus, and bulbocavernosus muscles.

At one time it was believed that failure of the discharge of semen after lumbar sympathectomy in men was due to the abolished upper lumbar sympathetic chain. However, Retief (14), in a study of male patients with extirpation of the sympathetic trunk from the T-9 to the L-3 segment, found that ejaculation indeed did take place, but in a retrograde fashion into the urinary bladder. The reason for this was that the internal vesical sphincter was not closed at the time of ejaculation due to the absence of impulses conducted through the sympathetic nerves. Kedia et al. (15) showed that denervation of the deferential ducts prevents peristalsis and aspermia results.

Pathophysiology and Symptoms

Referred pain is quite an important issue in reference to disorders of the genitourinary system. The bladder neck and trigone areas, for example, refer to the urethra, perineum, and glans of the penis or glans of the clitoris; however, pain of prostatic origin refers to the perineal area just behind the scrotum or to the rectum. Generally speaking, however, it is most difficult to localize or target a specific organ on the basis of subjective symptoms because of the intimate association of all the pelvic viscera and all their nerve supplies.

Pelvic pain is often relieved by warmth and sometimes increased by cold temperatures. Patients with urinary symptoms are best off staying in warm surroundings, taking hot sitz baths, and applying heat locally. Medications that increase the frequency of urination such as diuretics or increase central awareness may exacerbate symptoms referable to the urinary system. Thus, caffeine-containing foods and drinks such as coffee, tea, colas, and chocolate should be avoided because they are both central stimulants and diuretics.

Pain Related to the Bladder and Urethra

Pain related to urination is termed *dysuria* and is most often described as burning or scalding in character. It can occur at the beginning of urination, throughout urination, or at the end of urination and may persist after voiding is completed. Initial dysuria is related to lesions of the mucosa of the urethra such as in gonococcal mucositis or to denudation of perineal skin such as in herpetic ulcerations or excoriations due to intense scratching associated with pinworm infestations. When hypertonic solutions such as urine come into contact with a moist mucosal or epidermal surface stripped of its protective covering, a painful stimulus occurs. Total dysuria probably localizes the offending process to the urethra and bladder. Terminal discomfort may be caused by lesions of the bladder, urethra, or prostate. Strangury is a condition of excruciatingly painful, difficult, and slow passage of urine accompanied by spasm of the urethra and bladder. It is usually the result of severe inflammation.

Bladder Disorders. In men, pain caused by bladder disorders may be referred to the distal urethra or under the surface and glans of the penis. The latter occurs particularly when the bladder neck and prostatic urethra are the affected parts. In women, bladder lesions commonly produce referred pain in the urethra, perimeatal skin, and clitoral region.

Urinary frequency commonly accompanies other urinary symptoms and may be a symptom of infection or bladder obstruction when it occurs both at night and in the daytime. Nocturnal frequency, unaccompanied by daytime symptoms, is more likely associated with cardiac problems and nocturnal mobilization of fluid than disease of pelvic organs. Urinary urgency is an almost uncontrollable desire to urinate immediately. It is another irritative symptom due to inflammation, and approximately 10% of all individuals have a degree of bladder instability manifested as urgency (16). Adults who manifest daytime urinary frequency and urgency but do not have nocturia may be reacting to emotional or other stress.

Pain due to distension of the bladder has two components. The first is the intrinsic response to stretch and is felt suprapubically as an uncomfortable need to void. The second is due to lifting and stretching of the peritoneum overlying the bladder dome and is a more visceral and vague discomfort. This visceral sensation, mediated by the splanchnic nerves, is useful to paraplegics and others whose pudendal afferents and sacral nerve connections have been severed because they can readily learn to interpret this sensation as a need to empty the bladder. It may also contribute to the autonomic dysreflexia occasionally seen in such individuals.

Positional discomfort or pain related to activity can occur in patients with bladder calculi. The portion of the bladder with the greatest concentration of nerve endings in relation to area is the trigone. Therefore, patients with bladder stones may experience relief of irritation in the supine position when the stone rolls off the trigone onto another surface, or exacerbation of symptoms with jogging due to the stone bouncing on the trigone. Submucosal extravasation of urine through tears or cracks may be a part of the discomfort felt in interstitial cystitis (IC) and other entities. In these conditions, fixation of the normally mobile and elastic mucosal lining may occur as a result of scarring, with secondary tearing as the bladder distends and pulls the mucosa away from a point of abnormal fixation.

Urethral Disorders. The urethra has a mucosal lining and contains compound glands and ducts in the walls. Pain can occur as a result of acute inflammation secondary to infection, the presence of irritating chemicals such as bubble bath, cyclophosphamide or foreign bodies, and trauma, which may be self-inflicted or produced by iatrogenic instrumentation. Accumulation of secretions in one of the glands lining the urethra can also produce a sensation of fullness or discomfort in the perineum, vagina, or rectum, which, although rarely excruciating, can be severely annoying if it persists. Acute conditions are usually associated with terminal dysuria or even strangury and at times tenesmus. Chronic pain is referred to the perineum, urethral meatus, clitoris, or glans penis.

Pain Related to the Prostate and Seminal Vesicles

An inflamed or distended prostate may cause sensations of rectal discomfort, tenesmus, perineal pain, difficulty in voiding, decrease in stream size, frequency, and ultimately retention of urine, which is severely painful. Marked enlargement of the prostate can sometimes intrude on and compress the rectal lumen to the point of obstructing normal passage through the rectum. On the other hand, severe perineal discomfort and spasm of the levator or perineal muscles can precipitate urinary retention. This is most likely to occur in men following hemorrhoidectomy or in women after gynecologic surgery.

Disorders of the seminal vesicles can be associated with ipsilateral lower abdominal or groin pain as well as referred pain to the gonad, perineum, and penis. Significant lesions of the seminal vesicles that are unassociated with prostatic disease are extremely rare.

Pain Related to the Scrotal Contents and Penis

Infection is the most common cause of distension of the epididymis, which results in pain and tenderness. Chemical inflammation can occur as a result of retrograde flow of urine down the ejaculatory ducts. Such a scenario can occasionally occur traumatically during contact sports or when congenital or acquired obstructing urethral lesions create high proximal voiding pressures.

Pain caused by distension of the epididymis may radiate up the affected spermatic cord into the groin. Since the embryonic origin and nerve supply are almost the same as those of the kidney and renal pelvis, it should not be surprising that the pain may mimic renal colic. The physician should examine the genitalia of any patient

with flank pain and, conversely, check organs in the flank of patients with labial or scrotal pain when there is no local pathology.

Testicular pain can occur as a result of infection, typically viral, or by extension from epididymides infected with sexually transmitted diseases; in association with traumatic rupture or hematoma; and infarction from torsion. Such pain is severe and may be accompanied by nausea and vomiting. Acute congestion of the male gonadal structures as a result of sexual stimulation can also be painful. A smooth muscle contraction of the tough tunica albuginea of the testicle can produce such pain by increasing intratesticular pressure.

As indicated already, pain is frequently referred to the penis from the bladder, especially the bladder neck and trigone, urethra, prostate, and occasionally seminal vesicles. Thus, referred pain is the most common pain experienced in the genitourinary system.

PELVIC UROLOGIC DISORDERS

Diseases of the Bladder

Acute Bacterial Cystitis

Bacterial cystitis is the most common bacterial infection occurring in women, with 30% of women experiencing at least one episode of cystitis during their lifetime (17). Characteristic symptoms of urinary frequency and urgency, dysuria, and often hematuria are present with approximately 80% of cases due to antibiotic-sensitive *Escherichia coli* (18). Underlying structural problems should be ruled out if response to treatment is delayed, symptoms recur rapidly following cessation of antibiotic therapy, or if the symptoms recur three or more times per year. Minimum workup includes renal function and imaging of the urinary tract, especially if fever and pain are also present. Approximately one-third of patients presenting with cystitis have upper tract infections; therefore, a careful history to identify risk factors for subclinical pyelonephritis is important. The pain of acute cystitis lessens within hours of appropriate antibiotic therapy, with associated spasm often responding pharmacologically (phenazopyridine, Pyridium) or with direct heat (sitz baths, heating pads, or urinating in a warm tub). A differential diagnosis of acute dysuria must also include vaginitis or urethritis; therefore, a stepwise diagnostic approach, accompanied by inexpensive office laboratory testing (urinalysis, cytology, complete blood count) is necessary to begin delineating the cause.

Chronic Cystitis

Etiology. Chronic cystitis is most common in middle-aged women but may occur in anyone at any age. The differential diagnosis includes recurring acute bacteriuria with a previously unrecognized focus (e.g., infected stones), a congenital abnormality of the urinary tract, IC, female urethral syndrome, and urinary symptoms of psychosocial origin. The primary diagnostic criterion of chronic infective cystitis is persistence of detectable organisms in culture. This has commonly been accepted as colony counts of 100,000 organisms per mL of urine; however, chronic cases have been reported as clinically significant as low as 1,000 colonies per mL (19). An important criterion is the presence of white blood cells in the urine. Patients with chronic symptoms must be evaluated for anatomic lesions that could contribute to recurrences. These include vesicoureteral reflux, ureterocele, bladder diverticula, urethral diverticula, and vaginovesicular fistulas, as well as infected stones that might be seeding the bladder from the upper tract (20). If *nonpathogenic* organisms are repeatedly cultured in relatively pure growth, they should be treated (e.g., yeast, *Staphylococcus epidermidis*, a-hemolytic streptococci).

Diagnosis and Treatment. Chronic infectious cystitis symptoms are usually less severe than those of acute cystitis. Symptom levels usually vary with the degree of bacteriuria. Nocturia is common with chronic infection, with pain subsiding with antibiotic therapy. Pus may be emanating from a urethral diverticulum and should be looked for on physical examination. Treatment usually involves a loading dose of an appropriate antibiotic, which is then maintained in low dose (nitrofurantoin, 50 to 100 mg, or trimethoprim-sulfamethoxazole, 500 to 1,000 mg per day) for 6 months to years in some patients.

Noninfectious cystitis is clear of significant sediment and bacteria, is rarely nocturnal, and is often associated with depressive or psychosocial problems (e.g., IC). Other causes of depression should be sought out and treated and a multimodal approach initiated to assist with treatment (21).

Interstitial Cystitis

Diagnosis. IC is a medical enigma, the cause of which is unknown. The term IC was first coined by Skene in 1878. In 1915, Hunner described finding an “elusive” bladder ulcer in a group of patients with suprapubic pain, frequency, nocturia, and urgency that had persisted for an average of 17 years' duration. Hunner's ulcers, however, are rarely present, making this a painful bladder disease that can be challenging to diagnose and treat (22). Walsh (23) stated, “IC is a disease of extremes: extremely severe symptoms; extremes of overdiagnosis and underdiagnosis; etiologic theories varying from the abstruse to the fashionable; treatment ranging from the alpha of vitamin prescription to the omega of radical bladder substitution surgery; and sadly often, extreme confusion in medical thinking.” It characteristically presents with unremitting suprapubic pain that worsens as the bladder fills, combined with urinary urgency and frequency both day and night. There may be an associated feeling of incomplete emptying, malaise, and dyspareunia or pain after intercourse. Some patients describe a sensation of ground glass or razor blades in their bladder. Incontinence and dysuria are uncharacteristic. Oravisto's survey of the disease in Finland (24) found the disease to initially progress rapidly then stabilize at a given plateau. The presence of a marked inflammatory response, mastocytosis, and antinuclear antibodies in many patients (22,23,24,25 and 26) suggests that there may be an autoimmune component.

The initial presentation must be differentiated from bacterial cystitis and female urethral syndrome. IC patients typically describe relief during voiding, pressure or discomfort with bladder filling, frequency, urgency; have sterile urine; and are not relieved by antibiotics. Bacterial cystitis patients often describe burning with voiding or are unable to void; have frequency, urgency, and bacteria in urine; are relieved by antibiotics; and have symptoms unrelated to bladder filling (27). Patients with a recently defined urologic disorder called *female urethral syndrome* may have a variant of IC or have nontraditional cystitis infections such as *Chlamydia*. These patients complain of straining to void, urgency, frequency, hesitation, incontinence, retention, or both, and subpubic pain without a definable urologic or bladder abnormality and may have pelvic floor muscular dysfunction (22,28,29 and 30). A careful history offers some insight into these similar presentations. To make a diagnosis, IC requires endoscopy and overdistension of the bladder under regional or general anesthesia. Ordinarily, IC patients experience such pain with bladder filling that they cannot tolerate cystoscopy under local anesthesia; therefore, the bladder must be examined while only partly filled following overdistension. The typical punctate petechiae or glomerulations seen in many places in the bladder mucosa establish the diagnosis. Bladder biopsy must be taken to rule out *in situ* cancer of the bladder, which may have a similar presentation.

Long thought to be a rare disorder of postmenopausal women, IC is now known to be a relatively common malady occurring ten times more frequently in women than men and has been reported in children. Women in their 20s to 40s are most frequently afflicted, with an estimated 500,000 patients in the United States alone (22). Failure to consider IC is the most common reason the diagnosis is missed. The typical IC patient has seen five doctors and has had the disease 4 years before the correct diagnosis is made (22). IC patients are often in acute distress given the often continuous, unremitting pain that cyclically occurs as the bladder fills. This often exacts a heavy physical and psychological toll over the years. Therefore, the importance of a definitive diagnosis cannot be underestimated, as naming the culprit may begin the process of finding relief (22).

Etiology. Patients may experience symptoms, which can fluctuate between mild, moderate, and severe, and these symptoms may be constant or intermittent. Some patients may experience remission spontaneously for weeks, months, and even years. There is thought to be more than one cause for IC, which is why no single treatment works for all patients. Unlike painful bladder disorders of a specific nature (e.g., radiation cystitis, cyclophosphamide cystitis, carcinoma *in situ*), IC has an unknown etiology and variable pathogenesis and presentation. Older women typically have the *classic* form of the syndrome, with significantly reduced bladder capacity (often less than 400 mL under general anesthesia) due to detrusor fibrosis. Older men, however, despite classic symptoms, are often not even assessed for the disease. In one review, classic IC was misdiagnosed as prostatitis, benign prostatic hypertrophy, or both in a series of older men (mean age, 67.3) despite cystoscopic changes in 70% of cases (31). Younger women and occasionally young men tend to have *early* IC, with a larger bladder capacity and fewer abnormalities under cystoscopy. The presentations are not exclusive, however, and there is no evidence to suggest that one presentation evolves into another. Many causes have been proposed for IC, with several possibly contributing simultaneously. Infection, mastocytosis, defects in the bladder mucosal lining, toxic substances in the urine, vascular or lymphatic obstruction, inflammatory processes, and endocrinologic or neurogenic causes have also been suggested (22). Given these unknown variable histologic and historic concerns, treatment should be individualized and multimodal (21,22).

Treatment

Antidepressants. Antidepressants have been used widely in chronic painful conditions. Given their propensity for reducing pain, facilitating sleep, reducing dysthymia,

and known antihistaminic properties (which might combat the effects of mast cells), they have been applied widely in IC. The anticholinergic effects of these medications also increase bladder capacity and improve tone at the bladder neck (hence their use to treat incontinence and enuresis). Small doses of amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan), or nortriptyline (Pamelor) may be titrated to effect but rarely completely ameliorate the symptoms. Antidepressants are discussed in Chapter 85.

Sodium pentosan polysulfate (Elmiron) was the first oral medication approved by the Food and Drug Administration (FDA; 1996) specifically for use in IC. The bladder has a mucin mucoprotein lining, similar to heparin, made up of glucosaminoglycans, which prevent bacteria from sticking to the bladder wall. It has been proposed that a deficiency in this layer allows substances in the urine to migrate into the subepithelial spaces of the bladder and set up an inflammatory response; chemical hyperemia, mastocytosis, and histaminic release lead to eventual fibrosis. An oral analog of heparin, Elmiron may act like a synthetic glucosaminoglycan layer and may thereby increase the antiadherent surface (slipperiness) of the bladder lining, as well as *plug* any leaks in the wall fortifying bladder defenses. A dose of 100 mg three times a day has been suggested for an initial 3- to 6-month period. If pain relief is obtained, a maintenance dose may continue indefinitely.

Hydroxyzine (Atarax/Vistaril) is an anxiolytic and antihistaminic medication that affects mast cell degranulation, which is thought to play a role in some IC patients' symptoms. Atarax can decrease nocturia, daytime frequency, and some pain. Like the antidepressant classes of medication, slow titrations of low doses are recommended to avoid excessive sedation.

Narcotic Analgesics. Some IC patients with severe symptoms who have not responded to standard IC treatments have found relief from various narcotic preparations. With the emergence of many new nonnarcotic therapies, these should be reserved for patients in whom other conventional approaches have failed. Narcotics are discussed in Chapter 84.

Other Oral Medications. Many other medications, including antispasmodics, antiinflammatory agents, and muscle relaxants, have been used by many IC patients to relieve their symptoms.

Food Restrictions. Although not the cause, certain foods and drinks may aggravate symptoms. These include spicy food, alcohol, coffee, chocolate, tea, cola, and acidic items such as orange juice, carbonated drinks, tomatoes, and vinegar. Smoking should be avoided, as it is a well-known bladder irritant.

Bladder Instillations

HYDRODISTENSION OF THE BLADDER. As the first line of treatment, hydraulic distension of the bladder is both diagnostic and therapeutic. Under general anesthesia, the bladder is filled to a pressure of 80 cm of water and kept distended for 5 to 10 minutes. Short-term improvement occurs in about a third of patients (several weeks). This is usually reserved for severe exacerbations; prophylactic distension does not seem to improve long-term results. Bladder rupture has been reported under these circumstances (32). Although intentional rupture has not been advocated as therapy, Higson et al. (33) noted that patients whose bladders have been accidentally ruptured in this way do much better for a longer period of time afterward than those whose bladders remain intact during stretching.

DIMETHYL SULFOXIDE. Approved by the FDA in 1978 specifically for the treatment of IC, dimethyl sulfoxide (DMSO) is the most time-tested and proven remedy for IC (34). The treatment is given once a week for 6 to 8 weeks and as needed thereafter. It is instilled by catheter, and it is retained in the bladder for 15 minutes before voiding. Urethral burning has been reported and irritative symptoms may worsen directly after the procedure. It is excreted via the lungs within days of the treatment. DMSO is thought to relieve symptoms in two-thirds of patients via an anesthetic action on the bladder surface or through an antiinflammatory effect. It may also have cytolytic effects in the submucosal nerve plexuses while sparing the detrusor (35). Most patients require repeated courses of therapy. Some have used DMSO instillation in combination with heparin, corticosteroids, local anesthetics, and bicarbonate (22).

OTHER INTRAVESICULAR INSTILLATIONS. Dilute silver nitrate solutions and oxychlorosene sodium (Clorpactin WCS-90) have been used with mixed results for IC. Clorpactin instillation is extremely painful and requires general anesthesia. Hyaluronic acid (Cystitstat) can be instilled directly into the bladder and is thought to work by replacing the defective glucosaminoglycan lining of the bladder. Cystitstat is initially instilled once a week for 6 weeks and then biweekly when symptoms have stabilized. Clinical trials in the United States are ongoing as efficacy is not known at this time. It was originally designed as a treatment for bladder cancer and is instilled directly into the bladder and appears to work by boosting the immune system. Long-term benefit and untoward effects are unknown (22).

Treatment of Hunner's Ulcers. Hunner's ulcers, present in only a small percentage of IC patients, may be treated with laser, resection, or fulguration. Treatment does not appear to affect the severity of the presenting symptoms.

Transcutaneous Electrical Nerve Stimulation. Electrical stimulation is often used in the treatment of a variety of painful conditions and may be helpful in some IC patients. It may be used daily for up to 8 to 10 hours on the thighs, low back, and lower abdomen, with the primary advantages of reversibility and ease of application. Its mechanism in IC remains unclear. Transcutaneous electrical nerve stimulation is discussed in Chapter 98.

Denervation. In the first edition of this book, Bonica (5) noted that in the 1930s a number of respected clinicians, including Leriche and Mandl, reported relief of pain associated with severe chronic cystitis following a lumbar sympathetic block. These procedures had been prompted in part by the reports of Learmonth and Braasch (36), Nesbit and McLellan (11), and others that resection of the superior hypogastric plexus gave uniformly good results in patients with chronic intractable pain due to cystitis and associated vesical spasm. In view of the fact that the sensory supply to the bladder is primarily through the sacral segments, these authors suggested that relief of vesical pain following the operation was caused by interruption of the nociceptive and vascular supply to these structures. A decade later, however, Jacobsen et al. (37) concluded that “although partial or temporary relief of vesical pain often is observed, permanent relief followed only occasionally, and in this respect, the operation has been found wanting.”

Similar opinions were also published by White and Sweet (38). Repeated hypogastric plexus blockade has also been used with varying degrees of short-term success (39). Bonica (5) also reported complete temporary relief with transsacral S-2, S-3, and S-4 block with 0.15% tetracaine in patients with severe vesical spasm accompanied by intractable pain unresponsive to sympathetic blockade. Continuous infusions for prolonged analgesia in this region were also used to break the pain cycle in severe cases. Neurolytic and percutaneous and direct rhizotomy techniques in this region cause loss of bladder and rectal sensation and penile erection and orgasm; therefore, these approaches are impractical for definitive therapy.

Pudendal Nerve Blockade. Pudendal blockade was first described by Mueller in 1908 for use in obstetrics. Over time, a number of variations in technique have been described, including that of Klink and Kohl, who advocated transperineal and transvaginal approaches, respectively. These techniques evolved due to the repeated difficulty of successful block due to an inability to accurately target the nerve. McDonald et al. reported on the successful use of computed tomographically guided pudendal nerve blockade for diagnostic and therapeutic application in chronic pelvic pain conditions (40).

Surgery. Surgery for pelvic pain and associated dysfunctional voiding syndromes may be appropriate for a small minority (less than 10%) of patients whose symptoms are intractable and where lesser invasive, reversible forms of therapy have failed. In fact, no treatment to date, other than surgery, is significantly effective for the patient whose bladder has irreversible scarring and contraction and a significantly reduced bladder capacity. The healthy bladder holds 800 to 900 mL under anesthesia and 400 mL when the person is awake. Once the bladder capacity shrinks to less than 300 mL under anesthesia, the person may have a capacity of less than 150 mL while awake. In such cases, standard augmentation cystoplasty has been used in the past (41). In other patients, urine has been diverted to a bowel segment or through an intestinal conduit to the skin (42). Attempts at supratrigonal denervation by resecting the bladder from its trigone and reanastomosing it afterward have resulted in contracted useless bladders in some patients (22). However, *definitive* surgical intervention for the majority of these patients should be approached with caution, as it has not uncommonly failed to ameliorate persistent symptoms. It has been postulated that this may be in part due to a neuronal plasticity and wind-up phenomenon (43) (see Chapter 4).

Sacral Nerve Stimulation. Stimulation effects of the cauda equina were initially reported by Blume et al. while attempting to treat patients after failed back surgery (44). Since then the sacral portion of the cauda equina has been stimulated primarily for motor disorders such as voiding dysfunction (45). Stimulation of the sacral nerve roots has been applied by providing low-frequency stimulation to the anterior sacral nerve roots via open and percutaneous approaches through the posterior sacral foramen (45). In September 1997, S-3 sacral nerve stimulation via an external transforaminal approach was approved for urge incontinence by the FDA. This was followed by an FDA-approved investigational protocol for patients with symptoms of urinary urgency, frequency, and pain who had failed conventional IC therapies. However, despite improved bladder motor control and some associated pain relief, both methods have been associated with a high patient dissatisfaction rate. In a multicenter study for urge incontinence, 57 of the 155 patients (37%) experienced an unsuccessful trial of sacral nerve root stimulation. Of the 98 patients who underwent permanent implantation, 39% later required either an electrode revision or system explantation (Medtronic Inc., 1998, Interstim report). Alo' et al.

subsequently reported a modified craniocaudal intraspinal approach for selective lumbar and sacral nerve root stimulation in the treatment of chronic pain (46). This approach may in part address the inherent percutaneous electrode instability concerns described previously. Although preliminary studies using sacral nerve stimulation for IC have not yet been completed, initial results are promising (47).

Radiation Cystitis and Postirradiation Contracted Bladder

Etiology. The effects of bladder irradiation may be separated into two phases. The acute phase is an immediate inflammatory response to radiation consisting of edema, mild infiltration, and some hemorrhage, which usually clears in weeks to months. The chronic phase is a delayed obliterative endarteritis accompanied by bladder scar formation, contraction, and mucosal ulceration, which can occur from 1 to several years following radiation therapy, but usually within 3 years. Increasing use of radiation in pelvic malignancies has resulted in more disorders of this type, although better control of radiation fields has limited the incidence of chronic radiation cystitis.

Symptoms and Treatment

Acute Phase. The acute phase usually presents with symptoms that are similar to those of acute bacterial cystitis: frequency, dysuria, and urgency. The urine is usually sterile, and treatment with anticholinergic drugs such as propantheline, 15 mg four times a day, may help. Some patients require systemic medications such as sedatives or narcotics. Aspirin should be avoided, as it may worsen the bleeding of irradiated mucosa. Belladonna and opiate suppositories per rectum every 4 hours may give relief in difficult cases. Superimposed infection, if proven by culture, should be treated with appropriate sensitive antibiotics. Bladder catheterization and instrumentation should be avoided for the duration of therapy because of the increased risk of infection with the introduction of a foreign body, as well as the local inflammation and trauma that may ensue. If protracted, the acute phase can progress to the chronic phase and ultimately a contracted bladder.

Chronic Phase. The treatment of a painful contracted bladder, which may occur in the chronic phase of postirradiation cystitis, is difficult. The symptoms are similar to those of IC with the added difficulty of hemorrhage, which at times causes clot retention and life- threatening loss of blood. The latter may require endoscopic fulguration. For diffuse oozing, other methods such as balloon inflation within the bladder under regional anesthesia or instillation of protein-precipitating agents, such as 5% silver nitrate or even 10% formalin, have been tried. Augmentation cystoplasty with small or large bowel has been used with limited success in some patients. Urinary diversion has not been useful unless the bladder is also removed. Partial pain relief can be obtained in extreme cases with regional nerve blockade followed by S-3 nerve section or cordotomy in patients with a limited life span (48).

Chronic Tuberculous Cystitis

Tuberculous cystitis may present in severe form much like chronic radiation cystitis. These patients have pyuria with mixed infections, but the pyuria fails to clear with control of the usual pathogens. Tuberculous contacts should be gleaned from the history and if positive should be sought by culture and biopsy. Patients often respond to antituberculous drugs with symptomatic relief. Periodic assessment of the upper urinary tract is indicated as ureteral scarring and stenosis can occur in the presence of antituberculosis drugs. If disease progression occurs to late-stage bladder contraction despite therapy, augmentation cystoplasty or diversion may be necessary. Alternative medication or block therapies may be adjunctive.

Schistosomal Bladder Infection

Schistosomal infection of the bladder, caused by *Schistosoma haematobium*, produces symptoms similar to those seen in tuberculous and postirradiation cystitis with the addition of necroturia (passage of necrotic tissue) and, in late stages, urethral stricture. Cutaneous hyperemia usually accompanies initial infection with itching; late infection may mimic the myriad symptoms of chronic inflammatory processes involving the bladder and urethra. Urethral stricture, pitting and scarring of the glans penis, and palpable perineal fibrous tissue may also be present. The differential diagnosis is aided by exposure in endemic regions of North Africa and the Middle East. Radiographs of the urinary tract may show submucosal or intramural calcification of the affected bladder, ureters, seminal vesicles, and prostate. The disease may evolve into squamous cell carcinoma of the bladder. Treatment of schistosomiasis (bilharzias) is guided by specific antischistosomal agents such as trichlorfon (Bilarcil) and praziquantel (Biltricide), which are used orally. Advanced cases may require all of the measures described for tuberculous and radiation cystitis with or without removal of calculi, treatment of stricture, or both. Endoscopy should be performed on a periodic prophylactic basis to evaluate for recurrent stones and secondary cancer. The chronic and slow progress of this devastating disease may actually destroy some of the nociceptive vesicular fibers; however, pain may be a formidable element given the protean involvement of the urinary tract and accessory genitalia. Nerve blocks, rhizotomy, and cordotomy have all been used for palliation, as this disease is as aggressive as carcinoma of the bladder.

Cancer of the Bladder

In its early stages, transitional cell cancer of the bladder is typically painless. Pain occurs late in the disease usually as the result of metastases, scarring, or postirradiation changes. Bony metastases are treated similarly to that of other mucosal visceral tumors with local radiation followed by specific chemotherapeutic agents. Pain due to ureteral obstruction by intrinsic or extrinsic tumor may be debulked (e.g., local transurethral resection or endoscopic stenting) to facilitate drainage. A silastic stent may be left in place for months; however, it may be difficult to place retrograde and therefore may need to be placed via a nephrostomy antegrade. Pain from progressive disease may require cystoprostatectomy, cordotomy, presacral neurectomy, direct local or neurolytic blockade, pelvic irradiation, or a combination of treatments. Complications from these treatments are many, not the least of which may be erectile dysfunction. Treatment fortunately is available for this side effect including corpora cavernosa implants.

Diseases of the Urethra

Acute Urethritis in Men

Sexually transmitted disease is by far the most common cause of acute urethritis in men, and its symptoms respond dramatically to specific antibiotic therapy. *Chlamydia* infections can become chronic, but the symptoms are usually so mild that reassurance about the natural history of the disease is enough to satisfy all but the most guilt-ridden sufferers. Rarely does sufficient pain develop to require more than the usual management of acute pain; however, if the pain becomes severe and is unrelieved with the use of analgesic medication, several blocks of the pudendal nerve with a local anesthetic or continuous caudal analgesia limited to the sacral segments can be used for several days to provide relief. In the extremely rare patient who has severe persistent and disabling pain that is not relieved with temporary pudendal blocks, neurolytic block or neurectomy can be considered. It is important to note, however, that destructive procedures provide relief for on average 6 (to 12) months, after which the pain returns. Moreover, the neurolytic block can be followed by postchemical neuropathy including sexual dysfunction, neuroma formation, or both, which is likely to involve additional and even more severe pain.

Acute Urethritis in Women

Acute urethritis in women independent of cystitis is most frequently associated with sexually transmitted diseases such as *Chlamydia* infection, herpes, trichomoniasis, and gonorrhea. As in men, the usual response to specific antimicrobial treatment is prompt and gratifying pain relief. Genital herpes may recur with chronically painful lesions, which often require systemic relaxants; if absolutely necessary, a stepladder pharmacologic approach including narcotics (as is commonly applied in cancer pain) can be used. Urethral inflammation can also be produced chemically by bubble bath soaps (49).

Female Urethral Syndrome

The symptom complex termed *urethral syndrome*, which is also called *psychosomatic cystitis* and *chronic urethritis*, is the female equivalent of chronic prostatitis in men and probably acutely affects as many as half of the women aged 15 to 50 years who are said to have cystitis (29,50). Some even believe this is a complex subgroup of IC, vulvar vestibulitis, or both, where chronic urethral pressure and pelvic muscular variations have been shown (30,51). Because the causes of chronic urethral syndrome are multiple, treatment directed only at a single specific cause often fails, especially if it remains organ specific (52). Depression and stress appear to contribute to this entity, as do local trauma, dysfunctional voiding patterns, sexual frustration, vaginitis, concerns about sexually transmitted diseases, and guilt about sexual fantasies and feelings. It is also probable that a variety of minor local problems are operative including blocked and distended urethral glands, prolapsing urethral mucosa, postmenopausal epithelial changes, inflammatory polyps in the urethral mucosa, urinary frequency related to menstrual fluid retention and its diuresis, previous experience with cystitis or sexually transmitted disease, fear of recurrence, or cancerophobia triggered by minimal urethral symptoms.

Symptoms and Diagnosis. Characteristic symptoms include dysuria, burning on urination, and a burning or irritated sensation in the periurethral area or perineum. These symptoms may not necessarily be associated with urination but can be exacerbated by it. Symptoms are most prominent during waking hours, with little or no nocturnal disturbance. Typically, the urinary sediment is unremarkable, and urine cultures grow limited quantities of mixed flora or nothing. The following conditions must be considered in the differential diagnosis: IC, urethral diverticulum, urethral caruncle, stricture, vesicovaginal or urethrovaginal fistulae, vaginitis, vulvar and perineal cutaneous problems, chronic yeast infestation, pinworm infestation, postmenopausal mucosal and skin alterations, diabetic neuropathy, and tuberculosis. If the primary involvement is vaginal, a vaginal discharge usually precedes the urinary symptoms. Vaginal discharge occurring after treatment with antibiotics for urinary symptoms usually is secondary to yeast infestation. Examination of the perineum may reveal excoriation, herpetic lesions, urethral caruncle, or mucosal prolapse. In the case of a urethral diverticulum, gentle stripping of the urethra by stroking through the anterior vaginal wall may express pus through the urethral meatus. In patients with persistent symptoms of this type, an intravenous pyelogram should be obtained to make certain that there are no lesions of the upper urinary tracts producing referred symptoms. Allowing contrast medium to accumulate in the bladder and looking at a voiding film of the urethra is the least traumatic way of imaging this structure. Cystourethroscopy also is required in many of these patients to provide absolute assurance that no serious disease process is present to account for the symptoms (53,54 and 55).

Treatment. The most important aspect of treatment for female urethral syndrome is the process of ruling out serious illness or any potential for serious illness in the organs of the region (52). Carefully listening to the patient, who needs to feel that she is really being heard, followed by a gentle and thorough physical examination enhances the patient's confidence. Then appropriate diagnostic studies to confirm or deny the presence of local pathology must be obtained and reviewed. Lesions found must be discussed and addressed. These diagnostic and therapeutic maneuvers may take several sessions with the patient. If the problem is dysfunctional voiding or sexual behavior, retraining should be considered. Communication problems between partners should be discussed, and strategies for dealing with them presented. The patient can learn to relax the perineal musculature during urination by voiding while in a hot tub. Pelvic biofeedback may also assist with associated pelvic floor dysfunction (30). Encouraging the patient to raise her concerns about premature ejaculation or inadequate foreplay directly with her partner may be all the help necessary. Reassurance that no sexually transmitted disease is present is effective. A frank and practical discussion of the ways of dealing with a persistent problem such as herpes and referral to an appropriate support group are often helpful. Oral nystatin (Mycostatin) to clear the intestinal source of a perineal yeast infestation along with Lactinex powder to reseed the lactobacilli that may have been driven out by previous antibiotic therapy may also be helpful. If postmenopausal changes in the perineal skin and mucous membranes are seen and there is no contraindication, a combination of estrogens and periodic progestational treatment may be useful. Such treatment should be carried with support of a gynecologist. Conjugated estrogens (Premarin), 0.625 mg per day, and medroxyprogesterone acetate (Provers), 10 mg taken from the tenth to the twentieth of the month, provide satisfactory replacement. Before prescribing these, the physician must be aware of potential thrombotic complications and carcinogenicity.

Disease of the Prostate and Seminal Vesicles

Acute Prostatitis

Etiology. In middle-aged men, acute prostatitis is mostly of bacterial origin. Coliforms are the leading offender, although *Staphylococcus epidermidis* runs a close second and is probably the most common agent in diabetics and those with immunodeficiency disorders. Posterior urethritis and therefore (at least technically) prostatitis accompany 80% of the urethritis associated with sexually transmitted diseases. In younger men, the most common cause is sexually transmitted disease, with chlamydial infection and gonorrhea being the leading offenders.

Diagnosis. On presentation the patient has chills, fever, pain in the perineum and rectum sometimes severe enough to inhibit defecation, along with urinary frequency, dysuria, decrease in stream size, and possibly nausea and vomiting. If secondary seminal vesiculitis occurs, there may be pain in the groin. The urine is cloudy, and its sediment is loaded with pus and bacteria. The patient is sweaty, febrile, and obviously ill. The prostate is very tender and enlarged and has a *boggy* consistency, which is similar to the sensation encountered on palpating pitting edema of an extremity. If acute or subacute prostatitis is part of the differential diagnosis, rectal palpation of the prostate must be done with extreme care and gentleness as the potential is high for precipitating a bacterial shower into the bloodstream with sudden septicemia and shock.

Treatment. Treatment for acute prostatitis includes bed rest, extra fluids, appropriate antibiotics, and pain medication. Usually, oral nonsteroidal antiinflammatory agents alone or in combination with narcotics are sufficient, but occasionally parenteral narcotics are required. Hot sitz baths are helpful, and belladonna and opiate suppositories relieve bladder irritability and tenesmus. If retention occurs that necessitates catheterization, it is best to avoid the urethra and place a catheter into the bladder percutaneously above the symphysis with the aid of local infiltration anesthesia. If a urethral catheter must be used, the smallest one possible should be selected. Acute prostatitis rarely causes significant problems with pain relief; chronic prostatitis is another matter.

Chronic Prostatitis

Etiology and Symptoms. Chronic prostatitis, like urethral syndrome in women, probably involves several different underlying processes with similar symptoms, which are merged under one diagnostic label. Patients complain of fullness in the perineum, urethral burning, which may or may not be related to urination, rectal discomfort, and discomfort on ejaculation. In some patients, blocked ducts and trapped secretions in distended prostate glands probably are responsible for the symptoms. Loci of microscopic inflammation may also create symptoms. These same lesions, however, may be found incidentally in asymptomatic individuals whose prostates are histologically examined for unrelated reasons such as death due to trauma or coronary disease. Low back pain is such a common complaint among the general population that it probably is coincidental to chronic prostatitis, or it reflects a musculoskeletal response to the primary problem. Driving trucks, tractors, and construction equipment seems to exacerbate such symptoms.

Diagnosis. The diagnosis and management of prostatitic syndromes is a challenge to the clinician (56). Careful pain history and examination of the prostate fluid and quantitative segmented bacteriologic cultures lead to proper categorization into the recognized forms of the prostatitic syndrome (57,58,59 and 60). It has been suggested that transrectal prostatic sonography may also be a useful diagnostic adjunctive tool (61). However, nonbacterial prostatitis, vesiculitis, and prostatodynia must also be kept in mind within the differential diagnosis if causative organisms have not been identified (62,63). Prostatodynia is a complex of symptoms similar to prostatitis that occurs without objective findings that definitely implicate the prostate gland. Bladder disorders such as internal sphincter dyssynergia, bladder outlet obstruction, tension myalgia of the pelvic floor, or at times, stress and emotional issues may be associated (64,65,66,67 and 68). Much like IC, there is emerging evidence of abnormal T-cell reactivity in a subgroup of prostatitis patients that suggests an autoimmune component to the disease (69,70).

On examination, the prostate tends to be firm and fibrous or boggy. Secretions obtained at massage are variable, but in some patients white cells are found in large clumps. Prostate secretions should be cultured. They are normally absolutely sterile, so the presence of even a few organisms is significant, particularly if they are pathogens. Before the prostate is massaged to obtain secretions for culture, the urethra must be cleansed by partially emptying the bladder. The specimen so obtained is divided into two parts. The first 5 to 10 mL of urine is collected in a tube labeled *VB1* (voided bladder urine 1). Without interrupting the voiding process, the next 150 mL or so is collected in a container, and the last 5 to 10 mL of this portion is collected in a culture tube and labeled *VB2*. Voiding is interrupted, the prostate is then massaged, and secretions are collected in a sterile receptacle held under the meatus. This is labeled *EP1* (expressed prostatic secretion 1). If no secretions are obtained, the patient is instructed to void additional urine, which is collected in two parts, the first part being labeled *VB3* and the last part *VB4*. If, when cultured, there is a higher colony count in EPI or in VB3 than in VB1 or VB4, the bacteria almost surely originate in the prostate.

Therapy. When the four-glass test is positive (71), sensitivities on the culture should be obtained and appropriate antibiotic therapy used (trimethoprim and sulfamethoxazole, regular strength tablets four times a day for 5 days to load and twice a day for the next 45 days). Young individuals should be cultured for *Chlamydia* also. A 6-week course of tetracycline may be reasonable if one suspects chlamydial etiology. Patients who do not respond to such measures may be helped if accumulated secretions are expressed by periodic prostatic massage. Occasionally, such individuals have a urethral stricture that responds to dilation. Pain due to chronic bacterial prostatitis is usually persistent and annoying but not of an intensity to require potent narcotic analgesics. Most individuals in this group are more concerned about cancer or some other long-term danger. If they can be reassured that these are not present, they are generally willing to live with the problem (50). In severe persistent cases of abacterial chronic prostatitis and prostatodynia, however, unremitting refractory symptoms may be seen. For this better recognized growing subgroup of prostatitis patients, a number of new therapies including retrograde balloon dilation, transrectal and transurethral hyperthermia, pollen extract (Cernilton N), electric acupuncture, and low-intensity laser radiation have all been successfully described (72,73,74,75,76 and 77).

Prostatic Calculi

Patients with prostatic calculi are rarely symptomatic and often are picked up when hard nodules are palpated on routine rectal examination. If the stones are multiple,

are in contact with each other, and crepitate when palpated, the diagnosis is made on physical examination. A radiograph of the pelvis usually reveals the offending calcification in the region of the prostate, thus differentiating it from cancer. Patients with prostatic cancer occasionally are misdiagnosed as having calculi. This is most likely to occur if the physician overlooks changes in the size or character of palpable nodules on reexamination. If prostatic calculi become infected or symptomatic, they can be removed by resecting the tissue between the stone and the urethra, which frees the stone into the urethra or bladder, and then crushing the stone and evacuating the fragments (78).

Benign Prostatic Hypertrophy

Benign prostatic hypertrophy is included only for completeness. Other than the pain of urinary retention, for which treatment is straightforward, pain is not a characteristic problem of this disease. Common symptoms are perineal or rectal fullness and, of course, urinary frequency and dysuria. All of these disappear with removal of the underlying obstruction. Chronic calculous prostatitis in the face of benign prostatic hypertrophy may aggravate symptoms and complicate treatment (79).

Cancer of the Prostate

Epidemiology. The cause of cancer of the prostate is unknown, but this cancer affects all races and ethnic groups. Findings of occult cancer of the prostate in autopsy series increases dramatically after 50 years of age to over 80% of those older than 80 years of age (80). Only 1 in 400 individuals over the age of 80 years dies because of cancer of the prostate, whereas 10% of those discovered with the disease under age 60 succumb from it. According to Breslow et al. (81), the incidence of large latent cancer of the prostate is the same as the death rate from the disease in several different racial groups, whereas the incidence of small latent cancer is the same as the general mortality for these groups. The implication of this study is that large latent cancer behaves in a malignant fashion whereas small latent cancer does not.

Diagnosis. Many patients with cancer of the prostate are asymptomatic, their disease being discovered on screening rectal examination. Others present with characteristic obstructive symptoms, which tend to be more unrelentingly progressive than those of benign prostatic hypertrophy. Fifteen percent to 20% present with lumbar spine or pelvic pain due to metastatic bone disease as their first symptom. The prostate characteristically is hard or contains hard nodules on rectal examination, and biopsy of these areas of the prostate yields tissue that is positive for adenocarcinoma. Serum acid phosphatase may be elevated. Osteoblastic lesions may be seen on radiographs of the lumbar spine and bony pelvis or a positive bone scan is obtained.

Treatment. Pain associated with cancer of the prostate is usually related to obstruction or metastases. Advanced or acute obstruction can be relieved by catheter drainage and resection of obstructing tissue. Less acute obstruction in patients unsuitable for excision can be relieved by hormonal control therapy. Hormonal control therapy for pain from metastatic disease provides objective as well as subjective improvement in about 70% of the cases. Synthetic estrogen (stilbestrol) given daily is effective but may take 30 to 60 days to achieve complete palliation, whereas the dramatic relief resulting from orchiectomy occurs within a week after the procedure. Subsequent recurrence of pain may respond to alteration in estrogen dosage or in the type of estrogen. Dramatic claims for luteinizing hormone releasing hormone may prove to be exaggerated, but this drug, like orchiectomy, does not produce salt retention or thrombotic problems, which are common side effects of estrogens. Pain in localized areas of bone involvement, particularly periosteal elevation, responds well to irradiation. Patients with bone marrow replacement respond to transfusion and irradiation for varying periods. Thus far, the use of antimetabolites in advanced prostatic cancer has yielded disappointing results. The management of patients with pain due to terminal cancer is discussed in Chapter 40.

Seminal Vesicle Diseases

Primary disease of the seminal vesicles is extremely rare. Secondary disease related to congenital anomalies of the urinary collecting system is also rare. More common is involvement secondary to prostate infection or cancer. The symptom is pain in the groin on the affected side. The differential diagnosis should include ilioinguinal and genitofemoral neuralgias in patients who have had recent flank or groin surgery (82). Treatment is directed at the primary disease, such as prostatitis and cancer of the prostate.

DISORDERS OF THE EXTERNAL MALE GENITALIA

Diseases of the Epididymis

Acute Epididymitis

Etiology. Acute epididymitis is characteristically due to chlamydial organisms in men younger than 40 years and coliform bacteria in older men; thus, it is a sexually transmitted disease in sexually active young men, whereas in older patients it is usually secondary to obstruction or other changes. In prepubertal boys it can also be associated with urethral obstruction (83,84).

Symptoms and Signs. Typically, the history is one of gradual onset of dull pain in the scrotum followed in hours or days by symptoms of tenderness in the affected epididymis. It is soon followed by swelling and redness in the scrotum, and then symptoms of chills, fever, and malaise. The pain is partially relieved by assumption of the supine position. The pain, inflammation, tenderness, and swelling may radiate up the spermatic cord. There is usually a history of recent sexual exposure and urethral discharge. On examination, the scrotum is often swollen, red, and tender, particularly over the epididymis, which should lie posterolaterally even though it is three or four times normal size.

Differential Diagnosis. The differential diagnosis of acute epididymitis includes torsion of the testicle (85), mumps orchitis, incarcerated hernia, sudden hemorrhage into the testicle, and neoplasm. Pain associated with torsion of the testicle is sudden in onset and often occurs at night; there is no discharge and the urinary sediment is normal. The twisted testicle pain is not relieved by simple elevation. Bowel tones can be auscultated over the scrotum in instances of a prolapsed and incarcerated hernia.

Mumps orchitis is associated with a history of exposure to mumps, parotitis, and possibly elevated serum amylase values. The testicle should be the primarily involved organ; thus, the examination of the epididymis is normal. Acute testicular hemorrhage is typified by a history of trauma, and again, the epididymis is normal. Dramatic relief of epididymis pain is achieved by local anesthetic infiltration of the cord structures with 1% lidocaine or 0.25% bupivacaine. In addition to dramatic relief of pain, such a local block may permit a more thorough examination so as to determine the actual location of the pain in the epididymis.

If there is legitimate concern that the diagnosis may be torsion, the safest course is exploration. We have yet to see scrotal morbidity in individuals with epididymitis who were explored to rule out torsion. On the other hand, in some of these explorations, we have saved some testicles in patients who would have lost them if their torsion had been treated as straightforward epididymitis without the benefit of surgical exploration.

Treatment. Most young men with acute epididymitis are infected with *Chlamydia*; thus, the logical treatment is tetracycline therapy. Men over 40 years of age should be treated with specific sensitive antibiotics effective against coliform organisms as determined by identification cultures and sensitivities. Acute epididymitis is an extremely painful disorder and practically speaking incapacitates those engaged in any physical activity at work or in recreation. Treatment regimens can include up to 50 days of antibiotics, scrotal support, and depending on severity, bed rest or restricted activity for several weeks. Suboptimal treatment may result in the development of chronic epididymitis.

Chronic Epididymitis

Chronic epididymitis, the end stage of unresolved acute epididymitis, is a disabling condition in which the epididymis is chronically swollen, painful, and extremely tender to palpation. This condition can also develop in conditions of recurrent bacterial prostatitis or congenital urethral defects.

Treatment of chronic epididymitis may result in prolonged use of a scrotal support, several months of limited physical activity, and concomitant antibiotic therapy. Some patients require epididymectomy, and some even more drastic measures such as removal of both the offending testicle and epididymis. Before such surgery, several local anesthetic infiltration blocks of the spermatic cord should be tried to see if the pain cycle can be interrupted and perhaps relieved permanently. Infection of the spermatic cord, known as *funiculitis*, occasionally accompanies epididymitis. Chronic funiculitis is almost never seen independently and is usually treated by an

identical regimen as just outlined for epididymitis.

Diseases of the Testicle

Torsion of the Testicle and Spermatic Cord

Etiology. Although torsion is primarily a disease of adolescence and young adulthood, it occasionally occurs in both the very young (i.e., the newborn) and the elderly populations (85). The incidence in a busy general hospital is only a few cases (i.e., three or four cases) a year. Left-sided torsion is twice as common as the right side. The primary cause of torsion is a congenitally induced high insertion of the tunica vaginalis on the spermatic cord, which allows the testicle to rotate within the tunica. Depending on the degree of rotation, which can be as small as 90 degrees or as large as 720 degrees, vascular compromise with ischemia and eventual necrosis of the testicle and epididymis develop over time.

Diagnosis and Treatment. Testicular pain is the primary initial symptom of torsion of the testicle. It is sudden in onset, severe in degree, manifest by exquisite tenderness, and often occurs at night. Often, patients have had a previous similar episode or episodes of less severity, which have resolved spontaneously. On physical examination the affected testicle is often higher than the unaffected testicle; this is in contrast to the condition of epididymitis, in which the affected side is positioned lower. In the twisted testicle, the epididymis is in some position other than the normal dorsolateral location, and the degree of swelling and tenderness varies. Urinalysis is usually normal in patients with torsion, whereas the urine of patients with epididymitis usually contains white blood cells. Local infiltration of local anesthetic around the spermatic cord relieves symptoms and tenderness, allowing a more careful examination of the scrotal contents and possibly manual derotation.

The treatment is immediate derotation or detorsion. This must be accompanied by a surgical fixation to prevent subsequent episodes. The contralateral side should also be protected prophylactically, because the congenital defect underlying the condition is usually present bilaterally.

Torsion of the Testicular Appendages

Although there are four testicular appendages, the appendix testis, a vestigial structure on the upper pole of the testis, is involved in 95% of the cases of torsion. This small (0.1 to 0.5 cm in diameter) pedunculated structure twists on its pedicle, and ischemia with necrosis follows. The highest incidence is in prepubertal patients 10 to 13 years of age (85).

The patient presents with pain of sudden onset, initially localized to the upper pole of the testis. After several hours, however, the pain may be difficult to distinguish from that of torsion of the testicle and cord. Early, on physical examination, a blue dot may be seen through the scrotum over the twisted appendix testis. Local infiltration blockade of the spermatic cord permits a thorough examination, which is necessary to make the diagnosis and also temporarily relieves the pain. The urinalysis is normal. Surgical excision is indicated and results in prompt relief of pain; this aggressive approach can resolve any diagnostic doubts about the possibility of torsion of the spermatic cord.

Orchitis

Orchitis is another completely independent disorder of the male external genitalia and is most commonly caused by a viral agent after puberty. Mumps is by far the most common cause, but coxsackie and other viruses have also been implicated. Pain results from swelling of the testicular parenchyma within a tightly adherent and unyielding tunic. Often, a history of previous viral exposure and involvement of other organ systems precedes the development of testicular pain. There are no urinary symptoms, and, except for proteinuria, the urinalysis is normal. A fever to 39°C is common. Temporary relief may be obtained by infiltration of 1% lidocaine into and around the spermatic cord at the external inguinal ring, because it may resolve the exquisite pain and swelling due to inflammation of the orchitis. Local measures, such as heat and mechanical support, can also help alleviate pain in some patients.

Orchiodynia

Orchiodynia, also known as *orchidalgia*, *orchialgia*, and *testalgia*, is a rare disease of unknown etiology characterized by chronic pain in the testicle. Some patients have a history of trauma to the testicle, and occasionally this disorder occurs following vasectomy. The pain is usually nagging, persistent, and achy but only rarely and fleetingly severe. The pain may be perceived in the testicle but tenderness is variable. If the patient has a history of trauma or inflammation, scarring or atrophy may be evident on examination of the testicle.

Often simple reassurance that no malignancy or other serious or transmittable disease is present encourages the patient to live with the minor discomfort of orchiodynia. Two of the three patients seen by us with this disorder were relieved with infiltration of local anesthetics around the spermatic cord at the external inguinal ring. The injections were repeated two to three times at weekly intervals. Removal of the testicle in these cases is not recommended because the pain usually persists after the testicle is gone. For example, one 91-year-old man whom we have seen for years continues to complain periodically of pain in the testicle 40 years after that organ's removal and 30 years after an ipsilateral seminal vesiculectomy.

Diseases of the Penis

Paraphimosis

In paraphimosis, the redundant foreskin retracts behind the corona of the glans penis and constricts it. The result is similar to that of a tourniquet. Further swelling and edema of the glans make diagnosis and treatment difficult for those unaware of the mechanism of this disorder.

Reduction of the foreskin often is possible after pressure over the glans has reduced the edema and swelling. This is aided by judicious use of local anesthesia infiltrated under the skin and subcutaneous tissue circumferentially at the base of the penile shaft and around the dorsal nerves of the penis and the deep corporeal nerves. Because the nerves to the coronal skin and glans reach them via the corpus spongiosum, it is necessary to infiltrate the corona circumferentially as well. (These same maneuvers apply when anesthetizing locally for purposes of circumcision.) If the edema is great, the foreskin may be reduced following local block with the aid of Babcock's clamps placed on the contraction ring, or it may be necessary to perform a dorsal slit at the bedside. When the patient has recovered and the swelling is considerably reduced, elective circumcision is indicated (86).

Priapism

Priapism, a prolonged painful erection not associated with sexual stimulation, can occur idiopathically or secondary to medications or other disease processes. Patients with leukemia and lymphoma, those undergoing dialysis, and those being treated by heparinization are at increased risk. An initial prolonged episode usually is preceded by a number of short bouts of this disorder. On physical examination the corpora cavernosa are painfully engorged, but the corpus spongiosum and glans are not turgid.

All successful therapy of persistent priapism establishes some form of shunting mechanism between the corpora cavernosa, whose venous outflow is obstructed, and the corpus spongiosum of the glans or urethra, whose venous drainage is normal. In its simplest form, this is accomplished by needle excision of cores of tissue between glans and corpora cavernosa (87). If that fails, a formal shunt will have to be created between the corpus spongiosum and the cavernous bodies, or perhaps a corporosaphenous shunt. Unfortunately, impotence often follows such procedures (88), but this is correctable by insertion of one of the penile prostheses now available (89). Control of pain due to priapism may require administration of opioids or continuous caudal block. Various anesthetics and local measures formerly used in an attempt to treat the problem are not warranted by the meager clinical results obtained.

Peyronie's Disease

Peyronie's disease is characterized by induration and sometimes curving of the corpora cavernosa of the penis. An autosomal dominant inheritable form of the disease has been identified by Nyberg et al. (90). An HLA linkage and association with Dupuytren's contractures also have been established for this inherited form, which occurs as early as the third decade; the more common, less obviously inherited form presents in the fifth and sixth decades. Patients often have no symptoms, but the discovery of a hard plaque in the dorsal shaft raises fears of a malignant process. Some patients notice incomplete erection distal to the lesion and then

discover the plaque. Others have severe angulation on erection, making intromission painful or impossible. Characteristically, the symptoms wax and wane over time, making assessment of treatment results difficult.

The patients most likely to be satisfied with surgical correction are those unable to intromit because of severe angulation due to the plaque and those whose distal erectile dysfunction also creates problems with intromission. Both will probably require penile prostheses in the course of treatment. Those with minor degrees of deformity or curvature usually do well when informed of the natural history of the disease and realize the prognosis for them is good.

Herpes Progenitalis

Herpes progenitalis, one of the most common of the sexually transmitted diseases, causes pain due to the chronic recurrence of small blistering lesions on the skin of the shaft. The painful character of the skin lesion is short lived, but the pain of the social impact of the disease on the individual's life is not.

Treatment with 5% acyclovir (Zovirax) ointment applied locally may increase the interval between recurrence of lesions. Most large communities have support groups that are helpful for patients with herpes.

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CHAPTER 74

Pelvic and Perineal Pain Caused by Other Disorders

John S. McDonald and John D. Loeser

The preceding three chapters have discussed various acute and chronic painful conditions caused by pregnancy, diseases of the pelvic viscera, and by other gynecologic and urologic disorders. This chapter discusses pain caused by disorders of bone, joints, and muscles of the pelvis, nerves, and skin, and pain referred to the pelvis from other regions. Because many of these conditions occur in various parts of the body, they are discussed elsewhere in this book (see Part III and also Part IV, Chapter 27, Chapter 29, Chapter 75, and Chapter 77). Therefore, only issues relevant to the pelvis and perineum are presented in this chapter. The material is presented in five sections: Musculoskeletal Disorders; Pain of Neuropathic Origin; Painful Visceral and Dermatologic Disorders; Referred Pain; and Pain Primarily of Psychological Origin.

MUSCULOSKELETAL DISORDERS

Pain in the pelvis is frequently associated with trauma, infection, metabolic disease, or neoplasm involving the bones and joints of the pelvis. Muscular spasm and myofascial syndromes involving some of the muscles in the pelvis, particularly the pelvic diaphragm, are also common causes of pain.

Trauma

Sprains

Etiology and Symptoms and Signs. Sprains of one or more of the numerous ligaments of the pelvis as a result of accidental trauma or some other unusual exertion can be a source of pain. One of the most frequent types is sprain of the ligaments of the symphysis pubis (see Fig. 70-4). During pregnancy, the ligamentous tissues of the pelvis relax and stretch and, with an unusually large fetus or multiple fetuses, sufficient stress might be placed on the symphysis to be a source of pain. The pain is usually dull and aching in character, of mild to moderate intensity, and associated with localized tenderness in the pubic region. Occasionally, direct impact can cause bleeding, with consequent subcutaneous hematoma.

Sacroiliac joint sprain can occur as a result of excessive stress on the joint or because of injury. This condition usually produces pain in the low back and thigh (see Chapter 75).

Treatment. If the patient is seen soon after injury, application of ice to the region is useful to decrease bleeding and inflammation. The pain can usually be controlled by nonsteroidal antiinflammatory drugs (NSAIDs), given alone or combined with codeine or a more potent opioid. In patients who experience moderate to severe pain, it is useful to infiltrate the joint with a local anesthetic (e.g., 0.25% bupivacaine) combined with a corticosteroid. The local anesthetic produces relief of pain for 6 to 8 hours, and the corticosteroid decreases the degree of posttraumatic inflammation.

Fractures

Direct force applied to the pelvis can fracture this structure anywhere. Fractures that involve the pelvic ring are typically produced by compression and can either be single or multiple (1,2). Because a fracture tends to occur across a weaker part of the ring, it is especially likely to be at the obturator foramen or across the wing of the ilium, from the crest to the margin of the greater sciatic foramen. A single fracture in either location allows parts to lift and separate. Treatment is usually conservative. The pain is usually moderate and can be controlled by NSAIDs alone or in combination with a weak or strong opioid.

In contrast, severe trauma invariably produces an unstable pelvic ring fracture as part of multiple trauma. Fu and Mears (3) have noted that patients with multiple trauma who were managed in a community hospital setting, in which expert trauma surgeons were not available, had a high incidence of morbidity and mortality. The advent of rapid transport to specialized trauma centers and the development of effective techniques of internal and external fixation have markedly decreased this morbidity and mortality and have proven effective in reducing the pain, resulting in early mobilization with a consequent decrease in posttraumatic complications, earlier ambulating, and shorter hospitalization.

Pathophysiology. Watson-Jones (2) and, more recently, Pennal and Massiah (4), have classified unstable pelvic ring fractures according to the mechanism of injury. The most frequently encountered mechanism is a lateral compressive force that can produce one of several patterns of anterior or posterior injury. The anterior disruption can be a fracture of one or more pelvic rami, dislocation of the symphysis pubis, or both (3,4). The posterior injury disrupts the ipsilateral or contralateral ilium, sacroiliac joint, or sacrum. Occasionally, multiple posterior disruptions occur. The second mechanism involves an anteroposterior compressive force, which usually disrupts the symphysis pubis, with a wide diastasis. A third type of injury, the vertical shear disruption, is generally produced by the most violent indirect forces. Usually, the disruptive force is transmitted through a lower extremity by way of the hip joint to the pelvic ring (3). Radiologic evidence of a vertical shear fracture includes an avulsion fracture of the ischial spine, with superior migration of the entire hemipelvis. Injury of one or more branches of the lumbosacral plexus, particularly the ipsilateral L-5 root segment, is a frequent accompaniment to this type of injury.

Symptoms and Signs. Invariably, patients who present with an unstable pelvic ring fracture show evidence of other serious injuries to the intraabdominal organs, intrathoracic viscera, central nervous system, or limbs. Depending on the degree and severity of central nervous system injury, patients experience severe pain in multiple body regions. Massive hemorrhage might have occurred, manifested by the signs and symptoms of hypovolemic shock.

Diagnosis. Unless multiple radiographic views are taken, a pelvic instability might not be evident in the conventional anteroposterior pelvic view (3). Radiography should include pelvic inlet and outlet projections; if available, computed tomographic (CT) scanning is most useful because it reveals the pattern and degree of disruption of a severe pelvic ring fracture (3,4). Indeed, bone scans have revealed a number of so-called stable pelvic ring fractures accompanied by undisplaced fracture adjacent to the sacroiliac joint, and this appears to accompany every injury in which multiple pelvic rami are fractured.

Treatment. Fu and Mears (3) have presented impressive evidence that nonsurgical methods do not control osseous bleeding from the fracture site and do not permit early mobilization of patients. Consequently, patients have a high incidence of serious mental, urinary, and pulmonary complications; the latter causing delayed death in 10% to 30% of patients. Moreover, nonoperative procedures have been associated with a high incidence of serious chronic disabilities.

On the basis of these results and personal experience, Fu and Mears (3) have suggested that these patients undergo immediate reduction and stabilization of the fracture to minimize pain and hemorrhage, late pulmonary complications, and various chronic musculoskeletal disorders, which are frequently associated with these massive traumatic insults. Reduction and stabilization are best achieved by external skeletal fixation using an anterior fixation frame, which is simple to apply. In patients who are receiving emergency room care and who are in unstable hypovolemic conditions, rigid external pelvic fixation should be done as soon as blood and fluids have been replaced by intravenous administration. In patients who are stable, primary internal or external fixation of the posterior or anterior site of pelvic disruption should be carried out. In reporting their experiences with 20 patients, Fu and Mears (3) noted that 14 obtained marked relief of pain within a day after application of the frame, and an equal number were out of bed within a week after surgery. Intravascular techniques to control hemorrhage are important in the management of pelvic fractures (5). The management of pain after major trauma is discussed in Chapter 43.

Coccygodynia

Coccygodynia is a common problem and is characterized by pain in the *tailbone*, with radiation to the lower sacral and perineal areas. This condition afflicts women more frequently than men.

Etiology. Coccygodynia may follow a fall in the sitting position in which the patient lands on the coccyx, such as astride a log, or it can follow a direct blow to this region. One of the most frequent causes of coccygodynia is damage to the sacrococcygeal ligament during a difficult vaginal delivery (6). Any of these factors can cause a fracture or ligamentous sprain. Because the coccyx is quite movable and is supported by the sacrococcygeal ligaments, fracture is not as common as a sprain. A chronic sprain can follow repeated microtrauma caused by poor sitting habits, in which pressure is centered on the coccyx. Arthritis, osteitis, osteomyelitis, and other skeletal disorders involving the coccyx and lower sacrum, although rare, have been reported as causative factors. The differential diagnosis of coccygodynia is difficult and often unrelated to outcomes (7,8). Our clinical experience has suggested that psychosocial factors can play a large role in many patients who do not have a history of trauma.

Symptoms and Signs. Pain and tenderness at the tip of the spine or in the coccyx is the most frequent complaint. The pain can be severe, as in fractures, or it can be a dull ache accompanied by bouts of lancinating pain. The pain frequently radiates to the perineal, gluteal, and posterior sacral regions and occasionally down the posterior thigh along the course of the sciatic nerve. The pain and tenderness are aggravated by sitting on a hard chair, particularly in thin individuals with poorly developed gluteal muscles, and by movement of the coccyx by the examining index finger inserted into the rectum. The levator ani, coccygeus, and piriformis muscles are frequently in moderate to severe spasm. The tenderness and spasm may become generalized and involve all the myofascial and ligamentous structures of the posterior wall of the pelvis.

Diagnosis. Diagnosis is based on history and physical examination, including rectal examination. Occasionally, radiography reveals fracture, malalignment of the coccyx, or arthritic changes involving the sacrococcygeal joint. An infectious process is a very rare etiology.

Treatment. Treatment consists of massage, local heat, injection of the joint with a local anesthetic and corticosteroid, and, whenever indicated, psychological therapies. Thiele (9) reported permanent relief in most patients following a series of treatments consisting of massage performed through the rectum and hot sitz baths or diathermy. Usually six treatments given at 3- to 5-day intervals were sufficient. Local injection of hydrocortisone has been reported as effective. If the pain is severe, local infiltration, coccygeal nerve block, or a low caudal block, involving only the S-5 and coccygeal nerves, is effective. This can be repeated several times using a local anesthetic. If the block provides complete but only transient relief of pain, the procedure can be done with alcohol or with a cryoprobe (10) (see Chapter 104). It is unclear what the role of coccygectomy is in this pain syndrome. Because many of these patients are tense, apprehensive, and nervous, psychological assessment and treatment frequently constitute important components of care.

Infectious and Inflammatory Disorders

Osteomyelitis

Osteomyelitis in one or more of the bones of the pelvis, although rare, can cause pain localized to the pelvis. With acute infection patients are usually extremely ill, with high fever, malaise, lethargy, and often vomiting (11). Most patients have tenderness over the affected bone, which can be palpated. This condition is an uncommon cause of pain in the pelvis.

Arthritides

Infectious or septic arthritis and osteoarthritis may involve a sacroiliac joint, causing pain in the hip and buttock with reference to the groin. Degeneration of the interpubic disk can also cause pubic pain. Sutro (12) noted that pregnancy accentuated a degenerative process in the interpubic disk, and these patients can develop localized pain later in life. Arthritides are all discussed in detail in Chapter 27.

Paget's Disease of Bone

Paget's disease of bone, also known as *osteitis deformans*, is a localized disorder characterized by initial excessive resorption and subsequent active deposition of bone. The cause of Paget's disease is unknown. No disturbance of mineral or protein metabolism has been demonstrated; hence, it is not considered a metabolic bone disease. The condition is rare in those below the age of 40 years; among those older than 40 years, the prevalence is said to be approximately 3%, men being affected slightly more frequently than women (13). The pelvic bones are the most commonly involved, followed by the femur, skull, tibia, lumbosacral spine, dorsal spine, clavicle, and ribs (14).

Symptoms and Signs. The most common presenting symptom is pain, which can be bone pain from the active disease process or pain arising from secondary complications, such as nerve compression, fracture, or osteoarthritis. The bone pain is usually continuous and often interferes with sleep. When the pelvis is involved, patients usually experience pelvic or low back pain, or both.

Diagnosis. The diagnosis of Paget's disease is usually not difficult because of the bone deformity (13,14). Radiographic studies demonstrate lytic, sclerotic, or mixed changes. Laboratory studies might reveal an increase in the urinary hydroxyproline level, reflecting increased degradation of bone collagen consequent to elevated bone resorption.

Treatment. Treatment is directed at inhibition of osteoclastic activity, which produces symptomatic improvement and restoration of normal bone architecture. Three classes of drugs are now used to achieve this therapeutic objective: hormones, diphosphonates, and antibiotics. Calcitonin, a polypeptide hormone produced in the perifollicular cells of the thyroid, blocks bone absorption, decreasing skeletal turnover and leading to a mild hypocalcemia (13,14 and 15). The drug is given parenterally; symptomatic improvement is noted in a few weeks, reflected by a decrease in the serum alkaline phosphatase and hydroxyproline levels to 50% of pretreatment levels (15). Standard pharmacologic treatment of chronic pain with NSAIDs and, when necessary, opioids can be used.

Neoplastic Diseases

Primary Bone Tumors

The most common types of primary bone tumors of the pelvis are chondrosarcoma, followed by osteosarcoma, fibrosarcoma, giant cell tumor, and chondroblastoma (16,17). These neoplasms can produce pain that is usually continuous, dull, and aching in character; of moderate to severe degree; and generally localized to the region of the primary tumor. If the tumor encroaches on the sciatic nerve, obturator nerve, or both, however, the pain can be accompanied by neurologic symptoms and signs.

Diagnosis. Because patients with primary bone tumors of the pelvis might be candidates for local resection of the pelvis or for hemipelvectomy, it is essential for the surgeon to determine the local extent of the tumor as precisely as possible (17). Only then can the surgeon accurately predict whether patients require a local resection of part of the pelvis or hemipelvectomy. For a primary bone tumor, it is necessary to ascertain the intraosseous and extraosseous extent of the tumor, which cannot be done by physical examination alone. Consequently, it is essential to carry out extensive diagnostic imaging. The use of conventional radiography to determine the extent of the tumor is complicated by the depth of the pelvis and by its obstruction by soft tissue. Therefore, radiographs taken at 45 degrees of an anterior and posterior rotation provide more information than conventional anteroposterior views (17). Moreover, conventional tomography is more useful than conventional radiography for visualizing the intraosseous extent of the tumor. Skeletal scintigraphy is moderately useful for demonstrating the local intraosseous extent of the tumor in the pelvis. Angiography is helpful for defining the relationship of the tumor to the major intrapelvic vessels. CT scanning is the single most reliable diagnostic procedure for viewing the soft tissue extent of a primary pelvic bone tumor (17). Magnetic resonance imaging is particularly valuable in assessing soft tissue involvement.

Treatment. Local pelvic resection can be used for removal of a primary bone tumor. Marginal excision, a section at the periphery (margin) of the pseudocapsular tumor, is usually chosen for a benign tumor and also for a locally aggressive tumor such as a giant cell tumor or chondroblastoma (17). A wide excision is usually indicated for a low-grade malignancy such as a low-grade chondrosarcoma or a recurrent aggressive Paget's tumor, such as a giant cell tumor. Radical resection (in which the plane of dissection leaves a cuff of normal tissue and continuity with the tumor outside a normal anatomic compartment) is indicated for a high-grade malignant tumor. If the operative procedure is going to be used as an adjunct to other forms of treatment, as in the case of Ewing's sarcoma, the surgeon might elect to decrease the extent of the surgical incision from a radical to a wide excision. Local pelvic resection should not be performed for palliation or in the presence of metastasis because recovery is slow (17). A decision regarding the best therapeutic strategy for particular patients with specific primary bone tumors in the pelvis should always depend on the personnel and resources available and on a collaborative multidisciplinary and interdisciplinary effort.

Metastatic Disease of the Pelvis

Numerous studies have shown that the pelvis is one of the most important and frequent sites of metastasis from such primary tumors as breast, prostate, and, less frequently, thyroid, kidney, bronchial, and rectal tumors (18). Thus, Lenz and Freid (19) carried out radiologic and postmortem studies of 81 patients with skeletal metastasis from breast cancer and found that the pelvis was affected in 51 patients (63%). Among 50 patients with advanced breast cancer, metastasis to the pelvis occurred in 66% of patients (20,21).

Symptoms and Signs. The most frequent symptom associated with bone metastasis is pain, which characteristically develops gradually over weeks or months and becomes progressively more severe. The pain is usually localized and is typically more severe at night. Percussion tenderness at the site of involvement is a highly reliable clinical sign (22). Stretching of the periosteum of the involved bone, either by direct tumor expansion or by weakening of the bone by mechanical stress at the tumor site, precipitates pain in many patients. In most patients, bone metastasis is likely to involve other sites, and the initial site of pain might be elsewhere. In such cases radiographs must be obtained to rule out a pathologic fracture.

Pain is often positional in nature and can be temporarily relieved by shifting weight from the involved area. Expansion of a tumor located in the ischium can cause encroachment on the obturator or the sciatic nerve, or both, causing pain and neurologic deficits in the distribution of these nerves.

Diagnosis and Evaluation. The physical examination is one of the most important elements in the evaluation of patients with osseous metastasis. Patients with severe pain are often heavily medicated, and precise location of the pain requires interviewing and examining patients just before the next dose of medication is administered. Multiple areas of pain are often noted in patients with extensive bone metastasis. Routine radiographs do not reveal bone metastasis until the bone density has changed by 30% to 50%, so it is necessary to use more sophisticated radiographic imaging techniques such as CT and magnetic resonance imaging or radionuclide scanning (22). Occasionally, patients develop pain without bone scan or radiographic evidence. In such cases, it might be necessary to carry out a biopsy, if this is feasible.

Treatment. In general, bone metastasis requires treatment directed toward relieving the pain and preventing fracture of weight-bearing bones. Mauch (23) has firmly stated that, with few exceptions, a radical curative approach to the treatment of bone metastasis is unrealistic, and its attempt only risks treatment complications in patients with incurable disease. Before relying solely on opioid medication, anticancer therapy should be attempted (see Chapter 35, Chapter 36 and Chapter 37). Localized radiation therapy is a highly effective measure in treatment of bone pain, offering partial or complete relief in 75% of patients. Options for radiation and radionuclide therapy are discussed in detail in Chapter 37.

During radiation therapy for cancer, pain should be controlled with appropriate doses of systemic analgesics consisting of NSAIDs, which are specifically effective in the relief of bone pain and, if necessary, supplementation by weak or strong opioids (see Chapter 36). In patients whose pain is severe or excruciating, the use of continuous epidural opioid therapy achieved by the insertion of a catheter into the epidural space and by injection of an opioid should be considered.

Myofascial Disorders

Muscle Spasms

Pelvic muscle spasm in women was discussed in Chapter 72. A similar condition occurs in men, who experience pain in the perineum, rectum, and back that is associated with intense local spasm of the levator muscles. Acute transient muscle spasm can develop following injury to the perineum. In such cases the pain might be moderate, but occasionally is severe enough to disable patients completely. The pain is usually sharp and felt deeply in the perineum, with radiation to the coccyx, sacrum, and rectum. Patients respond to application of deep heat and massage. If the pain is severe enough, injection of local anesthetic into the spastic muscles might be required (see Chapter 102).

An alternate procedure involves administration of a low caudal analgesia limited to the lower three sacral segments. This is done by injecting 4 to 5 mL of a long-acting local anesthetic (e.g., 0.25% bupivacaine with epinephrine 1:200,000), which provides complete pain relief for 8 to 10 hours. In some patients it might be necessary to insert an epidural catheter through the sacrococcygeal hiatus and advance it to the S-3 level. This permits repeated injection of the local anesthetic or continuous infusion using an infusion pump.

Generalized perineal muscle spasm unrelated to trauma can persist and produce chronic dull aching pain felt deep in the lower abdomen, pelvis, perineum, rectum, and lower part of the sacrum (see Chapter 72). In many patients the pain is of mild to moderate intensity and can be exacerbated by intercourse and emotional tension. Drinkwater and associates (24) studied 14 patients with chronic perineal pain who had gained no lasting relief from various therapies and were considered to be on a “nothing further can be done” status. They examined the profile of pain personality, nonpain problems, and attitudes to treatment parameters. In addition to the clinical interview schedule, they administered the McGill Pain Questionnaire, Cattell's 16 Personality Factor (PF) Questionnaire, and the Claybury Battery. They found that the means of all variables in the McGill Pain Questionnaire exceeded (indicated more pain) those quoted by Melzack for menstrual, arthritic, cancer, dental, back, phantom limb, and postherpetic pain (see Fig. 71-1). On the average, the affective subclasses were more frequently used than the sensory subclasses. The mean was low compared with that in psychiatric groups, and the mean 16 PF profile showed significant conscientiousness. They found that all 14 patients were more responsive to behavioral psychological intervention than to psychotherapy. Apparently, most of the patients studied had perineal pain primarily as a result of psychological factors, and behavioral approaches such as stress management and muscle relaxation techniques were part of the general management plan. This is extensively discussed in Chapter 72.

Postoperative Muscle Spasm

Surgery on perineal structures or pelvic viscera, like operations on other parts of the body, invariably produces reflex spasm of skeletal muscles that result in moderate to severe pain. Usually, the muscle spasm and pain occur during the first and the second postoperative days. The treatment of such pain is discussed in

detail in Chapter 41.

Some patients who undergo laminectomy for removal of a herniated disk or for spinal stenosis have repeated bouts of severe muscle spasm in the low back, perineum, and upper thighs. Rather perplexingly, the reflex muscle spasm does not occur during the first 2 days after the procedure, but begins as soon as patients ambulate, perhaps on the third or fourth postoperative day. The spasm and associated severe pain last only a few minutes. These bouts are triggered by movement of the trunk, especially the pelvis, although sometimes they occur while patients lie in bed.

The mechanism of such abnormal reflex responses is unknown, but they might result from sensitization of the spinal cord neurons involved in reflex mechanisms, which is initiated by the surgery and sustained by a postoperative nociceptive barrage. Surprisingly, this problem is not discussed in textbooks of orthopedic surgery.

Therapy is directed toward decreasing the hyperreflexia with pharmacologic agents. Diazepam, given in doses of 10 mg every 4 hours, has proven to be highly effective in terminating the spasm and associated pain. Because this problem follows low back surgery, it is discussed in Chapter 76.

Myofascial Pain Syndromes

Pain in the pelvis and perineum can be provoked by myofascial pain syndromes with trigger points. Because the causes, pathophysiology, diagnosis, and treatment of myofascial pain syndromes with trigger points are discussed in detail in Chapter 29, only brief mention is made here of several syndromes that produce pain in the pelvis and gluteal region with reference to the perineum. These include trigger points in the lowermost portion of the external abdominal oblique, the lower part of the rectus abdominis, gluteus maximus, gluteus medius, and gluteus minimus (25,26 and 27). The pattern of pain produced by trigger points in the lowermost portion of the abdominal wall is depicted in Figure 69-5B. Pain is produced in the groin and testicle, with some radiation to the lower abdominal wall and upper part of the interior thigh.

Trigger points in the lateral border of the rectus abdominis muscle produce pain in the right or left lower quadrant, depending on which side the trigger point is located. Trigger points in the right lower rectus abdominis produce pain and tenderness in the region of McBurney's point, which simulates the pain of acute appendicitis (see Fig. 69-6A). Trigger points in the lowermost part of the rectus abdominis bilaterally produce pain in the hypogastric region. Through somatovisceral reflexes, trigger points can intensify the pain of dysmenorrhea or can cause other types of dysfunctions of the pelvic viscera (26).

Trigger points in one or more of the gluteal muscles and in the piriformis muscle frequently produce pain in the lower back over the sacrum and in the glutei, with spillover pain to the perineum and thigh. Because these syndromes produce pain primarily in the low back, lower limbs, or both, they are discussed in Chapter 75 and Chapter 77.

PAIN OF NEUROPATHIC ORIGIN

Pain originating in the pelvis and perineum was traditionally thought to be commonly due to organ pathology. In the last edition of this book, much of the discussion was focused on organ disorders, and there was a substantial section on pelvic pain without organ pathology. The pelvic pain sufferer was largely at the diagnostic and therapeutic discretion of the physician, who may have chosen conservative therapy if his or her specialty was medicine or neurology or who may have opted for radical therapy if his or her specialty was surgical. Unfortunately, many patients were repeatedly surgically treated with no resolution of their pain and with the disturbing epithet on discharge, “the pain may well be in your head.” We now believe that most chronic occult pelvic pains are caused by neuropathic disorders. Some of these include lesions of the spinal cord, meninges, lumbar or sacral nerve roots, and peripheral nerves that supply the pelvis and perineum. The pathophysiology, diagnosis, and treatment of most of these conditions have been discussed in detail in Chapter 72. Several peripheral neuropathies not considered in Chapter 72 are discussed in detail here.

Central Pain Syndromes

Lesions of the Spinal Cord, Meninges, and Epidural Space

Pelvic pain may be caused by lesions of the spinal cord, nerve roots, and peripheral nerves. These include intramedullary lesions located in the lower lumbar or sacral cord segments (i.e., conus medullaris). Tumor, multiple sclerosis, syringomyelia, abscess, and trauma can occur in this region. Pain from intramedullary lesions is usually spontaneous in nature, burning, diffuse, and poorly localized. It can be further characterized as continuous or explosive and can be associated with hyperalgesia, hyperpathia, and paresthesia. Mass lesions almost always produce back pain and tenderness as well as neurologic signs.

Extramedullary intrathecal lesions can be primary or metastatic. Examples include neoplasms, abscesses, and hemorrhages that initially produce pain localized to the low back and pelvis. The pain often becomes radicular and is aggravated by straining and coughing. Other signs include paravertebral tenderness, paresthesia, sensory loss, muscle weakness, and reflex loss in those lumbosacral spinal cord segments in which the lesion is located.

Epidural spinal cord and nerve root compression may also be produced by a primary or metastatic tumor, hemorrhage, or abscess, all of which may produce pressure on the conus medullaris. These invariably produce low back and pelvic pain, but often also involve the lower limbs. An unusual example of an iatrogenic injury occurred in a patient who had been heparinized and in whom lumbar puncture for subarachnoid block was followed by hemorrhage in the lower lumbar and sacral spinal canal. The patient developed neurologic, sensory, and motor dysfunction in the pelvis, lower limbs, and perineum.

Inflammatory conditions may also be a cause of pain; an example is arachnoiditis of the cauda equina; this condition is characterized by inflammation and fibrosis of the arachnoid membrane and scarring of the nerve roots. In most patients the condition involves multiple segments of the cauda equina, but occasionally it is limited to the roots of the lower three sacral and coccygeal nerves. It is manifested by pain, sensory deficits, and motor dysfunction in the *saddle region*, and is often associated with dysesthesia and paresthesia. This disease was seen much more often when oil-based myelographic agents were used; there is no effective therapy for this condition.

Lesions of the Roots or Spinal Nerves of the Lumbosacral Segments

Lesions of the roots of the spinal cord, or rootlets, produce a radiculopathy, consequent radiculalgia, or segmental pain. Such pain is quite characteristic, with a definite distribution pattern, and can be caused by acute and infectious processes such as herpes zoster, chronic infection, or metabolic or toxic neuropathy. Other etiologies include actual compression of nerve roots themselves by tumor growths, disk protrusions, vertebral fractures, osteophytes, and even pressure exerted by arthropathies; the latter cause encroachment by swelling due to inflammation.

Peripheral Neuropathy

Iliohypogastric, Ilioinguinal, or Genitofemoral Neuralgia

Etiology and Pathophysiology. This is a common peripheral neuropathy in patients who have had surgery or other types of traumas in the lower abdominal wall. The pain is engendered by retraction of these nerves that are located along an incision line. This results in stretch and compression neural injuries. The onset of pain is variable, perhaps related to the intensity of the injury. Many gynecologic patients, for example, have a Pfannenstiel incision that cuts across the regions of the ilioinguinal and iliohypogastric nerves. The actual injury may be from retraction in the lower corners of this incision, where the nerves are located. Many patients have histories of repeated abdominal exploration because of an initial diagnosis of intraabdominal pathology and recurrent operative interventions without resolution of pain. The *diagnostic laparotomy* is becoming less popular nowadays due to the widespread use of laparoscopy, but the latter procedure may also cause abdominal wall neuropathy due to placement of the scope at or near a nerve resulting in the same type of injury that occurs with laparotomy. Some patients may have many nerves injured.

The most common neuropathies in this area are of the iliohypogastric and ilioinguinal nerve. One must also consider injuries of the genitofemoral nerve, the lateral femoral cutaneous nerve, or even multiple nerves. The pathophysiology of the injury can be a stretch or tear or even partial avulsion; the nerve may atrophy and undergo fibrosis (28). Other rarer causes of neuropathy of these nerves include inflammatory disorders such as herpes and pelvic tumors that compress these nerves in the pelvic side wall. Neuralgia may also be consequent to unintentional section of one or more nerves, with development of a neuroma. Applegate wrote an

excellent paper on these neuropathies (29).

Symptoms and Signs. Neuralgia of one or more of these superficial abdominal nerves is characterized by a burning, aching pain in the distribution of the affected nerve. If the iliohypogastric nerve is involved, pain is produced in the inguinal and suprapubic regions, with occasional reference to the hip region. If the injury involves the ilioinguinal and genitofemoral nerves, the pain radiates to the inguinal region and to the anterior part of the labia majora in the female subject or to the scrotum and root of the penis in the male subject, as well as to the inner and anterior surfaces of the thigh. The pain pattern is variable but usually one of four patterns dominate and these include (a) incremental, typified by an increasing pain during the day and maximized with activity; (b) decremental, typified by maximum pain on awakening and gradual improvement during the day; (c) static, typified by a continuous and unchanging pattern throughout the day; and (d) sinusoidal, typified by an increasing and decreasing pattern throughout the day. All of these general patterns can be aggravated by forcible stretching of the affected part, coughing, sneezing, general tension in the abdominal muscles, or vigorous sexual intercourse.

On examination, pain can be triggered by pressure in a narrowly circumscribed area of an operative scar (28). Usually tenderness extends along the course of the nerve from the anterior superior iliac spine to the external genitalia. When the genitofemoral nerve is involved, the internal ring of the inguinal canal can be painful. Associated with pain is cutaneous hyperalgesia and occasionally hyperesthesia, especially to cold stimuli. In some patients, scratching the skin produces less or no reddening on the affected side as compared with the normal side, indicating a degeneration of afferent C fibers. A lesion of the hypogastric nerve can be associated with decrease or loss of the lower abdominal reflex. Similarly, the cremaster reflex may be absent on the affected side of involvement of the genital branch of the genitofemoral nerve.

Diagnosis. Diagnosis is made by history, characteristics of the pain, examination of abdominal scars, and the finding of a peripheral neuropathy. It is typical that the pain is aggravated when the examiner uses the blunt end of a pen to push straight downward along the course of the involved nerve. When these maximum tender points are identified, they are marked with a pen. The patient is asked to lift her head as pressure is placed gently on these marked positions. The pain should be considerably intensified by this maneuver. Infiltration of the affected nerve with a local anesthetic can eliminate the pain and thus help to confirm the diagnosis.

Treatment. The typical pattern of this type of pain is persistence without spontaneous remission (28). A series of local anesthetic nerve blocks with a long-acting local anesthetic, such as 0.25% bupivacaine with epinephrine, done on a scheduled basis for a series of five blocks, should be instituted. Nearly 60% to 70% of patients respond favorably to this therapy by itself. If a sensitive neuroma is detected, and its palpation produces aggravation of the pain, injection of a local anesthetic into the neuroma can relieve the pain and associated symptoms. We do not recommend neuroma injection with 0.5 mL of alcohol or phenol, because this has been associated with the risk of producing postinjection neuropathy. Resection of the nerve proximal to the region of injury or dorsal rhizotomy may be undertaken in severely disabled patients who do not respond to medications or local injections.

Obstetric Neuropathy

Femoral Nerve. The femoral nerve, derived from the L-2 to L-4 spinal nerves, comes off the lumbar plexus and takes form in the psoas muscle. It emerges from the lateral border of the psoas and courses inferiorly downward between the psoas and the iliacus muscles. The femoral nerve enters the thigh after coursing under the inguinal ligament and soon separates into a number of motor and sensory branches. It supplies major motor innervation to the quadriceps femoris muscle and major sensory innervation via the saphenous nerve. A large proportion of femoral nerve disturbances are iatrogenic and are related to surgical procedures (30,31 and 32). The femoral nerve can be injured either in its intrapelvic or extrapelvic portion. The most common cause of femoral nerve injury is abdominal pelvic surgery; abdominal hysterectomy is the single most common procedure to lead to this nerve injury (32). For some time, gynecologists and general surgeons alike have enjoyed the exposure and convenience of the use of self-retaining retractors. Unfortunately, the lateral blades can directly stretch or compress the femoral nerve itself or cause pressure and ischemia along the course of the psoas muscle and femoral nerve in the lateral pelvic wall (31,32 and 33). Factors that increase the likelihood of nerve injury during abdominal and pelvic surgery include thin, muscular patients, the use of a Pfannenstiel incision, and large lateral blades (32,33). Femoral nerve injury can also be associated with various transplantation operations where vascular injury may occur with resultant ischemia and or hematoma near the nerve (34). Laparoscopic operations and other general surgical, urologic, and vascular surgical operations can also be complicated by femoral nerve injuries (30,32,35). Orthopedic surgical procedures can damage the femoral nerve, due to compression of the nerve, hematoma formation, or inappropriate use of retractors. The heat of bone cement and compression during its application can also lead to nerve injury (36,37).

Pudendal Nerve

Etiology. The most common injury to the pudendal nerve occurs during childbirth as documented by the many studies that have originated from England in the 1980s. This condition has commonly been labeled *obstetric neuropathy* (38). Both reversible and irreversible damage due to childbirth has been well documented (39). There are other etiologies, however, and some of these include (a) unilateral pudendal neuropathy with neuralgia that results from trauma due to fracture of the ischial spine; (b) entrapment of the nerve or of some of its branches, which pass through the sacrospinous ligament; (c) nerve compression during its course in Alcock's canal; and (d) damage to the nerve during pudendal nerve block if the nerve is penetrated with a large, dull needle. Axons can be severed in a jagged fashion and intraneural hemorrhage can occur.

Bilateral pudendal neuralgia is extremely rare and can be the result of trauma such as during bicycle or horseback riding, or following injury of the type that occurs when the patient falls and straddles a blunt and firm object (Fig. 74-1). One or more branches of the pudendal nerve can be damaged when surgery or trauma results in scars in the perineal area occur.

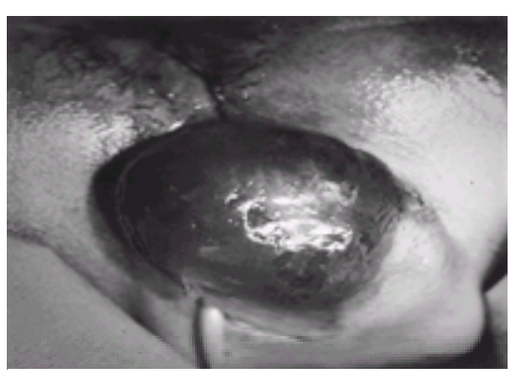

Figure 74-1. Acute traumatic vulvovaginal hematoma. The patient was seen for intense pain and inability to urinate. Treatment consisted of immediate evacuation of the hematoma and ligation of the bleeding sites by figure-eight sutures. The patient's recovery was rapid and uneventful.

Symptoms and Signs. Pudendal neuralgia is variable in reference to symptomatology but is usually characterized by mild to severe burning pain with occasional bouts of lancinating pain, cutaneous hyperalgesia, hypalgesia, deep tenderness, paresthesia, tingling, and subjective numbness. The cutaneous tenderness can be so severe as to prevent the patient from sitting or from engaging in sexual intercourse. Paresthesia can cause the patient to scratch, resulting in irritation of the skin.

Diagnosis. Diagnosis is made on the basis of the history and physical examination and, in the case of trauma or fracture, by radiographic evidence; palpation can reveal a scar involving the nerve or one of its branches. Diagnostic pudendal nerve block with a local anesthetic may allow confirmation of the diagnosis.

Treatment. Posttraumatic neuropathy consequent to needle penetration usually resolves over a period of weeks. Severe nerve damage by fracture can cause the neuropathy to persist for months. *Obstetric paralysis* usually resolves spontaneously in several months. The treatments for neuropathies as discussed in Chapter 19 are applicable to pudendal nerve injury pain. Periods of severe pain can be controlled by pudendal block achieved with 0.25% bupivacaine with epinephrine, using extreme care not to damage the nerve further with the needle.

Anorectal Dysfunction. Anorectal dysfunction is quite common among women. The onset is typically immediately after vaginal delivery, and the impact of the symptomatology increases with age. Women are often too embarrassed by their problem and thus do not talk about or complain to their doctors. Some do choose to

discuss the problem and often find lack of physician interest due to inadequate education and deficient understanding of the various diagnostic and therapeutic options. Anal incontinence causes involuntary loss of gas or feces and it is not a rare condition, occurring in approximately 10% of the population (40,41,42,43 and 44). The ramifications of this disorder cause emotional, psychological, and social problems of a severe nature that can disrupt personal and professional life. By far the most common etiology of anal incontinence is obstetric trauma. Vaginal delivery can damage the anal continence mechanism by direct injury to the anal sphincter muscles, damage to the motor innervation of the pelvic floor, or both (38,39,44). Vaginal delivery can result in significant injury to pathways of innervation of the pelvic floor musculature.

Sciatic and Obturator Neuropathy

Etiology. Neuropathy of the obturator or sciatic nerve, or of the pudendal plexus, can be caused by continuous pressure by the presenting part during a prolonged labor and vaginal delivery; or it can be caused by direct damage by the edges of the obstetric forceps during forceps delivery (45). Usually one or more nerves on one side are involved, but occasionally bilateral involvement occurs. Although obstetricians generally attribute the neuropathy to local anesthesia, most reported incidents have occurred with general anesthesia or no anesthesia at all (45). In some cases the condition developed in parturients who were managed with subarachnoid or epidural anesthesia, but careful evaluation of the symptoms and signs eliminated this cause (see following section).

Symptoms and Signs. Usually, soon after delivery, or 1 or 2 days later, the patient has a burning, aching pain in the distribution of the affected nerve and frequently motor impairment or loss; hence the term *obstetric paralysis*.

Diagnosis. Differential diagnosis is simple if one considers that the symptoms and signs in obstetric neuropathy have a peripheral nerve distribution. Often alleged to be due to spinal or epidural blocks, this concept is most unlikely. Involvement of the roots of a single peripheral nerve and the sparing of other nerves supplied by the same lumbosacral spinal segments is impossible as a complication of subarachnoid or epidural block because, with these procedures, the neurotoxic effect of the local anesthetic is bilateral and involves the roots of all anesthetized nerves.

Treatment. Treatment of obstetric neuropathy consists of rest and appropriate orthotic devices to assist ambulation. Recovery is usually slow but is complete in most patients. Pain is controlled with NSAIDs given over several weeks. If these are not sufficient, they can be supplemented with opioids for 2 to 3 weeks. Long-term beneficial effects can be obtained by referral to physicians who are aware of the pathophysiology of these conditions and who are skilled in their diagnosis and treatment. Unfortunately, such physicians are few and far between, because most have just not been trained in pelvic pain management.

Tumor Infiltration of the Lower Sacrum and Sacral Nerves

Etiology. Metastasis of a neoplasm or primary sacral tumors in the lower half of the sacrum can result in compression of the nerves that contribute to the pudendal plexus and nerves. In other cases the lumbosacral plexus can be compressed by the tumor or marked lymphadenopathy.

Symptoms and Signs. Pain in the distribution of the sacral nerves occurring in patients in their fifth, sixth, or seventh decade is frequently the result of the spread of bladder, gynecologic, or colonic cancer. The pain is dull, aching, and burning in character, is frequently located in the midline, and is associated with a burning or throbbing pain in the soft tissues of the rectal and perineal regions. The pain is aggravated by sitting and lying down.

Examination reveals tenderness over the sacrum and region of the sciatic notch, associated with sensory loss in the perianal region and in the genitalia, and can be accompanied by hyperpathia. The pain and sensory deficit can initially be unilateral but later can progress to bilateral sacral nerve involvement, with consequent sphincter incontinence and impotence.

Diagnosis. Diagnosis is made through the history, physical examination, and imaging, including radiography, CT, or magnetic resonance imaging of the pelvis, all of which show sacral erosion with a presacral mass.

Treatment. Treatment should begin with anticancer therapy (see Chapter 36). Pharmacologic agents, regional anesthesia, neurosurgical procedures, or a combination of these can be used to control the pain, depending on its severity and on the resources available. In patients who have severe unilateral pain, a trial or subarachnoid local anesthetic block followed by subarachnoid neurolysis can be useful (see Chapter 104). With precise technique and skill, analgesia can be produced predominantly on one side. Another option is cordotomy or myelotomy (see Chapter 106). In patients with bladder or anal sphincter dysfunction, alternative procedures include administration of a low caudal block with a local anesthetic; if relief is complete it can be followed by injection of 5% aqueous phenol, phenol in glycerin, or 25% alcohol. Cryoanalgesia is another alternative. Sacral rhizotomy either by radiofrequency or by open surgery can also be used (see Chapter 104).

Phantom Pelvic Visceral Pain Syndromes

Phantom Urinary Bladder Pain Syndrome

Review of the literature reveals that phantom urinary phenomena occur rarely following cystectomy, spinal cord injury, and hemodialysis, in which previous disease of the kidney, urethra, and urinary bladder was present.

Symptoms and Signs. Brena and Sammons (46) reported a case of a 38-year-old woman who complained of midline suprapubic pain that had started 1 year previously, after removal of the bladder for chronic severe cystitis. The patient described the pain as being continuous and feeling like “having a very full bladder,” with recurrent episodes of sharp, burning acute pain. She rated the degree of pain as 90 on a scale of 0 to 100 (0, no pain; 100, intensity of pain comparable with that of labor pain), and further stated that the discomfort was “tearing her nervous system apart.” Treatment with oxycodone, diazepam, and other mild analgesics was ineffective.

The patient's past medical history and social profile appeared normal except for a sharp decrease in social, recreational, and sexual activities because of the continuing pain (46). Physical examination revealed no abnormalities other than tenderness to palpation and a decreased pinprick pain threshold over the suprapubic region in both lower quadrants. She also had tenderness to palpation in the right flank, with a number of trigger points over the paravertebral area in the lumbar back region. Neurologic examination revealed no abnormalities. Brena and Sammons (46) made the important point that their patient had had continuous pain caused by the urinary tract infection prior to surgery. They cited three other reports pertaining to this phenomenon. One involved phantom urinary bladder following cystectomy for recurrent bladder tumors. Another report described seven patients with spinal cord injury who had experienced sensations of unpleasant urinary bladder distension after drinking water. The third report concerned 24 of 35 patients undergoing hemodialysis because of severe renal damage, with average urinary outputs of no more than 500 mL. These 24 patients experienced feelings of discomfort, bladder distension, and an urge to micturate.

Treatment. Brena and Sammons (46) managed their patient with a series of six lumbar sympathetic blocks with 0.25% bupivacaine combined with a course of six applications of transcutaneous electrical nerve stimulation, and relaxation-assertiveness training, given over a 10-day period. At the end of the treatment and at 3 and 6 months' follow-up, the patient reported that the phantom bladder sensation had been reduced to 25% of previous levels and that the suprapubic burning pain and tenderness were no longer present. It has been reported that regional analgesia carried out for several days prior to amputation in patients who had pain in the limb before the surgery and continued for several days postoperatively decreases the incidence of painful phantom sensations (see Chapter 102). This would suggest that patients who have severe urinary bladder pain (or severe pain as a result of other pelvic visceral disease) should receive continuous epidural analgesia extending from T-9 to S-5 for 48 hours prior to removal of the viscus and for 2 to 3 days postoperatively. Although the literature review suggests that phantom bladder is rare, it is likely that the condition has been underreported. Notwithstanding its low frequency, aggressive management with regional analgesia should be considered to relieve the discomfort of patients who experience these phenomena.

Phantom Anus Pain Syndrome

Boas (47) reported that, among 177 patients who had undergone abdominoperineal surgical resection, 40 patients (23%) developed characteristics of phantom anus perineal pain. Analysis of the characteristics of the pain, and especially of the time of onset, revealed that these patients fell into two subgroups, early onset and late onset.

Symptoms and Signs. Patients in the early group experienced phantom anus perineal pain within days or weeks of the surgery, and the pain was rated as having an intensity of 2.1 ± 0.8 on a scale of 0 to 4 (32). Of those in this group, 18 patients (75%) experienced aching pain, 8 (33%) had burning pain, and 4 (17%) had sharp or

stabbing pain. In a considerable number of those in this early group (seven patients) the pain was mild, but among those with burning pain about the nonexistent anus, the pain was of high intensity, having a score of 2.6 ± 0.5.

In the 16 patients who experienced pain months or years after the surgery, the pain had greater intensity (2.4 ± 0.9). In 14 of these 16 patients (88%) the pain was aching, 2 (13%) experienced burning pain, and 6 (38%) had a sharp or stabbing component to the pain; those in this last group (with the sharp stabbing pain) recorded high scores (2.8 ± 0.9). The most common factor that initiated or aggravated the pain in the entire group was sitting on hard surfaces, with tiredness being a significant contributing factor in 25% of all patients. Spontaneous pain was experienced by nine patients (38%) in the early group and by four (25%) in the late group. None of the patients experienced cutaneous numbness or hyperesthesia around the perineal scar.

Treatment. Fifty-eight percent of those in the early group and 69% of those in the late group noted that rest and use of cushions relieved the pain. Systemic analgesic drugs proved to be almost totally ineffective for the relief of early-onset–type pain, but helped some in the late-onset group. Boas (47) reported that intravenous lidocaine administered in doses of 1.5 to 2.0 mL per kg totally abolished the phantom anal pain for several hours. Subarachnoid block, with small doses of a hyperbaric solution of lidocaine, reduced the pain intensity but did not abolish the phantom sensation until the block extended to the T-10 to T-12 spinal cord levels. Boas (47) also noted that the phantom pain could be relieved by a combination of tricyclic antidepressants and antiepileptic drugs, suggesting a neuropathic origin for this pain syndrome.

PAINFUL VISCERAL AND DERMATOLOGIC DISORDERS

Various painful disorders of the skin and subcutaneous tissue can cause pain in the rectum, perianal region, perineum, and external genitalia. These have been discussed in Chapter 32, Chapter 66, Chapter 72, and Chapter 73 and are briefly presented here.

Proctalgia Fugax

This disorder is often a diagnostic enigma for physicians, because by the time the patient comes to the office for diagnosis and treatment, the pain has usually abated. The onset is sudden, is typified by severe stabbing rectal pain, is episodic in nature, and can occur day or night without warning. In some patients, there is sphincter dysfunction; in others there is a pudendal neuropathy. Some believe the etiology may be tied to an intussusception in the bowel. Other physicians, who are frustrated and unable to come up with any explanation, blame psychological problems for the disorder. Treatment can consist of taking an analgesic, applying heat to the area locally, and trying to abort the attacks by taking small doses of b-blockers. In one study of 38 patients 76% experienced complete relief, while another 16% had good relief and only 8% had no change in the status of pain (48).

Rectal and Anal Pain

In addition to fissure *in ano* and hemorrhoids, superficial ulcers of the rectum and anus can be caused by syphilis, tuberculosis, typhoid, dysentery, and, of course, malignant lesions. These conditions cause pain in the rectum, anus, and perianal region that is sharp and burning in character and is aggravated by defecation. These conditions can also be associated with tenesmus, diarrhea, blood or mucus, and spasm of the sphincter muscle. A careful proctoscopic examination can reveal fissure or hemorrhoids and establish the diagnosis.

Submucous Proctitis and Periproctitis

Submucous proctitis and periproctitis, fistula *in ano*, and rectal papillitis and cryptitis can also produce a sharp throbbing pain in the perirectal and perianal regions, but unlike proctalgia fugax that comes on spontaneously, they are aggravated by defecation or walking. The pain is associated with acute tenderness, swelling, and redness, and if the infection is severe, with fever, malaise, and other systemic symptoms.

Pruritus Ani

Pruritus ani from pinworms and other parasites, hemorrhoids, cryptitis, papillitis, and other superficial lesions causes moderate to severe intractable itching of the anal region. This produces the urge to scratch and initiates the vicious circle of scratch, which leads to more itching, which leads to more scratching, which leads to abrasion of the region and development of pain. The diagnosis is made by inspection of the offending cause by inspection, microscopic examination, and careful history.

Furuncles and Carbuncles

The perianal region can also be the site of acute furuncles and carbuncles, which are painful staphylococcal abscesses of one or more hair follicles in the hair-bearing area around the anus. Treatment of most of these dermatologic disorders is considered in Chapter 32. Obviously, if the condition is caused by bacteria, antibacterial drugs constitute the first phase of treatment. Patients with an infectious process, such as periproctitis, furuncles, or carbuncles, should have cultures made of the superficial pustules to determine the antibiotic sensitivity of the causative agent. During the primary therapy it is essential to control the pain, which can range in intensity from a minor annoyance to disabling discomfort, with appropriate systemic analgesics, including opioids if the pain is severe enough.

In case of severe, excruciating pain, temporary relief can be provided by administration of a continuous low caudal block except in cases of infection over or adjacent to the caudal hiatus. This procedure is especially useful for those with pruritus ani, because it provides complete relief of itching for several days and thus breaks the vicious circle mentioned previously. A low caudal block with 0.2% ropivacaine given in volumes of 3 to 4 mL produces analgesia of the last two or three sacral and coccygeal nerves, and thus eliminates the abnormal sensory input from this region without any substantial motor blockade. This treatment can be repeated several times to bring on a desired effect and break the severely painful cycle. Bristow and Foster (49) reported that 10 of 12 patients with severe spasmodic painful tenesmus were relieved with sympathectomy; this operation is rarely used today for this condition.

Dermatologic Disorders of the Perineum and External Genitalia

Injury to the skin caused by superficial trauma and dermatologic conditions can also involve the rest of the perineal area including the female external genitalia, or the scrotum and penis. These conditions include condyloma latum, which produces pain and tenderness if the warts are ulcerated and is associated with muscle spasms. Pain caused by trauma to the female perineum and genitalia is discussed in the section on vestibulitis in Chapter 72. In addition to injury, ulcers, chancroid, and condylomata lata can cause localized pain and swelling in the scrotum.

Another condition that can cause pain and discomfort in the pelvic and perineal area is hydrenadenitis suppurativa, a chronic painful suppurative inflammatory disease of the apocrine glands in the genitocrural area. This is discussed in Chapter 32. Treatment of hydrenadenitis suppurativa requires incision and draining of abscesses and palliative intralesional corticosteroid irrigation. Because this condition is often caused by multiple organisms, a broad-spectrum antibiotic should be used. The therapy of choice has been prompt diagnosis and surgical extirpation of the affected skin and subcutaneous tissue. During the primary therapy for the condition, pain and suffering should be controlled with NSAIDs or, if necessary, by oral opioids or regional anesthesia for short periods.

REFERRED PAIN

Pain Referred to the Pelvis

Pain in the pelvis can be referred from disorders of the abdomen, especially acute appendicitis, acute pyelitis, spasm of the lower bowel from acute infection or chronic bowel disorders, ulcerative colitis, diseases of the kidney and pelvis, pelvic peritonitis, chronic colitis, Meckel's diverticulum, regional enteritis, and lower rectoperineal tumors. These are all discussed in Chapter 66, Chapter 68, and Chapter 69. Less common pain referred to the pelvis includes diseases of the hip and sacroiliac joint, left psoas abscess, aneurysm of the left iliac artery, strangulated retroperitoneal hernia, lower abdominal abscess, and chemical or infectious peritonitis (see Chapter 69, Chapter 75, and Chapter 78).

Pain Referred to the Perineum

Pain referred to the perineum is frequently present with various pelvic gynecologic and urologic disorders, such as cystitis, prostatitis, and diseases of the uterus, and with other less common conditions. Similarly, diseases of the hip joint or upper thigh can sometimes cause pain radiating to the perineum (see Chapter 69).

PAIN PRIMARILY OF PSYCHOLOGICAL ORIGIN

Chronic Pelvic Pain without Obvious Pathology

In a significant number of patients who present with pelvic pain having characteristics of pain of gynecologic origin, no obvious organic pathology can be found, even with comprehensive clinical and laboratory examination. During the 1940s and 1950s various causative factors and hypotheses were presented, including pelvic vascular congestion, functional disturbance of sensory nerves, disturbance of the pelvic sympathetic system, and microscopic lacerations of the uterine ligaments, among others. In the second edition of this book, it was stated that ample evidence had been accumulated to suggest strongly that pelvic pain and associated symptoms without obvious pathology are caused primarily by psychopathology of one form or another. Psychiatric evaluation has shown that many of these women have borderline personality syndromes, neurosis, severe anxiety, depressive trends, and somatization. Chapter 72 addresses this issue and places the psychological aspects in contemporary perspective. It is more accurate to state that diagnostic studies have not identified an organic cause, and that because this pain has such a burdensome psychological impact, many patients have concomitant psychological problems. It is important to realize that the patients do not have psychological diseases that are the primary cause of their disorder, but, more correctly, that they have an ongoing severe pelvic pain problem that consumes tremendous energy and mental reserves and that taxes their psychological coping mechanisms. The history of childhood incest and abuse is common (50). We remain convinced that a neuropathic disorder is primarily responsible for chronic pelvic pain without discernible etiology. How childhood abuse and current stress facilitate such a neuropathic disorder is unclear. On the other hand, there are many women who have similar abusive histories who do not develop pelvic pain. This problem is discussed in Chapter 72.

Orchiodynia

Orchiodynia, also known as *orchidalgia* and *orchialgia*, is characterized by chronic pain in one or both testicles without any obvious pathology, even when the most modern methods of evaluation and laboratory testing are carried out. Although some patients give a vague history of an injury or vasectomy many years before, no abnormality can be found at the time of complaint. The pain is usually nagging, persistent, and achy, but only rarely and fleetingly severe. Evaluation by a physician expert in pelvic pain and in performing various diagnostic blocks should be undertaken in association with a psychosocial assessment.

Rectal and Perineal Pain of Psychiatric Origin

Approximately 10% of psychiatric patients who complain of pain have rectal or perineal pain, although this is usually mentioned as a secondary site of pain (28). Only approximately 2% of patients report pain in these parts as the primary site and, in such cases, the rectal pain is usually associated with severe depressive or schizophrenic illness, although it can be associated with somatoform symptoms. Such patients usually have pain and other symptoms elsewhere in the body (see Chapter 26).

Two types of pain are clearly of psychiatric origin: delusional or hallucinatory and hysteric or hypochondriac. Hallucinatory pain is attributed by the patient to a specific delusional cause, such as pain or a painful object in the rectum or perineum or in the vagina or penis. This type of pain varies from mild to severe and persists until the causal psychological illness remits. The pain can be aggravated by psychological stress. A comprehensive physical and laboratory examination reveals no structural lesion that could lead to the patient's symptoms.

Hysteric or hypochondriac pain is specifically attributable to the thought processes, emotional state, or personality of patients in the absence of an organic or delusional cause, or to a tension mechanism (24,28). This type of pain can be felt anywhere in the perineum or rectum, but, like other types of chronic pain of psychological origin, is extremely rare. In general, female subjects experience this type of pain more frequently than male subjects. Pain is described in simple sensory terms, but complex or affective descriptions are given by some patients. The pain is usually continuous throughout most of the waking hours but fluctuates somewhat in intensity, does not awaken patients from sleep, and usually lasts for more than 6 months. Pain is often present in other areas and can be associated with loss of function without a physical basis. The mechanisms underlying such pain symptoms remain obscure (see Chapter 26).

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CHAPTER 75

General Considerations of Pain in the Low Back, Hips, and Lower Extremities

Joseph M. Czerniecki and Barry Goldstein

Disorders of the lumbosacral portion of the spine, hip, and lower limbs cause pain, suffering, and disability more frequently than disorders in any other part of the body. The most frequent cause of pain and disability in this region is musculoskeletal disease or dysfunction of the low back and lower limbs, followed by neuropathic disorders and peripheral vascular disease. Knowledge of the causes, pathophysiology, and symptoms and signs permits the establishment of a correct diagnosis and the development of effective therapeutic strategies. The clinician should have a thorough knowledge of the functional anatomy and biomechanics of the lumbar spine, the sacrum, and the various parts of the lower limbs; of the anatomy and function of the lumbar and lumbosacral plexuses and the major nerves; and of the vascular structures in the pelvis and lower limbs.

This first chapter of Section F discusses the lumbosacral spine, including its functional anatomy and biomechanics; the vertebral (spinal) canal and its contents, specifically a description of the spinal cord and its relation to the various parts of the vertebral canal; nerves to the lumbar spine, pelvis, and lower limbs; sympathetic and somatic segmental and peripheral nerve supply to the hips and lower limbs; and finally, evaluation of the patient, with an outline summarizing the most important aspects and a table summarizing the pain characteristics and other symptoms and signs to help make a differential diagnosis. Various aspects of low back pain are discussed in Chapter 76 and neurologic pain syndromes are covered in Chapter 77. The functional anatomy and biomechanics of the hip joints and adjacent structures are presented in Chapter 78, of the thigh and knee in Chapter 79, and of the leg, ankle, and foot in Chapter 80.

BONY CONSIDERATIONS

Lumbar Vertebrae

Lumbar vertebrae consist of a ventral body and a dorsal neural arch; together they enclose the cauda equina, meninges, and other neurovascular structures. From the neural arch, three processes diverge for the attachment of ligaments and muscle; in the posterior midline is the spinous process while the transverse processes are found symmetrically on either side. The portion of the neural arch between spinous process and transverse process is the lamina, while the portion between transverse process and body is the pedicle. The vertical extent of the pedicle is less than that of the body, to allow room for passage of the spinal nerve (Fig. 75-1).

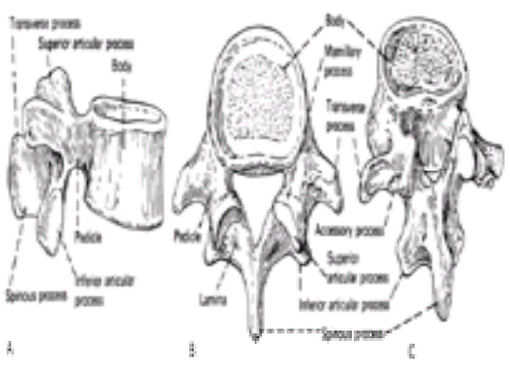

Figure 75-1. Anatomy of a lumbar vertebra. **A:** Lateral view. **B:** Superior view. **C:** Superolateral view. The body is wider transversely than anteroposteriorly, and the spinal canal is triangle shaped. Note the directions of the articular facets. See text for more details.

At the junction of the lamina and pedicle the superior and inferior articular processes of the facet joints project above and below. Motions of flexion and extension and lateral flexion occur at the facet joints (Fig. 75-2). When two adjacent lumbar vertebrae are separated, one sees how the inferior articular processes of the upper vertebra fit medially and posteriorly into the superior articular processes of the lower vertebra (Fig. 75-3). Therefore, each lumbar vertebra provides lateral stability to the overlying vertebra as a result of the buttresslike structure of the articular processes. The junction of the superior and inferior articular processes of a vertebra is termed the *pars interarticularis*. *Spondylolysis* is a term that describes a defect in the pars interarticularis that results most commonly from trauma (Fig. 75-4). Spondylolisthesis is a process by which the vertebra above is allowed to slide forward in relation to the lower vertebra as a result of spondylolysis.

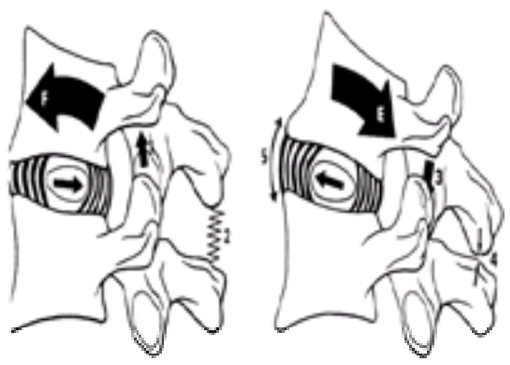

Figure 75-2. Flexion (F) and extension (E) and lateral flexion occur at the facet joints. During flexion of the spine, there is distraction of the facet joints (1) and stretching of the interspinous ligaments (2). During extension of the spine, there is compression of the facet joints (3), the spinous processes (4) come into closer proximity, and the anterior longitudinal ligament is under tension (5).(Reprinted from Kapandji IA. *The physiology of the joints*, 5th ed. Vol 3, Trunk and vertebral column. Edinburgh, UK: Churchill Livingstone, 1987, with permission.)

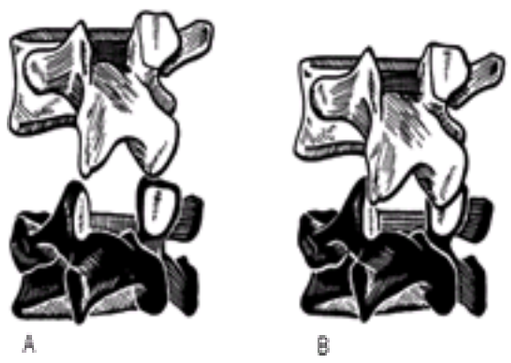

Figure 75-3. **A,B:** The articulations between adjacent vertebrae. See text for explanation. (Reprinted from Kapandji IA. *The physiology of the joints*, 5th ed. Vol 3, Trunk and vertebral column. Edinburgh, UK: Churchill Livingstone, 1987, with permission.)

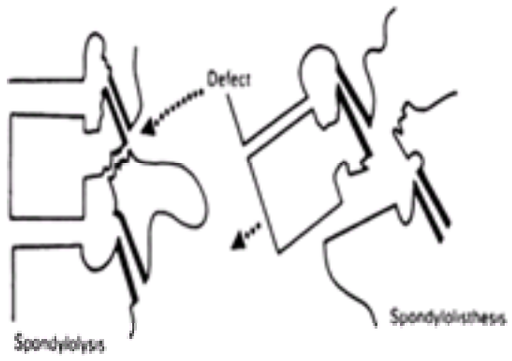

Figure 75-4. Isthmic spondylolisthesis. The basic lesion is a defect in the neural arch across the pars interarticularis. When degenerative changes occur in the subjacent disk, the vertebral body displaces forward, carrying with it the superimposed spinal column and leaving behind the inferior articular facets, lamina, and spinous process. (Reprinted from McCulloch J, Transfeldt E. *Macnab's backache*, 3rd ed. Baltimore: Williams & Wilkins, 1997:164, with permission.)

The lumbar vertebral bodies are kidney shaped when viewed from above and are large and strong. The strength of the body is derived from the dense bony cortex in addition to the trabecular structure of the medulla. The cortex of the superior and inferior aspects, the vertebral plateau, is thickened in the center and contains a cartilaginous plate. The periphery of the vertebral plateau forms a distinct thickened rim. It is derived from an epiphyseal growth plate that is separate from the vertebral body, which becomes fused to the body at about 15 years of age. Abnormal ossification of this rim leads to vertebral epiphysitis (Scheuermann's disease). The bony trabeculae of the vertebral body are oriented along lines of force. The vertical trabeculae link the superior and inferior surfaces of the vertebral body, the horizontal trabeculae link the lateral surfaces, and the oblique trabeculae link the inferior with the lateral surfaces. The intercrossing of these three trabecular systems constitutes zones of maximum structural rigidity. The anterior portion of the vertebral body lacks an overlapping trabecular structure and is therefore more easily fractured. This explains the commonly observed anterior wedge-shaped fracture of the vertebral body, which occurs secondary to axial compression loading, especially when the structural integrity is reduced as in osteoporosis.

Sacrum

The sacrum is a single osseous structure comprised of five fused vertebrae and their costal elements (Fig. 75-5). When viewed from the front it is triangular in shape, with the base of the triangle at the superior margin and the apex inferior. When viewed from the lateral aspect it is curved, with its concave surface anterior and its convex surface posterior. Fusion of the first and second vertebrae may be incomplete, which results in lumbarization of the first sacral vertebra. In contrast, the sacrum may also have an additional vertebral element that may be partially or completely fused to it. *Sacralization* of the fifth lumbar vertebra is the term applied to this process. The sacrum articulates with the ilium at the sacroiliac joint. The synovial portion of the sacroiliac joint has a complex articular surface and is stabilized by broad, strong ligamentous structures. Because of the shape of the articular surface, the ligamentous reinforcement, and the ring-shaped structure of the pelvis, only small movements occur at this joint. These movements are not well appreciated until there is a painful pathophysiologic process such as a trauma or inflammation resulting from ankylosing spondylitis, or Reiter's syndrome.

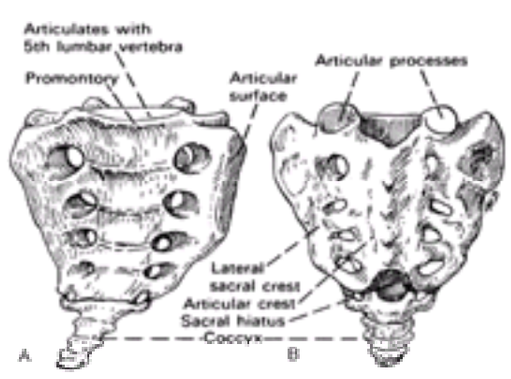

Figure 75-5. Anatomy of the sacrum and coccyx. **A:** Anterior view. The anterior (pelvic) surface is concave, which provides increased capacity to the pelvic cavity, and is crossed by four transverse ridges that separate the five segments of vertebral bodies. The four pairs of rounded anterior (pelvic) sacral foramina communicate with the sacral canal by the intervertebral foramina, through which course the anterior primary divisions of the first four sacral nerves and the lateral sacral arteries and veins. The coccyx is a triangular structure composed of four rudimentary vertebrae. **B:** Posterior view. The posterior surface is convex and is narrower than the anterior surface. In the midline is the median sacral crest, on which are mounted three or four tubercles of the rudimentary spinous processes of the upper three or four sacral segments. The posterior sacral foramina are located between the intermediate and lateral sacral crests, through which pass the posterior primary divisions of the upper four sacral nerves. Between the sacrum and coccyx is the sacrococcygeal hiatus.

Within the body of the sacrum, there is a central canal that tapers toward the distal end and is continuous with the central canal of the lumbar vertebrae, which are above. The sacral canal carries the most caudal nerve roots (S-1 to S-4) of the cauda equina (see Fig. 75-5). The ventral primary rami of each segmental nerve exit via the anterior foramina while the posterior primary rami exit via the posterior intervertebral foramina. The posterior foramina and the sacral hiatus are easily accessible for segmental injections and caudal anesthesia, respectively.

LIGAMENTS

The lumbar spine can be viewed as a series of stacked bony elements. From a functional perspective the bony elements must be held together in a manner that allows sufficient stability to allow the arms and upper body to be maintained in a stable upright posture but at the same time allow a high level of mobility. The stability of the spine is the result of the anatomic structure of the intervertebral disks, the shape and orientation of the facet joints, and the orientation and mechanical characteristics of the ligaments. The ligaments can be classified into two major groups: those that are long and straplike and extend over the length of the spine, such

as the anterior and posterior longitudinal ligaments, and those that are shorter and span only one or two segments (Fig. 75-6).

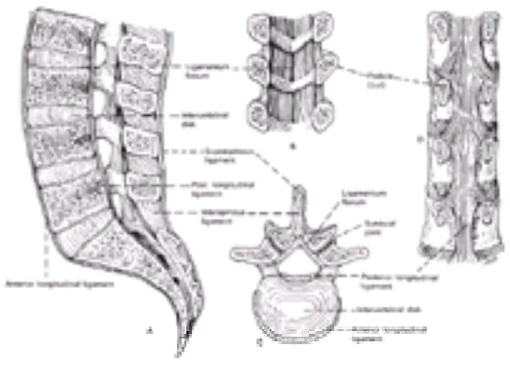

Figure 75-6. Ligaments of the lumbar vertebrae. **A:** Medial sagittal section of three lumbar vertebrae and their ligaments. The vertebral bodies are slightly higher anteriorly than posteriorly, and the intervertebral disk is also higher anteriorly than posteriorly. The interspinous ligaments are thin and membranous and interconnect with adjoining spinous processes, with their attachments extending from the root to the apex of each spinous process. Here they meet the ligamentum flavum anteriorly and the supraspinous ligament posteriorly. Whereas they are narrow and elongated in the thoracic region, they are broad, thick, and quadrilateral shaped in the lumbar region to conform to the shape of the spinous process. The supraspinous ligament is a strong fibrous cord that connects the apices of the spinous processes of the vertebrae. Fibrocartilage is developed in the ligament at its point of attachment to the tips of the spinous processes. The supraspinous ligament is thicker and broader in the lumbar than in the thoracic region. The most superficial fibers of the supraspinous ligament extend over three or four vertebrae, those coursing more deeply pass between two or three, and the deepest ones connect the spinous processes of neighboring vertebrae and become continuous with the interspinous ligament. **B:** Anteroposterior view of the laminae and intervening ligamenta flava in the lumbar region. The ligamenta flava connect the laminae of adjacent vertebrae and are thickest and strongest in the lumbar region. Each ligament consists of two lateral portions that begin on each side of the root of the articular process surrounded by the capsule and extend posteriorly to the point where the two laminae meet to form the spinous process. Each ligamentum flavum consists of yellow elastic tissue, the fibers of which are almost perpendicular to and are attached to the anterior and inferior surfaces of the lamina above and to the superior and posterior surfaces of the lamina below. **C:** Superior view of a lumbar vertebra showing the positions of the various ligaments in the lumbar region. The anterior longitudinal ligament almost covers the anterior surface of the body of the vertebra, whereas the posterior longitudinal ligament covers only a portion of the posterior surface of the vertebra. Note also the cut supraspinous and interspinous ligaments, ligamenta flava, and articular joints. **D:** Posterior aspect of the vertebral body. The laminae and spinous process have been removed to show the posterior longitudinal ligament in the lumbar region. The ligament broadens and becomes intimately adherent as it passes over each of the intervertebral disks and over contiguous margins of the vertebrae. It is narrow and thick over the center of the body, however, from which it is separated by the basivertebral veins. This ligament is broad in the cervical region but at the L-1 vertebral level it begins to narrow progressively, so that on reaching the last lumbar and first sacral interspace it is only half of its original width. See text for a discussion of the implications.

The anterior longitudinal ligament is a broad band that lies on the anterior surface of the vertebral bodies and extends from the anterior tubercle of the atlas to the upper part of the pelvic surface of the sacrum. It consists of several laminae of fibers, the deepest spanning one intervertebral segment, while the most superficial extend over several segments. The anterior longitudinal ligament is thickest centrally, and it becomes progressively broader as it passes in a caudal direction. It is firmly united to the periosteum of the vertebral bodies but is free over the intervertebral disks. The anterior longitudinal ligament functions to limit extension of the vertebral column. In anterior crush injuries of the vertebral bodies, the anterior longitudinal ligament is ordinarily not injured, so that when the injured region is placed in hyperextension, this ligament can act as a splint to hold and fix the bony fragments.

The posterior longitudinal ligament lies on the posterior surface of the vertebral bodies and is therefore within the central vertebral canal. It extends from the posterior aspect of the body of the axis superiorly to the sacral canal below. It is attached firmly to the superior and inferior margins of the vertebrae and to the intervening disks, but over the centers of the vertebral bodies, there is a space through which blood vessels course to and from the posterior aspect of the vertebral body. The posterior longitudinal ligament functions in part to limit flexion of the vertebral column.

The vertebral arches are united by the ligamenta flava, intertransverse ligaments, interspinous ligaments, and supraspinous ligaments. The ligamenta flava are elastic in content and distinctly yellow. They join the contiguous borders of adjacent laminae and are attached to the front of the upper lamina and to the back of the lower lamina. They are stretched by flexion of the spine. Their elastic nature prevents redundancy and buckling when the ligament is slack. Thickening (hypertrophy) of the ligament flava can contribute to compression of a nerve root at the intervertebral foramen.

Three collagenous, segmental ligaments further unite and stabilize the vertebral arch. The supraspinous and interspinous ligaments join adjacent spinous processes; the supraspinous fibers are superficial and join just the tips. They are extremely strong and limit flexion of the lumbar spine. The intertransverse ligaments run from transverse process to transverse process. They are thin and membranous in the lumbar spine. It is thought that they stabilize and limit intervertebral movement during lateral flexion.

The ligaments of the spine are richly innervated by both somatic and sympathetic fibers. A branch of the dorsal primary ramus, the sinuvertebral nerve, innervates all of the posterior ligaments and facet joints (1). A branch of the ventral primary ramus innervates the anterior longitudinal ligament. In spite of their extensive innervation, it is controversial whether or not pathologic processes affecting ligaments are a significant source of nociception for patients suffering from low back pain.

ANATOMIC RELATIONSHIPS OF THE ROOTS AND SPINAL NERVES

The anterior and posterior nerve roots pass through the subarachnoid space and converge to form the spinal nerve at approximately the level of its respective intervertebral foramen (Fig. 75-7). The course of the nerve roots becomes progressively longer and more obliquely directed the more distal the segmental level. Therefore, in the lumbosacral regions the nerve roots and spinal nerves travel an almost vertical course before exiting below the pedicle of the corresponding vertebrae. Each nerve root leaves the vertebral canal through an intervertebral foramen (Fig. 75-7B). These foramina are bounded anteriorly by the posterior border of the intervertebral disk and the adjoining parts of the vertebral bodies, superiorly and inferiorly by the pedicles of the two adjoining vertebrae, and posteriorly by the articular processes and the facet joint, which are linked by the capsular ligament and the lateral edge of the ligamentum flavum. In the lumbar region the foramina are elliptical in shape and are approximately five times the diameter of the nerve root (Fig. 75-8). They are therefore large enough to transmit the spinal nerve, blood vessels, and nerve branches that supply the vertebral column and surrounding soft tissues. Due to the ample vertical dimensions of the foramen (12 to 19 mm in the lumbar region), degenerative changes and loss of disk height tend to result in a smaller foramen, yet even complete collapse of the lumbar disk may produce little evidence of nerve compression. In contrast, the transverse extent of the foramina is much smaller (approximately 7 mm); therefore, any space-occupying lesion that narrows the transverse dimensions of the foramen (bony spur, hypertrophy of the ligamentum flavum, tumor, protruding disk) may more readily result in nerve root impingement.

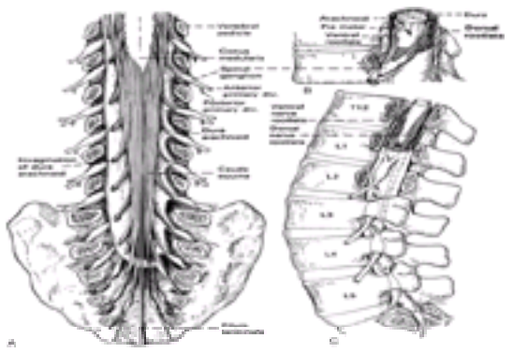

Figure 75-7. Detailed anatomy of the nerve rootlets and roots of the lumbar, sacral, and coccygeal nerves. **A:** Posterior view. **B:** Lateral view at midthoracic vertebral

level. **C:** Lateral view of the lumbar spine. The rootlets and roots of the lumbar, sacral, and coccygeal nerves course some distance before they leave the spinal canal. Gathered from their respective rootlets, they proceed caudad toward their respective intervertebral foramina and traverse the subarachnoid space within the dura-arachnoid sac in their own separate dura-arachnoid sleeves. As the nerve roots of the lumbar nerves descend in the spinal canal, they cross the disk immediately above the foramina through which they exit and then enter the foramina beneath the pedicles. After entry into the foramina on their extravertebral course, each root invaginates the dura-arachnoid and carries the sheath of each into the foramen, so that each of the two roots has its own separate investment of dura-arachnoid as far as lateral to the spinal root ganglion where the roots unite. At this point the two separate sheaths likewise merge so that the formed spinal nerve is invested by a single sheath, which continues for a short distance before it fuses with the epineurium of the spinal nerves. Within the foramen part of the dura fuses with connective tissue and thus anchors the dural sleeve to protect the nerve root from being stretched during movements of the spine. **C:** Within the foramen the smaller anterior (motor) root is located anteriorly and inferiorly near the intervertebral disk. After leaving the foramina the lumbar nerves incline caudad, laterally, and slightly anteriorly. The roots and dorsal ganglia of the S-1, S-2, and S-3 nerves lie in sheaths immediately external to the arachnoid- dura cisterna or cul-de-sac, while the roots and ganglia of the S-4, S-5, and coccygeal nerves lie within their sheaths in the body sacral canal at a considerable distance from the dural cul-de-sac.

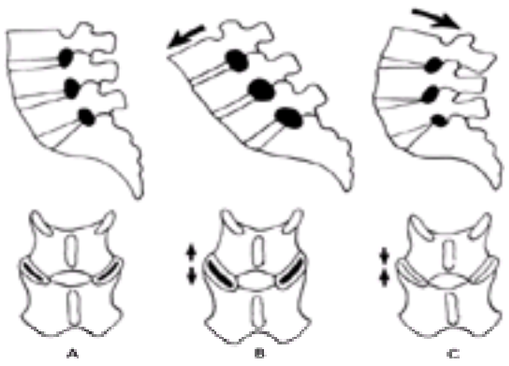

Figure 75-8. Flexion and hyperextension of the lumbar region. **A:** Normal posture showing the relation of the facets as well as the size of the intervertebral foramina and the configuration of the intervertebral disks. **B:** Flexion causes the facets to separate, thus allowing movement in the lumbar area in both lateral and rotatory directions. The intervertebral foramina enlarge and the anterior portions of the disks are compressed. **C:** Hyperextension. Facets approximate each other, thus completely eliminating any lateral rotatory movement and causing a significant decrease in the size of the intervertebral foramen. (Modified from Cailliet R. *Low back pain syndromes*, 3rd ed. Philadelphia: FA Davis, 1981.)

SPINAL CANAL

The shape of the posterior aspect of the vertebral body and the orientation of the pedicles and laminae determine the shape of the spinal canal (see Fig. 75-7). In the upper lumbar vertebrae the posterior aspect of the vertebral body is concave and the pedicles project directly back, creating a general oval shape to the canal. In the lower lumbar vertebrae, the posterior aspect of the vertebral bodies is slightly convex and the pedicles are in a more lateral orientation, therefore producing a more triangular-shaped canal.

The contents of the spinal canal vary depending on the segmental level. The tapered end of the spinal cord, the conus medullaris, may end anywhere between T-12 and L-3 but most commonly terminates at the L-1 to L-2 disk (Fig. 75-9). From its tapered end the filum terminale continues distally to the sacrum and coccyx (see Fig. 75-9). The lumbosacral nerve roots continue in a distal but slightly lateral direction to exit at their respective intervertebral foramina. Surrounding the lumbosacral nerve roots and the filum terminale are the meninges. External to the meninges is the epidural space. It is loosely filled with fat and connective tissue that *pads* the enclosed neural elements but also includes the internal vertebral venous plexus and the branches of the spinal arteries that supply the vertebral column, the dura, and the tissues of the epidural space. The internal vertebral venous plexus receives most of its tributaries from the large basivertebral veins, which drain the vertebral bodies.

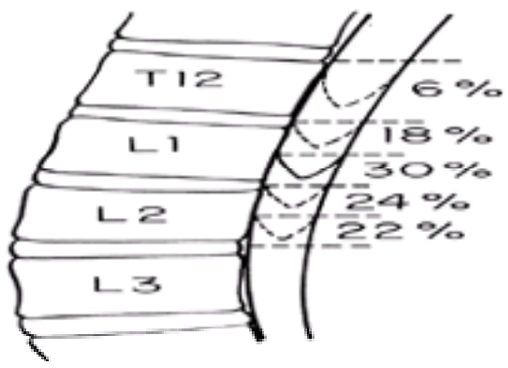

Figure 75-9. Various levels of the lowermost termination of the spinal cord shown in percentages as found in several autopsy studies.

Lumbar central spinal stenosis is a clinical condition that results from narrowing of the central canal and subsequent compression of the lumbosacral nerve roots. It may occur at a single or at multiple segmental levels; however, the L-4 to L-5 level is the most commonly affected. Central stenosis is produced mainly by a combination of osteophytes from the facets (the inferior facets most commonly) and disk degeneration with herniation, ligamentum flavum hypertrophy, or both. The typical symptoms are those of pain radiating into the buttocks and lower extremities, with or without sensorimotor complaints, that is exacerbated by standing or walking.

INTERVERTEBRAL DISK

The vertebral bodies of the lumbar spine articulate with one another through amphiarthrodial joints, which are termed *intervertebral disks* (Fig. 75-10). They are therefore by definition nonsynovial. In the transverse plane the cross section of the intervertebral disk is kidney shaped, corresponding to the shape of the vertebral body above and below. In the sagittal plane the disk is slightly thicker anteriorly than posteriorly, which may in part contribute to the lordotic posture of the lumbar spine (2).

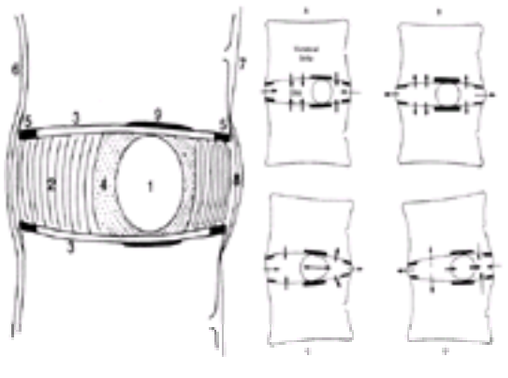

Figure 75-10. **A:** This diagrammatic representation of the intervertebral disk, in addition to presenting the customary nucleus pulposus (1), annulus fibrosus (2), and cartilaginous end-plates (3), also presents the zone of irregular connective tissues surrounding the nucleus (4), the epiphyseal rim (5), the anterior longitudinal ligament being continuous with the periosteum (6), and the posterior longitudinal ligament separating from the concave posterior vertebral body (7), the presence of Sharpey's fibers (8), and a thickened calcified layer capping the nucleus (9). **B:** The nutrient cycle to the disk is schematically depicted. (*A*) The weight is off the disk, permitting the polysaccharide molecules to imbibe fluids essential for nutrition. (*B*) The weight-bearing phase is represented, and the fluid is shown as being expressed from the disk. (*C*) Illustrated is backward bending, which may take place even at rest on an overly firm mattress. Here, while the front of the disk absorbs nutrient fluids, the back of the disk is unable to do so. (*D*) Forward bending, the reverse of Figure C, is illustrated. An additional feature of forward bending is that with sufficient fluid moving posteriorly, hydrodynamics of the disk are upset and the patient may become fixed in flexion. (Reprinted from Paris SV. Anatomy as related to function and pain. *Orthop Clin North Am* 1983;14:476–477, with permission.)

The intervertebral disk consists of two major portions: a central gelatinous portion, the nucleus pulposus, and a circumferential portion, the annulus fibrosus.

Nucleus Pulposus

The nucleus pulposus is enclosed by the surrounding annulus fibrosus at the periphery and by a cartilaginous end-plate on the adjacent vertebral bodies. It consists of water and connective tissue elements including collagen and proteoglycans, as well as cellular components. The proteoglycans and collagen are constantly being degraded and replaced by the cellular structures within the nucleus. Water is the most predominant substance in the disk, accounting for 90% of the total volume (3). Proteoglycans contribute 50% of the dry weight, while collagen contributes only 15% to 20% (4). Although the mechanical properties of the disk are dependent on all of these components, the water content is probably the most important, and it is largely determined by the hydrophilic nature of the proteoglycans. It does, however, also vary with the type and extent of mechanical loading, age, as well as other factors that contribute to the overall nutritional status of the disk.

Annulus Fibrosus

The annulus fibrosus is a structure that is largely made up of collagen. The collagen fibers are attached to the peripheral margin of the adjacent vertebral bodies. The structure of the annulus has been likened to that of an onion. It consists of a series of approximately 20 concentric layers or lamellae. The collagen fibers in each layer are in a parallel arrangement oriented obliquely at about a 50-degree angle relative to the surface of the vertebrae (5). In each consecutive layer the fibers are oriented in an opposite direction to those in the previous layer. In the adult spine the nucleus resides in a somewhat posterior position in the intradiskal space, and the lamellae are therefore thinned in this region. The outer margin of the annulus does have a limited vascular supply and neural supply. The innervation of the outer portion probably includes both nociceptive and mechanosensitive nerve fibers.

In the human the intervertebral disk is the largest avascular structure in the body. Nutrients enter the disk and waste products leave the disk largely by diffusion to and from vascular structures in adjacent tissues. The cartilaginous end-plate that separates the nucleus from the vertebral body above and below is the most important source for nutrients, with the peripheral margin of the annulus providing a secondary source. Smoking, increased age, and vibration result in an accumulation of metabolites and a reduction in oxygen use (4). Mechanical loading seems to enhance disk nutrition as well, as evidenced by studies of the effects of spinal fusion on disk metabolism (6,7).

Anatomic Changes in the Disk during Development

There is considerable controversy about whether the gross, histologic, and biochemical changes that occur in the lumbar spine with increasing age are pathologic or simply a consequence of normal aging. The anatomic changes that are typically seen with increasing age are an increase in collagen content and deposition of lipofuscin and amyloid in the nucleus. In addition, small concentric clefts form in the posterior portion of the annulus that may coalesce to form larger and more radially oriented clefts. The cartilaginous end-plate may show changes of thickening or defects and fissuring with associated Schmorl's nodes. These changes are associated with the development of marginal osteophytes at the edges of the vertebral body adjacent to the disk. Although classically the degenerated disk has a reduction in water content and a reduction in height, the disk height may be increased with age when there is concomitant osteoporosis. Osteoporosis leads to collapse of the vertebral end-plates and an increase in vertical dimension of the disk, especially the central portion (8).

Function of the Intervertebral Disk

The function of the intervertebral disk at its most rudimentary level is to simply allow multiplanar motion between the rigid structural elements of the vertebral bodies. The nucleus behaves as a viscous fluid, and in conjunction with the surrounding annulus, it functions as a shock absorber. Vertical loads cause the nucleus to distort uniformly in a circumferential direction, which subsequently results in distortion of the annular envelope and tension in the collagen fibers of the annulus. The healthy lumbar disk is extremely resilient to vertical loading; in fact, the bony vertebrae undergo fracture before there is evidence of disk injury.

There have been numerous investigations of the changes in intradiskal pressure during a variety of lumbar spine postures and activities (9,10 and 11). This information has been useful in increasing our understanding of the biomechanics of the spine and its ergonomic applications. It is uncertain what the relationship between disk loading, disk injury, disk degeneration, and low back pain might be (12).

FACET JOINTS

The facet joints of the lumbar spine are paired articular structures. Each anatomic motion segment is associated with one pair (Fig. 75-11). These joints are diarthrodial planar joints where the joint surfaces are covered with articular cartilage and the joint is enclosed by a capsule. The facet joints form an articulation between the inferior articular process of the vertebrae above and the superior articular process of the vertebrae below. This sometimes leads to confusion because when the facet joints are viewed in isolation, the inferior, more caudal portion is actually the superior articular facet because it is named from the vertebrae below, and the superior portion of the joint is formed from the inferior articular process of the vertebrae above.

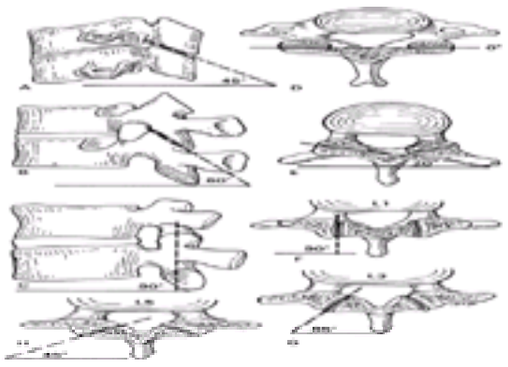

Figure 75-11. Planes of the articular facet surfaces of the vertebral arch joints. Lateral views show the angulation that determines the direction of movement permitted by the vertebral facet in the cervical **(A)**, thoracic **(B)**, and lumbar **(C)** regions. Depiction of the superior surfaces to show the facet planes horizontally. In the cervical region **(D)** they allow anterior flexion and extension, in the thoracic region **(E)** their angle permits an appreciable amount of rotation between consecutive vertebrae, and in the upper lumbar vertebrae **(F)** the facet planes are vertical. As they proceed caudad **(G,H)**, however, there tends to be a gradual transition in the angle of the superior articular process, which gradually faces more posteriorly and less medially, while the inferior articular process gradually faces more anteriorly and less laterally. The lumbosacral joint, the part farthest from the sagittal plane, allows some rotation of the lower part of the lumbar spine. (Modified from Hollinshead WH. *Anatomy for surgeons*, 3rd ed. Vol 3, The back and limbs. Philadelphia: Harper & Row, 1982; and Lindh M. Biomechanics of the lumbar spine. In: Frankel VH, Nordin M, eds. *Basic biomechanics of the skeletal system*. Philadelphia: Lea & Febiger, 1980.)

The facet joints are complex structures whose shape and orientation are not only difficult to define at any specific intersegmental level but they also change as one moves in a cephalad to a caudad direction. In the upper lumbar segments they are vertical with a predominantly sagittal plane orientation, while in the lower lumbar segments they are somewhat less vertical and are approximately halfway between a sagittal and a coronal plane orientation.

Throughout all of the segmental levels the shape of the superior articular process is concave while the inferior articular process is correspondingly convex. In the upper lumbar spine the superior articular process faces medially while the inferior articular process faces essentially laterally. In the lower lumbar spine as the orientation of the joint gradually becomes closer to the coronal plane, the superior articular facet faces both posteriorly and medially while the superior articular facet faces anteriorly and laterally.

The joint capsule encloses the facet joints and is relatively tighter anteriorly and more lax posteriorly. The multifidus muscle attaches in part to the posterior capsule and may exert a *tensioning* effect on the capsule (13,14). The superior capsule has been shown to be stretched and may be injured with axial loads, especially with the spine in extension (15). Attached to the interior surface of the joint capsule at the level of the superior and inferior joint recesses are fibrofatty or fibrous structures. They have been described as meniscuslike, and some authors believe that they may be a source of nociception if trapped between the joint surfaces. Other authors believe that they are too friable to exert tension on the joint capsule and therefore cannot be a source of nociception (16).

The facet joints and capsule are richly innervated through branches from the posterior primary ramus as it exits from the intervertebral foramina. The posterior primary ramus at a given segmental level sends fibers to the facet joint at that level but also to the facet joints above and below the level of the nerve exit (17) (Fig. 75-12). The innervation of the facet joints and capsule appears to be through mechanoreceptors as well as nociceptors, and there appear to be substance P–containing nerve fibers present (18,19).

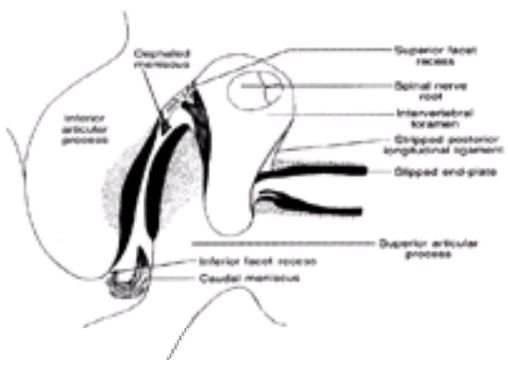

Figure 75-12. A segmental cross section through the facet joint and intervertebral foramen shows the mixed spinal nerve root high up in the foramen opposite a weakened upper portion of the facet capsule and superior articular recess. An inferior recess is at the caudal extent of the joint, as is a larger tonguelike projection of cartilage identified as a meniscus. This specimen also shows a slipped superior cartilaginous end-plate with a stripping of the posterior longitudinal ligament from the periosteum. (Reprinted from Paris SV. Anatomy as related to function and pain. *Orthop Clin North Am* 1983;14:479, with permission.)

Biomechanics and Function of the Facet Joint

The lumbar spine is a structure that includes five motion segments between L-1 and S-1. In the adult the lumbar spine typically adopts a lordotic posture and sits on the sacrum, which is angulated posteriorly. The posterior angulation of the sacrum results in the upper surface of S-1 being oriented 60 degrees to the vertical plane.

The function of the facet joints is to limit and guide the motion of the lumbar spine. The generally sagittal plane orientation of the facet joints markedly limits axial rotation in the lumbar spine. However, the relatively more coronal orientation at the L-5 to S- 1 junction may allow somewhat greater rotation to occur. Flexion of the lumbar spine can be influenced dynamically through the lumbar spine musculature and through the passive restraint of connective tissue. It is interesting to note that in spite of the significant stature of the interspinous and supraspinal ligaments, the facet joints provide the greatest limitation to full flexion. In anatomic studies where the facet joints have been excised, there is a marked increase in the mechanical stresses that the disk experiences (20). During full flexion, contact between the more anterior portions of the superior and inferior articular processes of the facet joints and tension in their joint capsules are the major restraint to motion. In full extension there is stretch applied to the superior aspect of the facet joint capsule, and there may be *bottoming out* of the inferior articular process on the laminae below (8).

The facet joints do not carry significant axial loads with the spine in a neutral position because of their vertical orientation. In extension, however, they have been shown to carry 16% to 20% of the total axial load. The actual anatomic structure of the facet joint that carries the axial load in extension is debated, and in fact it may be dependent on whether the spine and the disk exhibit degenerative changes (21). In the absence of disk degeneration the joint capsule carries significant loads, while in the presence of disk degeneration a greater portion of the load may be borne by the articular surface (22).

As noted previously, the lumbosacral junction is subject to significant shear stresses because of the lumbar lordosis and the posterior angulation of the sacrum. The L-5 to S-1 facet joint bears significant shear stress loads. These shear stresses may in part play a role in the increased incidence of spondylolysis and secondary spondylolisthesis.

LOWER EXTREMITY

General Considerations

The lower extremity predominantly functions to support and move the weight of the body through space. These include skeletal structures; articulations and their supporting structures; and muscle, nerve, and vascular structures. To make a correct diagnosis in the patient who presents with lower extremity pain, one must have a comprehensive understanding of the anatomy, functional biomechanics, and pain characteristics associated with nociceptive input from these structures. In addition, pain experienced in the lower extremity may have an origin in structures outside of the lower extremity; it is therefore important to have knowledge of common patterns of pain radiation and referral.

Osseous Structures

The lower extremity consists of 30 different osseous structures. These include the femur, patella, tibia, fibula, talus, calcaneus, navicular, cuboid, three cuneiforms, five metatarsals, five proximal phalanges, four intermediate phalanges, and five distal phalanges. The major functions of these skeletal structures are to provide structural integrity to the lower extremity; form articulations that allow mobility; form attachment points for muscle, ligaments, and joint capsule; and act as a storage site for calcium and other minerals and as a site for the genesis of hematopoietic tissues. Bone is a dynamic structure that is constantly being absorbed and generated by the osteoblasts and osteoclasts. Because of this, it can repair itself after injury, and its shape and structure are altered by the forces that are applied through it. The attachment points of muscle modify the shape of the bones of the extremities. A good example of this in the lower extremities is the tibial tuberosity, which forms a prominent area of bony enlargement at the attachment point of the patellar tendon. The profound muscle forces of the quadriceps, which are transmitted through the patellar tendon, result in the elevation of the tibia in this region. The bones of the lower extremities are predominantly long bones, with their length being greater than their width. The regions of a long bone include the diaphysis or shaft, the metaphysis, which is the region where a long bone expands as it nears the articulation, and the epiphysis, which is the portion immediately adjacent to the articulation. The long bones of the lower extremity include the femur, tibia, fibula, metatarsals, and phalanges. The other bones of the tarsal region are considered short bones. Pain arising from the osseous structures usually is experienced at the location of the lesion. A stress fracture, malignancy, or contusion usually results in pain where the lesion occurs. There may be some proximal or distal radiation; however, referral of pain of osseous origin to more distant sites is uncommon.

Articulations

All of the joints of the lower extremity are synovial joints with the exception of the distal tibiofibular joint, which is a syndesmosis. Synovial joints have common characteristics in that they are formed as an articulation between two osseous structures. The surfaces of the osseous structures that come into contact are covered with articular cartilage, and the joint is enclosed by a synovial lining, which produces synovial fluid for joint nutrition and lubrication. Exterior to the synovial lining is a joint capsule, which provides a strong connective tissue enclosure to the joint. The joint capsule is subsequently reinforced by ligamentous structures, which provide stability to the joint but also guide and restrain the motion of the joint. Synovial joints of the lower extremity typically allow greater ranges of mobility if the architecture of the joint results in a high level of intrinsic stability.

Hip Joint. The hip joint is an articulation between the acetabulum of the pelvis and the head of the femur. It is described as a ball and socket joint because of the shape of the articular surfaces. This joint has a high level of intrinsic stability because of the deep ball and socket architecture. The stability of this joint is further reinforced by strong ligaments, which span the perimeter of the acetabulum and attach to the neck of the femur. These ligaments are increasingly taut with extension of the hip, and if the center of mass is positioned appropriately relative to the hip joint, the upright posture with hip extension can be maintained with minimal muscle work. One can rely exclusively on passive tension in the ligaments to maintain this posture. Hip joint pain is commonly experienced in the anterior groin area with occasional referral to the anteromedial thigh and the knee. This referred pain pattern is related to the segmental innervation of the hip joint, which includes a significant component of L-3 and L-4.

Knee Joint. The knee joint is an articulation between three osseous structures: the femur, the tibia, and the patella. This joint has little intrinsic stability based on the architecture of the articular surfaces. Its stability is determined almost exclusively by strong ligamentous structures reinforced by dynamic muscle action and to a much lesser extent by the menisci, which deepen the articular contact area of the tibia. Because of its limited intrinsic stability there are greater constraints on its motion. Although its range of motion in the sagittal plane is between 5 degrees of hyperextension and 120 degrees of flexion, there is only a small amount of transverse plane motion and essentially no coronal plane motion. The patella and the patellofemoral joints' primary functions are to redirect the pull of the quadriceps. This effectively increases the extension torque of the quadriceps at any point in its flexion-extension excursion. This function is most important near full extension. In the case of a patient with a patellectomy, the absence of a patella may in fact lead to an inability to extend the knee in the last 10 degrees of extension in spite of having a strong quadriceps muscle.

The location, character, and quality of pain associated with pathophysiologic processes affecting the knee vary. Broadly speaking, painful processes that are caused by diffuse inflammatory conditions such as crystal-induced arthropathies or degenerative conditions such as tricompartmental degenerative arthritis will cause poorly localized knee pain aggravated by activity and relieved by rest. Other processes such as ligamentous meniscal or patellofemoral processes can result in localized pain in a portion of the knee that is reflected in the anatomic location of the structure.

Ankle Joint. The ankle joint is an articulation between the tibia, fibula, and talus. The most common description of this joint is a *mortise and tenon* joint. The mortise is composed of the tibia above and medially and the distal fibula laterally. The mortise of the ankle joint is composed of the dome of the talus. The mortise and tenon architecture of this joint allows for more intrinsic stability, especially in the coronal plane. The bony stability of this joint is further reinforced by the strong medial and lateral ligamentous structures. The motion that occurs at the ankle is predominantly in the sagittal plane.

Articulations of the Foot. There are many different articulations of the foot, each with unique biomechanical and functional characteristics. A detailed description of these is beyond the scope of this section. The general function of these articulations is to provide suppleness to the foot, particularly in the first half of the stance phase when force and impact absorption are critical. In the second half of the stance phase, when force transmission and propulsion of the body and the lower extremity into the swing phase are the most important functions, the articulations of the foot stiffen secondary to changes in the orientation of the articular surfaces and through dynamic action of the musculature.

Arterial Vascular Supply

The arterial supply to the lower extremity begins at the distal aorta, which bifurcates into the right and left common iliac arteries (Fig. 75-13). The common iliacs subsequently branch into the internal and external iliac vessels. The internal iliac perfuses the pelvic structures and the gluteal musculature through the gluteal arteries. The external iliacs continue through the pelvis, exiting under the inguinal ligament, and into the femoral triangle where they become the femoral arteries. Within the femoral triangle, the femoral artery lies between the more lateral femoral nerve and the more medial femoral vein and is easily palpable in this location. Within the femoral triangle, it gives off two major branches: the profunda femoral artery and the circumflex femoral artery. The profunda femoral artery supplies the musculature of the thigh, while the circumflex femoral passes posteriorly and laterally, supplying the posterior and lateral gluteal regions as well as sending a branch to the head of the femur. The femoral artery continues down the thigh in the adductor canal. At the distal end of the adductor canal it travels posteriorly and enters the popliteal fossa, where it becomes the popliteal artery. Within the popliteal fossa it gives off a number of geniculate arteries that supply the knee and its adjacent soft tissue structures. Exiting the popliteal fossa distally it divides into two major branches, the anterior tibial artery and the tibioperoneal trunk, which subsequently divide into the posterior tibial and peroneal arteries. The anterior tibial artery continues down the leg in the anterior compartment and emerges at the anterior aspect of the ankle joint and continues down the dorsal part of the foot as the dorsal pedis artery. The peroneal artery continues in the leg in the deep posterior fossa at the junction of the interosseus membrane and the posterior aspect of the fibula. The posterior tibial artery travels in a distal direction, lying on the tibialis posterior muscle. At the ankle it lies posterior to the medial malleolus into the plantar surface of the foot where it divides into the medial and lateral plantar branches.

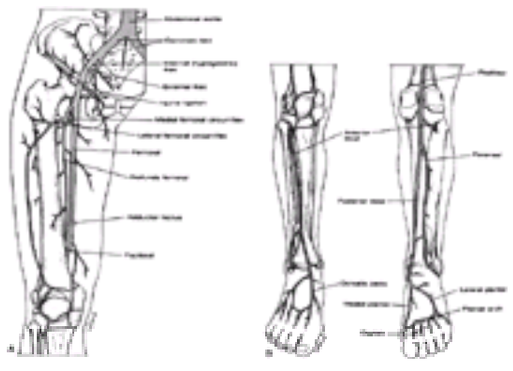

Figure 75-13. **A:** Arteries of the pelvis and thigh. **B:** Arteries of the leg and foot: anterior view (left) and posterior view (right). (Reprinted from Spence AP. *Basic human anatomy*, 3rd ed. Redwood City, CA: Benjamin/Cummings, 1990:320, with permission.)

Arterial supply to the lower extremity can be assessed clinically by palpation or through the use of Doppler evaluation. Typically, the vessels are assessed in regions where the artery is more superficial. This includes the dorsalis pedis artery on the dorsal aspect of the foot, the posterior tibial artery posterior to the medial malleolus, the popliteal artery in the popliteal fossa, and the femoral artery in the femoral triangle.

Pain syndromes that arise from impairment of arterial perfusion vary depending on the acuity and extent of the occlusive disease, the anatomic location of the occlusive disease, and the extent of collateralization (see Chapter 33). Acute arterial occlusion secondary to thrombosis in an area of atherosclerosis or secondary to arterial embolization results in the sudden onset of severe pain in the distal portion of the extremity. The limb is pale and cold to palpation, and there is severe impairment or absence of neurologic function. Chronic arterial occlusive disease results in two major types of pain, claudication and rest pain. The pain in both of these situations is the result of an inadequate blood supply to meet the metabolic demands of the tissues. With claudication, the pain occurs during exercise. Typically, the pain is predictable in onset at a certain walking distance or exercise intensity. It is described as cramping. With femoral-popliteal disease it is typically in the calf muscles, and in aortoiliac disease it may involve the buttock or thigh. Rest pain is typically anatomically located in the forefoot and toes. It occurs with recumbency or with limb elevation, and it is relieved by dependency—for example, when the patient hangs his or her leg over the edge of the bed. Rest pain occurs because limb perfusion is inadequate to meet the metabolic demands of the tissues even at rest. As the patient adopts the recumbent position there is a decrease in perfusion pressure secondary to a reduction in the hydrostatic pressure of the column of blood and pain occurs. When the patient drops his or her leg over the edge

of the bed, there is a slight increase in perfusion because of the hydrostatic pressure of the column of blood within the arterial tree, and the pain is typically relieved.

Venous System

The veins of the lower extremities can be broadly divided into two major groups: the superficial and the deep venous systems (Fig. 75-14). The deep system travels along with the arterial supply to the leg, beginning on the plantar aspect of the foot and extending proximally to travel with the peroneal, tibial, and posterior tibial arteries in the leg. Similarly it travels with the popliteal and femoral arteries in the popliteal fossa and within the adductor canal to the femoral triangle.

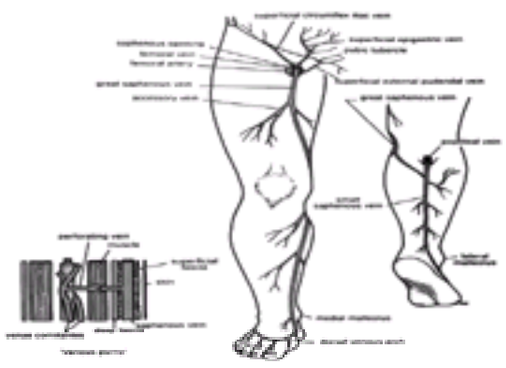

Figure 75-14. Superficial veins of right lower limb. Note importance of the valved perforating veins in the *venous pump*. (Reprinted from Snell RS. *Clinical anatomy for medical students*, 5th ed. Boston: Little, Brown and Company, 1995:523, with permission.)

The superficial venous system is external to the superficial muscle fascia of the leg and thigh. It consists of two systems: the greater and the lesser saphenous veins. The greater saphenous vein has its origin on the dorsum of the foot passing just anterior to the medial malleolus, then traveling up the medial aspect of the leg along with the saphenous nerve. It then moves just posterior to the knee and up the anteromedial aspect of the leg, where it perforates the superficial fascia of the leg and connects to the femoral vein. The lesser saphenous vein begins on the dorsal aspect of the foot and travels just posterior to the lateral malleolus. It then passes up the middle of the leg between the two heads of the gastrocnemius, where it penetrates the fascia of the leg in the popliteal fossa and joins the popliteal vein.

The veins of the leg are thin walled but do have a muscular layer. One of the important anatomic characteristics of the venous structures is the presence of valves, which function to support the column of blood. Valves are very important, especially in light of the fact that humans spend the majority of time in the upright position. The valves, in addition to supporting the column of blood, also assist in directing flow. Flow of venous blood is central and from the superficial to the deep system. Muscular contraction within the closed space created by the muscular fascia results in compression of the veins, and because of the anatomy and functional characteristics of the valves, blood is directed in a cephalad direction toward the inferior vena cava and heart.

Pain related to venous malfunction occurs in a number of pathologic conditions. Most commonly, in the case of valvular incompetence, there is a dull aching pain in the legs, especially in the lower half. The pain is aggravated by prolonged standing and walking and relieved by compression or elevation of the limbs. This pain may be associated with swelling as well as the characteristic changes of chronic venous stasis, which include pigmentation (brawny induration), with or without venous stasis ulcers, which typically occur in the supramalleolar region. In addition to chronic venous stasis, acute superficial thrombophlebitis may occur. Superficial thrombophlebitis results in localized thrombosis and inflammation in a segment of the superficial vein with symptoms of exquisite local tenderness in a portion of the leg in the anatomic location of either the greater or lesser saphenous veins, associated with tenderness, local edema, redness, and warmth.

Nerve Supply

General Considerations. Motor innervation of the lower extremity muscles follows specific organizational features. First, each segmental nerve root innervates more than one muscle, and all muscles are innervated by more than one nerve segment (23).

The cutaneous innervation of the lower limb is provided by nerves that have their origin in the lumbar and lumbosacral plexus. Differentiating between a peripheral nerve and dermatomal pattern of sensory loss requires knowledge of both the cutaneous nerves and segmental pattern of supply. Dermatomal segments are as follows: L-1, midpoint over the inguinal ligament; L-2, proximal medial thigh; L-3, medial knee; L-4, medial ankle; L-5, first web space on the dorsum of the foot; S-1, lateral heel; S-2, popliteal fossa; and S-3 to S-5, perianal skin (see Chapter 8). Peripheral nerve patterns are quite different than segmental patterns. The innervation of the buttocks by peripheral nerves is as follows: the superior cluneal nerves supply the upper buttock, the middle cluneal nerves supply the midportion of the buttock, and the inferior cluneal nerves curve around the lower border of the gluteus maximus to supply the inferior portion of the buttock. The innervation of the thigh is as follows: branches from the femoral nerve supply the anterior and medial thigh (except the proximal medial thigh is innervated by the obturator nerve), the lateral thigh is innervated by the lateral cutaneous nerve of the thigh, and the posterior cutaneous nerve of the thigh innervates the posterior thigh. The innervation of the leg is as follows: the medial leg is innervated by the saphenous nerve, the anterolateral leg is innervated by the lateral sural nerve proximally and the superficial peroneal distally, and the medial sural nerve supplies the posterior leg. The foot is innervated by the saphenous nerve medially, the superficial peroneal nerve dorsally (except the deep peroneal nerve supplies the skin over the first web space), the sural nerve laterally, and the plantar nerves on the plantar surface.

Lumbar and Lumbosacral Plexuses. In all vertebrates, each limb is organized into compartments; the skin and muscles of these compartments are supplied by limb plexuses. In the plexuses, spinal nerves interchange fibers so that the major nerve branches, distal to the plexus, receive contributions from two or more segmental spinal nerves. The evolution of plexuses was an important adaptive structural and functional advancement, allowing further complex neuromusculoskeletal behavior and protection from injury.

All of the vertebrates, including humans, have a similar organization of limb plexuses. From fish to reptiles to humans, each limb plexus has the following features in common: (a) several spinal nerves (connected to spinal cord enlargements) contribute nerve fibers to the plexus, intermingle, divide, and regroup; (b) each spinal nerve divides into a dorsal ramus and ventral ramus; however, only the ventral ramus contributes nerve fibers to the limb plexus; (c) each plexus divides into anterior divisions to supply flexor muscles and the overlying surface of the limb and posterior divisions to supply extensor muscles and the body wall over their respective surface; and (d) each plexus is an organized meshwork of sensory, motor, and sympathetic fibers and innervates most of the extremity. Some plexuses are remarkably complex (the skate has 26 spinal nerves contributing fibers to the brachial plexus), while others are quite simple, such as the lumbar plexus in the human.

The lower limb consists of a flexor and extensor compartment that meets at borders (preaxial and postaxial), marked out by veins. The great saphenous vein marks out the preaxial and the small saphenous vein at the postaxial border. The flexor compartment, innervated by anterior divisions from the plexus, has a richer nerve supply and includes an additional caudal nerve. The nerve supply to these muscles and body wall structures is derived from the *lumbosacral plexus*, which is formed by segmental nerves L-1 to S-4. The plexus is actually one plexus in the fetus but becomes subdivided by the developing pelvic girdle. The plexus is usually studied as two in the adult: the lumbar and the lumbosacral plexuses.

Lumbar Plexus and Its Major Branches. Five lumbar nerves emerge from their respective intervertebral foramina and contribute to the formation of the lumbar plexus (Fig. 75-15). This plexus lies within the substance of the psoas major on the posterior abdominal wall, and its branches emerge through the muscle (anteriorly), laterally, and medially. This is important to remember since the plexus and branches are vulnerable during surgical procedures (e.g., abdominal hysterectomy), disease processes (e.g., psoas abscess), or space-occupying lesions (e.g., abdominal aortic aneurysm) that involve the psoas muscle or posterior abdominal wall. For example, anticoagulant therapy that results in a retroperitoneal hemorrhage might involve one or more nerves of the lumbar plexus dependent on the location of the hematoma. Most of the branches from the lumbar plexus are destined to supply the lower limb but in passage give motor supply to the psoas (especially L-2 to L-3) and quadratus lumborum and sensory supply to the posterior parietal peritoneum. There are five branches of the lumbar plexus.

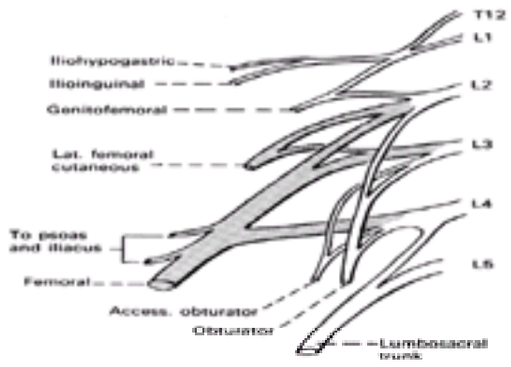

Figure 75-15. The lumbar plexus. The anterior primary division of the L-1 nerve splits into upper and lower branches, with the upper branch joined by a filament from the T-12 nerve to form the common trunk of the iliohypogastric and ilioinguinal nerves. The lower branch joins a branch of the L-2 nerve to form the genitofemoral nerve. The anterior primary division of the L-2 nerve also splits into upper and lower branches. The smaller upper branch takes part in the formation of the genitofemoral nerve, while the lower branch takes part in the formation of the femoral, lateral femoral cutaneous, and obturator nerves. The lower branch of the L-2 nerve, the upper branch of the L-4 nerve, and the undivided L-3 anterior primary division split into ventral and dorsal subdivisions. The dorsal branches form the femoral nerve while the ventral branches form the obturator nerve. The smaller branch of the anterior primary division of the L-4 nerve joins the undivided anterior primary division of the L-5 nerve to form the lumbosacral trunk or nervus furcalis, which takes part in the formation of the sacral plexus.

The *lateral cutaneous nerve of the thigh* is in close proximity to the femoral nerve at its origin and then diverges laterally to lie behind the iliacus fascia on the iliacus muscle (Fig. 75-16). It approaches the inguinal ligament, which it pierces medial to the anterior superior iliac spine, and terminates by supplying the lateral side of the thigh down to the knee. Meralgia paresthetica is a neuropathy, usually secondary to entrapment, of this nerve and results in paresthesias of the lateral thigh extending almost to the lateral knee. Treatment of this condition has included corticosteroid injection (at the point where the nerve pierces the inguinal ligament) and surgical release of the nerve (from the inguinal ligament, from beneath the iliacus fascia, or both).

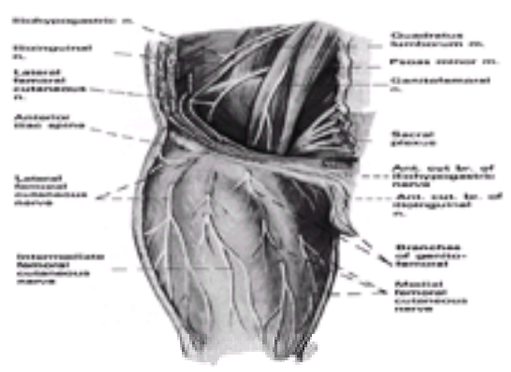

Figure 75-16. Anatomy of the iliohypogastric, ilioinguinal, genitofemoral, and lateral, intermediate, and medial femoral cutaneous nerves. See text for details.

The *femoral nerve* also emerges from the lateral aspect of the psoas muscle and is the great extensor nerve of the thigh (Fig. 75-16 and Fig. 75-17). The nerve travels in the gutter between the psoas and iliacus, supplies the iliacus, and passes beneath the inguinal ligament. It immediately breaks up into numerous branches and supplies both muscle and skin of the anterior thigh. Nerve conduction studies can sometimes be challenging because of this anatomy. Stimulation of the nerve proximal to the inguinal ligament might be difficult with abundant adipose tissue while stimulation distal to the inguinal ligament is often confounded by the early ramification of nerve branches. Motor fibers from the femoral nerve supply the pectineus, sartorius, and the quadriceps. Sensory fibers supply the hip and knee joints (Hilton's law) and most of the skin of the anterior and medial thigh, and the saphenous nerve innervates the skin of the medial leg and foot. In the setting of weak quadriceps, the distinction between a femoral neuropathy, lumbar plexopathy, and L-4 radiculopathy can sometimes be a challenge. In contrast to a femoral neuropathy, however, lumbar plexopathies typically involve the lateral cutaneous nerve of the thigh and might affect the obturator nerve, in addition to the femoral nerve. Contrasting, an L-4 radiculopathy would involve ankle extensors (dorsiflexors) and muscles innervated by the superior gluteal nerve, yet spare hip flexors and the skin of the anterior thigh.

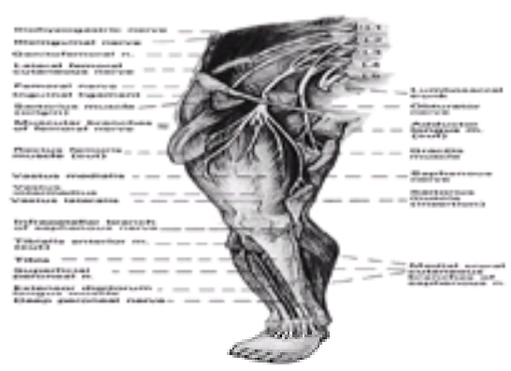

Figure 75-17. Anatomy of the femoral nerves. See text for details.

The *obturator nerve* forms medial to the psoas muscle and lies on the ala of the sacrum, travels along the side wall of the pelvis, and splits into two terminal branches prior to exiting the pelvis through the obturator foramen (anterior and posterior branches). In the thigh, the two branches split around the adductor brevis and terminate by supplying muscle and skin of the medial (adductor) thigh (Fig. 75-18). Motor fibers supply the obturator externus, pectineus (it often receives innervation from both the femoral and obturator nerves), gracilis, and the three adductors (brevis, longus, and magnus). Sensory fibers supply the hip joint and the lower medial side of the thigh. Obturator nerve blocks are less effective if the infusion of phenol or ethanol is superficial and does not affect the posterior branch, since the posterior branch supplies the large adductor magnus muscle. Positioning the needle just external to the obturator notch (foramen) yields the best results, as opposed to a bit more distal placement after the anterior and posterior branches diverge.

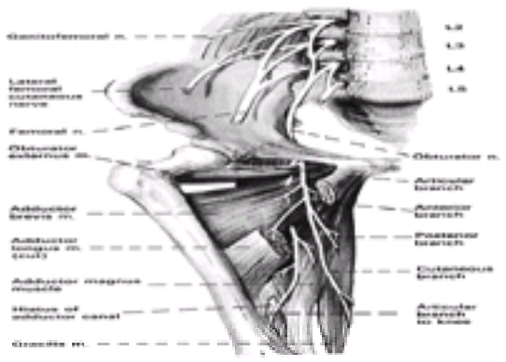

Figure 75-18. Anatomy of the obturator nerve. See text for details.

For completion, the *L-1 segmental nerve* and *genitofemoral nerve* (L-1, L-2) are worthy of mention as branches of the lumbar plexus (see Fig. 75-16). The L-1 segmental nerve is a typical spinal nerve that divides into its two terminal branches, ilioinguinal and iliohypogastric. These nerves supply the lowermost aspect of the abdominal wall (both muscle and skin) and then supply skin of the upper thigh and anterior scrotum. Injury to the nerves (e.g., abdominal surgeries) can result in denervation of the lowermost fibers of the abdominal wall (internal oblique and transversus abdominus) and result in a direct inguinal hernia. The *genitofemoral nerve* emerges through the substance of the psoas muscle and then supplies the cremaster muscle with motor fibers, while the sensory fibers supply the fascia of the spermatic cord and a small patch of skin on the anterior thigh (just distal to the midinguinal ligament). This nerve is of interest because it subserves the cremasteric reflex (L-1, L-2) and is thought to mediate referred pain from a ureteral stone. Indeed, renal colic may result in reflex retraction of the testis as well as radiation of pain into the groin and anterior thigh (see Chapter 68).

Lumbosacral Plexus and Its Major Branches. The lumbosacral plexus is formed by the lumbosacral trunk (from L-4, L-5) and sacral nerves (S-1 to S-4) on the surface of the piriformis muscle within the pelvis. Branches from the plexus arise from the roots and after the divisions as in the brachial plexus. There is remarkable symmetry that aids in learning the 12 nerves of the lumbosacral plexus. Six nerves branch from the roots, and six arise after the divisions. There are three nerves from the anterior and three from the posterior divisions (Fig. 75-19 and Fig. 75-20).

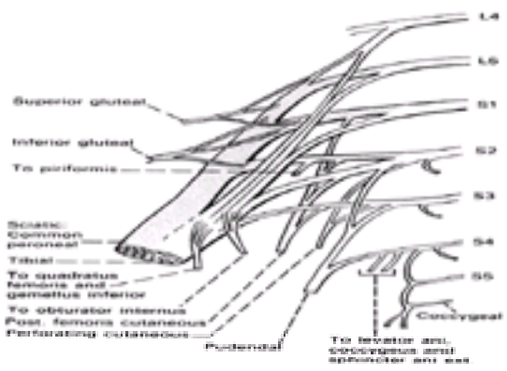

Figure 75-19. The sacral plexus. The large tibial nerve, the nerve to the quadratus femoris and gemellus inferior, the nerve to the obturator internus and gemellus superior, and part of the posterior femoral cutaneous nerve are derived from the anterior subdivisions. The common peroneal nerve, the nerve to the piriformis, the superior gluteal, the inferior gluteal, and part of the posterior femoral cutaneous nerves are derived from the posterior subdivision. The tibial and common peroneal nerves are the two terminal branches and are usually fused together as far as the posterior part of the thigh into what is commonly known as the great sciatic nerve (see Fig. 75-20). (Modified from Clemente CD, ed. *Gray's anatomy of the human body*, 30th Am. ed. Philadelphia: Lea & Febiger, 1985:471.)

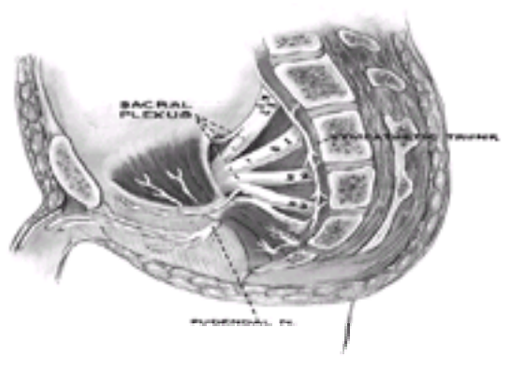

Figure 75-20. Sagittal view of the right pelvis showing the position of the sacral plexus, which is a large, broad, triangular structure lying in the posterior part of the true pelvis in front of the sacrum, from which it is separated by the piriformis muscle. Its broad base is formed by the anterior primary divisions and therefore coincides with the row of anterior sacral foramina and with the L-5 and L-4 paravertebral spaces, while its apex is composed of the great sciatic nerve as it lies in the great sciatic notch. The plexus is covered by the pelvic fascia and is in close relation with the pelvic viscera. Anterior to the plexus are the hypogastric vessels and some of their branches, the ureter, and the sigmoid colon. Some branches of the hypogastric vessels run between the anterior primary divisions before they unite to form the plexus.

The branches that arise directly from the roots of the lumbosacral plexus are primarily important when considering pelvic anatomy and function. The *posterior cutaneous nerve* of the thigh is the only one of significance when considering the lower extremity. It supplies the inferior buttocks (inferior cluneal branch) and the posterior thigh down to the popliteal fossa. Referred pain from the prostate and other derivatives of the cloaca are thought to be mediated along this nerve and must be distinguished from sciatica.

The nerves from the anterior divisions supply flexor and adductor muscles. Two of the three nerves from the anterior divisions are relatively unimportant (*nerve to* obturator internus and*nerve to* quadratus femoris). The *tibial component of the sciatic nerve* is the great flexor nerve of the lower extremity (Fig. 75-21). It supplies almost all of the flexor muscles of the thigh (except the short head of the biceps femoris) and all of the flexor muscles of the leg and sole of the foot. The tibial nerve is rarely injured in the thigh and leg except by penetrating, violent injuries. Complete division results in paralysis of flexor muscles of the leg (calf) and sole of the foot and loss of sensation on the plantar aspect of the foot. After a complete injury, the ankle and foot have a characteristic posture (calcaneovalgus) due to the unopposed action of ankle and foot extensors (dorsiflexors) and evertors.

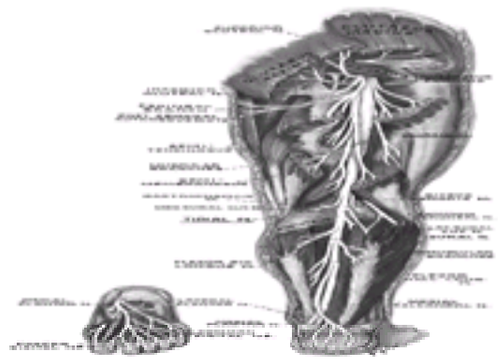

Figure 75-21. **A:** The plantar surface of the foot, depicting distribution of the two plantar nerves and their branches. **B:** Anatomy and distribution of the sciatic nerve and its branches, including the tibial and common peroneal nerves.

The nerves from the posterior division supply the extensor and abductor muscles of the lower extremity. The *gluteal nerves* are motor nerves that supply the gluteal muscles. Using the fact that the gluteus medius arises higher on the iliac bone (as compared with gluteus maximus) assists one in memorizing that the *superior gluteal nerve* innervates the gluteus medius, minimus, and tensor fascia lata. It also arises from a more rostral segment (L-4 versus L-5) than the inferior gluteal nerve. Injuries to the gluteal nerves might occur within the pelvis or after exit through the greater sciatic notch in the buttock. Intrapelvic injuries are typically caused by a mass or an injury that also affects other branches of the lumbosacral plexus (e.g., sciatic). Within the gluteal region, injuries are usually of the penetrating type, iatrogenic in nature by injection, or after violent injuries by gunshot or knife. Injury to the superior gluteal nerve results in weakness of the gluteus medius and minimus revealed by a positive Trendelenburg's sign when weight bears on the affected lower limb.

The *common peroneal nerve* is wrapped with the tibial nerve within the sciatic sheath and gives off one branch in the thigh to the short head of the biceps femoris (Fig. 75-22). In the upper aspect of the popliteal fossa, it branches from the tibial nerve and follows the lateral border of the popliteal fossa and then the medial border of the biceps, giving off genicular nerves to supply the knee joint and the lateral sural nerve. It then becomes subcutaneous just behind the head of the fibula, where it is commonly injured from direct pressure, repeated squatting, prolonged sitting in a cross-legged position, or traction after orthopedic injuries (e.g., medial dislocation of the knee). In the substance of peroneus longus, the nerve divides into its two terminal branches, the *deep and superficial peroneal nerves*. Each of these nerves may be injured within their respective compartment (deep peroneal within the anterior compartment and superficial peroneal within the lateral compartment) by various pathologies including fracture, compartment syndrome, and tumor and from extrinsic compression by tight-fitting clothes and footwear.

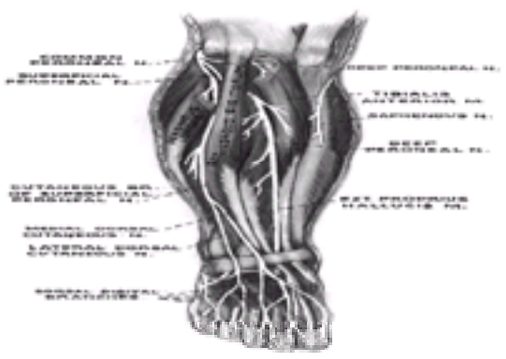

Figure 75-22. Anterior view of the leg showing the course and distribution of the common peroneal nerve into the superficial and deep peroneal nerves and their branches.

The*sciatic nerve* is, in fact, two nerves wrapped within one sheath. Sometimes, it divides into its two components as it enters the buttock and the two nerves simply course downward side by side. In this case, there is no difference in innervation; all of the branches to the hamstrings arise from the medial-lying tibial nerve with the exception of that to the short head of the biceps. In thinking about nerve blocks to the hamstring muscles, many patterns of innervation have been observed. Occasionally, a separate large motor trunk is formed within the pelvis and parallels the sciatic nerve into the buttock and thigh. Typically, separate branches arise at intervals from the medial aspect of the sciatic nerve, but the patterns are variable. Sunderland and Hughes, for example, found variability in the order in which the branches to the various muscles arose, together with an inconstant number of branches. As a case in point, they found a single branch to the long head of the biceps in 50% of the cases, two nerves in 40%, and three nerves in 10% (24).

The sciatic nerve is sometimes injured in its early course by pelvic fractures, dislocations or surgeries of the hip, and penetrating injuries, although the most common injury is from poorly placed gluteal injections. The majority of sciatic nerve lesions affects primarily the common peroneal nerve with a relative sparing of the tibial component. In the thigh, the nerve is rarely injured because extensive soft tissues protect it. As the nerve enters the popliteal fossa, however, it is somewhat more vulnerable to injury. At the apex of the popliteal fossa (a hand's breadth above the knee joint) the sciatic nerve divides into its terminal tibial and common peroneal nerves. Therefore, injuries at the level of the apex commonly damage both components of the nerve, while those below the apex more commonly affect the tibial nerve.

Sympathetic Innervation. The preganglionic fibers for the lower limb originate within the spinal cord (preganglionic fibers arise from the thoracolumbar outflow) from the lower segments (T-11 to L-2). The cell bodies are located in the lateral horn and the axons exit via the ventral roots (Fig. 75-23). They descend in the sympathetic chain to synapse in a ganglion.

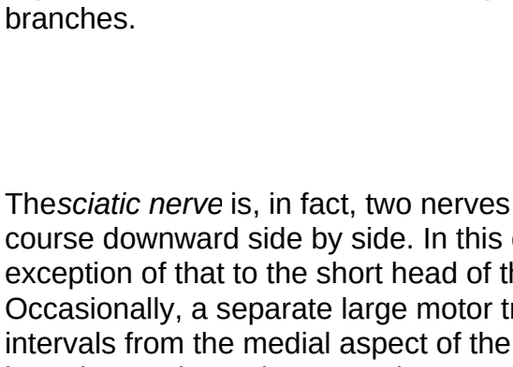

Figure 75-23. Origin and course of preganglionic (*solid lines*) and postganglionic (*dashed lines*) sympathetic fibers that supply the lower limbs. Preganglionic fibers at the T-6 to T-9 spinal cord levels pass cephalad to join those from T-2 to T-5 to supply the upper limb. (Reprinted from Bonica JJ. *Clinical applications of diagnostic and therapeutic nerve blocks.* Springfield, IL: Charles C Thomas, 1959:146, with permission.)

A postganglionic (gray ramus) sympathetic nerve joins each root of the lumbar and lumbosacral plexus after exit from the intervertebral foramina; these sympathetic fibers hitchhike through the plexus and its nerves. Thus, each dermatome of the lower limb is supplied via the cutaneous nerves by sympathetic fibers to innervate

blood vessels, sweat glands, and erector pili muscles. The postganglionic nerve arises from cell bodies in the appropriate sympathetic ganglion from the lumbar and sacral sympathetic chain.

Sympathetic innervation provides a valuable diagnostic aid in localizing nerve lesions. For example, the presence of autonomic disturbance in the lower limb localizes a process to a site distal to where the postganglionic fiber joins with the root. For example, a herniated nucleus pulposus does not affect sympathetic fibers because it compresses the nerve root, but a tumor in the retroperitoneal space presents with both somatic and sympathetic nerve dysfunction.

Muscle

The majority of the mass of the lower extremities is made up of muscle. The chief functional tasks of muscle are to maintain postural stability in standing and other ambulatory activities, and to generate concentric and eccentric contractions to produce and control movements of the lower extremities. The gross motor tasks include a spectrum of complexity, from simple movements to the highly complex tasks that are seen during sporting maneuvers.

A detailed analysis of the origin, insertion, and function of each muscle group is beyond the scope of this work. It is useful, however, to consider muscles as a potential source of nociception. To effectively make a diagnosis of the etiology of pain that is ascribed by a patient to an anatomic area that is muscular, one must consider both local and referred sources of pain.

Muscle and its supporting connective tissue structures are important and frequent sources of nociception in the lower extremities. Pain localized to muscle may be caused by local pathologies, or it may be referred from a nociceptive source in proximal articulations or osseous or neurogenic structures. Common causes of referred pain to areas of lower extremity muscle include radicular processes, peripheral nerve lesions, and spinal or hip arthritis.

Muscle as a Source of Nociception. There are many conditions that can result in muscle pain. A useful organizational structure that is helpful in assisting the clinician determine a diagnosis is to define the pain in terms of its acuity of onset, whether it is focal or generalized, and whether or not it is exercise related.

Focal Muscle Pain. Focal muscle pain is defined as pain arising in a single muscle group or muscle compartment. The most common cause of this type of pain is muscle trauma. The trauma can be broadly categorized into external trauma (i.e., arising from an impact of the muscle group with another structure) or internal trauma, resulting from forces generated by the muscle itself. Trauma to muscle from an external impact results in direct muscle injury, which leads to the development of a hematoma. The onset of pain is sudden and associated with the injury; however, the pain may increase over time as swelling increases. The diagnosis is usually obvious based on the history. Physical examination reveals an area of localized tenderness and swelling at the site of injury, with ecchymosis. Pain is exacerbated by any attempt at generating tension in the muscle either from active contraction or passive stretch. These injuries typically resolve spontaneously with full restoration of function; however, complications including calcification of the hematoma leading to myositis ossificans (25), and a compartment syndrome may occur. Trauma resulting from internal muscle forces results in muscle strain or a frank muscle tear. Typically, the injuries result from a forced lengthening of a muscle group that is being strongly contracted or from a powerful eccentric contraction from the muscle group (25). The lower extremity muscle groups in which this occurs more commonly are the gastrocnemius and the hamstrings. The history is one of sudden onset of pain that results in cessation of the movement. In a muscle strain there is partial rather than complete disruption of the muscle. A muscle *tear*, in contrast, results in a complete discontinuity in a portion of the muscle. This results in a rapid onset of swelling (within an hour or so) and ecchymosis with focal pain and tenderness. The pain is aggravated by any attempt to lengthen the muscle passively or by voluntary contraction of the muscle group. With resolution of the swelling there may be a palpable defect in the body of the muscle.

Tumor is an uncommon cause of muscle pain but must be considered in the patient who presents with progressive pain and localized swelling. Tumors arising from muscle cells are uncommon. Benign tumors of muscle (i.e., rhabdomyoma) almost never occur in the extremities (26). Malignant tumors, usually rhabdomyosarcomas, arise in the extremities more commonly. Typically, these are childhood neoplasms that present with a gradually enlarging mass that may or may not be painful, depending on the extent of tumor at the time of presentation (26). Because muscle is anatomically comprised of tissues other than those of muscle cell origin, tumors of fibrous, lipoid, vascular, and neural structures can also arise within muscle.

Muscle ischemia rarely leads to pain in a specific muscle group. The pain more commonly involves multiple muscle groups within an extremity. The most common underlying pathologic causes of ischemic muscle pain are atherosclerosis, thrombosis, and embolus. Acute embolus results in acute onset of pain with a cool, pale extremity with impaired motor and sensory neurologic function. Chronic ischemic disease may result in claudication, with pain in lower extremity muscles associated with exercise and relieved with rest. A less common cause of acute focal muscle pain related to ischemia is diabetic muscular infarction. In this condition patients with long-standing diabetes present with the sudden onset of acute thigh pain with swelling and muscle weakness. The most common muscle groups involved are the vastus lateralis and the adductors (27).

Acute Generalized Muscle Pain. Differential diagnoses to consider with the acute onset over days to weeks of diffuse muscle pain in the upper and lower extremities, often with a more severe proximal distribution, include infectious myositis, toxic myositis, and drug-induced myositis.

Viral and parasitic infections are the most common infectious causes of acute diffuse muscle pain. The more common viral infections that may result in myositis include influenza, coxsackievirus, and human immunodeficiency virus. With influenza and coxsackievirus infections, the muscle pain begins 1 to 13 days after onset of a flulike syndrome. Associated symptoms include fatigue, muscle weakness, and myoglobinuria. In human immunodeficiency virus myopathy the onset is much more gradual and progressive, with weakness rather than pain being the predominant symptom (28). Many different parasites can affect muscle. The three most common are trichinosis, cysticercosis, and toxoplasmosis. The general presentation is one of relatively acute onset of fever, muscle pain, tenderness, and weakness. Muscle swelling with or without distinct nodularity is a variable feature.

Alcohol is the most common toxin to cause a myopathy. The type of myopathy may be acute or chronic, depending on the extent and chronicity of alcohol intake. Acute alcoholic myopathy can result in the acute onset of muscle weakness and pain that is generalized. Pharmaceutical agents that can cause muscle necrosis are more likely to cause myalgias in addition to weakness as a presenting complaint. Agents that fall into this class include the cholesterol-lowering drugs lovastatin, clofibrate, and gemfibrozil, as well as ipecac when used chronically. Elevations in creatine phosphokinase and abnormalities in electrodiagnostic studies in patients taking these medications help to confirm the diagnosis (29).

Chronic Generalized Muscle Pain. Chronic generalized muscle pain has an onset that is more gradual, extending sometimes over weeks to months. Muscle weakness may or may not be a prominent feature depending on the underlying etiology. The more common causes in this group include polymyositis and dermatomyositis, polymyalgia rheumatica, fibromyalgia syndrome, and metabolic and endocrine myopathies (30). Polymyositis and dermatomyositis are autoimmune connective tissue disorders that can affect muscle in a fairly focal manner or may cause diffuse proximal muscle weakness with muscle pain. In polymyositis there is no cutaneous involvement, but swallowing difficulties may be the result of pharyngeal muscle involvement. With dermatomyositis there is a concomitant characteristic facial rash, with or without an erythematous scaling rash over the dorsum of the interphalangeal joints or the extensor surfaces of other joints. Diagnosis is made on the basis of history, physical examination in association with abnormal muscle enzymes, electromyography, muscle biopsy, or more than one of these tests. Polymyalgia rheumatica occurs in patients over 50 years of age, with a peak onset in the 70s. The characteristic clinical features include pain and stiffness, with more minor complaints of weakness, predominantly in the shoulder girdle musculature but also involving the muscles of the trunk and pelvic girdle. Fibromyalgia syndrome is discussed in detail in Chapter 30 but is included here for completeness. It is a syndrome of diffuse muscle weakness with myalgias and chronic fatigue with a high frequency of depressive symptoms. This syndrome is more common in women than in men. The underlying etiology is not known. Therapeutic interventions include tricyclic antidepressants, aerobic exercise, and behavioral strategies (31).

The majority of metabolic and endocrine processes that can affect muscle function cause weakness of the shoulder and pelvic girdle muscles as a primary complaint. Hypothyroidism and hyperthyroidism as well as hyperparathyroidism are more likely to cause diffuse muscle stiffness and myalgias in conjunction with the weakness (31).

Exercise-Induced Muscle Pain. During exercise, especially during intense or prolonged exercise, there are considerable metabolic and mechanical stresses placed on muscle. These can result in pain either during or in the postexercise period. The etiology of pain during maximal isometric contractions or with repeated maximal concentric or eccentric contractions is not known. Lactate accumulation and alteration of pH were believed to be the primary mediators of pain, but these are no longer believed to be the critical factors. It is possible that accumulation of other metabolites may be more important (32). A number of inherited abnormalities of muscle metabolism can predispose to muscle pain, fatigability, and weakness during and after exercise.

Pain can also occur in muscle in the period after cessation of exercise. This has been termed *delayed-onset muscle soreness*. Delayed-onset muscle soreness occurs

with a greater frequency after a period of unaccustomed exercise and in particular if there is a significant eccentric component to the exercise stress. The location of the pain is specific to the muscle groups that have been exercised eccentrically. Within the muscle group there may be increased pain in the region of the musculotendinous junction. The onset of muscle pain usually is 24 hours after exercise, with a peak at 48 to 72 hours after exercise, and a gradual diminution over the next 24 to 48 hours. It is believed that the etiology of the pain is related to injury to the muscle at an ultrastructural level because of the high forces the muscle is exposed to. The ultrastructural injury leads to localized muscle swelling and an inflammatory response.

Muscle cramp is a sudden onset of powerful involuntary muscle contraction of a muscle group that may be provoked by a minor voluntary muscle contraction with the muscle in a shortened position. Although it may be associated with neurologic or endocrine disorders, it is most commonly associated with exercise. It may occur either during or after a period of intense or prolonged exercise. When it occurs during exercise, it is more common during endurance activities such as marathon running or long- distance bicycle racing. In this context, electrolyte depletion and fluid volume loss are thought to be important contributing factors (32). Muscle cramp is thought to be associated with a hyperexcitability of the motor neuron. The exact portion of the motor neuron that is involved is controversial: It may be the terminal portion that is the source of the high-frequency discharge (33).

Referred Pain in the Lower Extremities. One of the most common sources of referred pain into the lower extremities is mechanical compression, injury, or irritation of a neural structure. The classic example of this is *sciatica* (i.e., pain referred into the posterior thigh and leg with or without pain in the foot related to radiculopathy). Pain in the lower extremity associated with radiculopathy is typically in the dermatomal distribution of the affected nerve root. With L-5 and S-1 lesions the pain is in the previously mentioned distribution. With an L-4 root lesion the pain is more in the distribution of the anterior thigh and medial leg, and with an L-3 root lesion the pain is in the distribution of the anterior thigh. Coughing, sneezing, or straining, which increases intradiskal and venous pressure, may aggravate pain of radiculopathy. The pain may be associated with symptoms of sensory deficit or motor weakness. Specific physical examination findings such as positive root tension signs, sensory disturbance, motor weakness, and reflex changes in the appropriate nerve root distribution may confirm the diagnosis.

Another common cause of referred pain in the lower extremities is related to nerve injury. These injuries include peripheral neuropathies, focal compressive neuropathies, vasculitis, or local direct trauma. The pain is typically referred in the distribution of the affected nerve. For example, the lateral femoral cutaneous nerve typically exits the pelvis just medial to the anterior superior iliac spine at the inguinal ligament and supplies sensation to the anterolateral thigh. This nerve is commonly injured at the point of exit from the pelvis. Injury results in the clinical syndrome with a burning dysesthetic pain in the anterolateral thigh, which is termed *meralgia paraesthetica*.

Pain in the Hip and Gluteal Region

The accurate diagnosis of hip and gluteal pain is a challenge; there are many soft tissue, joint, and neural tissues that subserve pain in the region. In this section, the regional anatomy is presented followed by an overview of common causes of pain in the hip and gluteal region.

Anatomy. The lower limb is articulated to the axial skeleton via the pelvic girdle. The femur joins with the pelvis at the acetabulum and the pelvic girdle articulates with the axial skeleton at the sacroiliac joint. Organizationally, it is useful to consider the pelvic girdle and sacroiliac joint separately from the gluteal and hip regions.

Surface Anatomy and Palpation. The tips of the anterior superior iliac spine and iliac crest are easily felt and may be visible. When the inguinal ligament is traced medially from the anterior superior iliac spine, the pubic tubercle is the first bony landmark palpated. The greater tuberosity of the femur lies quite posteriorly, a hand's breadth below the iliac crest, and is best palpated with the hip relaxed and in an abducted position. The ischial tuberosity is easily palpated when the hip is flexed but covered by the gluteus maximus and more difficult to palpate when the hip is in the extended position. Pain over the ischial tuberosity may represent ischial bursitis, inflamed with too much sitting (*weaver's bottom*). Directly beneath the visible dimples above the buttocks, the posterior superior iliac spines are readily palpated.

Pelvic Girdle. The bony pelvis constitutes the base of the trunk. It supports the abdomen and links the vertebral column to the lower limbs. It is a closed ring made up of three bony parts and three joints. There is a complete interdependence of the various elements of the pelvis, so that impairment at any level affects the structure as a whole and decreases its mechanical resistance. The three bony parts are the two paired iliac bones and the sacrum. The three joints are the two sacroiliac joints and the symphysis pubis that links the iliac bones anteriorly. The bony pelvis is quite different in male and female subjects. The female pelvis is broader and shorter, with a larger pelvic brim. The female bones are also more slender and make a wider subpubic angle.

As a whole, the bony pelvis transmits forces from the vertebral column to the lower limbs. The weight supported by L-5 is distributed equally along the alae of the sacrum and through the ischial tuberosities toward the acetabulum. Conversely, ground reaction forces are transmitted to the acetabulum by the neck and head of the femur. Some of these forces are transmitted across the horizontal ramus of the pubic bone and counterbalanced at the symphysis pubis by a similar force form the other side.

Since the pelvis is remarkably strong, fracture is rare except after the application of great force. Fractures are typically a result of compressive forces and break across the weakest parts of the ring, such as the pubic rami, wing of the ilium, and at the obturator foramen.

Sacrum and Sacroiliac Joint. The sacrum consists of five fused vertebrae that form a single triangular bone that supports the spine and forms the posterior wall of the pelvis. The base is formed by the upper surface of the first sacral vertebra and has an anteriorly projecting edge known as the promontory. The sacrum is markedly curved and tilted backward, so that its first element articulates with the fifth lumbar vertebrae at a pronounced angle. As the sacrum is broader above than below, it fits vertically between the two iliac bones like a wedge. The sacrum is suspended from these bones by sacroiliac ligaments (Fig. 75-24). As forces increase on the spine and sacrum (e.g., during standing), the sacrum is wedged more tightly between the iliac bones as a self-locking system.

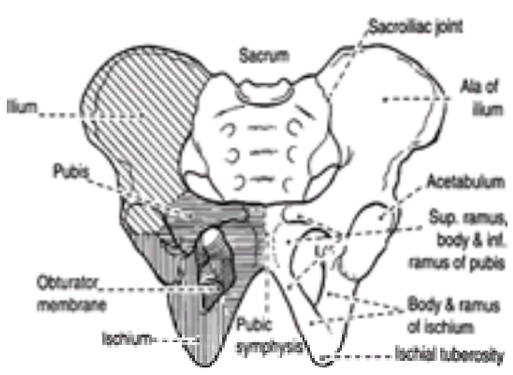

Figure 75-24. The bony pelvis, tilted slightly backward and seen from an anterior view. The three component bones of the pelvic girdle are shaded differently. (Reprinted from Rosse C, Gaddum-Rosse P, eds. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:308, with permission.)

The sacroiliac joint is synovial and a complex articulation between the sacrum and ilium. The articulating surfaces are crescent shaped and marked by corresponding elevations and depressions that fit one into another, thus restricting movement (Fig. 75-25). The joint is further stabilized by a long crest on the articular surface of the iliac bone that fits into a curved furrow along the articular surface of the sacrum. In addition to the osseous features, ligamentous factors promote stability at the sacroiliac joint. The sacroiliac ligaments surround the capsule of the joint and are separated into anterior, intermediate, and posterior portions. In general, these ligamentous bands are weak anteriorly and very strong elsewhere. The iliolumbar ligaments, attaching the transverse processes of the last two lumbar vertebrae to the iliac crest, and the sacroischial ligaments (e.g., sacrospinous and sacrotuberous) are considered accessory ligaments that add further stability to the joint.

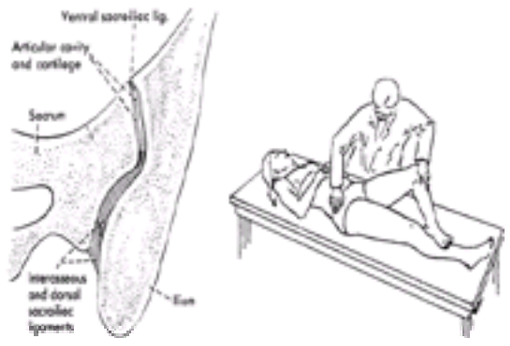

Figure 75-25. The sacroiliac joint. **A:** A schematic transverse section through the right sacroiliac joint. **B:** Testing the right sacroiliac joint. The joint is subjected to stress by pressing on the right anterior superior iliac spine and on the distal end of the left femur after the left hip has reached its limit of movement in the position shown. (Reprinted from Rosse C, Gaddum-Rosse P, eds. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:312, with permission.)

Significant forces and some movement occur at the sacroiliac joint, noted during pregnancy and by the individual who has pathology at the joint, such as sacroiliitis. The movements that occur include small degrees of sliding and rotational displacements. These movements and mechanical forces (e.g., compressive and distracting) are best appreciated when examining the effect of posture on the joints of the bony pelvis. The weight of the trunk during quiet standing acts on the promontory and causes the sacrum to rotate so that the base moves forward (inferiorly and anteriorly) and the apex (along with the tip of the coccyx) moves backward (34). The anterior sacroiliac, sacrospinous, and sacrotuberous ligaments are rapidly put on tension, thereby limiting any further movement. When standing on one foot, the pelvis on the side of the unsupported limb drops. This leads to shearing and rotational forces at the pubic symphysis and the sacroiliac joints, resisted by the ligaments so little actual movement occurs. However, significant movement might occur if the stabilizing ligaments of the sacroiliac joint are lax. This occurs following traumatic injuries to the pelvis, and pain might be felt at every step during walking. Inflammation or abnormal mobility may be a cause of low back pain.

On physical examination, direct examination of the sacroiliac joints is difficult. Therefore, provocative tests that compress and rock the joint are helpful in eliciting signs of sacroiliac joint disease (pelvic rock test, Gaenslen's sign, and Patrick-Fabere test) (see Fig. 75-25). If hip joint pathology is excluded, pain elicited by these tests in the sacral region is indicative of disease in the sacroiliac joint. Traumatic injury to the sacroiliac joints is rare. It is more common that infection (tuberculosis), tumor, or arthritis affects the sacroiliac joint. Sacroiliitis associated with rheumatologic disorders (e.g., ankylosing spondylitis and Reiter's syndrome) is well described and can be a cause of low back pain.

Gluteal Region. Pain in the gluteal region is common. In addition to many tissues that are direct sources of nociception, referred pain to the buttock from the lumbosacral spine has been well described.

The gluteal region consists of soft tissues that join the posterior aspects of the pelvis with the hip joint. The skin over the buttocks and lateral thigh is thick, tough, and poorly vascularized, making it a common site for carbuncles. An abundant layer of subcutaneous fat provides padding and support for weight bearing during sitting and is traversed by cutaneous nerves and small blood vessels. Deep to the adipose layer is deep fascia; a tough inelastic membrane. It varies widely in thickness over the limbs. In the lower extremity, the iliotibial tract is a well-developed region of deep fascia over the lateral thigh (Fig. 75-26). Tensor fascia lata and the gluteus maximus both insert into the iliotibial tract to act across both the hip and knee. The deep fascia is relatively avascular and is richly endowed with sensory fibers. It is exquisitely sensitive. Its nerve supply is that of the overlying skin and not of the underlying muscles. Traumatic injury, overuse, and inflammatory pathologies may cause pain in deep fascial structures.

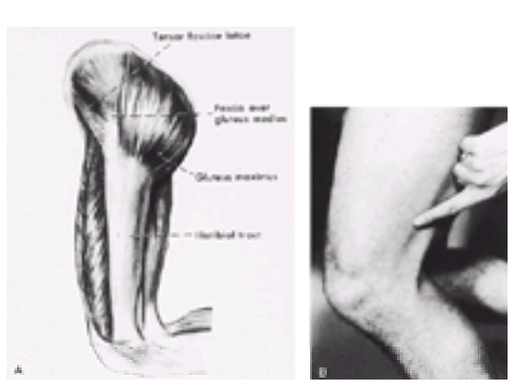

Figure 75-26. The iliotibial tract and the muscles associated with it. **A:** Lateral view of the thigh and gluteal region showing the iliotibial tract, tensor fasciae latae, and gluteus maximus. **B:** The iliotibial tract, seen anterior to the tendon of the biceps femoris, is an important factor in stabilizing the flexed knee when it is supporting the body weight. Note: the right leg is off the ground. (Reprinted from Rosse C, Gaddum-Rosse P, eds. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:320, with permission.)

The gluteal region serves as the origin for the major abductor, extensor, and lateral rotating muscles of the hip joint. Most of the muscles insert onto the greater trochanter or the iliotibial tract.

The gluteus maximus is the superficial muscle in the buttock and is a powerful extensor of the hip. It arises from the posterior aspect of the ilium and the sacrum and inserts into the iliotibial tract and the greater trochanter. The primary action of the gluteus maximus is powerful hip extension; it contracts during activities such as going upstairs and getting up from a sitting position. This contrasts with hip extension during quiet, level walking during which the hamstring muscles are the primary movers. The origin of the hamstrings on the ischial tuberosity is a possible source of pain in the gluteal region. Proximal hamstring sprain or rupture, hamstring tendinitis, and bursitis over the ischial tuberosity may lead to pain in the region of the buttocks, particularly over the ischial tuberosity.

Gluteus medius and minimus are the primary abductors of the hip (Fig. 75-27). Lying beneath the gluteus maximus, both muscles arise from the posterolateral surface of the ilium and insert into the greater trochanter. Abduction of the unsupported lower limb is often clinically tested when side-lying, yet gluteus medius and minimus usually function during walking (Fig. 75-28). Contraction of the ipsilateral hip abductors occurs during the stance phase and prevents the pelvis from dropping to the unsupported side. Weakness of the gluteus medius and minimus manifests as a positive Trendelenburg's test in which the pelvis drops away from the stance leg during walking or single-leg standing.

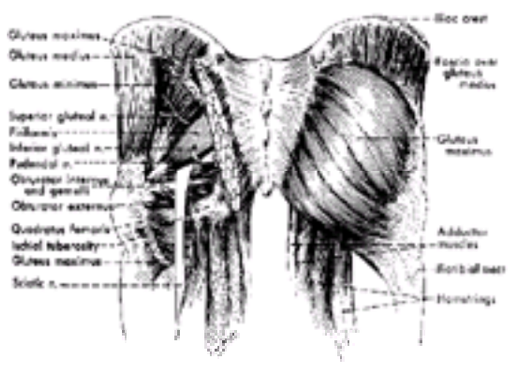

Figure 75-27. Muscles of the gluteal region seen from the back. On the left side the gluteus maximus has been resected and a wedge has been removed from the gluteus medius. (Reprinted from Rosse C, Gaddum-Rosse P, eds. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:321, with permission.)

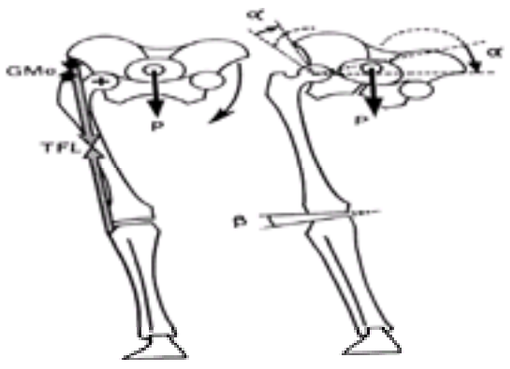

Figure 75-28. Explanation of Trendelenburg's sign. (Reprinted from Kapandji IA. *The physiology of the joints*, 5th ed. Vol 2, Lower limb. Edinburgh, UK: Churchill Livingstone, 1987:49, with permission.)

The tensor fascia lata (see Fig. 75-26) is a muscle that arises from the anterior part of the iliac crest and passes downward and backward to insert into the iliotibial tract. It functions as a flexor and medial rotator of the hip. Several short lateral rotators make up the deepest layer of muscles in the gluteal region and insert into the posterior aspect of the greater trochanter. The piriformis arises from the anterior surface of the sacrum and exits through the greater sciatic foramen surrounded by neurovascular structures that enter the buttock. The piriformis syndrome has been described as a condition in which the piriformis muscle irritates the sciatic nerve, causing pain in the buttocks and referred pain along the course of the sciatic nerve. Patients generally complain of pain deep in the buttocks, which is made worse by sitting, climbing stairs, or performing squats.

Hip Joint and Anterior Thigh. The hip is a stable ball-and-socket joint with spherical articular surfaces. The neck of the femur, which joins the shaft, supports the spherical head. The axis of the femoral neck is obliquely set and runs superiorly, medially, and anteriorly. In the adult it forms an angle of approximately 125 degrees with the femoral shaft. An increase in this angle, coxa valga, occurs in cases of congenital dislocation of the hip. A decrease in the angle, coxa vara, occurs in fractures of the femoral neck and in slipping of the femoral epiphysis. During standing, the coronal plane passes through the center of the femoral head and axis of the femoral condyles, which lie almost completely anterior to the femoral shaft and the axis of rotation at the knee. The head articulates with acetabulum, which is directed laterally, inferiorly, and anteriorly. Its inferior orientation results in an overhanging upper part of the socket, which sustains the greatest compression forces from the head. Therefore, the articular cartilage of the acetabular roof and of the femoral head are thickest superiorly. Dislocation of the hip occurs rarely. In cases of congenital dislocation of the hip, the upper lip of the acetabulum fails to develop adequately and the head of the femur slips out of the acetabulum onto the posterior surface of the ilium. Traumatic hip dislocation occurs after motor vehicle accidents in which the flexed knee strikes a fixed object, resulting in a posterior dislocation of the femur.

Femoral neck fracture is a common cause of hip pain in the elderly. More than 90% of such fractures occur in persons over 70 years of age. Fractures of the upper end of the femur may break the neck immediately beneath the head, through the neck, between the trochanters (intertrochanteric), or below the level of the trochanters (subtrochanteric). The location of the fracture determines whether the blood supply to the femoral head is interrupted with resultant avascular necrosis. This is a problem in the child and the older adult. In the child, the nutrient artery to the shaft of the femur terminates at the metaphysis; in other words, the nutrient arteries are end arteries and do not supply the epiphysis. Therefore, embolism, infarction, and osteomyelitis in the child may result in infarction. In the young child and middle-aged adult, the metaphysis has ossified, and rich anastomoses are established between epiphysis and metaphysis. However, the blood supply changes in the elderly. One of the two major sources of blood, the obturator artery, begins to wither away. Many of the anastomoses become tenuous and the main supply of the femoral head is through small arteries that arise from the trochanteric anastomosis and travel up along the neck of the femur. In the older person, fractures of the femoral neck interrupt the retinacular arteries and the head is deprived of its blood supply. The retinacular arteries may be injured in femoral neck fractures, dislocation of the hip, and slipping of the femoral epiphysis. In contrast, fractures outside the joint capsule (some of the intertrochanteric and all of the subtrochanteric fractures) leave these vessels undisturbed.

The capsule of the hip is loose but extremely strong, strengthened by three named ligaments, each ligament arising from a constituent of the innominate bone (iliofemoral, pubofemoral, and ischiofemoral). All of the ligaments have a coiled or spiral structure secondary to the rotation of the lower limb during development (35). The disposition of the ligamentous fibers runs in a clockwise direction from the hip to the femur, meaning that extension winds these ligaments around the neck of the femur and flexion does the opposite. Therefore, during extension of the hip, all the ligaments become taut as they wind around the femoral neck, clearly demonstrated when an individual with complete paraplegia stands with the hips in extension, *balancing* on the ligaments.

The primary flexors of the hip include psoas major and iliacus (Fig. 75-29). The iliacus muscle is a broad, powerful, fan-shaped muscle that lies beneath the extremely tough iliacus fascia where it arises from the iliac fossa. Its innervation is from the femoral nerve, which is en route to its destination, the anterior compartment of the thigh. In contrast, the psoas muscle arises from lumbar vertebrae within the abdominal cavity (from the posterior abdominal wall), has parallel fibers, and is designed more for excursion than power. The psoas muscle is innervated segmentally by branches from the lumbar plexus, particularly from L-2 and L-3. Weakness of the psoas muscle (e.g., psoas abscess, hematoma) localizes a peripheral nerve lesion to an extremely proximal site, within the lumbar plexus itself or at the level of the roots. During concentric contractions, the psoas is able to flex the thigh or the vertebral column, depending on which segment is fixed. It is important to recall some of the surrounding abdominal anatomy: The appendix overlies the right psoas major, an important clinical relationship to remember as the individual with appendicitis resists right hip extension, which stretches the psoas and causes pain. This is not to be confused with the patient who is tucked into a fetal position to prevent any movement or stretching of the peritoneum, an ominous sign of a perforated appendix.

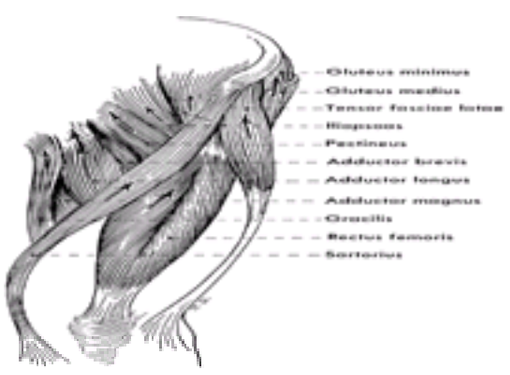

Figure 75-29. Flexors of the thigh. (Reprinted from Jenkins DB. *Hollinshead's functional anatomy of the limbs and back*, 6th ed. Philadelphia: Saunders, 1991:276, with permission.)

The rectus femoris is the one head of the quadriceps that arises from the pelvis and acts as a hip flexor. Two heads of origin attach to the anterior inferior iliac spine and an area just above the margin of the acetabulum. Rupture of the rectus femoris occurs in the young athlete after a forceful contraction of the quadriceps. The

sartorius is a long, straplike muscle that arises from the anterior superior iliac spine, forms the lateral boundary of the femoral triangle as it crosses the proximal thigh, and inserts on the medial tibia. Its action at the hip is flexion and lateral rotation. Rupture of the sartorius from its origin has been described in runners and presents as anterior hip/thigh pain.

The adductor compartment of the thigh consists of gracilis and three named adductors (e.g., brevis, longus, and magnus). All of the muscles originate from the pubis, are located medially in the proximal thigh, and insert into the femur. Sprains and ruptures occur with some frequency in dancers and athletes, particularly the adductor longus muscle.

The neurovascular bundle enters the anterior thigh beneath the inguinal ligament and enters an intermuscular space, the femoral triangle (Fig. 75-30). Pain is common in this region, and a knowledge of the contents of the femoral triangle is important in establishing an accurate diagnosis. The femoral artery can be felt pulsating at the midinguinal point, halfway between the anterior superior iliac spine and the pubic symphysis in the femoral triangle. A finger on the femoral pulse lies directly over the head of the femur, immediately lateral to the femoral vein and a finger's breadth medial to the femoral nerve. The relationship of the vessels and lymphatics within the femoral sheath are best remembered by the mnemonic *NAVEL* (nerve-artery-vein-empty space-lymphatic) (Fig. 75-31). A femoral hernia, more common in women than men, is a hernial sac that passes down the femoral canal and may form a swelling in the upper part of the thigh over the femoral triangle. The femoral artery initially lies in the femoral triangle and then enters an aponeurotic tunnel in the middle third of the thigh (adductor or subsartorial canal) opening through the adductor magnus (adductor hiatus) to enter the popliteal fossa. The upper 10 cm of a line joining the midinguinal point with a central point of the patella represents the artery in the femoral triangle, while the lower 15 cm of the same line defines the artery within the adductor canal. The canal also contains the femoral vein, the saphenous nerve, and the nerve to the vastus medialis. In the individual with femoral triangle pathology, many of these structures may be the source of pain.

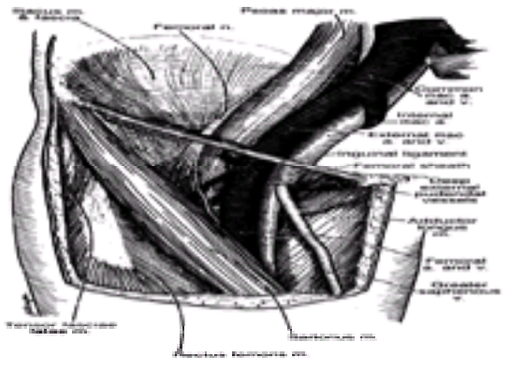

Figure 75-30. The boundaries and contents of the femoral triangle. (Reprinted from Woodburne RT, Burkel WE. *Essentials of human anatomy*, 9th ed. New York: Oxford University Press, 1994, with permission.)

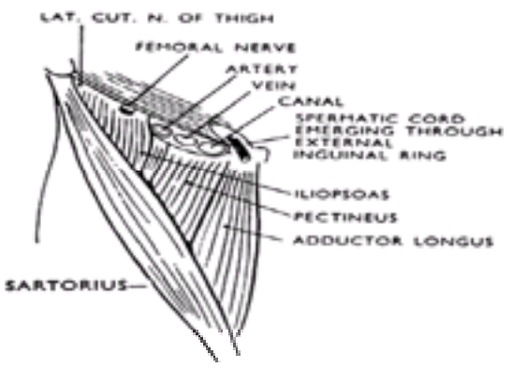

Figure 75-31. The femoral vessels are surrounded by the femoral sheath, a prolongation of extraperitoneal fascia, and lie just medial to the femoral nerve. On the medial side of the femoral sheath is the femoral canal, a potential space through which the lymphatics pass to the abdomen and into which the femoral vein can expand during increased venous return. (Reprinted from Shankar K, ed. Physiatric anatomic principles. *Phys Med Rehabil* 1996;10:605; as adapted from Ellis H. *Clinical anatomy: a revision and applied anatomy for clinical students*, 5th ed. Oxford, UK: Blackwell, 1971, with permission.)

Evaluation of the Patient Presenting with Hip or Gluteal Pain

Three characteristics of pain in the hip and gluteal region are particularly helpful in organizing the clinical evaluation: exacerbating factors, anatomic location, and temporal course of onset.

Organizational Approach. Most musculoskeletal pain is aggravated by local movement and relieved by rest. An individual who has mechanical hip disease most frequently complains of pain while weight bearing as the predominant symptom. Pain and a limp often accompany degenerative joint disease, inflammatory arthritides, a sprain or strain injury of muscle, a fracture, and ligament injury. Pain exacerbated by movement and mechanical loading suggests that there is an increase in tension or pressure in pain-sensitive load-bearing tissues. Pain that persists after activity suggests increasing pressure in a closed space, such as an increasing amount of purulent exudate within a joint capsule. Elucidating the source of pain requires a careful history and physical examination because there are many tissues that receive somatic pain afferents in the hip region (e.g., bone, capsule, synovial membrane, ligament, muscle, and tendon).

The referral of pain into the hip and gluteal regions may have an origin in a number of anatomic locations. Radicular low back pain with associated radiation to the hip and buttock regions occurs commonly. The pattern of pain referral varies depending on the level of nerve root impingement. Pain referral can be either in a sclerotomal or dermatomal pattern. Dermatomal patterns follow nerve root sensory innervation routes (e.g., L-3, L-4 root impingement refer to the anterior or medial hip, whereas L-5, S-1 root impingement refers to the posterior aspect of the hip). Sclerotomal patterns occur in the absence of nerve root impingement. For example, nociception from mesodermal tissues refers to other connective tissues derived from the same embryonic source. When a facet joint capsule or annulus fibrosus from L-5 or S-1 is stretched, pain may radiate into the sacroiliac area and buttocks.

Acute Atraumatic Pain

ACUTE ATRAUMATIC PAIN IN THE BUTTOCK. The major differential diagnoses to consider are presented here.

Claudication pain from internal iliac artery obstruction is usually seen in older adults. Symptoms occur as ischemia develops in the gluteal muscles and is progressively more severe as occlusion worsens. Pain with sustained contraction of the gluteal muscles assists with the diagnosis. Other physical signs of arteriosclerosis are often present in the lower limbs.

Referred pain from a herniated nucleus pulposus (L-5 and S-1) frequently presents as low back and buttock pain (see previous discussion). Provocative maneuvers that stretch the nerve root (straight-leg-raising test and Laséque's sign) reproduce the pain in the buttock and lower limb.

Ischial tuberosity bursitis is an inflammation of the bursa located between the gluteus maximus and underlying ischial tuberosity. Point tenderness over the ischial tuberosity is noted on physical examination.

Referred pain from pelvic disease sometimes is felt as pain in the buttock or posterior thigh. Pain such as that from prostate disease refers along the posterior

cutaneous nerve of the thigh since this somatic nerve arises from same segments as the pelvic parasympathetic nerves that innervate pelvic viscera.

ACUTE ATRAUMATIC PAIN IN THE LATERAL HIP. The major differential diagnoses to consider are presented here.

Trochanteric bursitis is usually a nonspecific, sterile inflammation of the subcutaneous trochanteric bursa (between the skin and the underlying muscle attachments to the greater trochanter) or the gluteus maximus bursa (between the gluteus maximus and the trochanter). Tenderness can be elicited by direct palpation over the greater trochanter. Resisted lateral rotation, abduction, and extension localize pain to the trochanter as well. Occasionally, bacterial infection, gout, or rheumatoid arthritis is the cause, and the appropriate laboratory tests should be conducted on aspirated fluid.

Iliotibial band overuse injury is often seen in dancers and is frequently confused with trochanteric bursitis. Pain is elicited by provocative maneuvers that stretch the iliotibial band such as passive adduction or lateral flexion of the trunk toward the uninvolved side.

Meralgia paresthetica is an entrapment neuropathy of the lateral cutaneous nerve of the thigh (L-2, L-3). The common entrapment points occur beneath the iliacus fascia and as the nerve pierces the inguinal ligament just medial to the anterior superior iliac spine. Pregnancy, obesity, tight-fitting clothing, and direct pressure from a body jacket are causes of meralgia paresthetica. Dysesthesia and often hypesthesia are present with light stroking of the skin within the distribution of the affected nerve.

ACUTE ATRAUMATIC PAIN IN THE ANTERIOR AND MEDIAL HIP REGIONS. Pain emanating from structures within the femoral triangle has already been described. There are also several muscles and associated bursae in the vicinity that may give rise to anterior or medial hip pain.

Lesser trochanter bursitis is an inflammation of the bursa found between the capsule of the hip joint and the overlying tendons of iliacus and psoas major. Provocative maneuvers stretch the overlying muscles (e.g., hip extension) or compress the bursa (adduction and flexion of the hip). Because there is occasionally a communication with the hip joint, intracapsular disease processes might affect the bursa as well. Aspiration of fluid and the appropriate diagnostic tests are necessary if pyogenic infection or rheumatic disease is suspected.

Psoas abscess or hematoma is occasionally present arising from disease in the spine or the retroperitoneal space. Pus arising from lumbar vertebrae tracks along the fascial sheath of the psoas major and presents as a painful swelling in the femoral triangle, sometimes being confused with a hernia.

In a *femoral hernia*, protrusion of peritoneum and intestine is forced through the femoral ring into the femoral canal, presenting as a painful mass. Careful auscultation often reveals bowel sounds, particularly early in the course prior to strangulation. Femoral hernias are more common in women than in men since the femoral ring is stretched in pregnancy and the normal septum of extraperitoneal tissue is no longer able to act as an effective partition in the abdominal wall.

Intraabdominal and intrapelvic disease processes may present as hip and thigh pain since muscles are sometimes directly irritated by visceral disease (e.g., inflammation from appendicitis irritating iliacus or psoas major). If there is significant muscle spasm, the resting posture of the lower limb is affected and stretching the affected muscle increases the pain.

Pyogenic and nonpyogenic arthritis are more common in children, although also seen in adults. A painful hip with fever is the usual presentation, although the diagnosis in an infant is much more challenging. Many organisms have been implicated. Historically, *Staphylococcus aureus* has been the most common organism in pyogenic infections. *Mycobacterium* is the most common nonpyogenic organism. Hematogenous spread, direct extension from osteomyelitis, and direct inoculation are all modes of entry into the joint. Permanent deformity and disability may result from acute septic arthritis if it is not detected early and treated aggressively. *Acute hematogenous osteomyelitis* sometimes precedes the development of a septic joint in children and is primarily a disease of growing bones. The metaphyseal region of the proximal femur is the most common site of infection and also leads to significant destruction of the hip joint if not diagnosed early and treated. The presentation is similar to septic arthritis in that the onset is acute and the infection progresses rapidly. Severe and constant pain in the hip is accompanied by unwillingness to bear weight on the affected limb.

Avascular necrosis occurs as a result of many disease processes that result in the interruption of blood supply to the femoral head. Fracture of the neck of the femur was discussed previously. There are many other diseases that mechanically interrupt the blood supply (e.g., slipped capital femoral epiphysis, hip dislocation), affect blood flow (e.g., sickle cell, arteriosclerosis), or result in secondary affects that impede blood flow (e.g., gout, radiation). Unilateral chronic hip pain is the typical presentation of avascular necrosis. Range of motion is normal until degenerative arthritis develops.

Rheumatoid arthritis is a chronic, systemic, inflammatory disease that chiefly affects the synovial membranes of multiple joints in the body (see Chapter 27). Pain and stiffness are characteristic complaints, particularly following a period of immobility. When the hip is involved, the synovium, surrounding bursae, and tendon sheaths are typically involved. The joint is painful in all areas and tender to palpation. Contractures develop and there is marked restriction of flexion and adduction.

Degenerative joint disease or osteoarthritis is a slow, progressive, articular disease that is characterized clinically by the gradual development of joint pain, stiffness, and limitation of motion. The most prominent pathologic change is the degeneration of articular cartilage. Osteoarthritis is classified as primary (or idiopathic) when it occurs without a known predisposing factor, or secondary when it follows an identifiable local or systemic underlying cause. The predominant symptom is progressive pain that is worse with mechanical loading of the joint and better with rest. There is tenderness to palpation in all areas of the hip. Typically, there is restricted range of motion in flexion, internal rotation, and abduction. The radiographic abnormalities of osteoarthritis include loss of joint space, appearance of subchondral bone cysts, formation of osteophytes, and eburnation (sclerotic bone formation). Osteoarthritis of the hip, also known as malum coxae senilis, usually occurs in older individuals. It may be unilateral or affect both sides; however, approximately 10% of unilateral cases progress to bilateral disease.

Crystal-induced arthropathies are debilitating illnesses seen worldwide and can be associated with a variety of other disease entities. Gout (inflammation caused by monosodium urate monohydrate crystals) is the most common crystal-induced arthritis. Pseudogout is an inflammatory disease caused by calcium pyrophosphate crystals. This disorder also causes acute and subacute monoarticular and pauciarticular arthritis. It has been associated with a variety of metabolic disorders, aging, and trauma. The hip is uncommonly involved in gout.

The *seronegative spondyloarthropathies*, previously called *rheumatoid variant diseases*, are a group of inflammatory joint disorders typically seronegative for rheumatoid factor and characterized by the involvement of sites of insertion of ligaments and capsules into bones (the enthesis). Clinical manifestations result in sacroiliitis, spondylitis (arthritis of the spine), and other abnormalities. This group includes ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, spondylitis associated with chronic inflammatory bowel disease, such as ulcerative colitis, and reactive arthritis following enteric bacterial infections (dysentery). All diseases in this group have a strong association with class I HLA-B27 antigen. The hip is involved in some of these diseases (e.g., ankylosing spondylitis) and bony ankylosis often results (see Chapter 27).

Pain in the Region of the Knee

To make a diagnosis in the patient who presents with pain in the region of the knee, one must have a detailed understanding of the anatomy of the knee and of the typical pain characteristics of each of the disease processes, as well as the physical examination skills to be able to elicit pain in the appropriate structures. In this section the anatomy of the knee is presented followed by a discussion of the more common causes of pain at the knee, with a subsequent discussion of the physical examination of the patient who presents with knee pain. Chapter 79 contains a detailed description of knee pain and its diagnosis and treatment.

Anatomy. The knee joint is commonly thought of as an articulation between the tibia and the femur, but the patellofemoral articulation should also be remembered.

Tibiofemoral Articulation. The articular surface of the distal femur can be broadly divided into a medial portion, a lateral portion, and a patellofemoral portion, which is somewhat more dorsal and in the midline (Fig. 75-32). In the sagittal plane the medial and lateral femoral condyles are cam shaped (i.e., they have a constantly changing radius of curvature). The posterior portion of the condyle has a shorter radius of curvature and the middle portion is most flat. The cam shape is important to the function of the knee in a number of ways. First, the cam shape determines the motion characteristics at the articular surfaces during flexion and extension. From a fully flexed position, as the knee extends, the joint surfaces of the tibia and the femur undergo a combination of rotation and gliding. The larger the radius of curvature of the cam, the greater the degree of gliding. Second, the cam shape does not allow there to be a single axis of motion in flexion and extension; the knee is therefore not a true hinge joint. The cam shape causes the actual instantaneous center of motion to change throughout the range of motion. Finally, the flattened portion of the cam of the femoral condyles is the portion that makes contact with the tibia during weight bearing in full extension. This flattened portion allows there to be a larger

surface area of contact and therefore reduced contact forces during weight bearing and ambulation.

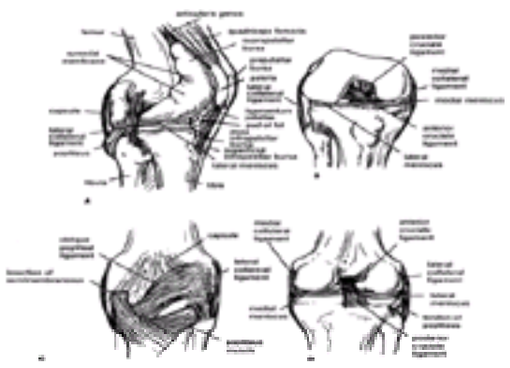

Figure 75-32. Right knee joint as seen from **(A)** lateral aspect, **(B)** anterior aspect, with joint flexed, and **(C,D)** posterior aspect. (Reprinted from Snell RS. *Clinical anatomy for medical students*, 5th ed. Boston: Little, Brown and Company, 1995:580, with permission.)

The articular surface of the proximal tibia consists of two elliptical areas that are shallow in contour and separated by a bony ridge called the intercondylar eminence. The two articular surfaces correspond to the medial and lateral femoral condyles. The depth and contour of the tibial articular surfaces do not correspond exactly to those of the femoral condyles. This is a disadvantage when one considers the optimization of surface area is important for minimizing focal abnormal loading of the articular cartilage. The menisci are paired semilunar or C-shaped cartilaginous structures that deepen the concavity of the tibial articular surface and thereby increase joint stability and the surface area of contact between the tibia and the femur. This minimizes abnormal loading of the articular cartilage. The intercondylar eminence forms the point of attachment of the *horns* of the menisci along with the tibial attachments of the anterior and posterior cruciate ligaments.

Ligaments. From the description of the architecture of the articular surfaces of the distal femur and proximal tibia, it is obvious that the tibiofemoral joint does not have a great degree of intrinsic stability. The stability of the joint is markedly augmented by strong ligamentous structures. Although there are many different ligaments, the four most important ligamentous structures that add to knee stability are the anterior and posterior cruciate ligaments and the medial and lateral collateral ligaments. The anterior cruciate ligament extends from the medial part of the posterior aspect of the lateral femoral condyle and travels distally and anteriorly toward the anterior aspect of the intercondylar eminence of the tibia. It functions to restrain anterior translation of the tibia on the femur as well as anterolateral rotation of the tibia on the femur. The posterior cruciate ligament travels from its origin on the anterior and lateral aspect of the medial femoral condyle to the posterior aspect of the intercondylar eminence of the tibia. Its function is to restrain posterior translation of the tibia on the femur and to limit hyperextension of the knee. The medial collateral ligament is a bandlike structure, which originates at the medial aspect of the medial femoral condyle above the joint line and attaches extensively on the medial aspect of the medial tibial condyle. The deep portion of this ligament has attachments to the medial meniscus and augments the stability of this structure. The major function of this ligament is to stabilize the knee to valgus stresses. The lateral collateral ligament is a cordlike structure that attaches to the prominence of the lateral femoral condyle above the joint line and attaches distally to the head of the fibula. This ligament stabilizes the knee to varus stresses.

Bursae. The knee has a number of bursal structures that may be a source of nociception at the knee. The function of the bursae at the knee as with bursae anywhere in the body is to reduce frictional forces between structures. Some of the bursae at the knee are subcutaneous and reduce friction between the external environment and underlying bony structures. Other bursae lie at deeper anatomic levels (e.g., between tendon and underlying bone and reduce frictional forces between these structures). From an anatomic perspective these bursae can also be divided by the anatomic regions of the knee where they lie: anterior, posterior, medial, and lateral. The anterior bursa includes the suprapatellar, the prepatellar, and the deep and superficial infrapatellar. The suprapatellar bursa lies superior to the patella on the anterior aspect and is continuous with the joint space. Therefore there is swelling in this bursa from any condition that causes a joint effusion. The remaining anterior bursae do not communicate with the knee joint. These include the prepatellar bursae, which is a subcutaneous bursa immediately superficial to the patella, the superficial infrapatellar, which is subcutaneous and immediately anterior to the patellar tendon, and the deep infrapatellar, which lies between the patellar tendon and the underlying portion of the proximal tibia. The posterior bursae include the semimembranosus bursa and the subpopliteal bursa. The semimembranous bursa is on the medial side of the popliteal fossa. It can exist either as a free bursa without a connection with the joint or as a projection of the synovial membrane of the knee joint. Its function is to reduce shear forces between the overlying semimembranosus tendon and the underlying gastrocnemius and posterior aspect of the tibia. Swelling in this structure results in a Baker's cyst, which can be seen as a swelling on the medial aspect of the popliteal fossa. The subpopliteal bursa, which is on the lateral side of the popliteal fossa, is a continuation of the synovium of the joint and is therefore in continuity with the joint. It lies immediately beneath the tendon of the popliteus, separating it from the underlying posterolateral corner of the lateral femoral condyle. The most important medial bursal structure at the knee is the pes anserine bursa. It lies at the proximal medial aspect of the tibia between the overlying pes anserine tendon, which is a common attachment of sartorius, gracilis, and semitendinosus, and the underlying flare of the medial tibial condyle, approximately 3 to 5 cm distal to the joint line. Two small bursae have been described on the lateral side of the knee—one that is located between the lateral collateral ligament and the lateral femoral condyle and one that is located between the lateral collateral ligament and the tendon of biceps femoris. These bursae are much less commonly involved in pathologic processes and therefore are much less commonly a source of nociception.

Patellofemoral Joint. The patellofemoral joint is an articulation between the distal femur and the undersurface of the patella (Fig. 75-33). The patella is a heart-shaped osseous sesamoid bone: It is formed within the tendon of the quadriceps muscle. The articular surface of the patella is posterior. It is typically divided into medial and lateral facets that articulate with the trochlea of the femur. The trochlea of the femur is the distal anterior portion of the femur. It is V shaped in the transverse plane corresponding to the complementary shape of the undersurface of the patella. The V-shaped structure assists the patella in *tracking* optimally on the distal femur during flexion and extension movements of the knee. The primary function of the patellofemoral joint is to act as a pulley and redirect the pull of the quadriceps muscle. As the quadriceps tendon passes over the patella and continues distally to its attachment on the tibial tuberosity, the patella redirects its pull to increase the effective torque of the muscle, especially in the last 10 to 15 degrees of extension.

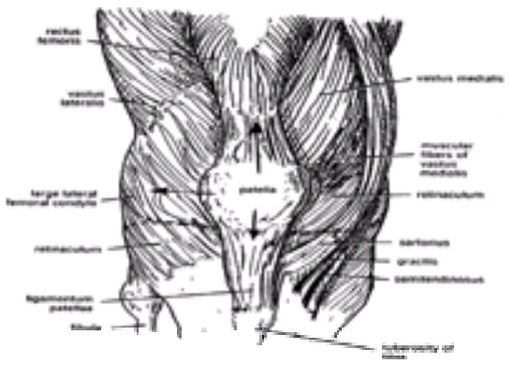

Figure 75-33. The quadriceps femoris mechanism. The lateral and upward pull of the powerful rectus femoris and the vastus lateralis muscles on the patella is counteracted by the lowest horizontal muscular fibers of the vastus medialis and the large lateral condyle of the femur, which projects forward. (Reprinted from Snell RS. *Clinical anatomy for medical students*, 5th ed. Boston: Little, Brown and Company, 1995:528, with permission.)

Muscles Acting at the Knee. The muscles that act across the knee can be broadly defined into extensor and flexor groups. The extensor group is the large quadriceps muscle, which includes the vastus lateralis, vastus medialis, vastus intermedius, and the rectus femoris (Fig. 75-34 and Fig. 75-35). These muscles have their origin on the femur, with the exception of the rectus femoris, which also crosses the anterior hip joint to attach near the anterior inferior iliac spine on the anterior aspect of the pelvis. The muscles come together to form a common tendon, the quadriceps tendon, that inserts into the proximal aspect of the patella. The tendinous continuation of these muscles is the patellar tendon, which originates on the inferior pole of the patella and attaches to a roughened area on the anterior aspect of the proximal tibia. The function of the quadriceps is to actively extend the knee or to control the rate of knee flexion under load. Concentric contraction occurs during

rising from a seated position, climbing stairs, or jumping upward. Eccentric contractions are those that are energy absorbing. Examples of eccentric contractions are climbing down stairs, sitting down from a standing position, or decelerating after a jump. In each of these cases the function of the quadriceps is to control or decelerate the mass of the body. The hamstring muscles, semimembranosus, semitendinosus, and biceps femoris are the most important posterior muscles of the thigh. They all have their origin on the ischial tuberosity at the posterior aspect of the pelvis, with the exception of biceps femoris, which has a second head that also has an origin on the posterior femur. Their insertions include the head of the fibula for biceps femoris, posteromedial aspect of the medial tibial condyle for semimembranosus, and the pes anserine tendon, which inserts on the medial tibial flare, for semitendinosus. The function of the hamstrings, as with the quadriceps, can be divided into concentric and eccentric functions. The concentric function results in active flexion of the knee and the eccentric function is to decelerate and control the forward progression of the tibia. A good example of the eccentric function is in the second half of the swing phase of gait when the hamstring decelerates the forward swinging tibia and foot prior to the next heel contact. The only other muscles that act across the knee are tensor fascia lata, popliteus, and gastrocnemius. Tensor fascia lata, which has its origin on the anterolateral aspect of the iliac crest, inserts into the iliotibial band. The iliotibial band passes on the lateral aspect of the lateral femoral condyle and the lateral knee joint line to insert onto a small bony prominence on the anterolateral aspect of the lateral tibial condyle. The insertion of this tendon and the location of the tendon near the axis of the knee joint give this muscle its relatively complicated functional characteristics. With the knee in full extension the iliotibial band passes anterior to the knee joint, allowing it to function as an accessory knee extensor. However, with the knee flexed greater than 25 degrees, the tendon of the iliotibial band passes posterior to the knee joint and therefore it functions as an accessory knee flexor. The popliteus muscle is a small triangular muscle that has its origin on the prominence of the lateral femoral condyle, and it passes downward and posteriorly to attach into the posterior proximal aspect of the tibia. Its function therefore is to externally rotate the femur on the tibia. The gastrocnemius muscle, which is primarily an ankle plantarflexor, also has weak actions at the knee. It must be remembered that the gastrocnemius muscle has its origin on the posterior aspect of the medial and lateral femoral condyles. The muscle belly travels distally toward the ankle in the posterior aspect of the knee. Because this muscle crosses the knee joint and it travels posterior to the knee axis, it functions as a week knee flexor.

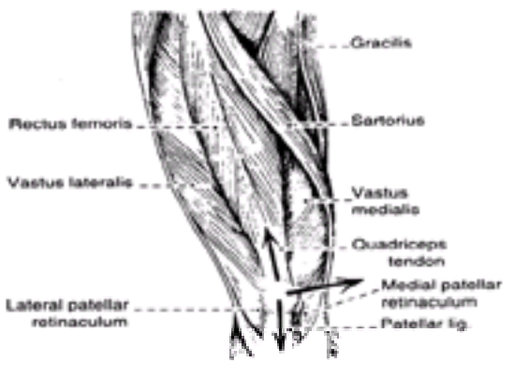

Figure 75-34. The quadriceps: The rectus femoris conceals the vastus intermedius. Note the insertion of some fleshy fibers of the vastus medialis into the medial side of the patella, which helps balance the pull on the patella by the quadriceps tendon and the patellar ligament. Arrows indicate directions of pull. (Reprinted from Rosse C, Gaddum-Rosse P, eds. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:356, with permission.)

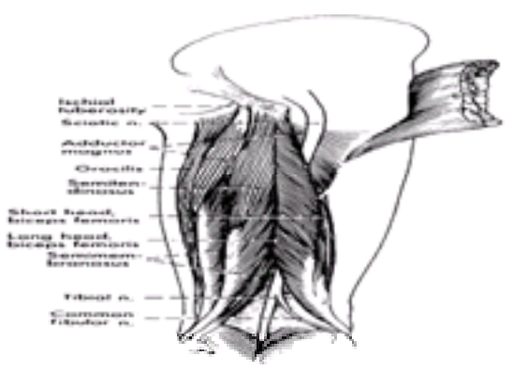

Figure 75-35. The posterior (hamstring) muscles of the right thigh. Gracilis, also shown here, belongs to the adductor group. (Reprinted from Rosse C, Gaddum-Rosse P, eds. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:362, with permission.)

Innervation. The innervation to the knee joint is derived from the major nerves that travel in proximity to the joint. There are branches from the femoral and saphenous nerves on the anterior and medial aspect and from the tibial nerve in the posterior aspect. Anterior pain at the knee joint may originate in the hip joint, which shares a common intervention with the anterior aspect of the knee, or by processes affecting the femoral nerve itself. Posterior pain in the knee in contrast may have its origin in processes that affect the tibial nerve or the first sacral nerve root.

Blood Supply. Blood supply to the knee is primarily through a vascular anastomosis involving the medial and lateral branches of the superior and inferior geniculate arteries, which are branches of the popliteal artery. This anastomosis is reinforced by some branches from the femoral and tibial arteries.

Evaluation of the Patient Presenting with Knee Pain

History and Physical Examination. As with most of musculoskeletal medicine, the diagnosis is made on the basis of establishing a history and performing a physical examination. The key elements of the history include pain location, severity, onset, aggravating factors, relieving factors, and associated factors. In the knee the associated factors that must be considered include weakness, sensory deficit, locking, and instability. An understanding of these elements usually allows the clinician to elucidate the underlying process that is leading to pain.

The physical examination of the patient presenting with knee pain should include an examination of both the intact and affected extremity. Because of the considerable variability in what is considered normal motion, strength, and ligamentous stability, the examination of the intact extremity allows one to determine what is normal for that individual. Depending on the nature of the presenting complaint and what is found on the examination of the knee, a more comprehensive examination of other joints as well as a neurovascular examination may be necessary to establish the diagnosis. Most of the local examination of the knee uses observation, palpation, and the performance of specific examination maneuvers that test the integrity of specific musculoskeletal structures and whether or not mechanical stress elicits pain.

Organizational Approach. There are a number of organizational schemes that are useful in assisting the clinician in arriving at a diagnosis. A useful organizational structure that can be used is to broadly define the pain in terms of its acuity versus chronicity, whether the origin is traumatic or atraumatic, and to determine the anatomic location of the pain. Acute pain has an origin of less than 24 hours in duration, while subacute or chronic pain has a longer period of onset and duration. A traumatic origin is that which has a sudden onset with clearly defined trauma, while nontraumatic pain may have its origin in mechanical loading and stress but the onset is not associated with a singular sudden traumatic event. The anatomic location of knee pain can be categorized as generalized, anterior, posterior, medial, or lateral.

Acute Atraumatic Generalized Pain. The patient presents with relatively sudden onset of pain that is experienced diffusely in the knee. When asked, the patient is unable to point with a single finger to any particularly painful region of the knee. The major differential diagnoses to consider are presented here.

CRYSTAL-INDUCED ARTHROPATHY (GOUT AND PSEUDOGOUT). There are a number of different crystals that may produce joint symptoms. The two most common are calcium pyrophosphate dihydrate, which produces symptoms of pseudogout, and monosodium urate monohydrate, which produces symptoms of gout (see Chapter

27).

Pseudogout most commonly occurs in a patient middle aged or older. Symptoms typically begin with recurrent acute bouts of joint pain and swelling. There may be secondary degenerative changes leading to chronic, subacute pain. The onset of the acute attack may be associated with surgery or severe acute medical illness.

Gout is the acute attack of joint swelling and pain as the result of deposition of disodium urate crystals within the joint. Classically, these symptoms begin at night and most commonly occur in the first metatarsophalangeal joint, but any joint, in particular other lower extremity joints, may be involved. As with pseudogout, the attack may be exacerbated by external environmental stressors.

SEPTIC JOINT. The knee is the most common joint involved in sepsis. The acuity of the onset of symptoms in a septic joint is dependent on the organism involved. In the majority of cases gram-positive cocci are the etiologic agent. Mycobacterium or fungi have a more subacute onset. Septic joints are seen at either extreme of age—childhood or senescence—and are more frequently seen in patients with a history of intravenous drug abuse, a history of intraarticular injection or aspiration, the presence of a joint arthroplasty, or trauma to the overlying soft tissue that allows bacterial invasion.

PALINDROMIC RHEUMATISM. The etiology of this syndrome is not known; some patients evolve into clinical diagnoses of rheumatoid arthritis or systemic lupus erythematosus. Its typical age of onset is in the fourth to sixth decade.

The presentation in each of these conditions is that of the acute onset of severe pain and effusion, often with warmth or redness of the overlying skin. There is little to differentiate the different disorders on physical examination. The patient with a septic joint may be febrile; fever is not associated with the other conditions. The knee is typically held in a flexed position if the patient is able to weight bear through the affected limb. There is an antalgic gait pattern with a shortened stance phase on the affected side. On palpation there is diffuse tenderness, and pain is exacerbated if the joint is taken through a range of motion. The range of motion is restricted in both flexion and extension.

The typical investigative procedure is to obtain radiographs and a complete blood count with differential and perform joint aspiration. The aspirate should be analyzed for a white count, Gram's stain and culture, and the presence of crystals.

Acute Traumatic Generalized Pain. The patient usually presents with the history of significant injury with immediate onset of pain. The pain is diffuse throughout the region of the knee and is difficult to localize to any single anatomic area.

The major differential diagnoses to consider are presented here.

FRACTURE WITH HEMARTHROSIS. Significant trauma to the lower extremity from a fall or direct impact to the extremity can result in bony injury to the distal femur, proximal tibia, or the patella. Fractures that do not involve the joint can usually be somewhat localized by the patient. However, fractures that extend into the joint space can result in a tense effusion secondary to bleeding into the joint space. As the pressure from the effusion increases, there is increasing diffuse generalized pain in the knee.

LIGAMENT INJURY WITH HEMARTHROSIS. The most common ligament injury to result in an acute hemarthrosis is an anterior cruciate ligament injury. This is an intracapsular structure within the knee that is supplied by a vessel within its body. A complete ligament injury results in disruption of the vessel; since it is an intraarticular structure, blood collects within the joint space resulting in a tense effusion. The most common mechanisms of injury are an acute hyperextension injury or a flexion rotation injury. The anterior cruciate ligament may be injured in sport activities, industrial accidents, and, to a lesser extent, motor vehicle accidents. Commonly, there is an audible *pop* at the time of injury as the ligament is disrupted.

The patient tends to keep the knee flexed approximately 30 degrees. Fracture makes it unlikely that the patient will be able to bear weight. Pain limits any effort at examination. Radiography reveals a fracture, is normal, or shows evidence only of an effusion with an anterior cruciate ligament injury. The joint may be aspirated to decrease pain. If this is done and the radiographs are normal, further physical examination maneuvers, in particular Lachman's test, which creates an anterior translation of the tibia on the femur, may reveal abnormal laxity secondary to the anterior cruciate ligament injury.

Subacute or Chronic, Atraumatic, Generalized Pain. These conditions are processes that result in a diffuse synovitis and a subsequent joint effusion without involvement of specific localized anatomic structures. The major differential diagnoses to consider are degenerative arthritis, rheumatoid arthritis, seronegative spondyloarthropathies, chronic crystal-induced arthropathies, and other less common collagen vascular disorders (see Chapter 27).

DEGENERATIVE ARTHRITIS OR OSTEOARTHRITIS. This is probably the most common cause of joint pain in the older patient population. Degenerative arthritis can be either primary or secondary. In patients with primary degenerative arthritis there is usually multiple joint involvement including the spine, hips, knees, and proximal interphalangeal and distal interphalangeal joints of the hands. It is usually symmetric. Secondary degenerative arthritis is either monoarticular or pauciarticular and involves joints with a preceding history of injury that predisposes the joints to secondary changes. The knee and hip are commonly involved in secondary degenerative arthritis. The patient typically presents with a history of progressive onset of pain over weeks, months, and years. The pain is aggravated by activity and relieved by rest. There may be a history of stiffness of the joint, particularly after a period of rest, which is clinically referred to as *gelling.* On physical examination the joint may have a mild flexion contracture. Typically, there is a mild to moderate effusion with pain at the end of range of motion. There may be palpable osteophytes at the joint margin and pseudolaxity secondary to loss of articular cartilage height.

RHEUMATOID ARTHRITIS. Rheumatoid arthritis is an autoimmune disease that affects women more than men, with an onset typically in young adulthood or middle age. It is a symmetric polyarticular disease with involvement of the small joints of the hands and feet, which also commonly symmetrically involves the wrists, ankles, knees, and elbows. Associated symptoms include morning stiffness and general constitutional symptoms of fatigue. On examination the joints are swollen and warm to palpation, and the small joints may be erythematous. Ultimately, with chronic rheumatoid arthritis, typical deformities of the hands, wrists, and feet develop.

SERONEGATIVE SPONDYLOARTHROPATHIES. Included in this group are ankylosing spondylitis, enteropathic arthritis, psoriatic arthritis, and Reiter's syndrome.

Enteropathic arthritis and ankylosing spondylitis are uncommon causes of knee pain. They predominantly involve the spine, the sacroiliac joints, and the hips. They can be a cause of knee pain, but typically there is obvious involvement of other structures at the time of presentation.

Reiter's syndrome is a subacute disorder associated with gut infections with organisms such as *Shigella*, *Salmonella*, or *Campylobacter*. It is also associated with chlamydial infections of the urinary tract. This syndrome results in arthritis, conjunctivitis, and urethritis. The joint involvement tends to be asymmetric, involving lower extremity joints with evidence for a synovitis with pain, effusion, and warmth.

Psoriatic arthritis has a number of variant forms that involve varying distributions of the spine, sacroiliac joints, and peripheral joints. One variant with peripheral joint involvement includes a symmetric process involving the distal interphalangeal joints of the hand. There is also a variant that causes a pauciarticular arthritis that may involve the knees. From a diagnostic perspective, essentially all patients have evidence for cutaneous involvement with psoriasis.

Acute Traumatic Regional Pain Syndromes

ACUTE TRAUMATIC ANTERIOR KNEE PAIN. The most common diagnoses that result in acute anterior knee pain include quadriceps tendon rupture, patellar tendon rupture, fracture of the patella, and dislocation or subluxation of the patella.

Quadriceps or patellar tendon rupture can occur at any age, although it is more common in younger individuals. Typically, the mechanism of injury is that of forced flexion of the knee in conjunction with a powerful contraction of the quadriceps mechanism. This might occur after a stumble or during sports activities. Associated problems that predispose to rupture include diabetes, corticosteroid use, or local injections of corticosteroids. Clinically, the patient presents with severe anterior knee pain with an inability to extend the knee. There is local swelling and tenderness in the area of rupture and a palpable defect. In the case of quadriceps tendon rupture, these physical examination features are present at the proximal edge of the patella, while in the case of the patellar tendon rupture they are seen between the inferior pole of the patella and the tibial tuberosity.

Fracture of the patella can occur secondary to direct trauma such as in the case of a fall on the flexed knee. It can also occur in a similar mechanism to quadriceps tendon rupture or patellar tendon rupture.

Dislocation or subluxation of the patella can occur when the patella subluxes or dislocates from its anterior position at the distal femur. Typically, the patella dislocates laterally. The mechanism of injury is one of forcible use of the quadriceps while the foot is planted on the ground, the knee is flexed, and the femur internally rotates on the tibia. In this position the patella is free from the trochlea of the distal femur and the pull of the quadriceps has a marked laterally directed force vector. The diagnosis is made by observation of the patella on the lateral aspect of the knee in the case of dislocation, although commonly the patella returns to its original position as the knee is extended. In this case anterior knee pain is present with an effusion and pain in the peripatellar region with a positive apprehension sign. The apprehension sign is positive when the clinician attempts to slide the patella laterally, reproducing the position of subluxation or dislocation, which creates distress in the patient.

ACUTE TRAUMATIC MEDIAL KNEE PAIN. The two most important considerations here are a medial collateral ligament injury or a medial meniscus injury.

Medial collateral ligament injury is the most common ligament injury at the knee. It occurs most commonly when there is a lateral impact to the knee region with the foot planted on the ground. The symptoms and presentation vary somewhat with the severity of the tear, but generally speaking there is an acute onset of medial knee pain; over the course of hours to days an effusion may develop, in conjunction with localized swelling, ecchymosis, or both on the medial aspect of the knee. Ligament assessment reveals varying degrees of laxity, while a valgus stress test is applied to the knee at 30 degrees of knee flexion.

Medial meniscus injuries occur in two circumstances: first, during sporting or vocational activities where there is a significant torsional stress to the knee with the foot planted on the ground, and second, during functional tasks that cause the knee to be hyperflexed as occurs during some lifting activities from the floor. The usual presentation is localized medial knee pain with the development of a knee effusion over 24 to 48 hours. Symptoms commonly subside spontaneously, although they may recur with locking of the knee and associated pain. Occasionally, the patient presents with the knee locked at some degree of flexion and with an inability to bend or straighten it from this position. In this context the meniscus is trapped between the articular surfaces of the tibia and femur with associated pain. Physical examination reveals a knee with a trace to moderate effusion and marked local tenderness on the medial joint line, with or without a positive McMurray's test.

ACUTE TRAUMATIC LATERAL AND POSTERIOR KNEE PAIN. Acute pain in these regions is much less common than anterior or medial. Acute lateral collateral ligament injuries can occur but are much less common than medial. The mechanism of lateral collateral ligament injury is an impact to the medial aspect of the knee with the foot planted. Similarly, the incidence of lateral meniscal lesions is also much less common than medial.

Pain in the Region of the Foot and Ankle

Anatomy. The foot and ankle include many osseous, articular, ligamentous, muscular, and soft tissue structures that allow for the complex functional tasks involved in gait and other bipedal activities. These are discussed in detail in Chapter 80. There are a number of key surface anatomic landmarks that can be identified on observation. The malleoli are prominent bony structures on the medial and lateral aspects of the ankle. The lateral malleolus is the distal portion of the fibula, while the medial malleolus is the distal and medial portion of the tibia. The tendons of the long flexors of the toes and the tibialis posterior tendon along with the posterior tibial artery and the tibial nerve pass posterior to the medial malleolus, while the tendons of the peroneus longus and brevis pass posterior to the lateral malleolus. The tendon at the posterior aspect of the ankle is the combined tendon of the gastrocnemius and soleus. There are a number of tendons that pass anterior to the ankle joint, including the tibialis anterior and the extensors of the hallux and the toes. The continuation of the peroneal nerve also passes anterior to the ankle along with the dorsalis pedis artery, which lies immediately lateral to the tibialis anterior tendon. From an architectural perspective the foot is made up of three arches: the medial and lateral longitudinal arches and the transverse arch. The arches of the foot are typically maintained through the underlying architecture of the osseus and articular structures that are supported passively through ligamentous structures and dynamically through a musculotendinous support system (Fig. 75-36). The medial longitudinal arch is obvious on the medial side of the foot. Its curvature is typically diminished during weight bearing. The transverse arch passes in a medial-lateral direction at the level of the metatarsal heads. The soft tissues of the plantar surface of the foot have a specialized architecture designed to dissipate the forces associated with weight bearing and propulsion. The superficial fascia is attached to the underlying plantar aponeurosis by connective elements or septa. There is adipose tissue that is loculated in these spaces and helps to function as *hydraulic* shock absorbers.

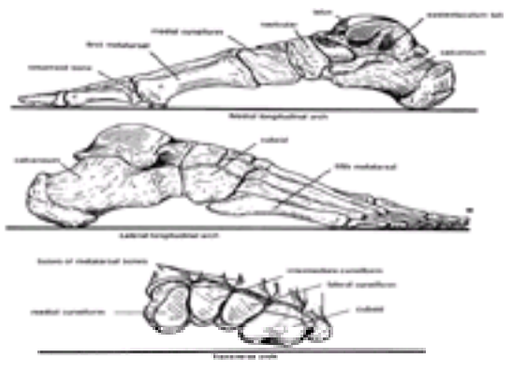

Figure 75-36. Bones forming medial longitudinal, lateral longitudinal, and transverse arches of the right foot. (Reprinted from Snell RS. *Clinical anatomy for medical students*, 5th ed. Boston: Little, Brown and Company, 1995:589, with permission.)

Hindfoot. The hindfoot osseus structures include the distal portions of the tibia and fibula, the talus, and the calcaneus. The two major articular structures in the hindfoot are the ankle or talocrural joint and the subtalar joint. The ankle joint is the articulation between the distal portions of the tibia fibula and the talus. From a structural perspective, this joint is commonly referred to as a mortise and tenon joint. The *mortise* component is made up of the medial malleolus, which is a non–weight-bearing structure; the tibial platform, which is the weight-bearing structure of the distal tibia; and the non–weight-bearing surface of the lateral malleolus. The *tenon* is made up of the dome of the talus. This joint tends to be a stable joint based on the architecture of the interlocking mortise and tenon. Because the dome of the talus is wider anteriorly than posteriorly, the osseus structures fit more tightly in a dorsiflexed position and the joint is therefore even more stable in a dorsiflexed than in a plantarflexed position. The major ligamentous support for the talocrural joint is through the medial and lateral ligament complexes. The medial ligament is the deltoid ligament, which attaches from the tip of the medial malleolus fanning out distally to attach from the medial aspect of the navicular, talus, and calcaneus. The lateral ligament complex comprises three distinct structures: the anterior talofibular ligament, which spans from the tip of the lateral malleolus to the talus, the calcaneofibular ligament, which travels from the lateral aspect of the calcaneus to the tip of the lateral malleolus, and the posterior talofibular ligament, which travels from the talus anteriorly toward the tip of the lateral malleolus. The motions that occur at the ankle joint are predominantly the sagittal plane motions of dorsiflexion and plantarflexion. The muscle groups that produce plantarflexion are the powerful gastrocnemius and soleus, and to a lesser extent the long toe flexors, tibialis posterior, and peroneus longus and brevis. The muscle groups that produce dorsiflexion are tibialis anterior and to a lesser extent the extensors of the toes.

The subtalar joint is an articulation between the undersurface of the talus and the dorsal aspect of the calcaneus. The articular surface is divided into three components or facets. Together these facets allow the calcaneus to glide in a medial-lateral direction underneath the talus. This motion is called hindfoot inversion (medial) and hindfoot eversion (lateral). The muscle groups that cause these motions are tibialis anterior and tibialis posterior, and peroneus longus and brevis, respectively.

The hindfoot performs a number of important functions during ambulation. During walking the foot typically makes contact on the posterolateral corner of the heel. The foot is dorsiflexed and in inversion. The impact of heel contact is absorbed in part by the specialized anatomic structures of the heel pad and by eccentric contraction of the tibialis anterior, which controls the rate of ankle plantarflexion at heel contact, and by eccentric contraction of the tibialis posterior, which controls pronation. In midstance phase the ankle plantarflexors contract eccentrically, controlling the forward rotation of the stance phase leg into dorsiflexion. Finally, in late stance phase a powerful contraction of the ankle plantarflexors generates a push-off function, which, along with the hip flexors, accelerates the leg forward into swing phase.

Midfoot. The midfoot osseus structures include the navicular medial cuneiform, intermediate cuneiform, and the lateral cuneiform, along with the cuboid. These

osseus structures articulate between themselves but also articulate with the talus and calcaneus proximally and the metatarsals distally. These complex articulations are commonly divided into two functional joints. The functional joints include the calcaneocuboid and the tarsometatarsal joints. These articulations allow the forefoot to be abducted and adducted on the hind foot and also allow rotations of the midfoot along the longitudinal axis of the foot. During the stance phase of walking, the alignment of these joint axes determines the rigidity of the midfoot. During early to midstance phase as the foot is pronated, the axes of these joints are aligned and therefore a greater level of mobility is allowed. The foot therefore is more supple during this portion of stance phase, which allows it to absorb medial lateral forces and allows the foot to accommodate to irregular terrain. In mid- to late stance phase the foot tends to supinate, which causes the axes of the calcaneocuboid and tarsometatarsal joints to become oblique to one another and results in a more rigid midfoot. This is of functional importance because the key functional necessity of the foot and ankle complex is power generation by the gastrocnemius soleus and transfer of energy across the foot to the ground. A more rigid midfoot at this point in the gait cycle allows for more efficient force transmission.

Forefoot. The forefoot osseus structures include the metatarsals and the phalanges. The joints of this region of the foot are the metatarsophalangeal joints and the interphalangeal joints. The motions of the metatarsal joints are predominantly into flexion and extension. The prime movers of these joints into flexion are the short toe flexors, which originate in the foot, and the long toe flexors, whose muscle bellies arise within the leg and pass posterior to the medial malleolus into the plantar aspect of the foot and subsequently attach to the toes. The prime movers of the joints into extension are similarly the long and short extensors. The short extensor—extensor digitorum brevis—arises from the dorsal aspect of the tarsals and attaches to the extensor expansion of toes 2 through 4 and the base of the proximal phalanx of the first toe. The long extensors—extensor hallucis longus and digitorum longus—arise on the leg and travel anterior to the ankle joint onto the dorsum of the foot and to the toes. The tendons are restrained as they pass near the ankle by retinacula, which function to prevent *bowstringing* of the tendons.

Blood Supply and Innervation of the Foot. The blood supply to the foot is based on two major arteries. The dorsalis pedis is typically the continuation of the anterior tibial artery in the leg, and the posterior tibial artery is the continuation of a vessel by the same name. The dorsalis pedis artery crosses the anterior aspect of the ankle just lateral to the tibialis anterior tendon and continues into the foot over the medial tarsal bones, where it subsequently lies in the space between the first and second metatarsal. A major branch travels laterally at the level of the proximal metatarsals from which each of the common digital arteries branches off and travels toward its respective web spaces. The posterior tibial artery crosses the ankle with a number of tendons on the posterior aspect of the medial malleolus. The artery divides into a medial and lateral branch. The medial branch travels distally toward the great toe, while the lateral branch travels distally and laterally, forming a plantar arch that divides into the digital arteries. Typically, there are connections between the plantar and dorsal vascular arches.

The innervation of the foot comes from four major nerves. The saphenous nerve, which is a continuation of the femoral nerve, travels down the medial aspect of the leg and supplies sensation to only the medial malleolar region of the ankle. The sural nerve is also a pure sensory nerve that travels down the midline of the leg in a subcutaneous position posterior to the lateral malleolus and supplies sensation to the lateral aspect of the foot and the fifth toe. The deep peroneal nerve travels in the anterior compartment of the leg, traveling across the anterior aspect of the ankle joint to provide sensation to the majority of the dorsum of the foot. The superficial peroneal nerves and the tibial nerve are mixed nerves. The superficial peroneal nerve travels in the lateral compartment of the leg and crosses the anterior aspect of the ankle, where it sends a motor branch to extensor digitorum brevis and subsequently continues distally to the first web space, where it functions as a sensory nerve. The tibial nerve courses posterior to the medial malleolus at the ankle along with the flexor tendons and the posttibial artery. All of these structures pass under a flexor retinaculum, which prevents subluxation. Immediately on exiting under the flexor retinaculum, the nerve divides into a number of branches. The medial and plantar nerves travel distally in the foot, supplying motor function to the intrinsic muscles of the foot and sensation to the medial and lateral aspects of the sole of the foot.

Evaluation of the Patient Presenting with Foot and Ankle Pain

History and Physical Examination. As previously mentioned, the key element to successful musculoskeletal diagnosis is through the history and performing a physical examination. The key element of the history is to define the character of the pain, including location, severity, onset, aggravating factors, relieving factors, and associated factors.

The physical examination of the patient presenting with foot or ankle pain, as with all articular structures, generally includes an examination of both the intact and affected extremity. Depending on the nature of the presenting complaint and what is found on the examination of the knee, a more comprehensive examination of other joints as well as a neurovascular examination may be necessary to establish the diagnosis. Most of the local examination of the foot and ankle involves observation, palpation, and the performance of specific examination maneuvers that test the integrity of specific musculoskeletal structures and whether or not mechanical stress elicits pain. These painful conditions are discussed in detail in Chapter 80.

Acute Atraumatic Hindfoot Pain. The differential diagnosis is similar to this classification at the knee. Acute atraumatic pain in the hindfoot is typically the result of bone or joint inflammation from infection, rheumatoid arthritis, seronegative spondyloarthropathies, or crystal-induced arthritis (see Chapter 27). The ankle and subtalar joints are less commonly involved in rheumatoid arthritis, and when involved, the involvement is usually symmetric in both lower extremities, and it usually occurs in the later stages of the disease. Similarly, pseudogout is relatively uncommon in the hindfoot articulations, but it has been described in these areas. Gout is relatively common in the ankle and has been reported to occur in up to 50% of cases. In all of these conditions, the presentation is one of pain, limitation of motion, limited weight bearing, warmth, erythema, and joint effusion.

Acute Atraumatic Midfoot Pain. The differential diagnoses to be considered are similar to hindfoot pain. Involvement of the intertarsal joints in these processes is much less common.

Acute Atraumatic Forefoot Pain. Rheumatoid arthritis commonly presents with a symmetric distal polyarthritis involving the small joints of the hands and feet. It is relatively common, therefore, to experience inflammatory involvement of the metatarsophalangeal and proximal interphalangeal joints of the toes. The presence of multiple joint involvement, especially involving the joints of the hands and feet, in the presence of general systemic features in conjunction with morning stiffness, should assist the clinician in arriving at this diagnosis. Gout is the most common crystal-induced arthritis to result in acute atraumatic pain and joint dysfunction in the foot. The most common joint involved is the first metatarsophalangeal joint. The presentation, as previously noted, is classically an onset at night with joint effusion, pain, redness, and limitation of range of motion.

Subacute Chronic Hindfoot Pain. Chondral or osteochondral fracture of the talar dome may occur with an inversion injury to the ankle because of impact with the medial aspect of the lateral malleolus. The typical history is one where there has been an inversion strain to the ankle and there is a lack of resolution of symptoms. The patient typically presents with pain that is aggravated by activity and relieved by rest and is located in the anterior or anterolateral portion of the ankle joint. On physical examination there may be a persistent ankle effusion with pain at the end of range of motion. There are few characteristic features that allow this diagnosis to be made on physical examination alone. A high index of suspicion is required to order the appropriate diagnostic tests. If the fracture includes the subchondral bone it may be visible on radiography; if, however, it involves only the articular cartilage, computed tomographic scan or magnetic resonance imaging may be necessary for diagnosis.

Retrocalcaneal bursitis occurs in the retrocalcaneal bursa, which lies between the Achilles tendon and the posterior aspect of the calcaneus at the point of insertion of the Achilles tendon on the calcaneus. *Superficial calcaneal bursitis* occurs in the superficial calcaneal bursa, which lies between the subcutaneous tissues and the posterior aspect of the calcaneus near the attachment of the Achilles tendon. These bursae may become inflamed and painful due to mechanical pressure from footwear.

Sever's disease is an osteochondritis similar to Osgood-Schlatter's disease at the tibial tuberosity, except that it involves the epiphyseal plate at the posterior aspect of the calcaneus. This condition results in pain at the posterior aspect of the heel. It typically occurs in a child about 8 years old. Physical examination reveals localized tenderness as well as pain on forced plantar flexion.

Achilles tendinitis, inflammation in the Achilles tendon, is usually the result of an overuse injury or repetitive trauma injury. It results in the subacute onset of pain in the Achilles tendon proximal to the calcaneus. Stiffness and crepitance may be associated complaints. Contributing biomechanical factors include excessive foot pronation and heel cord contracture. On physical examination there is usually localized tenderness to palpation and pain on resisted ankle plantarflexion and on passive ankle dorsiflexion. There may palpable crepitance or thickening in the tendon.

Subluxing peroneal tendons most often are secondary sequelae of inversion injury to the ankle with disruption of the connective tissue retinaculum at the lateral ankle. Inflammation and pain in the peroneal tendons result from this injury. Physical examination findings include local tenderness of the peroneal tendons at the lateral ankle, with subluxation of the tendons on resisted dorsiflexion and eversion of the foot. Peroneal tendinitis can occur as an overuse syndrome in the absence of

subluxation.

Tibialis posterior tendinitis is most commonly an overuse syndrome. The usual location of pain is at the medial aspect of the distal one-third of the leg, although pain may be localized to any portion of the tendon including its position posterior to the medial malleolus and near its insertion on the medial plantar aspect of the navicular. Associated biomechanical factors include abnormal pronation with hindfoot valgus. Physical examination findings that suggest tibialis posterior tendinitis include pain in the appropriate location along the medial aspect of the tibia, at the posterior aspect of the medial malleolus, or near its insertion on the navicular. Pain is increased, with the appropriate mechanical stressors to the tendon including maximum resistance and maximum stretch of this muscle group.

Plantar fasciitis is a condition that results in pain and limitations in ambulation. There is pain on the plantar surface of the foot near the calcaneus and in particular on the medial aspect of the insertion of the plantar fascia on the calcaneus. It is discussed in Chapter 80.

Painful heel pad results from pain arising from the soft tissues on the plantar surface of the heel. The location of the tenderness is usually posterior to the tender area seen in plantar fasciitis.

Degenerative arthritis of the ankle and subtalar joints can be caused by previous trauma to these joints, leading to secondary degenerative changes. The pain is subacute to chronic in its evolution and, as with degenerative arthritis at any joint, there may be stiffness after a period of immobility. The pain is typically aggravated by activity and relieved by rest.

Subacute and Chronic Midfoot Pain. Midfoot pain is much less common than either hindfoot or forefoot pain, and there are correspondingly fewer differential diagnoses to consider.

Köhler's disease is a condition of avascular necrosis of the navicular bone. The underlying etiology is unclear, but as the term *avascular necrosis* suggests, the suspected etiology is one of interference with blood supply to the bone.

Plantar fasciitis pain is typically maximal at the plantar surface near the calcaneus, but it is not uncommon for the pain to radiate to the plantar surface of the midfoot.

Degenerative arthritis can affect any of the intertarsal articulations of the midfoot. It is often seen after ankle or subtalar arthrodesis. Here, the rigidity of the fused articulation leads to abnormal loading of the remaining joints. The end result is premature degenerative changes and pain on weight bearing and ambulation.

Subacute and Chronic Forefoot Pain. The term *metatarsalgia* is a nonspecific term that refers to pain in the region of the metatarsal heads. It is a term that is used when other more specific diagnoses that also can result in pain in this region have been ruled out. The pain is thought to be the result of abnormal mechanical loading of the soft tissues on the plantar surface of the foot at the level of the metatarsal heads.

Interdigital (Morton's) neuroma leads to pain in the region between the third and fourth metatarsals and may radiate into the third and fourth digits.

Hallux rigidus is usually the end result of degenerative arthritis.

Hallux valgus with bunion is a foot deformity associated with a valgus malalignment of the great toe, and, if of adequate severity, may result in an overriding second toe. Because of the deformity, the medial aspect of the first metatarsophalangeal joint is subject to increased mechanical loads from footwear and a bursa commonly develops. Pain is localized to the first metatarsophalangeal joint.

Freiberg's disease is a relatively uncommon cause of foot pain due to avascular necrosis of the second metatarsal head. Its onset is usually in adolescence with pain associated with activity. Physical examination reveals pain and tenderness with or without enlargement at the second metatarsal head.

Stress fractures can occur in a variety of the osseous structures of the foot, but involvement in the metatarsal is most common. This is an overuse syndrome. An abrupt increase in the loading of the foot by increasing the repetition of loading, as occurs with increasing the distance walked or by increasing the magnitudes of the loads experienced by the foot, as occurs when running, may result in a stress fracture. The chief symptom is that of foot pain in the region of the metatarsals. The pain severity is activity related. On physical examination careful palpation along the length of each of the metatarsals shows a specific region of point tenderness.

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CHAPTER 76

A. Primary Care Approach to Acute and Chronic Back Problems: Definitions and Care

Stanley J. Bigos and Gerd Müller

This section is devoted to the management of acute low back and leg pain. It strongly espouses the viewpoint that most low back and leg pain is a self-limited and benign condition, unless inactivity leads to deconditioning. It does not review the myriad of treatments for acute low back pain, as these have been shown by clinical reviews to be of little, if any, value. Passive treatment modalities may transiently relieve symptoms because of specific or nonspecific effects, but they do not alter outcomes. They are, in general, a waste of the public's money.

Although we know something of the pathophysiology of low back and leg pain due to disk protrusion or mechanical instability, we do not have good evidence for the causes of nonspecific low back pain, which is the only diagnosis possible for more than 80% of our patients. In this section, Bigos puts forth the Agency for Health Care Policy and Research (AHCPR) guidelines and the evidence upon which they were based. The goal is to provide the pain management physician with the information necessary to optimally assess and treat patients with acute low back pain.

INTRODUCTION

Back problems generally are transient but can linger as the product of many physical (1,2,3,4,5 and 6) and nonphysical factors (7,8 and 9). The treatment and study of back problems have become models for other pain care issues. This section delineates possible contributing factors for back problems and then discusses the most dependable physical approach to care and a comprehensive nonphysical approach appropriate for the individual practitioner. Recommendations for physical care are based upon the most reliable information from the literature, whereas those for nonphysical care may present new issues for the practitioner. Multidisciplinary pain clinic approaches are discussed in Chapter 11, Chapter 18, and Chapter 109.

The approach presented in this chapter does not question whether the patient truly has pain. Epidemiologic studies of the incidence and prevalence of back symptoms remove such doubts. Practitioners should not neglect the nonphysical factors that influence a patient's response to symptoms and subsequent care. The literature abundantly describes the nonphysical factors encompassing premorbid and postmorbid societal pressures or psychosocial issues (8,10). We assume that clinicians understand that a myriad of combined dynamic individual and situational factors can alter patients' responses to both their symptoms and the care provided. Simplistic attempts to attribute symptoms to a specific factor are classic examples of Mayer's Law: “Where you stand on a particular subject depends upon where you (have to) sit” as is obvious from surveys of those with similar complaints but varied attribution according to type of work (Table 76A-1).

Site	Heavy work	Attributable to work	Light work	Attributable to work
Neck	39	31	45	29
Low back	43	32	42	18

Data from Johnson JA. Work-related and non-work-related musculoskeletal symptoms. *Appl Ergonomics* 1994;25:248-251.

TABLE 76a-1. Percent with complaints related to work

This section is designed to help clinicians practically define problems so as to minimize the duration and severity of the patients' pain and reduce the impact of nonphysical societal pressures. Nowhere in care is a defensible approach more important than for those slowest to respond. This chapter concentrates on reliability in both diagnostic procedure and therapy with the goal to provide help that is in the patient's best interest. The recommendations reflect the most reliable data available on effective treatment and the most practical approach to addressing patient fears.

This chapter presents historical and related developmental issues central to many past misconceptions about care. It reviews epidemiologic information important to patient education and other aspects of care. Treatment will be based upon treating the patient's activity intolerance rather than just the pain. Historical perspectives and occasional theoretical notes are central to the theme of modern back care. Other sections of this chapter address surgical, anesthetic, and psychosocial aspects

of the care of the low back pain patient.

EPIDEMIOLOGY OF BACK PROBLEMS AND HISTORY OF BACK CARE

Back problems are an extremely common medical issue, the most common and expensive orthopedic entity, most expensive industrial injury, and most common cause of disability for workers younger than age 45 years (11,12). Back problems are erratic in their interference with activities. For 90% of working persons, an episode limits regular activity for less than 30 days. Of those seeking medical care, 25% to 40% may have symptoms radiating below the gluteal fold, an indication of sciatica. Approximately 5% have neurologic changes detectable by physical examination, with approximately 2% having strong findings indicative of a good surgical outcome from nerve root decompression (via laminotomy or laminectomy). Half of those with the strong neurologic findings of herniated disk recover sufficient activity tolerance by 30 days to lose any interest in surgery.

Medical frustration with this commonly transient yet occasionally chronic entity is illustrated by up to a ninefold variation in use of evaluation and treatment modalities in different regions of the United States (up to a tenfold variation in different counties in the state of Washington) (13,14). Back problems are seemingly unavoidable (5,16,17,18,19,20,21,22 and 23). The back is one of the most frequent reasons for primary care visits (11) and accounts for approximately 20% of all industrial injuries and 40% to 50% of the costs for all industrial injuries (10,24). Yet, there is no typical, easily identified cause. Only 10% of the claims account for 80% of the cost due to disability, including time off work and permanent disability (10,24). This 80% figure is derived from a cross-sectional survey assessing memory of having a back problem. For approximately one-third of the population, the back no longer feels “young” by age 30; half lose this young feeling by age 35, and three-fourths by age 40 (11). Anyone who lives to 50 years of age can expect to have some limitations due to back problems. Studies indicate that more than half of working age adults admit to having at least 1 day of back limitations each year. A survey by Carey et al. in North Carolina found that more than 20% of respondents remembered back symptoms lasting for more than 1 month in the prior year (25). Sciatica has a slower than expected recovery and is strong tocsin announcing the loss of a young spine's tolerance for activity.

Back problems deriving from heavy physical demands are virtually unavoidable by age 50 years, but interestingly, some persons may not recall experiencing problems. Hultman studied the 20% of Swedes who denied prior back problems by 50 years of age (26). Interestingly, she found that this group had simply forgotten back episodes. Almost all had medical records indicating back treatment. This forgetful 20% had a common characteristic—they were able to work at their own pace, and most were farmers. No doubt they did heavy work. Yet, the farmer noticing a catch in the back has the luxury of deciding to sharpen tools for a day before returning to the fields. Conversely, such a person's memory might have been more accurate if a supervisor had demanded no return to work until the back was fully recovered.

MEDICAL FRUSTRATIONS WITH BACK PROBLEMS AND BACK CARE

Waddell et al. described many of the irrational aspects of back care based upon conventional wisdom (8,9,27). In earlier times conventional wisdom prompted physicians to treat patients with infection by bleeding them, well after the negative impact was obvious. One continuing irrational approach to back problems is the use of screening x-rays even though they provide information beyond what is expected from history and physical examination in only one in 2,500 cases (28). The tendency is to assume that normal aging changes seen on computed tomography (CT) or magnetic resonance imaging (MRI) are an indication of pathology, even in the absence of reliable physiologic evidence. Conventional passive treatments are still championed despite proof of the detrimental impact on both patient fears and physical activity tolerance. Moreover, “hard” work becomes the culprit for causing unpreventable back symptoms if we ignore expected age associations and obvious contributing factors in the backgrounds of hourly workers (29,30). History warns us that we should not be surprised by resistance to rational inquiries that fly in the face of conventional wisdom.

MEDICAL HISTORY OF THE “REST THEORY” CONUNDRUM

Medical hypotheses seemingly inflicted less harm on patients with back symptoms before back problems were declared an injury rather than a part of life. Waddell found in Oman, the Ivory Coast, Nepal, and other areas of the world that back pain is still considered to be a normal part of life, and compared with Western societies, is less debilitating (9,27,31,32,33,34 and 35). Many have posed the question as to why back problems have become such a problem in Western society (36,37,38). A nineteenth-century contributor to the development of Western attitudes was Hugh Owen Thomas, whose unverified “rest” theories have harmed more back patients than any other therapeutic approach (39). Rest not only debilitates the patient but also forces more aggressive considerations when activity tolerance worsens with inactivity. The impact of back problems was minimal until back pain evolved from being a part of life to classification as an injury for workers' compensation and insurance purposes (40,41). Once so categorized, Hugh Owen Thomas' theories came to the forefront with their adoption by orthopedists, who evolved as caregivers for such structural injuries. The unfortunate mantra— “rest to allow recuperation and avoid damage”—persisted despite its poor applicability to back problems.

Ironically, Thomas comes from a long line of Welsh bone setters, who tended to set bones or splint patients to keep them as functional as possible (39). He was the first member of his family to attend medical school but then took up his family's trade. He built his fame upon a hypothesis about the body's natural recuperative properties and based his noble model upon patients with tuberculosis in this era before the antitubercular drugs. This therapeutic approach incorporated rest, nutrition, and recuperation to reduce weight loss and improve the body's resources to fight the infection. Febrile and coughing episodes declined and the patient's energy eventually returned. The stress of physical activity was commonly associated with relapse. Although Thomas' treatise on the recuperative aspects of the body relates well to preantibiotic tuberculosis, he applied this approach to all painful entities, including back pain, and until recently, succeeding generations of clinicians failed to objectively test it. Ironically, his nephew, Robert Jones, became known as the “father of orthopaedic surgery” (42,43).

Tuberculosis or infectious agents cause a small percentage of today's back problems. We cannot evaluate the course of back symptoms by monitoring temperature, cough, and body weight (44). Rest fits poorly into reliable treatment regimens for noninfectious, nonfracture back problems because it debilitates protective muscles and further reduces the patient's ability to comfortably tolerate activity. Early motion with resumption of activity is one of the most important advances in the treatment of musculoskeletal injuries (45).

Biomechanical studies have not altered the treatment approach in a positive direction and perhaps are the source of other irrational theories. The National Institute of Occupational Safety and Health (NIOSH) published a lifting guide in 1980 with the best of intentions to protect workers from back injury. The guide was based on a consensus panel review of three cadaver studies, including one published in the United States in 1957. Another was published in 1962 in Japan, and the third was presented at a meeting but was never published in a refereed journal. The conclusions seem to be based on system failure in an unknown number of cadaver spines from persons at different ages. In an attempt to ensure safety for workers, the panel drew conclusions from these data without considering the differences of *in vivo* spines, including presence of vertebral blood, reinforcing musculature, and the surrounding body structures. Thus, the biomechanically stressed spines failed to correlate well with the experiences of living patients. Later studies of osteoporotic patients cast suspicion on such mechanical modeling; these patients seemed to tolerate activities for which the modeling data predicted fractures (6).

This 1980 guideline had little impact on reducing back problems, so NIOSH reconvened a new panel a decade later, but its recommendations followed a similar pattern of logic. Daily work task maximums were based upon data from estimating the chance of weight loss while on a fixed calorie diet (46). The consensus of this small panel unintentionally provoked rules about work as a cause provoking barratry rather than further science. Unfortunately, the lifting guide has caused unnecessary loss of employment by citizens before retirement age. Within 10 years it was revised with the same data (47). The first guide prompted NIOSH to launch a 10-year planning conference in 1985 that included the goal of eliminating back pain as an industrial injury by 1995 through known ergonomic principles (48). Time revealed the myopia of this effort. Prevention fervor now focuses on repetitive strain and cumulative trauma, factors based upon even less reliable scientific support (12,29,49,50,51,52 and 53).

Reliable data point away from these simplistic approaches. In the last 25 years, job-related requirements for range of motion (ROM), cumulative lifting weight, and maximum lifting weight have, on average, declined, but the disability pensions nevertheless increased by 2,600% to 3,300%. Additionally, in many countries with less strict lifting guidelines, the work force has a lower percentage of lost workdays due to back pain compared with countries with stricter guidelines. The nonphysical aspect of work injury claims is further evinced by increasing the sickness benefit by 20%, resulting in a 20% increase in lost workdays in Sweden (54).

Back injury claims are a complicated web of many factors. Experiencing back symptoms is a common, unavoidable part of life, and the demands and benefits of jobs involving physical labor require regular use of the spine. Reliable data show that a young- feeling back is lost by age 50 years, whether the life's work has been strenuous or not. The only real glimmer of hope for prevention of further debilitation or conditioning is to regain comfortable tolerance. Workers can improve protective muscles and avoid the debilitation of inactivity to reduce the amount of discomfort, recurrence rate, and days of limitations they experience (5,56 and 57). Disability

issues are further discussed in Chapter 17.

To overcome the negative impact of irrational prevention and treatment practices requires a sound scientific foundation. During the 1994 AHCPR Guideline (11) development process, we attempted to review the medical literature for reliable information. The AHCPR panel reviewed more than 11,000 abstracts and compiled evidence tables for those with sufficient information to evaluate reliability. The panel provided “Finding and Recommendation Statements” to interpret the literature and a guide for clinicians who care for a wide range of back patients. Back problems were defined as an episode of limited activity tolerance due to back or back-related leg symptoms. The term *back pain* alone may or may not include sciatica, with different risk factors presented for each condition. Risk factors for the first episode of back trouble, first back claim, repeated back claim, disability, and chronic disability do not coincide (Fig. 76A-1). Thus, the term *back pain* was avoided other than for those specific symptoms. Note especially the hierarchy of decisions made at each phase. The guide emphasizes meaningful measurements of limitation due to back symptoms. The treatment goal for both working and retired patients is to improve comfortable tolerance for needed physical activity.

Figure 76A-1. Level of back problems—related decisions. Note many levels of back problems including the annual percentage of the working population that is affected. Patient understanding can affect some early active decisions and perhaps avoid the later difficult passive decision issues.(From Bigos SJ. *Housestaff handbook for back problems*. Seattle: SpineMate Publications, 1996.)

To what extent do the presence of back symptoms and loss of activity tolerance relate to physical demands and the aging process (Fig. 76A-2)? The question requires a review and further explanation.

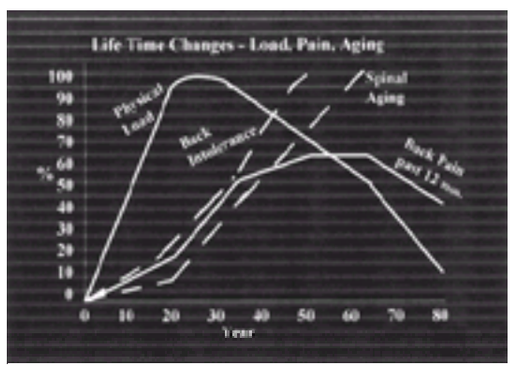

Figure 76A-2. Lifetime changes—load, pain, aging. Note relationships between maximum adult physical load, back pain, and back intolerance relative to spinal aging according to age. (Modified from Videman T, Battié MC, Gibbons LE, et al. Lifetime exercise and disk degeneration: an MRI study of monozygotic twins. *Med Sci Sports Exerc* 1997;29:1350–1356.)

LOSS OF ACTIVITY TOLERANCE DUE TO BACK SYMPTOMS: DEFINITION OF BACK PROBLEMS

Medicine has long preferred to treat discrete variables that can be eradicated, such as treating infection with antibiotics (58). Unfortunately, treatment of back problems is more like training for a marathon. Treatment outcomes are not discrete or dichotomous variables (sick or not sick) but a continuum of responses. As with a marathon, the more a person trains and the younger the age, the better the result. Yet, two persons with the same training may perform differently in the race due to individual variation (59). So it is with how patients cope with the loss of the “young” back's tolerance for physical stress. Despite the best conditioning and medical care available, one basketball star's career ended in his early 30s after he developed back symptoms, whereas another afflicted at the same age continued playing for 8 to 10 more years. Physical variation makes it difficult to predict comfortable activity tolerance in highly motivated athletes. Prediction becomes even more difficult with the addition of nonphysical stress and pressure in patients who are earning salaries far below the multimillion-dollar contracts of professional athletes.

Two challenges should now be evident: (a) It is difficult to predict the outcome of back problems, and (b) it is difficult to solve pain problems in patients who have become extremely inactive. Yet, data indicate a potential to make major differences in the outcomes of both acute and chronic patients if from the beginning we can avoid the debilitation of inactivity (55,57). Evidence confirms two important elements: (a) the need to convince the patient that there is nothing dangerous causing symptoms, and (b) that using the back is not only beneficial but safe. This section reviews potential causes of symptoms, which are the important ammunition needed to convince the patient about the safety of continuing with normal activity. This information also will help the clinician see the logic of the recommendations.

Lost activity tolerance is predicated on many issues. A patient's responses to questions about activity can be altered by perceptions, fears, prior experience, expectations, social or work situation, and medical understanding (60,61,62 and 63). The patient's eventual activity tolerance is a response to combinations of the unavoidable physical experiences and many nonphysical factors that have surfaced relative to considering back problems as injuries. Thus, activity tolerance provides a measurable index for monitoring the sum of medical and nonphysical issues that bear on treatment results (64). The rate at which a patient regains activity tolerance can also clarify the need to consider many issues relative to resumption of work that are important concerns for many back patients.

Understanding the Logic of Treatment for an Activity Intolerance

The knee offers an analogy applicable to the whole musculoskeletal system. With a knee problem, the quadriceps muscles must be conditioned, regardless of whether surgery is required. Pain subsides only after conditioning the thigh muscles sufficiently to compensate for whatever knee problem remains. Adequate conditioning of these protective muscles can return patients to rigorous professional athletics, not because the knee is like new but because muscular compensation is adequate to tolerate the required activity. The protective muscles must be conditioned to a state better than before the knee problem occurred. Until reaching that point, the knee continues to be painful, intolerant of activity, and irritated by even minor mishaps. The knee may become red and swollen with the stresses of conditioning. Sometimes fluid must be removed, which may prompt questions from the patient about why we recommend exercise when there seems to be something terribly wrong with the knee. Then, almost miraculously, as muscular capacity increases, the redness and swelling disappear, and activity tolerance begins to increase. The requirements of muscular conditioning are similar with the spine.

Until we condition protective muscles sufficiently to do their job, any activity is like gardening for the first time in spring after the winter's rest. We may not feel pain when we start gardening, but after our protective muscles fatigue, we are destined to pay a price either that night, the next day, or occasionally immediately. The severity depends on whether the muscles were already compensating for a problem (as in the knee analogy). Do we experience the pain because gardening is a dangerous activity or because something is seriously wrong? Pain more likely results from the lack of conditioning caused by the winter's rest. Only conditioning protective muscles with exercise or continuing to work in the garden eventually allows comfortable activity (although a person who hates gardening may never

overcome the aches or fears of pain).

Unfortunately, training or conditioning cannot be achieved without using the back. Such activity need not be dangerous, although it may not be totally comfortable. Regular use of the back can increase muscular capacity and bone mineral density and improve the capacity of other tissues, which improves the efficiency and the responsiveness of the musculoskeletal system.

Nonphysical Pressures

Costs to employers directly or through their insurance can drive nonphysical factors to exert stress on an employee. Financial pressures result from time loss and indemnity costs, which in some cases triple the medical costs (24). Employers also see lost production and the expense of replacing missing employees. For the employee, inability to resume regular work activities is commensurate with educational level or training and relates to options of facing failure. Lower education triggers a potential for long-term disability, retraining costs, and settlement awards. Avoiding debilitation by maintaining normal activity not only reduces time lost from work but also seems to speed recovery and reduce recurrence of back problems and future work time loss (55,57). Studies have found that activity tolerance can be improved by conditioning protective muscles (65,66), while for workers with strenuous jobs specific back muscle conditioning provides future protection from both symptoms and time loss (56). Unfortunately, it is a rare person who can tolerate using the back as a crane at a regular or rapid pace until retirement age. Thus, many workers with limited education or skills will face nonphysical pressures when they become back patients.

Epidemiologic data provide the assurance we need to give our patients about expectations and influence our care. An important issue for our patients and society, and the care we provide, centers around one issue—the loss of the young-feeling back. Once that occurs, the patient can derive comfort from a simple formula. The treatment section expands upon this theme after back problems are defined in the following section.

POTENTIAL ETIOLOGIES: ACTIVITY INTOLERANCE DUE TO BACK SYMPTOMS

The recommended approach focuses on handling the problem rather than searching for the cause. The clinician is advised to seek factors that may need to be addressed rather than seeking the cause of transient symptoms. As can be seen with the formula, structural and exposure-to-load factors must be considered, given the close relationship between structure and function (e.g., the worse the structural problem, the more conditioning is needed) (67,68 and 69).

Relative Anatomy of the Lumbar Spine

Possible compression of cauda equina or nerve roots below the first lumbar vertebral body is the concept that provokes the greatest concern regarding treatment and requires the most extensive evaluation. The lumbar nerve roots exit around and under the pedicles attaching the vertebral body to the posterior elements (Fig. 76A-3).

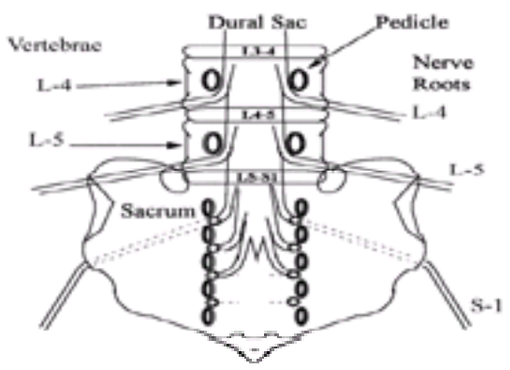

Figure 76A-3. The relationship of the dura, dural sleeves, and nerve roots to the pedicle and central spinal canal. (From Bigos SJ. *Housestaff handbook for back problems*. Seattle: SpineMate Publications, 1996.)

Note the relative relationships between pedicles, transverse processes, facet joints, and ligamentum flavum to the disk space neural foramen and neural contents of the dural sac, which includes the nerve roots (Fig. 76A-4).

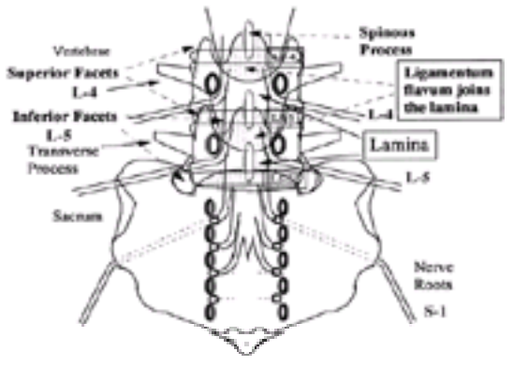

Figure 76A-4. The posterior elements—facet joints, lamina, spinous processes, and interlaminar space covered by the ligamentum flavum relative to neural contents. (From Bigos SJ. *Housestaff handbook for back problems*. Seattle: SpineMate Publications, 1996.)

Studying Figure 76A-5 and Figure 76A-6 relative to the neural contents in Figure 76A-4 explains why disk herniations usually catch the nerve root that exits at the next lower level nerve root foramen. For instance, herniation at L-4 to L-5 usually affects the L-5 nerve root that exits at the L-5 to S-1 foramen, and herniation at the L-5 to S-1 usually impacts the S-1 nerve root that exits through the sacrum.

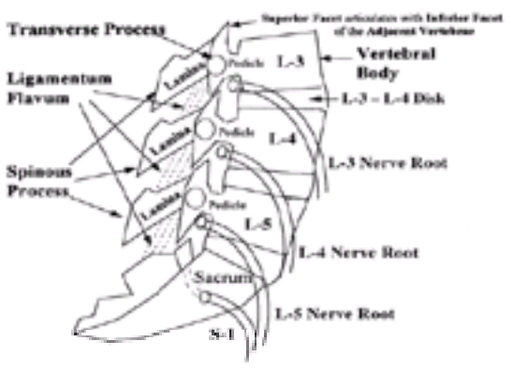

Figure 76A-5. The lateral relationship of the nerve roots to the foramen formed by the facet joints, pedicle, and vertebral body. (From Bigos SJ. *Housestaff handbook for back problems*. Seattle: SpineMate Publications, 1996.)

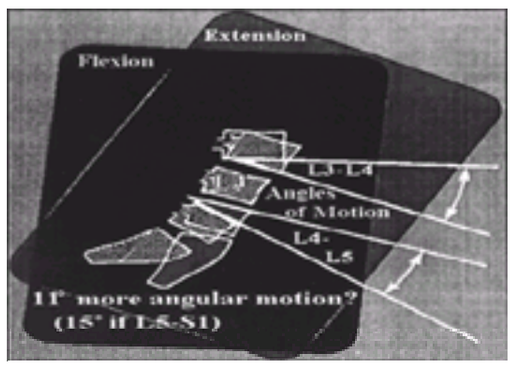

Figure 76A-6. X-ray angular motion of instability. Superimposing a vertebra adjacent to the motion segment to be measured (here, L-4) from lateral films taken at the extremes of motion. The end-plates or posterior bodies can be used to measure the change in angular relationship from hyperflexion to hyperextension. Stress shielding occurs when there are more than 11 degrees of motion than the adjacent segments. (From Bigos SJ. *Housestaff handbook for back problems*. Seattle: SpineMate Publications, 1996.)

The relationship of the pedicles as would be seen on a plain radiograph is also important. Their absence hints at tumor, which tends to affect the vascular pedicle's junction with the body of the vertebra. The pedicle is also an important landmark for finding the nerve root, as can be seen in Figure 76A-3.

A break in the pars interarticularis (between the upper and lower facet articulation of the same vertebra), termed *spondylolysis*, is found in approximately 7% of adults. Such a defect allows the body, pedicle, and superior facet to move forward in half the cases (known as *spondylolisthesis*), leaving the spinous process, lamina, and inferior facet behind to articulate with the adjacent superior facet (see spondylolisthesis in instability).

Aging of the Lumbar Spine

The first visible aging in the human body occurs in the disk. Before gray hair, balding, and wrinkles, changes usually occur in one of the lower two lumbar disks levels. Holt's diskograms found abnormalities in 34% of subjects by age 23 years (70). Necropsy studies found aging changes at one of the lower two levels of the lumbar spine in 75% of subjects by age 28 years and 100% by age 42 years (50,63). Magnetic resonance imaging (MRI) scans have since verified these prior studies (71).

Early disk aging should not be a surprise. The lower lumbar disks are the largest structures in the body without a blood supply after age 12 years (72). Nutrition of the disk relies on osmosis from the vertebral end-plate and periphery (72,73). Sixty percent of oxygen and glucose in a disk diffuse in from the end-plate vascular system and the rest from the periphery, whereas 60% of the sulfoxyl ions and glycosaminoglycans diffuse in from the peripheral disk vasculature and the remainder from the end-plate of the adjacent vertebral bodies. From a clinical standpoint, we can expect early aging in the lumbar spine; 40% of asymptomatic persons by 35 years of age have noticeable radiographic changes (28).

Approximately 15% of teenagers have disk changes seen on MRI, which is much more sensitive than radiography (74). Herniated nucleus pulposus is one expression of aging of the intervertebral disk. Disk aging causes greater demarcation between the outer grizzly annulus fibrosus and the inner jelly of the nucleus pulposus. Also, this nuclear material gradually loses its sulfoxyl ions and the ability of the glycosaminoglycans to hold water. Gradually, the disk becomes less of a hydrostatic cushion, and the nuclear material is transformed from this jelly to more of a crabmeatlike substance. During aging, the outer annulus fibrosis (grizzle) develops posterolateral cracks, where the inner nuclear material may escape into the spinal canal. Nuclear material can irritate the nerve roots both chemically and physically, causing pain and even dysfunction. Apparently approximately one of four to five herniations traps a nerve root and gives the clinical picture of sciatica that is amenable to decompression of the irritated nerve root(s) (74) [see Herniated Disk (45)].

Aging also occurs in the facet joints, but most commonly after changes in the intervertebral disk. Because the facet joints have a stabilizing effect on the spine, most persons lose motion with age, although individuals show marked variation, and loss of motion may be slower in women than in men (75). In rare instances, a relative increase in motion can occur either through stiffening segments above and below one with reasonable motion or through laxity of one segment that allows the adjacent segments to be shielded from stress and become relatively stiffer. Either process can lead to a loss of structural integrity. Both are opportunities for one segment to take most of the motion and become looser, while adjacent segments are shielded to become stiffer. Neurologic elements can be in jeopardy if structural integrity is lost at the loosest junction. This points to the problem of instability.

The aging process in the disk and facets can decrease the space available for neural contents and thus can cause symptoms, such as neuroclaudication, which may require surgery (see Neuroclaudication Due to Spinal Stenosis). The relativity of the aging process to clinical entities is also depicted in Figure 76A-2 (76). The concept of increased motion at one segment is based upon relative increased motion that allows measurable stress shielding of the adjacent segments—for example, the hypermobile segment takes up all the stress and allows 11 to 15 degrees (for L-5 to S-1) more motion than in adjacent motion segments (Fig. 76A-6) or more than 5- mm slipping translation (Fig. 76A-7).

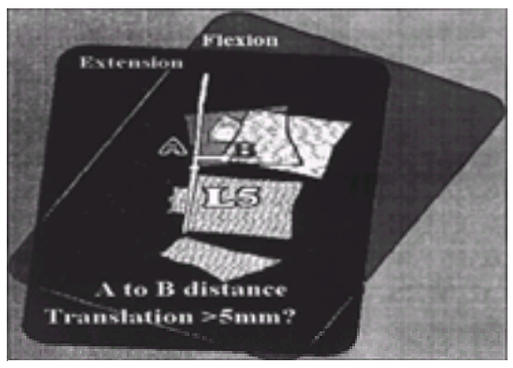

Figure 76A-7. X-ray translation of instability. Superimpose the vertebral image below the slip (here the L-5 image) from the hyperflexion and hyperextension lateral films. The amount of translation can be measured as the distance perpendicular from a vertical line relative to L-5 vertebrae. The distance A to B considering magnification should not normally be more than 5 mm in the lumbar or thoracic spine or greater than 3.5 mm in the cervical spine. (From Bigos SJ. *Housestaff handbook for back problems*. Seattle: SpineMate Publications, 1996.)

The techniques shown in Figure 76A-6 and Figure 76A-7 are used to evaluate potential long-standing instability. The attempt to obtain hyperflexion and hyperextension views can be dangerous after acute trauma and should be undertaken only by spine specialists.

The stress-shielding capacity of the hypermobile segment provides a mechanism to evaluate potential dangers to this lax area with hyperflexion and hyperextension lateral views of the spine (72,77,78). As noted in Figure 76A-6 and Figure 76A-7, we have laboratory baseline criteria for this stress shielding, although many patients meeting these criteria have few abnormal back symptoms. Thus, present treatment data make it difficult to justify using only our imagination to diagnose instability of the spine without added jeopardy of fracture or traumatic dislocation (79).

These extreme displays of lost segmental integrity have not been scientifically related to symptoms. As Swedish orthopedist Alf Nachemson has noted: “Instability

exists, but we do not know what it is and how we define it." We lack convincing data to predict a good outcome for fusion for back pain alone or for the results found on diskogram.

Spondylolisthesis must not be confused with loss of structural integrity and the question of instability (80). Spondylolisthesis is but a measurement of the slip of one vertebra upon the one below. Thus, such slippage requires hyperflexion and hyperextension lateral views. The most common spondylolisthesis or slippage is developmental in origin and is a defect in the pars interarticularis between the superior and inferior facet joint. This defect has not been found in newborn necropsy yet is present in approximately 5% of young schoolchildren and approximately 7% of late teenagers and retiring adults. Approximately half of those with the defect in the pars interarticularis develop a forward slip. Although this defect, known as *spondylolysis*, is potentially pathologic in adolescents and teens (81) due to the potential for slip, no significant risk or relationship to pain exists in adults. In adults the slips rarely progress, even without surgery (82). Once a slip occurs, aging changes commonly allow little motion. Only in cases of spondylolisthesis with slippage of more than 50% on the lower vertebral end-plate is further progression predictable in adulthood (83). Surgery is rarely required to avoid further slip and is not recommended for patients older than 30 years with less than 50% slip in the absence of neurologic findings, unless the slip is combined with hypermotion x-ray findings. Most of the time we are surprised how slips have stiffened in adults.

In summary, by age 35 years, 40% of persons without symptoms show aging changes on radiographs (11). MRI changes are noted in the disks of 15% of teens and 30% of adults by age 30 years (74). Necropsy findings indicate that we can expect a diskogram to be positive in 75% of persons at age 28 years and in everyone at age 42 years. Even when a patient has spondylolysis defects with spondylolisthesis of less than 50%, surgical considerations need to be based upon more than just anatomic findings. Thus, we must be careful in interpreting the anatomic findings if information is lacking on other aspects of the clinical picture.

PHYSIOLOGY: ELEMENTS OF PAIN

Neurologic Components: Diagnosis

The innervation of the spine is fundamental to the physiology of spine pain and is discussed in detail in Chapter 75. The sinuvertebral nerves are the primary innervation of the intervertebral disk. From the posterior primary nerve root these small branches can cross the midline and travel rostrally two levels and caudally three levels (2). The innervation pattern of this nerve alone helps explain the myriad of central, bilateral, or even shifting pain complaints that can originate from spinal structures. A more lateral branch from the nerve root is the posterior rami circumflex, which extends to the facet joints (84). Hypertonic saline injected into the facet joints can cause referred pain as low as the posterior knee area (85). The nerve root complexity and potential autonomic input may further explain various symptoms, including traveling aches, burning skin, deep boring pains, and shocks in various distributions, although we do not know the exact cause of such symptoms. Although we can block sinuvertebral nerves with caudal and epidural nerve root blocks or perform physical and chemical facet joint denervations, the results continue to be unpredictable in clinical studies.

Sciatica may result from both chemical and mechanical irritation of the nerve root. Chemical irritation causes the tougher nerve root to be easily irritated by the softer, crabmeatlike nucleus pulposus. The chemical explanation helps us to better understand the natural history of severe sciatica, which often abates long before there is significant shrinkage of nuclear fragments in the spinal canal (86,87 and 88). The effect of nerve root irritation can be measured through conduction studies such as somatosensory evoked potentials and electromyography (EMG), which help us to distinguish a source of sciatic and neuroclaudication symptoms from herniated disk or spinal stenosis. Unfortunately, our present knowledge of the nervous system explains the painful symptoms in only about 12% of our patients (11).

Physiology of Pain and Treatment: Loss of Muscular Protection

Scientific studies of muscle reveal that between 20 and 50 years of age up to 50% of certain muscular elements are lost through aging and inactivity (89). Thereafter the losses are more rapid, especially with extended periods of rest. Muscular protection lessens with increasing age and the elderly are more susceptible to debilitation with inactivity. The importance of muscular protection can be easily demonstrated by applying a walking cast to an athlete without a knee problem. When the cast is removed after 3 to 5 weeks, the athlete rarely can walk comfortably, let alone run up the stairs. The muscle wasting makes climbing stairs and walking on uneven ground difficult. Until the "well-rested" quadriceps, and especially its vastus medialis obliquus, can be reconditioned sufficiently, activity tolerance is compromised.

Physical conditioning improves comfortable activity tolerance. Preseason training is a painful time for most athletes. During the first few days the athlete struggles to get out of bed the morning after even a short session of competitive activity. By midseason comfortable rising in the morning follows even a maximum effort. The difference is muscular conditioning, which prevents fatigue. Muscle fatigue slows reaction time and reduces the force of contraction, which can hamper the ability of the muscle to protect its own fibers or the joints it spans. Whether the activity is gardening for the first time in the spring after a long winter rest or preseason athletic training, activity beyond the capacity of muscular protection can produce symptoms immediately, that night, or the next morning. Understanding physical conditioning can help patients eliminate misconceptions about work as a cause of back problems. Inactivity may affect not only the muscles and joints, but also the brain and spinal cord. Extreme rest to the point of severe debilitation may have an effect beyond reducing comfortable activity tolerance—it may generate pain. Modern societies can inflict such inactivity upon the body. Periods of inactivity negatively affect the heart; lungs; digestion; bone mass; muscles; and even neurotransmitters such as serotonin, enkephalin, and endorphin (90). Lack of normal input due to physical inactivity might, along with other changes, alter the ability of the brain to process information. Central changes may prompt the brain to interpret impulses from hypoactive muscles and joints as dangerous.

We know that inactivity can induce pain as seen in athletes during preseason training or gardeners in early spring. An extreme example may be sympathetic dystrophylike syndromes induced by inactivity. Beggars have been observed to immobilize an arm under a belt for numerous days until the hand becomes swollen and shiny enough to permit successful begging (I. McNab, *personal communication*, 1979). Physical findings are similar to shoulder-hand syndromes. Tentative active motion generates a grimace, and passive motion arouses protests of severe pain. The pain, stiffness, and swelling seem impossible to control. Treatment is physical activity, aided by pain-relieving procedures and medicines (see Chapter 20).

Chronic back pain patients have similar activity intolerance, although without evidence of swelling and redness. After but a few weeks of inactivity we confront a back conundrum. Recent studies give hope that most of these situations are avoidable by aggressively recommending against the debilitation induced by inactivity (55,57).

Work Activities

The relationship between back pain and work has led to repeated erroneous conventional wisdom statements. The first studies sought to identify defects on screening x-rays (91) and then ROM deficits on preemployment examinations. After researchers blamed the worker for being defective, the pendulum swung to calling back problems a preventable injury. This model set the stage for claiming work to be an injury agent for back problems. If work causes back problems, then we should somehow be able to prevent them in a portion of our population younger than 50 years of age. The association with work seems superficially obvious. Once the back inevitably loses its youthful vigor and an episode of pain occurs, the occurrence of another episode is common, easily triggered by continued activity that may fatigue protective muscles. Yet, the physiology of symptoms has been neglected in favor of a simplistic, mechanically oriented paradigm.

Nonphysical Pain Modulators (Psychosocial Responses)

We should not underestimate the influence of social pressures upon the filing of back injury claims (see Chapter 7, Chapter 17, and Chapter 25). Back-related claims have been studied the most because they are the most common and most expensive of injury claims. One difficulty is in the use of social or psychosocial terms that do not fit into our medical approach of explaining all problems from a single factor. Many authors use the term *psychosocial* quite loosely and even emphasize the importance of evaluating psychosocial factors (92). Unfortunately, they conveniently avoid recommending solutions about this aspect of the back problem. Clinical studies reveal that these "psychosocial" problems reflect a myriad of different and often dynamic factors, with marked individual variations in perceptions and experiences (from experience to disability). Psychosocial problems can result from work and societal expectations as well as the person's response can complicate continuation of work.

Fordyce long ago stated, "People don't hurt as much if they have something better to do." This observation helps us understand why rates of injury claims correlate more to difficulties between labor and management than to mechanical stresses at work (93). Studies show up to threefold increases in claims among workers who experienced labor-management stresses compared with workers with similar demographics and work requirements who did not experience such stresses (94).

A poor economy resulting in threat of layoffs, a change in technical work requirements combined with short duration of employment, and management attitudes better predicted injury claim rates than did variations in physical requirements (10,95). A 10% reduction in the population of middle-income workers and an expanding

lower-income group in the United States from 1970 to 1992 worsened the problem (96). This continued enticement for employers to reduce the number of employees or to terminate older employees before having to begin the balloon payment for retirement funds further exacerbates the situation, for both those who lose jobs and those who remain (36).

The options continue to shrink for workers who face combinations of physical or nonphysical failure at work. Well-trained technical workers are in demand and command higher wages; they file fewer claims and have more employment options. The professional or self- employed rarely make claims whether or not his or her work is strenuous. When facing failure with few options, most persons survive as best they can. Clinicians can expect aggressive survival behavior when a patient is forced to hold onto an injury claim due to a lack of work options or the absence of funded health care outside of the compensation system. Such survival behavior is manifested as embellished symptoms, blame, and latching onto any prior learned rhetoric that may be perceived as helpful. As professionals, we best serve by providing the most reliable and defendable recommendations available. This section is built upon the most reliable data about medical treatment of back and leg pain and the simplest basic concepts available to the individual practitioners who must manage these patients.

DATA-DRIVEN PHYSICAL LOW BACK CARE

It is not difficult to imagine that patients who seek our help have many agendas. The AHCPR panel developed patient discussion handouts covering a minimum of seven agendas that tend to arise within the first 6 weeks of care. Few patients are interested in an issue until it pertains to them, which explains the weakness of offering detailed pamphlets that try to cover all the issues. The agenda items follow a progression as symptoms continue. The agendas address such questions and statements as “What help can I get with symptoms?” “Is the problem dangerous?” “Why does it continue?” “Tell me about special tests.” “What do the special studies mean?” “Now what do we do?” and finally, “What if it does not work?”

Patient education requires specific themes reiterated as questions arise. Prospective studies reveal that the most important issues in the care of back patients center around convincing the patient that nothing dangerous is occurring and that the greatest threat is the debilitation of inactivity (55,57). We can improve the patient's ability to make a good decision irrespective of the physical or nonphysical nature of the problem. Through professional recommendations and compassion we can help patients define options to avoid failure. Thus, the early priorities are to assure the patient that activity is safe, to provide help with symptom control, and to emphasize that the best treatment is to avoid debilitation and safely build comfortable activity tolerance.

Defining Potential Dangers and “Red Flags”

Those who care for patients with back problems are responsible for addressing serious conditions that might be causing symptoms. If any are found, effective options for improving the patient's comfort should be used and efforts should be made to avoid worsening of the condition, including tolerance for activity.

Initial Evaluation

A goal of the initial evaluation for a patient with acute or chronic back pain includes diagnosis of potentially serious causes of back symptoms (Table 76A-2). Most of these efforts are aimed at identifying “red flags” of potentially dangerous conditions or seeking neurologic deficits in the minority of patients who have leg symptoms or identifying a structural deficit that might require attention or definition before treatment can begin. However, for approximately 88% of patients we are unable to provide a defendable pathoanatomic diagnosis that will withstand scrutiny.

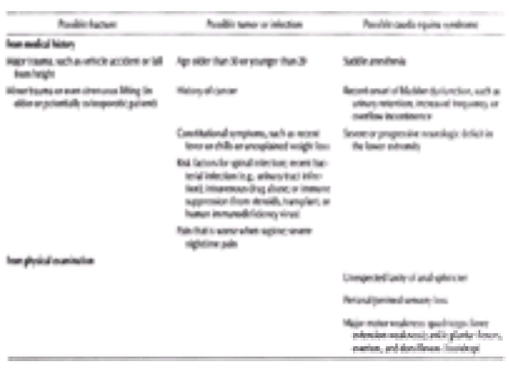

TABLE 76a-2. Red flags for potentially serious conditions

After ruling out “red flags,” the next step is to classify symptoms as back only (no neurologic involvement) or sciatica (neurologic) and then to provide the patient with an understanding of prognosis, workup, and treatment options for dealing with the limiting symptoms.

We can spot “red flags” through questionnaires addressing past medical history, review of systems, present medications, and such measures as the pain drawing with symptoms and an activity visual analog scale. This review is necessary to guide the physical examination and to assure ourselves we have placed the patient in the correct treatment paradigm. The patient, rather than a spouse or caregiver, should fill out the questionnaires. Answers in the patient's own handwriting can help avoid future contention about potentially contestable points.

Specific History

It is essential to take a specific history, if for no other reason than to assure the patient of the physician's thoroughness. Use of questionnaires as mentioned above can facilitate the acquisition of a complete history (see Chapter 12).

The patient should be asked “What symptoms are limiting you? Is it pain, weakness, numbness, stiffness, or other problems?” and “Where on the body have you experienced recent symptoms?” Other questions include the following: “Are the symptoms intermittent or constant?” and “How long have they been the same as now?” Probably the most important question is “How are you limited by the symptoms?” If the patient cannot clearly explain what he or she can't or won't do, it is important to pose questions that ask about specific limitations, as in the following examples:

“Without feeling like you are doing damage, how many minutes can you sit safely, how many minutes can you stand safely, how many minutes or blocks can you walk safely, and how many pounds or kilos can you lift safely?” These questions are best asked eye to eye early in the interview when expectations are highest and intentions least suspect. The reason is that the answers to these queries can help set the starting points for activity recommendations. Should responses be less than 20 pounds or 20 minutes, reassuring the patient that normal activities are safe usually resolves extreme activity restrictions, unless the patient is a true invalid. In the elderly, if walking is commonly limited to less than 20 minutes or 300 yards, ask the following question: “After you have walked as far as possible, can you just stand still to rest and relieve the pain?” If the answer is yes, consider a diagnosis of vascular claudication. This question is aimed at identifying neuroclaudication, which can be caused by spinal stenosis, which is especially common in the elderly. A diagnosis of true neuroclaudication requires the patient to sit, bend over, or squat for a few minutes to supposedly open up the neural canals before continuing walking or other activity.

It is also helpful to understand the patient's interpretation of prior spinal, musculoskeletal, or exercise limitations, including dates and time to recovery and the dates and results of each type of related diagnostic procedure, surgery, or injection.

“What do you usually do to stay in shape?” is another key question. Knowing exercise patterns in the past and present can bring you more quickly to a negotiation point and emphasize the importance of exercise early in the process. Another helpful piece of information stems from the question, “What has given you lasting comfort?” Other useful questions are the following: “What brings you to see me now?” and “Has something changed recently?” The answers will help to understand the patient's expectations about the present visit. If the patient is not working, try to determine what blocks return to work so you can help set goals relative to the prior information about sitting, standing, walking, and lifting. These few questions posed in a specific format can provide the physician with the required information and

avert the need for a belabored “fishing expedition.”

Physical Examination

The focused physical examination for low back pain need not take more than 5 minutes, even in a slow-moving patient.

Standing

1. Normal walking. Normal walking should be fast enough to stimulate the toe-clearing reflexes and eliminate many limps and deviations. Next, ask the patient to walk on heels (testing L-4 to L-5), then on toes (testing S-1 to S-2) before doing a squat and rise (L-2 to S-1), which provides a reasonable index of general strength and proximal muscle debilitation.
2. ROM. ROM is difficult to measure even with the Schober test. Thus, a better approach is to determine whether back muscles are uncoordinated or guarding. Since the introduction of diazepam (Valium), this condition has been called *muscle spasm*. Asking the patient to attempt spinal extension, side bending, rotation, and flexion allows an estimation of muscle fatigue and ROM to the degree that muscles remain in a shortened state on one or both sides at certain levels. A patient who shows extreme guarding and has had recent symptoms of fever and chills warrants investigation for infection of the spine or its appendages.
3. Waddell pain embellishment I, II. Tenderness and simulations can be performed and are discussed later in the section Nonphysical Interference.

Sitting

Sitting provides an opportunity to evaluate more basic neurologic functions. Ankle and knee reflexes can provide reliable objective data for the trained physician whether they are positive or negative; they do not rely on the patient's interpretation or volition.

1. Circumferential measurements. Measurements above and below the knee with differences of more than 1 to 2 cm can indicate possible atrophy. These measurements also require no patient volition or interpretation, so they can also be considered objective if differences between the sides are greater than 2 cm given the difficulty of accurately measuring a soft tissue cone. The remainder of the physical examination requires patient interpretation or volition and so provides the physician only with indexes of suspicion. In general, the examination helps to avoid missing nonback problems (vascular, abdominal, central neurologic, hip, or knee) or points toward a neurologic or nonneurologic workup if the patient is slow to recover.
2. Lower extremity joints. These joints can be evaluated in the sitting position by assessing hip rotation (loss of internal rotation, perhaps from hip degenerative joint disease) and knee stability when the knee is slightly flexed and extended (also note Table 76A-4, III). The clinician also should check for extremes of foot and ankle motion.

I. Tenderness: subcutaneous (or less) pressure to reproduce symptoms
II. Simulation
a. Simulation of loading the spine with the weight of your hands on top of the patient's head to reproduce back symptoms
b. Simulation of twisting the trunk when rotating the shoulders and hips in unison to reproduce back pain (can physiologically reproduce sciatica)
III. Distraction: sitting knee extension to test sciatic tension while distracting the patient with knee or foot examination as the reason for extending the knee (If the patient is comfortable during sitting knee extension, straight-leg raising should not be positive and, if it is, is of questionable significance.)
IV. Nonanatomic distribution of pain as seen on pain drawing (total body or outside the body) or giving away on muscle testing (intermittent efforts)
V. Overreaction: grimacing, complaints, or suffering displays inappropriate for situation or maneuver

From Bigos SJ. Household handbook for back problems. Seattle: SpineMate Publications, 1996.

TABLE 76a-4. Waddell embellishment tests

3. Muscle strength. A slight loss of strength is most detectable in large muscles—hamstring (L-5 to S-1), quadriceps (L-2 to L- 4)—compared with great toe extensors (L-5), toe flexors (S-1 to S-2), ankle dorsiflexors (L-4 to L-5), and ankle evertors (L- 5 to S-1).
4. Waddell embellishment IV. Giving away on muscle testing (discussed later, in Nonphysical Interference).

The supine position provides an opportunity to examine abdomen and pulses, which is especially important in elderly with or without positive “red flags.”

The most reproducible physical test pertinent to the goals of the back examination is straight-leg raising of each lower limb to seek sciatic tension signs. Ask the patient to tell you “stop” if it causes discomfort. The next question is the following: “Where is the pain? On the same side or the opposite one? In the back? In the hip, thigh, knee, or below the knee?”

Back pain during the straight-leg raising test is not pathognomonic of radiculopathy. It is rather a sign of unspecific low back pain.

At the level where raising becomes painful, further raising can help in evaluating the reliability of the patient's report of symptoms, as follows:

- Worse with plantar flexion? (It shouldn't be.) Or dorsiflexion of the ankle? (It should be.)
- Worse with external rotation? (It shouldn't be.) Or internal rotation of the whole limb? (It can be.)

Diagnostic Considerations

Opposite (or crossed) leg raise can irritate the symptomatic limb and is the strongest predictor of an anatomic lesion such as a herniated disk, although pain rarely augments with dorsiflexion and rotation. Because of the gradual onset of nerve root compression with neuroclaudication due to spinal stenosis, the sciatic tension signs are rarely positive (see Neuroclaudication Due to Spinal Stenosis).

No special studies need be considered in the absence of “red flags” or limitations of less than 4 weeks' duration, because 90% of patients regain reasonable activity tolerance from back symptoms and 50% of those with objective evidence of sciatica recover within a month (11). If the patient has been referred from another physician, review of the imaging and physiologic studies, if available, is essential.

It is important to remember that prior surgery makes imaging studies more difficult to evaluate and that conditions change over time. “Red flags” must be addressed before classifying a patient into the back treatment paradigm. A different paradigm must be used if tumor, infection, or metabolic disorders are suspected. They are best assessed through laboratory studies. New bowel and bladder symptoms or obvious multilevel neurologic dysfunction demand immediate neurosurgical consultation and consideration of MRI or myelo-CT scan.

Some fractures may be difficult to see on x-ray, but if suspicion remains high due to the history and continued severe limitations, a bone scan is more sensitive after 7 to 10 days of symptoms. During the acute stage, CT scan should be reserved for patients with a high suspicion of a serious problem on the basis of physiologic or historical indications demonstrated with x-ray film or CT scan.

The clinician can expand the medical examination as required by the specific leads obtained from the standard history and physical examination of the spine. The importance of the interview and the review of systems and past medical history forms cannot be overemphasized.

Once the examination is completed, the clinician can then categorize the patient according to present and future needs. A clinician can feel comfortable explaining the good news and expectations to a patient after ruling out “red flags” if the present episode of limitations due to symptoms has lasted less than 4 weeks. If limitations have persisted longer than 4 weeks, the clinician must decide, based upon limitations, improvement since onset, and threat to the patient's livelihood and mental well-being, whether special studies are warranted immediately or in the future. An executive with symptoms that interfere with racquetball or tennis but that are not a threat to livelihood can be followed for several months. A furniture mover with similar limitations but unable to work for a month would be at great risk of losing his or

her job if the clinician waited 2 to 3 months for the symptoms to resolve. Thus, history, physical examination, and special examinations are the foundation for the statement that there is no danger (psychological validation) in avoiding the debilitation of inactivity. The prescription of activity, rather than rest, is the cornerstone of the management of low back pain.

Medical Attention: Assurance, Comfort, Education

The goal of initial care is to keep the patient's activity as normal as possible to avoid the debilitation of excessive rest and to prevent potential socioeconomic complications. Assurance, comfort, and effective treatment need be addressed for all patients. The *New England Journal of Medicine* article by Malmivaara and colleagues indicates that approaches advocating rest may have been too conservative (55). This report emphasizes a need to assure the patient that there is no hint of anything serious (psychological relief) and to encourage the avoidance of further debilitation by continuing normal activity (physical help). Malmivaara et al. found that even when patients engaged in reasonably heavy work, the symptoms abated faster than for those who had 2 days of rest or who had passive correction techniques that were labeled exercise. If limitations linger, the clinician should provide further education about expectations and assure the patient that further diagnostic studies will be considered.

Assurance and Expectations

An example of how to reassure the patient is the following: “Medicine is pretty good at finding serious conditions and at this time we have no hint of any serious problem. Unless you become too debilitated by inactivity, your symptoms should resolve over the next few days. If you are in the slowest 10% to recover we will again consider special studies to help explain the reason for the delayed recovery. The reality is that no one has been able to explain the cause of back problems that limit approximately a third of us by age 30, 75% of us by age 40, and virtually all of us by 50 years of age. It is good news when we can't explain the exact cause of a back problem because the outcome is better and we can usually start sooner to build comfortable activity tolerance. Now we need to help you feel more comfortable without making your symptoms worse.”

Comfort and Help

Here is an example of advice regarding comfort: “There are many means of helping you with discomfort but nothing totally wipes out the pain and lets you go about your business as usual. Thus, we will recommend the best combination of methods to allow you to stay as active as possible to avoid debilitation and to minimize how much work you will have to do later to regain your physical capacities. It usually takes twice as long to regain conditioning as it does to lose it. Medication can take the edge off the pain. Acetaminophen blocks the pain highway at a different place than other medications, so it works well by itself or in combination. At worst, an episode of pain may last for up to 5 days. That is the longest you might need major help with comfort. Most often your medication will allow you to continue with normal activities. We will try to avoid medication that might cloud your mind or disrupt your normal activity any more than necessary.”

For patients who lack any hint of kidney or liver dysfunction and who are not elderly, a combination of acetaminophen and nonsteroidal antiinflammatory drugs is adequate and more effective than what are commonly considered “stronger” or more dangerous methods. If patients feel manipulation has helped before, remind them that it only helps symptoms and does not correct the problem without the addition of conditioning.

Work Recommendations (for Compassion, Not Safety)

A patient may not be able to tolerate the discomfort associated with required work activities. Compassion for the patient may necessitate some work limitations, for as short a time as possible, until the severest symptoms resolve or conditioning begins to improve activity tolerance. Whenever activities at work are limited for more than 3 to 4 days, an alternative activity (see Treatment: Maintaining or Building Comfortable Activity Tolerance) must be started to minimize the debilitative effect of the work restriction. The two medically justifiable parameters for recommending work limits involve lifting and sitting. The amount and time spent doing each can be negotiated based upon the report of specific limitations in the initial history (patient's perception of safely standing, sitting, walking, and lifting) and the recommendations of the AHCPR Guideline #14 with regard to the duration and progression of work activities. The main goal is to avoid debilitation through inactivity. Prolonged absence from work also leads to loss of physical and social skills, thereby impeding restoration of normal function.

Treatment: Maintaining or Building Comfortable Activity Tolerance

Remember the old Groucho Marx joke: “Doctor, doctor, after surgery will I be able to play the violin?” Doctor: “I would hope so.” Response: “Good! Cause I could never play it before.” Surgery, manipulation, injections, medication, or rest do not train anyone to play the violin, run a marathon, tolerate strenuous activity, or return comfortably to normal activity after being inactive for a while. Only conditioning allows a person to comfortably tolerate activities.

Unfortunately, there is no way to maintain or build activity tolerance without conditioning (see Why Conditioning: A Summary of Explanations for the Patient). Conditioning activities need not be any more dangerous for the spine than sitting at bedside before rising in the morning, but activity may not be totally comfortable. Patients need to understand the difference between hurt and harm (see Chapter 25). Discomfort with conditioning by walking or cycling usually points to a lack of muscular protection and emphasizes the importance of the conditioning activity (97,98,99 and 100). Whether due to inactivity or general or specific structural change, once activity tolerance is lost only conditioning can regain or improve comfortable performance. The three aspects of activity progression are the following: general conditioning for stamina, specific spine muscle conditioning, and general reconditioning, especially resuming work or specific activity conditioning (at work if possible).

General Conditioning for Stamina

General conditioning for stamina consists of speed walking or stationary cycling for 30 continuous minutes at a heart rate of 130 beats per minute (or 120 if older than age 40 years) or jogging for 20 minutes. *Note*: Severely debilitated patients or those with severe lower extremity joint problems may need to start with swimming, which can improve tolerance for essential terrain-oriented conditioning activities. Few severely debilitated patients profit sufficiently from swimming to avoid the walking or cycling needed to build reasonable activity tolerance.

After 5 days per week of conditioning for 6 weeks, general stamina can be maintained thereafter with 2 to 3 sessions per week of 30 minutes each. (Like an airplane, it takes much more energy to get up to altitude than to stay there; 2 days a week of conditioning will maintain it.)

Specific Spine Muscle Conditioning

Recommendations are based upon the original work of Biering-Sorensen (101) and have been best studied by Gundewall et al. (56). The patient should work up to a 4-minute isometric session per night.

Resuming Work or Specific Activity Conditioning (at Work if Possible)

There is no better way to avoid deconditioning than to continue normal activities, as has been demonstrated in prospective studies (55,57).

Education and Reassurance for Those Slowest to Recover

Providing information to patients is important and has long-lasting benefit (57). Assurances, expectations, and the importance of conditioning must be established with each patient. Initial validation and repeated reflection are essential parts of care. Numerous studies (41,102) prove the effect on outcome. Patient confidence is maintained by using validated information and reassurance that if significant improvement does not occur, special studies will be considered to help explain continued limitations persisting 4 weeks or more (11).

The next section is not an attempt to provide surgical guidance but offers information for nonsurgical clinicians who must explain workup and surgical aspects of care to patients. This overview is congruent with surgical information presented in other portions of this chapter.

DIAGNOSTIC CONSIDERATIONS FOR DELAYED RECOVERY

If back symptoms continue to limit activity, especially at work, for more than 4 weeks or if sciatica persists for more than 4 weeks, it is reasonable to consider seeking a cause. Obtaining physiologic evidence can help determine the likelihood that anatomic imaging might lead to a specific diagnosis (11). Anatomic studies alone can be confusing. Normal aging changes (present 30% of the time in asymptomatic 30-year-olds and found in virtually everyone by age 65) may be confused with a diagnosis. Thus, physiologic evidence helps to avoid the limitations of imaging studies (45).

Figure 76A-8, which correlates age with disk findings in normal subjects, illustrates this point. Table 76A-3 notes that imaging studies provide no physiologic evidence. Thus, a clinician who does not consider the whole picture may wrongly interpret aging changes as a cause for present symptoms.

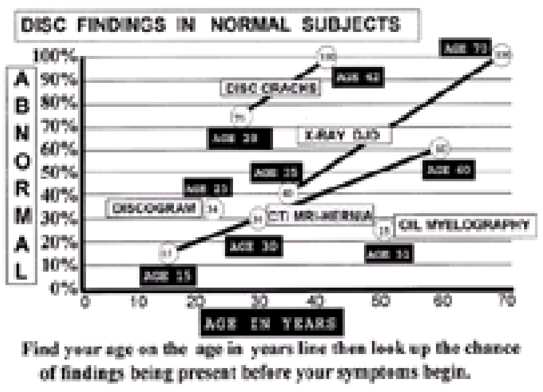

Figure 76A-8. Questionable radiographic diagnoses that increase in frequency with age from imaging studies of patients without symptoms. (CT, computed tomography; DJD, degenerative joint disease; MRI, magnetic resonance imaging.) (From Bigos SJ. *Housestaff handbook for back problems*. Seattle: SpineMate Publications, 1996.)

	Contributions of evaluation methods	
Technique	Physiologic evidence	Anatomic definition
History	+	+
Physical examination		
Circumference measurements	+	+
Reflexes	++	++
Straight-leg raise	++	+
Crossed straight-leg raise	+++	+++
Motor	++	++
Sensory	++	++
Laboratory studies (sedimentation rate, blood count, urine analysis)	++	0
Bone scan[a]	+++	+++
Electromyography/sensory-evoked potentials	+++	+++
X-ray[a]	0	+
Computed tomography[a]	0	++++[b]
Magnetic resonance imaging	0	++++[b]
Myelography[a]	0	++++[b]
Myelo-computed tomography[a]	0	++++[b]

0, no contribution; ++++, excellent contribution.
[a]Risk of complications (radiation, infection, etc.): [illegible]
[b]False-positive findings up to 50% without symptoms at age 50.
From Bigos SJ. *Housestaff handbook for back problems*. Seattle: SpineMate Publications, 1996.

TABLE 76a-3. Types of contributions toward making a specific diagnosis

A picture of a telephone does not tell you if it is ringing. A picture of a box does not tell you if it is filled with an anvil or foam. If you drop the box on your foot, then you know. You have some physiologic information. A picture of soft tissue or even bone abutting the dura does not show whether the pressure is sufficient to compromise the function of the nerve root. Only physiologic evidence tells us whether the nerve root is compromised. Surgery is effective in relieving pressure on compromised neural contents caused by either herniated disk or spinal stenosis. Imaging pictures guide the surgical approach by defining an anatomic cause for known physiologic compromise.

Physiologic Evidence

In the absence of fracture or dislocation, reaching a conclusion about surgical considerations is similar to television's “Wheel of Fortune” game show. The more letters on the board, the greater the chance of guessing the phrase correctly. Figure 76A-8 presents the chances at different ages of having an imaging test that is diagnostic before the development of symptoms. This chart is based on studies of subjects without symptoms. Table 76A-3 offers clues about how to procure physiologic evidence to avoid the possible confusion of relying on imaging studies alone.

- Laboratory studies (sedimentation rate, blood count, urine analysis) provide indications about a metabolic and more general screen for suspected potentially serious problems (103).
- Bone scan provides a nonspecific structural screen and sensitive physiologic information about bone and joint changes (bony reaction to change in structural loading with fracture/dislocation or architectural changes of tumor, infection, or spondylitis).
- EMG is indicated for constant or near constant limb symptoms of suggestive radiculopathy persisting for more than 4 weeks (an earlier test may provide false-negative results because changes will not be evident until the third or fourth week of symptoms) (see Chapter 13) (104). The diagnostician should look for more than multiple positive sharp waves or fibrillation potential (S-1 compromise can slow H-reflex) as evidence of motor nerve compromise (strongly consider anatomic studies if any muscle is 3+ or more). The physical examination should show obvious signs of a problem at L-5 or S-1 before the diagnostician seeks imaging verification. EMG is not needed if motor, sensory, and reflex tests indicate obvious L-4, L-5, or S-1 nerve root damage or compromise, which is strong physiologic evidence to explain a limitation due to leg symptoms persisting 4 or more weeks.
- Somatosensory evoked potentials (SSEP) can provide information on slowed nerve root transmission in patients with symptoms of neuroclaudication and EMG evidence of motor function changes. SSEP measurements tend to be more sensitive than EMG measurements, although less specific for active compromise of a nerve root.

Anatomic Imaging

Anatomic imaging is used to define a reason for physiologic evidence and to seek conditions that impose upon the neural content of the spinal canal and foramen. The most commonly used techniques are MRI or CT, which are not as invasive as myelography. With both we seek information about pressure upon the spinal cord above L-2 and upon nerve roots in the lumbar spinal canal or in the intervertebral foramen, through which they pass to exit the spinal canal before forming the lumbosacral plexus (see Chapter 14).

- X-ray screening is most useful for seeking a fracture or dislocation. Otherwise, beyond the expectations from history and physical examination, radiographs contribute information on serious pathology in but one in 2,500 cases (11,103). When a radiograph is positive for fracture or dislocation, the clinician may gain additional information with CT scan or MRI, depending upon the patient's clinical presentation and findings.
- CT scan defines bony pathology but may not allow definitive evaluation of the contents of neural canal (74).
- MRI best defines the potential anatomic reason for physiologic evidence, especially intradural and extradural defects; soft tissue visualization is better than that for bone but is potentially distorted by patients who cannot lie still for extended periods of time (15% of patients experience claustrophobia).
- Myelogram–CT scan may be used for patients who cannot lie still, are too claustrophobic for MRI, or who have had prior spinal procedures. This combination provides better intradural resolution than does CT scan alone.
- Myelography may be used when MRI is not possible. In this procedure, radiopaque material is injected into the spinal dural sac. Myelography is best combined with CT scan.

A reasonable approach to MRI interpretation is as follows:

1. Start with the MRI T1-weighted view. Parasagittal views are the best for evaluating fat in the foraminal canal, which vanishes before nerve roots can be compressed. The parasagittal MRI T1-weighted lateral images show fat as white in contrast to the nerve and other tissue in the canal.

   The parasagittal lateral views of the spine are usually displayed from left to right, so the first view in the upper left corner is of the far left aspect of the left foramen, with each picture thereafter moving to the right until the lowest right image is the rightmost aspect of the right foramen. Look for fat in the foramen because any pressure will eliminate the fat before affecting the nerve. Do not be alarmed unless you cannot find fat present in at least two views of the foramen in the parasagittal views. Remember to record the level according to the system in which the fifth vertebra is the one above the sacrum, the fourth is two above, and so on. The foramen is described according to the vertebral body above and below—for example, L-5 to S-1 foramen or interspace, L-4 to L-5.
2. Next, look at the parasagittal MRI T2-weighted lateral images, which make water seem white in contrast to other tissues. Thus, these images give views similar to a lateral myelo-CT, in which the myelographic dye makes the cerebrospinal fluid white, as does the T2-weighted image. Here, look at the contours of the spinal canal and potential indentations upon the white, fluid- filled dural sac, which contains the nerve roots before they exit through the foramen. One can also evaluate alignment of the vertebral bodies that form the anterior wall of the spinal canal.
3. Finally, evaluate the T2-weighted cross-sectional images to evaluate indentations upon the dural sac and its white, watery fluid contents and nerves. Think of the sac as a long water-filled balloon that should be convex unless resting upon something that flattens it out or indents it. We are most interested in the indentations that cause the sac to be concave, which may indicate pressure on the neural contents that could explain physical findings or EMG abnormalities relative to complaints of sciatica.

In summary, T1-weighted (fat-white) parasagittal lateral views let you look for fat in the foramen that is obliterated before there is pressure on nerve roots. T2-weighted (water-white) parasagittal views of the canal allow you to assess the contours of the vertebral alignment and compression of the white, water-filled dural sac. T2-weighted (water-white) cross-sectional views provide evaluation of the normally convex or flat dural sac, which might have a concavity due to pressure on the sac and its contents. Any doubts about the numbering or left to right or right to left display on parasagittal views should prompt a phone call to the neuroradiologist for verification.

An important point on all imaging studies is that overreading is a necessity for the neuroradiologist. Only such emphasis can satisfy all potentially interested parties who might review the scan; it also alerts the less adroit to points of interest, clinically significant or not. Radiologists frequently report normal age-related changes as pathologic.

Specific Impressions

Sciatica Due to Herniated Disk

The history of back and leg symptoms with strong physiologic evidence of nerve root compromise on physical examination or EMG (95% L-5 or S-1) and corresponding anatomic verification on MRI, CT, or myelogram are indications to consider surgical decompression by removing the offending disk material and any loose nuclear material within the disk (diskectomy), usually through hemilaminotomy (widening the opening between the lamina) (105,106). The patient who can function with less than 3+ EMG findings and who does not have surgery commonly recovers within a few months, with a recurrence rate of approximately 60% in the next few years.

Surgery can reduce the recurrence rate to approximately 10%, depending upon demands placed on the back, with strong findings that surgically treated manual workers miss fewer days due to back problems during the first 4 years after onset (106,107). After that period, there seems to be no difference in recurrence rates. Surgery is a luxury for speeding recovery when a patient has very strong findings. Generally, the more obvious the findings, the more certain the recovery. The greater the compromise of the canal, the better the results with surgery. Herniated disk recurs at the same level in 2% to 4% of cases. An important point is that surgery does not make the back feel 18 years of age again. Back functioning will still be limited depending upon muscular conditioning relative to what the back will be asked to do. The key is to make certain that herniation is the cause of symptoms. In many cases, removal of disk herniation may solve a problem present before symptoms began and that is not the cause of symptoms. In such cases surgery is not a solution and may even worsen the symptoms. Again, the lesson is to not rely exclusively on anatomic imaging studies alone.

For patients with prior diskectomy, reliance on physiologic information is even more important. First, scarring may alter imaging findings, while diminished physical findings may be related to the reduced nerve root mobility due to scar (108). Patients who did not respond to the first diskectomy present even more difficult management challenges (109). Theories abound as to why. Surgeons traditionally blame scar but every postoperative patient has scarring. The wrong diagnosis or postoperative diskitis may be the reason for failure (110). Great caution is required in diagnosing recurrence within a few months after surgery or assessing the patient whose symptoms worsen immediately after first diskectomy. Both situations can involve a myriad of issues. A surgically battered nerve root may produce EMG changes for more than a year and can be an enticement to attempt to decompress (uselessly) an already sensitive nerve root. An old adage was that positive sciatic tension signs plus one neurologic finding yielded a 65% chance of correct diagnosis. This adage is a dangerous guide for patients with a possible recurrent disk herniation. Acute EMG changes, not polyphasic waves, with corresponding imaging findings greater than would be produced by scar, are the safest indications of the need for another decompression. However, we must be guarded in our expectations of results relative to those expected with first procedure.

Neuroclaudication Due to Spinal Stenosis

The diagnosis of spinal stenosis is common, although it is but a physical finding related to the condition that is most amenable to surgery—neuroclaudication. The diagnosis is better determined by history than by imaging studies. Surgical results are most appreciated by older, retired patients who have experienced a gradually decreasing activity tolerance, especially in walking (neuroclaudication) and standing (related to extension of the lumbar spine), which cause leg or feet symptoms. These patients can find relief by flexion of the lumbar spine to decrease the ligamentous enfolding that crimps the intradural neural contents. If spinal stenosis occurs before age 60, consider the diagnosis of diabetes or other general metabolic problems or congenital stenosis due to short pedicles. Most patients have at least intermittent symptoms for months before seeking medical care.

Physical examination tends to be unimpressive and without evidence of sciatic tension signs of straight-leg raising; weakness and atrophy may be symmetric, as are the diminished reflexes. EMG changes tend to be minimal due to the gradual nature of the compression, but some positive sharp waves and fibrillation potentials are indicative of active disease. SSEPs can further help surgical planning by identifying levels of nerve root compromise to guide which nerve root foramina need special attention during surgical decompression (111). Anatomic studies, either myelogram MRI or myelo-CT scan, can verify central decompression (achieved through subtotal laminectomy with removal of the ligamentum flavum along with redundant anterior facet capsule, osteophytes, and sometimes diskectomy) (112). Foraminal decompression commonly requires removal of part of the anterior facet and perhaps partial removal of the inferior pedicle. The surgical decompression is not preventative and should be performed only when the patient feels compromised enough by the walking limitations to undertake the risks. Bowel and bladder compromise is an emergency indication for decompression. Those who respond best to surgery tend to be those who are most limited in walking distance (neuroclaudication less than 300 yards) and who must sit or squat to relieve the walking symptoms before continuing (113). Segmental fusion may be considered if there is accompanying retrolisthesis, spondylolisthesis, or (developmental degenerative slip) with motion.

Spondylolisthesis

In the American population, 3.5% have slippage of either L-4 vertebra on the L-5 or L-5 vertebra on the sacrum due to bony disruption between the facets (spondylolysis) early in life. A slip of more than 25% can compromise the nerves at the involved level. The limb findings and EMG changes are commonly more vague than with herniated disk and may be bilateral or unilateral. Surgical decompression is similar to that for spinal stenosis and fusion is usually required, as the disk tends not to show the aging signs and stability usually found in spinal stenosis. Thus, there is a greater chance of further slip with decompression given the usually underdeveloped facet joints. In general, the younger the patient (younger than age 30 years), the better the fusion result due to the decreased likelihood of a diagnostic dilemma posed by vague back symptoms. In instances of the latter, 25% to 40% of patients have vague leg symptoms, leading to the unverified misdiagnosis. Many patients without slip of 50% or more do not experience problems until the normal aging brings spinal stenosis, at which time the aging at slipped level leaves little residual motion.

Medical Arthritis (Seronegative Spondyloarthropathy)

Medical arthritis (seronegative spondyloarthropathy) (see Chapter 27) includes ankylosing spondylitis, Reiter's syndrome, psoriatic spondylitis, and their related

expressions of spinal symptoms (114). These tend to be multisystem diseases that require medical observation and the right combination of medication to keep the patient functioning. Once the vertebrae are stiff and brittle, minor trauma can cause fractures with serious consequences. Except for psoriatic arthritis, these disorders mostly occur in men, with onset between 20 and 40 years of age, and symptoms, especially stiffness, that are worse in the morning. After rising, it may take the patient an hour or more to reach the best attainable functional level, as the symptoms decrease with mild activity (83). The prudent clinician rarely considers surgery except for an unusual case of severe deformity (115).

Segmental Instability

The concept of increased motion at one segment is based upon relative increased motion that allows measurable stress shielding of the adjacent segments—for example, the hypermobile segment takes up all the stress and allows 11 to 15 degrees (for L-5 to S-1) more motion than in adjacent motion segments (Fig. 76A-6, x-ray angular) or more than 5-mm slipping translation (Fig. 76A- 7, x-ray translation). It is still controversial to fuse a motion segment that does not move after surgical decompression (116).

Nonphysical Interference

Spine-limited patients commonly find themselves facing dilemmas when they must use their backs as a crane to survive. Such dilemmas manifest in expressions of fear, anger, or survival behavior that we commonly view as unpleasant or even dishonest. Clinicians may observe altered views of self or others and concentration on the insurance industry injury contest for the assignment of blame more than a focus on the medical problem at hand. The threats of failure commonly lead to embellishment of symptoms. The safest interpretation is that the patient has reason to question whether the clinician has his or her best interest in mind. Embellishment and anger seem to be attempts to enlist help in the contest over liability. Increasingly, we are finding that these nonphysical factors, commonly termed *psychosocial*, are dynamic and reactive (117). It is important to remember, however, that nonphysical threats to the patient's self-esteem, livelihood, future, or other loss can significantly influence the patient's response to caregivers (8).

The Waddell tests and the clinician's personal impression are probably the best predictors of a slower than expected physical recovery. The potential combinations of nonphysical pressures, be they economic, psychological, or social issues, make a search for the specific cause impossible. No matter what the combination of perception and threat, the clinician should try not to be too judgmental. Recognize that survival behavior is a common response, although not very effective at the human level. In nature an animal's survival behavior is an aspect of being prey or predator. Sometimes such behavior is effective; other times it is not. A survival game must have a winner and loser, so both sides use betrayal to gain an advantage over the adversary. A bird feigns a broken wing away from the nest, a lizard changes color or fans out to appear larger, a zebra bears stripes, and a lion's coat is camouflage in high grass. All are a natural part of survival in the animal kingdom. Embellishment of symptoms is a more sophisticated expression of survival behavior that should not be interpreted as a deliberate attempt to deceive the physician, but as a tocsin that the patient feels trapped and is seeking help and understanding in the best way he or she knows.

Zero to two positive Waddell tests are normal, whereas three or more positives warn the clinician of nonphysical interference that can confuse the history and physical examination. In the latter case the clinician needs a more objective focus to avoid overreacting to nonobjective findings that require the patient's volition or interpretation. Clinicians should also be warned that nonphysical pressures may alter the patient's response to the care provided and perhaps lower the expectations related to outcome for both surgical and nonsurgical efforts (8,118). Although other approaches are available to the individual clinician, these simple tests can help to avoid overlooking potential difficulties (Table 76A-4).

The specific nonphysical reasons for slow recovery are usually numerous. Whatever the nonphysical reason for slowed or delayed recovery, the approach is the same: Overcome the fear of physical activity through validation and reflection techniques, and help the patient defuse reactions to the unknown by gathering enough data about options to encourage more logical decisions (see Slow Recovery Approach: Validation and Reflection).

FURTHER TREATMENT AFTER DIAGNOSTIC OR SURGICAL PROCEDURES

After seeking reasons for slow recovery, we return to a similar but altered treatment paradigm. Whether due to the period of reduced activity or to changes in the motion segment, the focus is now on gaining comfortable activity tolerance. No shortcut exists; the only recourse is conditioning to avoid fatiguing protective muscles and to prevent their owner from causing symptoms or irritation. After diagnostic or surgical procedures, nothing should stand in the way of the needed conditioning. The first step is to assure the patient as part of the validation and reflection process that there is nothing dangerous to fear and that comfortable activity tolerance can be gained only by overcoming or avoiding the debilitation of inactivity. This best approach is a gradual return to activities or exercise in conjunction with a gradual return to activities. In either case, there is no pill, massage, manipulation, injection, or surgery to provide comfortable activity tolerance. The only way to regain comfortable activity tolerance is through conditioning protective muscles.

Why Conditioning: A Summary of Explanations for the Patient

When Will the Pain Go Away?

Review the example of the knee. It makes no difference whether knee surgery is required. Recovery comes only after conditioning the thigh muscles to the point of compensating for whatever knee problem remains. Adequate conditioning of the protective muscles allows some patients to return to rigorous professional athletics, not because the knee is normal, but because there is adequate muscular compensation to tolerate the required activity. The protective muscles must be conditioned beyond their capacity before the knee problem. Until conditioned to that point, the knee continues to be painful, doesn't tolerate activity, and can be irritated by any minor mishap. The knee becomes red and swollen, sometimes requiring draining of fluid that prompts the patient to question the exercise regimen when there seems to be something terribly wrong with the knee. Then, almost miraculously, the redness and swelling resolve and activity tolerance begins to improve as the muscular capacity increases. It is similar with the spine.

Until our muscles can do their normal protective compensatory job, any activity is like gardening for the first time in spring after resting all winter. Once we tire or the muscles we are using begin to fatigue, we can pay for it that night, the next day, or even right away. The severity of symptoms depends upon whether protective muscles are already compensating for some change, as in the knee analogy above. At age 18, we're a little stiff; by 50 we may notice much more stiffness, but both result from the same physiologic phenomenon. It is not associated with dangerous activity or a serious problem, but only a winter's rest. It usually takes a few days or weeks of working in the garden, practicing a sport, or working at a demanding job before muscles become sufficiently conditioned to do their normal protective job of allowing comfortable tolerance.

Conditioning Requirements

Our best science indicates that conditioning involves addressing two weak links that can keep protective muscles from reacting fast enough to protect the spine. The most obvious is fatigue of the specific back muscles, which slows their reaction time. Also, if the owner of those muscles becomes even a little tired, general muscle reaction slows and coordination is impaired. Such explanation will help patients understand how a lack of general stamina can prolong symptoms and how training specific spine muscles provides protection from future problems.

Medical Goal

Nothing, surgical or nonsurgical, makes the back young again after a few weeks of limitation or significant sciatica. The goal of treatment is to gain sufficient muscular protection to reduce the frequency and severity of future back problems.

Conditioning

The conditioning process starts first with completion of general conditioning. These activities are done 5 days per week for 6 weeks and involve either continuous jogging 20 minutes or continuous walking or stationary cycling that keeps the pulse above 120 to 130 beats per minute for 30 minutes. After only 4 weeks of general conditioning, a second phase of specific back muscle conditioning can be started, with the patient working up to 4 minutes daily for 4 weeks to gain muscular protection. Both phases can be started at once but for deconditioned patients tolerance is much poorer.

A third phase is not focused on treatment of the spine but is an attempt to regain what we tend to lose when we are inactive due to back symptoms. Thus, this is a general reconditioning phase for arm, leg, and abdominal muscles. Dips for the arms can be performed in any armchair. Leg exercises include either squats at the sink or the old ski conditioning exercise of assuming the sitting position against a wall without a chair. The abdominal muscle conditioning demands only mild exercises. All can be performed in less than 5 minutes of effort and usually can be added after 4 weeks of specific spine muscle conditioning.

An additional phase II exercise for upper back and neck is also available. Once a person's shoulders will tolerate 100 continuous small arm circles done slowly, they are performed as rapidly as possible to involve the upper back and neck muscles. Canned goods (tuna to pears) and even weights can be added to further improve conditioning.

Work hardening should be reserved if at all possible for gradual return to activities at work. The basic concept is to have the patient perform as many specific but limited tasks as possible. If the patient is unable to tolerate one circuit of an activity, then repetitions need to be built with limited load (two-thirds to three-fourths of the requirement) until one circuit can be completed. Then the patient should begin two-thirds to three-fourths of full-load building with repetitions beyond what is required before gradually increasing the load to the normal level. The speed of progression and eventual end point may be predicated upon many physical and nonphysical factors. A work-hardening approach performed in the normal work milieu increases the chance of success and markedly reduces costs.

Slow Recovery Approach: Validation and Reflection

Patients are stymied by slow recovery or a parade of continuous obstacles to gaining reasonable activity tolerance through conditioning. If return to work is the expected outcome, the patient may well be struggling to survive in a confusing contest. The patient may perceive return to work as guaranteeing failure. A sense of being trapped in this contest causes patients to embellish symptoms and augment pain behavior. A clinician's harsh judgment can only worsen the situation. It helps to remember that survival in the jungle is based upon confusing the enemy. We commonly see patients make clumsy attempts to enlist our help. Patients may regard the clinician as a predator in the contest until we can convince them that we have their best interest in mind. We also must look at ourselves when we continue to see such behavior because it means we have not convinced the patient that we are not just another predator. No species chooses failure to resolve a contest. A person's failure to overcome limitations can be due to innumerable combinations of physical, emotional, cognitive, and social factors. Patients benefit more from our honest help than our judgment of their legitimacy (61).

Nonphysical Interventions

Validation and Reflection

When recovery is slow, review the history, physical findings, and special study findings to be sure no “red flags” have emerged. Validate again that there is no hint of anything serious standing in the way of building comfortable activity tolerance. As a helpful partner, use reflection techniques to explain the need to build activity tolerance through conditioning. Most important, use reflection techniques to show concern for slow progress and difficulty in reaching activity goals.

“If it is this difficult now (to regain activity tolerance), what is the chance that it will be easier as you get older? What will you do if, for any reason, you do not get back to your former job or activity? If there is any question, let's gather some information about your options, just in case. You may not need to know options immediately but they could be important for planning over the next few years or sometime before retirement age.” These statements provide the patient with validation and acceptance that you truly have his or her best interest in mind. Such acceptance is a turning point in any individual or multispecialty approach to the patient.

This validation and further reflection can help the patient feel much more in control, with the knowledge that he or she is not tied to a particular outcome if in a feared “return-to-work contest.” Offer to help the patient start a spiral notebook to record information about options (11) and review notebook progress on each visit. Only information and understanding deemotionalize decision making.

No Effort about Options/Further Reflection

Some patients may require coaxing to gather information about possible options. The patient's lack of response to a few suggestions to gather information provides another opportunity to show concern by providing reflection about the apparently inappropriate denial. In such cases, the clinician might state, “It is quite unusual for spine symptoms alone to keep someone from making a few phone calls to figure out how to save one's own livelihood and perhaps the future of his or her family. Usually other issues are involved. I think you need see a counselor to sort out the reasons for such behavior.”

If the patient trusts that you have his or her best interest in mind, the patient usually asks, “Reasons such as what?” The ensuing discussion provides an opportunity to review common reasons. The reason for such denial can be personal habits, denial, or social factors.

Approaching emotional issues can at first result in anger and avoidance. Referral for psychiatric evaluation and treatment can be helpful for both the patient and the physician.

DIFFICULTIES WITH THOSE WHO CANNOT FIND FAILURE ALTERNATIVES

“It Didn't Work!”

Those without reasonable options tend to demand the unavailable. Groves described the “hateful patient” in a number of scenarios (119). Most important, he related what he described as the passive-aggressive patient. Without showing distress, the patient smiles before responding to recommendations by saying, “Didn't work! Now what are you going to do?”

This patient does an excellent job of transferring the problem to the clinician. Thus, it is important to not chase the pain but attack the activity intolerance with activities no more stressful than sitting on the side of the bed before rising. Should this type of conditioning be uncomfortable in the absence of red flags, it can expose the present lack of muscular protection and validate further the importance of conditioning.

Validation that there is no dangerous problem and reflection about what you have to offer must include the expected result of gaining the ability to tolerate reasonable activity. Those who have unreasonable expectations about future tolerance may benefit from the stories of athletes such as the professional basketball players. The question always must turn to “But where are the people who can continue such strenuous activity after 60 years of age?” Equally important is to review the failure of medical science to explain the cause of symptoms in 88% of the patients we see. Thus, workup is not aimed at the cause of symptoms but to find serious conditions or alterable reasons for slow recovery—for example, either neurologic compression or lost structural integrity that can slow the conditioning needed to regain comfortable activity tolerance.

Anger

Patients trapped in failure have but two options. They can escape or become depressed. Without the emotional energy from accomplishment or the camaraderie of interacting with others, depressive tendencies are almost guaranteed.

A person who lacks a sense of accomplishment or even self-indulgence (considered selfish by most blue-collar patients) can head down a path toward depression unless interrupted. Anger can be a short-term interruption on this slippery path. Unfortunately, anger does not always strike its target and can confuse the clinician's efforts to determine the true sources of the patient's dilemma. Usually, simple questions such as “Is there something I've done?” or “You seem very angry” can refocus the patient's aggravation in the right direction and away from you. Should you sense an inappropriate disturbance, offer to help the patient with a referral to a counselor or psychologist. Sometimes the patient's anger is with your inadequacy to solve the problem. Fortunately, other than tarnishing of your name, anger dissolves and requests cease as soon as the patient finds an enabler. Thereafter, the patient may have unreasonable hopes about nonphysical problems and no longer feel a need to function. Unrealistic validation may allow avoidance, at least for a while. Some patients later return to you when the enabler's ability to support avoidance evaporates or fails to solve the external pressures related to the patient's failure to function. Then the clinician must resume further honest validation of

nothing serious and reflection toward improved conditioning.

CONCLUSION

Everyone who lives to age 50 experiences back problems. Occasionally, someone will challenge this statement. Simply point out that it is a rare person older than age 50 who could lay a driveway by hand over the weekend and then play basketball on Monday, as most of us could when we were 18 years of age.

Back problems affect society (i.e., all of us). We all pay for this most expensive industrial injury, musculoskeletal problem, and most common cause of disability under age 45. The person who moves furniture, carries cement bags, or must quickly unload heavy objects pays most directly. His or her livelihood and even the family future can be threatened by back problems. These symptoms may slow down the housewife because there is no one else to do her chores. The same symptoms may inconvenience the lawyer, administrator, or physician by interfering with a racquetball game or tennis match without threatening income or future. Back problems cost us all either in our personal productivity or in the prices of the goods we purchase because of the increased disability costs incurred by employers.

Where does medical care fit in? In recent years, some have questioned whether care for back problems is optimal. A ninefold difference in the use of different evaluation and treatment techniques in different parts of the country has been demonstrated in the United States, the country with the world's highest rate of back surgery. Newer and newer technology and growing numbers of providers and approaches to treatment have not halted the rising costs of back problems, even with the advent of managed care. More scientific information indicates that a limited physical understanding of back problems can compound nonphysical pressures. Medical science will have few solutions to the real problem until we realize that the back cannot be used as a crane until age 65 and that psychosocial problems are often not diagnosed but are the result of a complex combination of present and prior experiences.

The definitions and resultant treatment considerations can help the clinician avoid complicating the patient's problem by employing an honest scientific basis for medical recommendations. Back problems are rarely emergencies. The real decision maker continues to be the patient. We help most by giving the patient the clearest advice and understanding of what medical science finds reliable and warning against becoming physically debilitated by inactivity. Relying upon scientific literature can also avoid fingers pointed at the clinician when a patient must defend a lack of progress. This point brings us to our most difficult patients and greatest challenge.

Surviving an injury contest can greatly emotionalize the patient's life and decision making. Being able to assure patients that they “deserve the most dependable recommendations medical science provides” affords the clinician an opportunity to help the patient build comfortable activity tolerance and prepare for difficult decisions. Rather than facing the old paradigm of “Didn't work, Doc! Now what are you going to do?” a professional and a friend can remain an ally to the patient facing both the physical and the nonphysical aspects of return to work (119).

The literature supports the clinician who adroitly sets reasonable expectations and helps the patient avoid both physical and nonphysical pitfalls. Reliable data can help the clinician be more efficient and effective and remove the sting of having to see another time-consuming back patient. The prudent physician will

- Never be put in the position of being accused of treating only the patient's head. Red flags and examination information are always needed to assure the patient and the clinician that there is no physical problem to block conditioning.
- Remember the Groucho Marx joke, and that only conditioning begets comfortable activity tolerance.
- Realize that only the computer on the patient's shoulders can weigh the different (nonphysical) pressures, fears, and understanding needed to make a reasonable choice of options.

Nowhere in the literature have both elements of acute care been better illustrated than in the work of Malmivaara and Indahl (55,57). The nonphysical should be addressed with strong assurance that there is “no hint of anything bad that should stand in the way” of the most important aspect of physical treatment—“avoiding the debilitation of continuing activity by continuing normal activity as soon as possible.” For debilitated patients, the message of Gundewall (56) provides the next step for future protection, as discovered by Biering-Sorensen (101).

Perhaps as a friend as well as a clinician, we can help patients face serious decisions in a more informed and less emotional fashion. We can support the collection of information needed for making those decisions by avoiding harsh judgment when behavior varies in the emotional battle for survival through avoidance of facing real or perceived failure.

Despite the incentives for surgeons to perform surgery, we shall remember how rarely complications of dural leaks, ileus, blood replacement and reaction, discitis, battered root, and scarring are encountered after the conditioning needed to improve activity tolerance. This is particularly important when surgery makes so little difference in the final outcome except to speed pain relief in patients with very strong findings (107,120).

This section has tried to capture the essence of our strongest scientific data and the best elements of multidisciplinary approaches that can be provided in a practice. Those patients who are more disturbed, entrenched, abused by or abusing their local medical community or those requiring more hand holding may require a team approach (see Chapter 11). Other sections of this chapter cover treatment of pain and spine surgery. For pain patients with a lumbar spine component, we have stressed activity issues that are critical to the restoration of well-being.

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CHAPTER 76

B. Role of Surgery in the Treatment of Low Back Pain and Sciatica

Jeffrey J. Wise and Gunnar B.J. Andersson

Although it has been estimated that 60% to 80% of the population experience at least one episode of low back pain during their lifetime, the majority of these episodes are self-limiting (1,2). Regardless of treatment, low back pain episodes usually resolve spontaneously within a few weeks. The presence of leg pain (sciatica) influences the recovery rate negatively (1,3). The lifetime prevalence of sciatica is 2%, and 10% to 25% of these patients develop persistent radiculopathy (3). The lifetime prevalence of lumbar surgery in the United States is approximately 3% (3). The annual incidence of surgery in 12 countries is depicted in Figure 76B-1. In Scandinavia the surgery rate is only 1%, and in England even less. What accounts for this difference? Taylor et al. (4) noted substantial variations in spinal surgery rates by region in the United States, as well as the number of spine surgeons per capita. When is surgery on the spine indicated (5)?

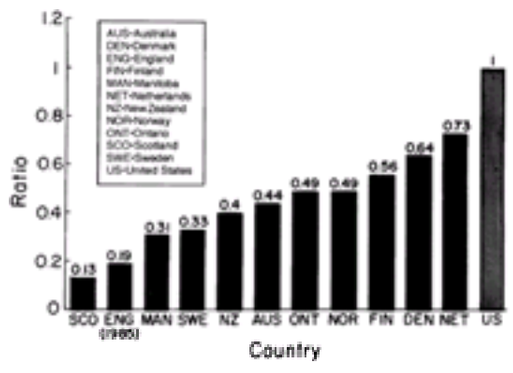

Figure 76B-1. Incidence of spine surgery in the United States. (From Cherkin DC, Deyo RA, Loeser JD, et al. An international comparison of back surgery rates. *Spine* 1994;19:1203.)

Surgery for lumbar disk disease should be performed only when nonoperative treatment fails, barring a few surgical emergencies. Nonsurgical management should be attempted for at least 4 to 6 weeks but may last as long as 6 months or more depending upon the patient's condition. Nonoperative treatment is addressed in a previous section of this chapter, and thus, will not be discussed here.

There are several major indications for spinal surgery: neoplasms, infection, inflammatory disorders, and deformity. Discussion of the surgical indications and operative procedures for all of these conditions is beyond the scope of this chapter. Rather, we examine the most common indications for spinal surgery, the degenerative conditions of the lumbar spine: herniated nucleus pulposus, spinal stenosis, and instability with degenerative spondylolisthesis.

SURGERY FOR THE HERNIATED DISK

Natural History

In considering the surgical treatment of any disease process, the natural history must first be determined. An intervention is not warranted if the natural history of the disease is not altered in a beneficial manner. Classically, disk herniations present as leg pain and/or numbness after an episode of acute low back pain. However, herniations may be asymptomatic (6). Leg symptoms, such as pain, numbness, or weakness after a dermatomal distribution, are referred to as *radiculopathy*. Back pain may occur concomitantly or may precede radicular pain by as little as a few hours or as long as a few days. Quite often, the initial low back pain diminishes and the leg weakness, numbness, or pain persists. Variations in pain patterns may be explained anatomically. The sinuvertebral nerve may be irritated from disk and annular material encroaching on the posterior longitudinal ligament or from direct compression of this nerve. Disk herniation can lead to activation of the inflammatory cascade that chemically irritates the nerve root, producing leg pain, numbness, or weakness. Isolated leg pain may result from a large extruded herniated disk fragment that directly compresses the nerve root.

The natural history of asymptomatic lumbar disk herniation is unknown, as is the natural history of untreated symptomatic herniations. This is so because in the presence of symptoms, treatment interventions have always occurred. Treatment may be as simple as activity modification, often combined with the use of over-the-counter medication. The natural history of the most severe variation of a herniated disk, the cauda equina syndrome, is also unknown (7).

Hakelius found in a 1970 study that 75% of patients with herniated nucleus pulposus responded to conservative treatment, usually within 10 to 30 days. Only 19% of patients went on to require surgical treatment (8). In 1983, Weber performed what is still considered the “classic” study on the treatment of lumbar disk herniation (9). This study is often misquoted as a natural history study, when in fact it is not. Two hundred eighty patients were studied, of which 127 were randomized to conservative and surgical treatment groups. Of the 280, 67 were selected for surgery based on their clinical symptoms, whereas 87 responded to conservative treatment and therefore were not randomized. Among the randomized patients, 17 crossed over from nonoperative to surgery in the first year (26%); at that time (1 year) 90% of the patients had a good outcome with surgery as compared with 60% with nonoperative treatment. However, at 4-year and 10-year follow-up intervals there were no statistically significant differences in outcome between the two groups. Weber's study also showed that the type of treatment did not alter recovery of motor or sensory functions. This confirmed Hakelius' earlier finding (8). With mild weakness, motor strength tends to return over a 3- to 6- month period. However, if the motor deficit is severe (less than grade 3 out of 5 strength), the recovery is often insidious and incomplete. If the onset of muscle weakness is temporally related to the onset of symptoms, then surgery is the treatment of choice.

When these studies are carefully analyzed, several methodologic flaws are found. The control group underwent significant clinical intervention—a 2-week hospital stay. Many patients were excluded based on their symptoms (54.3%). If patients in the nonoperative groups had disabling symptoms, they underwent surgery (26%). Because patients were transferred from the nonoperative treatment group during the study period, the outcomes of this treatment group were actually worse than reported. These studies demonstrate that short-term relief of symptoms is better with surgery, but the long-term patient outcomes are not significantly different when the conservative approach is compared with surgery, at least not in patients whose pain is not intractable. Tendon reflexes did not usually recover after either conservative or surgical treatment. Approximately one-third of the patients in both groups were left with some sensory deficit that did not influence their overall

function.

More recently, Saal and Saal reported 90% good or excellent outcomes for 64 patients with lumbar disk herniations (10). These patients were treated with epidural steroid injections and active physical therapy. Surprisingly, the results were not affected by either the size of the disk herniation or the presence of a neurologic deficit. Only three of 15 patients with an extruded fragment required surgery. They also reported a 75% to 100% resorption of the herniation in a smaller group of patients, whereas another 36% had a 50% to 75% decrease in size of the disk herniation (11). A follow-up study demonstrated that the larger the disk herniation, the greater the resorption (12). Thus, the presence of a disk herniation is not in and of itself an indication for surgery. And, when surgical risk is poor, patients can be advised that over time the chance of recovery is good.

Finally, disk herniations may be present without producing any symptoms at all. Two studies have demonstrated a large incidence (21% to 28%) of posterior or posterolateral disk herniations in asymptomatic subjects (6,13). In these same studies, disk bulges were found in 52% to 56% of patients. The asymptomatic herniations, like symptomatic herniations, are most common at the L-4 and L-5 levels and least common at the L-1 and L-2 levels. This distribution corresponds to that of disk degeneration— more caudal disk levels degenerate at earlier ages and to a greater degree. Thus, the presence of a disk herniation discovered on an imaging study is not an indication for surgery in the absence of clinical signs and symptoms that can be localized to the imaged abnormalities.

Indications

Interventions for medical conditions are expected to alter the natural history of a pathologic process. If there is no benefit to an intervention, the risks of the intervention cannot be justified. Interventions must also be cost effective. As stated above, patients who undergo surgery for a herniated lumbar disk tend to have more rapid relief of symptoms, but good long-term results are typically obtained in those patients who are treated conservatively. It must be stressed that the patients' diagnosis must be confirmed by history and must correlate with objective physical findings and imaging findings.

The only absolute surgical indication for lumbar disk herniation is the cauda equina syndrome (7). This syndrome is characterized by bilateral lower extremity weakness and pain, saddle anesthesia, urinary retention, and diminished rectal tone. Although there is little debate that surgery is indicated for a patient with a cauda equina syndrome, the timing of surgery remains somewhat controversial. Kostuik et al. showed that there was little difference in functional outcome whether surgery was performed within 6 hours or after an average of 3.3 days (7). Shapiro demonstrated better results if surgery was performed within 48 hours (14). In a metaanalysis of the literature, Ahn et al. found worse outcomes when surgery was delayed by more than 48 hours after the onset of symptoms (15). Once this diagnosis has been established, surgery should occur as rapidly as it can safely be performed. There is no role for observation in the treatment of a cauda equina syndrome, but there is also no reason for an unplanned rush to the operating room.

Several relative indications for surgery for lumbar disk herniation exist. These include gross motor weakness, particularly when progressive, loss of bowel or bladder function, recurrent incapacitating episodes of radicular leg pain, and severe leg pain persisting despite 4 to 6 weeks of appropriate conservative treatment. The best window of opportunity for successful surgery is before 3 to 6 months. Persistent symptoms may be due to chronic pathologic changes in the nerve root that are related to prolonged compression. Motor weakness is a relatively strong indication for surgery. Although Weber's study demonstrated that patients with a 75% to 100% resorption of the herniation and neurologic deficits may recover fully without surgery, his study did not include patients with severe motor deficits, and many surgeons believe (without real scientific proof) that recovery is accelerated with surgical intervention (9).

When evaluating recurrent radiculopathy as an indication for surgery, it is important to note that the likelihood of a recurrence increases with each recurrence. After the first episode of radiculopathy, 90% of patients' symptoms resolve and do not recur. After a second episode of radiculopathy, 90% of patients' symptoms improve, but 50% of patients will have recurrent symptoms. After the third episode, 90% of patients will get better, for a period of time, but 90% of these patients go on to have recurrent sciatica. Surgery, therefore, should be considered after the second episode of radiculopathy (caused by a disk herniation) and strongly recommended after the third.

If failure of conservative treatment is considered as an indication for surgery, the treatment should have been appropriate. Patients should undergo no more than 2 to 3 days of bed rest; a trial of nonsteroidal antiinflammatory medications taken regularly for 3 to 4 weeks; and possibly nerve root blocks, epidural injections, and physical therapy. After 4 to 6 weeks of such treatment, and only if the patient has appropriate physical findings such as a positive straight-leg raising test that are objectively confirmed on a radiographic study (computed tomography, magnetic resonance imaging, or myelogram), the patient may be considered a surgical candidate. This, of course, assumes that the patient does not develop a cauda equina syndrome or major motor deficits. Potential secondary gain issues, including worker's compensation claims and litigation, must be evaluated before determining a patient's suitability as a surgical candidate. In addition, a psychological evaluation may be appropriate for some patients (see Section C of this chapter). Patient selection is crucial to successful postoperative outcome. The point cannot be overemphasized that the patient's history must be substantiated by physical findings and radiographic studies. Patients with secondary gain issues have poorer surgical results, as do patients demonstrating nonorganic physical findings (16). In addition, patients with diabetes mellitus may have a relative contraindication to surgery, as their outcomes have been shown to be poorer than patients without diabetes (17).

In conclusion, there is a lack of prospective randomized data on surgical indications for lumbar disk herniation. In “Consensus summary on the diagnosis and treatment of lumbar disk herniation,” published in *Spine*, the panel recommended further prospective study to better define surgical indications and determine the timing of surgical intervention during the course of the symptomatic period (18). At the present, every patient must be evaluated on a case-by-case basis, taking into account the issues discussed above.

Alternatives and Procedures

There are two goals in the treatment of lumbar disk herniations: Relieve neural compression and avoid creating instability. One should look at this type of surgery as a procedure focusing on the nerve root and not on the disk. Success in treating lumbar disk herniations relies heavily on patient selection. The alternatives for treatment include the following:

A. Chemonucleolysis
B. Percutaneous diskectomy
    1. Mechanical
    2. Laser
C. Open surgery
    1. Posterior approaches
        a. Standard laminotomy and diskectomy
        b. Limited approach/microdiskectomy
        c. Far lateral diskectomy (Wiltse approach)
    2. Anterior approaches
D. Arthroscopic diskectomy

Chemonucleolysis

Chemonucleolysis was first used clinically by Lyman Smith in 1964. The procedure involves injection of chymopapain, an extract of latex of papaya. Chymopapain is a proteolytic enzyme that affects the proteoglycan-water aggregation in the nucleus pulposus. Proteoglycans are negatively charged molecules that combine with water. Glycosaminoglycan side chains are cleaved by the positively charged chymopapain molecule. Proteoglycans then lose their ability to hold water. The loss of water causes the disk to deflate and release pressure from the nerve root. Chymopapain has no effect on collagen molecules except in very high concentrations; thus, the majority of the disk is left intact.

Chemonucleolysis is indicated only for contained disk protrusions causing sciatic pain that have been unresponsive to conservative care. This injection is contraindicated when there are extruded and sequestered disk herniations and in patients with a cauda equina syndrome. Relative contraindications include previous chymopapain injections, previous surgery for lumbar disk herniation, spinal stenosis, severe degenerative disk or facet osteoarthritis, and spinal instability (spondylolisthesis) (19). Chymopapain should not be used during pregnancy or in disk herniations above L-1. The final contraindication to chymopapain injection is an immunoglobulin E–mediated sensitivity, which is present in 0.35% of patients. Chymopapain should therefore be avoided in patients with a history of sensitivity to products containing chymopapain, such as meat tenderizers, beer, cheese, and toothpaste. The procedure should be preceded by testing to identify

chymopapain-sensitive individuals.

Procedure. Chemonucleolysis is usually performed under local anesthesia with sedation as needed. The lateral position is recommended, although it may be performed with the patient prone. The correct level should be identified with fluoroscopy. The sacrum must always be visualized and the preoperative radiographs checked for lumbarization or sacralization of vertebra to ensure the correct level is approached. The correct needle insertion site is approximately 10 cm lateral to the posterior midline of the back and the angle of needle insertion is 45 degrees to the horizontal plane of the back. Under fluoroscopic guidance, the needle is advanced to the correct disk space. The tip of the needle should be centered in the disk space on both anteroposterior and lateral x-ray views. Once this position is verified, 0.75 to 1.00 mL of chymopapain is injected [1,000 units of chymopapain (Chymodiactin)]. Care must be taken not to injure nerve roots or to inject into the thecal sac, because chymopapain is neurotoxic.

The procedure is performed on an outpatient basis. Severe spasm and back pain may occur immediately after injection. This can be managed with muscle relaxants and oral analgesics. Lumbar corsets may be used for comfort. Exercise and physical therapy are begun after 4 weeks.

Automated Percutaneous Lumbar Diskectomy

Addressing a herniated disk through a needle is achieved by chemonucleolysis, as described previously. Drug- and technique- related complications triggered the interest in alternative methods, which did not involve the use of pharmaceuticals. First introduced in Japan in the mid-1970s, the use of a mechanical device to remove a herniation using a percutaneous method was approved for use in the United States and elsewhere in the mid-1980s. The first, more widely used device to accomplish this was the Nucleotome System (20). The technique involves inserting a trocar into the disk, passing a cannula over the trocar until it rests on the annulus, and then penetrating the annulus with a trephine. Once the annulotomy is made, a probe is inserted through the cannula into the disk. The probe is then activated to start the cutting and suctioning actions. The principle is to cut the disk into fragments, which are washed out through the probe. The probe is worked around inside the disk space to accomplish the maximum amount of disk removal. An alternative technique uses laser technology to remove disk tissue (21).

The results of percutaneous diskectomy using the above techniques remain open to question.

Standard Laminotomy and Diskectomy

Laminotomy with diskectomy has long been the “gold standard” for treatment of lumbar disk herniations. Approximately 300,000 procedures a year are performed in the United States. Patient satisfaction approaches 95% when selection is appropriate. Statistically, the complication rate is low. There is approximately a 5% rate of recurrent disk herniation at the same level, which may occur anytime from several hours to several years after the index operation. The infection rate appears to be less than 0.5%, the risk of neural injury is less than 0.5%, and the mortality rate is less than 0.1%. The most frequent complication is a dural tear, which after treatment does not influence the end result. However, if nerve roots are injured when the dura is torn, long-term pain and neurologic deficit may ensue.

Procedure. Although there are differences in how this procedure is performed, the following describes the authors' preferred method. The patient is placed in the kneeling position on an Andrews-type frame. This position allows the abdomen to hang freely, thereby diminishing epidural venous return and minimizing intraoperative bleeding. The procedure is performed under loupe magnification with the use of fiberoptic headlights. A 4-cm incision is centered over the midline of the back. The interspinous spaces may be palpated along with the iliac crest. Radiographic localization should be performed to identify the correct level. The lumbodorsal fascia is incised in the midline, followed by unilateral exposure of the spinous process and lamina of the level above and below the disk herniation. Subperiosteal dissection of the paraspinal muscles is performed laterally to the facet joint. Care is taken to preserve the facet capsule to avoid creating instability. A Taylor or self-retaining retractor is placed. The correct level is again confirmed by palpation or radiograph. The ligamentum flavum is then identified and elevated off of the inferior portion of the cephalad lamina with a curette. A hemilaminotomy is performed by removing a small amount of the inferior portion of the superior lamina (Fig. 76B-2). The end point of laminar resection is the area where the superior portion of the ligamentum flavum inserts. An angled elevator may then be passed from cephalad to caudal beneath the ligament in the epidural space. This maneuver separates the ligament from the underlying dural sac. Appropriate parts of the ligament are then removed with Kerrison rongeurs. Due to the distal takeoff of the S-1 nerve roots, an L- 5 to S-1 disk herniation may be approached by beginning the hemilaminotomy inferiorly on the S-1 lamina as opposed to superiorly on the L-5 lamina. In either case, the epidural space is visualized, and additional bone from the lateral aspect of the lamina is removed as needed to safely identify the lateral edge of the nerve root. The root may be immobile and erythematous when observed and can be mistaken for a disk fragment. The nerve root is gently mobilized medially with an elevator and, once mobilized, may be retracted with a nerve root retractor. A sequestered disk fragment should be visible at this point and may be removed with pituitary rongeurs (Fig. 76B-3). A bulge in the annulus fibrosus (protrusion) causing root compression may be incised and the disk space then entered with a pituitary rongeur to remove any free disk fragments. Nuclear material not easily removed should be left intact to preserve disk stability. At the end of the operation, the nerve root should be freely mobile from the takeoff on the thecal sac and out through the foramen. The foramen should be probed with a Woodson elevator or similar to ensure that no fragments have migrated that may compress the nerve root and to ensure that there is enough space in the foramen for the exiting nerve root. The epidural space should be probed ventrally as well to ensure that no free fragments remain. Hemostasis is achieved. The dura may be left exposed, covered with a substance such as Adcon (Gliatech Inc., Cleveland, OH) or with a free fat graft. The effect of an interposition membrane on final outcome has been studied (22). Clinical outcome does not depend on which material is used to prevent epidural fibrosis formation. The patient may be ambulatory with assistance the day of surgery and discharged or, more typically, stay overnight. Walking is encouraged postoperatively, while lifting, bending, and twisting are avoided for 4 to 6 weeks.

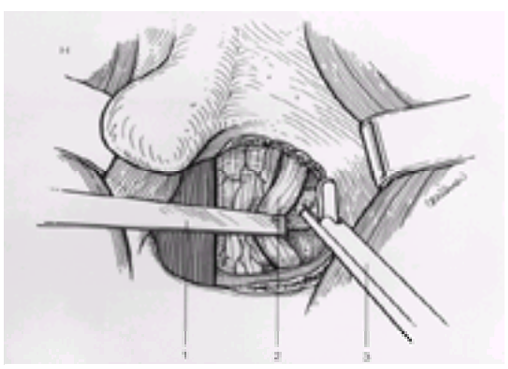

Figure 76B-2. Hemilaminotomy. (1, nerve root retractor; 2, spinal nerve root; 3, pituitary rongeur.) (From An HS, Riley LH, eds. *An atlas of surgery of the spine*. London: Martin Dunitz Ltd; and Philadelphia: Lippincott–Raven, 1998:188.)

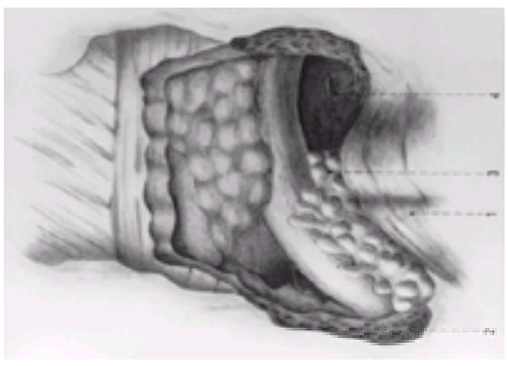

Figure 76B-3. Sequestered disk fragment. (1, zygapophyseal articulation; 2, resection extended caudally and laterally; 3, loose intervertebral disk sequestrum; 4, perforation site and height of the intervertebral space.) (From Reulen H-J. Neurosurgical operations. In: Bauer R, Kerschbaumer F, Poisel S, eds. *Atlas of spinal operations*. New York: George Thieme Verlag, 1993:332.)

Limited-Approach Diskectomy/Microdiskectomy

Limited-approach diskectomy/microdiskectomy is similar to the standard laminectomy, but the skin incision is only 1 to 2 inches long, extending from the midpoint of one spinous process to the spinous process at the next level. The fascial incision is just lateral to the midline so as not to destroy the competency of the supraspinous ligament. Subperiosteal dissection should proceed as with standard laminectomy. The microscope may then be moved over the operative field. Some surgeons may use the microscope from the outset of the procedure. The procedure from this point on is similar to the standard laminotomy except for the use of the microscope. Most studies have demonstrated no statistically significant difference in patient outcomes when comparing the standard laminotomy and microdiskectomy. Postoperative care is also similar.

Far Lateral Diskectomy (Wiltse Approach)

When a lumbar disk herniation is located foraminally or lateral to the foramen, it may not be amenable to removal through standard midline posterior approaches. In these cases, a paraspinal muscle-splitting approach is used, as recommended by Wiltse. The patient is positioned in the kneeling position as for the standard diskectomy. The skin incision is two finger's breadths or approximately 4.5 cm from the midline. The length of the incision may vary. The fascial plane of dissection is between the multifidus and longissimus muscles. The fascia between these muscles is incised and curved medially at the distal end and laterally at the proximal end to aid in retraction (Fig. 76B-4). Finger dissection should split the plane between these muscles, and the transverse processes may be palpated below. Self-retaining retractors are placed. The transverse membrane between the transverse processes is visualized. A Kerrison rongeur may be used to detach the membrane from the superior facet, pars interarticularis, and inferior portion of the transverse process. The nerve root is usually displaced laterally by the disk fragment. Pituitary rongeurs are used to remove free fragments of disk. The disk space may then be entered to remove any remaining free fragments. Postoperative care involves ambulation the night of surgery, overnight hospital stay, and avoidance of lifting and bending for 4 to 6 weeks.

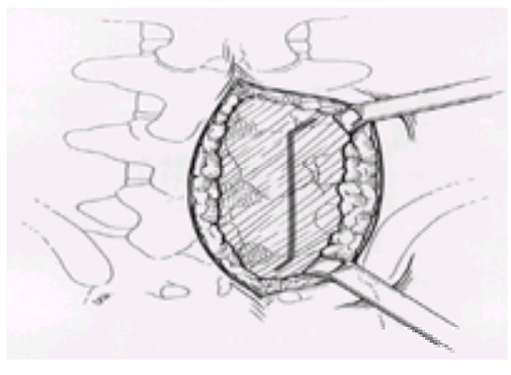

Figure 76B-4. The Wiltse paraspinal muscle-splitting approach. (From An HS, Riley LH, eds. *An atlas of surgery of the spine*. London: Martin Dunitz Ltd; and Philadelphia: Lippincott–Raven, 1998:196.)

Anterior Approach

An anterior approach, although possible, is rarely indicated for primary surgery on lumbar disk herniations. The surgical results are similar, but the risks and morbidity of this approach are much greater than posterior approaches and cannot be justified. The anterior approach is reserved for other anatomic abnormalities.

Arthroscopic Diskectomy

Arthroscopic diskectomy developed from biopsy techniques (23). This procedure is primarily used for disk protrusions at the L-4 to L-5 and L-5 to S-1 levels. Above these levels, disk herniations must be subligamentous to be removed safely. The procedure is contraindicated in patients with severe neurologic deficits, cauda equina syndromes, or migrated sequestered disks. Prior diskectomies and high-riding iliac crests may be relative contraindications to this procedure. No prospective randomized controlled trials have been performed comparing arthroscopic diskectomy with other techniques. Several authors have reported good results (24,25). It is a technically demanding procedure with a steep learning curve and should not be performed by surgeons without specialized training.

Procedure. The patient is placed prone on an adjustable radiolucent frame to flatten lumbar lordosis. The abdomen is left hanging freely to decompress Batson's plexus and reduce epidural venous bleeding. Fluoroscopy is used with the **C**-arm on the symptomatic side of the patient. Local anesthetics are used so that the patient is awake during the procedure and may respond as neural structures are approached. The triangular working zone on the disk surface is bounded by the nerve root superiorly and anteriorly, the transverse process inferiorly, and the superior facet medially. The skin entry point is identified by fluoroscopy and is at the disk level approximately 11 cm lateral to the midline. A 6-inch, 18-gauge spinal needle is passed at a 45-degree angle to the horizontal down to the disk space. The tip of the needle should be at the interpedicular level on the anteroposterior x-ray view. The needle tip should be at the posterior portion of the disk on the lateral x-ray view. Once the position is confirmed, the trocar is removed and a guidewire is passed through the spinal needle. The needle is removed, with the guidewire left in place. An arthroscopic cannula is then passed over the guidewire to the disk space. The annulus is identified. The nerve may then be probed with a small guidewire through the cannula. Cannulas are advanced into the disk space by cutting through the annulus with the trocars. Lidocaine-soaked patties may help alleviate annular pain. Pituitary rongeurs may be passed through the cannula, and under x-ray guidance, disk fragments are removed. A mechanical shaver also exists to aid in disk removal. The portals are closed with single stitches. Postoperative care is similar to standard diskectomy.

SURGERY FOR SPINAL STENOSIS

Clinical Syndromes

Spinal stenosis can be defined as a narrowing of the vertebral canal, lateral recesses, or vertebral foramina. Based on location, it can be divided into central (vertebral canal) or lateral stenosis. It can have different etiologies, most frequently degenerative, and does not always result in clinical symptoms. The most common symptom complexes are neurogenic intermittent claudication and radiculopathy.

Natural History

Patients with spinal stenosis tend to have an insidious onset of symptoms. Exacerbations may be produced by activity or trauma. However, very few natural history studies of lumbar spinal stenosis have been performed (6,27,28,29,30,31 and 32). Thus, predicting which patients will benefit from surgical intervention is difficult, if not impossible. Most of these studies include only small numbers of patients. In addition to the scarcity of clinical data, the natural history of spinal stenosis is further confounded by the limited knowledge of the pathophysiologic effects on compression of the spinal nerve roots and cauda equina.

In 1978, Blau and Logue reported on two patients with neurogenic claudication (26). One patient had no change in symptoms over a 7-year period and the other patient experienced a slight increase in difficulty ambulating with leg pain over 10 years. Several other small reports documented success of conservative treatment or insidious progression in the early neurosurgical literature. One study showed that a lumbar corset may provide relief of symptoms (27). In another study, myelography was found to be predictive of outcome with nonoperative treatment. Patients with complete or severe myelographic block fared poorly with conservative treatment (28). Five patients underwent conservative treatment after myelography. One patient had improvement in neurologic symptoms, whereas the other four patients remained stable. Over time, one patient's symptoms improved, whereas two remained the same and two deteriorated slightly. Obviously, the results of this study are not statistically significant due to the retrospective design and small sample size.

In 1991, Johnsson et al. performed a 3-year follow-up study on patients with lumbar stenosis, half of which were treated nonoperatively and half with laminectomy without fusion (29). Diagnosis was confirmed by partial block on myelograms. All patients showed evidence of neurologic injury by electromyography. They found that

in 32% of the patients the symptoms remained unchanged, 42% of the patients improved, and 26% deteriorated. The authors concluded that symptom progression was slow and conservative treatment could be safely exercised for 2 to 3 years. This study was followed by an observational study of 32 patients treated conservatively over a 4-year period (30). Only 15% of patients reported improvement in their pain on a visual analogue scale, whereas 70% remained unchanged. With respect to walking, one-third of the patients improved, one-third remained the same, and one-third deteriorated.

Another 35 patients were studied by Wardlaw and MacNab (31). These patients were treated nonoperatively, and success correlated both with a history of back pain of less than 5 years' duration and a history of leg pain for less than 6 months.

The largest study to date on nonoperative treatment of spinal stenosis was performed by Saal et al. (32). These data have yet to be published. Fifty-two patients were enrolled in this study. Nonnarcotic analgesics controlled pain in 33 of the 52 patients. Walking was unrestricted in 36 of the 52 patients. Only four patients ended up needing surgery.

None of these studies is prospective and randomized. In addition, the sample size is small in all of the studies. However, most patients seem to have symptoms that stabilize. Further study is required to validate the present natural history data. Currently, one cannot predict which patients will require surgical intervention. Once the natural history is known, risk factors for failure of conservative treatment can be identified. Current indications for surgical intervention for spinal stenosis are discussed below.

Indications for Surgery

The purpose of any surgical procedure for spinal stenosis is to improve function and diminish pain. As with all types of spine surgery, proper patient assessment is vital to surgical success. This is not a life-saving procedure, but one that should improve the quality of life. Each patient must be evaluated to rule out other causes of leg pain and claudication, such as peripheral vascular disease, referred hip or knee pain, or osteoarthritis of the hip or knee. The extent to which a patient's activities of daily living and lifestyle are affected is particularly important in deciding on surgical treatment.

As with lumbar disk herniations, a radiographic study that corresponds to the patient's symptoms is imperative before undertaking surgery. Patients should undergo at least 4 to 6 weeks of conservative treatment, including rest, nonsteroidal antiinflammatory medications, and physical therapy. Epidural steroid injections may be attempted, although they are controversial because of a lack of good scientific data about effect.

Persistent leg pain and poor function despite conservative treatment are the primary indications for surgery presuming other causes of pain have been excluded (33). Severe neurologic deficit is another indication for surgery (34). Duration of symptoms and response to conservative treatment should not delay surgical intervention when neurologic involvement is present. A relative indication for treatment is lifestyle alterations due to pain (33,34). If a patient has difficulty ambulating due to pain, surgery is indicated despite a lack of neurologic findings.

Contraindications to surgery may include poor overall medical health. However, chronological age is not an absolute contraindication to surgery (33,35). Physiologic age is a more critical factor. Radiographic findings in the absence of clinical symptoms are never an indication for surgery (6,36).

Most studies show a 70% improvement in pain and function as compared with preoperative levels. Patients should understand that the surgical procedure may not alleviate all of their pain. Some residual back and/or leg pain may persist after surgery. Preexisting degenerative arthritis may be a source of these persistent symptoms.

In general, surgery alleviates pain and improves function but may not reverse neurologic deficits. Results of surgery are better in patients with localized lesions rather than global changes. Postural improvement in symptoms was shown by Ganz to predict surgical success (37). Ninety-six percent of patients with postural improvement of symptoms had relief of pain after surgery. Only 50% of patients whose symptoms did not vary with posture had postoperative relief.

Several factors have been shown to predict poorer outcome in spinal stenosis surgery. Poorer outcomes may be expected if radiographic findings do not correlate with the patient's symptoms. Also, female gender, litigation, prior lumbar surgery, and concomitant spondylolisthesis have been associated with poorer outcomes (38,39).

Alternatives and Procedures

Alternatives to noninvasive conservative treatment of spinal stenosis include epidural steroid injections and surgical treatment. Surgical treatment for spinal stenosis involves decompression of the cauda equina, nerve roots, or both. Anatomically, compression may occur in several zones within the spine. Classic symptoms of neurogenic claudication are usually caused by central stenosis— that is, narrowing of the vertebral canal. This narrowing may be produced by thickening of the ligamentum flavum, osteophytes from the facet joints, and/or degenerative bulging/herniation of the intervertebral disk. Stenosis in the lateral recess usually produces radicular symptoms. The nerve root exits, after branching from the thecal sac, through the lateral recess, beneath the pedicle and out through the foramen. The lateral recess is bounded by the medial pedicle wall laterally, the posterolateral corner of the vertebral body, and the ligamentum flavum. Hypertrophy of the ligamentum flavum combined with a trefoil-shaped epidural canal creates the greatest risk for nerve root compression. Finally, foraminal stenosis involves the exiting nerve root only and produces radiculopathy. Foraminal narrowing may be caused by facet osteophytes, narrowing of pedicular distance between two levels because of loss of vertebral disk height, or disk bulging.

Surgical treatment for spinal stenosis must address the anatomic areas of nerve compression to be successful (40). In fact, a frequent cause of failure of surgical treatment is inadequate decompression in one of these anatomic regions or the failure to recognize that one of these regions is stenotic on preoperative films.

Principles

Every attempt should be made to identify the levels from which the patient's symptoms are produced. Not all radiographic stenotic levels must be decompressed. For most cases, the levels to be decompressed should extend from the pedicle above to the pedicle below the stenotic intervertebral segment. It is usually unnecessary to move more caudally to the lamina below or cephalad to the lamina above. For example, if stenosis is isolated to the L-4 to L-5 level, only the L-4 lamina need be resected. Decompression may proceed until a pulsatile dural sac is exposed. Central stenosis is decompressed in the midline and as far lateral as necessary. Lateral recess stenosis may require resection of the medial facet joint, whereas foraminal stenosis requires further facet resection. If an entire facet joint or greater than 50% of both facet joints at one level are removed to decompress the nerve roots, segmental instability may be produced (41). Instability is more likely to be created when intervertebral disk heights are normal. Degenerative disks with height loss and osteophyte formation may stabilize the segment. This is discussed below.

Laminectomy

The patient undergoes either general or spinal anesthetic and may be placed prone on either an operating room table with chest rolls, a Wilson frame, an Andrews table, or the Jackson table. The abdomen is left hanging freely to decompress the epidural veins. Care must be taken to keep pressure off of the eyes to prevent retinal ischemia. Compression stockings and/or sequential compression devices are used. The rate of deep venous thrombosis below the knee is 5% to 6% with stockings alone (42). The rate of proximal thigh deep venous thrombosis is much lower. Radiographs should be used to localize the correct levels for surgery; a midline incision is then made. The lumbodorsal fascia is identified and incised in the midline. Dissection continues subperiosteally to expose the spinous process, lamina, and facet joints bilaterally. The facet joint capsule is preserved. Leksell rongeurs are used to remove the spinous processes. A curette is then used to elevate the ligamentum flavum from the anterior surface of the inferior portion of the lamina (Fig. 76B-5). A Kerrison rongeur is used to resect the lamina from caudal to cephalad just medial to both facet capsules (Fig. 76B-6). A Woodson elevator may be used to ensure that the ligamentum flavum is not adherent to the underlying dura. This helps to prevent cerebrospinal fluid leaks. If the dura mater is adherent to the ligamentum, a high-speed diamond-tipped burr may be used to thin the lamina. If the lamina still cannot be elevated safely, it may be thinned to a flake of bone and left attached to the dura, as this should not cause neural compromise. Once the lamina is removed, the pedicle can be identified and the nerve roots found and traced out the foramen. If the lateral recess is narrow, the medial portion of the superior facet may be undercut to remove osteophytes and widen the foramen (Fig. 76B- 7). Alternatively, an osteotome may be used to resect the medial aspect of the facet joint.

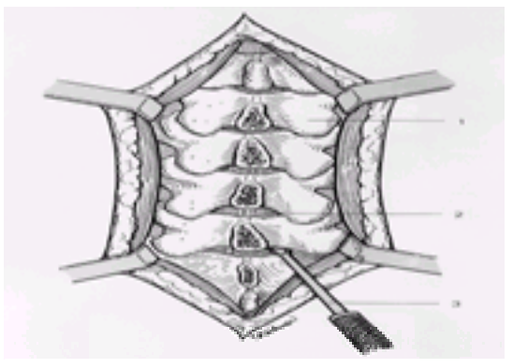

Figure 76B-5. Laminectomy in spinal stenosis. After exposing the ligamentation flavum, a curette or similar instrument is used to separate the ligament from the underside of the lamina. (1, L-2; 2, ligamentum falvum; 3, curette.) (From An HS, Riley LH, eds. *An atlas of surgery of the spine*. London: Martin Dunitz Ltd; and Philadelphia: Lippincott–Raven, 1998:192.)

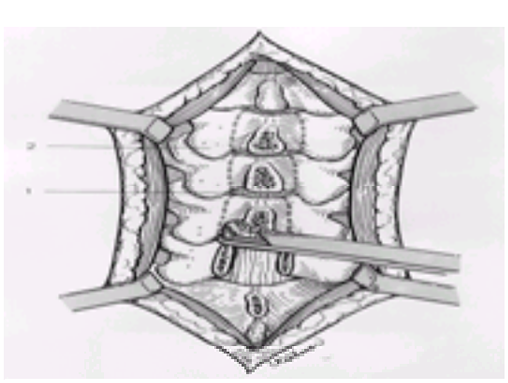

Figure 76B-6. Laminectomy in spinal stenosis. A Kerrison rongeur is used. Usually the laminectomy is done from caudal to cephalad. (1, ligamentum flavum; 2, L-2.) (From An HS, Riley LH, eds. *An atlas of surgery of the spine*. London: Martin Dunitz Ltd; and Philadelphia: Lippincott– Raven, 1998:192.)

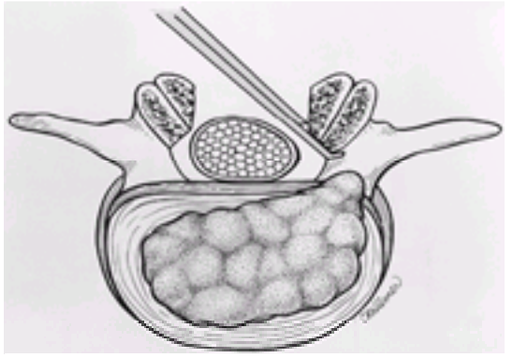

Figure 76B-7. Undercutting of the facet is usually done from the opposite side. (From An HS, Riley LH, eds. *An atlas of surgery of the spine*. London: Martin Dunitz Ltd; and Philadelphia: Lippincott–Raven, 1998:194.)

The disk space may then be inspected and any herniation removed. As long as the thecal sac is not compressed centrally and the symptomatic nerve roots are freely mobile from the thecal sac and out through the foramen, the decompression is complete. The procedure is repeated for additional stenotic levels. A free fat graft may be placed over the exposed dura or it may be left uncovered. Ambulation is begun the night of surgery in patients in whom fewer levels are decompressed. Walking is encouraged at home, although lifting, bending, and twisting are avoided for 4 to 6 weeks. Physical therapy is instituted as needed.

Limited Laminectomy

A limited-approach diskectomy dissection may be used if patient symptoms and radiographic stenosis are limited to one level and one side. Dissection is similar to a limited-approach diskectomy. The entire hemilamina on the affected side is resected, as is the ligamentum flavum. The facet may be undercut as needed to decompress the lateral recess and foramen, and the herniated nucleus pulposus is removed if present.

Fusion

The role and technique of fusion are discussed in the indications and techniques section on spinal instability.

SURGERY FOR DEGENERATIVE SPINAL INSTABILITY

Natural History

Defining degenerative lumbar spinal instability is difficult. No universally accepted description of what constitutes clinical lumbar instability has been provided. The set of clinical symptoms that is created by spinal instability has also not been defined. Several authors have attempted to describe instability through clinical, biomechanical, or radiographic definitions, but none has been uniformly agreed on. Regarding the lumbar spine, the most consistently used criterion for instability is either 10 degrees of angular motion or 4 mm of translation on controlled lateral flexion-extension radiographs (43). Determining the natural history of a diagnosis that cannot be defined is impossible. In this section, we restrict our comments to that spinal instability that presents as degenerative spondylolisthesis. In general, the natural history of degenerative spondylolisthesis is variable. It is not only the instability that is a problem in these patients, but narrowing of the spinal canal also occurs as one vertebra slips on its neighbor, causing stenosis (ring-on- ring phenomenon). Progressive loss of disk height also occurs (44). Rarely does the degenerative spondylolisthesis slip more than 30%.

There are at least two causes of degenerative spondylolisthesis. With aging, morphologic changes of the intervertebral disk and facet joints occur, which weaken the structure mechanically. Some facet joints are more sagittally oriented and are more likely to allow the slippage, which leads to degenerative spondylolisthesis (45). This type of spondylolisthesis occurs most commonly at L-4/ L-5. L-5 radicular pain is common as the slip progresses, due to compression of the L-5 nerve root. Lateral flexion-extension radiographs may show either increased translation or, more commonly, no abnormal motion.

Iatrogenic instability is created when decompression during a laminectomy is so significant that it produces an unstable motion segment. Biomechanical studies have demonstrated that removal of more than 50% of both facet joints or complete resection of one facet joint will destabilize a motion segment (41). In contrast, severe degeneration of the disk and osteophyte formation may stabilize the motion segment. Patients with spondylolisthesis and large disk spaces with minimal osteophyte formation will often be destabilized by posterior decompression (46).

Several studies have confirmed progression of spondylolisthesis (instability) after posterior decompression for spinal stenosis (46,47 and 48). These studies

demonstrated that the outcomes for surgery on spinal stenosis with degenerative spondylolisthesis are better when a fusion is added. Arthrodesis prevents progression of spondylolisthesis and stabilizes the decompressed segment, which may prevent back pain, leg pain, or both (49). An algorithmic approach to spinal stenosis and instability is shown in Figure 76B-8 (43).

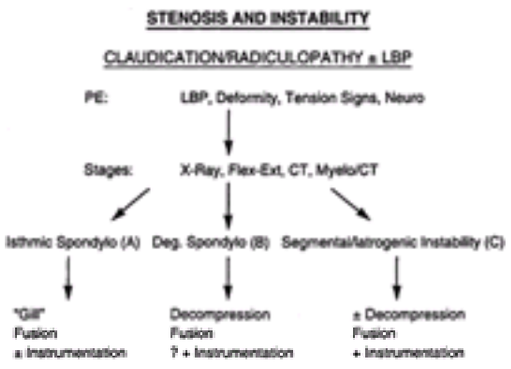

Figure 76B-8. Algorithm of the approach to a patient with spinal stenosis. (CT, computed tomography; Deg. Spondylo, degenerative spondylosis; Flex- Ext, flexion-extension; LBP, low back pain; Myelo/CT, myelogram/computed tomography; Neuro, neurologic findings; PE, physical examination; Spondylo, spondylosis.) (From Hanley EN Jr, Spengler DM, Wiesel S, et al. Controversies in low back pain: the surgical approach. In: Schafer M, ed. *Instructional course lectures*. Vol 43. Rosemont, IL: American Academy of Orthopaedic Surgeons, 1994:422.)

Indications

The indications for surgical treatment of spinal stenosis with degenerative spondylolisthesis are similar to those for isolated spinal stenosis. Degenerative spondylolisthesis has an undefined natural history and it is thus difficult to predict which patients require surgical intervention. One estimate of the percentage of patients with this condition that require surgery is 10% to 15% (50). According to Frymoyer, indications for surgery include cauda equina dysfunction with evidence of complete neurologic block at the corresponding level and progressive muscle weakness of functional significance (i.e., footdrop or quadriceps weakness). Progressive and incapacitating radicular pain and claudication failing to respond to conservative treatment are other indications (50). Radicular pain is a particularly important indication when activities of daily living are altered or sleep disturbance is present. Isolated back pain is not a good indication for the surgical treatment of this disease. Patients with isolated low back pain are best managed conservatively.

Several studies have examined the risk factors for poor operative outcomes (51,52). Instability was the most common cause of failure (52). Instability is likely to have diminished since the routine use of arthrodesis when decompressing spinal stenosis associated with degenerative spondylolisthesis was shown to be more effective (46). As one might expect, increased age, multiple medical comorbidities, and longer periods of observation of symptomatic patients were associated with increased risk of surgical failure (51,52 and 53).

As with all procedures on the spine, the patient selection process is crucial. Subjective complaints must be verified objectively with physical findings and corresponding lesions on roentgenographic studies. Surgery is not indicated in asymptomatic patients with a spondylolisthesis.

Surgery for spinal stenosis involves decompression of compromised nerve roots. When degenerative spondylolisthesis is present, most surgeons feel that a concomitant intertransverse process arthrodesis is indicated (54). A controversial issue remains if and when instrumentation should be used to augment the fusion.

In 1991, Herkowitz and Kurz demonstrated superior results in patients who underwent decompression with posterolateral intertransverse process fusion as compared with decompression alone (46). Fifty patients were prospectively randomized into the two groups. The groups were statistically well matched. At 3-year follow-up, back and leg pain was significantly better in the fusion group. In addition, the spondylolisthesis increased in only 28% of the patients with a fusion, whereas 96% of patients had slip progression without a fusion. Thirty-six percent of patients had a radiographic pseudarthrosis but the presence of a pseudarthrosis did not appear to affect the clinical outcome (“stable pseudarthrosis”). The only time a fusion may not be indicated is when patients have underlying systemic disease, which may greatly increase the risk of complications (53).

Newer fusion techniques have been advocated such as posterior lumbar interbody fusion and anterior lumbar interbody fusion, but no prospective, randomized controlled trials have been performed. However, fusion rates tend to be high with these techniques.

The use of instrumentation to augment fusion in these cases is more controversial (55,56 and 57). The purpose of internal fixation is to add additional stability to the spine, allow correction of deformity, protect neural structures, increase the fusion rate, and decrease rehabilitation time. However, pedicle screw placement is a technically demanding procedure. Screws are placed in a structure that is only a few millimeters larger than the screw. Improper positioning of screws can lead to loss of fixation and neurologic injury. In addition, pedicle fracture and screw breakage are known complications.

In one trial comparing instrumented with uninstrumented fusions, Fischgrund et al. found that while the fusion rate was higher with instrumentation, there was no statistically significant difference in clinical outcome (55). France et al. performed a multicenter, prospective, randomized study that also found no difference in patient outcome whether or not instrumentation was used (58). In contrast, a large cohort study on pedicle screw fixation concluded that the benefits of screw usage outweighed the risks (56). The instrumented group had an 89.1% fusion rate as compared with the 70.4% fusion rate without instrumentation. Improved spinal alignment, shorter time to fusion, better clinical outcome, and better neurologic recovery all characterized the instrumented group as compared with the uninstrumented group. Reoperations, medical complications, and deaths were similar between the two groups. Nork et al. found that patients who underwent decompression and instrumented fusion for degenerative spondylolisthesis had improved functional outcomes using standardized Short Form-36 questionnaires (59). This is the first study to examine functional outcomes in relation to surgical results. However, there was no uninstrumented control group with which to compare the results. Thus, at this point, no consensus can be reached on the use of instrumentation in augmenting fusion after decompression for degenerative spondylolisthesis.

Accepted surgical indications for the use of pedicle screw fixation usually include (a) correction of deformity (kyphosis, scoliosis), (b) fusion of motion segments after decompressive laminectomy, (c) recurrent spinal stenosis with iatrogenic spondylolisthesis, and (d) translational motion of greater than 4 mm in flexion and extension or greater than 10 degrees of angular motion as compared with adjacent levels on flexion and extension.

In the authors' experience, instrumentation is best used to augment fusions in younger patients and patients with large intervertebral disk spaces. In older patients with osteoporotic bone, instrumentation is best avoided to decrease the operating time and reduce complication risk and secondary hardware dislodgment. Many degenerative spines have narrowed disk spaces and bridging osteophytes, which may confer stability and thus obviate the need for instrumentation. Although no solid data exist, lateral flexion-extension radiographs may assist in the decision-making process. If no gross motion occurs, instrumentation may be avoided. With gross motion preoperatively, the likelihood of the spondylolisthesis progressing after decompression is high and the use of instrumentation should be considered.

Newer instrumentation techniques such as the use of metal (stainless steel or titanium) cages have been advocated. These are alternative techniques for obtaining a fusion, but no prospective randomized clinical trials have been performed. Decompression is still required to treat the stenosis. These modern trends will require further study prior to advocating their use.

Alternatives and Procedures

The alternatives for interventional treatment of spinal stenosis with degenerative spondylolisthesis include epidural steroid injections and surgery. Epidural steroid injections are discussed in Section D of this chapter. The surgical treatment involves decompression for the spinal stenosis. After decompression there is an increased likelihood of progression of the deformity without concomitant fusion, as well as poorer relief of back and leg pain (46). The majority of data now supports the addition of an arthrodesis to decompression for the treatment of spinal stenosis with degenerative spondylolisthesis.

Current alternatives include intertransverse process arthrodesis alone or in combination with instrumentation. Also, a limited- approach “lumbar laminaplasty” technique has been advocated.

Intertransverse Process (Posterolateral) Fusion

Patient setup for this procedure is similar to that for spinal laminectomy. The skin incision extends from one level above to one level below the fusion area. A decompression is performed as described in the section on spinal stenosis. The dissection is similar except that arthrodesis requires exposure of the transverse processes. Subperiosteal dissection is performed laterally down the lamina and over the facet joint, usually removing the capsule. Dissection proceeds cephalad around the pars interarticularis out over the dorsal surface of the transverse processes to be fused. Facet joints at the level above and below the fusion levels should be preserved, along with their capsules. Transverse processes should not be broken, and the intertransverse membrane should not be penetrated anterior to the transverse process during the dissection. The facet joints, lateral aspect of the superior facet, the pars interarticularis, and the dorsal surface of the transverse processes are decorticated using either an osteotome or power burr. This prepares the recipient bed for graft placement. The graft is then harvested from the iliac crest, usually through the same incision. If the patient has a wide pelvis, a separate incision is made directly over the crest. On one side the subcutaneous fat is elevated from the lumbodorsal fascia. The posterior superior iliac crest is identified. The fascia is split in line with the iliac crest and the muscle is dissected subperiosteally over the outer table of the ilium. An osteotome is used to remove corticocancellous strips of bone from the outer table of the ilium. Gauges and curettes are used to remove additional cancellous bone down to but not penetrating through the inner table of the ilium. The graft is then divided in half and packed between the decorticated transverse processes to be fused (Fig. 76B-9).

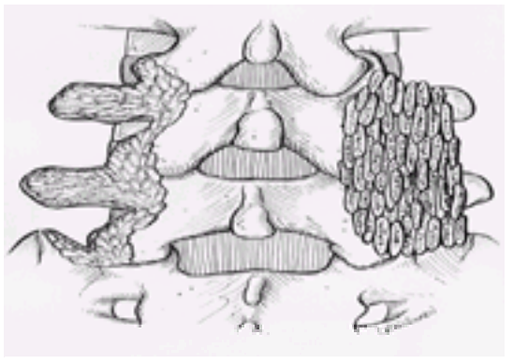

Figure 76B-9. Posterolateral fusion. Bone is placed over the transverse processes. (From An HS, Riley LH, eds. *An atlas of surgery of the spine*. London: Martin Dunitz Ltd; and Philadelphia: Lippincott–Raven, 1998:218.)

Postoperatively a lumbosacral orthosis is used for at least 3 months to stabilize the back and allow the fusion to heal. Ambulation and physical therapy are begun the day after surgery.

Instrumentation—Pedicle Screw/Rod Constructs

When a fusion is augmented with instrumentation, the setup and dissection are similar to those for arthrodesis (57). After decompression is performed, the pedicle screws are placed. The entry point for pedicle screw placement is identified. The entry occurs at the junction of the intertransverse process line horizontally and the lateral edge of the superior facet (2 to 3 mm lateral to the pars interarticularis) vertically (Fig. 76B-10). This point is 1 to 2 mm below the facet joint. A burr is used to open the dorsal cortex and a marker is placed. Radiographs are then taken to check the entry site and direction of the markers. Preoperative computed tomography or magnetic resonance imaging scans will help locate the entry point and direction of screw placement.

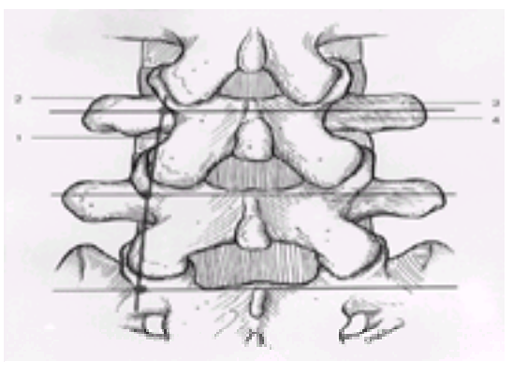

Figure 76B-10. Pedicle screw entry points. Typically the entry point is at the crossing of a vertical line connecting the lateral edges of the bony crest extending from the superior articular facets and a horizontal line which bisects the transverse process. (1, pars interarticularis; 2, transverse process; 3, interim edge of facet joint; 4, lateral edge of crest.) (From An HS, Riley LH, eds. *An atlas of surgery of the spine*. London: Martin Dunitz Ltd; and Philadelphia: Lippincott–Raven, 1998:231.)

A pedicle probe is used to sound the pedicle. The depth may be estimated from preoperative scans. Care must be taken to check the radiographs for cephalad/caudal direction of screw placement and to direct the probe medially. The most common error is to penetrate the lateral pedicle wall. Once the pedicle is sounded, a small probe is placed to palpate the medial, lateral, inferior, and superior walls of the pedicles. No holes in the pedicle should be present. If a hole exists, the entry path must be redirected. The hole is then tapped and reprobed to ensure that the tap did not violate a pedicle wall. If a decompression has been performed, the medial and inferior pedicle wall can be directly visualized to check for pedicle fracture. These two directions are the most critical, as the nerve root passes just medial and inferior to the pedicle.

At this point, the autogenous bone graft should be placed so that the hardware does not block its insertion. The screws are then placed. Screw diameter should be measured off of the preoperative studies. The screw diameter should fill the pedicle but be no larger than the inner cortical diameter of the pedicle. Ideally, all screws should be parallel to the end-plates.

Two types of connections are possible. Plates may be placed directly over the screws on each side of the spine. Washers then connect the plate to the screws (Fig. 76B-11). The second option involves connecting rods to the screws on both left and right sides. Many different implant systems are available. The rods should be bent into anatomic lordosis and fashioned to preserve sagittal alignment. Adding a cross connector between the left and right rods increases torsional rigidity. A brace may or may not be used postoperatively. Physical therapy is begun the day after surgery. The usual hospital stay is 3 to 4 days. The fusion usually takes a minimum of 6 to 9 months to fully consolidate.

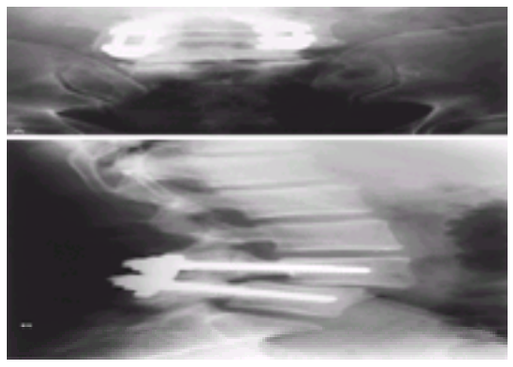

Figure 76B-11. Anteroposterior **(A)** and lateral **(B)** radiographs of a fusion with screws and plates.

Laminaplasty

A newer technique that has not yet gained wide acceptance is lumbar laminaplasty. This is a limited approach procedure indicated for one-level stenosis only. Bilateral nerve compression may be addressed. The significant advantage of this procedure is that stability may be preserved in patients with low-grade spondylolisthesis without performing a large fusion operation. The approach does not sacrifice the spinous process, the supraspinous ligament, one hemilamina, or either facet joint and thus preserves segmental stability.

A unilateral limited approach similar to that for a diskectomy is performed on the more symptomatic side. The lumbodorsal fascia is not incised in the midline but several millimeters toward the symptomatic side to preserve the supraspinous ligament. The hemilamina is resected as for limited laminectomy. An osteotome is then used to thin the spinous process on the more symptomatic side. The anterior surface of the spinous process is undercut to increase visualization to the contralateral side. Decompression is performed on the symptomatic side by removing the hemilamina and ligamentum flavum. The contralateral side may then be decompressed by retracting the thecal sac ventrally and using a Kerrison rongeur under direct vision to resect the ligamentum flavum and undercut the superior facet. Decompression is complete, but stability is preserved. This operation may be particularly useful for elderly patients in poor medical health who need symptomatic relief without the risk of a large fusion operation (60).

CONCLUSION

It should be understood, based on the preceding, that surgery for lower back pain is rarely indicated. In the majority of patients, pain will respond to nonoperative treatment. With the appropriate diagnosis, indications and technique, surgery can be extremely successful and return many patients to a high quality of life. When diagnosis, indications, and techniques are poor, disastrous results can occur. The right patient, right diagnosis, right indication, and right technique are the “four R's” of spinal surgery.

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CHAPTER 76

C. Failed Back Surgery Syndrome

Anne Louise Oaklander and Richard B. North

DEFINITIONS

Failed back surgery syndrome (FBSS) refers specifically to persistent or recurrent, chronic pain after one or more surgical procedures on the lumbosacral spine. *Failed back syndrome* commonly refers to the same condition, although it more properly describes persistence of back pain after unspecified treatment. The term *failed back* commonly is used to refer to both circumstances, but it implies functional failure of the back, as opposed to failure of treatment or surgery.

EPIDEMIOLOGY

Like other diseases with iatrogenic components, FBSS has a prevalence proportional to the prevalence of lumbosacral spine surgery. In the United States, where spine surgery exceeds 300,000 operations per year (1,2), 10% to 40% of lumbar spine operations result in FBSS (3,4 and 5). In the context of more than 25% point prevalence and more than 80% lifetime incidence of low back pain in the general population (6), the impact of these figures should create concern.

The first report of FBSS (7) followed the original description of surgical treatment of lumbar disk disease (8) by only 1 year. New invasive procedures such as percutaneous diskectomy and chemonucleolysis, while reducing some morbidities, have broadened the indications for treatment and thus added new categories of treatment failures. Finneson's aphorism “No matter how severe or intractable the pain, it can always be made worse by surgery” (9) should be kept in mind.

ETIOLOGIES

Patient Selection

Inappropriate or premature selection of patients for surgery is the most common cause of FBSS (10,11,12,13,14 and 15). Retrospective reviews of FBSS patients indicate that less than half had met standard criteria for their initial operation (11). Patients deterred from inappropriate surgery at the neurosurgical evaluation may continue to “doctor shop” until they find a willing surgeon. Thus, inappropriate behavior by both patient and physician can contribute to FBSS. The natural history of low back and sciatic pain, including that from disk herniation, is ultimately favorable in most cases, so if the indications for surgery are unclear, surgery can often can be delayed to attempt conservative management or to allow more time for decision making, with little effect on long-term outcome (16).

Nerve Injury

The second most common cause of FBSS is persistence of pain due to irreversible neural injury. This can occur despite appropriate patient selection and successful performance of the surgery. Preoperatively, it should be explained to the patient that the primary goal of surgery is to prevent further worsening rather than to reverse existing damage. In a patient who needs surgery (because spontaneous recovery is not expected) it is usually unrealistic to expect a complete return to full premorbid function with total absence of pain postoperatively. The surgeon and patient should discuss the odds of achieving various levels of pain relief. Equipped with realistic expectations, a patient with partial pain relief after surgery may consider this a satisfactory outcome rather than FBSS.

Persistent neural injury can be divided into two types; these can occur alone or in combination. The first, which largely affects the dorsal roots, consists of direct injury or death of neurons (e.g., due to spinal root compression by a herniated disk). Risk factors for this primary form of damage include the severity of the lesion, closer proximity to the neuronal cell bodies, and longer duration of the lesion. It has been noted that delaying decompression of acute disk herniation for longer than 6 months after onset is more likely to result in persistent postoperative pain. The condition of the patient, including age, coexisting neuropathy, and other medical factors, may also influence the recovery of neural function after surgical decompression. In general, the severity of loss of primary afferent neurons has been shown to be a risk factor for chronic neuropathic pain after several types of neuronal injuries (17,18).

In contrast, a second type of chronic neural injury can continue to improve long after surgery. It consists of transsynaptic changes in higher-order sensory neurons within the central nervous system (CNS). It has long been known that repetitively stimulating nociceptive nerve terminals leads to local sensitization and hyperalgesia but was only more recently appreciated that there are also effects on cells within the spinal cord and brain. The development of reliable animal models of neuropathic pain has enabled investigation of these chronic alterations in connectivity and organization; however, most have not been confirmed in CNS tissue from human pain patients. This postinjury response, described in detail in Chapter 19, includes reversible as well as irreversible physiologic changes such as central sensitization, complex pharmacologic changes, and frank anatomic changes within the spinal cord and brain (e.g., sprouting of nonnociceptive mechanoreceptive neurons into nociceptive pathways within the substantia gelatinosa) (19,20 and 21).

It is important to explain to patients that just as their muscles and bones require months to heal after their surgery, injured neural tissues may continue to normalize over months and years as well. One can also hope that partial pain relief after surgery will lead to improvements in psychosocial function, which may allow improved tolerance (and perhaps descending antihyperalgesic effects) of any residual pain. Sometimes one positive medical intervention is enough to shift the FBSS patient out of a downward spiral into an upward one that leads to improvement in quality of life. That pivotal treatment is more likely to be a rehabilitation program, treatment of depression, or medical control of pain than another surgery.

Technical Success of Surgery

A less common cause of FBSS is inadequate surgery. Examples include the persistence of unrecognized lateral recess stenosis or lateral disk herniation. A sequestered free disk fragment can be missed (22,23 and 24). Myelography can be definitive if the postsurgical magnetic resonance imaging (MRI) is equivocal.

Occasionally spinal instability can persist after fusion, most commonly because of failure of the fusion. Instrumentation (pedicle screws, plates, interbody cages) may reduce the incidence of this technical problem, but the clinical benefits are less clear. The use of tobacco is a major risk factor for failure of bony union; fusions may

be postponed until tobacco abstinence is achieved. Rarely, despite an apparently successful fusion of either the anterior or posterior spinous elements, some motion persists, and a second fusion may be beneficial.

New Damage to Nerves or Spine

Another type of FBSS consists of painful syndromes resulting from a new pathologic process initiated by the primary surgery. Well-recognized complications of spinal surgery include damage to nerves, dura, joints, and muscles, all of which can produce pain. Examples include the creation of segmental instability after a generous laminectomy, pars fractures, or pseudoarthrosis after an inadequate fusion (25,26 and 27). The acceleration of degenerative changes at levels adjacent to a spinal fusion (transition syndrome) is thought to result from added movement at adjacent levels, which of necessity occurs after fusion. Radiographic imaging of the spine during flexion and extension is often helpful in diagnosing this syndrome. In addition to the persistent neural damage discussed above, there are risks of *de novo* injuries to the nerve roots or spinal cord during surgery. Appropriate technique, including the use of intraoperative electrical monitoring when necessary, should minimize this complication.

Extensive Fusion

Extensive fusions or extensive instrumentation can produce secondary problems of posture such as loss of the normal lumbar lordosis (flat-back syndrome). Abnormal position can induce or accelerate degenerative changes and lead to new pain problems. Postural problems are readily diagnosed by x-ray, and postsurgical patients at potential risk for these syndromes may require periodic x-rays indefinitely.

Nonsurgical Complications

It should be noted that not all painful complications of the perioperative period result from the surgery itself. Invasive diagnostic studies or fluoroscopic procedures can also occasionally cause chronically painful complications. These include infections or arachnoiditis from procedures such as provocative discography, administration of epidural steroids, and myelography, which may have been mitigated in part by the transition from oil-based to water-soluble contrast media (1,28). Postsurgical scarring or inflammation of the meninges (arachnoid fibrosis or arachnoiditis) can produce patchy neurologic findings that are difficult to interpret. Although clumping of the lumbosacral nerve roots is sometimes visible on routine MRI, spinal myelography may demonstrate subtler cases. The value of epidural steroids for long-standing cases is unclear, as is the effectiveness of further surgical or percutaneous procedures attempting to “remove the scarring.”

PSEUDO FAILED BACK SURGERY SYNDROME

Patients or physicians may erroneously perceive their low back surgery as unsuccessful if their previous pain, or a new pain, returns after a pain-free interval after surgery. This may represent recurrent pathology at the level of surgery or at other levels (4,29). It is helpful to explain to patients that surgery does not protect against progression of underlying degenerative processes such as osteoarthritis, nor does it protect against the need for future surgeries. There are probably underlying biological variables, such as in the structure of collagen, that predispose certain individuals (or families) toward recurrent back problems. Patients who have had one low back surgery are at increased risk for having another in the future (5). It is not clear whether this represents an underlying susceptibility or a high prevalence of FBSS, but probably it reflects both. Identification of biological risk factors predictive of a poor outcome from back surgery would help to minimize future FBSS.

The pain that can accompany axonal regeneration can be mistaken for FBSS. Although new neuronal cell bodies cannot be created in adults, the damage is often to the axon (e.g., compression of a nerve root), which can regenerate if not too severely damaged. If the cell body of the sensory neuron in the dorsal root ganglion survives the trauma, it may be able to regrow new axonal processes once the compression is surgically relieved. Axonal regeneration can be associated with persistence or worsening of pain. This is attributed to accumulation of sensory transductive molecules at the distal ends (growth cones) of the regenerating axons. The clinician may be able to identify how far regeneration has proceeded along a peripheral nerve by tapping over the nerve until paresthesias are produced (Tinel's sign). The maximum rate of regeneration corresponds to the rate of fast anterograde axonal transport [approximately 1 mm per day (30)], and thus this phase of recovery can last for months or more than a year. This pain and paresthesias must be distinguished from FBSS pain, as in fact they are a sign of recovery. They should not be considered an indication of worsening nor provoke reoperation. Rare patients can have persistence of their radicular pain for months after surgery with total or near-total resolution of pain once reinnervation of the distal target is completed.

DIAGNOSTIC EVALUATION OF THE PATIENT WITH FAILED BACK SURGERY SYNDROME

Because poor diagnostic evaluation leading to inappropriate primary surgery is one of the major causes of FBSS, it is imperative that further diagnostic evaluations be correctly performed and interpreted, despite the added complexity of diagnosis of FBSS patients. For these reasons FBSS patients are often referred to a tertiary care center experienced in dealing with difficult pain patients and equipped for specialized diagnostic testing that may be required. Figure 76C-1 summarizes the diagnostic evaluation of the FBSS patient, consisting of history, physical examination, diagnostic imaging studies, and ancillary evaluations. Because this material is covered in depth in other chapters, we discuss only those issues specific to FBSS patients. In general, the diagnostic evaluation of FBSS patients should follow the same pathways as for other back pain patients; some additions are noted below (see Chapter 12, Chapter 16, Chapter 75).

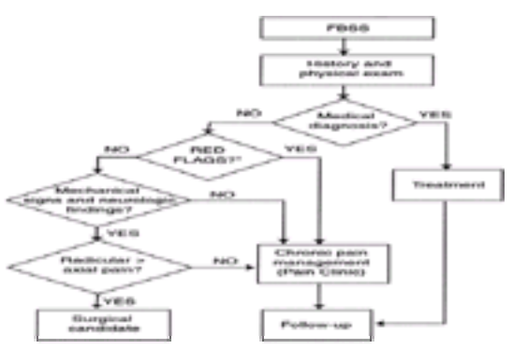

Figure 76C-1. An algorithm for the assessment and management of patients with failed back surgery syndrome (see text). (FBSS, failed back surgery syndrome; RED FLAGS, multiple operations without good indication and with poor results, psychosocial issues, inappropriate medications, etc.) (After North RB. Chronic low back pain and failed back surgery syndrome. In: North RB, Levy RM, eds. *Neurosurgical management of pain*. New York: Springer-Verlag, 1997:342.)

Medical History

As in other areas of medicine, a properly taken history is more cost-effective than any diagnostic procedure. In addition to the standard approach to patients with low back pain (see Chapter 12 and Chapter 75), additional information should be obtained from FBSS patients, including relevant reports of previous surgeries, films, and physical examinations. It is critical to know whether a current neurologic abnormality or abnormal x-ray indicates new or progressive disease or are residua of a previous problem that was already definitively treated. It is particularly important to take a detailed history of the patient's pain characteristics. The low back pain of 5 years ago may have different characteristics and causes than the current low back pain. The progression (or not) of the pain syndrome, including pain-free intervals and effects of various treatments, should also be noted. The psychosocial history should also be obtained to understand the effects of the FBSS pain on the individual's functioning. Issues related to secondary gain, psychiatric problems (see Chapter 26), or both should be clarified. Any pending or former lawsuits connected with the primary low back surgery should be identified.

Prior records and operative notes, when available, are invaluable. As noted earlier, the patient whose pain persists despite surgery that was clearly indicated and properly performed differs substantially from the patient whose pain persists after procedures whose basis is unclear.

Physical Examination

Physical examination should include pertinent musculoskeletal, neurologic, and tension signs and also functional signs. The standard medical and psychological criteria applied to select patients likely to benefit from a primary neurosurgical procedure still apply. Other considerations specific to FBSS patients are discussed below. One important issue is the detection of physical findings predictive of poor outcome of a repeat surgical procedure (31). Abnormalities such as weakness or sensory loss that appear and disappear at various times, change location, or are manifest only during the formal examination but not as the patient uses the “affected” part are suggestive of secondary gain or psychological problems and argue against repeat surgery until these issues are better understood. However, some so-called nonphysiologic or functional findings can result from objective pathology—for example, patchy “nonanatomic” sensory loss is common with lumbar arachnoiditis. Hyperalgesia after nerve injury can present as “superficial” lumbosacral spine tenderness. Although it predicts a poor response to standard lumbar spine surgery (32), the cause is physiologic rather than behavioral. Like other physical findings, these must be considered in context.

In patients with prior surgeries, it can be difficult to distinguish among residual effects after successful treatment (e.g., persistent footdrop after nerve root compression), abnormalities that remain untreated (e.g., lateral recess stenosis), and iatrogenic problems. In a patient who may never have met the standard indications for his or her first operation, the yield of reoperation to correct iatrogenic problems is probably low. Documentation of previous examinations is critical. If asked, the patient often knows valuable information about the duration and progression of any abnormalities noted on examination. Deep tendon reflexes, in particular, often remain abnormal despite adequate surgical decompression, with or without persistent pain, and so, although objective, they have limited specificity.

Diagnostic Imaging Options

A diagnostic imaging decision tree is summarized in Figure 76C-2. Chapter 14 and Section A of this chapter review in detail the use of diagnostic imaging before a first low back surgery. Although the same principles generally apply to FBSS patients, the interpretation of imaging studies is more difficult in FBSS patients because they may have superimposed anatomic abnormalities produced by their primary surgery and they may have had instrumentation that compromises the quality of certain imaging modalities.

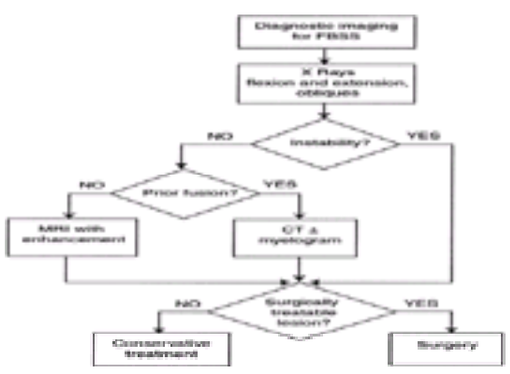

Figure 76C-2. An algorithm for the use of imaging studies in patients with failed back surgery syndrome. (CT, computed tomography; FBSS, failed back surgery syndrome; MRI, magnetic resonance imaging.) (After North RB. Chronic low back pain and failed back surgery syndrome. In: North RB, Levy RM, eds. *Neurosurgical management of pain*. New York: Springer-Verlag, 1997:343.)

The specificity of imaging studies in identifying clinically significant abnormalities in FBSS is limited, just as it is limited in the general population. The longest experience has involved myelography—exclusively with water-soluble contrast agents in recent series and often combined with computed tomography (CT)—in assessing candidates for reoperation. Long-term outcome assessments have been reported for patients selected for treatment on this basis (12).

Intravenous contrast-enhanced imaging studies can distinguish between postsurgical scarring and recurrent, retained, or new disk. CT was used first for this purpose (33,34); as experience accumulated, it became clear that this technique showed abnormalities even in asymptomatic patients (35). In current practice, CT for this purpose has been largely supplanted by gadolinium- enhanced MRI. In a comparison of the two modalities in 130 reoperation cases, MRI was said to be more useful than CT (36); in practice, of course, imaging techniques commonly complement one another.

It has been known for more than a decade that MRI with gadolinium helps to differentiate between postsurgical scar and recurrent or retained disk fragments (37), a distinction to which some authors give special attention (38). The association between pathologic findings on MRI and clinical symptoms, however, is not always clear, even when the identification of pathology is accurate, as confirmed by repeated surgery (38,39). In part, this simply reflects the limited yield of repeated operation for anatomic abnormalities that may have caused irreversible neural injury. Beyond this, however, it is clear that many abnormalities seen on contemporary imaging studies are asymptomatic, in the FBSS population as in the normal population (40). Even patients studied after successful surgery have significant morphologic abnormalities, some simulating recurrent disk herniations with mass effect (41,42). Direct comparisons between postoperative MRI studies in symptomatic and asymptomatic patients have shown no significant differences (43,44 and 45). Postsurgical scar is associated to some extent with symptoms, but it is not clear whether this correlation reflects a cause-effect relationship (scar causing pain) or common cause (pathology causing pain and also causing scar). Adjuncts to surgery to reduce postsurgical scarring assume the former; prospective studies are under way in an attempt to show their usefulness.

MRI avoids the potential morbidity of subarachnoid contrast studies, which have been implicated in the etiology of arachnoid fibrosis (1). MRI has limitations, however, in defining bony anatomy, which often can be better visualized by plain x-ray and CT. Three-dimensional reconstruction of CT information can be useful in the assessment of fusions (46).

The specificity of diagnostic imaging studies in FBSS (and for low back pain in general) is not well established, but chronic low back pain that is not explained by medical disease or ongoing FBSS is commonly considered an indication for imaging in some form. Imaging tests are often repeated, year after year, as the FBSS patient journeys from one pain treatment center to another.

Ancillary Aids to Diagnosis

Additional forms of evaluation may be useful in certain FBSS patients. The usefulness of electromyography in differentiating acute and chronic muscle denervation is an example: Nerve conduction studies can be helpful in assessing the location and severity of damage to nerve roots. Unfortunately, they predominantly detect impulse transmission in large myelinated fibers. The small-diameter axons conducting nociceptive impulses are better assessed in small punch skin biopsies, which, when immunolabeled, permit visualization and counting of small nociceptive endings in the skin (17,18). The utility of this method for evaluation of radicular injury has not been explored.

In some patients with repeated episodes of pain and unsuccessful surgeries, there are underlying medical conditions that predispose to chronic pain. Examples include peripheral neuropathies, treatable arthropathies such as gout and rheumatoid arthritis, and connective tissue disorders such as the Ehlers-Danlos syndrome. Examining other organ systems and taking a complete medical history will sometimes indicate that the FBSS patient needs more comprehensive medical evaluation rather than another surgery. Recognizing these underlying conditions is important in selecting patients for further surgical and nonsurgical treatment; in some cases, one can hope that disease-specific treatment will improve the patient's pain.

Psychological Testing

Psychological factors should be routinely considered in evaluating patients with FBSS (11,47,48), as in patients contemplating an initial surgery (see Sections B and C of this chapter and Chapter 16, Chapter 24, Chapter 25 and Chapter 26). Several authors have reported poor outcomes of reoperation in patients with psychological problems (32,49,50,51,52 and 53). These assessments have mostly been retrospective; however, prospective psychological studies can be difficult to design and interpret (54). Abnormal psychological findings or test results are commonly assumed to represent a premorbid trait (55,56,57 and 58); however, chronic pain and

other serious diseases commonly have psychological sequelae such as major depression, even in patients with no prior psychiatric history. Therefore, abnormal results of psychological testing in pain patients may reflect a consequence rather than a cause of the pain (59).

In fact, psychological testing can be used as an outcome measure in itself—for example, changes in Minnesota Multiphasic Personality Inventory profiles have been reported after successful treatment of chronic low back pain (60). Accordingly, depression and other psychological findings in a patient who has failed treatment should not be assumed to be primary and thus a contraindication to reoperation; they should be evaluated and treated separately. If concerns arise about whether psychological problems are causing pain or vice versa, it can be quite helpful to refer the patients for treatment of their psychological problems and reevaluate them once their psychological problems are better controlled or at least better understood. When considered as one among many potential prognostic factors, psychological testing explains only a fraction of the overall variance in treatment outcome, and it should be considered as one among other selection criteria. We have found standardized psychological testing helpful in identifying comorbidities requiring treatment, but in patients whom we have identified as candidates for a specific procedure (e.g., spinal cord stimulation) it explains a very small fraction of the variance in treatment outcome (48). Accordingly, we consider its prognostic value limited, at least in patients carefully selected by other means.

Diagnostic Blocks

Radiologic testing is increasingly successful at identifying anatomic abnormalities but still provides no information about the clinical significance of those abnormalities. The dissociation between abnormal radiologic findings in the low back and clinical significance is notorious and probably contributes to the performance of inappropriate back surgeries (and thus FBSS). The admonition to “treat the patient, not the x-ray” is critical for FBSS patients. For this reason, temporary diagnostic blocks using local anesthetics can be helpful in contributing functional information about the source of pain to the diagnostic evaluation. FBSS patients frequently have more than one anatomic abnormality in the lumbosacral spine, often at several levels. Their original surgery may have created additional anatomic abnormalities such as scarring or abnormal alignment. Because diagnostic and therapeutic decisions are more difficult in FBSS patients and the outcome of revisional surgeries worse than for the primary surgery (32,52), it is appropriate to invest more effort in identifying which (if any) of the visualized anatomic abnormalities are actually contributing to the pain.

A series of nerve root blocks can be useful in the evaluation of FBSS patients with multilevel anatomic abnormalities. It can be helpful to keep the patient unaware of exactly which level is being blocked; the use of anesthetics with different durations of action or of saline control blocks can also increase diagnostic utility (61). By knowing which abnormalities are contributing to a patient's pain syndrome, surgery can be limited to those levels rather than undertaking a higher-risk, multilevel procedure.

One caveat is that temporarily abolishing the patient's pain by blocking neuronal activity at a specific location does not equate to knowing that those neurons are the “pain generators,” or primary site of pathology. For instance, a patient with allodynia may experience relief of pain by a nerve root block, which temporarily eliminates incoming messages from the painful area; however, if the major pathophysiologic abnormality is within the dorsal horn of the spinal cord, a procedure directed at the primary afferent axons (e.g., foraminotomy or neurectomy), of course, will not address it directly.

In practice, temporary blocks with local anesthetic have had limited prognostic value in selecting patients for ablative surgery. Loeser reported limited predictive value of nerve root blocks before rhizotomy (62), and our experience with dorsal root ganglionectomy is similar—favorable response to blocks did not translate into long-term pain relief (63). Temporary nerve blocks have been noted to afford temporary pain relief even when performed distal to root or peripheral nerve lesions presumed to be pain generators (64,65 and 66) and even when performed contralateral to the site of a unilateral lesion (67). This phenomenon is not easily explained in terms of placebo or systemic effects of local anesthetics; it is more likely to relate to a central mechanism that responds to temporary interruption of a major afferent input. Response to a single temporary block may be a necessary condition, but is by no means sufficient to localize a pain generator or predict the results of a surgical procedure. Data on the predictive value of a negative response to a nerve block are lacking.

The usefulness of temporary blocks in the absence of defined anatomic abnormalities, such as with trigger point injections into muscle, has not been shown to have predictive value for reoperation. Repeated temporary local anesthetic blocks are generally not a useful treatment option for chronic pain.

Provocative Diskography

The rationale for performing provocative diskography is to determine whether mechanical loading of individual disks reproduces an individual patient's characteristic pain. Because negative results of diskography at a given level argue against the usefulness of diskectomy or fusion, diskography can be especially helpful in avoiding further unnecessary surgery in FBSS patients. It can also be helpful in minimizing the number of levels at which surgery is performed in a patient with multilevel disk abnormalities. Strongly positive results at a single level with negative results at other levels can give both patient and physician more confidence in the likelihood of success of a contemplated surgical procedure at that level. As with other diagnostic blocks, inappropriate responses can identify patients with behavioral factors, who should not be considered for repeat surgery at that time. Diskography remains, in spite of 30 years' use, a diagnostic study of uncertain reliability.

TREATMENT OPTIONS

FBSS can be a difficult and frustrating syndrome to treat. Many FBSS patients have had pain for a long time, have had multiple interventions fail, and often have financial and psychosocial difficulties because of their chronic pain. Additionally, patients may travel from great distances, which complicates the logistics of diagnosis and long-term follow-up. Many physicians avoid FBSS patients. In general, an algorithm should be followed, starting with conservative and reversible treatments and progressing logically toward more invasive and/or irreversible procedures only if needed. It may be appropriate to refer patients to centers that specialize in the less common procedures. Often, combining approaches (e.g., rehabilitation plus medications) is more successful than instituting either alone. It is important to emphasize to the patient that a logical progression of treatment options is being followed, and if one approach fails, other options remain. The multidisciplinary treatment options for FBSS are many, so it should never be necessary to abandon or tell a patient with FBSS (or other types of chronic pain) that nothing more can be done. This raises the frightening possibility that the pain will persist indefinitely. When a clinician has nothing further to offer within his or her specialty, the patient should be referred to a colleague with more expertise or an alternative approach to offer. Even when a patient's pain is intractable, a relationship with a reliable and trusted clinician who understands the patient's plight and who is willing to help with the associated issues that accompany chronic disease can provide great solace to the patient and tremendous professional satisfaction to the clinician.

Evaluation of the literature on treatment of FBSS is not straightforward, because different outcome measures are used, and methods of obtaining follow-up vary widely (68). The most common assessment is the patient's self-reported pain relief; other measures reflect pain relief indirectly. Patient satisfaction with treatment (“Would you go through this operation again for the same result?”) is also commonly assessed (4,12,25,32,69). A common criterion for “success” is a minimum of 50% estimated pain relief. Medication requirements usually are considered, as are abilities to engage in various activities of daily living. Return to work is given particular emphasis by rehabilitation programs (70) and is considered by many surgical series as well. When data from disinterested third-party interviews are compared with office and hospital records, the latter appear to overestimate the results of treatment (71,72,73 and 74). Reports of the outcome of reoperation and behavioral/rehabilitation programs are commonly based upon chart review, but a few have used disinterested third-party interviews (12,25,32,70).

Medical Options

A trial of conservative treatment is usually the first option for most patients with true FBSS. Options include medical treatment, rehabilitation, and management of other contributing medical factors, such as obesity or depression. Rehabilitation is central to the management to FBSS patient regardless of candidacy for any neurosurgical procedure. The results of an aggressive rehabilitation/behavioral program are very often favorable, as assessed by disinterested third-party methods (70), and may obviate the need for reoperation. In general, these programs are applicable to all patients with FBSS; they complement neurosurgical intervention in selected cases. This type of comprehensive diagnosis and treatment is presented in Chapter 11, Chapter 18, and Chapter 109. The methods used to treat primary low back pain, described previously in this chapter, are usually appropriate for FBSS patients as well. Medical management of FBSS patients (and chronic pain in general) is underused due to lack of education of both physicians and the public about medical options for treating pain. Patients who have already had one unsuccessful surgery should be even more strongly considered for a detailed trial of medical management. This may take months, or even several years, because there are many drugs that help some of these patients, but no one medication or class of medications has universal efficacy.

Patients with current or previous alcohol or drug dependency problems should be evaluated and treated, if necessary, before consideration of any procedure. However, addicts are not immune from legitimate indications for repeat surgery or from the need for chronic medical management of pain. A patient who has been well controlled on methadone maintenance or who has completed a rehabilitation program is much easier to diagnose and manage than someone acutely abusing drugs

or alcohol. Collaboration with a specialist in addiction medicine can be helpful in ensuring that these difficult patients are being appropriately treated. A skilled practitioner may be able to successfully manage both conditions simultaneously. Because FBSS patients, by definition, have continued chronic pain, they are very likely to be using pain medications, including opioids. Although physical tolerance can develop (as with some other types of medications), the majority of these patients do not display behavioral signs of addiction. Use of chronic opioid analgesics is not a contraindication for reoperation. Actually, aggressive medical management, including the chronic use of opioids where appropriate, should be more often tried as a means of avoiding further surgery, particularly in individuals with a low probability of pain relief after reoperation. Some patients can be treated satisfactorily with stable doses of opioid analgesics over long periods of time. Unfortunately, most clinicians are not taught how to medically manage chronic pain. They should not hesitate to refer to a pain specialist and should be prepared to resume the management of their patient once a stable drug regimen has been instituted. Abstinence from opioid analgesics often is used as an outcome measure (4); accordingly, it easily can be overemphasized as a prognostic factor.

Percutaneous Fluoroscopic Procedures

An increasing variety and number of percutaneous fluoroscopic procedures are being performed for FBSS patients. This must be motivated in part by reimbursement rates, because there is a paucity of information about the indications for and success rates of these procedures. As these procedures become more common, it is imperative that they be rigorously evaluated and that standard methods be developed. This is most advanced for the facet denervation procedure.

Degenerative disease of the zygapophyseal joints (where adjoining vertebrae overlap dorsal to the spinal canal) is an underappreciated cause of low back pain and of pain radiating to the buttocks or upper legs. Patients with pain of facet origin usually present with axial and predominantly proximal radicular-type pain, worsened by lumbar extension, and not associated with sciatic tension signs or unexplained neurologic findings. Because these joints are innervated by terminal twigs of the medial branch of the posterior primary ramus, it is presumed that these “nonanatomic” sensations are due to convergence upon second-order sensory neurons within the spinal cord. Particularly in the case of FBSS patients, where reoperation is intrinsically less desirable than a primary surgery, it can be useful to determine whether facet arthropathy contributes to their low back pain. Because this problem can be effectively addressed by low-risk percutaneous radiofrequency lesioning, it is often worthwhile to consider this nonsurgical option. In some patients with multifactorial pain, reducing the total pain burden by percutaneous facet denervation enables the patient to better tolerate his or her remaining pain.

Assessed by disinterested third-party interview, facet denervation has been “successful” (at least 50% relief of pain) in just under half of our patients at 3-year follow-up (67). This result, in fact, compares favorably with our experience with reoperation. Furthermore, in our experience, the morbidity of facet denervation has been nil. In other series, patients with a history of prior low back surgery reportedly respond less well to facet injections or denervations (75,76,77,78,79,80,81,82,83 and 84), but this has not been the case in our experience. The selection of patients by temporary diagnostic blocks, however, shows limited specificity.

There are much fewer data about other percutaneous fluoroscopic procedures for FBSS patients. They have an appeal because they avoid a surgical procedure, but most ablative surgical procedures for FBSS have poor results (see below). Data supporting the use of epidural steroids, lysis of adhesions, radiofrequency lesioning, and phenol injections into either nerves or dorsal root ganglia are preliminary and allow no definitive conclusions as to their usefulness.

Surgical Approaches

Surgical options for FBSS patients fall into three categories:

1. Anatomic procedures, which attempt to correct the pathology responsible for generation of pain
2. Ablative procedures, which attempt to block pain transmission by destroying some portion of the nervous system
3. Augmentative procedures, which reversibly modulate activity in the nervous system by electrical or chemical means

Anatomic Procedures

It is important to remember that the favorable outcomes after reoperation are less likely than for primary surgeries (12,32), and thus reoperation should be considered only for a distinct, well-defined minority of FBSS patients. Persistent or recurrent chronic pain may be attributed to a surgically remediable lesion, and surgery should be proposed only after thoughtful diagnostic evaluation and after failure of more conservative treatment.

Occasionally, patients require reoperation urgently after a primary low back surgery. These conditions, which should not missed, can be difficult to diagnose because of routine postoperative pain. Usually they present with new signs or symptoms in addition to the ongoing pain. Diskitis, abscesses, or other infections are usually associated with the systemic clinical and laboratory signs of infection. Perhaps most urgent is epidural hematoma. These patients usually present with widespread lumbosacral dysfunction, including leg weakness and bladder and bowel dysfunction. Immediate decompression may allow these devastating complications to reverse. Neural structures, including the spinal cord or nerve roots, may also be impinged upon by a retained disk fragment or newly implanted hardware. Rarely, instrumentation can induce stenosis at adjacent segments, which can require immediate revision.

Patient Selection for Surgery. The American Association of Neurological Surgeons (85) and the American Academy of Orthopedic Surgeons (86) have published criteria for patient selection for elective lumbosacral spine surgery. These are applicable to FBSS patients as well as to patients without prior surgery. They include the following:

1. Failure of an extended program of conservative therapy
2. An abnormal diagnostic imaging study (myelogram, CT, MRI) showing nerve root or cauda equina compression and/or signs of segmental instability consistent with the patient's presenting symptoms and physical findings
3. In patients with radicular pain complaints, conformity to physiologic dermatomal or sclerotomal patterns and one or more of the following: (a) corresponding segmental sensory loss, (b) motor loss in the appropriate segment(s), or (c) abnormal deep tendon reflexes in appropriate segment(s)

In patients who have previously undergone surgery, it can be difficult to distinguish the residual effects of prior insults that have been treated definitively (e.g., persistent hyporeflexia after disk surgery), abnormalities that have remained untreated (e.g., lateral recess stenosis), and iatrogenic problems. In a patient who may never have met the standard indications for his or her first operation, the yield of reoperation to correct iatrogenic problems is low.

Outcome of Repeated Lumbosacral Surgery. A number of reoperation series have been reported, with the range of “success” rates varying from 12% to 100% (12). The absence of standard outcome measures in these studies made metaanalysis and assessment of prognostic factors difficult (87). Adverse outcome and loss of neurologic function are only rarely reported but may be common (12,32,88). Morbidity, as recorded in office and hospital records, was minimal, but patients commonly report regression in neurologic function, activity levels, and medication requirements after surgery (12). A review using disinterested third-party interview methods suggested a long-term rate of “success” (at least 50% pain relief and patient satisfaction, at 5-year mean follow-up) of one-third (12). This is significantly less than that reported for other less-invasive options such as spinal cord stimulation (89). In prospective, randomized comparison with reoperation, spinal cord stimulation is significantly more effective by multiple outcome measures (67). It is not clear how patients who choose reoperation would have fared without surgery, but it is evident that selection of patients for repeated operation should proceed conservatively.

Decompression and Fusion. Reoperations may be considered in two broad categories: decompression and fusion. Large series of decompressive reoperations, specifically identifying those without fusion, have reported widely varying success rates, as above. Among decompressive reoperations, recurrent disk herniation at a previously operated level can be reoperated with generally good results. Repeat microdiskectomy has been successful in more than 80% in some series (90), and within one large reoperation series, previous diskectomy was a favorable prognostic factor (12). Central or lateral recess stenosis that was overlooked or undertreated at an initial surgery or that may have evolved at adjacent levels is a common indication for reoperation.

The role of fusion in lumbar disk disease is not well defined; there has been no prospective, randomized trial of fusion (91). Notwithstanding this, outcome studies have reported a significant association between technically satisfactory fusion and clinically satisfactory outcome (92). Likewise, repair of pseudarthrosis is highly successful clinically when successful technically adequate (93). Of course, this is vulnerable to bias of ascertainment—patients with persistent symptoms are most likely to be evaluated extensively, with some resulting diagnosis made.

Prognostic Indicators. A number of prognostic factors have been identified for patients undergoing repeated operation; they may or may not be significant for individual patients and should be considered in overall context. For example, women have been reported to do better than men (4,12). This is a statistically significant

but clinically minor consideration. Relatively favorable outcomes have been reported in patients with a history of good results from prior surgeries (25,32,50,52,94); this is not surprising to the extent that patients who respond favorably to a query about the operation under study are more likely to respond favorably to similar questions about prior operations. Patients who have undergone a small number of prior operations (32,52) reportedly do better after reoperation. Epidural scar requiring surgical lysis is an adverse prognostic factor (32,50,95,96). Operative or myelographic findings of disk herniation have been reported as favorable indicators (4,25,32,94,95,97). Patients with radicular pain reportedly have fared better than those with primarily axial pain for reoperation as for other treatments (*vide infra*) (32,98). Patients with a pseudarthrosis of a prior fusion appear to have inferior outcomes (49,94). The role of spinal instrumentation, like the role of fusion in the management of FBSS, is a matter of considerable controversy; like the technical details of reoperation, it is beyond the scope of this discussion. Patients who are still working immediately before surgery have been reported to have superior outcome from reoperation (12,94); workers' compensation status may (4,49,50,53) or may not (12,94) be associated with poor outcome.

Ablative Procedures

Persistent postsurgical lumbosacral pain can occur on the basis of continuing disease or injury in a ligament, joint, muscle, or disk (chronic nociceptive pain), or it can reflect abnormal function of a previously injured neural structure. This type of neuropathic pain is pathologic in that it persists after tissue healing and serves no physiologic function. Abnormal neural activity, which is interpreted as pain, can originate in a neuroma (99) or in dorsal root ganglia (100,101). Large myelinated afferents, which normally do not signal pain, have been shown to be involved in hyperalgesia after nerve injury (102). Any of these mechanisms of pain generation would be expected to respond to ablation of primary afferent neurons. However, the animal models of pain have taught us that significant changes within the CNS accompany perturbations of peripheral input (21). Persistence of these mechanisms may underlie the frequent treatment failures reported after these ablative procedures.

The results of open surgical ablative procedures for FBSS have been disappointing. A few series have reported favorable short- term results (62,103,104,105,106,107,108 and 109), but extended follow-up has demonstrated only modest results (62,106,108). It has been shown that dorsal rhizotomy does not interrupt all afferent input; contrary to the “law” of Bell and Magendie, there are numerous ventral root afferents with cell bodies in the dorsal root ganglia (110). These afferents may allow persistent input from peripheral pain generators to persist after dorsal rhizotomy. Removal of the entire dorsal root ganglion should thus be more effective than rhizotomy. This has not been confirmed in practice. The longest published follow-up (more than 5 years) in patients assessed by third-party interview showed no “successes” (63); other series have shown variable efficacy (111,112,113 and 114). Presumably the failure of these procedures to relieve pain testifies to the importance of central pathophysiology. Ablative procedures can compromise the results of other neurosurgical procedures. For example, implantation of a spinal cord stimulator has a lower yield after dorsal root ganglionectomy (63). Primary afferent ablation also depletes opiate receptors on dorsal horn neurons and might thereby compromise future pharmacologic therapy. With the exception of percutaneous facet neurotomy, ablative procedures have had a relatively poor outcome for FBSS and significant morbidity. Minimally invasive, reversible treatments such as spinal cord stimulation have a more favorable ratio of benefit to risk. It should be noted that the pathologic human tissues, such as dorsal root ganglia, that are removed during these procedures are exceedingly valuable to scientists investigating pain pathogenesis and that arrangements should be made preoperatively to make these tissues available to qualified investigators.

Augmentative Procedures

The rationale behind these approaches (described in detail in Chapter 99 to Chapter 101) is reversible modulation of sensory input (noxious as well as nonnoxious) to the CNS, or processing in the CNS, in an attempt to inhibit pain generation or hyperalgesia. “Neuromodulation” may use electrical stimulation or chemical infusion techniques. Although originally based on the gate control theory (20), the actual anatomic and biochemical mechanisms underlying electrical stimulation are not fully understood.

Implantable devices for pain control have the advantages of being minimally invasive and reversible. Thus, they are intermediate on the continuum between medical management and surgery.

Spinal cord stimulation is a reversible “neuroaugmentative” technique that has been successful in a majority of FBSS patients for up to 20 years (74). It compares favorably with reoperation (89) as assessed retrospectively, and more recently by prospective, randomized study (67). Spinal cord stimulation is traditionally more effective for radicular than axial low back pain (115), but with ongoing improvements in devices and their implementation, axial pain is more accessible (116). FBSS has been the most common indication for spinal cord stimulation (74).

Transcutaneous electrical nerve stimulation was developed to screen patients for implanted stimulation techniques; it uses external electrodes and follows the same rationale. Its prognostic value is limited, but it gives patients useful experience and is itself adequate therapy in some. Therefore, it is commonly prescribed before considering an implant.

Other neuroaugmentative methods less commonly used in FBSS include implantable peripheral nerve stimulators. These are usually considered in patients with pain attributable to a single well-defined nerve injury. Implantations usually need to be proximal to the injury and thus may not be helpful for radiculopathies. Thus, FBSS patients are not the group most likely to benefit from this approach. FBSS is also one of the most common indications for implantation of chronic electrodes into various locations in the brain. In contrast to the other augmentative procedures, this is one of the more invasive techniques, and so it is usually used only when many other treatment options have failed. This approach is discussed in more detail in Chapter 101. The use of implanted pumps for subarachnoid infusion to deliver opiates intrathecally (and, it is hoped, to minimize systemic complications) has been reported in small numbers of patients with FBSS; reported successes (117,118,119 and 120) have been tempered by reported complications (121,122,123 and 124). Patient selection criteria await further study and precise definition, as discussed in Chapter 103.

CONCLUSION

FBSS presents a challenge to the clinician as well as the patient. Inappropriate primary surgery is the most common cause. Diagnosis is more difficult than in unoperated patients. A logical progression of treatment options should be followed, starting with rehabilitation and medical management. The majority of patients will not need reoperation, and those who do will have a worse outcome, as a group, than those undergoing their first low back surgery. Thus, the onus is on the clinician to diagnose and treat these patients skillfully and with compassion. Patients commonly require referral to a multidisciplinary pain center or to other specialists for attention to all facets of the FBSS.

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CHAPTER 76

D. Psychological Screening of Spine Surgery Candidates: Risk Factors for Poor Outcome

Andrew R. Block

Although only approximately 1% of individuals who experience back pain ever require surgery (1), approximately 280,000 spine surgeries are performed each year in the United States (2). Approximately 85% of these procedures involve laminectomy and diskectomy and 15% are spinal fusions. Spine surgery often brings dramatic improvements in the patient's experience of pain and functional abilities. For example, Malter and colleagues, examining the effectiveness of laminectomy and diskectomy in the treatment of spine pain, found that those patients receiving surgery had significantly greater quality of life at 5 years postoperation than did patients provided conservative care alone (3). The results of this study also showed that the cost-effectiveness of laminectomy and diskectomy exceeded that of the medical treatment for hypertension, as well as that of single artery bypass grafting in coronary heart disease. Hence, there is real utility in spine surgery.

Unfortunately, the results of surgery for chronic low back pain are not uniformly positive. Turner et al., reviewing all published research on spinal fusion, found that only approximately 65% to 75% of all patients achieved satisfactory clinical outcomes. In these studies, poorer outcome was associated with a number of factors, including greater numbers of fused levels and the use of instrumentation (4). Similarly, Hoffman and colleagues, in a literature review on laminectomy and diskectomy, found that the mean success rate of this procedure for relief of spine pain was 67% (5).

Poor surgical results can have significant impact on the patient, the physician, the employer, and the third-party payer. The patient, of course, continues to remain disabled, with perhaps even greater pain, increased medication dependence, and more emotional difficulty than prior to the surgery. The pain may be so great, or the surgery so unsuccessful, that reoperation is required, as is the case in 10% of those who undergo laminectomy and diskectomy (5), and 23% of those who undergo spinal fusion (6).

The patient after failed surgery places many demands on the health care system, often requiring increasing medications and expensive multiple treatments. Patients often feel frustrated and discouraged. The physician may become angry with the patient for not responding to treatment, and the employer is always concerned about his or her obligation to pay compensation to a permanently disabled worker.

There has been a growing interest in identifying those patients at risk for having a poor response to surgery aimed at relieving chronic back and leg pain. If a means for such identification could be developed, not only would patients be spared the burden of suffering a failed procedure, but significant cost savings also would accrue. If one considers that approximately 235,000 laminectomy and diskectomy procedures are performed each year and approximately 25% of these result in failure, then approximately 58,750 patients each year continue to experience pain (2). The average cost of a laminectomy and diskectomy, including hospitalization and postoperative rehabilitation, is approximately $18,000 (7). Therefore, a screening procedure that correctly predicted all laminectomy and diskectomy failures would save 58,750 × $18,000 = $1,057,000,000 per year, in health care costs alone, minus the costs of the screening procedures.

PSYCHOSOCIAL FACTORS ASSOCIATED WITH POOR SURGICAL OUTCOME

The research on surgical outcomes for chronic pain has increasingly demonstrated that among the strongest predictors of poor results are psychosocial factors. Many elements of the patient's personality, emotional state, and history can combine with contingencies in the patient's social and vocational environment to militate against good surgical results. The purpose of this section is to alert physicians to the potential presence of such psychosocial risk factors and review their effects on surgical outcome.

Personality and Emotional Factors

There are many pathologic physical conditions that can lead to the experience of low back pain. It is the goal of the spine surgeon to correct such conditions, or to minimize their ability to generate perceptible pain. Pain, however, is a subjective experience, and correction of the objective pathology underlying it may fail to achieve relief. The literature, as well as clinical experience, reveals that the pain may linger even after technically successful surgery. Obviously, factors far beyond the operating room in the realm of the patient's psychological makeup and social situation likely contribute to the inconsistent outcomes observed.

Perhaps the strongest set of factors that have been shown to influence the manner in which individuals perceive and react to back pain is related to basic personality characteristics. The American Psychiatric Association (1997) defines *personality* as “deeply ingrained patterns of behaviors, which include the way one relates to, perceives and thinks about, the environment and oneself” (8). According to this description, personality can exert wide-ranging influences over both thoughts and actions. These characteristics can determine, for example, whether people typically become depressed, anxious, or angry in response to stress. Personality may also influence one's need to maintain control, to draw attention to himself or herself, or to withdraw and become sullen. More germane to presurgical psychological screening (PPS), personality factors can exert strong influences on perception of the pain, the emotional impact of pain, and the actions one takes to achieve pain relief.

Personality factors can be reliably identified through the use of *objective* psychological tests, such as the Minnesota Multiphasic Personality Inventory (MMPI). The MMPI has been frequently used in studies attempting to predict outcome following spine surgery. Table 76D-1 lists the major studies that have used the MMPI with spine surgery patients. The results demonstrate that elevations on several MMPI scales have been found to be associated with poorer surgical outcomes. In examining this table we must recognize that the MMPI not only assesses enduring personality traits, but also more acute emotional reactions. For example, depression, as assessed by the MMPI, may be a reaction to the pain and lifestyle changes engendered by the spine injury or may be more of a chronic feeling state. The results of the MMPI cannot be used to make such a differentiation. However, as is discussed in the following section, the relatively enduring nature of many of the traits displayed on the MMPI may significantly influence the outcome of spine surgery.

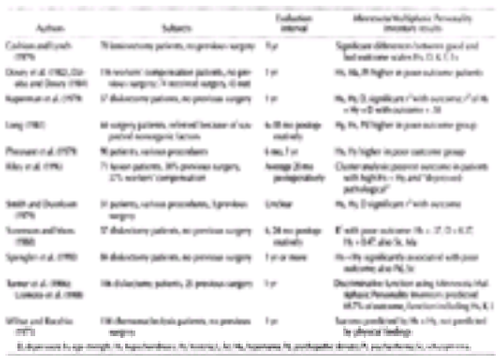

TABLE 76D-1. Studies examining the relationship of Minnesota Multiphasic Personality Inventory to spine surgery outcome

Pain Sensitivity: Minnesota Multiphasic Personality Inventory Scales for Hypochondriasis and Hysteria

A large body of research has demonstrated that chronic pain patients frequently display excessive *pain sensitivity*. For example, research has found that patients with functional gastrointestinal pain syndromes may be hypersensitive to pain signals arising from the gut. Using balloon distension of the esophagus in patients with noncardiac chest pain, Barish and colleagues found that distension caused pain in 56% of patients compared with 20% of normal controls (9). Similarly, Coffin and colleagues reported that patients with nonulcer dyspepsia showed greater sensitivity to balloon distension of the stomach than did normal subjects (10). Fibromyalgia patients, too, have been shown to be more pain sensitive than normal subjects to pressure, noxious heat, and electrical impulses (11). Finally, Schmidt and Brands reported that chronic low back pain patients were extremely sensitive to a cold pressor test (immersion of the forearm into an ice water bath), reporting higher pain levels and tolerating the ice water for a shorter period of time than did a control, nonpatient group (12).

Pain sensitivity, as a personality factor, can be assessed by the MMPI Hypochondriasis (Hs) and Hysteria (Hy) scales (13). These scales are the ones most commonly elevated in general chronic pain syndromes and in spine surgery candidates (14). The major difference between the two scales is that Hy, in addition to pain sensitivity, measures a tendency to deny psychological and emotional problems, as well as to minimize discomfort experienced in social situations. There is a strong correlation (*r* = .53) between the two scales, and thus they are often both elevated at about the same level.

We (15) have administered the MMPI to low back pain surgical candidates undergoing three-level lumbar diskography, and found that Hs and Hy elevations were associated with false-positive reports of pain (pain reproduction on injection of normal-appearing disk). Interestingly, the majority of patients who had such false-positive pain reports at one disk level also had concordant pain reports (i.e., pain reproduction on injection of an abnormal or disrupted disk) at another level. These results demonstrate that excessive pain sensitivity significantly influences pain perception even in patients with objectively identifiable pathophysiology.

Most studies examining the value of the MMPI in predicting spine surgery outcome have found at least one, if not both, of the scales Hs and Hy to strongly predict poor surgical outcome (see Table 76D-1). In some studies the predictive value of these two scales far exceeds that of medical diagnostic tests, such as radiography, computed tomographic scans, or neurologic signs (16). Such results parallel those in other chronic pain syndromes, finding that Hs and Hy elevations predict poor treatment outcome for syndromes as diverse as temporomandibular joint dysfunction, gastrointestinal disorder, and nonsurgical back pain (17,18,19 and 20).

Anger: Minnesota Multiphasic Personality Inventory Scale for Psychopathic Deviate

Anger and chronic pain are often intertwined. The anger experienced by chronic pain patients can sometimes be quite severe. Fernandez and Milburn, for example, asked chronic pain patients to endorse the intensity of 10 different emotions they were experiencing and found that anger was given the highest ratings of all emotions assessed (21).

Anger as a personality trait is assessed by the psychopathic deviate (Pd) scale of the MMPI, which also evaluates rebelliousness toward authority and aggressiveness (13). Elevations on the Pd scale have been found in at least five studies to be associated with poor surgical outcome (16,22,23,24 and 25). There are numerous reasons why anger may have a negative impact on reduction of pain. First, anger may lead to maladaptive lifestyle changes, such as poor health habits, lack of physical exercise, or excessive use of drugs or alcohol (26). Such maladaptive behaviors may have a negative impact on the patient's commitment to postoperative rehabilitation. Furthermore, anger has been shown to have an adverse effect on many health conditions, such as cardiovascular disease, headaches, asthma, and many others (27,28). Such adverse effects may be mediated by excessive activation of sympathetic nervous system efferents or changes in the immune system, perhaps influencing the healing process (27). Finally, anger directed at specific individuals or institutions may maintain pain symptoms beyond the expected period of healing. DeGood and Kiernan have found chronic pain patients who are angry and blame their employer for their injuries report high levels of emotional distress and have poorer response to treatment (29). It may be that for patients who experience intense anger, continued postsurgical pain reports may be tied more closely to such feelings than to any improvement in the pathophysiologic basis of the pain.

Clinical Depression: Minnesota Multiphasic Personality Inventory Scale for Depression

Many chronic pain patients experience some level of depression. For up to 85%, the intensity of this emotional experience is sufficient to meet the diagnostic criteria for clinical depression (30). Depressive symptoms include depressed mood, diminished interest in almost all activities, weight loss or gain, insomnia or hypersomnia, agitation or psychomotor retardation, fatigue or energy loss, feelings of worthlessness or guilt, impaired concentration, and recurrent thoughts of death [adapted from *Diagnostic and Statistical Manual*, fourth edition (DSM-IV)] (8). Depression can be assessed by scale D of the MMPI. Elevations on scale D are found in most studies to be associated with poor outcome of elective spine surgery (22,23,25), although in several studies no relationship was reported (16,31,32 and 33).

Chronic pain patients who are depressed may fail to respond well to spine surgery for a number of reasons. First, individuals with depression have been found to be more likely to focus on negative rather than positive events (34). Kremer and colleagues (35) demonstrated that such tendencies can affect the chronic pain patient's perception of the improvements in function that result from treatment. In this study, activity levels of patients undergoing interdisciplinary rehabilitation were unobtrusively observed by trained staff members. Patients also recorded their own activity levels on an hourly basis. Although all patients demonstrated objective improvement in activity levels as a result of treatment, those who were depressed tended to underreport their improvements. Thus, depressed patients who undergo spine surgery may also fail to see the gains they have made. Depression has also been shown to be associated with a low threshold for induced pain (36). Perhaps the surgical patient may be focused on the body and hypervigilant for pain even if its pathophysiologic basis has been corrected and the nociceptive stimulation greatly reduced.

In examining depression, it may be critical to consider whether the symptoms predate the back injury or are of relatively recent onset. For many patients, depression may be a personality style or a chronic emotional condition (i.e., dysthymia). For others, depressive symptoms, such as decreased concentration, sleep disturbance, and weight change, may be a direct result of the experience of protracted pain or disability (37). Chronically depressed patients may respond more poorly to any surgical procedure aimed at pain relief compared with those patients whose depression is reactive to their medical condition and symptoms. Surgical recovery in more acutely depressed patients may actually be facilitated if clinical depression is adequately treated, through a combination of antidepressant medication and short-term psychotherapy. The improvement in depressive symptoms, including a likely decrease in pain sensitivity, may lead the patient to feel relieved by surgery beyond the correction of pathologic changes in the spine.

Chronic Anxiety and Obsessions: Minnesota Multiphasic Personality Inventory Scale for Psychasthenia

Chronic back pain engenders many difficulties for the patient. Often patients are quite anxious, worrying about paying their bills and fearing that they will lose their jobs. They may be concerned about the many changes in family interaction caused by pain and limitations. Most of all, the spine surgery candidate has to face uncertainty about improvement in pain and functional ability. Such fears and worries, combined with more chronic tendencies toward emotional distress, obsessions, and compulsions, are assessed by the MMPI psychasthenia (Pt) scale. Patients with Pt elevations tend to be stubborn, rigid, and self-critical (DSM-IV, 1994). In four studies, Pt elevations have been found to be associated with adverse outcomes of spine surgery (see Table 76D-1). It may be that to the extent that the patient has chronic tendencies toward worrying and experiences high levels of anxiety, any improvements resulting from spine surgery may be denigrated, while continued minor

symptoms or irrational fears may become the focus of attention.

General Comments on the Minnesota Multiphasic Personality Inventory

The use of the MMPI with chronic pain patients has generated a great deal of controversy. One criticism of this test arises from its theoretical psychoanalytic underpinnings. Indeed, early use of the MMPI with chronic pain patients attempted to distinguish between those patients who had organic pain and those with *psychogenic pain*, pain arising from the conversion of some unresolved psychosexual or developmental conflict into a physical symptom (38). Gamsa has cautioned that there is little evidence to support such *dualistic* Freudian speculations (39). Nonetheless, the large body of research just reviewed demonstrates that the MMPI, stripped of its theoretical underpinnings, is effective as a predictor of surgical outcome. Unfortunately, as Main and Spanswick correctly point out, MMPI results are often communicated to physicians, not on an actuarial, probabilistic basis, but rather categorically in dualistic terms, indicating the presence or absence of some psychiatric syndrome or dysfunction traits (40).

A number of other criticisms of the MMPI, identified by Main and Spanswick (40), rest on methodologic grounds, including the representativeness of the populations used in developing the MMPI, the nature of items used, overlap between MMPI scales, and doubts about the worth of some of the MMPI scales. Although all of these criticisms certainly are valid, the MMPI has proven to be an effective tool. Even Love and Peck (41), who heavily criticize use of the MMPI with chronic pain patients, state, ". . . a relationship does seem to exist between MMPI scores and response to medical treatment. This suggests that the MMPI should be included in the assessment and planning of surgical interventions."

COGNITIVE FACTORS

Although the MMPI assesses general personality and emotional factors, it is neither designed specifically to address the problems of chronic pain patients, nor does it assess specific patient thought patterns and pain-coping strategies. A growing body of research, however, demonstrates that patients' thoughts and beliefs concerning their pain can strongly affect treatment outcome (42,43). Such cognitions and coping strategies have been demonstrated to influence the level of pain experienced by the patient, level of functional ability, and adjustment to the pain and efforts to overcome it (43,44 and 45).

Coping Strategies

Coping strategies may be defined as specific thoughts and behaviors individuals use to manage their pain or their emotional reactions to pain (46). Coping strategies may affect the patient's level of attentiveness to pain, the ability to persist in the face of pain, and the extent to which the patient feels entitled to be taken care of as a result of the pain. There are a number of questionnaires available to assess pain-related coping strategies, including the Vanderbilt Pain Management Inventory and the Ways of Coping Checklist (46,47). However, the largest body of research on coping in chronic pain (and the only research directly applied to surgical screening) has used the Coping Strategies Questionnaire (CSQ) (48).

Gross administered the CSQ preoperatively to 50 lumbar laminectomy candidates (49). Patients who obtained good results from surgery indicated on the CSQ that they felt better able to control the pain and also indicated they were more self-reliant. Other coping strategies assessed by the CSQ, such as hoping and praying and catastrophizing, were associated with poor surgical outcomes. These results are consistent with several other studies demonstrating that more passive coping strategies and perceived lack of pain control tend to be associated with greater pain levels, higher opioid consumption, greater levels of depression, and poorer treatment outcome (48,50,51). Additional studies on cognitive aspects of pain, using questionnaires other than the CSQ, have identified similar findings. Worse subjective symptoms and poorer treatment outcome are found in chronic pain patients who tend to have negative self-statements, tend to catastrophize (e.g., greatly overestimate the impact of minor negative events), and have strong beliefs that all pain should be avoided (44,45,52). Taken together, these studies demonstrate that pain and its impact are mediated by the manner in which the patient thinks about the experience of pain and the strategies he or she has available to cope with the pain.

BEHAVIORAL FACTORS

Back pain clearly is influenced by personality factors, emotional states, and cognitions, as well as anatomic factors. The patient's experience of pain, and the display of behavioral indications of pain, can also be influenced by the responses of others. Pain behavior always occurs in a social context, communicating to observers that the patient is in distress. Observers, in turn, may react to such behavior with attempts to relieve the patient's pain, help him or her to avoid further problems, or be supportive of limitations in activity. Employers, and even the insurance system, may also inadvertently support pain behaviors through provision of disability benefits or time off of work. Unfortunately, such solicitous responses from others, while well-intentioned, may serve to reinforce or reward pain behaviors, increasing the likelihood that patients will continue to show and experience pain (53). Failure to alter reinforcement of pain behavior may contribute to prolonged disability after spine surgery and noninvasive treatment of spine injury.

Spousal Reinforcement of Pain Behavior

Spouses may feel strong empathy with the patient, experiencing an increase in their own arousal level when the patient appears to be experiencing pain (54,55). Such physiological and cognitive responses to pain displays may motivate the spouse to behave toward the patient in a solicitous fashion, unwittingly reinforcing pain behavior. Reinforcing actions might include taking over the patient's jobs or responsibilities, giving the patient medication, and encouraging rest while discouraging activity. Family members may be more likely to pay attention to the patient when the pain appears greatest, and to ignore the patient at other times, such as when the patient is engaging in alternative *well behaviors*.

A number of studies have shown that responses by the spouse can exert a strong influence on patients' pain behaviors. Block and colleagues, for example, found that patients who receive a high level of attention or solicitous responses from their spouses were more likely to report high pain levels in the spouses' presence than were patients with nonsolicitous spouses (56). Lousberg and colleagues extended this result, finding that patients with solicitous spouses showed decreased physical exertion on treadmill performance in the presence of the spouse (57). Similar results have been obtained in a number of other studies (58,59). By extension, it would appear that spousal solicitousness may have a negative impact on surgical recovery and should be assessed prior to surgery, by measures such as the West Haven-Yale Multidimensional Pain Inventory (60).

Family members may provide emotional disincentives for improvement in another way. Numerous studies have demonstrated that marital distress is high among chronic pain patients (61,62). We have shown that dissatisfied spouses have more negative outcome expectations for the patient and tend to attribute the patient's pain to psychological causes (54,63). It is likely that spouses who are dissatisfied would be less supportive of the patient. Social support, particularly from the spouse, has been found to be an important influence on compliance with medical treatment recommendations (64) and recovery from invasive surgery, such as hip replacement (65). Thus, patients who report high levels of marital distress or have unstable or unsupportive marital relationships may have a poorer surgical prognosis. Marital dissatisfaction should be assessed in the surgical candidate, using measures such as the Locke-Wallace Marital Adjustment Inventory, which focuses on marital satisfaction (66).

Litigation

Kennedy, in a frequently cited quotation about patients involved in litigation, coined the term *compensation neurosis*, "a state of mind born out of fear, kept alive by avarice, stimulated by lawyers, and cured by verdict" (67). Studies of chronic pain patients do not support this concept of compensation neurosis. Yet, it is clear that cultural and social factors can influence chronic pain behaviors. In countries other than the United States, where litigation for accidents is uncommon, continuing pain from injuries is less common. In Lithuania, where few drivers are covered by insurance, virtually no individuals involved in car accidents report disabling *whiplash* type pain at 1 to 3 years postaccident (68). In New Zealand, which has a no-fault system for work-related injuries, workers experience less intense pain and have fewer emotional and behavioral difficulties than do injured workers in the United States (69). Thus, patients who are in litigation do appear to have greater pain complaints and levels of disability than do nonlitigating patients.

However, when an examination is made of the effects of litigation on treatment outcome, the results are complex. Schofferman and Wasserman found that low back and neck pain patients improved despite litigation (70). Norris and Watt found no statistically significant changes in the symptoms of litigating patients after their claims were settled (71). For conservative pain management it appears that, while litigating patients may have significantly increased pain complaints, for most claimants, disability from injury does not resolve following the settlement of litigation (72).

Despite the previously mentioned results, it appears that litigation surrounding an injury can exert greater influence on spine surgery outcome than on the conservative treatment of pain. Finneson and Cooper found that both “history of law suits for medicolegal problems” and “secondary gain” predicted negative results of disk surgery, a result corroborated by Manniche et al. (73,74). Junge et al. found that Swiss patients who were applying for disability pensions had poorer diskectomy outcomes than did nonapplicants (75). Such results do not mean that litigation patients are making up their symptoms (i.e., malingering), because surgical candidates do have a pathophysiological basis for the pain. Furthermore, an often-cited survey of orthopedic and neurosurgeons by Leavitt and Sweet found that malingering occurred in less than 5% of patients (76). However, the results with litigating surgical patients imply that, in some cases, reinforcement of pain in the form of anticipated financial gains may increase sensitivity to pain, making patients “somatically hypervigilant” (77) and less responsive to treatment.

Workers' Compensation and Disability Payments

A more immediate source of potential reinforcement for pain comes in the form of workers' compensation and other disability payments to those injured on the job. Such payments often begin at the time of injury and continue until the patient has been declared to have reached *maximum medical improvement*. A number of studies have shown that spine surgery outcome is reduced in patients receiving workers' compensation payments (78,79 and 80). Hudgins, for example, examining patients 1 year postlaminectomy, found that those receiving workers' compensation were the least likely to be working and to report pain relief (81).

Poor treatment results among workers' compensation patients, however, may not arise solely from economic considerations. Rather, workers' compensation patients have a number of additional issues that may lead to reports of high pain levels and poor treatment outcome. First, these patients have frequently been unable to work for extended periods at the time of surgery. Research on chronic pain has clearly shown that the length of time a patient has been nonfunctional strongly influences treatment outcome. Dworkin et al., using multiple regression to examine the relationships among compensation, litigation, and employment status (time off work) in 454 patients undergoing treatment for chronic pain, found that only time-off work (and not workers' compensation or litigation) predicted treatment outcome (82). Responses to treatment by patients receiving workers' compensation may be influenced by job and workplace factors such as job dissatisfaction (83), heavy physical job demands (75,78), and high levels of anger or blame toward the employer (29). Regardless of the cause, workers' compensation is so widely recognized as a risk factor that Frymoyer and Cats-Baril have proposed that *compensability* is one of the strongest predictors of excessive disability among back injury patients (84). Thus, compensation status should be noted as a potential risk factor for poor outcome following surgery. We should be cautious, however, in noting that compensation is a *relative risk* factor and may not be predictive of treatment response in any particular case. Rather, it should be included as one factor along with others described throughout this chapter (see Table 76D-3).

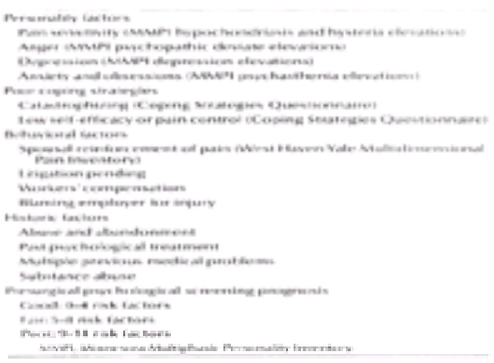

TABLE 76D-3. Presurgical psychological screening risk factors for poor surgical outcome

Historic Factors

The ways in which individuals respond to and cope with painful spine injuries are strongly influenced by their previous life experiences. Research has demonstrated a number of historic elements in the background of the spine surgery candidate that can negatively impact surgical recovery.

Abandonment and Physical and Sexual Abuse

A disproportionately high number of chronic back pain patients have been the victims of abuse or abandonment as either adults or as children. In one study, more than half of the patients evaluated at a multidisciplinary pain clinic had a history of at least one form of such abuse. In 90% of the cases the abuse occurred during adulthood (85). These figures are substantially higher than the base rate in the U.S. population.

One unfortunate consequence associated with victimization is that such patients respond poorly to spine surgery. Schofferman and colleagues (86) found an 85% failure rate from spine surgery among patients with a significant history of childhood abuse and abandonment, compared with a 5% failure rate among patients lacking such a traumatic history. A study by Linton (87) suggests that experiences of sexual and physical abuse may predispose individuals, especially women, toward chronic pain, thereby reducing overall spine surgery results. This study surveyed a sample of the general population in Sweden, as well as chronic pain patients, about their history of physical and sexual abuse. All subjects, whether patients or not, were also questioned about any chronic pain symptoms they might have had. Among the female chronic pain patients, 35% had an abuse history. Many of the nonpatient women also reported experiencing chronic pain. For nonpatient women reporting “pronounced pain,” frequency of physical abuse was 8% and frequency of sexual abuse was 46%. For the nonpatient women reporting no pain, frequency of physical abuse was 2% and frequency of sexual abuse was 23%. Further analyses of the results determined that the chances of developing chronic pain were increased fivefold by physical abuse and fourfold by sexual abuse. In this study there appeared to be little association of abuse with pain for the men. Surgery may eliminate the physical cause of pain; however, prior history of abuse continues to be present and may confound the outcomes of surgery.

Premorbid Psychiatric Diagnosis and Emotional Distress

Many chronic pain patients have diagnosable mental health problems. Kinney et al. (88), for example, found that among those reporting low back pain, 100% with chronic pain and 61% with acute pain had diagnosable psychological conditions. Lower incidence rates were reported by Coste and colleagues (89). As noted earlier in the discussion of depression, psychological problems may predate the injury. For example, Fishbain and colleagues found that 58.4% of the chronic pain patients they studied had diagnosable long-term personality disorders, while Reich and colleagues reported a 37% incidence of such disorders (90,91). Preexisting psychological problems, whether emotional or personality based, have been found by a number of authors to be associated with poor results from spine surgery (92,93). It would seem likely that patients with preexisting psychological problems, especially those who have had prior psychiatric treatment, might be less well equipped to deal with the stress and difficulties involved in recovering and rehabilitation following spinal surgery.

Previous Medical Use

Not only is a history of previous psychological treatment associated with poor outcome, but a preinjury history of multiple physical problems also does not bode well for surgical outcome. A number of authors have found that patients who report many illnesses and physical symptoms do not respond well. Frymoyer et al. (94), for example, found that a history of multiple physical complaints was associated with high levels of back-related disability. Ciol and colleagues (95) reported that higher numbers of previous hospitalizations were associated with greater risk of lumbar spine reoperations in a Medicare population. Wiltse and Rocchio (33) determined that high scores on the Cornell Medical Index, a measure of past illnesses and current bodily symptoms, were associated with poor outcome of chemonucleolysis.

The influence of previous medical problems on surgical outcome appears to parallel results reported earlier in this section noting that excessive pain sensitivity, as assessed by the MMPI Hs and Hy scales, is also a predictor of poor surgical outcome. It appears that patients whose personality and medical history predispose them toward reporting many physical symptoms may have more difficulty experiencing a reduction in back pain and disability as a result of spine surgery, perhaps related to their preoccupation with bodily processes and hypervigilance to noxious sensations.

Substance Abuse

Excessive use and abuse of opioid medication and alcohol appear to be red flags for poor surgical outcome. To the extent that patients depend on such substances, their responsibility for pain relief and improvements in functional ability through participation in postoperative rehabilitation may be diminished. It is clear that many chronic pain patients use excessive amounts of opioids. For example, Polatin and colleagues (90,93) found that 19% of spine pain patients entering a work-hardening program had a substance abuse history, and even higher rates were reported in other studies. Unfortunately, there is little research addressing the relationship of substance abuse and spine surgery outcome. The only study to directly report such results is that of Spengler and colleagues (96), who examined 30 of their spine surgery failures and found that 25 were “continually abusing medication and alcohol.”

Determining when a patient is abusing drugs or alcohol is not as easy as it might seem. In recent years there has been an increasing acceptance of the use of analgesic substances, including opioids, in patients with chronic pain. A number of studies have demonstrated that chronic opioids provide significant pain relief in chronic pain patients (97,98). Thus, some surgical candidates may be taking doses of opioids at the time of evaluation, which, just a few years ago, would have been considered unacceptable. One could argue that patients who are denied opioids by their physicians are not necessarily abusing substances when they seek pain relief through street drugs or alcohol. After all, if prescription opioids provide significant pain relief, is the patient at fault for seeking relief through other means when a physician will not prescribe such medication? Extensive use of substances should only be considered a risk factor if the patient meets DSM-IV criteria for substance abuse, and especially when these medications or alcohol provide inadequate pain relief and do not help to maintain the patients' functional ability (8).

SUMMARY AND APPLICATION

A growing body of research (94) reviewed in this chapter indicates that psychosocial factors can strongly influence spine surgery outcome. These results suggest that PPS should be included as a component of the diagnostic process in many spine surgery candidates. Table 76D-2 provides a set of general referral guidelines that a physician can keep in mind when considering the need for PPS. When the surgeon, comparing a patient with other spine surgery candidates he or she has evaluated, judges that the patient displays four or more of these points listed in Table 76D-2, a referral for PPS should be initiated. Such a referral is especially critical to the extent that the planned surgery is highly invasive (involving multiple levels, instrumentation, and so forth), is exploratory, involves a reoperation, or when the pain is particularly protracted (greater than 1 year in duration).

Excessive pain behavior
Symptoms inconsistent with identified pathology
High levels of depression or anxiety
Sleep disturbance: insomnia or hypersomnia
Excessively high or low expectations about surgical outcome
Marital distress or sexual difficulties
Negative attitude toward work or employer
Emotional lability or mood swings
Inability to work or greatly decreased functional ability (<1 mo)
Escalating or large doses of narcotics or anxiolytics
Litigation or continuing disability benefits resulting from spine injury
Referral considerations
0–1 items: not necessary to refer unless desired by patient
2–3 items: consider referral for presurgical psychological screening
4+ items: strongly consider referral for presurgical psychological screening

TABLE 76D-2. Referral guidelines for presurgical psychological screening

The major psychosocial factors contributing to poor surgical outcome are listed in Table 76D-3. PPS surgical prognosis is based on the number of these risk factors identified. Research from our laboratory has found that patients with nine or more risk factors are at risk for poor surgical outcome. In our study, 204 spine surgery candidates underwent PPS, using a semistructured interview and psychological testing including the MMPI. Outcome of spine surgery was assessed at approximately 6 months postoperatively. Poor outcome (measured in terms of continued pain greater than 4 on a 10-point scale, continued use of opioid medications, and severe activity restrictions) was obtained in 83% of patients having nine or more risk factors. Poor results were obtained in only approximately 18% of patients with fewer than nine risk factors. Such findings parallel those of other researchers who found, using a similar *scorecard* approach to identifying risk factors, that patients with a high level of overall risk respond poorly to spine surgery (16,73,75). For a more complete discussion of determination of prognosis, as well as psychological intervention in surgical candidates, see Block (7).

The results reviewed in this chapter demonstrate that spine surgery may not be very effective when applied to patients having a high level of psychosocial risk. For such patients, more conservative intervention appears more appropriate and effective. Through the use of PPS the surgeon can reduce the costs arising from futile procedures and can help the high-risk patient avoid a downward slide into increasing pain and disability. Based on the PPS, surgeons may decide to (a) deny elective surgery; (b) postpone elective surgery until psychosocial factors are addressed; or (c) proceed with surgery but involve psychologists early during rehabilitation.

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CHAPTER 76

E. Epidural Steroids for Low Back Pain

Miklavz Erjavec

"In this age of accountability it is imperative that therapies with questionable benefits be critically evaluated.'

Kepes, 1985 (1)

In 1953 the French team of Lievre et al. reported the first use of epidural steroids for the treatment of sciatica (2). In 1961 in the United States, the report by Goebert et al. appeared to confirm the promising results epidural steroids offered in individuals suffering from radicular pain (3). Since that time, physicians sympathetic to the suffering of patients with spinal and radicular pain syndromes have been enthusiastic in their support of this promising nonsurgical approach to the treatment of an all-too-often refractory condition. Has there been overzealous endorsement of epidural steroids? Spaccarelli tabulated the results of 26 noncontrolled epidural steroid studies performed up to 1996 and noted that in those studies 65% of patients demonstrated improvement (4). If this is so, then why is it that with the proliferation of pain clinics and physicians with added training in pain management performing tens of thousands of epidural steroid injections per year, we see an ever-increasing prevalence of low back pain and its associated disability (5)? More and more pain clinics are treating patients who have failed to respond to epidural steroids.

The answer probably lies in the hazard of uncontrolled clinical trials and our limited ability to scrutinize the available literature in a truly scientific manner (see Chapter 81 and Chapter 82). Lievre et al. reported epidural steroid injections in only 46 patients with an ill- defined clinical diagnosis of "sciatica." The dose and volume of injected hydrocortisone were not stated and there was no control group. Eight patients said they had very good results, 15 had good results, eight had a mediocre response, and 15 were considered failures. This has initiated a 50-year binge for the medical use of a novel treatment on hundreds of thousands of patients worldwide without the benefit of a properly conducted, prospective, blinded, randomized clinical trial. Could Goebert have understood the connotations of his statement with regard to his own epidural steroid study when he said, "There is no yardstick for measuring pain, but, unquestionably, many of these patients had real pain that was relieved by the treatment"?

The difficulties in studying the benefits of epidural steroid injections are numerous. First, one has to look at the natural history of back pain. Waddell stated that, at some stage in their lives, 80% of the human race will experience low back pain, and a total of 80% to 90% of low back pain will recover in 6 weeks irrespective of the administration or type of treatment (Fig. 76E-1) (5).

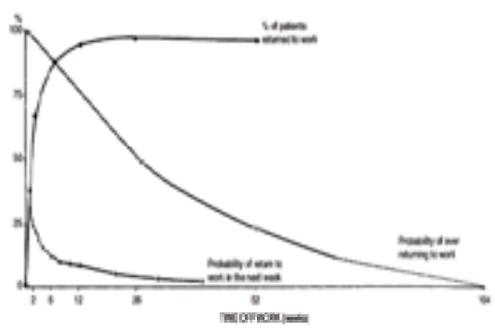

Figure 76E-1. Return to work as a function of time away from work because of low back pain, showing the proportion of patients returning to work with time and the diminishing probability of returning to work in the short term or ever. (From Waddell G. 1987 Volvo award in clinical sciences. A new clinical model for the treatment of low-back pain. *Spine* 1987;12:632–644, with permission.)

Thus, the power of a study involving epidural steroids in the first 6 weeks after the onset of low back pain needs to be enormous if one wants to demonstrate an effect greater than that of the natural history of back pain alone. Next is the difficulty in identifying homogeneous study populations. Should patients with all causes of low back pain with or without radiculopathy be included in a study sample— those with bulging disks, protruded disks, herniated disks, spinal stenosis, foraminal stenosis, facet disease, osteophytes, back strain or sprain, or facet subluxation, for example? We know that 37% of a population with no spinal or radicular pain were found to have disk abnormalities on myelographic imaging, so one must ask what is the association between radiological pathology and pain (6)? Are two patients with similar pain syndromes, one with radiologic evidence of spine pathology and the other without, eligible as subjects in the same study? Which one has a greater chance of a positive response? There is also the unquestioned influence of psychosocial factors when dealing with chronic pain syndromes. Bigos et al. showed in a longitudinal prospective study of 3,020 aircraft assembly workers that apart from preexisting back problems, job dissatisfaction and a high score on the hysteria scale of the Minnesota Multiphasic Personality Inventory have the highest predictive value in determining which workers would report a back injury (7). It has been extremely difficult to control for such psychosocial factors in efficacy studies using epidural steroids.

The problems in producing scientifically sound studies are numerous, and those who do large numbers of these procedures have been remiss in reporting their outcomes in a useful way. We will now address the proposed mechanisms of action of epidural steroids and the evidence to support those mechanisms and then examine the few well-controlled clinical studies and their wide range of results. It is interesting that recommendations for the use of this currently widely used but often clinically disappointing treatment vary enormously from person to person and committee to committee, even though all have reviewed the same literature.

PROPOSED MECHANISMS OF ACTION OF EPIDURAL STEROIDS

In assessing a patient with radicular pain one, should attempt to elucidate the pathologic processes responsible for the patient's symptoms. In simple terms, pathologic processes leading to pain can be divided into the following:

1. Degenerated or herniated disk
2. Nerve root compression by disk or bone
3. Irritation or inflammation of the nerve root
4. Sustained neuronal activity due to nerve injury or central changes

Several elegant radiologic studies using myelograms, computed-assisted tomography, and magnetic resonance imaging have demonstrated the presence of varying degrees of spinal pathology, including herniated nucleus pulposus, foraminal stenosis, and nerve root compression in asymptomatic individuals (6,8,9). The common age-related prevalence of radiologic evidence of degenerated and herniated disks in asymptomatic individuals should caution one against attributing radicular symptoms to radiologic defects. Even when a herniated disk is believed to be responsible for a patient's symptoms it is dangerous to conceptualize the herniated disk as a space- occupying lesion that has been proven to resolve with the application of epidural steroids.

It is not known how often nerve root compression is responsible for radicular symptoms of pain. A nerve root may be put under compression by a disk herniation, usually only when disk material extends laterally into the intervertebral foramen. The axis of rotation of the spine during flexion and extension is located anterior to the spinal canal such that the spinal canal lengthens approximately 7 cm in forward flexion in the average adult. The dura is firmly anchored at its cranial end to the base of the skull and distally is relatively fixed by way of fibrous tissue between the root sleeves and the intervertebral canal. Thus, neural tissues do not slide up and down the spinal canal during spinal motion but undergo a change in length by passive stretch (10). The spinal cord ends at approximately the L-1 level in the average adult. Because 95% of lumbar disk herniations occur at the L-4 to L-5 or L-5 to S-1 levels, there is ample room for disk lesions to expand before actual compression of spinal nerves occurs (11).

Experience gained by neurosurgeons doing spinal surgery under local anesthesia shows that inflamed nerves are exquisitely sensitive to manipulation (touch, stretch), whereas simple compression of normal nerves results in a painless loss of motor and sensory function (12). These findings suggest that pain associated with disk pathology is not due to compression but rather to tensile forces put on nerves that are fixed within the spinal canal and whose length must increase (particularly in flexion or during straight-leg raising) to accommodate the presence of a herniated disk. It is difficult to conceptualize a possible mechanism of action of epidural steroids on pain caused by tensile forces on spinal nerves if, indeed, tensile forces are a cause of pain. It is also difficult to understand how steroids can relieve the compressive forces on nerves by lesions such as osteophytes, foraminal stenosis, and spondylolisthesis.

There is good evidence in the literature that radicular pain can be produced by the inflammatory effects of the nucleus pulposus on nerve roots. Saal et al. looked at the phospholipase A_2 activity of the disk material of patients undergoing diskectomy. Phospholipase A_2 is an enzyme responsible for the liberation of arachidonic acid from cell membranes at sites of inflammation, which is considered to be the rate-limiting step in the production of prostaglandins and leukotrienes (13). They found phospholipase A_2 activity from disk material to be up to 100,000-fold more active than any other phospholipase A_2 yet described. McCarron et al. injected homogenized nucleus pulposus into the epidural space of dogs. The dural sac, spinal cord, and roots were then examined by gross inspection and microscopic analysis. There was clear evidence of an inflammatory response to the injected nucleus pulposus material in the study dogs as compared with dogs whose epidural spaces were injected with normal saline as a control (14).

Several anatomic characteristics of nerve roots and spinal nerves make them more susceptible to inflammation than peripheral nerves (Fig. 76E-2) (12).

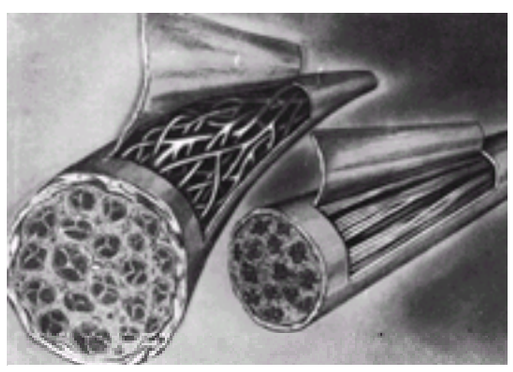

Figure 76E-2. Anatomic differences between a peripheral nerve (*left*) and a nerve root (*right*). See text for discussion. (From Murphy RW. Nerve roots and spinal nerves in degenerative disk disease. *Clin Orthop* 1977;129:46–60, with permission.)

Peripheral nerves have a dense epineurium consisting of loose elastic and fatty tissue that serves a protective role, shielding the nerve from mechanical pressure. This property is well developed in areas of bony prominences, such as where the peroneal nerve travels around the fibula. Peripheral nerves also have a perineurium, a dense sheet of fibrous tissue in which bundles of collagen are arranged in a circular, oblique, and longitudinal arrangement. On the inner surface of the perineurium is a layer termed the *perilemma*, which functions as a diffusion barrier against chemical irritants. The nerve root has no perineurium, and the other protective structures are either thin or lacking. The fibers in a peripheral nerve repeatedly divide and fuse to form plexi along the nerve length, giving them the ability to withstand stretch in response to tensile forces. Nerve root fibers run in parallel and are more susceptible to deformation from tensile forces. Peripheral nerves are well vascularized by the vasa vasorum. Nerve roots have a tenuous vascular supply consisting of a distal system from segmental branches in the vicinity of the dorsal root ganglion that runs proximally and a proximal system from the vasa corona that runs distally, with a relative area of hypovascularity in the middle (12). Another anatomic feature is the poor lymphatic drainage of nerve roots. It is easy to understand how nerves with little protective coverings are susceptible to the intense inflammatory effects of disk material. Furthermore, due to the sparse blood and lymphatic supply of nerve roots, it is difficult for the products of inflammation to be removed once they begin to accumulate, thus predisposing the nerve fibers to inflammation, invasion by fibroblasts, and, ultimately, intraneural fibrosis.

The antiinflammatory effects of steroids include a decrease in edema, fibrin deposition, local migration of leukocytes, phagocytic activity, capillary proliferation, fibroblast proliferation, and deposition of collagen and its cicatrization. It is intuitive to expect that inflamed nerves, whose existence is often confirmed at the time of surgery, should respond to the antiinflammatory effects of steroids. This leads to the puzzling question of why epidural steroids do not produce an effect in all patients with radicular symptoms. One obvious answer is that the pain is not truly radicular in origin—for example, those individuals with low back pain radiating into the buttock or to the knee. This type of pain may be attributable to processes such as myofascial and facet pain syndromes, which should be clinically distinguished from pain of radicular origin. Another possible explanation is that chronic nerve inflammation from exposure of nerves to a herniated disk or the chronic seepage of disk material from degenerated and desiccated disks produces chronic inflammation, which results in intraneural and perineural fibrosis. Holt correlated the histology of disk degeneration with adjacent spinal nerves in a cadaver study (15). When the disk was histologically normal, the adjacent nerve was also normal in 92% of cases. When the disk was degenerated, the adjacent nerve showed intraneural fibrosis in more than 60% of cases, a correlation statistically significant at the .001 level of confidence (15). In patients having surgery for herniated lumbar disk, Lindahl and Rexed demonstrated intraneural fibrosis in 78% of dorsal nerve roots taken for biopsy (16).

Thus, nerve roots and spinal nerves may be susceptible to stretch, ischemic, and inflammatory injuries, with little ability to clear the resulting inflammatory elements that accumulate, leading inexorably to an end-stage process of intraneural and perineural fibrosis that may not be amenable to any form of therapy. The role of epidural steroids in this situation can be questioned. Patients who respond to epidural steroids may represent those individuals who have a limited exposure to the inflammatory effects of disk material. Patients who demonstrate dramatic but short-lived improvement in symptoms may have chronic exposure to disk material, with return of symptoms as the effects of steroids dissipate. And lastly, those with no relief may be suffering from neural fibrosis, which is refractory to all known forms of medical therapy. As some patients do show dramatic improvement with epidural steroids the challenge in the future will be to identify which group of patients do respond. This, of course, depends upon being able to effectively determine the etiology of the patient's pain. Whether epiduraloscopy will be proven useful remains to be determined by proper trials.

There is a group of patients who have radicular pain with no demonstrable radiologic lesion, or similarly, had apparently successful surgical correction of spinal pathology and suffer persistent postoperative radicular pain. A popular recent explanation for this is the phenomenon of central neuroplasticity, as discussed in Chapter 3, Chapter 4 and Chapter 5. Nerve injury may lead to a state of central hyperexcitability or spontaneous activity in neurons such that pain may be perceived after a nociceptive impulse has ceased or normal neuronal activity is exaggerated and/or modified such that it is represented centrally as a painful phenomenon (17,18 and 19). Central nervous system changes are sometimes used by those who are proponents of the addition of local anesthetic to steroids in an attempt to “reset” neuronal activity. Some also believe that the addition of local anesthetic or opioids to epidural steroids may allow relaxation of paraspinal muscle spasm and block the nerves to facet joints, allowing for reduction of minor joint subluxations (20). However, two studies have not been able to detect any difference between normal saline and local anesthetic injected into the epidural space for the relief of low back and radicular symptoms (21,22). Some physicians advocate the use of local anesthetic with epidural steroids as a means of confirming correct placement of the injection into the epidural space by evidence of sympathetic and sensory block.

In this author's opinion, addition of a local anesthetic is of questionable benefit and adds the unnecessary risks of allergic reactions and the problems associated with local anesthetic toxicity or inadvertent administration into the intrathecal space. Furthermore, some patients will develop a motor block and will be unable to ambulate immediately, causing an unnecessary delayed stay in the treatment area. Sympathetic and proprioceptive blockade can also lead to troubling symptoms. An

interesting occurrence is the complaint by alarmed patients of marked increase in their pain coinciding with the resolution of local sensory block usually late in the evening well after the patient has left the treatment center. This could represent a patient's perception of worsening pain in contrast to several hours of relief from sensory block, or the consequences of preferential prolonged block of pain inhibitory fibers, or a central pain state.

There are numerous reports from the radiologic literature on the high failure rate of needle placement within the epidural space when positioned without the use of fluoroscopy and contrast material (23,24). This is not an experience familiar to most well- trained anesthesiologists, and the author sees little role for non–pain-trained physicians performing epidural steroid injections, particularly if it comes at the added expense and risk of fluoroscopy and the injection of contrast material.

NONRESPONDERS

An alternative approach to determining who will benefit from a treatment, when it is recognized that all recipients of the treatment do not respond, is to try to determine in whom the treatment is not beneficial. This has been looked at in two studies on epidural steroids.

Jamison et al., in an uncontrolled study, evaluated 249 patients referred to a pain center with low back and radicular pain attributed to a variety of different diagnoses (25). Each patient was given a comprehensive pain questionnaire and Brief Symptom Inventory Checklist to complete and underwent a thorough physical examination as well as a computed tomography scan, magnetic resonance imaging, and/ or electromyography. Patients were assessed for pain intensities after one epidural injection of methylprednisolone, 120 mg, in 0.5% lidocaine, 3 mL, and normal saline, 3 mL, at 1 day, 2 weeks, and 1 year after treatment. Mean visual analogue scores were 5.55 pretreatment, 4.5 one day after treatment, and 4.15 two weeks after treatment. Two weeks after treatment 155 patients reported a decrease in pain, 42 reported no change in pain, and 52 reported an increase in pain. Presence or absence of specific diagnoses or physical findings was not predictive of short-term response. Four factors were identified that best predicted poor outcome 2 weeks after treatment:

1. Greater number of previous treatments for pain
2. More medications taken
3. Pain not increased by activities
4. Pain increased by coughing

One hundred thirty-one patients were assessed at 1-year posttreatment. Factors that predicted no benefit 1 year after treatment were the following:

1. Pain does not interfere with activities.
2. Unemployment due to pain.
3. Normal straight-leg raise test before treatment.
4. Pain not decreased by medication.

Results of physical examination and presence or absence of structural pathology did not predict outcome at 1 year.

Hopwood and Abram looked at 33 factors derived from patient evaluation and physical examination in 209 patients undergoing epidural steroid injections to investigate factors that may influence outcome (26). Patients underwent an injection of epidural triamcinolone, 50 mg, in 1% lidocaine, 3 to 5 mL, and received a second or third injection if they received little or no relief from their previous injection. Univariate analysis showed an increased risk of treatment failure with the following:

1. Lower levels of education
2. Smoking
3. Lack of employment at start of treatment
4. Constant pain
5. Sleep disruption
6. Nonradicular diagnosis
7. Prolonged duration of pain
8. Change in recreation activities
9. Extreme values on psychological scales

EPIDURAL STEROID OUTCOME STUDIES

Epidural steroids have been the subject of many studies and reviews; controversy has focused upon their efficacy (Table 76E-1) (1,4,27,28,29,30,31,32,33,34,35 and 36).

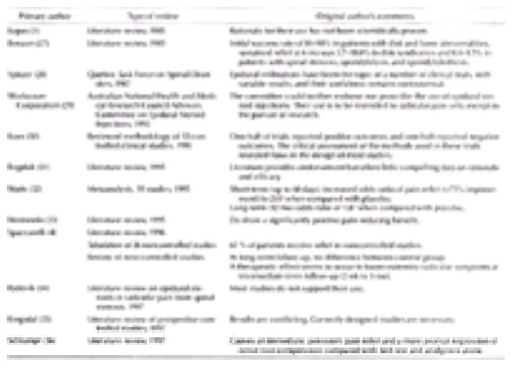

TABLE 76E-1. Reviews of the epidural steroid literature and the author's comments

It is worrisome that the reviewers listed in Table 76E-2 (22,37,38,39,40,41,42,43,44,45,46 and 47) have all had access to essentially the same literature, and yet they have produced a wide range of opinions on the efficacy of epidural steroids. Inspection of published reviews of this procedure reveals a trend: The more critical and discerning an author is with regard to the methodology of the epidural steroid studies, the less the author promotes epidural steroids as having a positive outcome. This point can best be illustrated in a review by Koes et al. (30). This group reviewed the efficacy of epidural steroids in 12 randomized clinical trials appearing in the literature before 1995, assessing the methodologic quality of these 12 trials by rating each study on a possible 100 points based on established criteria for generally accepted principles of interventional research (30). Out of a possible 100 points, four studies scored more than 60 points, four studies scored between 50 and 60 points, and four studies scored less than 50 points (see Table 76E-2).

Primary author	Points scored out of 100	Efficacy of epidural steroids
Snoek (41)	72	Negative
Matthews (42)	67	Slightly positive
Breivik (43)	63	Positive
Cuckler (44)	62	Negative
Bush (40)	59	Positive
Serrao (45)	52	Negative
Klenerman (46)	50	Negative
Dilke (38)	50	Positive
Rocco (47)	49	Positive
Ridley (39)	47	Short term only
Beliveau (37)	45	Negative
Yates (22)	17	Positive

*Reviewed by Koes, their results and methodologic score out of a possible 100 points.

Modified from Koes BW, Scholten RJ, Mens JM, et al. Efficacy of epidural steroid injections for low back pain and sciatica: a systematic review of randomized clinical trials. Pain 1995;63:279–288, with permission.

TABLE 76E-2. Twelve controlled clinical trials on epidural steroids [a]

The median score was 52 points, indicating the overall questionable methodology of the trials. The Dilke (38) and Snoek (41) studies will be used to illustrate common methodologic shortcomings. Dilke randomly assigned 100 consecutive inpatients to a treatment group who received methylprednisolone, 80 mg in 10 mL of isotonic saline into the epidural space, and a control group who received isotonic saline, 1 mL, in the interspinous ligament. The injections were repeated once if necessary. In the treatment group, 21 of 35 patients reported pain relief, whereas 11 of 36 patients in the control group reported pain relief, 60% and 31%, respectively, reporting pain relief in each group. At 3 months, one out of 44 patients had severe residual pain in the treatment group and six of 38 had severe pain in the control group. Three of 36 patients did not return to work in the treatment group, and 14 out of 35 did not return to work in the control group. Major methodologic flaws included the lack of differentiation between new-onset, chronic, and recurrent pain in the inclusion criteria. Approximately 30% of the patients are unaccounted for in the results. Decision for duration of bed rest, cotherapies, suitability for return to work, or need for surgery were all at the discretion of multiple clinicians in charge of their own patients, with no standard criteria for each of the aforementioned decision-making processes. Dilke stated that the trial did reveal significant differences in favor of the treated group with respect to pain relief and disability.

In 1977 Snoek studied 51 patients with acute herniated disk and neurologic deficits documented by myelography (41). They were randomly assigned in a double-blinded prospective fashion to receive an epidural injection of methylprednisolone, 80 mg, or isotonic saline, 2 mL, epidurally. Two hundred patients were assessed for suitability for the study. One hundred forty-nine patients were excluded for reasons consisting of motor paralysis, cauda equina syndrome, intolerable pain, or previous surgery. Follow-up at 48 hours showed no difference between the two groups with regard to pain relief, consumption of analgesics, and improvement in neurologic function. Interestingly, Green et al. (48) demonstrated that in patients responding to epidural steroid injections, 37% will respond in 2 days or less, 59% will respond between 4 and 6 days, and 4% will respond after 6 days. Snoek's follow-up at 48 hours may have missed many potential responders. Snoek then followed up long term with a chart review between 8 and 20 months, noting that the incidence of patients continuing on to surgery in each group was the same—14 in each group, for a total of 28 of 51 patients. This high surgical rate leads one to question the threshold criteria for surgery in his institution. One must question the fate of the 149 of the initial 200 patients who were excluded from the study for reasons of intolerable pain, motor paralysis, and so forth. Physical therapists blinded to the study rated 70% of the treatment group as improving, whereas they rated 42% in the control group as improving. This may be attributable to the fact that the physical therapists were assessing patients beyond 2 days. Thus, an intermediate period that may have shown a difference was unavailable to Snoek.

After commenting on the methodologic shortcomings of clinical epidural trials, Koes states that the benefits of epidural steroid injections, if any, seem to be of short duration only (30).

One noteworthy study has appeared in the literature since the reviews stated in Table 76E-2 were written. Carette et al. performed a randomized, double-blind prospective study on 158 patients who either received three epidural injections of methylprednisolone, 80 mg in 8 mL of isotonic saline, or three injections of isotonic saline, 1 mL (49). All patients had experienced a first or recurrent episode of sciatica that had lasted a minimum of 4 weeks but less than 1 year. *Sciatica* was defined as the presence of constant or intermittent pain below the knee. Signs of nerve root irritation (positive straight-leg test, defined as reproduction of radicular pain by elevation of the leg), nerve root compression (motor, sensory, or reflex deficits), or both had to be present, with computed tomography evidence of a herniated nucleus pulposus at a level corresponding to the symptoms and clinical findings. Functional disability was also assessed, requiring patients to have a score of greater than 20 on the Oswestry Low Back Pain Disability Questionnaire. Differences in improvements between the groups were not significant, except for improvements in the finger-to-floor distance (p = .006) and sensory deficits (p = .03), which were improved in the methylprednisolone group. After 6 weeks, the only significant difference was the improvement in leg pain, which was greater in the methylprednisolone group (p = .03). After 3 months, there was no significant difference between the groups. The Oswestry scores had improved by a mean of –17.3 in the methylprednisolone group and –15.4 in the placebo group. At 12 months, the cumulative probability of back surgery was 25.8% in the methylprednisolone group and 24.8% in the placebo group. In this study, the assumption was made that recurrent and new onset of radicular symptoms in patients with symptoms between 4 weeks and 1 year represent a homogeneous study group. This may be an unwarranted assumption, particularly when one recalls Waddell's data regarding the natural history of low back pain. This study otherwise surpasses all others performed thus far from a methodologic point of view. Patients suffering from radicular symptoms due to nerve root irritation may obtain short-term relief from epidural steroids. As seen in many epidural steroid studies, this author considers that an illusion of “cure” is created when those patients who fail either the epidural steroid or control treatment go on to receive surgery or improve due to the natural history of the disease.

A new approach to epidural steroid injection, termed the *epidural perineural selective nerve root technique*, has been developed and reported by Kraemer et al. (50). This double-needle technique uses an introducer needle to pass through the skin and interspinous ligaments in an oblique interlaminar approach. A 29-gauge spinal needle is passed through the introducer such that the needle tip enters the lateral aspect of the anterior epidural space. An argument is made that, in radiocontrast studies using the conventional posterior approach to the epidural space, fluids flow along the route of least resistance, which is likely away from the area one wishes to inject. Kraemer states that in his radiologic contrast investigations using the conventional posterior approach, only a small amount of injected material reached the affected transversing and exiting nerve root on the side of the anterior epidural space. He argues that the perineural technique also reduces the amount of steroid needed, as the steroid is injected directly on to the affected nerve root, thus avoiding the potential complications posed by larger quantities of steroids. The initial results of this new technique in two prospective controlled studies appear promising (50).

To date, there are no studies comparing the effects of different steroids or different doses or volumes of injectate.

COMPLICATIONS

Complications from epidural steroid injections are rare (51) but can be disastrous when they do occur. Complications can be divided into those attributable to epidural needle placement, to local anesthetic, and to steroid adverse reactions and idiopathic causes (Table 76E-3) (3,37,38,39,40 and 41,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90 and 91).

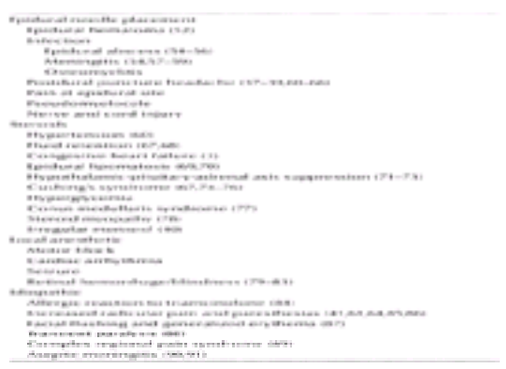

TABLE 76E-3. Complications of epidural steroid injections

Complications secondary to needle placement and local anesthetic injection are well described in the anesthesia literature. The mechanism of retinal hemorrhage is unknown but may well be attributable to a rise in cerebrospinal fluid pressure, which is then transmitted through the optic nerve sheaths to the posterior retinal venous circulation (83).

The role of steroids as a causative agent in arachnoiditis remains controversial. There are reports in the literature of arachnoiditis related to the use of intrathecal steroids (78,92,93,94 and 95). The presence of polyethylene glycol as a preservative agent in methylprednisolone has been implicated in cases of sterile meningitis, arachnoiditis, and pachyarachnoiditis when injected intrathecally (93). Latham et al. examined the histopathologic effects of intrathecally administered betamethasone in sheep and found that evidence of arachnoiditis did not appear until high doses were used and concluded that intrathecal injection of betamethasone in the low

doses used in humans is unlikely to cause arachnoiditis (96). To date there are no reports of arachnoiditis in patients who have received epidural steroid injections.

Less controversial is the observation that frequent epidural steroid injections clearly produce prolonged suppression of the hypothalamic-pituitary-adrenal axis. Jacobs et al. showed that a single dose of 80 mg of epidural methylprednisolone markedly suppressed plasma cortisol levels and the ability of the adrenal glands to secrete cortisol in response to synthetic adrenocorticotrophin for up to 3 weeks (72). Similarly, Kay et al. demonstrated acute and chronic adrenal suppression in patients receiving epidural triamcinolone, 80 mg weekly for 3 weeks. Full recovery of adrenal function occurred in 3 months (73). Cushing's syndrome has been reported with as little as one epidural injection of methylprednisolone, 60 mg. The consequences of systemic effects of steroids should engender caution in advocating the use of repeated epidural injections of steroids. Diabetics can lose good blood sugar control after a single epidural steroid injection.

Finally, as an aside, the author knows of an unreported case of osteomyelitis and pseudomeningocoele formation as a complication of epidural steroids.

CONCLUSION

Given the conflicting results of numerous studies, it is difficult to make broad-based recommendations regarding the role of epidural steroid injections in the treatment of low back pain. The extremes are represented by scientific purists who may never have firsthand experience of the desperation of those in pain and who argue that the literature has not established a role for epidural steroid injections. At the opposite pole are those who sustain a clinical career performing numerous epidural steroid injections on a purely empiric basis. Should one deny a request for an epidural steroid injection from a conservative surgeon who wishes to explore all possible nonsurgical approaches before embarking on a surgical intervention in a patient with a complex medical problem? On the other hand, the author has been approached by an individual who saw his anesthesia income declining and wished to supplement it by performing epidural steroid injections at the end of his ever-shrinking daily operating room responsibilities. His probe into the world of pain medicine was limited to how much steroid and at what level. This practice is mentioned only to be severely condemned and is discussed in Chapter 11.

The author believes that epidural steroid injections are but one tool in the multidimensional approach to the treatment of low back pain. This is truly a complex (26) problem, one that only physicians with a strong understanding of the biopsychosocial influences on pain are capable of assessing and treating effectively.

After a comprehensive assessment of a patient referred for epidural steroids, the pain management physician should determine whether the patient has a condition that may respond to this modality. After a full explanation of the associated risks involved and the probable short-term results that are expected, it may be reasonable to proceed with one epidural injection. A partial response suggests that further epidural steroid injections may have a cumulative benefit. The myth of requiring a series of three injections probably originates in a paper by Brown (97) in 1977, in which he stated, “more than 3 injections do not seem to provide additional benefit.” Somehow this statement has been construed to the common request for “a series of three.” The pain physician should use the opportunity of a request for epidural steroid injections to assess and address any other issues that may be contributing to pain and disability. These issues frequently include depression, inappropriate bed rest and use of medications, work issues, sleep and physical activity habits, and so forth. The initial visit is also an opportune time to explore a patient's understanding of low back pain and to provide education about the natural history of low back pain and the necessary elements of a physical rehabilitation program to restore physical function. After this has been completed and the patient has agreed to proceed, any relief of pain should be regarded as a window of opportunity to improve upon all the issues mentioned above.

Difficulties arise when patients receive short-term relief and continue to request additional epidural steroid injections. The risk of systemic side effects of steroids are real, and the practice of multiple epidural steroid injections is probably unwise. In this situation it is prudent to reassess the clinical problem and look for an appropriate next step in a treatment algorithm. This may tax even the most experienced of pain physicians. The physician with an armamentarium limited to blocks will have little else to offer in this frequently encountered situation. The proper role of epidural steroid injections in the treatment of low back pain and leg pain has not yet been determined. Those who wish to heavily use this interventive technique should design and implement appropriate outcome studies.

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CHAPTER 77

Pain of Neurologic Origin in the Hips and Lower Extremities

John D. Loeser

Pain of neurologic origin in the hips and lower extremities, often referred to as *lumbar* and *lumbosacral neuralgia*, includes a broad category of painful conditions localized to the lumbar and first two sacral nerve distributions. Neuralgia restricted to the lumbar area is relatively uncommon; most of these pains also involve sacral segments. These pain syndromes are thought to be caused by pathologic processes that involve the lumbar and sacral segments of the spinal cord, the nerve roots, the lumbosacral plexus, or the peripheral nerves (see Fig. 75-7). The information in this chapter is presented in two major sections: (a) general considerations, including an overview of etiology, symptoms and signs, diagnosis, and treatment, and (b) specific causes of lumbosacral neuralgia. More detailed information can be found elsewhere (1,2 and 3).

GENERAL CONSIDERATIONS

Etiology

Pain of neurologic origin in the hips and lower extremities is a symptom secondary to diseases that most commonly involve the nerve roots or the lumbosacral plexus. Pathology in the spinal cord or peripheral nerves is identified less often. Although sciatica is written about as if it were common, most low back and leg pain originating in the back is not caused by radicular disease at the L- 5 and S-1 levels, and most of what is called “sciatica” is a misnomer. The vast majority of hip and leg pains are of musculoskeletal origin, and their pathophysiology is not well understood. Further discussion of this topic can be found in Chapter 28, Chapter 29, and Chapter 76.

Pain of neurologic origin in the hips and legs can be best considered on the basis of the site of pathology: (a) lesions of the spinal cord and dura, (b) lesions of the spinal nerve roots, (c) lesions of the formed spinal nerves, (d) lesions of the lumbosacral plexus, and (e) lesions of one or more peripheral nerves.

Symptoms and Signs

The characteristics of the pain in these conditions are a function of the location of the offending lesion. Intrinsic lesions of the spinal cord rarely present with pain, but are more likely to be characterized by motor and sensory loss. Bowel and bladder dysfunction is usually an early sign; in the male, sexual dysfunction is common. Lesions of the dorsal roots usually produce a pain syndrome that has a dermatomal pattern and is exacerbated by mechanical factors. Lesions of the formed spinal nerves are uncommon; in addition to dermatomal pain, the motor and sensory changes are a function of the nerve involved. Lumbosacral plexus lesions are relatively rare and cause both local and referred pain, as well as sensory and motor changes. Peripheral nerve lesions are characterized by focal pain at the site of nerve damage and pain referred into the distribution of the nerve. Sensory and motor deficits are determined by the innervation pattern of the involved nerve.

Sensory alterations generally accompany the pain of any lesion involving the nervous system. Variations in the type of sensory loss are not terribly helpful in locating the lesion. Anesthesia, hypesthesia, paresthesia, hyperesthesia, hyperalgesia, and dysesthesia can all be associated with almost any type of nervous system lesion.

Motor deficits are frequently observed. Weakness of the muscles, loss of tone, atrophy, and reflex changes can all be seen. If the ventral root axons are significantly compromised, fasciculations can be observed. Abnormalities of sympathetic nerve function are common when the nerves to the legs are involved, including loss of sweating and piloerection and a cool extremity. A diffuse, deep, aching pain in the hip can also indicate sympathetic involvement.

Local tenderness can help to indicate the site of the lesion. Movements of the lumbar spine and hip that lead to increased mechanical pressure can exacerbate the pain. If a nerve in the leg is mechanically traumatized, movements and local pressure can aggravate the symptoms.

When the lesion has been present for a month or more and the nerve damage has been sufficient to disrupt axons, a *neuroma* sign can be present at the lesion site. Percussion over the nerve in this area produces paresthesias that are perceived in the cutaneous distribution of the nerve. If the lesion has been present long enough for some regeneration to occur distal to the site of the injury, *Tinel's sign* can be elicited: Percussion over the nerve distal to the injury site results in paresthesias in the cutaneous territory of the nerve. Tinel's sign can be used as an indication of the continuity of the nerve and the presence of some regenerating axons.

If the offending lesion is near the body surface it can be palpated, or the overlying skin contours can be altered. Deeper lesions might not be accessible to physical examination. The lesion itself can cause local pain because of tissue damage.

Diagnosis

The diagnosis of the cause of pain of neurologic origin in the hips and legs is based primarily on the history and physical examination. The strategies for obtaining a thorough history and carrying out a detailed physical examination are discussed in Chapter 12. Neurodiagnostic studies such as electromyography, nerve conduction velocity and reflex tests, somatosensory evoked potentials, and thermography are often valuable adjuncts that can help to locate the lesion precisely (see Chapter 13 and Chapter 14).

When the history has been obtained and the general physical examination has been done, the examiner should focus on the region of pain. The back, abdomen, groin, buttocks, and entire lower extremities should be inspected, with the physician searching for a loss of normal contours, muscular atrophy, or other deformities. Rectal or vaginal examination is important when sacral segments are involved in a chronic pain syndrome. Atrophy should be documented by measurement of the thigh and calf circumferences a fixed distance above and below the patella. Painful areas should then be palpated to locate regions of tenderness or of pain reproduction. The effects of movement at the major joints must be ascertained. Limitation of movement usually suggests disease of the joint or of the surrounding muscles, tendons, or ligaments. Most pains in this area are found to be in the low back, buttock, hip, and proximal leg. They are most often of musculoskeletal origin, in spite of the pattern of radiation, which suggests sciatic nerve involvement.

Examination of the lumbar and sacral neural segments is obviously critical in patients with pain symptoms in the lower body and legs. A knowledge of the dermatomes and patterns of muscular innervation is required (see Chapter 8).

Radiographic and imaging studies can be helpful in delineating mass lesions and sites of trauma. Computed tomography (CT) and magnetic resonance imaging (MRI) have helped greatly in locating internal pathologic processes. Magnetic resonance neurography is particularly helpful in localizing a peripheral nerve lesion (4). MRI scanning has largely replaced myelography in the diagnosis of intraspinal lesions.

Paravertebral somatic nerve blocks with a local anesthetic can be helpful in locating a lesion when other studies are not conclusive (see Chapter 102). If myofascial pains are suspected, trigger point injections can be both diagnostic and therapeutic. Indeed, presumptive treatment with physical measures can allow the cause of the pain to abate; vague pain states without specific findings do not need to be studied in great detail the first time that the patient is seen.

SPECIFIC CAUSES OF LUMBOSACRAL NEURALGIA

Lesions of the Spinal Cord

Intrinsic Spinal Cord Lesions (XXVI–4)

Neoplasms or cysts of the thoracolumbar spinal cord can lead to pain in the abdomen, low back, perineum, and lower extremities. Lesions intrinsic to the spinal cord rarely present with pain; neurologic deficits are usually the initial complaint, and profound sensory and motor loss can be found without any pain complaints. Segmental pains can be present and are probably caused by stretching of the dorsal roots by the enlarging intrinsic mass. In the male, sexual dysfunction is a frequent early sign. Because the pain can involve the lower lumbar segments, the patient might be thought to have disk disease; for this reason the conus must be visualized in any imaging study.

The common cause of an intrinsic spinal cord lesion is a tumor (5,6 and 7). Other causes include syringomyelia, congenital or posttraumatic cysts, and vascular malformations. Unrecognized congenital abnormalities of the spinal cord can also produce low back pain and neurologic deficit; CT or MRI scanning and other studies can help to establish the diagnosis. A significant percentage of patients with repaired meningomyelocele or lumbosacral lipomeningomyelocele develop symptoms of a tethered spinal cord; pain and progressive neurologic deficit are the common presentation of such a condition (8). Surgical repair usually alleviates the symptoms and prevents further neurologic loss. Midline cutaneous and subcutaneous abnormalities should alert the physician to the possibility of an underlying congenital abnormality of the spinal cord.

Extramedullary Intradural Lesions

Lesions extrinsic to the spinal cord but within the dura are not common; most occur in the thoracic region and not in the lumbar and sacral segments. Neurofibroma and meningioma are the most common neoplasms, but almost any tumor of neural or glial origin, as well as congenital cysts, can be present (9). Neurofibromas usually start on a root and present relatively early, with radicular pain and neurologic loss. Meningiomas usually start ventral or dorsal to the spinal cord, and radicular signs are often late to develop. Ependymoma of the conus region can begin within the spinal cord but can expand into the subarachnoid space and compress nerve roots, leading to pain and neurologic deficits. Radicular lumbosacral pain is too often assumed to be caused by herniated nucleus pulposus at L-5 or S-1; a tumor at the level of the conus medullaris can also produce radicular pain and neurologic loss. For this reason, every imaging study performed for suspected lumbar disk disease should also include views of the conus.

Diagnosis of intramedullary or extramedullary intradural lesions is established by myelography, CT, or MRI. Electrodiagnostic studies can also be helpful. Treatment is exclusively by surgical removal, because these lesions are almost all benign and are not sensitive to radiation or chemotherapy (Fig. 77-1).

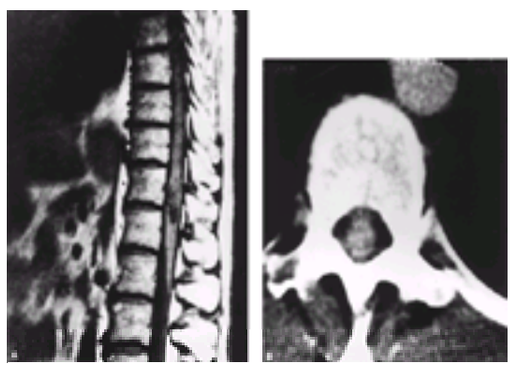

Figure 77-1. **A:** Intramedullary tumor (hemangioblastoma) at T-10 to T-11 as seen on midsagittal projection of magnetic resonance imaging scan. The tumor is the low-signal ovoid region within the higher-signal spinal cord. In this scan, cerebrospinal fluid is dark; fat and bones are white. **B:** Axial computed tomography scan with intravenous enhancement at T-10 to T-11. Swollen spinal cord with enhancing mass is obvious.

Meningeal Carcinomatosis (XXVI–11)

Leptomeningeal metastases from solid tumors elsewhere in the body can produce severe radicular pain and loss of function. The pathology is direct invasion of the nerve roots by tumor cells; a discrete mass might not be present. The most common primary tumors are carcinoma of the lung or breast, malignant melanoma, lymphoma, and leukemia. Both children and adults can suffer from this type of tumor spread. Diffuse spinal pain and headache are common. The diagnosis is confirmed by finding malignant cells in the spinal fluid. Treatment is by radiation or chemotherapy, depending on the primary lesion. Pain relief is sometimes obtained with narcotics; anticonvulsants can also be helpful (10).

Extradural Spinal Lesions (XXVI–4)

Herniated lumbar disk (see below) is probably the most common type of extradural lesion; tumors and abscesses also occur in this space. Extradural neoplasms are probably metastases from a primary lesion elsewhere in the body. Lung, breast, prostate, and thyroid neoplasms are the most common solid tumors. The patient usually has back pain before the development of signs of nerve root or spinal cord compression. The epidural deposit might be the first sign of the malignancy, or it might occur late in the course of the patient's disease. Diagnosis is established by myelography, CT, or MRI. Chemotherapy, radiation therapy, and decompressive laminectomy can all be used; the histology of the lesion determines the most effective therapy.

Epidural abscess is less common in the present antibiotic era than it was 50 years ago. There is often a history of bacteremia after a surgical procedure or of infection in the pelvic area, although epidural abscess can occur without any recognized antecedent infection. The patient almost always has severe back pain; neurologic deficits follow the pain if the lesion is not treated aggressively. The use of surgical decompression and appropriate antibiotics usually yields good results if the decompression is done before devastating neurologic loss has occurred (11).

Lesions of the Nerve Roots

Herniated Nucleus Pulposus (XXVI–1)

Certainly the most popular cause of lumbosacral radiculopathy, herniated nucleus pulposus (“ruptured disk”), is now recognized as a relatively uncommon cause of lumbago and sciatica (3). The pioneering work of Mixter and Barr (12) led to the realization that these common symptoms could be a result of extrusion of a fragment of disk into the spinal canal; formerly, surgeons had observed disk material in the spinal canal but thought it to be a form of neoplasm. Mixter and Barr (12) also described the value of myelography in establishing the diagnosis of ruptured disk.

In the past 20 years it has been recognized that many other structures in the back can produce both low back pain and pain referred to the sciatic nerve distribution. It is also well established that the pathologic changes that have been described in older texts as the basis for chronic pain are, in fact, found in many people who have never had any symptoms. Hence, there is only a loose association between the structural lesions and the patient's symptoms. Nonetheless, compression of the dorsal roots or of the dorsal root ganglion can lead to pain; herniated nucleus pulposus is a common cause of this syndrome (13). The role of herniated nucleus pulposus in

low back pain is discussed in greater depth in Chapter 76.

Etiology. Herniated nucleus pulposus is caused by trauma, the aging process, or both. If workers are compensated for on-the-job injuries, almost all disk disease will be ascribed to some type of minor traumatic event that happened at work. The actual role of trauma is not well understood because ruptured disks can occur in sedentary as well as heavy-labor settings. Degrees of disk disease are seen: degeneration of the disk, bulging of the annulus fibrosis, rupture of the disk through the annulus, and free fragment rupture of the disk into the spinal canal (Fig. 77-2). In general, the severity of symptoms is related to the extent of the pathology. Furthermore, as Spangfort (14) has clearly shown, the results of diskectomy are much better in patients who have free fragment disk ruptures. Disk degeneration and bulging of the annulus are a part of the aging process and occur in everyone to some degree.

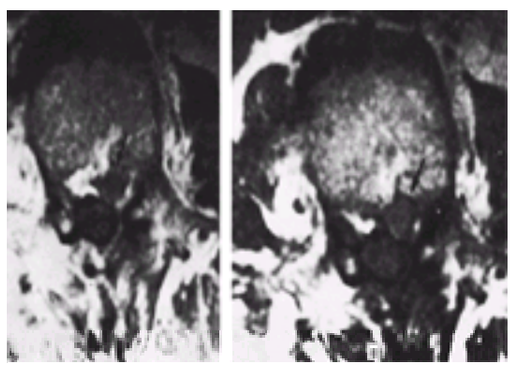

Figure 77-2. Free fragment disk L2-L3 rupture as seen on axial magnetic resonance imaging scan. Scar tissue from prior surgery enhances; disk fragment does not. **A:** Unenhanced scan. **B:** Gadolinium-enhanced scan. Arrow points to free fragment of disk. The patient had severe left L-2 radicular pain and paresthesia.

Symptoms and Signs. The outstanding symptom of herniated nucleus pulposus is pain. Most patients have had several episodes of low back pain before they develop pain that radiates to the buttock and leg in a segmental pattern. A specific episode of lifting, straining, or twisting is identified as the cause by most patients. The exact distribution of the pain depends on the root involved (Fig. 77-3). The S-1 root is most frequently compressed and leads to pain that radiates from the low back to the buttock, posterior thigh, lateral leg, lateral ankle, lateral foot, and fifth toe. The L-5 root is the next most frequently compressed and leads to pain in the low back, posterolateral thigh, dorsal foot, and medial toes. The L-4 root is the third most commonly involved and leads to pain in the low back, anterolateral thigh, and medial leg and foot to the first toe. Only rarely are more rostral nerve roots compressed by a herniated nucleus pulposus, because ruptures of disks above the L-3 to L-4 interspace are uncommon. The pain is aggravated by sitting, twisting, or lifting and is usually relieved by walking or lying down. Coughing, sneezing, and straining on the toilet typically exaggerate the pain.

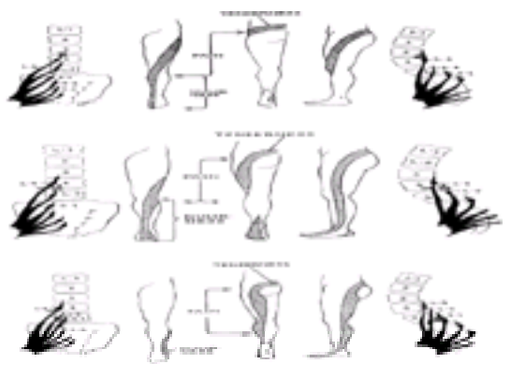

Figure 77-3. Dermatome hypalgesia, pain, and tenderness in the distribution of the lower limb from herniation of intervertebral disks. **A:** Pattern of distribution of the L-4 segment from herniation of the L-3 intervertebral disk. **B:** Dermatome hypalgesia, pain, and tenderness in the distribution of the L-5 segment resulting from herniation of the L-4 intervertebral disk. **C:** Dermatome hyperalgesia, pain, and tenderness in the distribution of the S-1 segment resulting from herniation of the L-5 intervertebral disk. (Modified from Keegan JJ. Dermatome hyperalgesia associated with herniation of the lumbar intervertebral disc. *J Bone Joint Surg* 1944; 26:238–248.)

Paresthesias are often perceived in the distribution of the compressed nerve root. These are of greater localizing value than the pain or sensory or motor deficits. Decreased light touch and pinprick sensations are sometimes noted. Motor changes are usually subtle but can be more pronounced. Weakness, atrophy, fasciculations, and reflex changes can occur (Table 77-1).

	Location		
Symptoms and signs	L4	L5	S1
Pain	In gluteal ("hip") region below iliac crest	In gluteal ("hip") region between sacral tuberosity and femoral trochanter	In medial gluteal ("hip") region over sacral tuberosity
Pain radiation	Anterior thigh and leg	Lateral thigh and leg	Posterior thigh and leg
Tenderness	Over spinous and transverse processes of vertebrae	Over spinous and transverse processes of vertebrae	Over spinous and transverse processes of vertebrae
Subjective numbness	Anterior leg, great toe	Lateral leg, three middle toes	Posterior leg, little toe
Hypalgesia	Over entire segment	Over entire segment	Over entire segment
Reflex changes	Patellar tendon reduced or absent	Usually no alteration	Achilles tendon reduced or absent
Motor weakness	Dorsiflexors of great toe	Dorsiflexors of ankle and toes	Plantar flexors

TABLE 77-1. Single nerve root syndromes of the lower lumbar and upper sacral segments

Mechanical signs of nerve root irritation are also present. These include reproduction of the pain on straight-leg raising, tenderness to percussion over the adjacent spinous processes to the herniated nucleus pulposus, paravertebral muscle spasm, lumbar scoliosis, and loss of lordosis.

A small percentage of patients sustain a massive free fragment rupture of a disk and suffer from a cauda equina syndrome, with multiple nerve root involvement and severe pain. This is the only case in which a herniated nucleus pulposus is a surgical emergency.

Diagnosis. Classic presentations of lumbar disk disease can be diagnosed from the history and physical examination (3). Atypical cases can be more difficult to discriminate from other pathologic processes that involve the back. Careful neurologic examination will usually locate the lesion. Radiculopathy caused by disk disease rarely involves more than one nerve root, and the signs and symptoms are usually unilateral. Low back pain usually precedes the development of leg pain.

Bowel and bladder symptoms are uncommon except in cases of large free fragment rupture, although subtle cystometrographic abnormalities have been well described in many patients with typical single-level disk disease. Intradural and epidural neoplasms, spinal infections and neoplasms, and retroperitoneal neoplasms and infection must be considered in the differential diagnosis. All these are much rarer than herniated nucleus pulposus. In addition, pain syndromes originating from

the joints of the spine, ligaments, or muscles must also be kept in mind. Pain that radiates into the lower extremity is not pathognomonic of herniated nucleus pulposus and nerve root compression.

Treatment

Conservative Therapy. The treatment of herniated nucleus pulposus should always be conservative, except in the case of a massive free fragment rupture with cauda equina compression (15). There is little evidence to show that any form of therapy improves on the natural history (see Chapter 76). The role of steroids is equivocal (16,17). Although some studies have indicated that the use of oral or epidural steroids hastens recovery from radicular pain caused by disk prolapse, others have not been confirmatory. Furthermore, the influence on later symptoms and signs (i.e., Is the natural history of the disease altered?) remains to be determined. As is so often the case, what is lacking is not the results of treatment but, instead, the natural history of the disease being treated. Prolonged bed rest and inactivity are deleterious. Narcotics and sedative-hypnotics can be of value for a few days, but their long-term use adds to the patient's disability. The patient should be told to avoid strenuous activities that stir up the pain but to resume normal activities as soon as possible.

Surgical Therapy. The major problem with lumbar disk disease is pain. The severity of the neurologic deficit rarely mandates surgical therapy. Only when the pain complaints are severe and unremitting should a surgical procedure be considered. If the diagnosis is straightforward, a diagnostic study such as myelography, CT or MRI, or electromyography is warranted only when the decision has been made to operate. Such studies only locate the lesion, and it should be remembered that they play no role in determining who needs surgery. All the myelographic, CT, and MRI changes that characterize lumbar disk disease are often found in people who do not have and might never have had significant low back and leg pain. These diagnostic studies never determine the need for surgery; they only locate the pathology in a patient who has already met the criteria for diskectomy (Fig. 77-4).

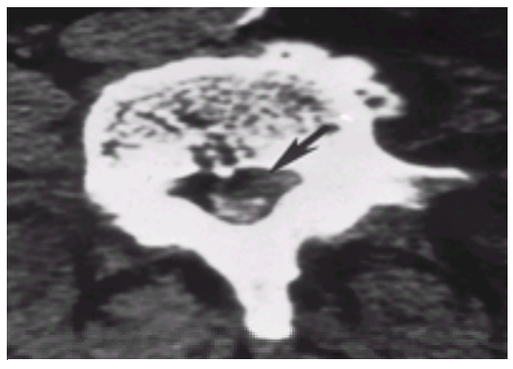

Figure 77-4. Axial computed tomography scan using intrathecal contrast agent showing that the dural sac is displaced posteriorly by a larger, herniated disk fragment (*arrow*). The patient had low back pain radiating to both legs, which was made worse by standing or walking.

The traditional open surgical method of removing a herniated lumbar disk has seen several modifications in the past 20 years. Microdiskectomy has its proponents; a percutaneous technique for mechanically removing the disk has been described (18). Enzymatic degradation of the nucleus pulposus by injection of chymopapain has also been popular. All of these procedures remove the disk, but none has been shown to offer major advantages. Each method carries some risk of complications. No matter how one removes a disk, the key to success is patient selection. Spangfort (14) showed that the relief of both leg and back pain was correlated with the findings at surgery: Free fragment disk ruptures had a 90% likelihood of relief of sciatica; bulging disks had a 60% likelihood of pain relief, and leg pain was more likely to be relieved than low back pain. The lack of randomized prospective allocation trials prohibits comparisons of results of different surgical strategies (19,20 and 21).

Relief of leg or back pain is not synonymous with return to work. Little evidence has shown that fusion of an otherwise normal lumbar spine improves the outcome for patients who have had a herniated nucleus pulposus and a diskectomy. Disk disease is a small component of the problem of low back pain in the modern industrialized state. Chapter 76 contains a more thorough discussion of low back pain and its attendant disability.

Spinal Stenosis (XXVII–3)

Spinal stenosis, also known as *neurogenic claudication*, is a painful syndrome that was first clearly described by Verbiest in 1954 (22). Bilateral lower extremity numbness, weakness, and pain, in association with low back pain, are present in varying degrees after walking or when standing erect. The symptoms are exercise induced and rapidly clear with rest. Vascular claudication occurs after exercise regardless of posture; neurogenic claudication occurs primarily in the erect position (23). The severity of the pain complaint usually exceeds the magnitude of the neurologic deficits (24).

The diagnosis can be confirmed by provocative physical testing and corroborated by myelography, CT, or MRI (Fig. 77-5). The causes of spinal stenosis are multiple, and accurate predictors of outcomes are not yet established (25). Conservative therapy can lead to excellent outcomes, but some patients prefer prompt surgery (26). Decompressive surgery is often effective treatment; stenosis of the spinal canal and of the neural foramina can be present to varying degrees, and surgical therapy must resolve the anatomic problems in each patient. Spinal stenosis and its treatment are also discussed in Chapter 76.

Figure 77-5. Myelogram showing pattern of spinal stenosis. The segmental narrowing is caused by encroachment of the enlarged ligamenta flava.

Arachnoiditis (XXVII–10)

One of the most disastrous complications of disk disease, myelography, trauma, subarachnoid hemorrhage, infection, or spinal surgery is the development of arachnoiditis involving the cauda equina (27). It is not understood why only a small percentage of patients who have one of these inciting causes develop inflammatory changes in the nerve roots and the surrounding arachnoid. Furthermore, not everyone with the histologic findings of arachnoiditis has a pain syndrome.

Etiology. Although any of the causes listed above can precede the development of arachnoiditis, none of them does so with any regularity. In addition to these factors, the following causative influences have been thought to be involved: syphilis; bacterial, fungal, or disk space infection; intrathecal drug therapy; herniated nucleus pulposus; spinal stenosis; radiation therapy; intradural tumor; and spinal anesthesia. It is not known whether patients who develop inflammation in the arachnoid that progresses to fibrosis have an alteration in their immunologic responses. The initial inflammatory process can proceed to severe scarring, both within the arachnoid and within the nerve roots themselves. The process can be restricted to one nerve root or can involve various parts of the cauda equina. Arachnoiditis has become

much less common since myelography has been largely replaced by MRI scanning.

Symptoms and Signs. The major problem with arachnoiditis is severe, unremitting pain in the low back and legs. Varying degrees of motor and sensory loss can be present, and in some patients the scarring process in the arachnoid is associated with progressive, profound neurologic loss, although this is relatively uncommon. The pain is aggravated by movements or positions that stretch the lumbar nerve roots. Most patients say that exercise aggravates their pain and rest relieves it.

Diagnosis. The development of chronic low back and leg pain in a patient who has been exposed to any of the causative factors should lead to the suspicion of arachnoiditis. Patchy neurologic deficits that involve multiple nerve roots are common. Diagnostic studies should reveal the absence of other structural lesions and the presence of nerve root matting or clumping and filling defects in the arachnoid. This is often a diagnosis of exclusion and is sometimes made without any real evidence.

Treatment. No controlled studies have demonstrated effective treatments for arachnoiditis. Some patients have responded to epidural and intrathecal steroids, usually administered with a local anesthetic. Because steroids do not affect collagen that has already been laid down to form a scar, it is difficult to explain their purported efficacy in arachnoiditis (28). Surgical lysing of the scarred nerve roots has also been undertaken, with variable results at best (29,30). Some patients lose neurologic function after this operation. Because arachnoiditis is probably a form of deafferentation pain, ablative surgical procedures are not indicated in most patients. Spinal cord stimulation has led to symptomatic improvement in many but not all patients (31,32).

Fractured Lumbar Spine (XXVI–5)

Fractures of the lumbar spine represent major trauma. They are associated with acute pain that can be expected to abate as the injury heals, but some patients develop a chronic pain syndrome. Persistent pain should raise the suspicion of instability at the site of injury. Trauma to the lumbar and sacral spine can also result in damage to the cauda equina and lead to deafferentation pain. Arachnoiditis and nerve root scarring can also follow trauma, and severe pain can ensue.

Lumbosacral Plexus Avulsion

Avulsion of the lumbosacral plexus or contusion of the roots that form the plexus is less common than major injuries to the brachial plexus. The lumbosacral plexus is more protected than the brachial plexus, and avulsion only occurs with massive trauma (33). These roots originate in the conus medullaris; avulsion can lead to myelopathy because of compromise of the blood vessels that feed the spinal cord and enter the dura in association with the nerve roots. A history of major trauma is almost always present, and the neurologic deficits occur immediately. Pain is present initially, and in some patients a denervation pain develops in the anesthetic areas of the body.

The management of this chronic pain is difficult. It does not respond well to narcotics, but anticonvulsants are sometimes valuable. Ablative surgical procedures are usually not helpful; dorsal root entry zone lesions are probably the most effective (see Chapter 106).

Postherpetic Neuralgia (XXVI–3)

Herpes zoster can involve the lumbar and sacral dermatomes and can lead to severe pain in the acute phase and chronic pain if postherpetic neuralgia develops. This common pain syndrome is discussed in Chapter 22; nothing is unique about its occurrence in the lower extremities. Inflammatory and degenerative changes are found in the peripheral nerves, dorsal roots, and dorsal horn of the spinal cord. Medical and surgical management can be difficult.

Tabes Dorsalis (XXVI–9)

Tabes dorsalis (tabetic neurosyphilis) is the cause of lancinating pains in a radicular pattern that can involve the lumbar and sacral dermatomes (34). It is much less common in the present antibiotic era, occurring predominantly in those of middle age, because it takes several decades for the infection to progress to this stage. Patients describe severe, shocklike pains that are of brief duration but can recur frequently. Both hypesthesia and hyperesthesia can be found in the areas of pain. Signs of spinal cord dysfunction are usually present. This pain syndrome is almost pathognomonic; tests for syphilis are positive.

The lightning pains can be ameliorated by anticonvulsants; diphenylhydantoin, gabapentin, and carbamazepine are most commonly used (see Chapter 23). Cordotomy has been reported to have a high success rate for cases in which medications are not effective (see Chapter 106).

Diabetic Pseudotabes (XXVI–9)

Diabetics can develop various neuropathies and myelopathies, including what is called *diabetic pseudotabes*. The exact cause of the neurologic signs and symptoms is not understood. The patient has signs of posterior column dysfunction (proprioceptive loss), radicular sensory loss, and radicular lancinating pains. Pseudotabes is distinguished from tabes dorsalis by the presence of abnormalities of sugar metabolism and the absence of positive tests for syphilis. Optimal management of diabetes seems to lessen the likelihood of occurrence of this form of neuropathy. Symptomatic relief can sometimes be obtained with anticonvulsants (see Chapter 23).

Lesions of the Lumbosacral Plexus

Lesions of the lumbosacral plexus are rare, because its location protects it from most trauma. Any lesion of the plexus can produce pain that is increased by deep palpation or by exercise that stretches the plexus or involves the psoas muscle. A sudden onset of severe pain and unilateral lumbosacral plexopathy can be a result of rupture of an abdominal aortic aneurysm or of the development of a retroperitoneal hemorrhage in a patient who is taking anticoagulants. Most other causes of plexopathy are of gradual onset.

Neoplasms (XXVI–8/503X4b)

Intrinsic Tumors. Tumors of the lumbosacral plexus present with neurologic deficits and pain that is usually referred to the distribution of the involved nerves. Most of these intrinsic lesions are benign schwannomas or neurofibromas, which can be solitary or part of a more generalized phakomatosis. Malignant degeneration rarely occurs. CT and MRI are of great diagnostic assistance; electromyography localizes the lesion functionally. Treatment involves surgical excision and repair of the plexus with cable grafts, when appropriate. Pain from a tumor of the plexus is sometimes relieved by narcotics; anticonvulsants can also be helpful, because often a component of deafferentation pain is also present.

Extrinsic Tumors. Retroperitoneal neoplasms can invade the lumbosacral plexus and produce severe pain and progressive neurologic deficits. Lymphoma, sarcoma, and uterine carcinoma (in women) are the most common types of tumors that invade the plexus and produce pain. Typically, the pain is perceived both deep in the abdomen and pelvis and in the distribution of the plexus to the groin and lower extremities. Aggressive medical (and sometimes surgical) treatment is needed to alleviate this type of cancer pain (see Chapter 35 and Chapter 36).

Lumbosacral Plexitis

Pain and neurologic deficits can develop rapidly in the lumbosacral plexus without any apparent injury or anatomic lesion and are assumed to be caused by a viral inflammation of the lumbosacral plexus (35). The disease is self-limiting and usually has a favorable prognosis. Symptomatic therapy is indicated; some have advocated the use of steroids (36).

Postradiation Plexopathy

Radiation therapy of the lower abdomen and pelvis can lead to lumbosacral plexopathy secondary to fibrosis. It is sometimes difficult to discriminate between tumor recurrence, surgical scarring, and radiation-induced fibrosis. MRI or CT helps to rule out tumor recurrence and make the diagnosis of plexopathy more likely. Radiation-induced pain rarely develops in less than a year after therapy; the latency period can be several years (1).

Symptoms and Signs. Sensory changes are usually found earliest in those with radiation-induced plexopathy; the amount of sensory and motor loss varies and can be slowly progressive. Radiation-induced skin changes are almost always observed.

Treatment. The treatment of radiation-induced plexopathy is not successful in most patients. The condition is rare, and proven therapies do not exist. Some patients respond favorably to analgesics, and anticonvulsants and antidepressants help others. Ablative surgical procedures are sometimes helpful; neurostimulation of either spinal cord or brain has been reported to be successful.

Contusion or Stretching

The lumbosacral plexus is not often contused or stretched by external trauma because it is well protected. The most common cause of such an injury is childbirth—hence the female preponderance (37). Either the fetal head or the forceps used to deliver the head can contuse or stretch the plexus; the lower segments are more likely to be involved. The pain and neurologic deficits are usually of several months' duration and abate spontaneously. The upper portion of the plexus can be damaged during delivery if the hips are maintained in flexion and abduction for a prolonged period. Pelvic surgery or external trauma can also damage the lumbosacral plexus (38).

Penetrating Trauma

Gunshot wounds or low-velocity penetrating injuries can directly damage the lumbosacral plexus, but this is a rare traumatic injury. Neuromas and scarring around the plexus can follow the acute injury and lead to chronic pain. Proper management requires adequate visualization of the plexus at the time of debridement so that the nature of the injury can be identified and plans for restorative surgery can be developed. Repair of the damaged plexus is the best method of preventing chronic pain. Secondary procedures to lyse the scar from within and around the nerve are sometimes helpful. Some patients respond to pharmacologic management with narcotics, anticonvulsants, or antidepressants. Ablative surgical procedures are rarely indicated. Electrical stimulation of the spinal cord or brain is sometimes helpful.

Lesions of the Peripheral Nerves

Acute Trauma

Any of the nerves of the leg can be injured by blunt or penetrating trauma. The injury itself is painful because of the surrounding tissue damage, and neurapraxia develops immediately. The likelihood of neurologic deficit and of the development of chronic pain is a function of the severity of the nerve injury. Chronic pain can develop if a neuroma is formed at the site of axonal disruption or if the nerve becomes chronically entrapped in a scar.

Prevention of chronic pain is associated with prompt repair of the nerve (39). If surgical exploration does not result in pain relief, local injections of steroids can be helpful for some patients.

Chronic Trauma

The most common cause of chronic nerve trauma is mechanical compression by surrounding structures; these are known as *entrapment syndromes* (40,41). Although it is possible for any nerve at any point in its course to be entrapped, most entrapments occur at specific sites on specific nerves. The more common lower extremity entrapment syndromes are described in Table 77-2.

Nerve	Location of pain	Sensory changes	Weakness	Usual cause
Lateral femoral cutaneous (meralgia paresthetica)	Anterolateral thigh	Anterolateral thigh	None	Entrapment under inguinal ligament
Saphenous	Medial leg, knee	Medial calf	None	Entrapment at adductor canal
Obturator	Proximal medial	Proximal medial	Adduction	Entrapment at obturator canal
Sciatic (piriformis syndrome)	Buttock, lateral and posterior leg, knee	Lateral and posterior leg, knee	Hamstrings, all distal muscles	Entrapment by piriformis muscle
Peroneal	Lateral knee, retro leg, and foot	Lateral leg, dorsum of foot	Foot drop/flexors	Entrapment at fibular head
Deep peroneal (anterior tarsal tunnel)	Dorsum of foot	First dorsal web	None	Entrapment by flexor retinaculum
Posterior tibial (posterior tarsal tunnel)	Plantar foot and toes	Plantar foot and toes	Intrinsic flexors	Entrapment at tarsal tunnel
Interdigital (Morton's neuroma)	Toes (usually third and fourth)	Opposing toes surfaces	None	Entrapment at metatarsal head

TABLE 77-2. Lower extremity entrapment syndromes

Etiology. The pathophysiology of nerve entrapment is almost certainly ischemia of the nerve. A mild degree of pressure for a short period produces a rapidly reversible dysfunction. Variations in the amount of pressure might be responsible for the intermittent symptoms that are so characteristic of these lesions. The lesion is electrophysiologically characterized by slowing of conduction velocities; histologic findings include segmental demyelination and remyelination (42).

Symptoms and Signs. Entrapment neuropathies are responsible for focal neurologic deficits, local and radiating pain, and paresthesias. Any of these three components can predominate, or they can be absent. The lost axons probably cause the motor and sensory loss; the paresthesias and pain of course require functional axons. Thus, the electrophysiologic changes do not correlate well with the pain or paresthesias.

Usually the symptoms of an entrapment neuropathy develop after unusual exercise of the appropriate body part. Once present, the symptoms frequently wax and wane without obvious cause. The neurologic deficits are usually slowly progressive; the pain and paresthesias vary. The pain might not be only local, but can radiate proximally and distally from the site of entrapment.

Diagnosis. Entrapment neuropathies can be diagnosed on the basis of history and physical findings and are corroborated by electrodiagnostic studies (43). Both early and late responses of nerve conduction and electromyography might be required for accurate location (see Chapter 13). Magnetic resonance neurography and the identification on MRI of denervated muscle can also be helpful (4) (Fig. 77-6).

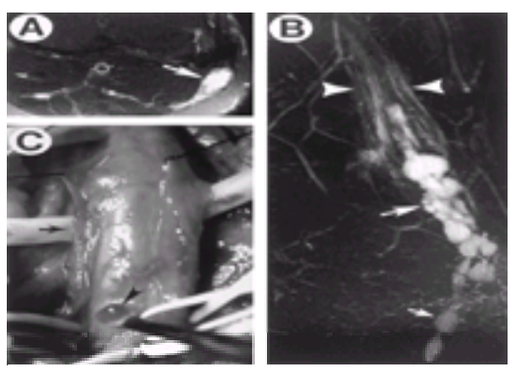

Figure 77-6. Magnetic resonance neurogram of cysts of the peroneal nerve. **A:** Axial T2 fast-spin echo (FSE) image with high spinal cystic lesions (*arrow*) within common peroneal nerve. **B:** Coronal T2 FSE multiplanar reconstruction showing high signal intraneural cysts (*small arrows*) and splayed nerve fascicles (*between arrowheads*). **C:** Intraoperative photograph demonstrating enlargement of peroneal nerve and cyst (*black arrowhead*). (From Kuntz C IV, Blake L, Britz G, et al.

Magnetic resonance neurography of peripheral nerve lesions in the lower extremity. *Neurosurgery* 1996;39:750–756, with permission.)

Treatment. Both nonsurgical and surgical therapies have been effective for entrapment neuropathies. Mild lesions related to repetitive movements can be managed by appropriate changes in occupation or recreation. Splinting or bracing can be effective for some lesions. Local injection of steroids can be beneficial. When these measures fail, surgical decompression is often curative. If major damage to the nerve has already occurred, decompression might not alleviate the loss of function or the pain.

Specific Nerve Entrapment Syndromes

Lateral Femoral Nerve Entrapment (XXX–1)

Entrapment of the lateral femoral cutaneous nerve is known as *meralgia paresthetica*. It was one of the earliest entrapment syndromes to be described. The nerve is derived from the L-2 and L-3 roots and travels across the pelvic side wall to enter the thigh at the lateral end of the inguinal ligament, which is the common site of entrapment. This nerve has no motor fibers; the symptoms are purely sensory.

Etiology. Entrapment usually occurs where the nerve passes underneath or through the inguinal ligament at the origin of the ligament and attaches to the anterior superior iliac spine. Human studies have revealed that in a significant percentage of individuals the nerve passes from the pelvis to the thigh through the fibers of the inguinal ligament rather than below it (43) (Fig. 77-7). Other causes are chronic trauma in those in certain occupations, intrapelvic pathology with compression along the long course of the nerve, and occupations that require standing with the side of the anterior superior spine held against a hard object (e.g., barbers) (44).

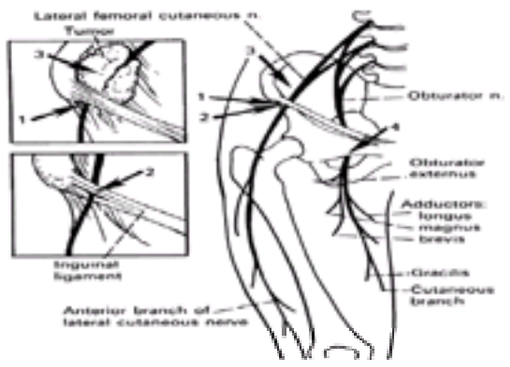

Figure 77-7. Sites of entrapment of the lateral femoral cutaneous and obturator nerves: the most common site of entrapment of the lateral femoral cutaneous nerve as it passes below the inguinal ligament (1); site of entrapment of the lateral femoral cutaneous nerve as it passes within the ligament (2); site of entrapment of the lateral femoral cutaneous nerve in the pelvis by a tumor (3); site of entrapment of the obturator nerve (4). (Developed by JJ Bonica and M Domenowske from data in Kopell HP, Thompson WAL. *Peripheral entrapment neuropathies*. Baltimore: Williams & Wilkins, 1963.)

Signs and Symptoms. The patient usually complains of both pain and paresthesias in the upper lateral thigh. The pain is described as burning or tingling and is localized to the skin and not to deep structures. Light stimulation of the skin is often described as very unpleasant (allesthesia). The pain and paresthesias are aggravated by standing and walking or by extending the hip; sitting or lying with the hip flexed can alleviate the symptoms. Many patients complain of the paresthesias without describing pain in the thigh; others have neither pain nor paresthesias but only sensory loss. The area of sensory loss is usually only in the center of the large territory of this nerve; the region of altered response to stimulation is often greater.

Diagnosis. Sensory action potentials can demonstrate conduction delay, temporal dispersion, or absence of responses (see Chapter 13). Electromyography should not reveal abnormalities of the quadriceps muscle or femoral nerve. No motor or sensory abnormalities should be present elsewhere in the leg. Retroperitoneal mass lesions should be excluded by physical examination or appropriate imaging studies. In fact, the presentation of burning and tingling in the lateral thigh is rarely caused by anything other than entrapment of the lateral femoral cutaneous nerve.

Treatment. Symptoms are usually mild, and reassurance and accurate diagnosis often suffice. Patients should be advised not to wear constricting garments such as corsets or belts. Obese patients should be advised to lose weight. If the onset of symptoms is associated with a new exercise activity, patients should be advised to find another, less stressful exercise.

The role of nerve blocks with or without steroids at the level of the inguinal ligament is unclear, because no controlled studies have been carried out. Whether temporary relief of symptoms alters the long-term prognosis is unknown. Some patients have remission of their complaints without any treatment. Although surgical decompression and nerve resection were once common, they are often not successful. Indeed, the pain complaints usually increase after transection of this or any other peripheral nerve.

Femoral Nerve Entrapment (XXX–3)

The femoral nerve can be compressed by various neoplasms and vascular diseases, but it is not involved in an idiopathic entrapment syndrome. Most of these lesions are intrapelvic and not occult. The nerve can also be damaged by extreme flexion or hyperextension at the hip. The femoral nerve is derived from the L-2, L-3, and L-4 roots and travels across the retroperitoneal space to exit the pelvis at the femoral triangle in close proximity to the femoral artery and vein.

Signs and Symptoms. Pain is not usually a symptom of femoral nerve entrapment. The major findings are quadriceps weakness with severe gait impairment and decreased sensation over the anterior thigh and medial calf. Pain can be at the site of the causative lesion rather than in the distribution of the nerve itself.

Diagnosis. The presence of hip flexor weakness indicates a lesion of the lumbosacral plexus or spinal roots and discriminates femoral nerve entrapment from femoral neuropathy. Electromyography, sensory action potentials, and nerve conduction velocity studies can help to locate the lesion. Imaging studies (CT or MRI) can be helpful in identifying intrapelvic or retroperitoneal pathology.

Treatment. Because entrapment is almost always caused by a pathologic lesion impinging on the nerve, treatment is aimed at that lesion. Explorative surgery to relieve pain is usually fruitless; only if a structural abnormality is present will surgery help.

Saphenous Nerve Entrapment

The saphenous nerve is a sensory branch of the femoral nerve that travels through the adductor canal of the thigh and penetrates the fascia just above the knee to supply the skin of the medial calf and ankle and often the medial portion of the foot dorsum. Idiopathic entrapment occurs where the nerve exits from the adductor canal in the distal thigh (subsartorial tunnel).

Symptoms and Signs. Saphenous nerve entrapment is characterized by burning or aching pain in the medial calf that can radiate into the entire distribution of this nerve. The patient does not have any weakness. Use of the knee can exacerbate the pain or the sensory changes.

Diagnosis. The diagnosis of saphenous nerve entrapment is based on the complaint of pain and sensory changes in the territory of this nerve without involvement of any other branches of the femoral nerve. Sensory action potentials can be helpful; mass lesions in the adductor canal can be seen on CT scan or with MRI. Prior

surgery in the area of the knee can lead to entrapment in the postoperative scar.

Treatment. Severe symptoms have been treated successfully by exploration and decompression of the exit zone of the saphenous nerve from the adductor canal. This is a rare entrapment neuropathy, and few data are available concerning its natural history and treatment outcomes.

Obturator Nerve Entrapment (XXX–3)

Entrapment of the obturator nerve usually occurs at the obturator membrane as this nerve leaves the pelvis and enters the thigh (see Fig. 77-7). Most obturator nerve lesions are traumatic; idiopathic entrapment is rare. Sacroiliac and sacrum pathology can encroach on the obturator nerve as it traverses the pelvis.

Symptoms and Signs. The patient complains of pain in the upper medial thigh, with possible associated sensory loss in the medial thigh and weakness of the adductor muscles. The latter can lead to a wide-based gait with the leg held in an abducted position. Rarely, the pain radiates to the knee or even below it.

Diagnosis. Sensory and motor findings can be confirmed by electromyography and nerve conduction studies. Space-occupying lesions in the retroperitoneal or pelvic regions can be seen with MRI or on CT.

Treatment. Most obturator nerve entrapment is caused by a lesion, and extirpation of the lesion is the goal of therapy. Entrapment at the obturator membrane can be approached surgically.

Sciatic Nerve Entrapment (XXX–4)

The sciatic nerve can be compressed at many sites along its course from the sciatic notch to the point at which it divides into the peroneal and posterior tibial nerves, just above the popliteal fossa. This nerve is derived from the L-4 and L-5 roots and the S-1, S- 2, and S-3 sacral roots. The nerve leaves the pelvis through the sciatic notch, where it immediately underlies the piriformis muscle and is above the obturator internus muscle. This is the most frequent site of sciatic nerve entrapment, where it has been called the *piriformis syndrome* (Fig. 77-8).

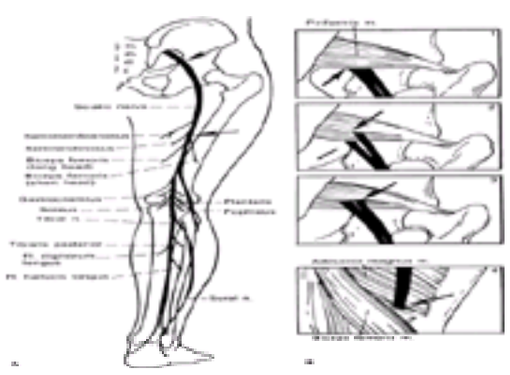

Figure 77-8. Sites of entrapment of the sciatic nerve. **A:** Posterior view of lower limb showing the position of the sciatic nerve and its branches. Arrows indicate sites of sciatic nerve entrapment. **B:** Insets with details. Inset 1. Arrow shows the most frequent site of entrapment. This occurs because of compression by the piriformis muscle, which lies just above the sciatic nerve as it passes from the pelvis through the greater sciatic foramen; beneath the nerve itself is the obturator internus muscle. It has been shown that inward rotation of the thigh causes compression of the sciatic nerve against the tendinous origin of the piriformis muscle. Spasm of the piriformis muscle (inset 1) can also cause compression. In 12% of individuals the nerve passes between parts of the piriformis muscle (insets 2 and 3), the peroneal nerve portion of the sciatic nerve being most frequently involved. Compression can also be caused by a myofascial band in the distal portion of the thigh between the biceps femoris and the adductor magnus muscles trapping the nerve (*arrow,* inset 4). Other causes include muscle fibrosis induced by repeated injections of pentazocine, compression of the nerve in the pelvis during anticoagulant therapy, and compression of the nerve from leakage of acrylic plastic into the region posterior to the hip joint during total hip replacement. (Developed by JJ Bonica and M Domenowske from data in Kopell HP, Thompson WAL. *Peripheral entrapment neuropathies*. Baltimore: Williams & Wilkins, 1963.)

Symptoms and Signs. Sciatic nerve entrapment by the piriformis syndrome can lead to buttock pain and pain that radiates in the distribution of the sciatic nerve to the foot. Motor loss can lead to instability of the foot and a severe gait dysfunction. The pain is usually described as aching and cramping. Paresthesias can be present in the sciatic nerve sensory territory.

Diagnosis. Piriformis syndrome can be diagnosed by determining the site of sciatic nerve compression on clinical, imaging, and electrodiagnostic grounds. The nerves and muscles innervated by the nerve roots before the lumbosacral plexus are spared; electromyography can be helpful in showing no involvement of the paraspinal muscles. Electromyography and nerve conduction velocity studies in the extremity, however, cannot locate the site of the lesion between the plexus and mid- thigh. The physical findings and history so typical of herniated nucleus pulposus are not found in patients with sciatic nerve entrapment (see Chapter 75). Unilateral symptoms and signs are rare in patients with spinal stenosis. Unfortunately, many patients with sciatic nerve entrapment are initially treated as if they had a herniated nucleus pulposus.

Treatment. If the diagnosis of piriformis syndrome is confirmed by diagnostic studies and the patient has significant neuropathic signs, the piriformis muscle should be detached from its origin and any fascial bands constricting the nerve should be transected.

Peroneal Nerve Entrapment

The peroneal nerve is a component of the sciatic nerve; it separates from the posterior tibial nerve approximately 8 cm proximal to the popliteal fossa. The peroneal nerve can be compressed as it courses around the fibular head in the upper calf and passes through a fibrous tunnel between the edge of the peroneus longus muscle and the fibula (Fig. 77-9). Trauma is a more common cause of peroneal neuropathy. Other causes include compression from improperly applied plaster casts, tight stockings, bandages, or garters. Peroneal damage can result from certain practices that produce compression and ischemia of the nerve, such as sitting, squatting, or kneeling when picking strawberries or weeding a garden for long periods, which result in compression by the tendon of the posterior part of the peroneus longus at the level of the head of the fibula. The peroneal nerve can also be compressed by various masses, including tumors of the nerve itself or tumors of the bone or ganglia arising from the superior tibiofibular joint.

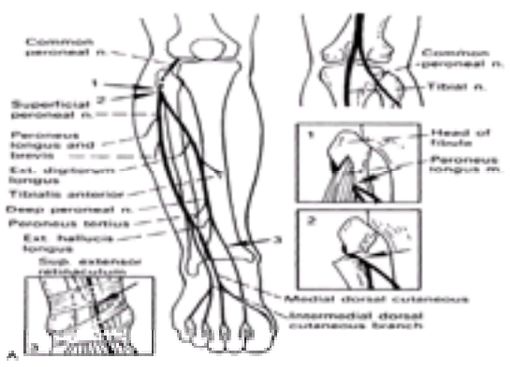

Figure 77-9. Entrapment of the peroneal nerve. **A:** Posterior view of the knee depicting the beginning of the common peroneal nerve as it separates from the tibial nerve and winds around the head of the fibula. **B:** Anterior view of the lower leg showing the common peroneal nerve winding around the head of the fibula and then dividing into superficial and deep branches. Arrows indicate sites of nerve entrapment. Inset 1 shows entrapment as the nerve passes through a fibrous tunnel

between the edge of the peroneus longus muscle and the fibula. Inset 2 shows entrapment caused by fracture of the fibula. Inset 3 shows entrapment of the deep peroneal nerve by the superior extensor retinaculum. (Developed by JJ Bonica and M Domenowske from data in Kopell HP, Thompson WAL. *Peripheral entrapment neuropathies*. Baltimore: Williams & Wilkins, 1963.)

Symptoms and Signs. Entrapment of the peroneal nerve usually presents with a deep, aching pain in the lateral distal knee. Pain can radiate into the foot, especially with pain at the fibular head, and slowly progressive sensory and motor loss is common. The sensory loss can vary from no loss to anesthesia over the lateral calf and dorsolateral surface of the foot. The skin distribution of the peroneal nerve is variable, but hypesthesia is commonly noted in the lateral calf and foot dorsum, including the medial three toes. Weakness of the foot dorsiflexors and everters can be present. Peroneal palsies caused by trauma are usually painless. Electrodiagnostic studies show both motor and sensory changes restricted to the peroneal nerve distribution. If the posterior tibial nerve is spared and both the superficial and deep branches of the peroneal nerve are involved, the lesion is at the fibular head.

Treatment. If entrapment of the peroneal nerve is confirmed, surgical decompression is warranted. Pain can be relieved effectively, and return of peroneal nerve function is commonly seen. Significant peroneal nerve dysfunction mandates a foot brace so that the patient can ambulate effectively.

Entrapment Neuropathies of the Foot (XXX–5)

Three entrapment neuropathies of the nerves of the foot have been well described: The deep peroneal nerve can be compromised in the anterior tarsal tunnel, the posterior tibial nerve can be damaged in the posterior tarsal tunnel (Fig. 77-10), and the interdigital nerves can be damaged by adjacent metatarsal heads (Morton's neuroma). Local anesthetic injections can help to establish the diagnosis; electrodiagnostic studies have not been reported in significant number. Surgical decompression of tarsal tunnel syndrome has been reported to yield good results (38). Morton's neuroma is treated by excision of the common interdigital nerve when conservative measures have failed to relieve the metatarsal pain.

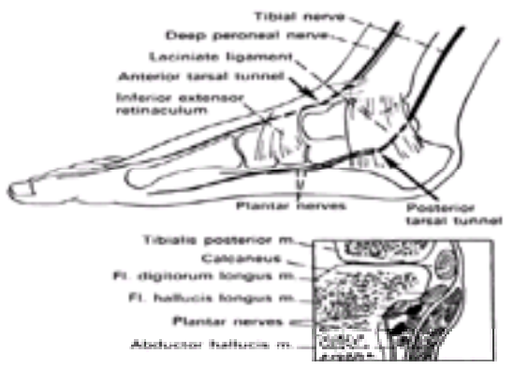

Figure 77-10. Entrapment of the tibial nerve in the posterior tarsal tunnel, which contains the tibial nerve, its posterior tibial artery, and tendons of the tibialis posterior, flexor digitorum longus, and flexor hallucis longus. The syndrome usually has a traumatic basis such as fracture and dislocation of the ankle, but symptoms might not develop until some time after the injury. Nonspecific tenosynovitis or thrombophlebitis can affect other contents of the tarsal tunnel and produce compression of the nerve. The anterior tarsal syndrome is an entrapment of the terminal portion of the deep peroneal nerve as it runs below the dense superficial fascia of the ankle. Inset: Cross-section of the ankle showing the contents of the posterior tarsal tunnel. (Developed by JJ Bonica and M Domenowske from data in Kopell HP, Thompson WAL. *Peripheral entrapment neuropathies*. Baltimore: Williams & Wilkins, 1963.)

Neoplasms

Tumors of the peripheral nerves can present with both local and referred pain and with sensory and motor changes in the distribution of the nerve (45). The typical history is of gradually progressive sensory and motor loss and pain in the region of the tumor. These tumors are usually slow-growing benign lesions, although they can become sarcomatous (46). Ganglion cysts may be found throughout the course of the sciatic nerve, but are most common in the popliteal fossa. They grow slowly and often present with symptoms similar to an entrapment (47). The treatment is surgical excision.

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CHAPTER 78

Pain in the Hip

John M. Clark

Many different diseases, either alone or in combination, can cause pain in the region of the hip. Most, but not all, of these diseases are musculoskeletal in origin. Disorders of the lumbosacral spine commonly cause buttock and thigh pain. More rarely, diseases of the urogenital and gastrointestinal systems will present as groin and thigh pain. This chapter covers musculoskeletal conditions other than those originating in the spine (Table 78-1). The purpose is to assist a practitioner confronted with the complaint of hip pain, and for that reason diagnostic features are emphasized. Pediatric hip disease, tumors, and most traumatic conditions are discussed only briefly.

Degenerative arthritis
Nontraumatic necrosis of the femoral head
Septic arthritis/osteomyelitis
Trochanteric bursitis/iliotibial band syndrome
Iliopsoas tendinitis/iliopectineal bursitis
Psoas abscess, tumor, or hematoma
Tear of the acetabular labrum
Painful pubic symphysis
Painful sacroiliac joint
Piriformis syndrome
Stress fractures of the femur and pelvis
Hip pain in pregnancy
Paget's disease

TABLE 78-1. Conditions that cause pain in the hip region

DEFINITIONS OF HIP PAIN

Clinicians and patients use the term “hip pain” differently, and this leads to confusion. Technically, the hip is the synovial joint and the ligaments that give it stability. To the layperson, however, the *hip* is the gluteal region, or buttock. Therefore, many patients who present complaining of hip pain actually suffer from extraarticular conditions, such as sciatica. Once the exact pain pattern is established, the diagnosis may be obvious. Conversely, diseases in the hip joint typically refer pain to the thigh and knee. For these reasons, one should clarify the patient's complaints early in the evaluation process so that further examination and testing can be focused. Use of pain diagrams is particularly helpful in this process.

ANATOMY AND MECHANICS OF THE HIP

The hip is a spherical ball and socket joint that routinely supports loads between three and 10 times the body weight. The joint shape provides a large arc of motion but requires stout ligaments and large, powerful muscles for movement and stabilization.

Muscular Anatomy

Hip muscles are classified by the motion they control (Fig. 78-1, Table 78-2). All of these muscle groups are powerful. The muscles that effect hip abduction are also those that support the pelvis and trunk during one-legged stance. For this reason, deficits in abductor strength cause significant dysfunction. The most important hip flexors are rectus femoris (part of the quadriceps), iliacus, and psoas (Fig. 78-2). The psoas and iliacus converge, forming the large iliopsoas tendon (Fig. 78-3). Complete loss of active flexion, as can occur after a stroke, will usually necessitate the use of crutches for walking. Powerful hip extension is necessary for stair climbing and rising from a chair.

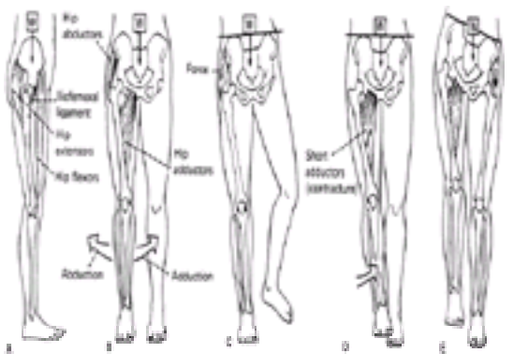

Figure 78-1. Simplified schematic of the pelvis and lower limbs and their relation to the major muscle groups at the hip. **A:** Lateral view showing the flexors and extensors. **B:** Anterior view showing the abductors and adductors. **C:** Abductors of the hip on one side balance the pelvis when the opposite leg is lifted [the force exerted by these muscles; this operates at the hip in addition to the weight of the body (W)]. **D:** Contracture of hip adductors prevents the leg from achieving the neutral (vertical) position in the abduction-adduction plane. **E:** Because walking requires the walking limb to be vertical, an adductor contracture causes the pelvis to be elevated, thus producing a fixed tilt that results in an apparent shortening of the leg. (Modified from Rosse C. The hip region and the lumbosacral plexus. In: Rosse C, Clawson DK, eds. *The musculoskeletal system in health and disease*. Hagerstown, MD: Harper & Row, 1980.)

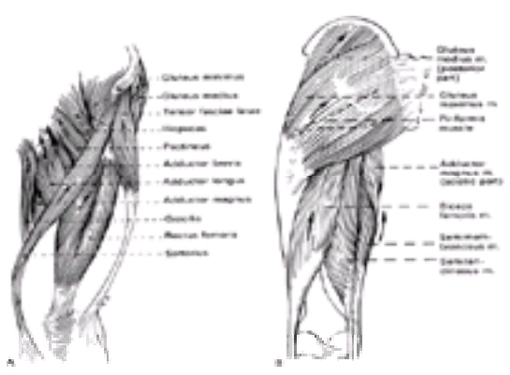

Figure 78-2. Muscles of the hip. **A:** Anterior view showing the flexors and adductors of the hip and extensors of the knee. The iliacus, together with the psoas major, forms a chief flexor. The iliacus originates from the pelvic surface of the ilium and then joins the psoas major, which originates from the last thoracic and all lumbar vertebrae. The common tendon inserts on the lesser trochanter. The rectus femoris, although primarily an extensor of the knee, is an effective hip flexor. The pectineus arises from the pectineal line of the pubis and inserts along the line leading from the lesser trochanter to the linea aspera. The sartorius arises from the anterior superior iliac spine and inserts on the proximal part of the medial surface of the tibia. The abductors also contribute to hip flexion. **B:** Posterior view showing extensors of the hip. The gluteus maximus originates over a wide area of the back of the bony pelvis and inserts into the gluteal tuberosity of the femur. The hamstring muscles, the semimembranosus, the semitendinosus, and the biceps femoris originate in the ischial tuberosity and insert below the knee. Consequently they also act as flexors of the knee joint. (From Hollinshead WH. *Anatomy for surgeons.* Vol 3, The back and limbs. Philadelphia: Harper & Row, 1982, with permission.)

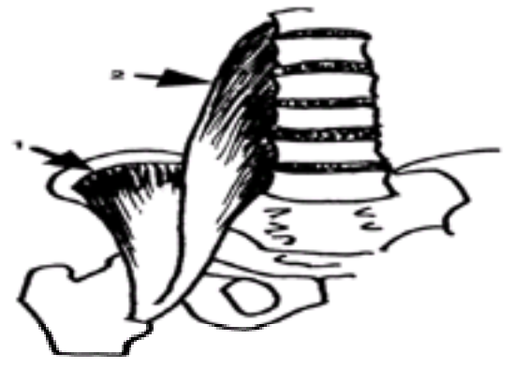

Figure 78-3. Anatomy of the iliacus and psoas muscles and the iliopsoas tendon. The iliacus arises from the entire internal iliac fossa and is joined by the psoas muscles, which arise from the lumbar vertebral bodies. Together they form one large tendon that inserts into the femur at the lesser trochanter. The tendon can snap where it passes over the anterior hip joint or the pubic symphysis (*arrows*). (1, iliacus; 2, psoas.)

Action	Muscles	Innervation	Nerve roots
Abductors	Tensor fascia latae Gluteus minimus and medius	Superior gluteal nerve	L-5–S-1
Extensors	Gluteus maximus Hamstrings	Inferior gluteal nerve Sciatic nerve	L-5–S-1
Flexors	Rectus femoris Iliopsoas	Femoral nerve Segmental nerves	L-2–L-4
Adductors	Adductor magnus Longus and brevis	Obturator nerve Sciatic nerve	L-2–L-4

TABLE 78-2. Major planes of hip motion and muscles controlling them

Capsule

The hip joint capsule is composed of ligaments running from the pelvis to the base of the femoral neck. The most important of these ligaments is the iliofemoral ligament, which is anterior and takes the form of an inverted Y (Fig. 78-4). This ligament normally acts as a passive restraint against hyperextension and permits a person to “lock” the hip in extension. The capsular ligaments spiral medially around the femoral neck as they span between pelvis and femur. For these reasons, the capsule tightens as the hip is extended and internally rotated, effectively reducing the volume of the joint capsule.

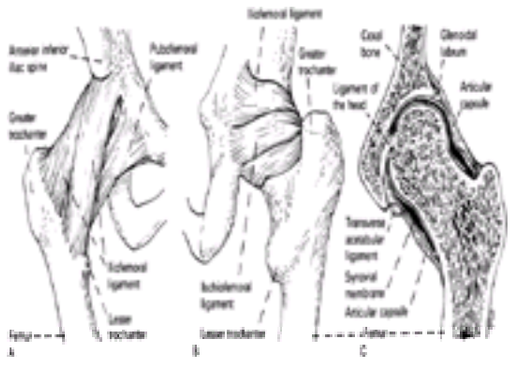

Figure 78-4. Chief ligaments of the capsule of the hip joint. **A:** Anterior view. **B:** Posterior view. **C:** Schematic coronal section through the hip joint showing the synovial membrane, which lines the capsule and covers the femoral head, ligament of the head, and intraarticular fat. (**A** and **B** modified from Clemente CD, ed. *Gray's anatomy of the human body*, 30th Am ed. Philadelphia: Lea & Febiger, 1985; **C** modified from Hollinshead WH. *Anatomy for surgeons.*Vol 3, The back and limbs. Philadelphia: Harper & Row, 1982.)

Skeletal Anatomy

Developmentally, each half of the pelvis is formed from three bones: the ilium, the ischium, and the pubis (Fig. 78-5). These three bones meet at the acetabulum. During growth the bones are separate, and the border between them in the acetabulum is called the *triradiate cartilage*. At approximately 17 years of age, the triradiate cartilage fuses to form a single bone called the *innominate bone*, although the regions of the pelvis are still identified as pubis, ilium, and ischium. Narrow processes of the pubis and ischium, called *rami*, converge anteriorly, forming the obturator ring.

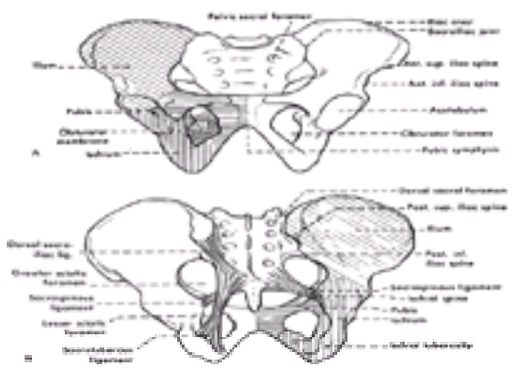

Figure 78-5. The bony pelvis. **A:** Anterior view. **B:** Posterior view. The two hip or coxal bones are separated posteriorly by the sacrum, thus making the pelvic girdle. Each hip bone consists of the ilium, ischium, and pubis, which are shaded differently. The three bones diverge from the acetabulum in different directions, with the winglike ilium projecting upward from the acetabulum. Its iliac crest, palpable along its length, terminates anteriorly in the anterior superior iliac spine and posteriorly in the posterior superior iliac spine. The posterior superior iliac spines are at the level of the S-2 spinous process and indicate the position of the sacroiliac joint, which cannot be palpated. The summit of the iliac crest is at the level of the L-4 spinous process. The ischium projects posteriorly and has two important landmarks, the ischial tuberosity and the ischial spine. Note the sacrospinous and sacrotuberous and other ligaments and the greater and lesser sciatic foramina. The body of the pubic articulates anteriorly with its fellow of the opposite side across the pubic symphysis, which is in the medial plane, while posteriorly the superior ramus fuses with the ischium and ilium in the acetabulum and the inferior ramus fuses with the ramus of the ischium. The two pubic rami embrace the obturator foramen, which is almost completely filled by the obturator membrane. (From Rosse C, Gaddum-Rosse P, eds. *Hollinshead's textbook of anatomy*, 5th ed. Philadelphia: Lippincott–Raven, 1997:308, with permission.)

Anteriorly, the two halves of the pelvis are joined by a fibrous joint called the *pubic symphysis*. Posteriorly the iliac wing is attached to the sacrum at an interface called the *sacroiliac joint*. The upper half of the sacroiliac joint is a fibrous joint similar to the pubic symphysis. The lower half contains a synovial space and is a true diarthrodial joint. Under normal circumstances, the pubic symphysis and sacroiliac joint move minimally. Both joints are held together by heavy ligament systems. These ligaments must be altered by disease, trauma, or pregnancy to permit significant displacement.

Surface Anatomy

In most people, the anterior superior iliac spine and the pubic tubercle can be palpated because little subcutaneous fat is deposited anteriorly over these structures, even in obese subjects (Fig. 78-6). The inguinal ligament connects these landmarks, and the center of the hip joint is located at the midpoint between them. The pulse of the femoral artery is palpable 1 cm below the midpoint. The posterior superior iliac spine is usually palpable and can be located by following the iliac crest back from the anterior superior spine. The posterior spine marks the upper extent of the sacroiliac joint—that is, the junction of the sacrum with the ilium. The buttocks are separated by the natal cleft, and the crease forming the inferior limit of each buttock is called the *gluteal fold*. These creases are created by suspensory ligaments between skin and deep fascia, and not by the gluteal musculature. The ischial tuberosity is palpable at the center of the gluteal fold but is more easily felt when the hip is flexed to a right angle.

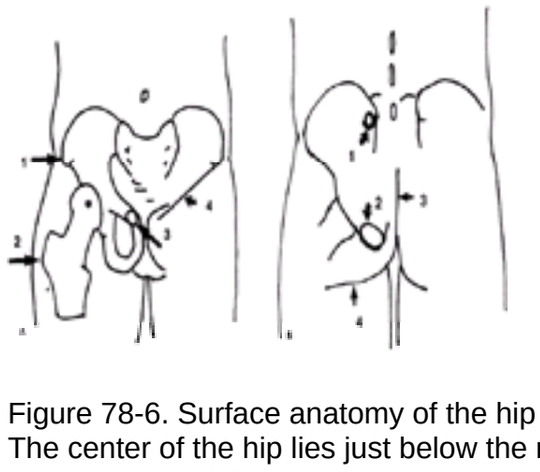

Figure 78-6. Surface anatomy of the hip region. **A:** Anterior view. The iliac crest and the anterior iliac spine (1), and the greater trochanter (2) are usually palpable. The center of the hip lies just below the midpoint of the inguinal ligament (4), connecting the pubic tubercle (3) to the anterior spine. **B:** Posterior view. The posterior superior spine (1) is palpable at the medial aspect of the posterior iliac crest and sometimes is visible as a dimple. This spine marks the upper lateral margin of the sacroiliac joint. The ischial tuberosity (2) is palpable just above the gluteal fold (3) and medial to the natal cleft (4).

Mechanics of the Hip

The center of gravity of the body is located in the sacrum (roughly in the body of the second sacral vertebra) (see Fig. 78-1). When erect, the weight of the upper body passes through the sacrum, across the sacroiliac joint through the ilium, and into the hip joint. Of course, when standing at rest on both feet, body weight is distributed

evenly onto both hips and lower extremities. When a person is walking, running, or climbing, the hip joint is constantly moving, and much of the time the entire body weight is supported by only one extremity. During these periods of one-legged stance, the trunk would tip to the opposite side were the pelvis not fixed by the abductor muscles.

The load on the hip includes both the body weight and the muscle forces. Large muscle forces are required to stabilize and move the hip. The joint load during normal gait or when standing on one foot is 2.8 times the body weight. During running and climbing, this load reaches six times body weight. Because the hip flexor muscles are located close to the axis of rotation, a simple straight-leg raise generates a load of one body weight on the hip. The magnitude of these mechanical forces has an important impact on hip disease and pain patterns.

EXAMINATION OF THE HIP REGION

Examination must be thorough, but is usually simple and logical.

Gait, Posture, and Limps

Normally, when a person stands on one leg, the pelvis on the opposite side tilts up slightly. This can be felt by resting one's index fingers on the iliac crests. If the hip abductor muscles are nonfunctional, the opposite side of the pelvis will drop down. This is called a *positive Trendelenburg sign*, and if the opposite hip and shoulder drop while walking on an affected hip, the result is a *Trendelenburg gait*. Generally, the Trendelenburg sign is not associated with pain.

If the hip hurts, a patient strives to reduce the load on the joint. Because load is greatest when standing on one foot, walking is altered to limit the length of time spent in the stance phase. The result is a hopping pattern, generally known as an *antalgic gait*. The same effect would be caused by a painful knee or a tack in the shoe. Another way to reduce pain is to limit the muscle force required to stand on the hip. This is done by throwing the body center over the affected hip, obviating the need to use the abductor muscles. This pattern is the opposite of the Trendelenburg sign because the opposite side of the pelvis rises up and the trunk tilts to the affected side. This is called an *abductor lurch*, and is specific to the hip joint.

Patients with significant hip or spine symptoms often do not stand erect or cannot lie flat. Atrophy of the thigh and calf can be seen but should be documented by measurement of circumference. The gluteal muscles and buttocks are best examined with the patient standing erect. Because the buttock is formed by fat deposition, the outline of each gluteus maximus must be palpated. All scars must be recorded and explained if possible.

Motion

Normal motion of the hip varies among individuals and with age. Flexion and extension are subtly augmented by motion of the spine. For these reasons, reference guides to normal motion are marginally helpful. The average person should be able to flex one hip to the point that the thigh rests on the chest while the opposite hip is extended fully, keeping the thigh on the examination table. The knee must be flexed because the hamstrings limit hip flexion if the knee is straight. Deficits in extension appear as the angle between the examination table and the thigh when the opposite hip is maximally flexed; this is called the *Thomas test* (Fig. 78-7).

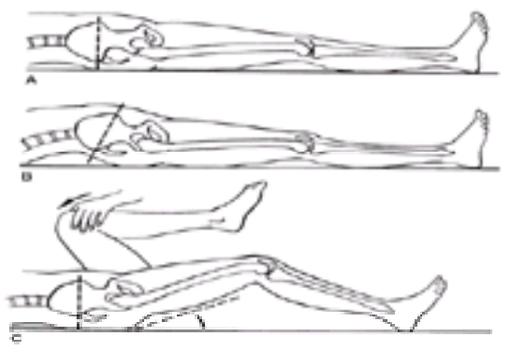

Figure 78-7. Diagnosis of hip flexion contracture using the Thomas test. **A:** The patient lies supine on a hard surface, with the hips and knees extended. If no contracture is present the pelvis remains neutral, with the anterior superior iliac spine lying vertically above the posterior superior iliac spine (*dashed line*). **B:** The patient has a flexion contracture, so the patient must arch the back to keep the legs on the table, thus compensating for the forward tilt of the pelvis. **C:** The Thomas test. To test the right hip, the left thigh is flexed passively until the anterior superior iliac spine lies directly over the posterior superior iliac spine. This places the pelvis in the neutral position and brings the lumbar spine down flat on the table. If a flexion contracture is present the right thigh cannot remain on the table and makes an angle with it that equals the angle of the deformity. (Modified from Rosse C. The hip region and the lumbosacral plexus. In: Rosse C, Clawson DK, eds. *The musculoskeletal system in health and disease*. Hagerstown, MD: Harper & Row, 1980.)

Precise measurements of hip rotation are best done with the subject prone and the hips extended fully and the knees flexed approximately 90 degrees. In this position, the hips can be tested simultaneously, first in maximal internal rotation, then in maximal external rotation. (One knee must be extended slightly to permit one leg to pass the other when testing external rotation.) By this method, asymmetries are apparent, and the angle of motion is clearly visible as the angle between the leg (tibia) and the vertical. When a patient cannot lie prone due to contractures or illness, measurement in the supine position is possible, using the foot axis, rather than the leg, to record the angle of rotation.

Because the spine will move and because the pelvis may tilt while lying, pelvic position must be monitored while testing hip abduction and adduction. One way to accomplish this is to place the thumb and long finger of one hand onto the anterior superior spines while moving the hip with the other hand. This test is best accomplished by asking the subject to abduct and adduct the hip actively. Full adduction or abduction is achieved when the pelvis starts to move.

Particularly at the start of an examination, it is better to ask the patient to demonstrate motion, giving ample time to comply. Guarding of a painful joint cannot be overcome by brute strength. Both hips should be examined, especially because asymmetry may be the best clue to lost movement, masses, or atrophy.

SPECIFIC CONDITIONS

Degenerative Arthritis

Osteoarthritis (OA) (Fig. 78-8) is by far the most common cause of hip pain and dysfunction (1,2 and 3). The incidence and severity of hip arthritis are closely related to age; the incidence increases steeply after the age of 65 years. Approximately 75% of hip replacements are for OA, and the average age at surgery is 70 years. In most cases, the arthritis is idiopathic. Rare heritable disorders of cartilage collagen have now been identified, and afflicted subjects suffer generalized OA as young adults.

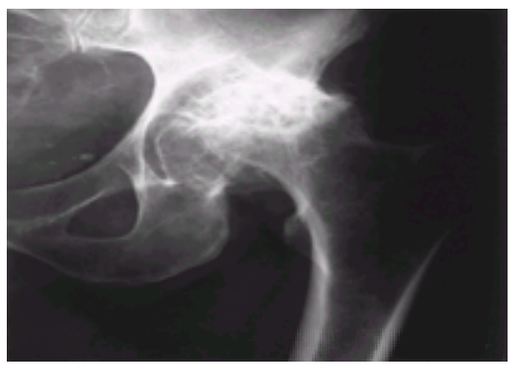

Figure 78-8. Degenerative arthritis. This is an example of severe osteoarthritis with lateral migration, joint space destruction, and cysts.

The incidence of hip arthritis is low (1%) in Hong Kong Chinese in comparison with white European populations (7% to 25%). In the knee, obesity is a known risk factor for development of OA, but such a relationship has not been established for the hip. Obesity increases the intensity of pain from hip arthritis, probably because the joint is subjected to proportionately greater loads in heavier people.

Hip OA can complicate trauma or developmental abnormalities that deform the shape of the articular surfaces. Despite appropriate treatment, hip pain is a common sequel of congenital dislocations, slipped femoral epiphysis, and Perthes disease. Late symptoms present any time from the third to sixth decades, depending on the severity of the anatomic anomaly. Oftentimes, patients are unaware of their deformities, and the diagnosis is not made until the painful hip is x-rayed. High-energy trauma, specifically femoral head and neck fractures, acetabular fractures, or fracture dislocations, also leads to secondary OA. Such trauma is rare and the cause is obvious.

The cardinal symptoms of hip OA are pain with use and loss of motion. The pain is most commonly centered in the groin and medial thigh (60% of cases) but can also be in the buttock (17%), the lateral thigh (8%), or the knee (2%). The patient may complain of stiffness and sharp pain early in the day followed by some resolution of these symptoms with activity. The pain returns as the day goes on, depending on the intensity and duration of use. Eventually, arthritic hips cause severe rest pain and sleep disturbance. Stiffness presents in a variety of ways, most commonly as difficulty reaching the foot, crossing the legs, and standing fully erect. In most people, hip arthritis evolves over several years.

The most sensitive physical sign of hip OA is loss of motion. Because a swollen or inflamed hip joint is more comfortable in flexion and external rotation, patients favor that position and gradually lose extension and internal rotation. Forced internal rotation usually elicits pain, even when motion is full. Global stiffness and a limp occur relatively late in the course of the disease. At that point, thigh muscle atrophy will be visible.

The diagnosis of hip OA is confirmed by radiography. The first visible change often occurs in the subchondral plate of the acetabulum. The density of the plate is normally uniform and symmetric in comparison with the opposite hip. Due to pressure concentration in the arthritic hip, the plate will thicken and appear sclerotic in a focal area, usually at the lateral edge of the acetabulum. Osteophytes, joint space narrowing, and lateral migration of the femoral head in the socket also occur early but can be difficult to appreciate. Cysts usually form late, after the loss of articular cartilage. In a rare cystic form of OA, multiple subchondral cysts are observed before loss of joint space and osteophyte formation.

Loss of the joint space due to wear of the articular surfaces is the critical feature of OA. In the hip, this joint narrowing is usually seen at the superior, lateral edge of the joint; this is called a *lateral pattern* because the femoral head migrates laterally. In the somewhat less common central pattern, the head moves medially as the joint space in the center of the hip narrows. When cysts and osteophytes are seen in the absence of joint space narrowing, one should consider a computed tomography (CT) scan to look for narrowing in the posterior aspect of the joint, or evidence of a labral tear anteriorly. Weight-bearing films are not particularly helpful.

At times, the pain of a degenerative hip cannot be differentiated from coexisting radicular low back pain. In this circumstance, diagnostic injection of anesthetic into the hip joint using fluoroscopic guidance is helpful. With bupivacaine, this procedure should ablate any pain originating in the hip joint for at least 4 hours.

The treatment of hip OA depends on severity and the age of the patient. Young patients are best treated symptomatically with antiinflammatory drugs and activity modification. The central intent of the conservative approach is to reduce loads on the damaged joint cartilage. Weight loss can be very effective for the moderately obese. Use of a cane in the opposite hand is the single most useful measure available short of surgery.

Osteotomy—that is, surgical alteration of the bony anatomy around the joint—is sometimes indicated in the treatment of hip OA. In general, this is challenging surgery best suited for relatively young patients in whom definite structural abnormalities are present and the arthritic change is not advanced. For patients older than age 60, hip replacement is a proven treatment for disabling hip OA.

Nontraumatic Necrosis of the Femoral Head

Sometimes a segment of subarticular bone in the femoral head dies (Fig. 78-9) (4,5). The most common known cause of this condition is disruption of blood vessels during fracture of the femoral neck. The bone circulation can also be obstructed by red blood cells in sickle cell anemia and by nitrogen bubbles in decompression illness. High-energy radiation therapy kills the bone directly. The precise mechanism leading to bone necrosis has not been identified in some circumstances. Most of these idiopathic cases are associated with corticosteroid treatment (60%) or alcohol abuse (20%). Patients with hyperlipidemia, diabetes, hyperuricemia, liver disease, vasculitis, and Cushing's disease are at risk as well, but this group represents only a small fraction of idiopathic cases. In some cases no risk factor can be identified. Because the etiology is variable and often unclear, this disease is now referred to as *osteonecrosis* (ON), but the term *avascular necrosis* is still in use.

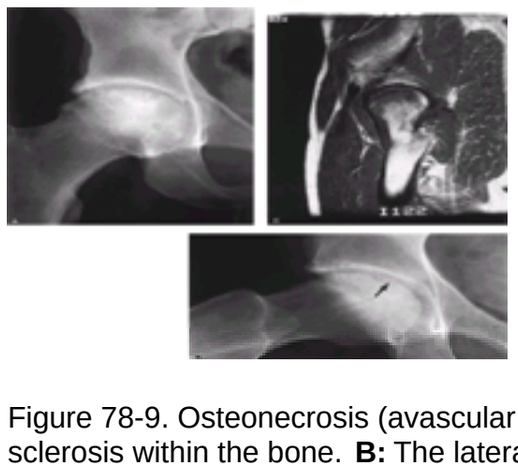

Figure 78-9. Osteonecrosis (avascular necrosis) of the right hip. **A:** The anteroposterior radiograph shows collapse of the femoral head as well as typical cysts and sclerosis within the bone. **B:** The lateral view demonstrates the anterior location of the lesion and a “crescent sign” (*arrow*), caused by fragmentation of the dead subarticular bone. **C:** On magnetic resonance imaging, the low signal in the femoral head is caused by displacement of normal marrow fat. The subarticular fracture is seen as a dark black line.

ON is a particular problem after renal transplantation—it has been reported in 29% of cases. The incidence is related to the total dose of oral corticosteroid given and perhaps for that reason is less common with heart and liver transplant. The precise relationship between steroid dose and incidence is currently unknown.

Idiopathic ON can cause pain in two ways. If the affected area of bone is large enough, it will fracture before it has healed. The fracture usually leads to collapse of

the articular surface and mechanical dysfunction of the hip joint. The symptoms of collapse are similar to severe OA. Occasionally, fragments of loose cartilage or dead bone will cause catching or locking symptoms. Deep, aching rest pain is sometimes present before fracture and collapse. For reasons that are poorly understood, marrow pressure is often elevated in the early stages of the disease. The rest pain is thought to be a symptom of this increased intraosseous pressure.

Diagnosis of ON is relatively straightforward when fracture or collapse has occurred because these conditions are apparent on simple radiographs. Usually, a wedge-shaped area of the superior femoral head is sclerotic or cystic. Before collapse, a thin rim of subchondral bone may fracture free from the head, creating a *crescent sign*. A collapsed segment and the crescent sign are often better seen on a frog-leg lateral view of the hip because the lesions are located anteriorly on the femoral head.

In the absence of visible collapse or fracture, ON lesions may appear as osteopenic or sclerotic areas on radiographs. Often, however, the radiograph is normal. In this circumstance, bone scans can be helpful, but are nonspecific. At present, magnetic resonance imaging (MRI) is the most sensitive method for confirming the diagnosis of ON. The necrotic segment of the femoral head appears as a dark area due to displacement of the normal marrow fat. The area of abnormality will be larger early in the course of the disease, probably because of edema in the surrounding living bone.

The time course of the MRI changes after renal transplants suggests that most cases of ON do not progress to fracture or collapse. In one study, 29% of transplant patients exhibited changes, but only 6% required hip replacement (6). The lesions probably stabilize within a year after the initial corticosteroid exposure.

For purposes of determining prognosis, staging systems based on radiographs and bone scans have now given way to simpler systems based on MRI scans. The risk of segmental collapse and subsequent destruction of the hip joint depends on the size and location of the lesion. Lesions that occupy more than approximately 25% of the head have a poor prognosis, especially if located in the classic superior-lateral position in the weight-bearing region. Lesions of 20% or less demonstrate a remarkably good prognosis, despite ongoing steroid exposure. In some cases, the symptoms and MRI changes resolve completely. When coupled with pain and visible osteopenia, this syndrome has been called *transient osteoporosis*.

No one knows the precise relationship between corticosteroid (or alcohol) exposure and ON. Apparently, the patients at greatest risk are those who receive large doses of oral steroids for immunosuppression or for treatment of diseases such as asthma or polymyalgia rheumatica. Some investigators believe that the presence of a vasculitis, as in systemic lupus erythematosus, is a critical risk factor. Because ON is relatively rare, MRI cannot be used as a screening test, especially as a substitute for radiography. The primary indication for MRI would be hip pain in a patient with a clear risk factor such as sickle cell anemia, exposure to steroids, chronic alcoholism, lupus, local radiation treatment, and so forth who does not have a clear-cut diagnosis after radiologic study.

The pain of ON can sometimes be relieved temporarily by *core decompression*, a surgical procedure in which a drill is passed into the femoral head. This procedure is still done with the hope that it might improve the prognosis of the disease. Unfortunately, the effectiveness of decompression has not been confirmed by prospective studies that also consider the size of the lesion (7).

Currently, the most promising therapy for larger lesions is placement of impacted bone graft and a vascularized fibular strut into the lesion. Lipid-clearing agents and biphosphonates may play a role in prophylaxis against collapse, but strong clinical evidence for a pharmacologic approach is absent.

Trochanteric Bursitis (Iliotibial Band Syndrome)

The lateral thigh is enclosed by a sheet of specialized fascia extending from the iliac crest to the lateral tibial plateau. The fascia is known as the *iliotibial band* or the *fascia lata*. Where it runs over the greater trochanter the fascia is separated from the bone by a large bursa. Both the gluteus maximus and the tensor fascia latae insert into the fascia lata and exert great tensile forces there during gait. Therefore, pressure between the fascia and underlying bone can be great.

Inflammation of the greater trochanteric bursa (trochanteric bursitis) is a common cause of pain in the hip region, and the pain can be surprisingly severe (8,9). Afflicted patients usually cannot lie on the affected side or sit comfortably due to tenderness. Usually, this tenderness is accompanied by pain with activity. The pain may be local, directly over the trochanter, but often radiates along the entire course of the fascia. Some subjects will complain of pain in the iliac crest, and others will experience pain to the knee. The tight iliotibial band may also snap over bony prominences at the knee.

The common feature of trochanteric bursitis is tenderness over the bursa itself. Anatomically, the bursa covers the posterior half of the greater trochanter, and the tenderness is localized there. Sometimes, patients will have a contracture of the fascia lata. In this circumstance, adduction is restricted when the hip is fully extended. The Ober test for this contracture is performed with the subject lying with the affected side up. The hip is passively extended and abducted, then adducted while held in extension. This maneuver brings the iliotibial band into line with the greater trochanter, where it will restrict adduction if tight. When the hip is then permitted to flex, a tight band will often snap as it slips anteriorly off of the trochanter.

When the pelvis tilts, the fascia lata is stretched tightly over the trochanter on the higher side. Therefore, trochanteric bursitis can be caused by a long limb or by weakness of the abductor muscles (which allows the pelvis to drop on the opposite side) or even by walking in a cast. For this reason, the examination should include a test for abductor strength and leg length.

Trochanteric bursitis and a contracture of the iliotibial band often accompany other conditions such as degenerative arthritis of the hip or a lumbosacral radiculopathy. Whenever the diagnosis is unclear, injection of the bursa with local anesthetic is helpful. The injection usually can be performed in clinic with a 1.5-inch needle and should immediately relieve the symptoms of bursitis. MRI can demonstrate enlargement of the bursa, but this test is probably not necessary unless other coexisting conditions are suspected.

The primary treatment of trochanteric bursitis is correction of all inciting causes. Physical therapy can strengthen the abductor muscles and stretch the fascia/iliotibial band and should also include passive modalities such as ultrasound and local heat. A shoe lift under the short limb can help immediately. Corticosteroid injection is effective when physical therapy fails to eradicate the symptoms. Surgical lengthening of the iliotibial band or excision of the bursa may be indicated in the most resistant cases.

Neuralgia of the Lateral Femoral Cutaneous Nerve (Meralgia Paresthetica)

The lateral femoral cutaneous nerve arises from the lumbosacral plexus and follows a retroperitoneal course over the iliacus muscle before entering the thigh. The nerve exits the pelvis by passing under or through the attachment of the inguinal ligament on the medial aspect of the anterior superior iliac spine and is subject to injury at this exit point.

The symptoms of injury to the lateral cutaneous nerve are numbness, hyperesthesia, and dysesthesias in the distribution of the nerve. The surgical options include transection and decompression, with transection providing more reliable relief (10,11 and 12). Tumors within the iliacus and psoas can present as meralgia paresthetica, but are rare. They should be considered when symptoms are persistent, however. The condition is discussed in greater detail in Chapter 77.

Space-Occupying Lesions of the Iliopsoas Compartment

The iliopsoas compartment contains the iliacus, psoas major and psoas minor muscles, as well as the femoral and lateral femoral cutaneous nerves. Hematomas, abscesses, and malignancies within this compartment cause lower abdominal pain and hip pain (13,14,15 and 16). The hip pain will present as irritation of the iliopsoas—that is, pain with passive extension and active flexion. Dysfunction of the femoral nerve may also be present.

Abscesses within the iliacus and psoas muscles can be caused by direct extension from infections of the spine or peritoneal cavity. This is a recognized complication of Crohn's disease and appendicitis, and right-sided abscesses are more common because the cecum overlies the right iliacus muscle. Pyomyositis of the iliacus may develop without an obvious local source, however. The abscess can track along the iliopsoas tendon into the perirectal space and medial thigh, where it is visible as a mass effacing the gluteal fold. Due to communication among the iliopectineal bursa, the iliopsoas tendon sheath, and the hip joint, an iliopsoas abscess and septic hip can coexist.

Hematomas have been described in patients with bleeding disorders or anticoagulation and with athletic injuries. The most devastating consequence of a large

hematoma is irreversible femoral neuropathy.

Diagnosis depends largely on a thorough history and awareness of a risk of retroperitoneal abscesses or poor coagulation. MRI and CT greatly facilitate recognition of these conditions but cannot differentiate among them. CT-guided aspiration or biopsy of this region is now technically straightforward. Treatment, of course, depends on the underlying problem.

Hip Pain in Pregnancy

Pain in the region of the hip may develop late during pregnancy (17,18). Due to increased body weight and the general relaxation of ligaments supporting the pelvis, the sacroiliac joints and pubic symphysis can become unstable. Although painful, these conditions are benign and usually reverse in the months after delivery. The symptoms are pain in the joints themselves and a sensation of movement where before there was none. The corsets used to treat low back pain in pregnancy are sometimes helpful.

Transient osteoporosis is a rare cause of groin or anterior thigh pain that typically appears in the third trimester of pregnancy. The patients tend to be older, first-time mothers. The condition derives its name from the loss of bone density seen on radiographs of the hips and spine. The precise etiology of the bone loss in unknown, although some subjects have preexisting risks for osteoporosis. One or both hips can be painful; for some reason, the left hip is preferentially involved.

The hip pain increases with time and may require use of crutches. The femoral neck can fracture spontaneously in this disease, although the incidence of this complication is unknown and evidently small. MRI is probably the optimal method of diagnosis. The changes are those of nonspecific marrow edema and could be confused with osteonecrosis.

Painful Symphysis Pubis

Chronic inflammation of the pubic symphysis occurs spontaneously, during pregnancy, after trauma, or after urogenital surgery (19). The precise etiology of the condition is often unknown and probably varies. Like sacroiliiitis, it can be a manifestation of a systemic inflammatory illness, specifically ankylosing spondylitis. Cases of idiopathic inflammation are sometimes called*osteitis pubis*(Fig. 78-10). Some cases are clearly related to instability caused by trauma or pregnancy. Runners and other athletes develop the condition from overuse. Some cases clearly are infectious, although the incidence of this is thought to be low. Inflammation of the symphysis is clearly related to surgical procedures that violate the joint, such as bladder suspension and placement of a suprapubic catheter.

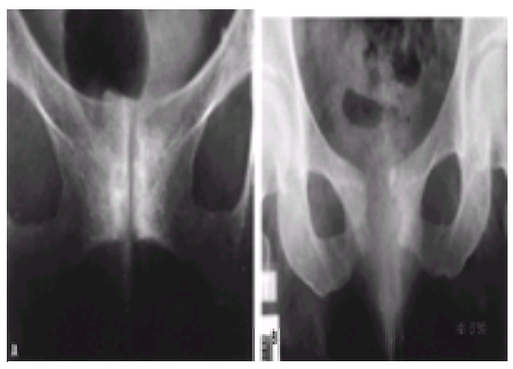

Figure 78-10. Osteitis pubis. **A:** This is a typical case showing cysts, sclerosis, and irregularity of the joint margins. **B:** A case of septic arthritis after placement of a suprapubic catheter. The joint and adjacent bone are eroded.

Pain in the pubic symphysis presents as medial groin pain radiating down the medial thigh on one or both sides. The pain is activity related and can be severe. The abdominal muscles and hip adductor muscles attach to the pubic symphysis; thus, pain can be elicited by use of these muscles. The symphysis is tender to palpation and, when unstable, can be felt to move slightly or click when stressed.

Lysis and sclerosis of the bone adjacent to the symphysis appear on radiographs within weeks of the onset of symptoms. In the presence of a suggestive history and examination, these findings are diagnostic. When symptoms persist despite rest and antiinflammatory drugs, biopsy or suppressive treatment for osteomyelitis may be considered. Refractory cases have responded to excision of the symphysis, but this is a rarely performed operation.

Painful Sacroiliac Joint

The sacroiliac joint is subject to degenerative arthritis, chronic inflammatory disease, and traumatic instability (Fig. 78-11) (20). Sacroiliitis is a feature of ankylosing spondylitis and other systemic inflammatory conditions associated with the HLA-B27 antigen. The joint may also develop an isolated inflammatory disease called *osteitis condensans ilium*. This unusual condition is named for the x-ray appearance of sclerosis in the adjacent iliac crest.

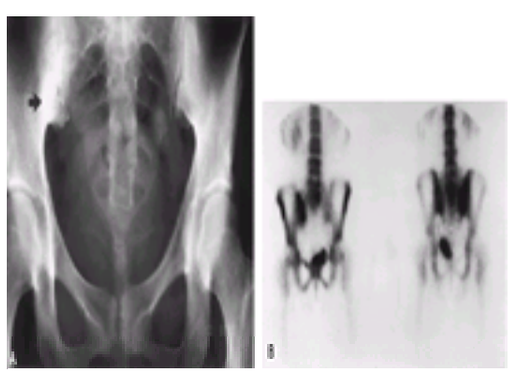

Figure 78-11. Osteoarthritis of the sacroiliac joint. **A:** The right sacroiliac joint (*arrow*) appears irregular due to formation of large cysts in the adjacent ilium. **B:** This technetium bone scan demonstrates increased uptake on both sides of the right joint.

Mechanical dysfunction of the joint, as occurs during pregnancy, is difficult to distinguish from low back pain. Primary degenerative arthritis of the sacroiliac joint is rare and usually the result of major pelvic trauma. Years ago, fusion of the joint was a common treatment for low back pain, but the incidence of this procedure declined as the mechanisms of radicular spinal disease were recognized. Now, fusion is recommended only after the more common causes of medial buttock pain are excluded.

Mechanical pain in the sacroiliac joint can be reproduced with Patrick's test, in which the hip is forced into external rotation by placing the ankle on the opposite thigh and pushing down on the knee. A positive test produces pain in the joint. The x-ray appearance of the sacroiliac joints is sometimes difficult to interpret because normal joints can be irregular and asymmetric. Bone scans will show increased bone turnover around arthritic joints. Currently, the most definitive test for pain originating in the sacroiliac joint is local anesthetic block. The presentation of infection in the sacroiliac joint is discussed in the next section.

Septic Arthritis/Osteomyelitis

Any joint or bone can become infected. Usually, organisms are carried into the synovial space and bone through the bloodstream or by a foreign object entering the joint. For example, the hip can be violated during attempts to catheterize the femoral artery or vein. Rarely, osteomyelitis of an adjacent bone will break through into a joint. After the knee, the hip is the second most common site of joint infection.

The risk factors for septic arthritis (Fig. 78-12) and osteomyelitis include advanced age, skin infections, intravenous drug abuse, surgery (joint replacement), and immunosuppression (14,21,22,23 and 24). Patients with inflammatory arthritis are particularly susceptible to the complications of joint sepsis because their arthritic joints contain excessive fluid and avascular debris and because they often are immunosuppressed. Gonococcal arthritis of the hip is rare.

Figure 78-12. Septic arthritis. **A:** The radiograph shows complete loss of the joint space and some irregularity of the femoral head. **B:** The bone scan (posteroanterior view) shows markedly increased uptake of technetium on both sides of the joint.

In immunocompetent patients, septic arthritis of the hip causes severe pain, particularly with motion. To reduce intracapsular pressure, the hip will characteristically be held in a flexed, externally rotated position. Sepsis of the sacroiliac joint in adults is usually apparent as tender, erythematous swelling posteriorly over the joint. The presentation of infection in the pubic symphysis is discussed under the heading Painful Pubic Symphysis. Septic arthritis of the hip is an emergency. The infection flourishes in the avascular environment of the joint space and will rapidly destroy the articular surfaces unless the joint is drained surgically. In contrast to most other joints, surgical drainage is usually the preferred option for treatment of hip infections because infections there do not reliably respond to aspiration alone and because the vascularity of the femoral head is endangered by intracapsular pressure elevation.

In general, infection should be considered in any adult with spontaneous, acute hip pain, but especially in those with specific risks. Often, systemic symptoms of infection are present, and the peripheral white cell count, erythrocyte sedimentation rate, and C-reactive protein level are elevated. The definitive diagnostic test for a septic joint is aspiration, with examination of the fluid for white cells and organisms. Bone scan and MRI will demonstrate abscesses in bone, and the diagnosis is made by biopsy. Aspiration of the hip and sacroiliac joints is difficult and benefits from radiographic control of needle placement. If fluid cannot be withdrawn, arthrography or irrigation is needed to ensure that the needle is in the joint space.

Tears of the Acetabular Labrum

With the advent of hip arthroscopy and MRI, pathology of the fibrocartilaginous labrum has been identified as a cause of hip pain and snapping (25,26,27 and 28). Symptomatic tears of the labrum can occur during traumatic dislocations of the hip, but most cases of hip pain ascribed to the labrum are spontaneous or related to relatively modest twisting injuries. The pain usually is located anteriorly. More than half of the time, a click is described, with associated pain radiating toward the knee.

On examination, pain and a clunk can be evoked by passive extension and internal rotation from a flexed, abducted position. This maneuver helps distinguish a torn labrum from a snapping iliopsoas tendon. A minority of patients will have an extension deficit. The current choices for diagnosis are CT-arthrography or MRI-arthrography. Because asymptomatic individuals can have MRI abnormalities of the labrum, false-positive scans will occur. Arthroscopy of the hip is now used for diagnosis and treatment of loose bodies in the hip, and labral tears have been effectively treated by this technique.

Stress Fractures

Stress fractures (Fig. 78-13 and Fig. 78-14) occur in the absence of overt trauma and are caused by fatigue of the bone during a repetitive or unusually strenuous activity (29,30 and 31). A classic example of this is the “march fracture” of the metatarsal in new military recruits. Poor bone quality is now recognized as an important risk factor. For example, stress fractures occur in amenorrheic female athletes due to their diminished bone density. Stress fractures are classified as incomplete, complete but nondisplaced, and displaced. Especially because incomplete fractures are often invisible on radiographs, these injuries can be difficult to recognize.

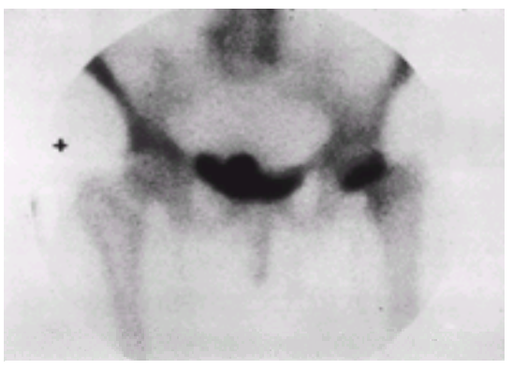

Figure 78-13. Osteoporotic stress fracture. Bone scan of a 72-year-old woman with normal hip radiographs and left groin pain. The scan reveals increased uptake of technetium in the left femur, evidence of a stress fracture at the junction of head and neck (+, right).

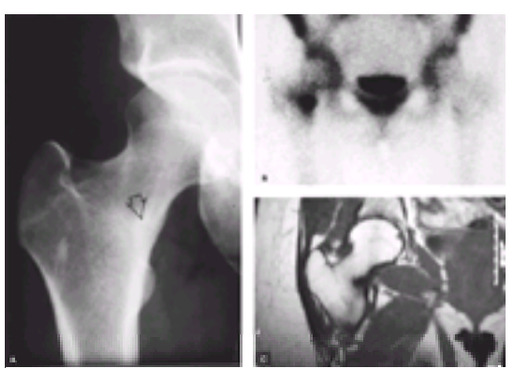

Figure 78-14. Overuse stress fracture in a 27-year-old runner. **A:** The radiographs shows sclerosis and widening of the cortex of the medial femoral neck (*arrow*). **B:**

On bone scan, the area immediately adjacent to the fracture has the greatest uptake of tracer, but the entire femoral neck is abnormal. **C:** Magnetic resonance imaging is useful because the exact location of the injury is delineated and other possible conditions, such as tumor, infection, and bursitis, are eliminated.

Stress fractures of the proximal femur generally occur in two groups: runners and the osteoporotic elderly. The most common site is the femoral neck. Early recognition of these injuries is important because the prognosis for uneventful healing is far better when the fracture has not displaced.

Femoral stress fractures in running athletes are rare but due to the serious nature of the injury should be considered in any athlete who spontaneously develops pain in the hip region. The symptoms are pain with weight bearing, stiffness, and a limp. Patients may complain of a “groin muscle pull” because the pain commonly radiates down the medial thigh.

The incidence of stress fractures of the femur in the elderly is unclear because fractures of the osteoporotic hip can occur with minimal trauma. One study has suggested that some patients fall because the femoral neck fractures spontaneously and many of these events are preceded by pain (32). In any case, elderly people sometimes can walk on a nondisplaced hip fracture, and these fractures often are not apparent on x-ray. As in the younger runner, the cardinal symptom is pain with activity.

The physical diagnosis of proximal femoral stress fractures is difficult because the severity of symptoms is related to the inherent stability of the fracture. Minimally displaced or incomplete fractures may be painful only when standing. Usually, straight-leg raising is painful or impossible. Most femoral stress fractures are located within the capsule of the hip joint and will cause pain when the hip is forcefully rotated internally.

The pubic and ischial rami also may fracture spontaneously or with minimal trauma, such as kicking or a fall onto the side. In athletes, the injury can be confused with a groin muscle strain because the adductor muscles originate on the obturator ring.

The first diagnostic test should be high-quality radiographs. With time, the fracture lines become visible due to subtle resorption or callus formation. Fractures of the femoral neck often cannot be seen on oblique views. To place the femoral neck parallel to the plane of the film, the anteroposterior view must be made, with the hip internally rotated 15 degrees (toes touching). Because this can be painful, films often do not meet this standard.

In the presence of normal, inadequate, or equivocal films, a bone scan or MRI is needed to confirm or rule out a fracture. MRI is the most accurate study available, but it is relatively expensive. Bone scans are not reliable in the first 24 to 48 hours after fracture and can give false-positive readings when periarticular inflammation is present.

Stress fracture should be considered in all cases of acute, activity-related hip pain. Association with a period of increased physical activity, suspected or documented osteopenia, incidental trauma, or a past history of stress fractures should lower the threshold for obtaining an MRI scan. All of these patients should cease painful activities and possibly use crutches until the diagnosis is clarified.

Iliopsoas Tendinitis/Iliopectineal Bursitis/Snapping Iliopsoas Tendon

The iliopsoas tendon passes anteriorly over the hip joint and the pubic ramus. In that region, the tendon is surrounded by a synovial sheath and separated from the bone and capsule by a bursa. The bursa is sometimes called the *iliopectineal bursa*. Pain in the groin has been attributed to inflammation of both the iliopsoas tendon sheath and the iliopectineal bursa (33, 34 and 35). These conditions are rare, and anatomic differentiation between them is difficult.

The iliopectineal bursa enlarges when inflamed (Fig. 78-15). Enlargement has been observed in rheumatoid arthritis and septic arthritis. An enlarged bursa can be palpated and has been observed to occlude the femoral vein. Because the bursa sometimes communicates with the hip joint synovial space, diseases of the hip can present as iliopectineal bursitis.

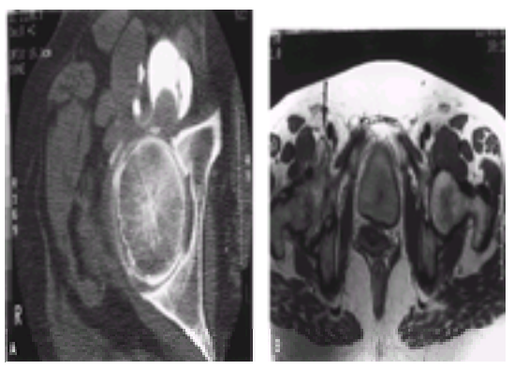

Figure 78-15. Iliopectineal bursitis/iliopsoas tendinitis. **A:** This computed tomography arthrogram demonstrates communication between the hip joint and an anterior bursa (*arrow*). The bursa surrounds the psoas tendon. **B:** On a magnetic resonance imaging scan the bursa appears as a mass extending anteriorly beneath the femoral artery. Such a mass (*arrow*) can be palpated and may compress the femoral vein.

Tendinitis of the iliopsoas tendon is also associated with a fluid collection over the anterior aspect of the hip. This tendinitis occurs in running or kicking athletes and causes groin pain with active flexion.

One form of iliopsoas tendinitis is associated with painful snapping. The assumed mechanism is snapping of the tendon over the iliopectineal eminence, a prominence on the pubic ramus (see Fig. 78-3). Unlike snapping of the iliotibial band over the trochanter, this snap is felt deep in the groin. It occurs with stretch or contraction of the iliopsoas, but a discrete evocative maneuver has not been elucidated.

Diagnosis of abnormalities of the iliopsoas appear as peritendinous or intratendinous fluid on MRI scans of the hip. No one knows how often such changes are present in asymptomatic patients. Because of potential communication with the hip synovial space, hip pathology should be excluded by plane films. Abnormal lateral excursion of the iliopsoas tendon can be seen under fluoroscopy when contrast is injected into the tendon sheath. Ultrasound is used to identify the fluid collection and abnormal tendon motion.

Piriformis Syndrome

As it exits the pelvis, the sciatic nerve passes under or through the belly of the piriformis muscle. Some clinicians have attributed a specific form of sciatica to entrapment of the nerve by the muscle (36). In this syndrome, sciatica and deep pain in the buttock are elicited by positions or activities that stretch the piriformis muscle. Specifically, flexion, adduction, and internal rotation of the hip or flexion and abduction against resistance are used as evocative maneuvers. Case reports have described electromyographic and MRI abnormalities. Some patients respond to stretching exercises, and surgical release of the tendon is sometimes recommended.

The prevalence of piriformis syndrome is unknown. To date, nerve compression by the piriformis muscle has not been reliably verified by anatomic studies.

Paget's Disease of Bone

Paget's disease causes progressive, sometimes painful deformities of bone (Fig. 78-16) (37). The etiology is unclear, although a viral origin is suspected. The disease is focal and axial, affecting the skull, spine, femur, and tibia preferentially. Within the affected areas, bone turnover and blood flow are elevated. Prevalence of the disease in the United States is estimated at 3%, but not all of these subjects are symptomatic.

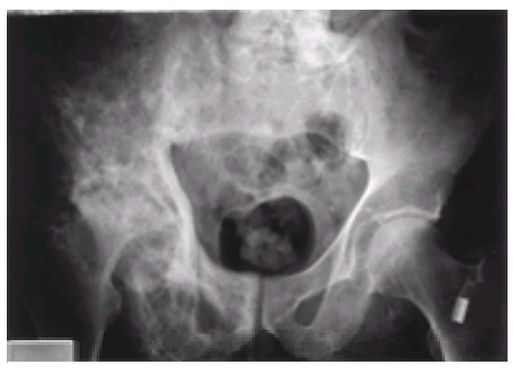

Figure 78-16. Paget's disease of the right hemipelvis. Enlargement of the bone and coarse, distorted trabecular patterns are typical of the disease. The hip joint is severely arthritic due to deformation of the acetabulum.

Paget's disease can cause aching pain in the region of the diseased bone or bones. Complications of the disease are also painful and require specific attention. When Paget's disease deforms the pelvis, the hip joint can become severely arthritic. Stress fractures occur in affected bones, particularly in the upper femur. A small proportion of long-standing cases will undergo sarcomatous degeneration.

The diagnosis is usually made from radiographs. After an early osteolytic phase, the characteristic bony changes of thickened trabeculae and generalized hypertrophy are readily visible. Serum alkaline phosphatase and urinary hydroxyproline levels are elevated. Hip arthritis, fractures, and tumors should be considered whenever the pain of Paget's disease is severe or changing. Fractures and arthritis are usually visible on directed x-rays. Sarcomas can be difficult to see in badly diseased bones, but rapid changes in appearance, cortical erosions, and soft tissue invasion should arouse suspicion.

Tumors

Primary tumors are a rare cause of hip pain. Symptoms depend on size and location. Tumors should be considered especially when the pain is chronic or when rest or night pain is predominant (38). The majority of malignant bony tumors are metastatic and therefore are more common in older patients.

Pigmented villonodular synovitis (Fig. 78-17) and synovial chondromatosis are aggressive but benign synovial tumors. Both conditions are rare and will destroy the hip over time. The major symptom is hip pain with use, and restricted motion worsening as the tumor grows. Chondromatosis can be recognized on radiographs due to the presence of calcifications in the periarticular soft tissues. Pigmented villonodular synovitis is best seen on MRI, where the presence of iron creates a characteristic stippling of the tissue.

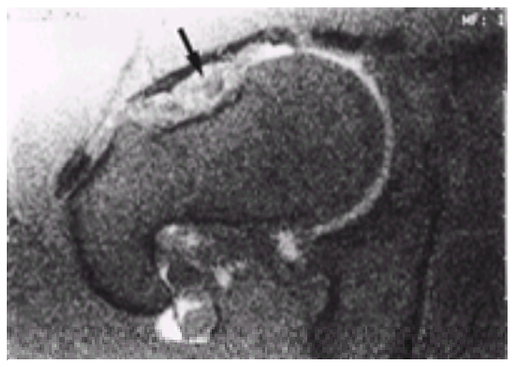

Figure 78-17. Pigmented villonodular synovitis. This synovial tumor was not apparent on radiographs but is seen here as a synovial mass on magnetic resonance imaging scan. Anteriorly, the mass, which has dark stippling, displaces the joint capsule (*arrow*).

CHILDREN

Hip pain in children is often the associated with serious and acute conditions requiring immediate specialty care. The spectrum of causes and presentation are different from adults. Each of the diseases causing pediatric hip pain is complex, controversial, and subject to swift changes in the approach to diagnosis and therapy (39). For these reasons, the following discussion is relatively brief.

Infections

Osteomyelitis and septic arthritis (of the hip and sacroiliac joints) are more common in children than in adults. Unlike in adults, septic arthritis of the hip and sacroiliac joints often occurs in the absence of an identifiable source or associated disease process. Risk is greatest in the first 6 years of life. The mechanism is believed to be hematogenous seeding. Similarly, osteomyelitis is usually caused by blood- borne organisms. The end vessels penetrating growth plates seem to trap organisms, especially after nondisplaced fractures. Perhaps for this reason, the onset of pain is often traced to an injury, and infection is sometimes discounted for that reason. Osteomyelitis and septic arthritis of the hip can coexist because the bone infection can penetrate this joint.

Depending on the age of the child, a limp or refusal to move the hip may be the only sign of infection. Hip pain frequently refers to the knee in children. Except for the limp, the examination in osteomyelitis may be benign. Infections of the hip joint cause escalating pain on motion, and the child holds the hip in flexion/external rotation. Warmth, tenderness, and a mass over the sacroiliac joint usually accompany infections there. Laboratory tests are essential for diagnosis. Sedimentation rate, c-reactive protein, and white cell count are usually abnormal, and radiographs are not. As in the adult, successful aspiration of the joint is necessary when septic arthritis is suspected. Inability to obtain fluid is not equivalent to a negative aspiration, and confirmation of needle placement is necessary in that circumstance. Bone scan and MRI will locate osteomyelitic areas.

As in adults, the treatment is timely surgical drainage of a septic hip. Antibiotic therapy is sometimes adequate for osteomyelitis and sepsis of the sacroiliac joint.

Toxic or Transient Synovitis

Toxic or transient synovitis is a benign, acute inflammatory condition afflicting the hip in younger children. The presentation is identical to septic arthritis. The child may have recently recovered from the flu. Generally, the sedimentation rate is moderately elevated. Aspiration reveals sterile fluid with lymphocytes rather than polymorphonuclear white cells. Treatment is rest and observation.

Fractures

Until growth ceases, fractures through the growth plates are possible. The most commonly involved sites are the proximal femoral epiphysis, the anterior inferior iliac spine, and the ischial tuberosity. Slip of the proximal femoral epiphysis is the most serious of these conditions. Although this is a fracture, the injury usually cannot be traced to a specific traumatic event. The known risk factors are male sex, obesity, rapid growth, and collagen abnormalities, specifically Marfan's disease. The peak age range is 11 to 14 years. Injury to the proximal epiphysis must be considered in any older child or growing young adult with a limp and irritable hip. Limited internal rotation is the cardinal physical sign, and laboratory studies will be normal. Diagnosis can be made from carefully positioned anteroposterior and frog lateral radiographs, in which the femoral head is displaced posteriorly and inferiorly. Because the disease can be silent and bilateral, symmetric abnormalities are possible. Treatment of a slip is usually surgical pinning.

Avulsions of the ischial tuberosity and anterior inferior spine are traumatic injuries usually incurred in sports. The inferior spine is the origin of the rectus femoris muscle, and forceful hip flexion can pull the spine off. Similarly, the ischial tuberosity is the origin of the hamstrings, and forceful extension, such as blocking in football, is the primary mechanism for injury. Pain during resisted hip flexion or extension is the key physical finding and presenting complaint. The radiograph will show separation of the ossified muscle origin. Because these injuries are sometimes chronic, the radiograph may reveal apparent enlargement of the spine or tuberosity, leading to concern about infection or tumor. Usually, careful history and a typical appearance are sufficient to clarify the diagnosis.

Perthes Disease

Perthes disease is a relatively rare condition unique to children and most common in boys aged 4 to 10. Although unproved, the commonly accepted etiology is vascular insufficiency leading to softening, fragmentation, overgrowth, and deformity of the femoral head. As in most other acute conditions, the symptoms may be a limp, knee pain, or painfully restricted motion of the hip. Enough cases are preceded remotely by an episode of toxic synovitis that a causal relationship is suspected. The presentation of Perthes disease usually is not acutely painful. The diagnosis is made when characteristic abnormalities of the femoral head are seen on radiographs. The prognosis of the condition is determined by the radiographic size and location of the affected lesion as well as the age of the child. Treatment options are numerous and vary with severity of the deformity.

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CHAPTER 79

Painful Disorders of the Thigh and Knee

Michael H. Metcalf and Roger V. Larson

The thigh and the knee joint provide an enormous amount of function. The bony architecture, combined with the surrounding soft tissue envelope, allows stability in three planes while maintaining a stable, weight-bearing platform. Essential to the changing motions and forces around the knee are the muscles of the thigh and soft tissues such as the capsule, ligaments, menisci, and articular cartilage. These provide the shock-absorbing and restraining qualities that keep the bony architecture in proper alignment.

Everyday actions of walking, climbing stairs, and raising from a chair, as well as athletic tasks of jumping, running, and side-to-side motion, depend on the integrity of this vital area. Any disease process or trauma to the bones or soft tissue envelope can significantly impair the ability to perform basic tasks. The thigh and knee are most commonly involved in musculoskeletal disorders because they must function under the extremes of physiologic stresses that, over time, result in degenerative changes. In addition, the thigh and knee are frequently involved in traumatic insults from sports participation, vehicular accidents, and falls from height. Infections, inflammation, and primary and metastatic neoplasms can also affect the knee and thigh. All of these conditions may result in chronic pain, suffering, and disability.

Proper diagnosis and treatment of disorders of the knee joint and thigh are essential for a successful return to full function. Proper diagnosis requires a thorough knowledge of the anatomy and biomechanics of all of the structures, as well as the pathophysiology and mechanism of injury and disease.

This chapter is divided into four major sections: Basic Considerations, including a classification of painful disorders and a discussion of the anatomy, biomechanics, and function of these structures; Clinical Evaluation of the Patient; Painful Disorders of the Thigh; and Painful Disorders of the Knee. More detailed information can be found elsewhere (1,2,3,4,5,6,7,8 and 9).

BASIC CONSIDERATIONS

Classification of Disorders

Almost all conditions causing pain around the thigh and knee result from traumatic, degenerative, vascular, congenital/developmental, neoplastic, or infectious processes. Table 79-1 and Table 79-2 classify various painful conditions of the thigh and knee primarily according to cause and pathophysiology. Pains caused by peripheral vascular diseases, neurologic disorders, reflex sympathetic dystrophy, and myofascial syndromes are discussed elsewhere. The remainder of those conditions listed in Table 79-1 and Table 79-2 are discussed in the last two sections of this chapter.

Type of disorder	Examples
Traumatic	Fracture; rupture of the quadratus femoris; muscle contusion; reflex muscle spasm; myofascial pain syndromes
Infectious	Acute osteomyelitis; chronic osteomyelitis; other bone infections
Metabolic or endocrine	Paget's disease; osteomalacia; osteoporosis
Neoplasic	Benign tumors: osteoma, chondroma; malignant primary tumors: giant cell tumor, osteosarcoma, Ewing's tumor, multiple myeloma; metastatic cancer

TABLE 79-1. Classification of painful disorders of the thigh

Type of disorder	Examples
Traumatic	Fracture; dislocation; meniscal tear; capsular or ligamentous tear; rupture of the quadriceps tendon
Inflammatory or degenerative	Arthritic gyogenic arthritis, rheumatoid arthritis, osteoarthritis, tuberculous arthritis, brucellic arthritis, neuropathic arthritis; syncitic acute traumatic synovitis, pigmented villonodular synovitis, osteochondromatosis, chronic synovitis, recurrent synovitis; bursitis: prepatellar bursitis, deep patellar bursitis, pesanserine bursitis, Baker's cyst
Avascular or necrotic	Osteonecrosis; embolism; circulatory insufficiency
Congenital	"Laxity" syndromes; Ehlers-Danlos syndrome; Blount's disease; varus-valgus deformities
Developmental	Patellar alignment; Osgood-Schlatter disease
Neoplastic	Primary benign tumors: osteoid osteoma, primary malignant tumors: osteosarcoma, chondrosarcoma, fibrosarcoma, giant cell tumor, Ewing's tumor, multiple myeloma
Miscellaneous	Osteochondritis dissecans, loose bodies in the knee, Pellegrini-Stieda disease
Referred pain	Diseases of the hip, spinal stenosis, other lumbosacral spinal disorders

TABLE 79-2. Classification of painful disorders of the knee

TABLE 79-2. Classification of painful intraarticular disorders of the knee joint

Anatomy, Biomechanics, and Function of the Thigh and Knee

Anatomy of the Thigh

Bony Anatomy. Figure 79-1 illustrates the anatomy of the femur, the largest of the long bones, with the corresponding origins and insertions. The anatomy of the proximal femur is described in Chapter 78. The femoral shaft is slightly anteriorly bowed beginning distal to the lesser trochanter. It maintains a relative tubular shape until the distal flaring of the medial and lateral condyles (5). In the normal standing position, the femoral shaft inclines medially to allow the knee to be centered under the femoral head and over the center of the ankle, thus creating the mechanical axis of the lower extremity. This angle of obliquity varies from 3 to 15 degrees (average, 10 degrees) when measured along the femoral shaft compared to a line drawn perpendicular to the joint line (5).

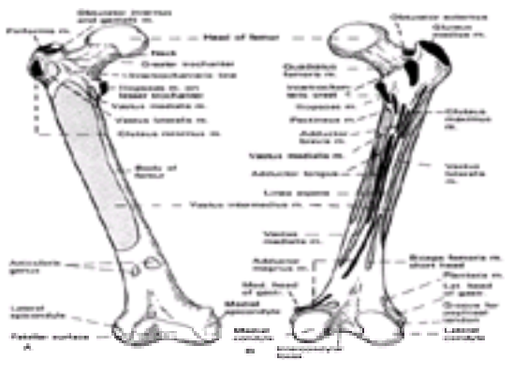

Figure 79-1. Anatomy of the femur and its muscular attachments. **A:** Anterior view. **B:** Posterior view. The body or shaft of the femur is almost cylindric but is a little broader proximally than in the center and is broadest and flattest distally. It is slightly arched, convex anteriorly, and concave posteriorly, where it is strengthened by a prominent longitudinal ridge, the linea aspera. This forms the prominent posterior border of the shaft and projects as an elevated longitudinal ridge or crest along the posterior aspect of the middle third of the bone. This crest consists of medial and lateral lips and a narrow rough intervening band. The distal extremity of the bone is greatly expanded in all directions to form the medial and lateral condyles, which are joined together anteriorly but separated posteriorly by the intercondylar fossa. The black areas are muscle insertions, and the stippled areas are sites of origin of muscles. The upper three-fourths of the anterior surface gives rise to the vastus intermedius, and the lower fourth of the bone surface is separated from the muscle by the intervention of the synovial membrane from the knee joint and by the suprapatellar bursa. The articularis genus muscle arises above the bursa. **B:** On the posterior surface the medial lip of the linea aspera gives rise to the vastus medialis, and the lateral lip and its prolongation give rise to the vastus lateralis. The adductor magnus is inserted into the linea aspera. Two muscles are attached between the vastus lateralis and adductor magnus, the gluteus maximus above and the short head of the biceps femoris below. Four muscles are inserted between the adductor magnus and vastus medialis, the iliacus and pectineus proximally and the adductor brevis and adductor longus distally. (Modified from Hollinshead WH. *Anatomy for surgeons,* 3rd ed. Vol 3. Philadelphia: Harper & Row, 1982:631, 633.)

The distal end of the femur consists of the medial and lateral condyles, which articulate with the tibia and patella to form the knee joint. The medial condyle projects approximately 0.5 cm below the level of the lateral condyle when the femur is held vertically. This difference allows the obliquity of the femoral shaft. Both condyles project more posteriorly than anteriorly to allow flexion of the knee joint.

Compartments. Figure 79-2 demonstrates the division of the musculature of the thigh into compartments and indicates the positions of the various muscle groups, nerves, and blood vessels. In contrast to the upper extremity, where intermuscular septa clearly separate the flexor and extensor compartments, the extensor muscles in the thigh almost completely surround the femur at their origins, leaving only the linea aspera for the attachment of other muscles. With the exception of the short head of the biceps femoris, the knee flexors of the thigh do not arise from the femur, instead taking origin from the ischium. The adductors occupy a large medial compartment that inserts to the femur as far distal as the adductor tubercle. Other relationships are demonstrated in Figure 79-5.

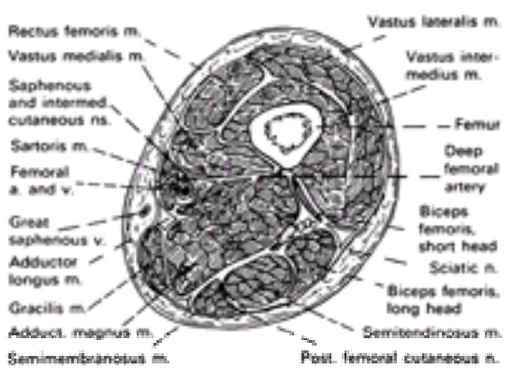

Figure 79-2. Transverse section through the middle third of the right thigh showing the division of the musculature into compartments and the position of the arteries and vessels. The vastus intermedius covers almost the entire circumference of the femur, except for the linea aspera posteriorly. The sciatic nerve is located deep in the posterior compartment that underlies the biceps femoris and semitendinosus muscles. At this level, the branches of the femoral nerves include the saphenous and intermedius cutaneous nerves, which are on the medial aspect of the thigh. (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985:561.)

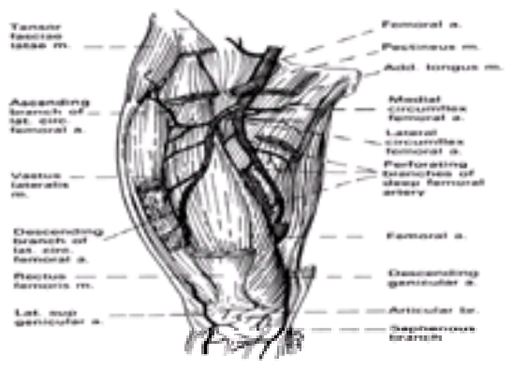

Figure 79-5. Anatomy of the femoral artery and its branches. The femoral artery, a continuation of the external iliac artery, enters the femoral triangle midway between the symphysis pubis and anterior superior iliac spine as its emerges from underneath the inguinal ligament, which forms the base of the triangle. In the femoral triangle, the artery is medial to the femoral nerve before it breaks up into its many branches. At the lower end of the femoral triangle, the femoral artery is cut to show the takeoff of the deep femoral artery, which is the chief source of blood for the thigh and its musculature. The lateral and medial circumflex arteries are branches of the deep femoral artery and encircle the proximal end of the femur to supply the hip joint. The deep femoral artery then descends posteriorly to the floor of the

adductor canal; as it descends, it gives off muscular branches and perforating arteries, which arise throughout its course. These perforate the adductor magnus and distribute blood to muscles in the posterior compartment.

The fascia lata (deep fascia of the thigh) forms a strong fibrous sheath around the thigh. It attaches superiorly along the iliac crest, inguinal ligament, conjoint ramus, ischial tuberosity, sacrotuberous ligament, and sacrum and inferiorly to Gerdy's tubercle on the tibia (7). Just below the inguinal ligament, the fascia lata covers the femoral triangle, where the femoral artery, vein, and lymphatics pass through the saphenous opening—an aperture in the fascia lata. At the back of the knee, the fascia lata covers the popliteal fascia, which covers the popliteal fossa.

Muscles. Table 79-3 lists the most important muscles that control motion of the knee and leg and their nerve supply. The prime movers of the knee joint are the bulk of the thigh muscles, which are important dynamic stabilizers of the knee joint; they also provide power for flexion and extension. A number of the muscles that move the knee also cross the hip and therefore provide dual functions for coordinated movements across two joints. Through postural reflexes they can recruit appropriate muscles for stabilizing the joints and balancing the trunk at the hip and knee. In addition, these muscles provide the power for active rotation of the tibia.

Region/muscle group/ function	Peripheral nerve supply	Segmental nerve supply*
Extension		
Rectus femoris	femoral	L-2, L-3, L-4
Vastus medialis, intermedius, and lateralis	femoral	L-2, L-3, L-4
Sartorius	femoral	L-2, L-3, L-4
Leg flexion		
Semitendinosus	Sciatic (tibial)	L-5, S-1, S-2
Semimembranosus	Sciatic (tibial)	L-5, S-1
Biceps femoris (long head)	Sciatic (tibial)	L-5, S-1, S-2
Gracilis	Obturator	L-2, L-3
Biceps femoris (short head)	Sciatic (peroneal)	S-1, S-2, S-3
Gastrocnemius	Sciatic (tibial)	S-1, S-2
Medial rotators		
Semitendinosus	Sciatic (tibial)	L-5, S-1, S-2
Semimembranosus	Sciatic (tibial)	L-5, S-1
Sartorius	Femoral	L-2, L-3, L-4
Gracilis	Obturator	L-2, L-3, L-4, L-5
Lateral rotators		
Biceps femoris		
Popliteus	Tibial	L-4, L-5, S-1, S-2, S-3

*Underlined vertebrae indicate the primary roots supplying the muscles.

TABLE 79-3. Function and nerve supply of muscles responsible for movement of the knee and leg

Extensors. The major muscle of the extensor group (Fig. 79-3) is the quadriceps femoris (rectus femoris, vastus medialis, vastus intermedius, vastus lateralis). The sartorius muscle also helps to extend the knee. Acting in unison, these muscles extend the knee. They also serve as secondary stabilizers of the knee (with the posterior cruciate ligament) to resist posterior tibial translation. The bony anatomy allows the quadriceps to relax when standing with the knee fully extended; however, if the foot is elevated off the ground in the same position, the muscle is tonically contracted (7).

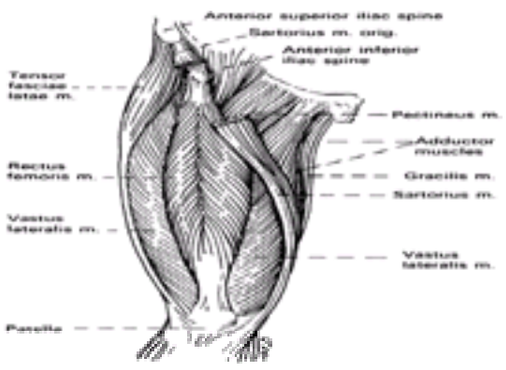

Figure 79-3. Extensor muscles of the knee. The rectus femoris originates from the anterior inferior iliac spine, whereas the vasti arise from the shaft of the femur. All four muscles converge onto a common tendon that crosses the knee joint and attaches to the tibial tuberosity by way of the patella. The common tendon of the quadriceps femoris comprises three lamina: the superficial layer from the rectus, the middle layer from the tendons of the vastus lateralis and medialis, and the deep layer from the vastus intermedius. The sartorius, a ribbonlike muscle, passes across the length of the thigh superficial to the quadriceps. It arises at the anterior superior iliac spine and inserts into the anterosuperior medial portion of the tibia. See Figure 79-1 for sites of origin and Figure 80-1 for sites of insertion of these muscles. (Modified from Hollinshead WH. *Anatomy for surgeons,* 3rd ed. Vol 3. Philadelphia: Harper & Row, 1982.)

Flexors. The chief flexors of the knee (Fig. 79-4) are the hamstrings (biceps femoris, semitendinosus, semimembranosus). These muscles also serve as secondary stabilizers (with the anterior cruciate ligament) to resist anterior tibial translation. The gracilis muscle also flexes the knee in addition to adducting the thigh and medially rotating the leg. The gastrocnemius also helps to flex the leg, in addition to plantar flexing of the foot.

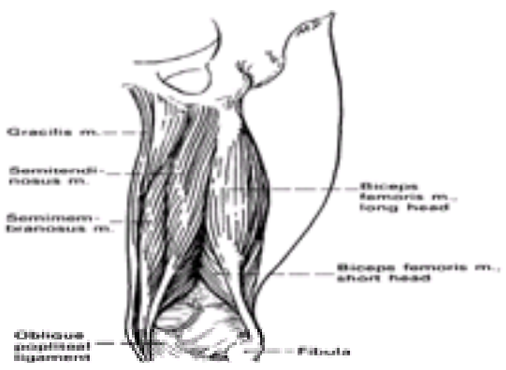

Figure 79-4. Flexor muscles of the knee. All three hamstring muscles arise from the ischial tuberosity and insert into the following structures. The semitendinosus muscle inserts into the medial aspect of the body of the tibia just posterior to the insertion of the gracilis and sartorius. These three muscles form a tendon complex sometimes called the *pes anserinus,* to which the anserina bursa is associated. The semimembranosus muscle inserts into the back of the medial tibial condyle, with the straight part of the tendon attaching to the medial meniscus as it crosses it. As it goes through its insertion, it gives off an expansion that runs obliquely, superiorly, and laterally across the posterior aspect of the knee joint to form the oblique popliteal ligament. The long head of the biceps femoris wraps around the lateral posterior medial side of the attachment of the fibular collateral ligament to the fibula, whereas the short head is attached to the tibia and to the fibular collateral ligament. The gracilis muscle is a long straplike structure located on the medial side of the thigh that arises from the lower part of the body of the pubis close to the symphysis and inserts into the medial surface at the upper end of the tibia below the medial condyle. See Figure 79-1 for sites of origin and Figure 80-1 for sites of insertion of these muscles. (Modified from Hollinshead WH. *Anatomy for surgeons,* 3rd ed. Vol 3. Philadelphia: Harper & Row, 1982.)

Rotators. Medial rotation of the tibia is produced by the semimembranosus, semitendinosus, sartorius, and gracilis muscles, whereas lateral rotation is produced by

the biceps femoris and popliteus muscles.

Blood and Nerve Supply. The blood vessels of the thigh are shown in Figure 79-5. The segmental and peripheral nerve supplies to the skin, muscles, and bones are described in detail in Chapter 8,Chapter 12, and Chapter 75. As is true for other long bones, the femoral shaft has dual circulation, with both small periosteal vessels as well as larger nutrient arteries providing blood supply. The nutrient arteries enter the upper half of the femur and give off long descending branches.

The nerves that supply the periosteum of the femoral shaft consist of filaments derived from the nerves that supply the muscles surrounding the bone. More distal innervation is from the corresponding nerves that supply the knee joint (see Nerves, later in this chapter).

Anatomy of the Knee

Bony Anatomy. The knee is the largest joint in the body. Although structurally it resembles a simple hinge joint, its movements are much more complex. In addition to flexion and extension, rotation and gliding movements occur at the knee. The bony architecture provides little inherent stability, which makes the knee vulnerable to injury. Stability is maintained by ligaments, muscles, and tendons as well as the menisci and joint capsule.

The knee joint consists of the articulations of three bones (femur, tibia, and patella) within a common cavity. The knee joint contains three compartments. The medial compartment consists of the articulation of the medial femoral condyle with the medial tibial plateau. The lateral compartment consists of the articulation of the lateral femoral condyle with the lateral tibial plateau. The patellofemoral compartment consists of the articulation of the retropatellar surface with the femoral trochlea. Disease processes may affect one or all three compartments of the knee. The articulating surfaces are covered with articular cartilage. In addition, the medial and lateral compartments have a fibrocartilaginous meniscus interposed between the articulation's surfaces.

Articular Surfaces. Figure 79-6 illustrates the articular surfaces of the knee joint. Note that the two rounded condyles are eccentrically curved, having a smaller radius of curvature posteriorly than anteriorly. Moreover, the curve of the lateral condyle is slightly greater, but shorter, than the medial condyle. The difference in curvature produces a difference in the movement of the two condyles and accounts for the medial rotation of the femur on the tibia that occurs with full extension of the knee (screw-home phenomenon) (7). The two femoral articular surfaces are confluent anteriorly through the articular surface of the patella but are widely separated posteroinferiorly and posteriorly by the intercondylar notch. The two epicondyles are two roughened convex prominences that surround the condyles proximally. The medial epicondyle receives the attachment of the medial collateral ligament of the knee joint, and the lateral epicondyle receives the attachment of the lateral collateral ligament and popliteus tendon.

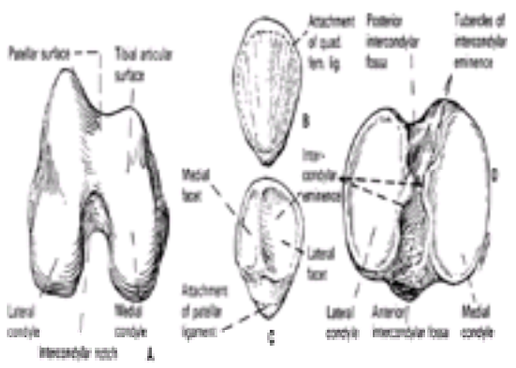

Figure 79-6. Articular surfaces of the knee joint. **A:** The articular surfaces of both condyles of the femur participate in the formation of the articular surface of the patella, which is larger on the lateral than on the medial condyle. Posteriorly, they are separated from each other below the intercondylar line by a deep intercondylar fossa. The articular surface of the lateral condyle is wide, whereas that of the medial condyle is longer and more highly curved posteriorly. **B:** The quadratus femoral ligament is attached to the periphery of the anterior surface of the patella. **C:** The posterior surface of the patella presents a smooth articular area covered with cartilage and divided into two facets by a vertical ridge, which lies adjacent to the groove on the anterior surface of the femur. The lateral patellar facet is broader and deeper than the medial facet. **D:** The upper surface of each tibial condyle is an articular surface that is almost ovoid and slightly concave. The two condyles and their articular surfaces are separated anteriorly by a slight depression of the anterior intercondylar fossa (or notch), which runs from the anterior to superior surface of the bone, and posteriorly by a more marked depression, the posterior intercondylar fossa (or notch). Between the anterior and posterior intercondylar fossae, the condyles and their articular surfaces are separated by a raised area, the intercondylar eminence, which has medial and lateral tubercles. Posteriorly, the articular cartilage extends over the smooth lip of the lateral condyle, but otherwise the articular surfaces are confined to the tibial plateau.

The tibial plateaus also consist of medial and lateral divisions. The surface of the medial plateau is slightly concave, whereas the surface of the lateral plateau is slightly convex. The lateral plateau is slightly higher than the medial plateau, secondary to the increased size of the medial femoral condyle compared to the lateral. Between the femoral condyles and the tibial plateau are the menisci, which are attached to the tibia by meniscotibial ligaments and to the femur by the meniscofemoral ligaments. The medial meniscus accounts for approximately 50% of the articulating surface in the medial compartment and the lateral meniscus approximately 70% of the articulating surface in the lateral compartment between the tibia and femur.

The patella is a roughly triangular bone (see Fig. 79-6). The quadriceps attaches to the superior pole through the quadriceps tendon, whereas the patellar ligament arises from the inferior pole and attaches to the tibia at the tibial tubercle. Anterior to the patella is a large prepatellar bursa, and the posterior surface is covered by articular cartilage with two main smooth facets to allow smooth gliding motion within the femoral trochlea.

Joint Capsule. The articular capsule of the knee is a complex structure that does not form a complete fibrous sleeve around the joint. Instead, the fibrous capsule consists of muscle, tendons, and ligaments between which a few capsule fibers that interconnect the articulating bones are found (5). Its inner surface is lined by synovial membrane, but this lining is often separated from the fibrous-ligamentous layer by other structures within the joint, such as fat pads and menisci.

The articular capsule is shown in Figure 79-7. In the anterior view, the fibrous layers of the capsule are seen to be completely lacking above the patella and deep to the tendon of the quadriceps femoris muscle. The fibrous capsule blends with the tendons of the vasti medialis and lateralis, the fascia lata, and its iliotibial band, which constitutes the medial and lateral patellar retinacula. *Anteriorly,* the capsule is reinforced by the patellar ligament, which is the central portion of the common tendon of the quadriceps femoris that continues from the patella to the tuberosity of the tibia. *Posteriorly,* the capsule consists of vertical fibers that arise above from the margins of the femoral condyles and the borders of the intercondylar fossa of the femur and descend to attach to the posterior margin of the tibial condyles. The capsule is reinforced from a tendinous expansion of the semimembranosus and oblique popliteal ligament. *Laterally,* capsule fibers stretch from the border of the lateral femoral condyle above to the aspect of the tibial condyle and head of the fibula below. The lateral collateral and popliteofibular ligaments reinforce the lateral capsule. *Medially,* the capsule attaches above to the margin of the medial femoral condyle and below to the corresponding margin of the tibial condyle. The medial collateral ligament reinforces the medial capsule.

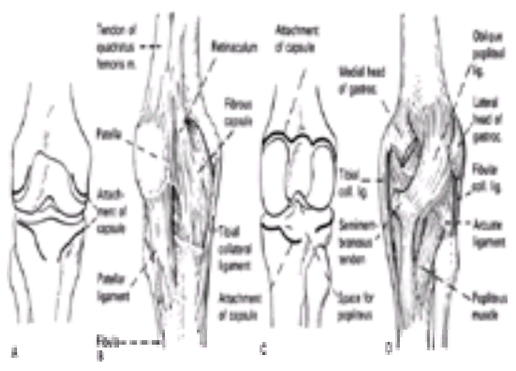

Figure 79-7. Articular capsule and some external ligaments of the knee joint. **A:** Anterior view. As shown by the thicker lines, the fibrous layers of the capsule are completely lacking above the patella. The synovial membrane is found deep to the tendon of the quadriceps. **B:** Anterior view. At the level of and inferior to the patella, the anteromedial and anterolateral aspects of the fibrous capsule blend with the expansion of the tendons of the vastus medialis and vastus lateralis muscles, as well as with the fascia lata and its iliotibial band. These structures constitute the medial and lateral patellar retinacula, which fill the intervals between the patellar and collateral ligaments and descend to attach to the anterior rim of the tibial condyle. The patellar ligament is the central portion of the common tendon of the quadriceps femoris that is continued from the patella to the tuberosity of the tibia. The ligament is a strong flat band approximately 8 cm long that is attached above to the apex and adjoining margins of the patella and the rough depression, on its anterior surface and below to the tuberosity of the tibia. Superficial fibers are continuous over the front of the patella with those of the tendon of the quadriceps, whereas the medial and lateral portions of the tendon pass from each side to the patella to be inserted into the proximal extremity of the tibia along the side of its tuberosity. These portions merge into the capsule to form the medial and lateral patellar retinacula. **C:** Lines of attachment of the capsule on the side and posterior to the cruciate ligaments. The gap in the tibial attachment of the capsule provides a hiatus for the exit of the popliteus muscle from the joint. **D:** Posterior view. The capsule consists of vertical fibers that arise above from the margins of the femoral condyles and from the border of the intercondylar fossa of the femur and descend to attach to the posterior margin of the tibial condyles. Blending with the capsule fibers posteriorly and above are the tendons of origin of the two heads of the gastrocnemius muscle. The popliteus muscle arises by a strong tendon approximately 2.5 cm long from a depression at the anterior part of the groove on the lateral condyle of the femur. The edge of the capsule, which arches over the muscle, is known as the *arcuate ligament*.

Accessory Ligaments. The major ligaments of the knee are independent of its capsule (Fig. 79-8). One pair, the medial and lateral collateral ligaments, is extraarticular; another pair, the anterior and posterior cruciate ligaments, is intraarticular (2,7).

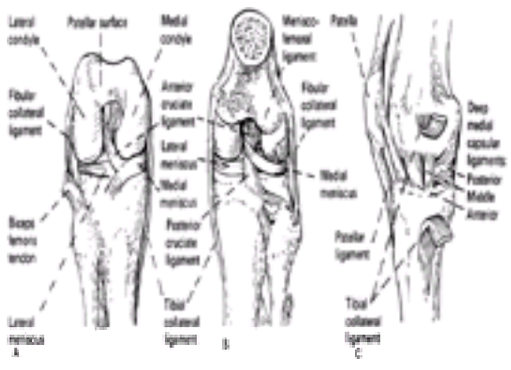

Figure 79-8. Accessory ligaments and menisci of the knee joint. **A:** Anterior view. **B:** Posterior view. **C:** Medial view. The two collateral ligaments, the anterior and posterior cruciate ligaments, and the medial and lateral menisci are interposed between the two bones. The superficial portion of the medial collateral ligament has been cut **(C)** and the ends reflected to show the deep section, which is composed of anterior, middle, and posterior ligaments. The anterior portion consists of parallel fibers that cover the anterior aspect of the joint, extend anteriorly into the extension mechanism, and attach loosely to the medial meniscus. These fibers are slightly relaxed during knee extension but tighten during flexion. The middle portion has distinct fibers and is composed of superior and inferior divisions. The superior (meniscofemoral) segment is thicker and fixes the medial meniscus to the femur, whereas the inferior (meniscotibial) segment is looser and permits the tibia to move on the meniscus. The posterior ligament consists of thin, indistinct, and fan-shaped fibers that pass posteriorly to aid in the formation of the posterior popliteal capsule. They are attached to the posterior aspects of the medial meniscus and blend with the semimembranosus muscle. (**A** and **B** modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985. **C** modified from Cailliet R. *Knee pain and disability,* 2nd ed. Philadelphia: FA Davis, 1983.)

The medial collateral ligament is composed of a superficial and a deep section. The superficial section is a broad flat band that extends from the medial femoral epicondyle to the proximal tibial metaphysis. Along its posterior edge, the superficial ligament fuses with the deep section, which is adherent to the joint capsule. The medial meniscus is attached to the deep section, along with the joint capsule (7). The medial collateral ligament is the primary restraint to valgus rotation.

The lateral collateral ligament is a cordlike structure that runs between the lateral femoral epicondyle and the tip of the fibula. It has no connections with either the deep capsule or the lateral meniscus. The lateral collateral ligament receives fibers from the popliteofibular ligament, which is a static portion of the popliteus tendon that arises from the posterior fibular head.

The anterior cruciate ligament runs from the intracondylar notch of the lateral femoral condyle to the anterior tibial plateau in front of the posterior cruciate ligament (Fig. 79-9). Its main function is to prevent anterior translation of the tibia in respect to the femur (Fig. 79-10). It is nearly isometric, in that it maintains tension throughout the range of motion of the knee.

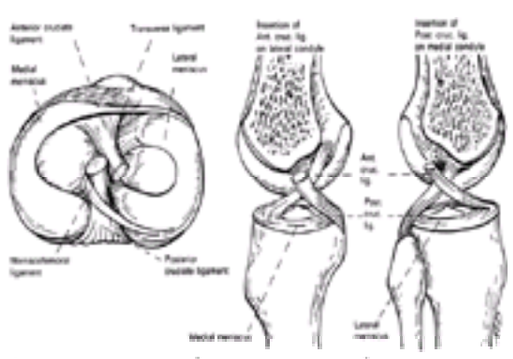

Figure 79-9. Menisci and cruciate ligaments. **A:** Superior view of the top of the right tibia. The medial meniscus is approximately 10 mm wide, with its posterior horn wider than the middle portion and its curve wider than that of the lateral meniscus. The anterior horn of the medial meniscus connects to the anterior ridge of the tibia, the anterior intercondylar eminence, and the anterior cruciate ligament by fibrous ligamentous tissue and, by way of the transverse ligament, connects to the anterior horn of the lateral meniscus. The lateral meniscus is 12 to 13 mm wide, and its curvature is greater than the medial meniscus, causing it to resemble a closed ring. Both its anterior and posterior horns insert directly into the intercondylar eminence and connect to the posterior cruciate ligament by fibrous tissue. Most of the posterior horn inserts into the femoral intercondylar fossa by way of the meniscofemoral ligament (of Wrisberg), which proceeds superiorly and medially and blends with the posterior cruciate ligament. **B,C:** Medial and posterior views of the cruciate ligaments. The anterior cruciate ligament is attached to the anterior part of the intercondylar eminence and passes posteriorly into the intercondylar fossa to attach to the medial side of the lateral condyle of the femur. The posterior cruciate ligament is attached to the posterior part of the intercondylar eminence and passes anteriorly in the intercondylar fossa to attach to the medial aspect of the medial condyle of the femur.

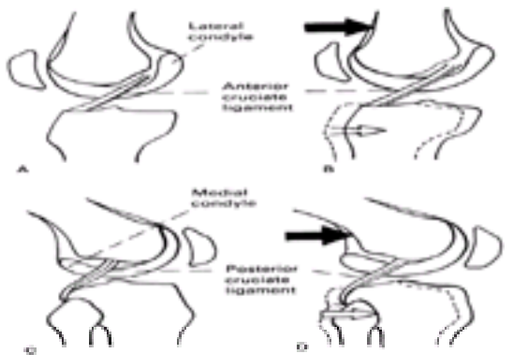

Figure 79-10. Function and restriction imposed by the cruciate ligament. **A:** A medial view of the right knee shows the attachment of the anterior cruciate ligament. **B:** Pressure on the lower part of the femur (*black arrow*), which tends to produce hyperextension, is prevented by the ligament. **C:** A lateral view of the right knee shows the attachment of the posterior cruciate ligament. **D:** Pressure posterior to the femur (*black arrow*), which would tend to displace the femur anteriorly, is prevented by the cruciate ligament. It also aids in normal knee flexion by acting as a drag force. (Modified from Cailliet R. *Knee pain and disability,* 2nd ed. Philadelphia: FA Davis, 1983.)

The posterior cruciate ligament runs from the intracondylar notch of the medial femoral condyle to the posterior tibial plateau behind the anterior cruciate ligament. It is the primary restraint to posterior translation of the tibia on the femur. It is composed of several bands that are tensioned at differing degrees of knee flexion.

Menisci. The menisci are two fibrocartilaginous semilunar wedges that partially divide the joint cavity and deepen the shallow articular facets of the tibia. Their concave inner margins are markedly thinner than their convex peripheral rims, which fuse with the capsule. Both menisci are anchored by their anterior and posterior horns to the intercondylar eminence. The upper and lower surfaces of the menisci are in contact with the articular cartilage of the femoral and tibial condyles, respectively, and both surfaces are moistened by synovial fluid.

The lateral meniscus becomes attached posteriorly to the medial condyle of the femur by the posterior meniscofemoral ligament (of Wrisberg), the anterior meniscofemoral ligament (of Humphrey), or both. The lateral meniscus is not rigidly attached. Its movements are guided by the movements of the femur, and its mobility is enhanced by the popliteus muscle, which can retract the meniscus over the smooth edge of the lateral tibial condyle. The medial meniscus is less mobile than the lateral meniscus, partly because of its attachment to the medial collateral ligament (7).

The menisci are penetrated by nerves derived from the capsular plexus but are avascular except for their most peripheral zone. The lack of blood supply to the rim of the menisci result in decreased ability to heal (4).

Synovial Membrane. The synovial membrane lines the inner surface of the capsule and covers all intraarticular structures except the menisci. Its attachment closely follows the articular margins (Fig. 79-11). The cruciate ligaments, popliteus tendon, and a large fat pad behind the patellar ligament are therefore intracapsular, but are extrasynovial. The synovial membrane projects from both medial and lateral borders of the articular surfaces of the patella as two fringelike folds to the interior of the joint. These alar folds converge and continue as a single band, the infrapatellar synovial fold (or ligamentum mucosa), attaching to the anterior aspect of the intercondylar fossa of the femur. At the upper posterior aspect of the joint, the synovial membrane forms true pouches, or bursae, which lie deep to the origin of the gastrocnemius muscle (Fig. 79-12).

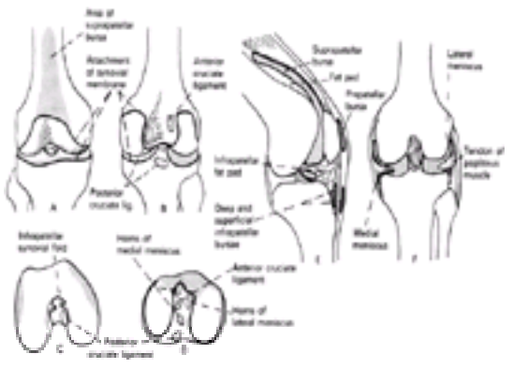

Figure 79-11. Attachment of the synovial membrane and its reflection on the surface of the bone. **A:** Anterior view of the knee joint. **B:** Posterior view of the knee joint. **C:** Articular surface of the femur. **D:** Articular surface of the tibia. The thick black lines show the boundary of the synovial membrane; the gray areas indicate its reflection on the surface of the bones. **E:** Sagittal section. **F:** A frontal section shows the boundaries of the synovial membrane (*thick black lines*) and some of the bursae around the joint. (Modified from Hollinshead WH. *Anatomy for surgeons,* 3rd ed. Vol 3. Philadelphia: Harper & Row, 1982.)

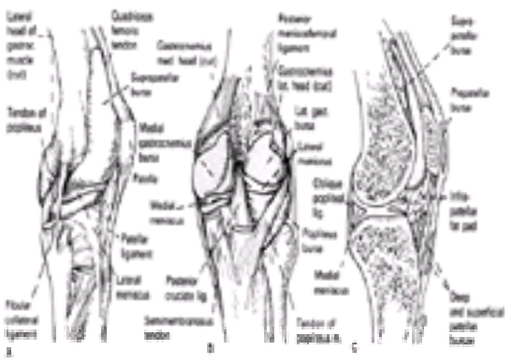

Figure 79-12. Synovial membrane of the right knee joint. **A:** Lateral view. **B:** A posterior view shows the distended synovial membrane (*indicated in gray*). Posteriorly, a smaller extension of the synovial cavity is interposed in the form of bursae between the popliteus muscle and the tibia as that muscle exits from the joint. The lateral gastrocnemius bursa lies between the lateral head of the gastrocnemius muscle and the capsule; the medial gastrocnemius bursa lies between the medial tendon of the gastrocnemius and the capsule. **C:** A sagittal section of the knee joint shows the synovial membrane and some of the bursae of the knee joint. As the membrane is draped over the fat, it is raised up into an infrapatellar fold and forms a ridge over which the two limbs of the U-shaped synovial cavity communicate with each other. The anterior conjoined portion of the cavity of the synovial membrane sweeps upward from its femoral attachment to cover the anterior surface of the femur; then, 7 to 8 cm above the patella, it reflects anteriorly onto the quadriceps tendon and attaches to the superior margin of the patella, thus producing the suprapatellar bursa or pouch. (**A** and **B** modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985. **C** modified from Rosse C, Clawson DK. *The musculoskeletal system in health and disease.* Hagerstown, MD: Harper & Row, 1980.)

The synovial membrane passes downward from the femur on both sides of the joint, lining the capsule at its points of attachment to the menisci. It then passes downward over the proximal surface of the menisci to their free borders, which are not covered by synovial membrane, and then along their distal surfaces. At the posterior part of the lateral meniscus, the synovial membrane forms a small sac, the popliteal recess, between the groove on the surface of the meniscus and the

tendon of the popliteus muscle. The membrane is then reflected across the cruciate ligaments.

Bursae. A number of bursae are related to the knee joint (see Fig. 79-12). Anterior to the knee are four bursae: (a) the large subcutaneous prepatellar bursa, which is interposed between the patella and the skin; (b) the small deep infrapatellar bursa, which lies between the upper part of the tibia and the patellar ligament; (c) the superficial infrapatellar bursa, which is between the lower part of the tuberosity of the tibia and the skin; and (d) the suprapatellar bursa, which lies between the anterior surface of the of the distal femur and the deep surface of the quadriceps that usually communicates with the knee joint.

Lateral to the knee joint are also four bursae: (a) the lateral gastrocnemius bursa, which sometimes communicates with the joint between the lateral head of the gastrocnemius muscle and the capsule; (b) the inferior biceps femoral bursa, which is between the lateral collateral ligament and the biceps femoris tendon; (c) the popliteus bursa, which lies between the popliteal tendon and the lateral condyle of the femur and is usually an extension from the synovial membrane of the joint; and (d) a bursa between the fibular collateral ligament and the tendon of the popliteus muscle.

Medial to the knee joint are five bursae: (a) the medial gastrocnemius bursa, which is between the medial head of the gastrocnemius and the capsule, sends a prolongation between the tendon of the medial head of the gastrocnemius and the tendon of the semimembranosus, and communicates with the joint; (b) the anserine bursa, superficial to the medial collateral ligament and deep to the tendons of the sartorius, gracilis and semitendinosus; (c) a bursa deep to the medial collateral ligament, which is between it and the tendon of the semimembranosus; (d) a bursa between the tendon of the semimembranosus and the medial tibial plateau; and (e) a bursa that is occasionally found between the tendons of the semitendinosus muscle.

Nerves. The knee joint is supplied by a large number of articular fibers from muscular branches of the femoral, obturator, tibial, and common peroneal nerves (Fig. 79-13). The articular branches of the femoral nerve to the knee joint arise from the saphenous nerve and from the nerves to the three vasti muscles. The branch from the saphenous nerve, which can contain some fibers from the anterior division of the obturator nerve, is distributed to the anteromedial part of the knee joint, and a branch from the nerve to the vastus medialis is distributed to the medial part of the joint. A branch from the nerve to the vastus intermedius is distributed to the suprapatellar part of the knee joint, and a branch from the nerve to the vastus lateralis is distributed to the anterolateral part of the joint. The amount of overlap is significant, and anastomoses among these branches are often seen (10).

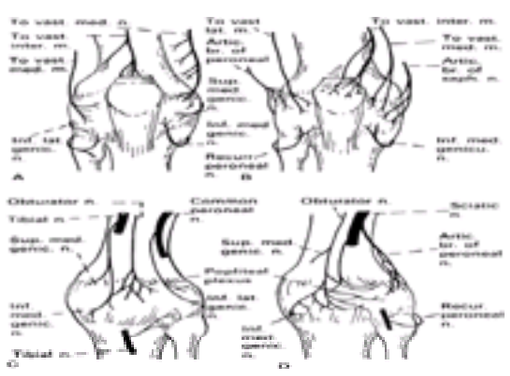

Figure 79-13. Nerves that supply the knee joint. **A,B:** Anterior views. **C,D:** Posterior views. See text for details. (Modified from Gardner E. The innervation of the knee joint. *Anat Rec* 1948;101:109–130.)

The branch from the obturator nerve is usually derived from its posterior division, follows the femoral and popliteal arteries to the knee joint, and is distributed especially to the posteromedial part of the capsule. The tibial nerve provides a single large branch that breaks up into subsidiary branches, which accompany various genicular vessels or run directly to the capsule to supply its posterior part. A single branch from the common peroneal nerve is distributed to the anterolateral part of the capsule.

The recurrent branch of the peroneal nerve arises at the point of division of the common peroneal nerve into its superficial and deep branches and is mainly distributed to the periosteum of the anterolateral surfaces of the tibia and the tibiofibular joint. In addition, some of the subsidiary branches follow blood vessels to the knee joint and supply the infrapatellar fat pad and adjacent capsule. The horns of the menisci, but not the body, are well innervated, as is the posterior meniscofemoral ligament of Wrisberg (7).

Blood Vessels. The arteries of the knee joint are branches of the vessels that enter into the anastomosis around the joint that receives contributions from the femoral, profunda femoral, and popliteal arteries (Fig. 79-14).

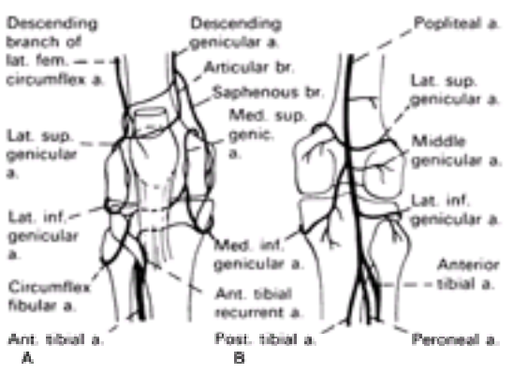

Figure 79-14. Blood supply of the knee joint. **A:** The arteries that supply the knee joint include the descending genicular branch of the femoral artery, which gives off saphenous and articular branches that supply the joint; the descending branch of the lateral femoral circumflex artery, which is a branch of the deep femoral artery; the lateral and medial superior genicular arteries and the lateral and medial inferior genicular arteries, which are branches of the popliteal artery; and the recurrent branch of the anterior tibial artery. Occasionally, a posterior tibial recurrent artery is present, which helps to supply the joint. **B:** The fibrous capsule is perforated posteriorly by the middle genicular artery, which supplies particularly the tissue of the intercondylar region—that is, the cruciate ligaments and attachments of the menisci. The menisci have minimal vascularity at their extremities, whereas the rest of the menisci are avascular. (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985.)

Movement and Stability of the Knee Joint

Movement. The tibiofemoral joint range of motion is greatest in the sagittal plane, where the range from full extension to full flexion is from approximately 0 to 140 degrees (11). Knee flexion and extension are accompanied by a gliding motion of the tibia on the femur with simultaneous rotation: External rotation of the tibia on the femur occurs during knee extension, and internal rotation occurs during knee flexion.

In the transverse plane, the range of motion of the knee increases from full extension of the knee up to 90 degrees of flexion. In full extension, almost no rotation is possible because of the interlocking of the femoral condyles and the tibial plateau. At 90 degrees of flexion, external rotation of the knee ranges from 0 to approximately 45 degrees and internal rotation ranges from 0 to approximately 30 degrees. Beyond 90 degrees of flexion, the range of motion in the transverse plane decreases, primarily because of restriction by the ligaments and other soft tissues.

In the frontal plane (abduction/adduction), much less motion secondary to the ligamentous restraints is seen. The maximal motion in this plane is obtained with the

knee flexed to 30 degrees, but even here it is limited to a few degrees (11).

The range of motion of the knee in the sagittal plane during level walking has been measured at approximately 5 degrees of flexion at the beginning of stance, at heel strike, and at the end of stance phase just before toe-off, whereas 75 degrees of flexion were observed during the middle of the swing phase (12). During normal gait, the knee is never fully extended. The range of motion required to do various other activities is varied: 0 to 83 degrees during stair climbing, 0 to 90 degrees during descending stairs, 0 to 93 degrees sitting, 0 to 106 degrees tying a shoe, and 0 to 117 degrees lifting an object (13,14).

Stability. Stability of the knee joint is crucial to proper function of the knee. Because the bony surfaces have a negligible influence on stability, the integrity of the ligaments and muscles is essential (2,7). In relaxed standing, the knee depends on its ligaments for stability, with the reinforced part of the capsule and the cruciate ligaments being the chief factors in preventing hyperextension. Once the weight-bearing knee is flexed, muscle force is essential to maintain stability. Even a few degrees of flexion are accompanied by contraction of the quadriceps, whose power can maintain stability in the knee despite considerable laxity of the ligaments. The quadriceps is important in stabilizing the patella. Because the femoral shaft articulates with the tibia at an angle, the pull of the quadriceps tends to displace the patella laterally. This is prevented by the prominent trochlea of the lateral femoral condyle and by the attachment of the vastus medialis into the medial border of the patella.

In the flexed position of the weight-bearing knee, the femoral condyles have a tendency to slip anteriorly on the tibial plateau, but this is prevented by the anterior cruciate ligament. The iliotibial tract is also important in knee function, particularly when weight is borne by the flexed knee. Because it is attached to the anterior surface of the lateral tibial condyle, the iliotibial tract can transmit forces to the knee from the gluteus maximus and tensor fasciae lata. The pelvis, with the femur, is balanced on the sloping tibial plateau by the gluteus maximus and tensor fasciae lata by way of the iliotibial tract.

Kinetics. Kinetic analysis is used in any situation, static or dynamic, to determine the magnitude of the forces on a joint that are produced by muscle, body weight, connective tissue, or externally applied loads. By kinetic analysis those situations that produce excessively high forces can be identified.

During walking, just after heel strike, the joint reaction force ranges from two to three times body weight and is associated with contraction of the hamstring muscles (11). During knee flexion, at the beginning of the stance phase, the joint reaction force is approximately two times body weight and is associated with contraction of the quadriceps muscle, which acts to prevent buckling of the knee. The peak joint reaction force occurs during the late stance phase, just before toe-off, when it ranges from two to four times body weight and is associated with contraction of the gastrocnemius muscle.

During the gait cycle, the joint reaction force shifts from the lateral to the medial tibial plateau, which sustains the peak force in the stance phase. In the swing phase, when the force is minimal, it is sustained primarily on the lateral plateau. The larger size and greater thickness of the medial plateau allow it to sustain the higher forces imposed on it during walking and other activities. Although the tibial plateaus are the main load-bearing structures in the knee, the cartilage, menisci, and ligaments also bear loads. The menisci help to distribute the stresses imposed on the tibial plateau.

CLINICAL EVALUATION OF THE PATIENT

The thigh and knee are frequent sites of painful disorders. In addition to the many mechanical injuries it can sustain, the knee is prone to almost every type of inflammatory and degenerative joint disease. Moreover, the metaphyseal regions of the femur and tibia are common sites of osteomyelitis and neoplasia. To make a correct diagnosis and carry out the appropriate therapeutic strategy, the patient must be evaluated thoroughly (Table 79-4).

TABLE 79-4. Evaluation of the patient with knee pain

History

As with all aspects of medicine, a proper diagnosis begins with a careful history. If a history of trauma is elicited, the mechanism of injury can provide important clues about destructive damage. The amount of force absorbed and the direction of force help to define injury.

A history of pain must be carefully characterized. Knowledge of the onset, distribution, intensity, quality, and aggravating and relieving factors assists in narrowing the differential diagnosis. Pain can arise from bone, muscle, or joint tissue. In addition to local trauma and overuse syndromes, pain may result from degenerative, congenital, infectious, vascular, neurologic, neoplastic, and systemic diseases. It may also be a referred phenomenon from the hip joint or spine. Weakness, stiffness, swelling, deformity, restricted movement, and clicking or locking of the knee joint are all important factors to define.

Physical Examination

A systematic approach to the physical examination of the thigh and knee is essential to confirm the history. The painful extremity should always be compared to the uninvolved (if unilateral symptoms) side to better establish “normal” for the particular patient. Inspection, palpation, range of motion, strength testing, sensory examination, ligament stability, and associated joints are all important components of the physical examination (see Table 79-4).

Inspection

Exposure of the extremity is essential for an adequate examination. The color and texture of the skin, with notation of any bruising or scars, can provide information not initially obtained in the history. The alignment of the femur, tibia, and patella should be noted. Mild degrees of genu valgum and genu varum are common in children, and normal growth usually corrects the deformity, unless it is excessive, in which case congenital disease of the bone should be considered. Hyperextension (genu recurvatum) results from muscle imbalance, a growth abnormality, or an unhealed ligamentous injury, all of which may distort the mechanics of the joint. The levels of the two patellae should be compared while the patient is in the relaxed standing position. Foot alignment should be noted. The contour of the soft tissues in the thigh and around the knee, with comparison of the muscles in both relaxed and isometric contraction, should be noted. Finally, the patient's gait should be closely observed for alterations in the normal pattern.

Palpation

All anatomic structures should be palpated, being especially gentle over painful and swollen joints. Abnormalities in skin temperature or texture and local tenderness or swelling can provide clues to underlying pathology.

With the quadriceps relaxed, the relatively flat patellofemoral articular surfaces should permit manual side-to-side displacement of the patella. The medial and lateral joint lines should not be tender. Insertions of muscles and ligaments, as well as bursae, should be palpated. Roughness of the articular surface can be evaluated by passively flexing and extending the knee with a hand over the patella. A grating sensation (crepitus) may signify underlying pathology. The crepitus can be magnified

by having the patient extend the knee against gentle resistance.

Generalized swelling is nonspecific and has several basic causes, including thickening or enlargement of the bone, fluid within the joint, and thickening of the synovial membrane. A hot, diffuse, tender swelling may suggest underlying osteomyelitis or a malignant primary tumor. Swelling around the knee joint should be differentiated from an intraarticular effusion. A large effusion will elevate the patella and obliterate the normal medial and lateral contour of the patella. The ballottement test (Fig. 79-15) is helpful in diagnosis of an effusion. Aspiration and examination of the intraarticular fluid can differentiate between traumatic (blood), inflammatory (serous), and infectious (pus) etiologies of effusions. Palpation of the soft tissues may demonstrate thickening of the synovial membrane, especially in the suprapatellar pouch.

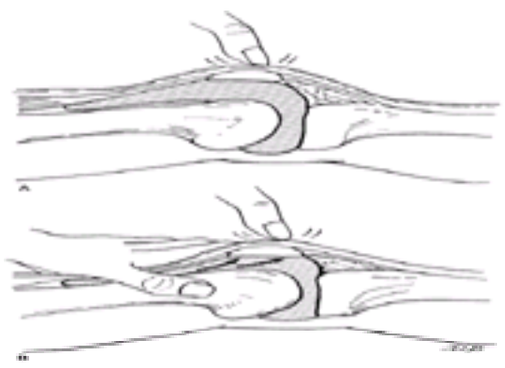

Figure 79-15. Technique of ballottement of the patella and of testing for the presence of a large effusion into the joint. **A:** With a large effusion (*shaded area*), the patella is greatly elevated, enabling ballottement of the patella against the femoral condyle with the second finger. **B:** With moderate effusion (*shaded area*), the patella may not be elevated. Thus, fluid must be displaced from the suprapatellar pouch and the site of the joint cavity by compressing the region with the left hand. When the patella is elevated, ballottement can be carried out with the second finger of the right hand. (Modified from Rosse C. The thigh and the knee. In: Rosse C, Clawson DK, eds. *The musculoskeletal system in health and disease.* Hagerstown, MD: Harper & Row, 1980.)

Range of Motion

Accurate assessment of the range of motion is an important part of the physical examination. The unaffected extremity is used as the control, as both the passive and active range of motion are evaluated. Any pain or crepitus with motion should be noted. Normally, the range of motion is from full extension with flexion being limited by the posterior soft tissues of the buttocks, thigh, and calf.

Muscle Strength

Motor strength is graded on a scale of 0 (no active muscle twitch) to 5 (full strength over a complete range of motion). Resistive testing of extension is easier to test with the patient sitting, whereas testing of flexion is easier with the patient prone (Fig. 79-16). In general, the knee flexors and extensors of a patient are considerably stronger than the arms of even the most robust examiner. Therefore, relative strength should always be compared to the opposite side. In addition, observation of ability to perform a deep knee bend and to toe and heel walk can provide additional information.

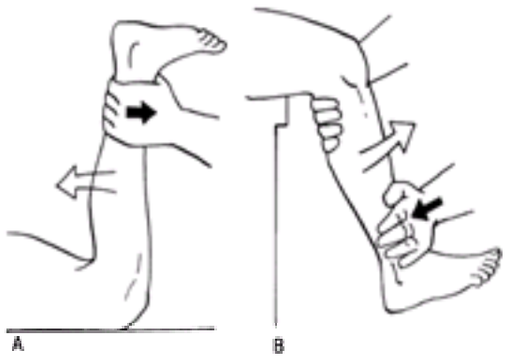

Figure 79-16. Testing the strength of the muscles of the knee. **A:** The flexor muscles are tested with the patient lying prone and the leg partly flexed. The patient attempts to further flex the lower leg toward the thigh against the resistance offered by the examiner. **B:** The extensor muscles are tested with the patient sitting at the edge of the examining table. The patient attempts to extend the knee against the resistance of the examiner.

Muscle atrophy can be assessed by measuring the thigh circumference. A mark made on the anterior thigh, 10 cm proximal to the superior pole of the patella, provides a repeatable assessment of muscle bulk. Both right and left sides should be measured.

Sensation

Decreases in light touch, temperature, and vibration at the thigh and in the lower leg and foot can help identify peripheral and central neurologic pathology. Reflex testing of the patellar tendon and Achilles tendon should be symmetric. Achilles reflexes typically are decreased or absent in the elderly. An abnormal Babinski test should be identified.

Stability

Patient relaxation is the key to obtaining a good assessment of ligamentous stability. Wide variation among the population is seen in the “tightness” of the knee ligaments, and therefore, both knees must be compared. Medial and lateral collateral ligament testing is performed with the knee at 30 degrees of flexion (Fig. 79-17). Anterior and posterior drawer tests are performed with the knee at 90 degrees of flexion and the foot anchored on the table (Fig. 79-18). A Lachman test, performed with the free leg at 30 degrees, has been shown to be more sensitive than the anterior drawer test in diagnosing anterior cruciate insufficiency (15).

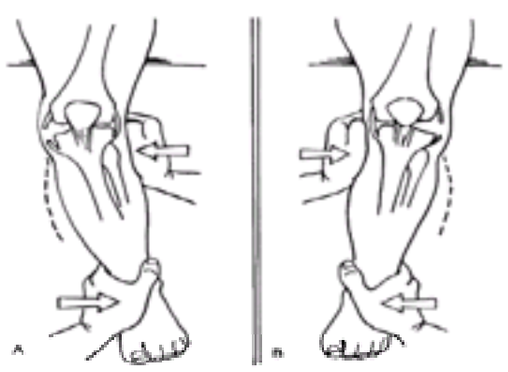

Figure 79-17. Testing the collateral ligaments of the knee. **A:** With the left knee slightly flexed to eliminate the stabilizing effect of the cruciate ligament on the extended knee, the tibial collateral ligament is tested by grasping the patient's ankle with one hand and using the other hand as a fulcrum at the knee. Abduction force

is then applied at the ankle in an attempt to produce a valgus deformity of the knee. **B:** The examiner tests the lateral collateral ligament by attempting to produce a varus deformity. (Modified from Rosse C. The thigh and the knee. In: Rosse C, Clawson DK, eds. *The musculoskeletal system in health and disease.* Hagerstown, MD: Harper & Row, 1980.)

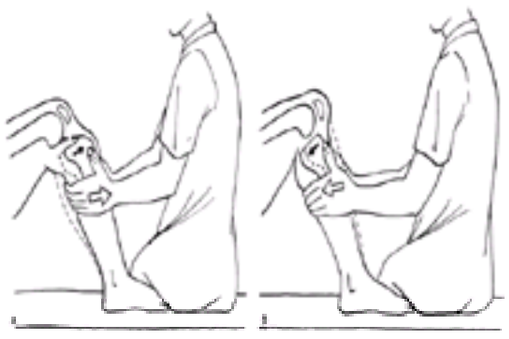

Figure 79-18. Testing the cruciate ligaments of the knee. **A:** With the patient lying supine on the examining table, the knee flexed to approximately 120 degrees, and the foot stabilized, the examiner grasps the upper end of the tibia with both hands, with the fingers interlocked behind and the tip of each thumb placed on each tibial condyle. The examiner tests the anterior cruciate ligament by attempting to displace the tibia anteriorly on the femur. If the ligament is torn, a forward displacement of the tibia occurs (anterior drawer sign). **B:** The integrity of the posterior cruciate ligament is tested in the same manner by attempting to produce posterior displacement of the tibia.

Other Areas

Because the knee is a common site of referred pain, the spine, hips, ankles, and feet must be carefully evaluated when assessing knee pathology.

Imaging

Anteroposterior and lateral radiographs of the thigh or knee provide a good general screening. Tangential views of the patella (sunrise view) can assist with patellofemoral symptoms. Oblique views (45 degrees) can help diagnose osteochondritis dissecans or fractures. Weight-bearing anteroposterior views are helpful when looking at compartmental involvement of osteoarthritis. A 45- degree flexion, weight-bearing posteroanterior view helps delineate lesions of the true posterior femoral condyles.

Depending on clinical suspicion after history and physical examination, additional imaging studies may be needed. Radioisotope bone scanning provides a sensitive but nonspecific assessment. Magnetic resonance imaging (MRI) can assist with soft tissue abnormalities, including ligaments, menisci, infection, and neoplastic processes. Computed tomography provides more detailed assessment of complex intraarticular fractures. Imaging studies of hips, spine, and feet may be necessary to diagnose pathology.

Arthroscopy

Arthroscopy has developed into both an adjunctive tool for diagnosis and an instrument for therapeutic intervention. Although arthroscopy has traditionally been performed in the operating room with regional or general anesthesia, experience is growing with office use with local anesthesia (16).

PAINFUL DISORDERS OF THE THIGH

Traumatic Disorders

Fractures

Etiology. Femoral shaft fractures are generally secondary to high-energy mechanisms. Pathologic fracture should be suspected when a femoral shaft fracture is seen after minimal trauma. Frequently, patients have additional injuries secondary to the high energy absorbed. Life-threatening causes of hypovolemic shock must be ruled out before assuming that the femur fracture is an isolated injury. However, even isolated femur fractures may result in hypovolemic shock and fat embolism syndrome.

Diagnosis. A careful assessment of the skin must be performed to ensure that the fracture is not an open injury, with an associated higher infection risk. Appropriate antibiotics followed by careful irrigation of the wound are key to decreasing infection risk.

Treatment. Definitive treatment of femoral shaft fractures depends on patient, fracture, and surgeon variables (17). Younger children are usually treated with external immobilization in a hip spica cast. Older, skeletally immature children usually require a period of traction followed by immobilization or operative stabilization. Skeletally mature patients are almost uniformly treated with operative fixation. Closed, percutaneous intramedullary nailing has had excellent results for several decades (18) (Fig. 79-19). Open plating and external fixation are additional methods that can be used depending on the particular fracture pattern and the surrounding soft tissue. Regardless of the technique, early fixation allows early mobilization and decreases the rate of problems associated with long bed rest.

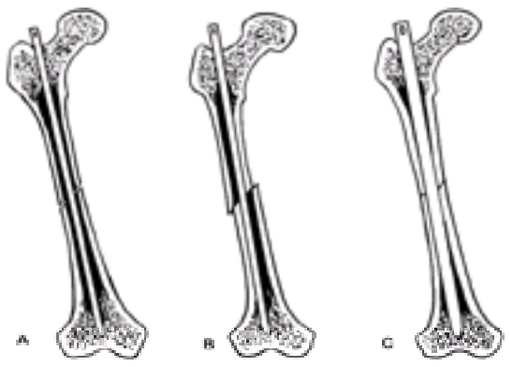

Figure 79-19. Internal splinting of the shaft fracture with a narrow intramedullary rod **(A)** often results in displacement and shortening **(B)**. Intramedullary reaming and nailing with a large rod allows better cortical contact and stability, thus minimizing this complication **(C)**. (Modified from Bucholz RW, Mooney V. Fractures of the femoral shaft. In: Evarts CM, ed. *Surgery of the musculoskeletal system.* Vol 3. New York: Churchill Livingstone, 1983.)

Pain Control. The intensity and duration of pain vary with the type of fracture and the associated soft tissue damage. A nondisplaced fracture produces moderate pain, whereas displaced fractures produce continuous, severe, deep pain and sharp, well- localized, superficial pain. The key to pain control is immobilization of the

fracture. Immobilization can be initially performed with external splinting; however, it is best accomplished with longitudinal traction, either skin or skeletal.

Initial pain control is provided systematically during transport and evaluation of the patient. Once the patient has been immobilized, effective pain relief can be attempted with opioid infusion. Patient-controlled analgesia is an excellent method of delivering pain control. When available, a continuous epidural analgesia produced by an opioid combined with a dilute solution of a local anesthetic, given in sufficient amounts to produce analgesia of the site of injury (T-10 to S-5 for the femur and knee joint) can provide pre- and postoperative analgesia. The need for ongoing assessments of compartments may preclude the use of epidural anesthesia.

Operative anesthesia is most commonly general; however, a regional anesthetic obviates the risk of vomiting or regurgitating gastric contents into the lungs. It also prevents massive nociceptive input and the neuroendocrine stress response. An alternative method of anesthesia is a sciatic-femoral-obturator nerve block.

Postoperatively, either patient-controlled anesthesia or continuous analgesia with a dilute solution of a local anesthetic and an opioid should be continued to provide effective pain relief, prevent the neuroendocrine stress response, and permit early motion and rehabilitation (19).

Contusions

Etiology. Contusions are the most common injury sustained to a muscle. They usually occur during an athletic event resulting from a direct blow to the muscle.

Diagnosis. A mild contusion of the quadriceps is associated with localized tenderness and pain with active contraction or passive stretching of the involved muscle. A moderate contusion is associated with increasing local edema in addition to pain. A severe contusion is associated with continuous pain, gross swelling, and disability.

Treatment. Initially, the goal is to minimize hemorrhage with rest, ice packs, compression, and elevation. This regimen is continued for 24 to 48 hours, during which no exercises beyond isometric quadriceps contractions are performed. After the phase of inflammation is passed, the goal is restoration of range of motion. Depending on the severity of the contusion, weight bearing may need to be limited with crutches. Active range of motion exercises are continued until full extension and flexion and a normal gait are obtained. The final phase is progressive resistance exercises until full strength is regained.

Muscle Strain

Etiology. Muscle strain is a common injury occurring when a muscle is forcibly contracted. It can occur passively, but muscle strain more commonly occurs with the active, eccentric loading of muscles. Muscles that cross two joints seem to be at particularly high risk (rectus femoris and hamstrings in the thigh). Myotendinous junctions are frequently involved (20).

Diagnosis. Patients typically complain of pain while participating in athletics. They may describe a popping sensation and have difficulty ambulating. Tenderness to palpation is found usually at the distal or proximal end of the muscle. Pain with passive stretch, swelling, and ecchymosis are often present. The degree of symptoms correlates with the degree of injury.

Treatment. Prevention of the injury with proper warm-up and stretching is best. As with contusions, rest, ice, compression, and elevation are the mainstays of early treatment. Gradual stretching exercises are continued until full range of motion is obtained, and return to activity with proper preparticipation warm-up is advised. Antiinflammatory medications are useful during the initial period.

Tendon and Muscle Ruptures

Etiology. Quadriceps and patellar tendon ruptures occur when the muscle rapidly contracts with the knee flexed. Rupture usually occurs through an area of weakened tendon secondary to age-related disorders (20). Direct trauma can also result in rupture.

Diagnosis. Patients complain of immediate pain and inability to ambulate. On physical examination, extensive swelling and a palpable gap are noted. Radiographs of the knee often demonstrate an abnormal position of the patella.

Treatment. Complete ruptures must be repaired surgically. Repairs are more effective if done early, as chronic ruptures contract and make an end-to-end repair more difficult. Patients are usually immobilized for 6 to 8 weeks postoperatively and then gradually allowed to return to activities once full range of motion is obtained. Partial ruptures are best repaired if diagnosed in the acute phase; chronic partial ruptures may respond to nonoperative rehabilitation.

Reflex Spasm of the Quadriceps

Etiology. Various injuries and a few disease states can provoke bouts of reflex spasm of the quadriceps or hamstrings that can cause transient severe pain. The reflex spasm can be a result of impact injuries to the muscles or can be associated with acute or chronic diseases of the hip and occasionally of the knee joint. Postoperative spasm can be excruciating and may occur on the second, third, or fourth postoperative day.

It has long been recognized that acute tissue damage caused by injury of muscle often provokes reflex spasm of the muscles that are supplied by the same and adjacent spinal cord segments as the site of injury. Until recently, these reflexes were believed to be produced as a result of continuous nociceptive input from the site of injury, stimulating interneurons in the dorsal horn and motor neurons in the anterior horn, with a consequent increase in skeletal muscle tension and spasm. It has been shown that massive nociceptive input not only stimulates various spinal cord neurons, the axons of which pass to the brain, but also sensitizes dorsal horn neurons, interneurons, and motor neurons, persisting for days and even weeks (21). The increased sensitivity decreases the threshold of these cells, and as a result, they can be activated by innocuous sensory stimulation such as light touch or proprioception (movement), which under normal conditions has no effect.

Diagnosis. Reflex spasm is probably one of the factors responsible for the production of hyperalgesia and allodynia in complex regional pain syndromes and for the abnormal motor response. It explains why such spasm occurs days after the pain from the surgical wound has diminished.

Treatment. The usual doses of potent opioids are ineffective in preventing or relieving the intense reflex muscle spasm and the associated severe pain. Even patient-controlled intravenous opiate analgesia may not provide sufficient relief. Intraspinal opioids dampen the reflex spasm, but only interruption of the afferent and efferent limbs or the reflexes with local anesthetic can adequately relieve the spasm and prevent or eliminate the pain. This is usually best achieved with administration of continuous epidural analgesia that extends from T-10 to the S-2 segments, either through repeated boluses or by continuous infusion. This blocks all nociceptive input from the hip joint, the area of the surgical incision, and the efferent somatomotor and sympathetic fibers to the thigh. This method of postoperative pain relief not only completely relieves pain and prevents the reflex spasm but also permits earlier mobilization and reduces the length of hospitalization (19).

Infections

Acute pyogenic osteomyelitis frequently involves the metaphyseal regions of the femur. The infection can enter either through an open wound (open fracture) or, more commonly, through the bloodstream (hematogenous osteomyelitis) (1,9). The distal femoral metaphysis is more prone to osteomyelitis than the proximal metaphysis. Children are more susceptible than adults, secondary to the large area of enchondral ossification. Chronic osteomyelitis is almost always a sequel to an acute infection that has been neglected or has been refractory to treatment.

Both acute and chronic osteomyelitis produce moderate to severe pain, fever and malaise, lethargy, and other constitutional symptoms. Local pain, draining sinuses, heat, swelling, tenderness, and erythema over the involved area are diagnostic hallmarks. Laboratory tests including white blood cell count, sedimentation rate, and C-reactive protein (CRP) may be elevated. Blood cultures typically fail to identify the causative organism. Radiographs may reveal a lytic bone lesion late in the course. Bone scanning reveals increased uptake in the lesion.

Antibiotics and surgical debridement are the usual treatment regimen for most pyogenic osteomyelitis.

Metabolic and Endocrine Disorders

The femur can be affected by various metabolic bone diseases, including osteoporosis, osteomalacia, osteitis fibrosa, and osteosclerosis. Nonmetabolic diseases including Paget's disease may also affect the femur. These conditions are discussed in Chapter 95.

Neoplasms

The knee and thigh represent one of the most common sites in the body for bone and soft tissue neoplasms. Benign and malignant bone and soft tissue tumors, as well as metastatic lesions, must be considered in the differential diagnosis of all patients with new onset of pain. Neoplasms of both the thigh and the knee are discussed in this section. As with most diseases, the diagnosis of neoplasia requires a through history and physical examination. Although the majority of patients present with pain, the presentation varies from an incidental finding on radiographs to severe constitutional symptoms. A complete description of all bone and soft tissue tumors is beyond the scope of this text (22,23); however, a brief description of diagnosis and treatment of some of the more common tumors follows.

Benign Bone Tumors

A simple bone cyst presents as a well-demarcated lytic lesion in the metaphysis of long bones, primarily in children. Many respond to a single injection of corticosteroids, with multiple injections or bone grafting occasionally required.

An aneurysmal bone cyst presents as an eccentric, lytic, expansile lesion in the metaphysis, primarily of adolescents. Treatment is careful curettage and bone grafting. Local recurrence is as high as 25%.

A nonossifying fibroma presents as an eccentric lytic metaphyseal lesion with a well-demarcated sclerotic rim. These lesions typically resolve without treatment. Curettage and bone grafting have been recommended for lesions greater than 50% of the bone diameter to prevent fracture.

Osteochondromas arise as an aberrant focus of cartilage near an epiphyseal center. They appear as a surface lesion with continuous cortex involvement of the underlying bone. They have a low rate of malignant degeneration (less than 1% if isolated, 10% if multiple). Symptomatic lesions should be excised.

Enchondroma typically appear as well-circumscribed lesions with calcifications within the medullary canal. Treatment is curettage and bone grafting, with wide resection for the small percentage with malignant transformation.

Chondroblastomas typically present as a lytic lesion of the epiphysis with occasional spread to the metaphysis. Most respond to curettage and bone grafting, with a small percentage of local recurrence and distant metastasis.

Osteoid osteomas are small diaphyseal lesions with a sclerotic border surrounding a zone of translucency. They are classically painful but respond to nonsteroidal antiinflammatory drugs (NSAIDs; particularly aspirin). Definitive treatment is *en bloc* resection.

Fibrous dysplasia is not a true neoplasm but tends to be locally aggressive. Typically, it presents as a ground-glass-appearing lesion, but there is a broad range of appearance. Thirty percent of the cases have involvement at multiple sites. Observation is most common with resection and bone grafting for more aggressive lesions.

Giant cell tumors are commonly an aggressive, expansile lytic lesion, without a sclerotic margin, of the epiphysis of skeletally mature bones. Curettage and bone grafting have led to recurrence rates as high as 50%, and therefore *en bloc* resection is often required.

Eosinophilic granulomas are vary widely in appearance. Typically, they do not require treatment unless there is impending fracture or they are close to an articular surface.

Paget's disease represents abnormal bone remodeling that presents in the fifth decade of life. These lesions are blastic appearance on radiographs. Less than 1% develop malignant degeneration. Paget's disease is treated with diphosphonates, calcitonin, and methotrexate.

Benign Soft Tissue Tumors

Pellegrini-Stieda disease is ossification of a subligamentous hematoma after injury to the medial collateral ligament, primarily at the insertion on the medial condyle of the femur. Medial pain and tenderness with thickening at the medial epicondyle are usually present. Radiographs reveal calcified deposits within the ligament. Rehabilitative stretching and strengthening are typically successful. Persistent pain may respond to aspiration, with surgical removal of the ossified tissue reserved for cases unresponsive to conservative measures (1).

Myositis ossificans represents calcifications within the soft tissue, typically after a traumatic episode. It most commonly occurs within the quadriceps after a contusion with hematoma formation. It must be differentiated from osteosarcoma. Resection of myositis ossificans is usually not needed.

Ganglia present as an outpouching of the synovial lining of an adjacent joint. Treatment is initially with aspiration and cortisone injection, but this is often unsuccessful; the lesion then requires surgical resection.

Pigmented villonodular synovitis is a proliferation of the synovium in middle-aged adults. It usually presents as recurrent monoarticular effusions. Limited resection is associated with high local recurrence. Complete synovectomy is considered the standard of care and can usually be done by arthroscopic means.

Synovial chondromatosis usually presents with pain and catching symptoms within the knee of young adults. Radiographs reveal multiple calcified loose bodies. Treatment consists of complete synovectomy. This condition must be differentiated from chondrosarcoma, which requires resection.

Malignant Bone Tumors

After multiple myeloma, osteosarcoma is the most common primary malignant bone tumor. It affects patients in the second decade of life, with 60% occurring during the adolescent growth spurt. Wide variation is seen in the radiographic appearance, but these tumors typically have areas of osteolysis, ossification, and periosteal reaction. Osteosarcoma is currently treated with chemotherapy and wide resection, with limb salvage when possible. Treatment and response depend on subtype.

Chondrosarcoma is the third most common primary malignant bone tumor. It occurs primarily in the fourth, fifth, and sixth decades of life. It appears as a destructive lesion with central areas of calcification. Most are resistant to chemotherapy and radiation, but they rarely metastasize. Radical resection is the treatment of choice. Adjuvant chemotherapy is also used for high-grade lesions.

Fibrosarcomas are lesions occurring in the third through fifth decades of life. They appear as lytic lesions, without calcification or periosteal reaction. This lesion is resistant to radiation. Amputation has been the definitive treatment, but wide resection, limb salvage, and chemotherapy have been tried.

Ewing's sarcoma is a round cell tumor classically affecting males younger than 20. Constitutional symptoms are frequent. It appears as a permeative, destructive lesion with ill-defined margins. Treatment involves neoadjuvant chemotherapy, radiation, and surgical resection.

Multiple myeloma is the most common malignant bone tumor. It typically affects elderly patients who present with pain or pathologic fracture. It classically appears as a punched-out lesion radiographically. Treatment is with multiagent chemotherapy and surgical stabilization.

Lymphoma is a painful lesion that affects a broad age range. Bone destruction and soft tissue involvement are common. Radiation and chemotherapy are mainstays

of treatment; surgery is needed for selected lesions.

Malignant Soft Tissue Tumors

Malignant fibrous histiocytoma is a poorly differentiated bone and soft tissue tumor. Thirty percent arise within benign conditions. The distribution of this lesion is bimodal with primary lesions occurring in young adults and secondary lesions found typically in the sixth and seventh decades. They appear as highly destructive lesions with soft tissue expansion. Treatment is with chemotherapy and resection.

Synovial sarcoma presents as a painful swelling around a joint in young adults. Lesions are rarely found within the joint. Radiographs reveal spotty calcifications within a paraarticular mass. Treatment is with wide resection. The benefit from chemotherapy is unclear.

Multiple types of fibrosarcomas are known. They present as soft tissue masses in the adult population. Treatment consists of surgical resection and chemotherapy.

Metastatic Neoplasms

Primary tumors that readily metastasize to bone include lung, breast, prostate, kidney, thyroid, and gastrointestinal lesions (24). The metastasis typically creates a lytic lesion on plain radiograph, although many are found on routine bone scans for follow-up of primary lesions. Severe local pain and pathologic fracture are the main concerns. Radiotherapy is often effective for a time and can promote union of the pathologic fracture. Metastasis from the thyroid can respond to radioactive iodine, whereas breast and prostate metastasis may respond to hormone therapy and other modalities.

Pathologic fractures are extremely painful and have a high incidence of morbidity. Prophylactic stabilization with a full-length reconstruction nail decreases pain and facilitates nursing care.

PAINFUL DISORDERS OF THE KNEE JOINT

Fractures

Etiology

Fractures around the knee can lead to prolonged disability. The normal range of motion requires smooth surfaces for painless gliding motion and weight-bearing. Displaced intraarticular fractures rapidly progress to premature degenerative arthritis. In addition, displaced extraarticular fractures can lead to joint malalignment with subsequent alterations of normal joint mechanics. Appropriate diagnosis and treatment are critical for the long-term outcome of these fractures.

Fractures around the knee are classified by location and involvement of the intraarticular surface. Distal femur fractures include supracondylar, intercondylar, and condylar fractures. The degree of comminution within the fracture is an important consideration. Proximal tibial fractures may involve the medial plateau, lateral plateau, both plateaus, or proximal metaphysis without extension into either plateau (Fig. 79-20). Patellar fractures can be transverse, vertical, or comminuted.

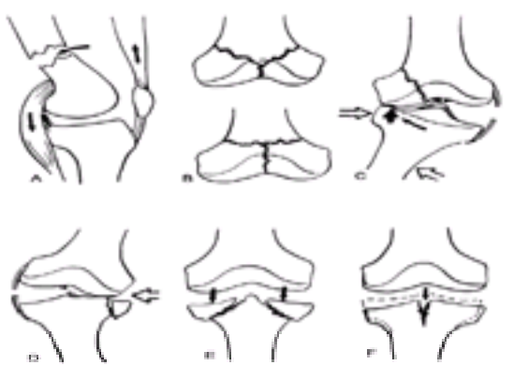

Figure 79-20. Various types of fractures of the bones of the knee joint. **A:** Supracondylar fracture with the gastrocnemius pulling the distal fragments posteriorly into the popliteal fossa and the hamstring and quadriceps pulling to shorten the femur. **B:** Intercondylar fracture of the distal femur: Y fracture (*top*); T fracture (*bottom*). **C:** Condylar fracture from severe valgus (varus) stress. Force applied to the knee joint or laterally to the tibia (*arrows*) can cause fracture of the femoral condyle, tearing of the opposite collateral ligament, and tearing of either or both of the cruciate ligaments, with compression of the meniscus. **D:** Fracture of one tibial plateau. Direct trauma to the tibial plateau, such as a fall on extended legs, can cause a Y fracture **(E)** or a T fracture **(F)** of the plateau. (Modified from Cailliet R. *Knee pain and disability,* 2nd ed. Philadelphia: FA Davis, 1983.)

Diagnosis

Pain after a traumatic event is the predominant symptom. It is generally limited to the knee region but can spread to the lower thigh and leg. Swelling and inability to bear weight are frequently encountered. Tenderness, crepitus, and edema are seen on physical examination. A careful neurovascular examination should be performed, because nerve and vessels are in close proximity to fractures within this area.

Anteroposterior and lateral radiographs are usually diagnostic. Computed tomography scans provide additional information of the extent of intraarticular involvement. MRI is better for assessment of soft tissue abnormalities.

Treatment

Basic principles of pain control and immobilization have been previously discussed. Longitudinal traction is typically not required; however, proper splinting to avoid painful movement across the fracture site is paramount while obtaining additional studies typically needed for these complex fractures.

Fracture fixation requires adequate exposure to judge the reduction of the intraarticular fragments. Anatomic reduction, stable fixation, and early motion are keys to improved outcome. Multiple methods of fixation including internal plates and screws, intramedullary rods, and external constructs are available for fixation. The best construct depends on the fracture pattern and individual surgical experience.

Postoperative care is focused on early mobilization. Careful examination of postoperative swelling within the compartments of the leg is crucial to avoid compartment syndrome. As described, adequate pain control assists in early mobilization.

Dislocations

Etiology

Complete dislocation of the knee joint is a rare, high-energy event. Ligamentous structures must be torn to allow complete dislocation. Direction of the tibia in relation to the femur describes the type of dislocation as posterior, anterior, and less commonly medial or lateral. These injuries are associated with a high incidence of neurovascular injury. Proper identification of the dislocation is important to preventing further injury.

Patellofemoral dislocations are much more frequent than complete knee dislocations. The patella is typically laterally dislocated. Diagnosis is occasionally difficult

because many relocate spontaneously before presentation. Proximal tibiofibular joint dislocation is a frequently overlooked injury that may lead to chronic symptoms.

Diagnosis

A high index of suspicion is required to properly diagnose dislocations. Often, the dislocations have been reduced. Careful isolation of each ligament will define the injury. Radiographs remain the proper screening tool, although they may not reveal fractures in purely ligamentous injuries. Patellofemoral dislocations are diagnosed with history and tenderness, primarily medial to the patella. Careful examination of neurovascular structures must be performed. Ankle-arm blood pressures should be obtained, with angiography reserved for injuries suspicious for vascular insult. MRI is useful in identifying soft tissue pathology.

Treatment

Preservation of blood supply to the lower leg and foot is the primary concern. Dislocations should be reduced and immobilized as soon as possible. Patellofemoral dislocations are immobilized with the knee in extension for 2 weeks and then started on a motion and strengthening program. Knee dislocations are highly unstable. During the course of treatment, diligent monitoring of the neurovascular structures is essential. Fractures are treated as described under Treatment, in the section on Fractures. Ligamentous injuries are dealt with as described in the next section.

Ligamentous Injuries

Etiology

Ligamentous injury commonly occurs after both contact and noncontact injuries to the knee. Injuries include a spectrum of minor sprains from tearing of a few fibers to complete tears of the ligament. Children typically present with avulsion injuries, whereas adults sustain midsubstance injuries. The direction of the force is helpful in predicting the ligaments injured. Often, multiple ligaments are injured with increasing force (Fig. 79-21).

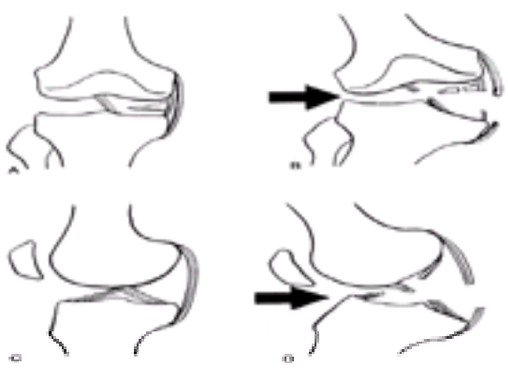

Figure 79-21. Severe ligamentous sprain. **A:** Anterior view of a normal joint. **B:** Severe lateral stress disrupts the medial collateral ligaments, medial meniscus, and anterior cruciate ligament—this is known as the *unhappy triad*. **C:** Lateral view of normal joint. **D:** Severe anterior stress. This can produce hyperextension of the joint and disrupt both the anterior and posterior cruciate ligaments and the posterior capsule. Examination reveals a positive drawer sign. (Modified from Cailliet R. *Knee pain and disability,* 2nd ed. Philadelphia: FA Davis, 1983.)

Diagnosis

Pain and a feeling of instability of the knee are common after ligament disruption. A “popping” sensation, as well as an audible pop, may be present. An immediate effusion is highly suggestive of an intraarticular ligament tear, and aspiration typically demonstrates a hemarthrosis. Tenderness over the medial or lateral aspect of the knee suggests involvement of the medial or lateral collateral ligament. Stability testing reveals laxity compared to the uninjured extremity; however, it is often difficult secondary to pain, especially in the presence of a tense effusion. Radiographs may reveal an avulsion injury in younger patients or may reveal medial or lateral joint space widening. MRI is a helpful diagnostic adjuvant. Examination under anesthesia provides additional information about the degree of injury (15).

Treatment

Isolated medial collateral ligament injuries are treated with protective weight-bearing with relative immobilization in a hinged knee brace to allow 30 to 60 degrees of active/passive motion for the first 3 weeks. Return to activity is limited until a full range of pain-free motion is obtained (15). Care must be taken to identify more severe injuries that include injury to the anterior collateral ligament.

Mild injuries to the lateral collateral ligament are treated with bracing and progressive exercises. More severe injuries can result in posterolateral rotatory instability, which should be repaired or reconstructed surgically.

Treatment of isolated injuries to the anterior cruciate ligament depends on multiple patient variables, including patient age, future demand to return to high-risk activities, associated injuries, and general laxity and alignment of the knee. Surgical reconstruction is required for patients with associated injuries (multiple ligament tears, meniscal tears) or those who desire to return to high-risk cutting and jumping sports. Proper positioning of the graft and postoperative rehabilitation are essential. Nonoperative treatment consists of bracing, strengthening exercises, and activity modification (15).

Isolated injuries to the posterior cruciate ligament are usually treated nonsurgically. Bracing and rehabilitation are usually successful. Reconstruction should be performed in patients with instability recalcitrant to conservative measures as well as patients with multiple ligament involvement (typically posterolateral).

Meniscal Injuries

Etiology

Meniscal injuries are encountered frequently in active adults. Classically occurring with a combination weight-bearing with rotatory stress, these injuries can occur secondary to both contact and noncontact injuries. Peripheral lesions occur in response to tension forces, whereas lesions to the body occur with compression (15).

Diagnosis

Pain localized to the joint line with or without mechanical symptoms of catching or locking suggests a meniscal tear. Joint line tenderness, effusion, and catching sensations may be reproduced on physical examination. Radiographs are typically normal. MRI results are technique-dependent but have been shown to be helpful. Diagnostic arthroscopy allows direct visualization of the pathology, including assessment of the stability of the meniscus.

Treatment

Studies suggest that as much of the meniscus as possible should be preserved at surgery to prevent premature degenerative disease. In general, partial-thickness tears, small tears in the vascular periphery, and stable tears should be left alone. Larger tears within the vascular periphery should be repaired, and large unstable tears out of the vascular periphery should be resected. Repairable tears with an associated anterior cruciate deficiency will fare better if the ligament is reconstructed (15).

Arthritides

Pyogenic Arthritis

The knee joint is prone to infectious involvement secondary to direct trauma or surgical intervention or from hematogenous spread from the distal femoral metaphysis, a site of frequent osteomyelitis. Systemic symptoms of fever with a recent infection elsewhere may be present. Typically, the knee is warm, swollen, tender to palpation and painful with range of motion. White blood cell count, erythrocyte sedimentation rate, and CRP are helpful in making the diagnosis but are not always elevated. Plain radiographs are typically normal. Bone scan may reveal increased uptake. Aspiration for culture before initiating antibiotics is mandatory. Younger children can be managed with serial aspirations. Adults who have had a prior total knee arthroplasty require open debridement with possible removal of components. Directed antibiotic therapy is usually curative.

Rheumatoid Arthritis

Rheumatoid arthritis is felt to be an autoimmune reaction to synovium (see Chapter 27). As such, it commonly leads to knee symptoms. Pain, stiffness, and swelling may be mild to debilitating. Mechanical deformities of alignment can occur. The goal of treatment is to reduce pain and enhance function. NSAIDs with modest doses of narcotics are usually successful; however, arthroscopic synovectomy or total knee arthroplasty may be necessary for progressive dysfunction.

Hemophilic Arthritis

Nontraumatic or minimally traumatic hemarthrosis is the common presentation with hemophilia. The knee is frequently involved. Frequent episodes can lead to synovial thickening and chronic knee symptoms. Aspiration of the hemarthrosis once the coagulation levels are corrected decreases symptoms. Improved control of the underlying coagulopathy helps prevent recurrence.

Other

Tuberculosis, human immunodeficiency virus, fungal infection, and Lyme disease are other infectious causes of acute arthritis of the knee. Systemic lupus, spondyloarthropathies, crystal deposition diseases, and sickle cell disease are all systemic diseases that may affect the knee. These also affect other joints and are discussed in more detail in Chapter 27.

Osteoarthritis

Etiology

Although degenerative joint disease is the most common cause of arthritis in the knee, the underlying etiology remains unclear. Generally, osteoarthritis is grouped into two categories: (a) primary (secondary to intrinsic mechanical, immune, vascular, or cartilage defect) and (b) secondary (secondary to trauma, infection, or congenital disorders). Primary osteoarthritis progresses more slowly, has an older age of onset, and is usually polyarticular when compared to secondary osteoarthritis. Deterioration and loss of the articular surface are followed by development of sclerosis, osteophytes, subchondral cysts, and narrowing of the joint space.

The pain associated with degenerative arthritis is secondary to inflammatory changes, synovitis, and mechanical pain from distortion of the capsule secondary to osteophytes. Pain is usually dull and aching, usually worse in the morning and after periods of rest, and usually improves with 30 to 60 minutes of activity.

Diagnosis

The diagnosis of degenerative joint disease is made from the history and radiographic signs. The classic radiographic signs are sclerosis of the joint line, osteophyte formation, subchondral cyst formation, and loss of the joint line. Radiographs do not always correlate with the severity of the symptoms. Computed tomography and MRI are useful to rule out other pathologic processes.

Treatment

The goal of treatment is pain control, with an accompanying increase in the ability to perform daily activities secondary to decreased pain. NSAIDs and salicylates remain the mainstay of medicinal therapy. Longer-lasting NSAIDs that allow once- or twice-a-day dosing have not proved to be more effective than traditional aspirin or ibuprofen. Some do have a lower incidence of gastrointestinal upset and offer a simplified dosing regimen. Thermal therapy has been shown to be effective for some patients. Overweight patients benefit from weight reduction.

Operative measures are reserved for patients who have failed conservative measures. Arthroscopic debridement and removal of loose bodies temporarily relieves symptoms. Younger patients who have unicompartmental disease and wish to remain active have benefited from high tibial osteotomy to alter the weight-bearing area of the joint. Total knee arthroplasty is effective at reducing pain and has a greater than 95% survivorship after 10 years (25).

Bursitis

Etiology

As noted, many bursae surround the knee, any one of which can become inflamed and cause pain. The pain may be acute and secondary to trauma, or it may be chronic and secondary to prolonged microtrauma. Pain is secondary to local inflammation and can be reproduced by pressure on the overlying soft tissues.

Diagnosis

The key differential diagnosis in patients with classic symptoms is between bursitis and an intraarticular process. Prepatellar bursitis is characterized as tenderness over the patella and a fluid mass that do not change in characteristics with range of motion. Inflammations in other bursae are not as easily diagnosed. A high index of suspicion must be held when there is a history of symptoms that are worse with motion and reproducible tenderness to palpation is found over the suspected bursae.

Treatment

Typically, conservative treatment will resolve symptoms. Rest, NSAIDs, and compressive dressings should be tried. Aspiration is reserved for more severe cases and should be followed with a compressive dressing in an attempt to oppose inflamed surfaces. In chronic bursitis, however, fibrosis, synovial thickening, and the formation of painful nodules may cause pain unresponsive to conservative measures. Surgical excision of the entire bursae may be required (9).

Synovitis

Etiology

Like bursitis, synovitis can be acute or chronic. Acute synovitis is most often caused by trauma, although foreign bodies, gout, and pseudogout are other common etiologies. Chronic synovitis lasts months and sometimes years and can be associated with rheumatoid arthritis, infection, ankylosing spondylitis, and other systemic disorders. It may also occur postoperatively (15).

Diagnosis

Synovitis produces a painful effusion and invariably causes decreased range of motion. Chronic synovitis may cause muscle atrophy secondary to disuse. A careful history of recent trauma, associated medical problems, and symptoms at other joints will help identify the cause. Radiographs help rule out foreign debris. MRI is not necessary, but diagnostic arthroscopy can readily identify the presence of synovial inflammation.

Treatment

Rest, NSAIDs, compression dressings, and occasionally aspiration are conservative treatment measures that are typically effective. Isometric quadriceps exercises should be performed to prevent atrophy. For chronic synovitis that is unresponsive to conservative measures, complete synovectomy has been performed, usually by arthroscopic means. Open mechanical procedures are often complicated by pain and hemarthrosis; however, arthroscopic laser or thermal ablation has shown promise (16).

Osteochondritis Dissecans

Etiology

Osteochondritis dissecans involves the subchondral bone and overlying cartilage. The origin is unclear but is thought to be traumatic. It typically involves the lateral aspect of the medial femoral condyle, with less than 1 to 2 cm of involvement. Early stages reveal subchondral injury without interruption of the articular surface. In late stages, the entire osteoarticular fragment may separate and create a loose body within the knee. The condition is most common in adolescence and occurs less frequently with increasing age. Males are more often affected than females (26,27).

Diagnosis

Pain and recurrent swelling are the most common symptoms. Catching and locking occur as the fragment separates. Standard radiographs may not visualize the fragment, and therefore oblique views are helpful. MRI can better demonstrate the lesion.

Treatment

Symptomatic lesions in adolescence are treated with immobilization for up to 3 months. Fixation of large fragments is recommended. Smaller loose bodies can be removed arthroscopically. Subchondral drilling and bone grafting are newer modalities (28).

Loose Bodies

Etiology

A loose body is any free-floating debris within the knee. The multiple etiologies include trauma, osteoarthritis, meniscal tears, osteochondritis dissecans, synovial chondromatosis, and tuberculosis.

Diagnosis

Loose bodies often cause a history of recurrent catching and locking of the knee. Patients can frequently disengage the loose body with manipulation of the knee. Physical examination is frequently normal except for a slight effusion. Radiographs may identify the loose body if it is osseus, but they represent the location of the body only at the time the radiograph was taken.

Treatment

Treatment is directed at symptoms. If symptoms are mild and infrequent, observation may be warranted. Removal of the loose bodies is typically performed via an arthroscope. Careful examination of the entire joint is necessary to avoid missing any fragments (28).

Baker's Cyst

Etiology

Popliteal cysts can be produced either by herniation of the synovial membrane through the capsule or by communication of fluid with the bursa around the knee. They may arise in children or adults and may be associated with an underlying disease such as rheumatoid arthritis.

Diagnosis

Popliteal cysts typically present as a tender, swollen area in the posterior knee. Although they are frequently found on routine examination, they must be differentiated from a vascular thrombosis or soft tissue tumor. Cysts are typically translucent. Radiographs are not usually helpful, and ultrasound and MRI provide more information.

Treatment

Small cysts in children frequently resolve. Treatment for chronic or symptomatic cysts should be directed at the underlying cause. When the cyst is associated with a significant effusion, correction of intraarticular pathology (i.e., meniscectomy for posterior horn meniscal tears) is usually sufficient. If the cyst does not appear to communicate, an open resection is needed (29).

Patellofemoral Pain

Etiology

Patellofemoral pain is a difficult condition to diagnose and treat, owing to the wide variety of symptoms. Generally thought of as an overuse injury, maltracking of the patella within the femoral trochlea and medial quadriceps muscle weakness are currently viewed as significant factors. Abnormal tracking increases the proportion of force absorbed by the patella and may lead to degenerative changes within the patellofemoral compartment.

Diagnosis

This condition is classically described as anterior knee pain. The onset of symptoms may be acute, but patients more frequently present with chronic pain. Difficulty with stair climbing and descending, kneeling, prolonged sitting, or squatting is a frequent complaint. Physical examination may demonstrate tenderness of the peripatellar tissues, crepitus with knee range of motion, and malalignment of the patella. A tangential view of the patella (sunrise view) should be obtained, although it is often nonspecific. An MRI can rule out other internal knee abnormalities but is not specific for patellofemoral pain.

Treatment

The majority of patients respond to rehabilitation. Strengthening of the medial quadriceps musculature is emphasized. Gradual return to athletic participation is essential. Some success has been reported with special taping procedures. Gross malalignment may need surgical correction. Lateral retinacular release, tibial tubercle medializations, and even patellectomy have been performed.

Tendinitis

Etiology

Patellar tendinitis is the most common tendinitis affecting the thigh and knee. As with other areas of the body, tendinitis is an overuse injury that occurs with repetitive motions, such as running, jumping, and climbing. It is common in repetitive motion sports such as basketball, tennis, soccer, and weightlifting. It is felt to be secondary to eccentric loading of the myotendinous junction.

Diagnosis

Diagnosis is confirmed by a history of pain with repetitive motions. Tenderness may not be reproducible if the tendinitis is in an early stage. Radiographs are not necessary initially but are useful for patients who do not respond to initial treatment.

Treatment

Initial treatment consists of rest, ice, compression, and NSAIDs. Ultimate improvement depends on the strengthening and stretching of the involved muscle. Returning to sports participation too soon leads to recurrent symptoms. Conditioning is essential to prevention of recurrence.

Apophysitis

Etiology

Apophysitis is similar to tendinitis but occurs in skeletally immature children. Repetitive loading through the unfused apophysis results in a traction injury. The tibial tubercle is the most common site (Osgood-Schlatter disease), but it can also occur at the distal pole of the patella (Sinding-Larsen-Johansson syndrome) and other apophysis in the body.

Diagnosis

History of infrapatellar knee pain and tenderness to palpation of the involved apophysis are diagnostic. Radiographs occasionally demonstrate enlargement of the tibial tubercle and assist with ruling out other pathology.

Treatment

Apophysitis is usually self-limiting as the child reaches skeletal maturity. Proper stretching and warm-up before activities, with ice and compression after participation, may decrease symptoms. Neoprene sleeves and NSAIDs may provide additional relief. Rarely, long leg casting may be required for severe symptoms.

Congenital Diseases

Multiple congenital and developmental abnormalities affect the growing child. Gait abnormalities can be the result of hip, thigh, knee, leg, or foot abnormalities. A complete discussion of the many abnormalities is beyond the scope of this chapter. A careful history (including pregnancy and family diseases), physical examination (with close observation of gait and leg length discrepancies), and basic screening radiographs often assist in the appropriate diagnosis. Any pain with ambulation is abnormal in a child and warrants further investigation.

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CHAPTER 80

Pain in the Leg, Ankle, and Foot

Alastair S. E. Younger and Bruce J. Sangeorzan

Leg, ankle, and foot pains are common reasons for physician consultation. Only backache and headache result in more frequent visits to primary physicians (1,2). Foot and ankle pain is the second most common complaint seen by orthopedic surgeons after back pain (3). Orthopaedic conditions cause the largest number of chronic conditions in the U.S. population, with 14% of patients having an orthopaedic complaint (4). Flat feet cause activity limitation in 1.5% of the population. Comparatively, orthopaedic impairment of the lower extremity (all conditions) causes limitation in 5.0% of the population (4). Hereditary problems, poor posture, poor footwear, trauma, infections, and arthritis are common underlying causes of foot pain. This broad number of etiologies and the complex anatomy of the leg, ankle, and foot make diagnosis and treatment of foot and ankle conditions a challenge. A thorough knowledge of the anatomy, biomechanics, and function of this area is required for effective treatment.

The material in this chapter is presented in five major sections: Basic Considerations, including classification and epidemiology of foot and ankle pain and a review of local anatomy, function, and biomechanics; Evaluation of the Patient, expanding the information in Chapter 12; Painful Disorders of the Leg; Painful Disorders of the Ankle and Heel; and Painful Conditions of the Foot.

BASIC CONSIDERATIONS

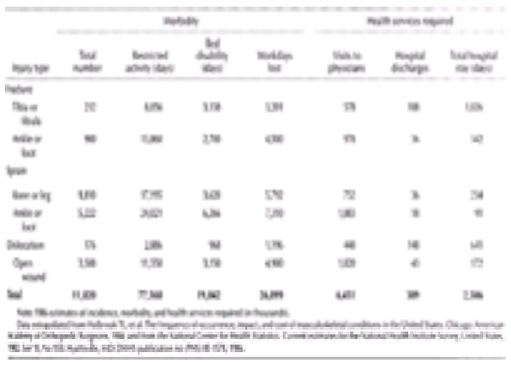
Etiology

Table 80-1 lists the most important painful disorders that affect the leg, ankle, and foot. Those listed in the first three major categories are discussed in this chapter. Those in the fourth and fifth categories are covered in Chapter 19, Chapter 20, Chapter 21, Chapter 22 and Chapter 23, Chapter 28, Chapter 29 and Chapter 30, Chapter 33, and Chapter 77.

TABLE 80-1. Classification of painful disorders in the leg, ankle, and foot

Epidemiology

The National Ambulatory Medical Care Survey 1980–1981 (1) estimated that in 1986 acute pain in the knee, leg, ankle, and foot resulted in approximately 5 million visits to physicians in the United States. This is second only to the number of physician visits caused by ear pain. Chronic painful conditions in the foot and ankle result in nearly 4 million visits to physicians, representing 10% of all visits for chronic painful conditions (2). Estimates have been made for the type, number, morbidity, and health services required by various musculoskeletal disorders and injuries of the leg, ankle, and foot (Table 80-2).



Injury type	Morbidity: Total number	Morbidity: Restricted activity (days)	Morbidity: Bed disability (days)	Morbidity: Workdays lost	Health services required: Visits to physicians	Health services required: Hospital discharges	Health services required: Total hospital stay (days)
Fracture							
Tibia or fibula	212	6,876	3,118	1,334	578	108	1,026
Ankle or foot	900	11,860	2,750	4,500	970	74	542
Sprain							
Knee or leg	5,810	57,195	3,420	5,792	752	36	234
Ankle or foot	5,222	24,021	6,264	7,210	1,082	58	911
Dislocation	176	2,886	960	1,776	448	148	640
Open wound	2,500	11,750	3,750	4,900	1,020	40	172
Total	11,820	77,568	19,842	26,099	4,451	389	2,586

Note: Title estimates of incidence, morbidity, and health services required (in thousands).

Data extrapolated from Holbrook TL, et al. The frequency of occurrence, impact, and cost of musculoskeletal conditions in the United States. Chicago: American Academy of Orthopaedic Surgeons, 1984, and from the National Center for Health Statistics. Current estimates from the National Health Interview Survey, United States, 1983. Jan'll, No.155. Hyattsville, MD: DHHS publication no (PHS) 85-1571, 1984.

TABLE 80-2. Musculoskeletal injuries involving the leg, ankle, and foot

Table 80-2 also lists the incidence of musculoskeletal injuries involving bones, joints, and soft tissues of the leg, ankle, and foot (1,2). These injuries, together with arthritis and other conditions affecting the leg, ankle, and foot, are among the most frequent causes of pain and disability in the United States. Similar trends are expected in other industrialized nations. The economic impact is significant and, taking into account the 1984 cost for workdays lost, visits to physicians, and hospital stays for acute injuries and pain, amounts to approximately $2.4 billion (3). This number does not take into account the economic impact of arthritis, infections, tumors, and other chronic painful conditions. The estimated cost for all conditions probably exceeds $8.5 billion (5).

Anatomy and Function of the Leg, Ankle, and Foot

Although the anatomy of the lower and upper extremities shares similarities, the functions are very different (6). The distal part of the upper limb is structured for versatility of movement, whereas the lower limb is built for weight-bearing and locomotion. Evolution and embryologic development demonstrate rotation and extension of the lower limb that position the foot for erect stance. Therefore, the flexor aspect of the leg faces posteriorly and the extensor aspect, anteriorly. In the anatomic position, the thumb is on the hand's lateral margin, whereas the great toe is on the foot's medial margin (6). The sole of the foot faces backward, and the palm of the hand faces forward. The foot is positioned at right angles to the leg. Flexion of the foot is described as *plantar flexion* and extension is called *dorsiflexion* (6).

The total body weight during weight-bearing is transmitted though the ankle and foot. Thick heel and toe pads act as shock absorbers during walking and running, and the joints are capable of making adjustments necessary for fine balance on various terrain (7). In some forms of strenuous physical activity, the ground reaction force is five times body weight. Because of the mechanics of the foot and ankle, the forces in the ankle are two to three times larger than the ground reaction force. Peak ankle joint forces may exceed 15 to 20 times body weight (7).

Anatomy

Tibia and Fibula. The tibia and fibula, two parallel bones, constitute the skeleton of the leg corresponding to the radius and ulna. However, unlike the radius and ulna, little motion occurs between the lower limb bones at the proximal and distal articulation (6). The fibula does not articulate at the knee as the radius does at the elbow. The fibula acts mainly as an origin for muscles and has little weight-bearing role (8) (Fig. 80-1).

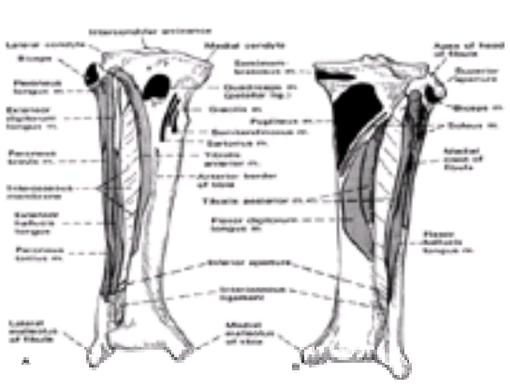


Figure 80-1. Anatomy of the tibia and fibula showing the sites of origin (*gray areas*) and insertion (*black areas*) of the muscles that move the ankle and foot. **A:** Anterior view. **B:** Posterior view. The lateral condyle has a raised area into which most of the iliotibial tract inserts. The facet for articulation with the head of the fibula is on the curved inferior surface of the lateral condyle. The semimembranosus muscle inserts on the medial condyle into a posteriorly placed deep transverse groove. The anterior border and medial surface of the tibia are largely subcutaneous. The posterior surface gives origin to most of the soleus, tibialis posterior, and flexor digitorum longus muscles. The posterior tibia receives the insertion of the popliteus and two of the hamstring muscles. The medial border of the tibia extends into the medial malleolus. This has an articular surface on the medial side continuous with the distal tibia. These articular surfaces, with the lateral malleolus formed by the distal fibula, form the ankle mortise articulating with the dome of the talus. The fibula articulates with the lateral border of the distal tibia at the fibular notch. The proximal head of the fibula is subcutaneous and rises laterally to its apex; the facet for its articulation with the tibia is on its medial crest. The lateral malleolus is the expanded lower end of the fibula and is also subcutaneous. Its medial articular surface forms the lateral part of the ankle mortise. (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985.)

The tibia and fibula articulate at proximal and distal tibiofibular joints and are joined together by the capsules of both joints as well as the intraosseous membrane. The superior tibiofibular joint is a synovial joint between the head of the fibula and a posterolateral part of the lower surface of the lateral tibial condyle. The anterior and posterior ligaments of the head of the fibula run upward and medial to the tibia and strengthen its capsule (see Fig. 80-1). This joint is innervated by the common peroneal nerve and the nerve to the popliteus muscle, a branch of the tibial nerve.

The interosseous membrane consists of thin but strong fibers passing downward and laterally joining the interosseous margin of the tibia to the sharp medial border of the fibula (see Fig. 80-1). The membrane separates the muscles of the anterior compartment from the posterior compartment and forms a large surface for the origin of muscles in both compartments. Above the proximal end of the membrane, just below the superior tibiofibular joint, is a large oval aperture for passage of the anterior tibial vessels to the anterior compartment. Close to its distal end (approximately 5 cm above the lateral malleolus) is a smaller aperture for the perforating branch of the peroneal artery. Between the adjacent distal ends of the tibia and fibula, the membrane is continuous with the crural tibiofibular interosseous ligament.

The tibiofibular interosseous ligament is composed of thick, short, strong fibers that run from the tibia to the fibula ending short of the articular margin of the ankle joint (6,8). The interosseous ligament is much stronger than the interosseous membrane. It prevents separation of the distal tibia and fibula and stabilizes the ankle joint. Rosse (9) has pointed out that the ligament is so strong that, when these forces are excessive (e.g., in an eversion injury), the fibula fractures distal to the ligament rather than the ligament rupturing. These injury patterns depend on the ratio of the strength of the ligaments and bones. Very old and very young patients will fracture bone, whereas the patients between these ages are more likely to tear ligaments. The tibiofibular interosseous ligament allows rotational displacement of the malleolus, with greater motion occurring at the proximal tibiofibular joint (see Fig. 80-1) (7).

The inferior tibiofibular joint is a fibrous joint stabilizing the distal end of the fibula in a groove on the lateral aspect of the tibia. It is essential for the integrity of the ankle joint. The inferior tibiofibular joint is stabilized by the interosseous ligament and the thinner, weaker anterior and posterior inferior tibiofibular ligaments, placed superficially on the front and back of the joint. The joint is innervated by the tibial and peroneal nerves as outlined in Hilton's law (6).

Muscles of the Leg and Foot

Muscular Compartments of the Leg. Figure 80-2 illustrates the compartments of the leg at midcalf level (10). The muscles within these compartments provide movement at the ankle, tarsus, and toes and flexion at the knee (gastrocnemius). The muscles are arranged in a manner similar to that of the prime movers of the wrist and carpus. The anterior compartment contains the extensors; the deep posterior compartment contains the flexors of the toes and tarsus. The superficial posterior compartment contains the flexors of the ankle, the triceps surae (6). A third compartment containing the peroneal muscles is present laterally for which there is no counterpart in the forearm. Each compartment is supplied by a nerve. The tibial nerve supplies the flexor compartment, the deep peroneal nerve supplies the extensors, and the superficial peroneal nerve supplies the peroneal compartment. Table 80-3 lists the muscles of the leg and foot, their function, and their nerve supply.

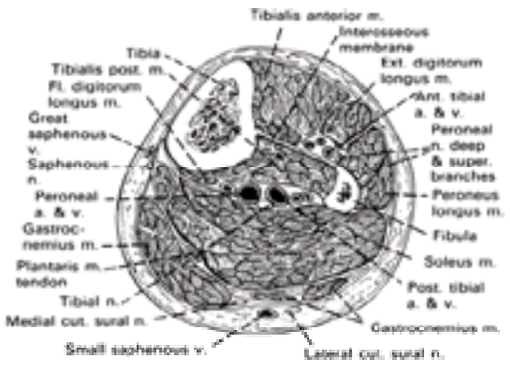


Figure 80-2. Transverse section of the leg at midcalf showing the three major compartments covered by the deep fascia of the leg, which is also known as the *crural fascia*. The anterior and posterior compartments are separated by the interosseous membrane. The anterior and posterior crural intermuscular septa enclose the peroneus longus and brevis, which separate the peroneal compartment from the anterior and posterior compartments. Note the location of the major vessels and nerves. (Modified from Eycleshymer AC, Schoemaker DM. *A cross-sectional anatomy.* New York: Appleton- Century-Crofts, 1911:96.)

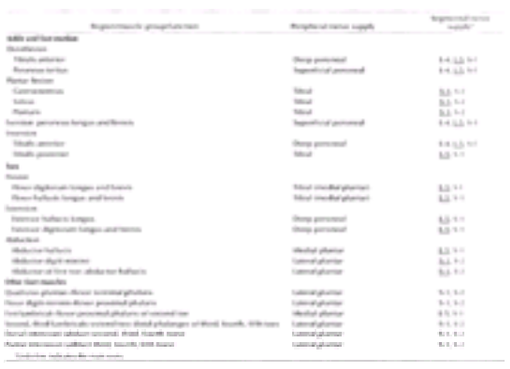


TABLE 80-3. Muscles of the leg, ankle, and foot and their nerve supply

Prime Movers of the Ankle

FLEXOR COMPARTMENT (PLANTAR FLEXORS). Figure 80-3 shows the muscles of the back of the leg (11). The gastrocnemius, soleus, and plantaris act together as the triceps surae within the superficial posterior compartment. These three muscle bellies are the most powerful plantar flexors of the foot (6,8). Other muscles pass behind the axis of the ankle but, because they are smaller and have a less efficient lever arm, they are less powerful plantar flexors of the ankle (6,8). These muscles include the tibialis posterior, peroneus longus and brevis, flexor hallucis longus, and flexor digitorum longus.

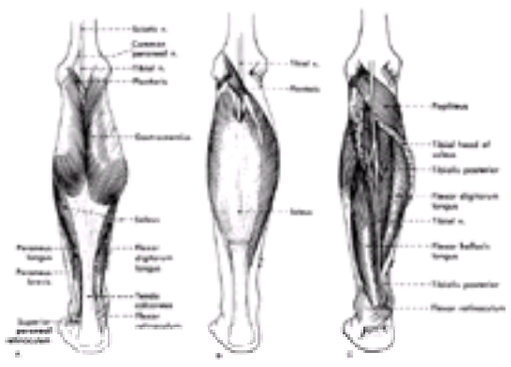


Figure 80-3. Posterior muscles of the left leg. All are plantar flexors, although some also act to flex and invert the foot or toes. **A:** The gastrocnemius muscle is superficial, with heads originating from the posterior aspect of the medial and lateral femoral condyles. Each head inserts onto the soleus, together forming the Achilles tendon, which inserts into the posterior surface of the calcaneus. **B:** The second layer consists of the soleus and plantaris muscles. The soleus arises from two heads, one on the tibia and the other on the fibula and interosseus membrane. A tendinous arch unites the two heads from which additional fibers arise. Under the fibrous arch runs the tibial nerve. Its muscular fibers end in a broad aponeurosis into which the gastrocnemius muscle inserts. The plantaris arises from the lateral condyle of the femur, passes obliquely medially, and forms a thin tendon that inserts just medial to the tendo calcaneus on the calcaneus. **C:** The deep muscles of the calf showing the tibial nerve. The soleus, gastrocnemius, and plantaris form the superficial posterior compartment. The tibial nerve is superficial to the muscles of the deep posterior compartment. The tibialis posterior arises from the interosseous membrane and from the adjoining parts of the posterior surfaces of the tibia and fibula (see Fig. 80-1B). The tendon lies deep to the flexor digitorum longus and lies beside it in a tendon sheath on a groove on the medial malleolus. The tendon passes deep to the flexor retinaculum and superficial to the deltoid ligament. It inserts into the tuberosity of the navicular bone with fibers going to other bones in the midfoot (see Fig. 80-15). This muscle (with the tibialis anterior) inverts the foot. The flexor digitorum longus arises from the tibia and the flexor hallucis arises from the fibula. Both tendons enter the sole of the foot behind the medial malleolus, and both are invested in tendon sheaths. The common tendon of the flexor digitorum longus splits into four tendons with their own sheaths to insert into the base of the distal phalanges of the second, third, fourth, and fifth toes, and the flexor hallucis inserts into the base of the distal phalanx of the great toe. These muscles flex the toes (see Fig. 80-15 for insertions of these muscles). (Reprinted from Rosse C. *Hollinshead's textbook of anatomy,* 5th ed. Philadelphia: Lippincott–Raven Publishers, 1997:371, 372, with permission.)

EXTENSOR COMPARTMENT (DORSIFLEXORS). The tibialis anterior and peroneus tertius are the two main dorsiflexors of the ankle and also act on the midtarsal joint. The extensor hallucis longus and extensor digitorum longus act primarily to extend the great toe and lesser toes, respectively. They also weakly dorsiflex the ankle and midtarsal joints (Fig. 80-4) (7). The tibialis anterior is the bulkiest muscle in the anterior compartment and acts to dorsiflex and invert the foot. The peroneus tertius arises with the muscle belly of the digital extensor but, because its tendon inserts into the base of the fifth metatarsal, dorsiflexes the ankle (Fig. 80-5).

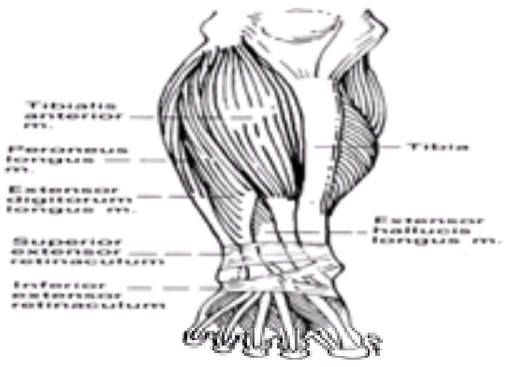


Figure 80-4. Anterior muscles of the leg. The tibialis anterior arises from the inferior surface of the lateral condyle of the tibia and the adjacent interosseous membrane. It inserts into the medial cuneiform after passing under the extensor retinaculum. It is the largest anterior compartment muscle. The extensor digitorum longus and extensor hallucis longus arise from the anterior surface of the tibia and pass under the superior and inferior extensor retinacula. The extensor digitorum longus divides into four separate tendons that split around the four smaller toes and insert into the volar plate of the proximal interphalangeal joints. These tendons therefore act to extend the toes at the metatarsophalangeal joint but not at the interphalangeal joints. The extensor hallucis longus inserts into the distal phalanx of the great toe. The peroneus tertius arises from a small area on the anterior tibia and adjacent interosseous membrane. The tendon passes under the extensor retinaculum lateral to the extensor digitorum brevis and inserts into the fifth metatarsal base. The tibialis anterior acts as an ankle dorsiflexor and inverter, whereas the peroneus tertius acts as a dorsiflexor and everter (see Fig. 80-15 and Fig. 80-16 for insertions of these muscles). (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985.)

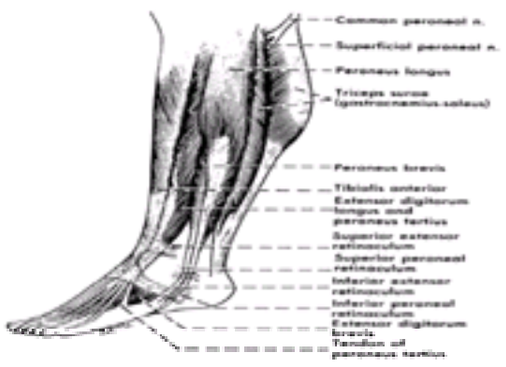


Figure 80-5. Lateral muscles of the left leg. The two anterolateral compartment muscles are the peroneus longus and peroneus brevis arising from the head and upper two-thirds of the lateral surface of the tibia (see Fig. 80-1A). The two tendons pass behind the lateral malleolus, lateral to the axis of the subtalar joint. The brevis inserts into the base of the fifth metatarsal. The longus enters the sole of the foot in a groove of the cuboid bone and crosses the sole before inserting into the base of the first metatarsal and the bones around it (see Fig. 80-16 for the insertions of these muscles). The brevis muscle everts the foot, and the longus acts to plantar flex the great ray and everts the ankle. (Reprinted from Rosse C. *Hollinshead's textbook of anatomy,* 5th ed. Philadelphia: Lippincott–Raven Publishers, 1997:377, with permission.)

Extrinsic Flexors and Extensors of the Toes. The superficial flexor of the arm is analogous to the soleus. The soleus muscle belly forms a tendon inserting onto the calcaneus. The tendon insertion continues distal to the heel, forming in the same plane the flexor digitorum brevis, which inserts into the middle phalanx of the toes similar to the profundus in the hand. Therefore, only one common extrinsic digital flexor is found in the calf, the flexor digitorum longus (see Fig. 80-3C), analogous to the flexor digitorum profundus in the forearm (6) (see Fig. 80-4). The flexor hallucis longus corresponds to the flexor pollicis longus. The flexor digitorum longus arises from the tibia, and the flexor hallucis arises from the fibula (see Fig. 80-1B); the tendons pass on the medial side of the heel and enter the sole of the foot through the tarsal tunnel behind the malleolus (Fig. 80-6). Also contained in the tarsal tunnel are, from medial to lateral, the tibialis posterior tendon, the digitorum longus, the blood vessels, the tibial nerve, and the hallucis longus. The tendons are invested in synovial sheaths and are kept in place by the flexor retinaculum, which is much thinner than the corresponding structure in the wrist (6,10) (see Fig. 80-6). The flexor tendons insert into the distal phalanges. The anatomic arrangement of synovial and fibrous flexor sheaths in the toes through which the tendons pass is similar to that of the fingers.

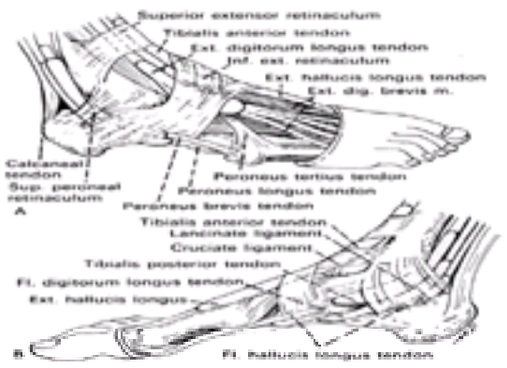


Figure 80-6. Synovial sheaths of the tendons around the ankle. **A:** Anterolateral aspect showing the tendons and synovial sheaths of the tibialis anterior and extensor digitorum longus passing under the superior and inferior extensor retinacula. Beyond the sheath, the extensor digitorum longus divides into four tendons. The extensor hallucis longus inserts into the base of the distal phalanx of the great toe. Note the insertion of the peroneus tertius onto the bases of the fifth metatarsal (see Fig. 80-16B). The peroneus longus and brevis have individual synovial sheaths that pass under the peroneal retinaculum. **B:** Medial aspect showing the synovial sheaths of the tibialis posterior, flexor digitorum longus, and flexor hallucis longus passing behind the medial malleolus. These tendons are covered by the flexor retinaculum covering the end of the tibial nerve and the beginning of two plantar nerves. This is a site for entrapment of these nerves. (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985.)

The extensor hallucis longus and extensor digitorum longus are located in the anterior compartment (see Fig. 80-4). Both originate from the fibula and insert into the toes through the dorsal digital expansions, analogous to those in the fingers, and act mainly to extend the metatarsophalangeal (MP) joints (see Fig. 80-16). The tendons are held in place in front of the ankle by the superior and inferior extensor retinacula and are enclosed in a synovial membrane (see Fig. 80-4). Unlike the hand, an additional short extensor muscle exists on the dorsum of the foot extending all of the toes.

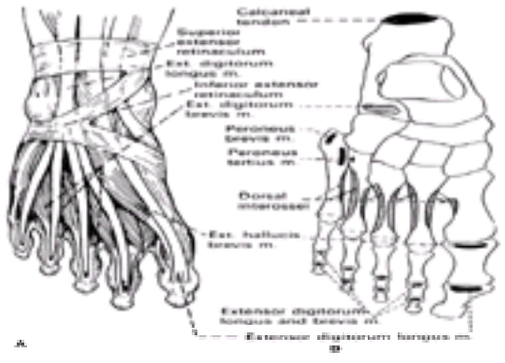


Figure 80-16. **A:** Muscles of the dorsal surface of the right foot. **B:** Dorsal view of the bones of the foot showing the origins of the intrinsic muscles (*striped*) and the insertions of the intrinsic and extrinsic muscles (*black*). (Modified from Hollinshead WH. *Anatomy for surgeons,* 3rd ed. Vol 3. Philadelphia: Harper & Row, 1982.)

Inverters and Everters. The peroneus brevis is the primary everter of the foot (see Fig. 80-5). The peroneus longus inserts mainly into the base of the first metatarsal on the plantar aspect having passed around the lateral border of the cuboid. It acts primarily to plantar flex the great ray and everts the ankle as a secondary function. Both peroneal muscles arise from the fibula and pass behind the lateral malleolus. The brevis inserts into the base of the fifth metatarsal.

The tibialis posterior, the deepest muscle in the flexor compartment, is the principal inverter of the foot (see Fig. 80-3). In this function it is substantially assisted by the tibialis anterior (see Fig. 80-4).

Many other muscles act to invert and evert the foot at the subtalar and midtarsal joints. Even the tendo Achilles can act to both invert or evert the foot in severe cavus deformity and flatfoot, respectively. As a flatfoot deformity progresses, the muscles acting to invert the foot have less mechanical advantage and those acting to evert the foot have greater mechanical advantage, explaining the rapidly progressive nature of severe flatfoot.

Figure 80-6 illustrates the synovial sheaths of the tendons and retinacula around the ankle joint.

Nerve and Blood Supply of the Leg. Figure 80-7 depicts the major arteries and nerves of the leg (6,8). The anatomy and distribution of the tibial and peroneal nerves are described in detail in Chapter 77. The leg and foot receive their arterial blood supply from the lower portion of the popliteal artery and its two terminal branches, the anterior tibial and posterior tibial arteries. The popliteal artery has two lower branches, the lateral and medial inferior genicular arteries. Both of these vessels terminate in the circumpatellar anastomosis and contribute to the blood supply of the knee and the surrounding ligaments. The anterior tibial artery arises from the posterior tibial artery and passes anteriorly through the superior aperture of the interosseous membrane. It descends to the ankle sitting on the interosseus membrane in the anterior compartment and has the dorsalis pedis artery as its terminal branch.

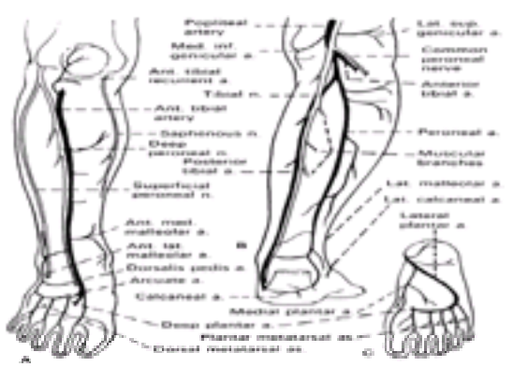


Figure 80-7. Nerve and blood supply of the leg. **A:** Anterior view.**B:** Posterior view. **C:** Plantar surface of the foot. The anatomy of the nerves is described in Chapter 70. (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985.)

The anterior tibial artery gives off (a) the fibular artery before it passes through the interosseus membrane, which supplies the soleus and peroneus longus muscles; (b) the anterior tibial recurrent artery, which terminates in the patellar plexus; (c) numerous muscular branches that supply the muscles of anterior compartment; and (d) the anterior medial and lateral malleolar arteries, which supply the ankle joint. The terminal branch, the dorsalis pedis artery, gives off the lateral and medial tarsal arteries and the arcuate arteries (see Fig. 80-7).

The posterior tibial artery descends in back of the leg as far as the ankle, where it divides into the medial and lateral plantar arteries. It lies between the deep and superficial posterior compartments alongside the tibial nerve. Along its course it gives off (a) the large peroneal artery, which gives off numerous muscular branches, nutrient arteries to the tibia and fibula, and perforating and communicating branches; (b) a large nutrient artery to the tibia; (c) muscular branches to the soleus and deep muscles in the back of the leg; (d) the posterior medial malleolar artery, which contributes to the malleolar arterial network and blood supply to the talus, and several large medial calcaneal arteries.

Anatomy of the Ankle and Foot

Skeleton. The foot is an intricate structure composed of 28 articulating bones similar to the bones of the hand and modified for weight-bearing (Fig. 80-8). The bones of the ankle and foot are the tarsals, metatarsals, and phalanges. The tarsal bones differ from the carpal bones of the wrist, but the metatarsals and phalanges are similar to the metacarpals and phalanges of the hand (6,11). The bony skeleton of the foot is divided into the forefoot, the midfoot, and the hindfoot. The metatarsals and phalanges form the forefoot; the navicular, cuboid, and cuneiforms form the midfoot; and the talus and calcaneus form the hindfoot.

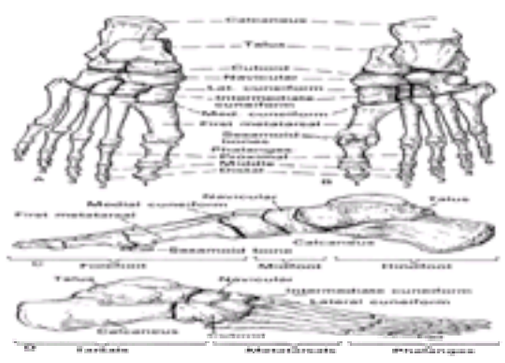


Figure 80-8. Bones of the ankle and foot. **A:** Superior surface. **B:** Plantar surface. **C:** Medial view. **D:** Lateral view. The seven bones of the hindfoot and midfoot, which constitute the tarsus, are arranged in two rows, with one bone between them. In the posterior row the talus sits on the calcaneus, and in the distal row the cuneiform bones and cuboid lie side by side. The navicular bridges the two rows on the medial side. The talus articulates with tibia and fibula so all force within the foot must pass through the talus. Normally the calcaneus and the heads of the five metatarsals are the weight- bearing points of the foot **(C,D)**. The skeleton of the foot has an arch between the calcaneus and metatarsal heads, with the arch being much higher on the medial side **(C)** than on the lateral side **(D)**. The calcaneus, the largest bone of the foot, forms the contour of the heel. The calcaneus supports the talus and transmits the ground reaction force applied to the heel. The calcaneus

forms a lever arm for the insertion of the Achilles tendon. The tubercle of the navicular is palpable 3.5 cm anterior to the medial malleolus. Its posterior concave surface articulates with the head of the talus, and its anterior or distal convex surface articulates with the three cuneiform bones. The cuboid articulates with the fourth and fifth metatarsals anteriorly, the lateral cuneiform and navicular bones medially, and the calcaneus posteriorly. The three cuneiforms, together with the cuboid forming the distal row of tarsal bones, are in line with the three medial rays of the foot and articulate with the corresponding metatarsals. The arrangement of the metatarsals and phalanges is similar to the corresponding segments of the hand. (Modified from Hollinshead WH. *Anatomy for surgeons,* 3rd ed. Vol 3. Philadelphia: Harper & Row, 1982.)

The talus has a body, neck, and head (Fig. 80-9) (8,12). Most of the body, the large trochlea, articulates with the tibia and fibula, together forming the ankle joint. The talus is hard to palpate. The calcaneus is the largest tarsal bone and forms the heel. It supports the talus and articulates with the cuboid laterally. Various parts of the calcaneus are palpable. The sustentaculum tali, a finger's breadth below the tip of the medial malleolus, supports the talus and can be identified as a buttress projecting medially from the calcaneus. Both the medial and lateral walls as well as the tuberosity can be clearly felt. The sinus tarsi is a depression between the body of the talus, the neck of the talus, and the calcaneus opening laterally just anterior and inferior to the lateral malleolus (13).

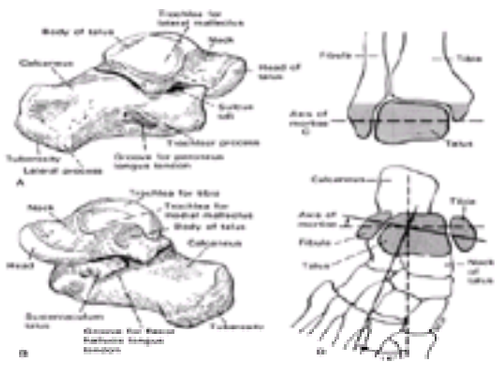


Figure 80-9. Anatomy of the right talus and calcaneus showing their relationship to the tibia and fibula, to other bones of the tarsus, and to the proximal ends of the metatarsals. **A:** Lateral view.**B:** Medial view. The talus has a body, a neck, and a head. **C:** The superior aspect of the large trochlea tali and both sides of the body articulate with the tibia and fibula, together forming the ankle mortise. The tibia contacts the entire superior aspect of the talus, with the medial malleolus extending one-third of the way down the medial aspect of the talus. The lateral malleolus covers the lateral aspect of the body of the talus. The rounded head of the talus fits into the concavity of the navicular bone. The inferior surface of the neck forms the roof of the tarsal canal, the floor being formed by the calcaneus. The tarsal canal separates the nonarticular portions of the talus and calcaneus. The talar neck is situated between the head and trochlea and fits closely between the two malleoli. The axis of rotation of the ankle is oblique to both the long axis of the foot and tibia. **D:** From above, the talus is wedge shaped, with the anterior portion wider than the posterior portion. The longitudinal axis of the joint is perpendicular to the axis of the mortise and forms an external “toe-out” of 16 degrees. (**A** and **B** modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985, with permission. **C** and **D** modified from Cailliet R. *Foot and ankle pain,* 2nd ed. Philadelphia: FA Davis, 1983.)

The navicular is a disk-shaped bone, identifiable by a tubercle that is 3.5 cm anterior to the medial malleolus, level with the sustentaculum tali. It can be identified by following the tibialis posterior tendon distally. It articulates with the talus proximally and the medial and middle cuneiforms distally. The three cuneiforms articulate with the medial three metatarsals. The cuboid articulates with the lateral two metatarsals and is palpable just proximal to the prominent tuberosity of the fifth metatarsal.

Joints

ANKLE JOINT. The ankle joint is a hinge, uniaxial, or ginglymus joint (6,12). It is formed above by the lower end of the tibia and the medial malleolus and the lateral malleolus of the fibula. The mortise articulates with the talus on its convex proximal surface and the flat medial and lateral facets. A cast of the ankle mortise duplicates all contours of the articular surface of the talar body, and hence is one of the most constrained joints of the body (6). A good fit is maintained throughout the whole range of plantar flexion and dorsiflexion. No lateral play or accessory motion occurs in any position. The distance between the malleoli does not change in dorsiflexion, although a small amount of lateral rotation of the fibular malleolus is permitted by the obliquity of the tibiofibular interosseous ligament, accommodating the wider anterior talus during full dorsiflexion (7).

The bones are connected loosely by the articular capsule. The medial deltoid ligament complex and lateral collateral ligament complex provide stability to the ankle joint (Fig. 80-10) (8). Part of the medial deltoid ligament and the lateral calcaneofibular ligament stabilizes the subtalar joint (14). The deltoid ligament inserts into the spring ligament stabilizing the talonavicular joint.

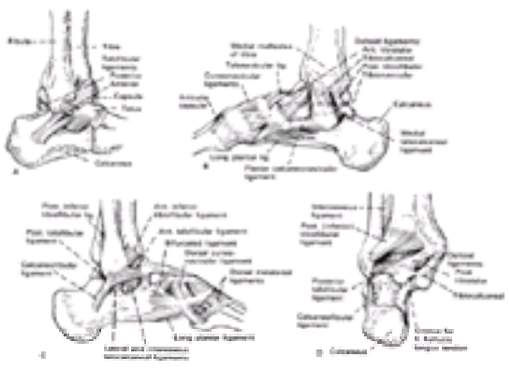


Figure 80-10. Anatomy of the capsule and ligaments of the right ankle joint. **A:** Lateral view: The articular capsule surrounds the joint, attaching above to the borders of the articular surface of the tibia and malleoli and below to the talus around its articular surface. **B:** Medial view: The medial collateral “deltoid” ligament fans out in a triangular shape from medial malleolus, attaching into the navicular anteriorly and the calcaneus and talus posteriorly. The deltoid ligament has superficial and deep portions. The superficial anterior portion is the tibionavicular ligament. The superficial posterior portion is the tibiocalcaneal ligament inserting into the sustentaculum tali. The anterior and posterior tibiotalar ligament inserts into the talus and forms the deep portion of the deltoid ligament. The deltoid ligament is covered by the tendons of the tibialis posterior and flexor digitorum longus. **C:** Lateral view: The lateral collateral ligament consists of three discrete bands. The short anterior talofibular ligament arises from the anterior margin of the lateral malleolus and inserts onto the lateral aspect of the talar neck. The posterior talofibular ligament, stronger and deeper than the anterior ligament, runs almost horizontally from the posteromedial aspect of the lateral malleolus to insert in a prominent tubercle on the posterior surface of the talus, lateral to the flexor hallucis longus tendon. The calcaneofibular ligament, the strongest of the three, is a narrow rounded cord passing from the apex of the lateral malleolus to a tubercle on the lateral surface of the calcaneus. **D:** This posterior view of the ankle joint showing the posterior inferior tibiofibular, posterior talofibular, posterior tibiotalar, and tibiocalcaneal ligaments. (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985.)

The articular capsule surrounds the joint. It inserts superiorly on the articular border of the tibia and malleoli and inserts inferiorly on the talar articular surface (see Fig. 80-10A). The anterior and posterior capsule is thin.

The collateral ligaments provide side-to-side stability to the ankle (see Fig. 80-10B,Fig. 80-10C). Inversion and eversion injuries may rupture the lateral or medial

collateral ligaments or fracture the malleoli. In a young adult, fracture dislocation includes rupture of the deltoid ligament, disruption of the distal tibiofibular syndesmosis, and fracture of the fibula just above the joint (15). Occasionally, the medial malleolus may be avulsed without injury to the deltoid ligament. The lateral ligaments rupture during an inversion sprain, the most common form of ankle sprain. The anterior talofibular ligament is ruptured first in the plantar flexed position. The interosseous ligament running between the talus and the calcaneus aids the stability of the subtalar joint (see Fig. 80-10C). The posterior fibers of the deltoid ligament prevent excessive dorsiflexion, whereas the anterior talofibular ligament prevents excessive plantar flexion (see Fig. 80-10B,Fig. 80-10D).

INTERTARSAL JOINTS. Movements at the ankle joint are limited mainly to plantar flexion and dorsiflexion. Inversion, eversion, forefoot abduction and adduction, and the combined movements of supination (inversion and abduction) and pronation (eversion and adduction) occur at the other joints (8,10). Most of this motion occurs throughout the subtalar joint, the talonavicular joint, and the calcaneocuboid joint. The motions of these joints are closely tied, with the talonavicular joint allowing the most combined motion. Because three of the arches of the foot involve these joints, they are under particular strain during weight-bearing. The plantar ligaments of these joints are particularly strong (8). The plantar surface of the foot has strong intertarsal ligaments that bind the bones together and help to prevent collapse of the arch. The arch is further maintained by the short muscles of the foot, the plantar aponeurosis, and the long tendons passing into the sole of the foot from the leg (Fig. 80-11C) (7). The posterior tibial tendon and the peroneus longus muscle have particular roles in maintaining the arch of the foot.

Figure 80-11. Ligaments of the ankle and foot. **A:** This coronal section through the right ankle and subtalar joints shows the talocalcaneal interosseous ligament, the deep portion of the deltoid ligament, the tendons and muscles in back of the heel, and the structures coursing beneath the malleoli. **B:** Oblique view of the ankle, subtalar, and transverse talar joints and the tarsometatarsal joints. **C:** Ligaments of the sole of the foot illustrated with the peroneus longus and both tibialis tendons. The long plantar ligament arises from the plantar aspect of the calcaneus and passes anteriorly in a fan-wise fashion. The deep fibers stretch to the plantar tuberosity of the cuboid bone. The most superficial fibers insert into the bases of the second, third, fourth, and fifth metatarsal bones. The plantar calcaneocuboid (short plantar ligament) is a strong ligament lying deep to the long plantar ligament. It extends from the plantar aspect of the anterior tubercle of the calcaneus to the plantar surface of the cuboid behind the peroneal groove. The plantar calcaneonavicular, or spring ligament, is a broad band of fibers that connects the calcaneus and navicular. (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985.)

The subtalar joint allows inversion and eversion of the heel and lies between the calcaneus and talus with two or three facets within the joint. The transverse tarsal joint links the hindfoot and midfoot. This joint allows inversion and eversion of the forefoot, forefoot adduction and abduction, and a small amount of forefoot flexion and extension (6). The talonavicular and calcaneocuboid joints together form the transverse tarsal joint. Independent movements are not possible in any of these joints (8). The subtalar joint and the lateral and medial components of the transverse tarsal joint are enclosed by an independent fibrous capsule lined by synovial membrane (Fig. 80-11).

Multiple ligaments stabilize the midtarsal joints (see Fig. 80-11B). The cervical ligament is located in the sinus tarsi and is attached to the neck of the talus and the upper surface of the calcaneus (8). One limb of the bifurcate ligament, the dorsal calcaneonavicular ligament, arises anterior in the sinus and connects the calcaneus and navicular. The other limb, the dorsal calcaneocuboid ligament, connects the calcaneus and cuboid bones. The plantar calcaneocuboid ligament (the short plantar ligament) maintains the calcaneocuboid joint during weight-bearing.

The long plantar ligament (see Fig. 80-11C) arises from the plantar surface of the calcaneus anterior to the calcaneal tuberosity. Its deep fibers insert on the plantar surface of the cuboid wall, and the superficial fibers continue to the bases of the second, third, fourth, and fifth metatarsal bones. These fibers form the roof on the groove on the plantar surface of the cuboid, making a tunnel for the tendon of the peroneus longus muscle. This ligament reinforces the lateral longitudinal arch (4,5,8).

Other intertarsal joints are found between the navicular and cuneiform bones, the cuboid and cuneiform bones, and among the cuneiforms (6). These can all form one continuous joint cavity, although the navicular cuneiform and cuboid to lateral cuneiform joints can be separate. These joints are supported by weaker dorsal interosseous ligaments and stronger plantar interosseous ligaments. The cuneiforms are supported by the weak transverse dorsal intercuneiform ligaments and by the stronger plantar intercuneiform ligaments.

JOINTS OF THE MIDFOOT AND FOREFOOT. The tarsometatarsal joints lie between the three cuneiforms and cuboid bones proximally and the bases of the five metatarsal bones distally. These joints are strengthened by the dorsal and plantar tarsometatarsal ligaments and by interosseous ligaments between the metatarsals and between the cuneiforms (see Fig. 80-11B).

The bases of the metatarsal bones are connected by the dorsal plantar and interosseous intermetatarsal ligaments. These help stabilize the midfoot and are ruptured in a Lisfranc midfoot fracture dislocation. The heads of the metatarsal bones are interconnected on their plantar aspects by the deep transverse metatarsal ligament. Some fibers of this ligament attach to the base of the proximal phalanx and the metatarsal heads. The range of extension is greater in these joints than the range of flexion, although movement is fairly minimal.

The MP joints are strengthened by the plantar and collateral ligaments. The anatomy of the interphalangeal (IP) joint corresponds to that in the hand (5,8).

Nerve and Blood Supply of the Joints of the Ankle and Foot. Figure 80-12 shows the nerve supply of the foot and ankle. The ankle joint is supplied by the deep peroneal, tibial, and saphenous nerves (5,14). The intertarsal joints are supplied by the superficial and deep peroneal nerves (15). The saphenous nerve supplies the joints on the medial border of the foot. The lateral and medial plantar nerves have branches to the plantar aspects of the joints.

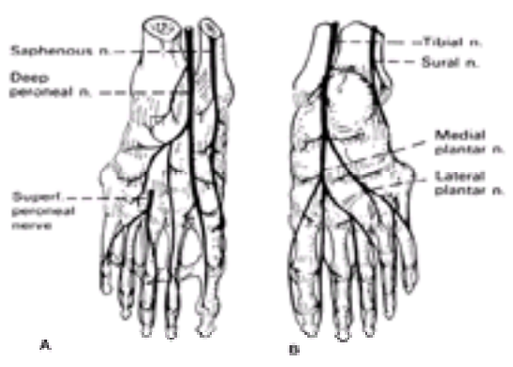


Figure 80-12. Nerve supply of the ankle joints and joints of the foot. **A:** Dorsal view.**B:** Plantar view. Many fibers supply the ankle. See text for details.

The blood vessels supplying the ankle joint are the malleolar branches of the anterior tibial and peroneal arteries. The other joints of the foot are supplied by the dorsalis pedis artery and its branches, the medial and lateral plantar arteries, and the plantar arch.

Fascia and Intrinsic Muscles of the Foot

Plantar Aponeurosis and Plantar Fascia. The superficial fascia forms a tough thick padding over the sole of the foot. The fascia is thin on the dorsum of the foot (4,5,8). The plantar aponeurosis is attached posteriorly to the calcaneus and fans out anteriorly toward the toes (Fig. 80-13). It sends fibers to the skin forming septa within the sole of the foot (4,5,8). The sides of the aponeurosis continue with intermuscular septa that separate the intrinsic muscles of the first and fifth digits from a central compartment containing the flexor tendons and the lumbricals. Additional sagittal septa over the metatarsal heads distally connect the plantar aponeurosis to the deep transverse metatarsal ligament. The tunnels formed between the septa, the plantar fascia, and the metatarsal heads alternately contain the flexor tendons or the lumbricals and digital vessels and nerves. The lumbricals, digital vessels, and nerves are protected from compression by the metatarsal heads.

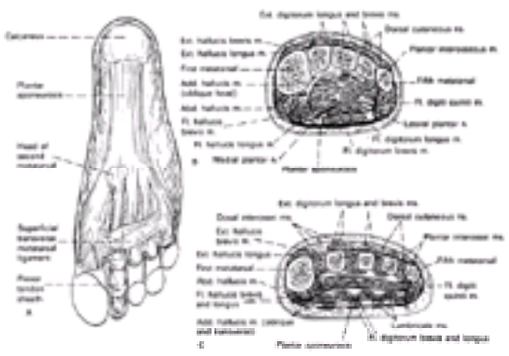


Figure 80-13. The plantar aponeurosis and bones and muscles of the right foot. **A:** Inferior view: The plantar aponeurosis arises from the posterior calcaneus and divides at the midfoot into bands inserting around the five toes. **B:** This cross section through the posterior metatarsal arch shows the fascial compartments and relationships between the bones, supporting ligaments, and muscles. The plantar aponeurosis and associated fascia are shown in black. The aponeurosis is thick on the plantar surface and thin on the lateral and dorsal aspects of the foot. **C:** Cross section at the anterior metatarsal arch. (**A** modified from Hollinshead WH. *Anatomy for surgeons,* 3rd ed. Vol 3. Philadelphia: Harper & Row, 1982. **B** and **C** modified from Eycleshymer AC, Schoemaker DM. *A cross-sectional anatomy.* New York: Appleton-Century-Crofts, 1911:159.)

Intrinsic Muscles. Figure 80-14 depicts the intrinsic muscles of the plantar aspect of the foot. Figure 80-15 shows the origins of the intrinsic muscles and the insertions of the intrinsic and extrinsic muscles. Figure 80-16 illustrates the muscles of the dorsum of the foot and the origins of the intrinsic muscles. The flexor digitorum brevis and extensor digitorum brevis act to flex and extend the toes when the long flexors are ineffective at extremes of plantar flexion and dorsiflexion. The lumbricals act to flex the MP joints and extend the IP joints and are weak in claw toe deformity. The interossei assist the lumbricals and have a minimal role in moving the toes in abduction and adduction.

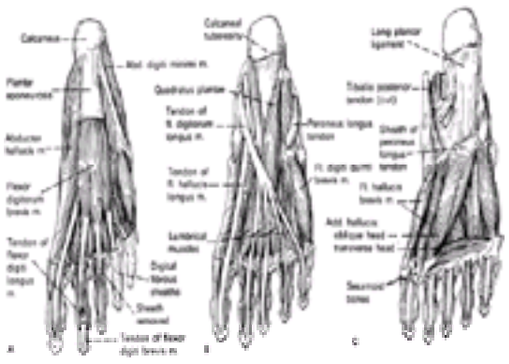


Figure 80-14. Plantar muscles of the right foot. **A:** The first layer consists of the abductor hallucis, flexor digitorum brevis, and abductor digiti minimi. **B:** The quadratus plantae and lumbrical muscles form the second layer. The tendons of the flexor digitorum longus and flexor hallucis longus lie over these muscles. **C:** The third layer consists of the flexor hallucis brevis, adductor hallucis (oblique and transverse heads), and flexor digitorum brevis. The fourth layer consists of the plantar and dorsal interossei (not shown). (Modified from Clemente CD, ed. *Gray's anatomy of the human body,* 30th Am ed. Philadelphia: Lea & Febiger, 1985.)

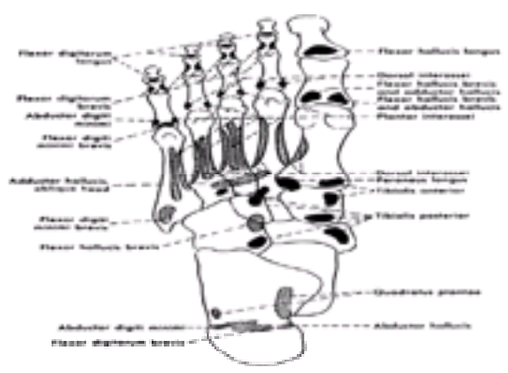


Figure 80-15. This plantar view of the bones of the right foot shows the origins of the intrinsic muscles (*striped*) and the insertions of the extrinsic and intrinsic muscles (*black*). (Reprinted from Hollinshead WH. *Anatomy for surgeons,* 3rd ed. Vol 3. Philadelphia: Harper & Row, 1982, with permission.)

Nerve and Blood Supply of the Foot. Figure 80-17 depicts the nerve supply of the foot. Cutaneous sensation of the sole is supplied by the medial and lateral plantar nerves and by the medial calcaneal branch of the tibial nerve. A strip of the lateral side of the foot is supplied by the lateral dorsal cutaneous branch of the sural nerve, itself a branch of the tibial nerve. The saphenous nerve supplies a thin part of the skin and fascia on the medial aspect of the midfoot. Motor innervation of the intrinsic muscles is primarily from the L-5 and S-1 segments through the medial and lateral plantar nerves (see Table 80-3). Most of the cutaneous innervation of the dorsum of the foot lies within the distribution of the superficial peroneal nerve medial and lateral branches. A twig from the deep peroneal nerve supplies adjacent sides of the first interdigital cleft. The saphenous nerve supplies the skin along the medial side of the foot, and the sural nerve supplies the skin along the lateral edge of the foot. (The segmental nerve supply to the skin, muscles, and bones of the foot is depicted in Fig. 75-20, and the peripheral nerve supply is shown in Fig. 75-21.)

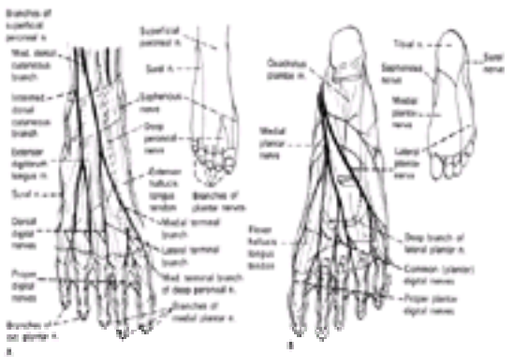


Figure 80-17. Nerves of the foot. **A:** Dorsal view.**B:** Plantar view. See text for details. (Modified from Goss CM, ed. *Gray's anatomy of the human body,* 29th Am ed. Philadelphia: Lea & Febiger, 1959.)

Blood reaches the foot by terminal branches of the anterior and posterior tibial arteries. Many anastomoses exist between these vessels (see Fig. 80-7). The dorsalis pedis artery and its branches supply the dorsum of the foot as the terminal branch of the anterior tibial artery. The plantar surface is supplied by the medial and lateral plantar arteries arising from the posterior tibial artery. The dorsalis pedis artery gives off medial and lateral metatarsal arteries, supplying the front part of the ankle joint. It anastomoses with the first tarsal and deep plantar arteries, the arcuate artery, and the plantar arch (see Fig. 80-7). These in turn give off vessels to the first through fifth plantar metatarsals. Each plantar metatarsal artery gives off two digital arteries, which supply the dorsal and plantar aspects of the joints of adjacent toes.

Arches of the Foot. The foot has four arches, two longitudinal and two transverse. The medial and lateral longitudinal arches are formed by the wedge-shaped bones, which together with their ligamentous support form the arches (Fig. 80-18). The plantar aponeurosis acts as a bowstring or tie rod, as do the long and short plantar and spring ligaments. The medial arch is dome shaped and is higher than the lateral arch (see Fig. 80-8). The posterior transverse or midtarsal arch is formed by the navicular, the three cuneiforms, the cuboid, and the bases of the metatarsal bones. This arch is maintained by ligaments and tendons binding the metatarsal bases. The integrity of these plantar ligaments maintains the arch (16). The anterior metatarsal arch formed by the metatarsal heads is maintained by the deep transverse metatarsal ligaments.

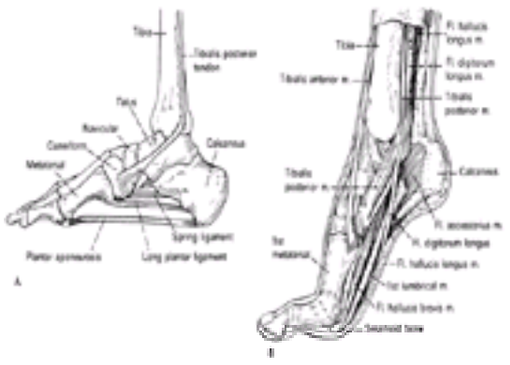


Figure 80-18. **A:** The structures maintaining the longitudinal arches of the foot. All ligaments are shown in the same sagittal plane from the same side. **B:** Dynamic stabilization of the medial arch. With the foot plantar flexed, as in walking, the heel is raised and the toes remain on the ground. The sesamoid bones and the flexor hallucis brevis tendons act to support the first metatarsal. The quadratus plantae lines the hollow between the flexor hallucis longus tendon and the heel. The tibialis posterior provides dynamic support in stance by inverting the hindfoot and locking the subtalar joint. This transforms the foot into a rigid lever for toe-off.

Movement and Biomechanics of the Foot

Movement. In the neutral or anatomic position, the foot forms a 90-degree angle with the tibia (6). Plantar flexion increases and dorsiflexion decreases this angle. This motion occurs mainly at the ankle joint and partially at the midtarsal joint. The total range of motion of the ankle joint in the sagittal plane is approximately 45 degrees but varies widely (17). Ten to 20 degrees of this range of motion are in dorsiflexion, and the remaining 25 to 35 degrees are in plantar flexion. The dorsiflexion range is increased with knee flexion as the gastrocnemius muscle passes behind both the knee and hip. The axis of the ankle joint slopes posteriorly and inferiorly on the lateral side (6,8,16,17). As a result, the foot adducts during plantar flexion and abducts during dorsiflexion. Toeing in and out can also be produced by tibial rotation (9,18).

Inversion and eversion turn the sole of the foot medially and laterally, respectively (6,13) (Fig. 80-19). This side-to-side rotation of the foot occurs at the subtalar and transverse tarsal joints around an anterior posterior axis deviating from the sagittal plane. During inversion the heel deviates medially; during eversion it deviates laterally (see Fig. 80-19A). In addition, this motion involves the forefoot, and its deviation is gauged by the line of the second metatarsal in relation to the tibia (see Fig. 80-19B). Because the axis of inversion and eversion is not strictly in the sagittal plane, the foot adducts during inversion and abducts during eversion through the transverse tarsal joint.

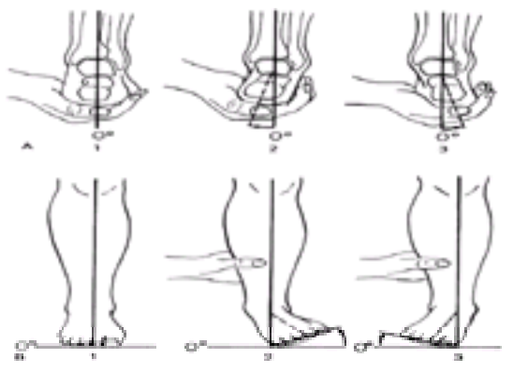


Figure 80-19. Inversion and eversion. **A:** In the neutral position, the vertical axis of the heel is aligned with the longitudinal axis of the tibia (1). By grasping the calcaneus with the hand, the entire heel can be moved inward (inversion) 20 degrees (2) or outward (eversion) 10 degrees (3). Excessive inversion may indicate laxity or tear of the calcaneofibular ligament and excessive eversion indicates tear or laxity of the deltoid ligament. **B:** Inversion and eversion of the forefoot. In the neutral position, the line of the second metatarsal is aligned with the midline of the tibia (1). Inversion is associated with adduction (2), and eversion is associated with abduction of the forefoot (3). (Modified from the American Academy of Orthopedic Surgeons. *Joint motion: method of measuring and recording.* Chicago: American Academy of Orthopedic Surgeons, 1965.)

These movements displace the metatarsals in relation to one another and involve the transverse tarsal joint and the joints distal to it (16,17). The foot cannot be adducted without inverting, nor can it abduct independent of eversion. In the neutral position, the heads of the metatarsals are in the same horizontal plane. Adduction associated with inversion elevates the head of the first metatarsal and depresses the head of the fifth metatarsal, whereas abduction associated with eversion has the

opposite effect (Fig. 80-20).

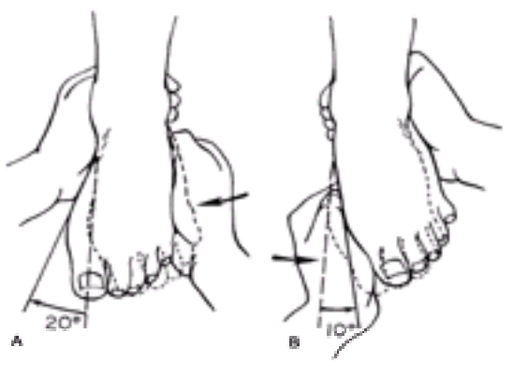


Figure 80-20. Testing for adduction **(A)** and abduction **(B)** of the forefoot. This takes place primarily at the transverse tarsal joint. The patient's foot is held at the calcaneus. The forefoot is moved medially and laterally. Under normal circumstances, adduction accompanies inversion and abduction accompanies eversion. (Modified from Hoppenfeld S. *Physical examination of the spine and extremities.* New York: Apple-Century-Crofts, 1976.)

Biomechanics. The foot adapts to uneven ground and allows the center of gravity of the body to be positioned over the center of support. The fit and construction of shoes affect shock absorption and the support of the foot. Footwear available today is designed specifically for such activities as sports, aerobics, walking, running, and dancing and provides the support, fit, control, shock absorption, and in some cases, splinting necessary for the specific activity. Wearing a shoe that is not designed for a vigorous form of activity can be a source of pain.

Foot biomechanics analyzes the alignment and magnitude of forces acting on the foot. The foot has 26 bones, 19 muscles, and 107 ligaments forming four arches (medial and lateral longitudinal and posterior and anterior transverse) (14). The shape of the foot relates to the supporting ligaments, muscle forces, and loading environment. Foot alignment during weight-bearing determines the loading environment to which the foot is subjected. The alignment of the foot is determined by the shape of bony structures, ligamentous tension, coordination of the musculotendinous units, and alignment of the leg in general.

The foot can be thought of as a tripod, with the os calcis providing one point of support and the heads of the fifth to first metatarsals providing the other two points of support (Fig. 80-21). The weight-bearing line normally passes through the ankle joint into this tripod area. If the weight-bearing line passes outside the area, problems arise. For example, in a pronated foot, the weight-bearing line falls medial to the foot and the hindfoot goes into eversion. Structures on the medial side of the foot are placed in tension. When the weight- bearing line falls laterally in a supinated foot, the ankle becomes inverted and overloads the lateral ligaments and the lateral border of the foot. Medial knee pain can occur in a supinated (or cavus) foot by causing overload of the medial side of the knee. Thus, abnormal foot biomechanics in an active individual can eventually lead to local or more widespread discomfort (6,16,18,19).

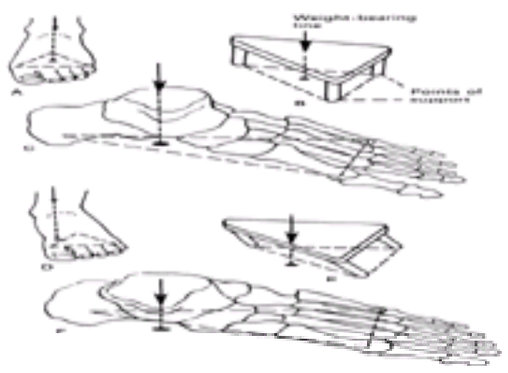


Figure 80-21. Weight-bearing alignment of the foot. A tripod is formed by the heads of the first to fifth metatarsals anteriorly and the calcaneus posteriorly. **A–C:** The normal weight-bearing line falls within the base of the tripod. **D,E:** In pronation, the weight-bearing line falls medial to the foot. **F:** The structures on the medial side of the foot are placed under tension.

EVALUATION OF THE PATIENT

A large segment of the population seeks health care because of pain in the distal lower limb (4). Comfortable feet are usually taken for granted. A small foot problem can dominate a person's perception of health. Feet vary in size, shape, posture, and soft tissue tension, thus changing the presentation of the pain. Problems are exacerbated as modern shoes are often designed more for fashion than for fit, support, or comfort.

For some patients and conditions, some minor therapeutic measures can greatly relieve pain in the foot. A patient with a painful ingrown nail is as grateful for the relief provided by cotton placed between the nail and the nail fold as the arthritic undergoing successful total hip arthroplasty. Physicians can do a great service to a patient by being aware of and using the general principles for treating pain described in this chapter.

Evaluation of the patient with pain in the lower extremity should be carried out using the principles in Chapter 12 and Chapter 75. Table 80-4 summarizes the major points of the history and clinical examination. The proximity of most of the structures in the foot and ankle to the skin facilitates diagnosis (6,13,20). Pain in the leg and foot can be caused by systemic disease. Radiating pain may result from disorders of the low back or deficient arterial supply (13). As a result, a general history and physical examination should be carried out. The following discussion presents a method for routine evaluation of the foot and ankle. Gait is examined as the foot and ankle form part of the locomotor system (16).

History

The clinical evaluation requires a detailed history of the pain. The patient should ideally be given a questionnaire before examination because this will help the patient communicate the complaint.

The patient is asked to describe the pain as it presently affects him or her. The location, intensity, quality, temporal profile, and aggravating and relieving factors should be elicited. The patient is asked to point exactly to the location of the pain and to trace the distribution of any radiation. Pain aggravated by walking or running and relieved by rest is often arthritic in nature if present for more than a couple of months. Occasionally, the pain may be caused by circulatory insufficiency, tumor, infection, or stress fracture. Some measure of the intensity of the pain should be used, such as the 1 to 10 intensity scale (0 being no pain and 10 being the most severe pain imaginable). Any relation of the pain to weather (e.g., arthritis), other joint involvement (e.g., systemic disease), or a general illness should be ascertained.

The quality of the pain helps in the diagnosis. Local pathology has sharp, well-localized discomfort. More diffuse aching about the leg or whole foot can be caused by systemic disease. The temporal profile of the pain is elicited (i.e., intermittent or continuous). Is the overall trend one of improvement, worsening, or no change? If the symptoms are deteriorating, therapeutic intervention should be earlier and more aggressive.

The functional disability should be assessed. The effect of pain on activities of daily living, work-related activities, and recreational activities is recorded. In each category, the physician should ask enough questions to develop a clear picture of the type of loading environment and degree of physical stress that the foot, ankle,

and leg must absorb during a typical day and the duration of exposure before symptoms appear. This is particularly important in patients suspected of having calf pain caused by peripheral vascular disease and in patients with pain in the ankle and foot caused by bone or joint pathology.

The patient is asked about the initiation and time course of the pain. Pain of acute onset is often related to specific events, such as trauma or overuse. A sedentary person beginning an aerobic dance course can be expected to have pain in the leg, ankle, and foot. Gradual development of pain without a precipitating event might reflect a systemic problem or structural abnormality that the person has had for many years that is just becoming symptomatic.

The treatment so far is recorded. Treatments benefiting the patient and those not assisting will aid diagnosis and further management. Many patients with foot and ankle problems have selected footwear to alleviate their problems. Others require education as to appropriate footwear. The physician should examine the shoes worn for recreational, day to day, and work use.

Physical Examination

Both legs should be exposed from the knee down. I use a nine-point physical examination checklist: exposure, gait, standing, inspection sitting, palpation, range of motion, special tests, joints above, and distal neurovascular examination.

Exposure

Both limbs should be visible from the knee down for the physical examination. Patients with loose clothing can roll up their trouser legs. Patients otherwise should be examined in a gown. Both socks and shoes should be removed after the patient has been observed walking with shoes and orthoses, if used.

Gait

While the patient walks, note any effects of pain on gait and observe the timing of the three phases of gait: foot-flat, toe-off, and swing phase. Observe the progression of weight-bearing and any asymmetry of motion between the left and right. Toes that lie in a normal position during stance can assume a claw toe or hammertoe configuration during swing-through or push-off. The patient is asked to walk on tiptoes and on the heels. Pain in the forefoot will prevent tiptoe walking. Muscle weakness or dislocation within the midfoot region will also prevent toe walking. Heel walking is prevented by equinus contractures at the ankle, often caused by arthritis or a tight Achilles tendon. Painful conditions of the forefoot or hindfoot may restrict both heel or toe walking, and such restrictions will assist the examiner in assessing the severity of the patient's disability.

Standing

With the patient standing, the position of the hindfoot and forefoot is observed. Excessive abduction of the forefoot occurs in symptomatic adult flatfoot (16). The degree of splaying or spreading of the forefoot is compared with the shoe size. Excessive supination, cavus or high arch pattern, and the presence of excessive pronation are noted. The posture of the foot should be recorded with the patient standing because the arch is usually restored once the patient is non-weight-bearing and the dynamic deformity no longer apparent.

Inspection

The patient sits on the edge of a high examination table in a well-lit room. The examiner should sit on a low stool with the patient's feet at waist level so they can be comfortably viewed. The position of the foot with respect to the knee is examined. The patella should be in vertical alignment with the first interosseous or interdigital space. External rotation of the forefoot is the more common disorder secondary either to forefoot adduction or external rotation of the tibia, a common postfracture malunion (13,17). Significant variation occurs between patients, and the pathologic side thus should be compared to the normal side. Internal rotation of the forefoot occurs in cavus foot disorders and clubfoot. The normal relaxed foot will hang in slight plantar flexion. Abnormal signs include local areas of increased or decreased temperature, loss of hair, abnormal coloration (e.g., blanching, blotching, or cyanosis, as seen in peripheral vascular disease), or localized areas of redness from shoe pressure. The skin texture should be examined, especially for excessive or diminished sweating. These skin changes are altered by peripheral vascular disease, complex regional pain syndromes, and peripheral neuropathies. The nails are inspected for evidence of infection within the nail or nail bed.

The heel and sole of the foot are examined. Subtle differences, such as swelling about the origin of the plantar fascia, are best appreciated by comparing one side to the other (20). Inspection of the foot for callosities, corns, areas of redness, and increased skin thickening will indicate areas of excessive load.

The shoes are inspected for excessive wear. Normal wear at the heel is slightly lateral to the midline. Excessive wear at the heel or sole associated with medial or lateral drift of the upper surface of the shoe indicates abnormal foot posture and dynamics. The interior of the shoe, particularly the toe box, should be inspected for signs of toe pressure. Foot orthotics and braces should also be examined. The shoes are inspected for their appropriate fit. Patients will present in everything from high-fashion high heels to custom-made orthopedic shoes.

Palpation

Palpation begins in the heel region (see Table 80-4). The Achilles tendon and bony landmarks are palpated. Bursitis and insertional tendonitis cause pain at the calcaneal level (Fig. 80-22B). Sometimes the defect in a ruptured Achilles tendon can be palpated. Plantar fascitis causes pain on the plantar aspect of the calcaneus (Fig. 80-22C). Each of the tendons passing around the heel on the medial and lateral side is palpated along its course during resisted active contraction.

TABLE 80-4. Evaluation of the patient with pain in the leg, ankle, and foot

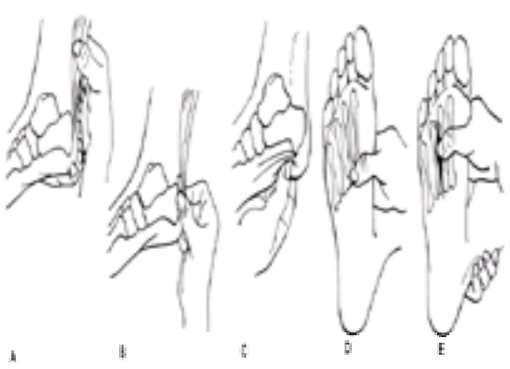


Figure 80-22. Pain in isolated regions of the sole may indicate a specific diagnosis. **A:** Palpation of the Achilles tendon. **B:** Palpation of the calcaneal bursa. **C:** Palpation of the calcaneus at the origin of the plantar fascia can elicit pain caused by plantar fasciitis. **D:** Palpation of the heads of the metatarsals for metatarsalgia. **E:** Shooting pain between the metatarsal heads may indicate a Morton's neuroma.

Examination of the sole of the foot includes palpation of the arch (Fig. 80-22D). Tenderness immediately proximal to the tuberosity of the navicular suggests a sprained spring ligament. Tenderness elicited by pressure on the metatarsal heads suggests neuroma, metatarsalgia, or calluses (Fig. 80-22E). Usually the head of the second metatarsal is the most painful in metatarsalgia. Synovitis of the associated MP joint may also be palpable.

Range of Motion

In examining the active and passive ranges of motion, side-to-side comparisons are made because large variations in normal exist between patients. The presence of pain or crepitus during passive range should be recorded. Arthritis in any joint will cause restricted range of motion. Movement should be separately tested at the ankle, subtalar, midtarsal, and MP joints. In claw toe deformity the IP joints are examined to determine if the contracture is flexible or fixed. Excessive laxity at the first tarsometatarsal joint can decrease the weight borne by the hallux and transfer more weight to the second metatarsal head (21).

A tight gastrocnemius muscle occurs with many foot pathologies, including flatfoot and diabetes. A tight gastrocnemius muscle causes a difference in dorsiflexion at the ankle with the knee flexed and extended. The subtalar joint should be locked for this examination by inverting the hindfoot. An excessively tight gastrocnemius muscle prevents dorsiflexion above neutral with the knee extended.

Figure 80-23 depicts the method of examining movement at the ankle and midtarsal joints and toe movements. To test the range of plantar flexion and dorsiflexion, the examiner grasps the heel with one hand and stabilizes the foot with the other. Although considerable variation exists, at least 15 to 20 degrees should be in dorsiflexion and 20 to 25 degrees in plantar flexion (17). The two sides should be compared.

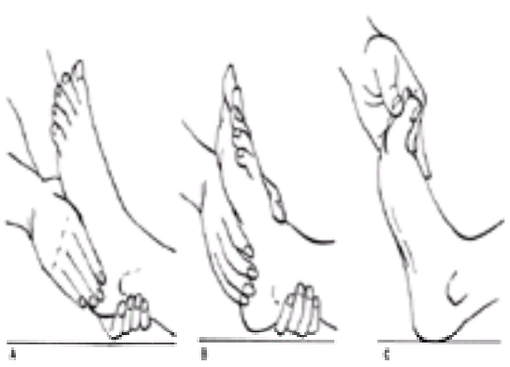


Figure 80-23. Examination of motion at the ankle, midtarsal, and metatarsophalangeal joints. **A:** Examination of ankle movement. The examiner's hand grips the hindfoot and calcaneus rather than the forefoot so that the movements of the subtalar and metatarsal joints are eliminated. The normal range of ankle movement varies, but in the average normal foot it is 20 to 25 degrees for dorsal flexion and 25 to 35 degrees for plantar flexion. **B:** Examination of metatarsal movement. The examiner grasps the Achilles tendon firmly so that the subtalar movement is eliminated. The other hand lightly grasps the midfoot near the bases of the metatarsals and the patient is asked to twist the foot alternately inward and outward into inversion and eversion. Normal rotation should be 15 to 20 degrees on each side of neutral. **C:** Examination of the normal range of motion at the metatarsophalangeal joint of the big toe. This should be nearly 90 degrees; less than 60 degrees of dorsal flexion is considered abnormal. (Modified from Adams JC. *Outline of orthopedics,* 10th ed. Edinburgh, UK: Churchill Livingstone, 1986.)

Tests for active range of motion and strength are shown in Figure 80-24. The results of these tests also provide an indication of the muscle power in the various functional units.

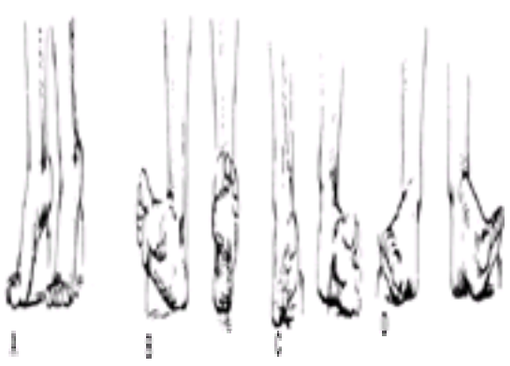


Figure 80-24. Rapid method of testing active range of motion and the strength of muscles controlling movement of the ankle and foot. **A:** Test of plantar flexion and toe motion: The patient is asked to walk on the toes. **B:** Test of dorsiflexion: The patient is asked to walk on the heel. **C:** Test of inversion: The patient is asked to walk on the lateral borders of the feet. **D:** Test of eversion: The patient is asked to walk on the medial borders of the feet. (Reprinted from Hoppenfeld S. *Physical examination of the spine and extremities.* Upper Saddle River, NJ: Prentice Hall, Inc, 1976, with permission.)

Special Tests

Coleman Block Test. The Coleman block test determines the origin of hindfoot varus in a cavus foot. The patient initially stands on the floor, and the hindfoot position is recorded. The patient then stands with the lateral border of the foot and heel supported on a block. If the deformity is fixed or secondary to loss of motion in the subtalar joint, the hindfoot position will not correct. In some cases, the hindfoot varus is secondary to a plantar-flexed rigid first ray with a flexible hindfoot, at which point the heel will correct to normal.

Single Heel Raise. The single heel raise test assesses the function of the posterior tibial tendon. The patient stands on one leg and places both hands on a table or bench for support. Upon standing on tiptoes the hindfoot should invert. If the hindfoot remains in valgus, either the tendon is ruptured or the muscle is too weak to invert the heel because of pain or a severe flatfoot deformity (16).

Thomas Sign. After rupture of the Achilles tendon, the soleus and gastrocnemius are no longer connected to the calcaneus. When the muscle is squeezed midcalf it will shorten. When the tendon is intact the foot will plantar flex. No plantar flexion is seen if the tendon is ruptured (17).

Inversion Stress Test and Anterior Drawer. To test the stability of the ankle, the leg is grasped with one hand and the heel moved anteriorly. Excessive anterior motion of the talus suggests that the anterior talofibular is torn (see Fig. 80-10). Figure 80-19 illustrates measurement of eversion and inversion. Excessive inversion, the more common disorder, indicates a tear in the calcaneofibular ligament or tear of the lateral stabilizers of the subtalar joint. Excessive eversion indicates disruption of

the deltoid ligament (17). Figure 80-20 illustrates measurement of adduction and abduction.

Joints Above. Pain and deformity in the knee and spine can be referred to the calf and ankle. Furthermore, foot disorders can cause problems at the knee. An equinus contracture of the ankle results in recurvatum of the knee and a stretched out capsule. A cavus-adducted foot results in the patient walking with the hip externally rotated, increasing the pressure on the medial aspect of the knee (17).

Distal Neurovascular Examination. Determining the state of the peripheral circulation is an essential part of the examination that is often forgotten (7). A palpable posterior tibial or dorsalis pedis pulse indicates adequate vascularity in most patients. Occasionally, vasculitis may cause skin ischemia with normal pulses in patients with diabetes, rheumatoid arthritis, or pyoderma gangrenosum. In the absence of pulses, capillary refill may crudely estimate the degree of insufficiency. A reasonably accurate assessment can be made by checking the skin temperature and texture. Severe arterial insufficiency of the leg and foot causes loss of hair, coarse nails, painful ulcers of the toe tips, and thin shiny inelastic skin (Chapter 33). If ulcers are present and painless, diabetes should be suspected.

If a peripheral vascular disease is suspected, special studies should be carried out, including ankle pressure recordings, Doppler ultrasound analysis, and other tests (Chapter 33).

Neurologic Examination

Although having the patient walk on the toes, heels, and lateral and medial edges of the foot provides a rough estimation of muscle strength, the strength of each muscle should be tested individually. The power of the triceps surae can be tested by opposing plantar flexion or by observing elevation of the heel while the patient attempts to stand on tiptoe. The ankle jerk test objectively reveals the integrity of the muscle and the nerve pathway. The dorsiflexors of the ankle can be tested by opposing dorsiflexion. Similarly, the power of the extrinsic flexors and extensors of the toes can be evaluated by opposing their action. Tone and clonus should be examined, particularly in the rheumatoid patient, as cervical cord compression may occur.

Sensory examination begins with light touch, comparing side to side and proximal to distal. If this is normal, further examination is unnecessary. The distribution of the sensory nerves and lumbar dermatomes is examined. The deep branch of the peroneal nerve passes through the anterior compartment and supplies the first web space. Intact sensation on the dorsum of the foot confirms an intact L-4 root and intact superficial branch of the peroneal nerve passing through the peroneal compartment. The tibial nerve passes through the deep posterior compartment and divides into the medial and lateral plantar nerves supplying the respective borders of the sole of the foot and the dorsum of the toes. The sural nerve and the saphenous nerve supply respective borders of the medial side and lateral side of the foot.

If light touch is abnormal, a more detailed examination including pinprick, proprioception, temperature, vibration sense, and possibly monofilament testing is performed (Chapter 76). Painful areas should be evaluated for the presence of neuroma by gentle tapping (Tinel's test). Foot trauma often produces injury to the sensory nerves, either by contusion or stretching. The superficial branch of the peroneal nerve can be seen in thin patients by inversion and plantar flexion of the foot.

The calf circumference should be measured. Any decrease of more than 2 cm is objective evidence of muscle atrophy, which is most often a sign of disease atrophy resulting from pain or, less often, peripheral neuropathy. Focal areas of increased warmth, swelling, and tenderness indicate inflammation, which then must be localized to a particular joint, tendon, or tendon sheath complex. Crepitation over a tendon sheath during active motion is pathognomonic of acute tenosynovitis.

Radiographic Examination

The radiographic examination includes routine radiographs and special views. Stress radiographs of the ankle are occasionally indicated. When possible, weight-bearing radiographs are desirable, including anteroposterior and lateral views. An oblique view of the foot or a mortise view of the ankle should also be obtained. Care should be taken to note abnormalities in the structural alignment of the foot, condition of the joints, mineralization, and any overlying soft tissue abnormalities. Special views show the sesamoids (Fig. 80-25), calcaneus (calcaneal axial view), subtalar joint (Broden view), Lisfranc joint (lateral oblique view of the foot), and views of tarsal coalitions (internal oblique view) (16).

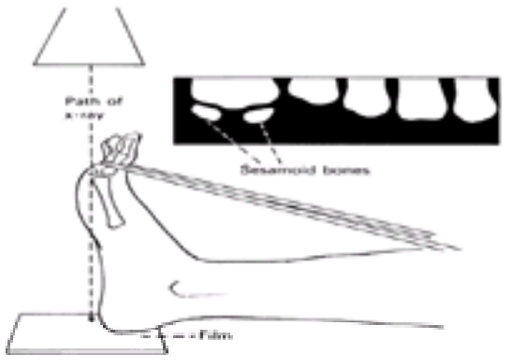


Figure 80-25. The sesamoid bones and joints can be assessed using a sesamoid view.

Stress radiographs are occasionally indicated. Anteroposterior and lateral stress radiographs of the ankle should be taken on both the affected and normal sides. The views are then compared to note any joint subluxation. Stress views can also be performed to visualize the subtalar joint using a 40-degree internal rotation Broden view. Finally, stress views may be performed on the midfoot to assess an occult Lisfranc joint injury (16).

Footwear Trial

When strain, overuse, or overload syndromes are suspected, a trial of supportive footwear provides a good diagnostic test. The patient's feedback helps to determine the best shoe orthotic correction and prescription (22) (Fig. 80-26 and Fig. 80-27).

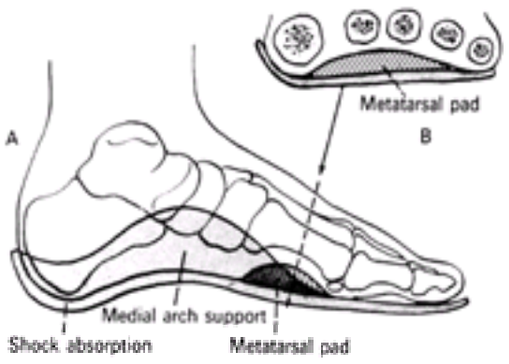


Figure 80-26. Two commonly used orthotics. **A:** Medial arch support. **B:** A metatarsal pad reduces forces under the metatarsal heads.

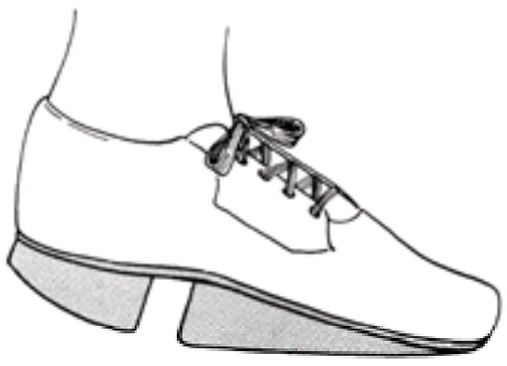


Figure 80-27. Wearing a shoe with rocker-bottom heel and sole helps to reduce the motion of the forefoot during toe-off.

Special Examinations

Bone Scan, Computed Tomography, Ultrasound, and Magnetic Resonance Imaging

Bone scans are useful in the investigation of a persistently painful foot when no abnormality is seen on plain radiographs. They help the physician to identify any underlying problem and to identify the site on which further investigation should be focused. Problems visualized include stress fractures, infection, or fractures not seen on plain radiographs, such as Lisfranc injuries or lateral talar process injuries. Midfoot arthritis can also be difficult to examine and see on plain radiographs; bone scans may assist in the diagnosis. If the bone scan is abnormal and the diagnosis still not certain, computed tomographic (CT) scans will allow the precise anatomy to be outlined. Tomograms may occasionally give more information than a CT scan. CT scans are of use in outlining the anatomy of malunions and nonunions, osteochondral defects, and the extent and degree of necrosis associated with osteomyelitis. Arthrography and tomograms have been largely replaced by CT scans. Arthrography is still of value during the aspiration of joints for sepsis or during local anesthetic blocks to confirm correct positioning of the needle.

If the bone scan is negative and symptoms are significant, magnetic resonance imaging (MRI) is of benefit. MRI is the best method of viewing soft tissue lesions. MRI is particularly valuable in the assessment of soft tissue tumors, both in assisting the diagnosis and outlining the anatomy. Almost all tumors should be imaged this way, as clinical examination does not differentiate a ganglion from a cystic malignant synovial cell sarcoma (23,24 and 25). Apart from soft tissue tumors, MRI is of value in assessing tendons, tendon sheaths, and joint capsules. Smaller lesions, such as a Morton's neuroma or the capsule of the IP joints, may not be seen by the resolution of scans used today. MRI is very sensitive and may find changes of doubtful clinical significance. Any finding should correlate with the history and physical examination. Cartilage lesions are often poorly visualized.

Ultrasound is of value in localizing abscesses, and these can be drained under ultrasound control. Although the resolution of ultrasound is not as good as that of MRI, the test can be performed in more centers and can be done faster and is more accessible on an emergency basis. Tendons and tendon sheaths can be assessed by ultrasound, with less clarity than MRI.

Arthroscopy

Arthroscopy of the ankle may be performed as a diagnostic procedure. Subtalar and first metatarsophalangeal (MTP) joint arthroscopy is being performed in some centers (26). Diagnostic arthroscopy of the ankle is indicated for patients having mechanical symptoms and recurrent effusions with normal investigations. Loose bodies can be missed by both CT and MRI, and the resolution of MRI is not clear enough to assess the chondral surface or impingement of the joint capsule. Excision of capsular lesions such as an anterolateral band seems to provide symptomatic relief. Removal of loose bodies and smoothing of raised chondral defects provide clinical relief (26). Anterior osteophytes and osteochondral defects can also be treated during arthroscopy.

Electromyography

Electromyography and nerve conduction velocity testing, particularly across the tarsal canal, help to evaluate the tarsal tunnel for entrapment (27). Doppler testing provides useful information about the adequacy of circulation at the digit level. In some cases, more proximal lesions, such as entrapment of the peroneal nerve at the level of the fibular head, can have a profound effect on foot and ankle function. Electromyography will help diagnose the cause of weakness and level of injury. Complex regional pain syndromes and compartment syndrome may cause similar disorders.

Diagnostic Blocks

If two or more joints are abnormal or the integrity of an old fusion site is questioned, injection of a low concentration of a local anesthetic (e.g., 0.5% lidocaine or 0.25% bupivacaine) into the joint or fusion site can help to localize the source of pain. For example, an injection into the talonavicular joint may differentiate between talonavicular and ankle joint arthritis. When the pain follows peripheral nerve patterns, a localized entrapment neuropathy should be suspected.

Laboratory Tests

Rheumatoid factor and sedimentation rates are of value in assessing patients with symptoms suggestive of an arthropathy or arthritis (25). If infection is suspected in an otherwise healthy patient, erythrocyte sedimentation rate and C-reactive protein are sensitive and specific tests assisting in the diagnosis (28). Plantar fascitis may be caused by a rheumatologic disorder and should be assessed by serology (16).

Joint fluid analysis and joint biopsy may also be performed. Joint aspiration, particularly of the MP joints, ankle, and subtalar joints, is easily performed. If infection is suspected, at least three separate specimens should be sent to a laboratory for culture. The correct position of the needle should be confirmed by arthrography. Joint fluid is sent for cell count, culture, and sensitivity and for crystal analysis looking for uric acid (gout) or calcium pyrophosphate (pseudogout) crystals. When osteomyelitis is suspected, needle or open biopsy of the small joints can be done for pathologic analysis. Table 80-5 summarizes the physical findings and diagnostic tests for painful foot and ankle conditions.

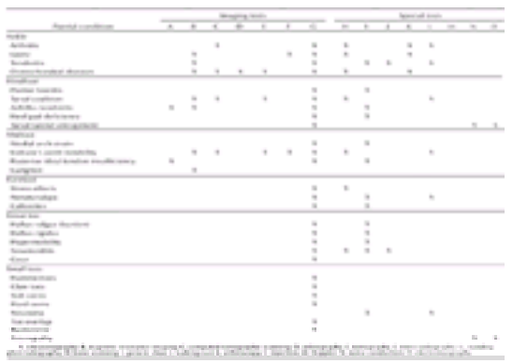


TABLE 80-5. Diagnostic tests for ankle and foot pain

PAINFUL DISORDERS OF THE LEG

Fractures

The tibia and fibula are two of the most frequently fractured long bones in the body. In younger patients, considerable energy is required to fracture these two bones, resulting in significant soft tissue damage. Fractures may be secondary to motorcycle, car, and pedestrian accidents. Falls from heights and sporting injuries account for most of the other injuries. The tibia has little soft tissue coverage and a poor blood supply (15). As a result, soft tissue coverage can be difficult to achieve and the bone may be devascularized by the trauma of the injury. For all open tibia fractures, chronic infection occurs in 10%, nonunion in 15%, and amputation in 5% (15) (Fig. 80-28). For tibial fractures requiring secondary plastic surgical procedures to close the wound, amputation rates approach 50%.

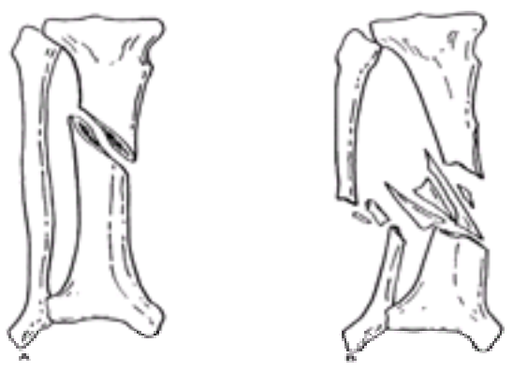


Figure 80-28. Fracture of the tibia. **A:** Long spiral fracture is typical of a low-energy torsion injury such as those occurring during a ski injury. **B:** Comminuted fracture of the tibia with wide displacement of the tibia from the fibula and associated fibula fracture is characteristic of a high-energy fracture commonly associated with motor vehicle accidents and indicates severe soft tissue injury. (Modified from Chapman MW. Fractures of the tibial and fibular shafts. In: Evarts CW, ed. *Surgery of the musculoskeletal system.* New York: Churchill Livingstone, 1983.)

Symptoms and Signs

Pain is the predominant symptom of fracture of the leg. Depending on whether the fracture is open or closed, associated signs such as swelling and bleeding are noted. Associated injuries should be ruled out. Plain radiographs of the splinted leg in two planes should include the ankle and knee.

Treatment

The treatment of the pain of fracture is discussed in Chapter 43. Immobilization of the limb in the emergency department, using a plaster splint before radiography, is the most effective method of early pain control. A small dose of intravenous short-acting benzodiazepine and narcotic will allow comfort for clinical examination and application of the splint.

These fractures require early stabilization by intramedullary nailing or plate fixation. The occasional stable or minimally displaced fracture may be managed in a cast. Postoperative management may be with intramuscular opioids or patient-controlled analgesia (see Chapter 41). An alternative is the use of intraspinal opioids or continuous epidural analgesia, which can be started before radiography and orthopedic therapy (closed or open). A compartment syndrome can occur preoperatively or postoperatively. The distal neurologic function needs to be observed closely, and excessive pain with increasing analgesia requirements is a warning sign of this complication (15).

Acute Compartment Syndrome

If the pressure within a soft tissue compartment exceeds the tissue perfusion pressure, cellular ischemia will result, and if ignored, cell death will follow. The tissues most sensitive to pressure are muscle and nerve. The intracompartmental pressure above which cellular perfusion will decrease is 30 to 40 mm Hg. Compartment syndromes occur after closed fractures, crush injuries without fracture, elective surgery, electrocution, and burns. Some occur after tissue ischemia and reperfusion after more proximal arterial injury or drug overdose, loss of consciousness, and prolonged immobility. Injection of irritants such as industrial agents or secondary to drug abuse can also result in compartment syndrome (15).

Compartment syndromes may occur after excessive elevation of a limb, particularly in patients with low blood pressure. When the leg is lowered, the reperfusion can cause a compartment syndrome. Patients with regional blocks are at particular risk because the insensate limb may be excessively elevated or one compartment may be crushed by positioning. In general, a limb should not be elevated more than 10 cm above the level of the heart.

Symptoms and Signs

Severe pain in the awake patient is characteristic of compartment syndrome. No amount of sedation will control the pain. Patients often undergo a “character change” and can be very abusive, hence the missed diagnosis in some cases. Nerves passing through the compartment lose their function, resulting in loss of skin sensation in that nerve's distribution. Passive stretch of the muscles in the compartment increases pain. Later, loss of muscle function occurs. Distal pulses and distal capillary refill are normal, as the compartment pressure will never reach the arterial perfusion pressure and blood from vessels passing through other compartments ensure distal perfusion through anastomoses in the foot. The diagnosis is clinical in the awake patient because pressure measurements may be unreliable. Comatose or intubated patients require pressure measurements to assist in the diagnosis.

Treatment

Immediate compartment release is required, and compartment syndrome is one of the few immediate orthopedic emergencies. All occlusive dressings must be released to the level of skin, and this may effect adequate treatment. Delay will result in further cell death and potential long-term disability. Prevention includes the careful positioning and monitoring of patients with peripheral nerve blocks.

Analgesia may be given once the diagnosis has been made. Once the compartment has been released, the patient may be difficult to rouse because of the loss of stimulation and the residual narcotic.

Stress Fracture

Tibial stress fracture occurs at the level of the mid- to proximal shaft in patients with no previous surgery (15). Military recruits, the elderly, and endurance sports participants are at risk. Patients with pantalar fusions are at risk for stress fracture at the distal tibia. Patients with previous hardware are at risk for stress fracture through old pin sites.

Diagnosis

Patients may have an underlying history of osteoporosis, previous inactivity, or change in activity level. The pain is often poorly localized and diffuse in nature. Clinical and radiographic examinations may be normal. Increased activity in the region is visualized by a bone scan, narrowing the diagnosis to tumor, infection, or stress fracture. A CT scan will rule out tumor and may confirm the stress fracture. Immobilization of the limb may also be diagnostic. MRI is of additional benefit if the

diagnosis is still in question.

Treatment

Stress fractures should become relatively pain-free once the limb is immobilized. Nonsteroidal antiinflammatory drugs (NSAIDs) can assist with pain control. Strong narcotics should not be required. Once the diagnosis has been made, cast immobilization usually allows bony healing in 6 to 10 weeks.

Rupture of the Calcaneal Tendon

Rupture of the calcaneal (Achilles) tendon is often overlooked (16), because the initial physician may dismiss the symptoms as those of a sprain.

Etiology and Pathophysiology

Rupture of the tendon is usually caused by excessive stress of the muscle while running or jumping. It can also occur as a result of external trauma. The rupture is nearly always complete and is usually found approximately 5 cm above the insertion of the tendon. If left untreated, the tendon may unite spontaneously but in a lengthened and dysfunctional position (29,30).

Symptoms and Signs

The patient is often an aging athlete in the 40- to 50-year-old age group. At the time of injury, there is sudden severe pain in the midcalf. Many report “being hit” in the back of the leg, but on turning around find no one there. The patient usually can walk, but with a limp (30). On examination, tenderness is noted at the site of rupture, with general thickening from effusion of blood and edema, and a gap may be palpated in the course of the tendon. The power of plantar flexion at the ankle is greatly decreased, but some strength remains through the action of the tibialis posterior, the peronei, and the toe flexors (6). Patients with late presentation report loss of strength going up and down stairs and being unable to run owing to the weakness.

Diagnosis

The retention of some power of plantar flexion can cause the unwary physician to make an incorrect diagnosis (17). The Thomas sign is the most efficient diagnostic test. The patient kneels on a chair, and the belly of the gastrocnemius is squeezed. On the affected side the foot does not move, whereas on the normal side the foot plantar flexes. In the chronic condition, the patient is unable to lift up the heel on the affected side during single leg stance (16,29). If the diagnosis is still in doubt, ultrasound can be used to rule out the injury.

Treatment

Immediately after the injury, the pain may be moderate in severity and nonopioid analgesics are sufficient. In some patients, however, the pain is severe and it is necessary to use strong opioid analgesics. Patient-controlled analgesia, intraspinal opioids, and epidural analgesia can be used (see Chapter 43).

Rupture of the Achilles tendon can be treated by immobilization in plaster for 5 weeks with the foot in slight equinus to relax the tendon and help prevent lengthening (29). Surgery entails repair of the tendon. Surgery is indicated for younger and more athletic patients or in cases of delayed diagnosis. Tension on the suture line is reduced by immobilizing the ankle in plantar flexion for 2 weeks followed by a below-knee plaster with the ankle at a 90-degree angle for 4 weeks (29). The operation should be done with continuous epidural anesthesia to prevent the neuroendocrine stress response, and the anesthesia should be continued for 24 to 48 hours to provide postoperative pain relief.

Rupture of the Anterior Tibialis Tendon

Acute and chronic rupture of the anterior tibialis tendon is rare. The rupture occurs between the extensor retinaculum and the insertion of the tendon (31). The patient experiences limitation of dorsal flexion and has a footdrop gait. Operative repair is the procedure of choice (31).

Posterior Tibial Tendonitis and Rupture

Etiology and Pathophysiology. Rupture of the posterior tibialis tendon can occur acutely as a result of an injury, either penetrating or nonpenetrating in nature. A secondary flatfoot deformity can result. More often, the tendon is dysfunctional because of severe flatfoot deformity. The resulting wear on the tendon may cause pain, synovitis, and in some cases, rupture. Rheumatoid arthritis affects the tendon owing to loss of the bony support to the arch as well as direct involvement of the tendon. Pigmented villonodular synovitis may affect the tendon sheath.

Symptoms and Signs. Acute rupture is associated with sudden pain on the medial aspect of the ankle and valgus instability. A painful flatfoot may develop (16). Examination reveals tenderness behind the medial malleolus.

Diagnosis and Treatment. The diagnosis is suspected from the history and physical examination. Early surgical repair is advocated by some (32,33). Nonsurgical treatment with an arch support and a medial heel wedge should be attempted but may not be effective (34). If the posterior tibial tendon is irreparable, a tendon transfer of flexor digitorum longus and some form of arch stabilization procedure such as a triple arthrodesis might be necessary (32). While awaiting surgery, pain is controlled by NSAIDs alone or in combination with opioids, or continuous epidural analgesia is initiated and used for the operation and for postoperative pain relief (see Chapter 41 and Chapter 43).

Shin Splints

Shin splint is a lay term used to describe pain along the anterior or posterior part of the tibia. The pain can be caused by a tibial stress fracture (15). More frequently a strain of the anterior or posterior tibial muscles resulting from overuse of the lower extremities is the cause. Exertional compartment syndrome may cause similar symptoms. The condition is described in Chapter 33.

Infections of Bone

The tibia is one of the most common sites of hematogenous osteomyelitis in pediatric patients. In adults, osteomyelitis occurs occasionally from hematogenous spread and usually occurs secondary to compound fractures or other forms of direct contamination (e.g., drug abuse). The fibula is less often affected. Once established, chronic osteomyelitis requires complete debridement and a full course of antibiotics.

Syphilitic infection of bone is now rare in Western countries. When it does occur, however, the tibia is often the bone affected (35). The infection can take the form of localized gumma or diffuse periostitis and is characterized by gradually enlarging swelling and moderate to severe pain. Adams (35) has noted that the possibility of syphilis should be borne in mind because the swelling is easily mistaken for tumor.

Bone Tumors

Musculoskeletal tumors often occur in metaphyseal bone. Within the tibia, tumors are more likely to occur at the proximal end. Tumors are divided into benign, benign aggressive, and malignant categories (36).

Benign lesions affecting the tibia include enchondromas, adamantinoma, fibrous dysplasia, aneurysmal bone cysts, and unicameral or solitary bone cysts. Most do not require surgery. Some may require biopsy for diagnosis, and some may require surgery for complications such as fracture.

Benign aggressive lesions are characterized by giant cell tumor. Giant cell tumors affect patients in the 20- to 40-year age group and occur right next to a joint

surface. Although the tumor rarely metastasizes, local recurrence is common. Initial treatment involves local excision with adjuvant treatment such as cold cryotherapy and possibly radiation. Occasionally, more radical surgery is required, particularly after recurrence or fracture. Knee fusion or arthroplasty is sometimes required.

The tibia is a site for sarcomas and primary malignant lesions affecting young adults. Ewing's sarcoma, osteogenic sarcoma, malignant fibrous histiocytoma of bone, and occasionally chondrosarcoma affect the tibia (36). The proximal tibia is more often involved than the distal tibia. The prognosis is fortunately better for these more distal lesions, in part owing to earlier diagnosis. Metastatic disease to the tibia is relatively rare. The treatment of cancer pain is discussed in Chapter 35, Chapter 36 and Chapter 37. Modern treatment of these tumors, including Ewing's sarcoma, includes radical resection (36). Usually the limb can be salvaged, particularly with the use of preoperative radiation. Reconstruction can be achieved with allograft and fusion or prosthetic joint replacement. A combination of surgery, local radiation, and chemotherapy is used for these sarcomas.

Acute Rupture of the Gastrocnemius Muscle

Rupture of the gastrocnemius muscle is usually the result of a vigorous contracture while the knee is extended and the foot forcefully dorsiflexed such as can occur during tennis (tennis leg) (30). Occasionally, the rupture is caused by a direct blow. The rupture usually occurs in the substance of the medial head of the gastrocnemius or at the musculoaponeurotic junction.

Signs and Symptoms

The rupture is characterized by sudden pain and a popping sensation. The medial aspect of the muscle is tender. The patient cannot walk without a limp or crutches. Examination reveals a palpable gap in the muscle. In some cases, a posterior compartment syndrome may result secondary to the hematoma. The condition should not be confused with a deep vein thrombosis, because anticoagulants will only increase the symptoms.

Diagnosis and Treatment

The diagnosis is made through the history and physical examination. The control of pain is similar to that for rupture of the Achilles tendon. Nonsurgical treatment using a cast in equinus is the treatment of choice. Compartment syndrome should be managed surgically as soon as diagnosed.

Other Painful Disorders

Other painful disorders of the leg (see Table 80-1) are discussed elsewhere. Intermittent claudication pain in the calf caused by arterial insufficiency in the lower limb as a result of peripheral vascular disease is discussed in Chapter 33. Myofascial pain syndromes with trigger areas frequently involve the calf or anterior leg muscles and cause pain (Chapter 29 and Chapter 79).

PAINFUL DISORDERS OF THE ANKLE AND HEEL

Posttraumatic Pain

Pain caused by acute injuries can result from fracture or dislocation of the bones of the ankle joint or from tear or actual rupture of the surrounding ligaments. In all these conditions, the pain is acute, usually moderate to severe, and requires management with a combination of NSAIDs and strong opioids (Chapter 43) (see Table 31-3).

Ankle Sprains

Ankle sprains are one of the most common presenting complaints to emergency departments and constitute a frequent cause of pain and disability. Many injuries are secondary to sport. Basketball and volleyball players are at particular risk. High-friction surfaces predispose to lower extremity injuries.

Lateral Collateral Ligament Injuries. Most ankle sprains involve the lateral collateral ligaments, and almost all are treated nonsurgically (15). Although isolated ligamentous injuries are common, they are occasionally associated with fractures. A lateral ligament tear may be associated with a medial malleolar fracture.

Symptoms and Signs. Ankle sprains are characterized by sudden, sharp pain. After the injury, the patient may be unable to walk or run. Swelling becomes marked within 6 to 12 hours of injury; the patient cannot bear full weight on the injured leg. Examination reveals the swelling as well as tenderness to palpation of the injured ligament. Ecchymosis is present in the foot and the lower leg. Care should be taken to correctly locate the source of pain, because other injuries, such as a Lisfranc joint injury, may be misdiagnosed owing to incomplete physical examination.

Diagnosis and Treatment. The diagnosis and treatment of ankle sprains are discussed in Chapter 43.

Deltoid (Medial) Ligament Tears

Medial injuries are more severe and associated with greater trauma than lateral injuries, because the deltoid ligament is much stronger than the lateral collateral ligaments. Deltoid ligament injuries can occur in isolation, but they are more commonly associated with lateral malleolar fractures, disruption of the distal tibial-fibular syndesmosis, or both (15). Occasionally, a subtalar dislocation can be associated with a deltoid ligament injury. A subtalar dislocation may be associated with a lateral talar process fracture.

Diagnosis. Pain is localized to the medial side of the ankle. Swelling and ecchymosis in the medial malleolar region can be seen. Complete examination should be performed to exclude associated injuries.

Treatment. The pain can be managed by antiinflammatories, although occasionally stronger narcotics are required. Isolated deltoid ligament injuries are managed nonsurgically, but the associated fractures usually require surgical intervention.

Distal Tibiofibular Syndesmosis Injuries

Occasionally, injuries occur in isolation to the distal tibiofibular joint. This is associated with a feeling of ankle instability and giving way. The diagnosis is often made late.

Symptoms and Signs. Patients complain of localized pain in the region of the distal tibia. Often, an internal rotation twisting injury on a stable foot causes the disruption. Early radiologic examination may show widening of the ankle mortise and talar shift. Late presentation can be diagnosed with a careful history and physical examination.

Treatment. In both early and late cases, the pain outside activity is not severe. However, the syndesmosis needs to be stabilized using a screw to prevent late talar shift and subsequent development of ankle arthritis.

Subtalar Instability

Occasionally, subluxation or dislocation occurs through the subtalar joint. Late instability may be misdiagnosed as ankle instability (16).

Symptoms and Signs. The signs and symptoms of subtalar instability are very similar to those of lateral collateral ligament injuries. The acute subtalar dislocation may spontaneously reduce, and only a careful history will indicate the joint of instability. Late cases may present with recurrent instability, and an inversion stress view of the subtalar joint may assist in the diagnosis.

Treatment. Acute treatment of pain may be achieved similar to lateral collateral ligament injuries. Subtalar joint stabilization by ligament reconstruction may be required.

Recurrent Ankle Instability

Recurrent ankle instability results in apprehension and persistent discomfort. Initial treatment consists of ankle-strengthening exercises and ankle braces. Many cases resolve with time. On occasion, surgical reconstruction is indicated (15).

Ankle Fractures

Etiology and Pathophysiology. Ankle fractures vary in severity from undisplaced lateral malleolus fractures to severely comminuted intraarticular injuries of the distal tibia (15). Isolated malleolar fractures involve less energy than fractures of the tibial midshaft. These injuries often occur as a result rotation of the body on a fixed foot. Distal tibial plafond injuries involving the metaphyseal region may or may not involve the joint. These injuries are associated with significant trauma in younger patients and have a potentially poor prognosis. Figure 80-29 shows several variations of ankle fractures involving the malleoli or the lower part of the fibula (37). Medial injuries are either bony (through the medial malleolus) or ligamentous (through the deltoid ligament).

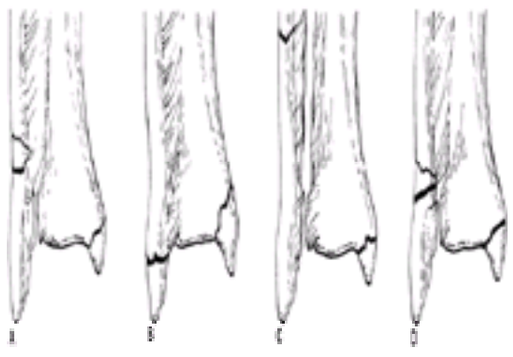


Figure 80-29. Types of ankle fractures as outlined by Launge-Hansen. This allows the treating physician to understand the nature of the injury creating the fracture pattern. **A:** Supination-eversion injury. **B:** Supination-adduction injury. **C:** Pronation-eversion fracture. **D:** Pronation-abduction fracture. (Modified from Yablon IG, Segal D. Ankle fractures. In: Evarts CW, ed. *Surgery of the musculoskeletal system.* New York: Churchill Livingstone, 1983.)

Treatment. Fractures involving the ankle joint require anatomic reduction so that late degenerative changes are prevented. For displaced fractures, open reduction internal fixation is usually required because any residual displacement or instability results in late degenerative changes.

Undisplaced fractures require cast immobilization. Operative intervention can be performed under regional anesthesia allowing postoperative pain relief. Alternatively, a general anesthetic with postoperative nerve block is used. Intraarticular distal tibial fractures are complex cases requiring up to 4 hours of surgery, and they require prolonged postoperative analgesia and elevation. In contrast, patients with isolated lateral malleolar injuries are usually discharged within 24 hours after the procedure. More detailed discussion of the management of pain caused by these fractures is contained in Chapter 43.

Ankle Arthritis

Various arthritic conditions can affect the ankle joint (see Table 80-1). Osteoarthritis is the most common degenerative condition of the ankle. Many cases occur after trauma in young patients. Spontaneous pyogenic arthritis with subsequent degeneration is uncommon and may be caused by tuberculosis. Rheumatoid arthritis is the most common generalized rheumatologic disorder affecting the ankle joints (25). Seronegative arthritis such as ankylosing spondylitis, psoriatic arthritis, and systemic lupus erythematosus may also affect the ankle joint. Gouty arthritis, pigmented villonodular synovitis, and synovial chondromatosis may affect the ankle in isolation. Hemophilic arthropathy and neuropathic arthritis are common enough to merit investigation in patients with unusual presentation. Diabetic neuroarthropathy can affect the ankle and is often associated with pain. The diabetes may as yet be undiagnosed at the time of presentation. Chapter 27 includes a more in-depth discussion of arthritis.

Osteoarthritis of the Ankle Joint

Degenerative destruction of articular cartilage is less common in the ankle than the knee and hip. Pain is the usual presenting symptom localized over the joint. Swelling is associated with the pain. The pain is mechanical in nature, aggravated by activity, and relieved by rest. On examination the joint is found to be slightly thickened from marginal bony hypertrophy and synovitis. Motion is often limited secondary to the development of osteophytes and a thickened capsule. Radiography reveals the typical features of osteoarthritis including joint space narrowing, sclerosis of the bone adjacent to the joint, hypertrophy or osteophyte formation at the joint margins, and cyst formation.

Treatment of osteoarthritis is discussed in Chapter 27.

Dislocation of the Peroneal Tendons

Etiology and Pathophysiology. Dislocation of the peroneal tendons is a condition resembling a severe lateral collateral ligament sprain (16). The injury can occur in snowboarders owing to a forceful contraction of the tendons while the ankle is dorsiflexed and everted. The peroneal tendon passes behind the lateral malleolus and is held by an overlying retinaculum. Forceful dorsiflexion with simultaneous peroneal contraction can rupture the retinaculum and dislocate the tendon.

Symptoms and Signs. The patient may present immediately after the initial injury. The tendons may be dislocated or relocated. Often, the patient presents late with a history of lateral ankle discomfort and a feeling of snapping or popping over the lateral side of the joint. Peroneal tendon subluxation occurs with the foot dorsiflexed and everted, unlike recurrent lateral collateral ligament injuries in which the foot is plantar flexed and inverted.

Diagnosis and Treatment. Occasionally, the retinaculum requires repair after acute injury. More often the tendons stabilize with cast immobilization. The pain is managed with NSAIDs alone or in combination with a mild or strong opioid. Delayed surgical repair may be indicated for recurrent subluxation.

Posterior Heel Pain

Etiology and Pathophysiology. Inflammation of the bursa under the Achilles tendon may occur with ill-fitting shoes (38). Some patients have an abnormally shaped calcaneus and have trouble finding comfortable shoes. In other cases, spontaneous degeneration of the Achilles tendon insertion occurs. Similar degenerative change may affect the Achilles tendon more proximally and is associated with tenosynovitis.

Symptoms and Signs. Exquisite pain and tenderness over the posterior aspect of the heel and under the skin are common features. This pain is aggravated by direct palpation and pressure (see Fig. 80-22B). The bursa may be visibly inflamed and is often distended with fluid. With chronic bursitis, the walls of the bursa and the overlying skin are thickened. Patients complain of pain on resisted dorsiflexion of the foot, such as getting up from a squat or climbing stairs.

Diagnosis and Treatment. Diagnosis is made by the history and physical examination, including careful evaluation of the shoe fit. Treatment begins with proper-fitting shoes with moderately low heels. The moderate to severe pain of acute bursitis is relieved by the application of ice and NSAIDs. In acute bursitis associated with severe pain, the swollen bursa is drained by needle aspiration followed by injection of a local anesthetic and steroid. Moleskin placed over the thickened skin prevents

further friction. In some cases it is necessary to cut out the back of the shoe or raise the heel inside the shoe. Surgical excision of the bursa is rarely indicated. In contrast, insertional tendonitis may require surgical debridement. Steroids should not be injected into the tendon itself because rupture may occur.

Osteochondritis Dissecans

Etiology and Pathophysiology. Osteochondritis dissecans is an osteochondral defect of traumatic or developmental origin. It involves the talar dome anterolaterally or posteromedially (15). Although a talar lesion can occur at any age, it most often affects adolescents and young adults, with a peak influence in the third decade. Although this condition occasionally develops spontaneously, trauma is often seen in association with the symptoms. Berndt and Harty (39) produced impressive experimental evidence of the traumatic origin of this condition, which they termed *transchondral talar fracture* and classified according to severity (Fig. 80-30).

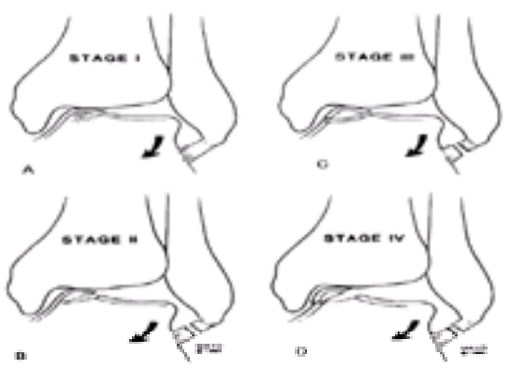


Figure 80-30. Classification of osteochondral fracture of the talus as outlined by Berndt and Harty. **A:** Stage I: A cyclic compression fracture of the medial talar dome with intact lateral ligaments. The articular cartilage remains intact while underlying trabecular bone becomes necrotic. **B:** Stage II: Incomplete fracture of the bone and cartilage with associated rupture of lateral ligaments. **C:** Stage III: Complete osteochondral fracture with an undisplaced fragment. **D:** Stage IV: Complete osteochondral fracture with displacement of fragment within the ankle joint. (Reprinted from Stauffer RN. Intra-articular ankle problems. In: Evarts CW, ed. *Surgery of the musculoskeletal system.* New York: Churchill Livingstone, 1983, with permission.)

Symptoms and Signs. Initially the patient can experience mild to moderate ankle pain, with some “catching” with motion that the patient frequently attributes to “mild ankle sprain” (15). If the bone lesion loosens, intermittent locking, chronic pain, and swelling occur.

Diagnosis. Many osteochondral talar fractures are missed at first presentation, either because radiographs of a routine ankle sprain are not taken or because the talar fracture is overlooked. Tomographs or CT of the talus demonstrates the location and extent of the lesion.

Treatment. If the condition is diagnosed early a conservative or nonsurgical approach can be considered. Patients in the later stages of the disease require surgical treatment. Curettage of the lesion removes all loose cartilage, and drilling of the subchondral bone promotes ingrowth of new fibrocartilage. Even though a large area might be affected, the new surface created by the fibrocartilage appears to hold up well. Pain is usually relieved, allowing full activities to be resumed.

PAINFUL CONDITIONS OF THE FOOT

Arthritis

The joints of the foot can be affected by pyogenic arthritis, rheumatoid arthritis, gouty arthritis, and osteoarthritis or degenerative joint disease. Although gouty arthritis is most common in the joint of the great toe, it can also occur in other joints. The two most common types of arthritis that affect the joints of the foot are considered here: degenerative arthritis and inflammatory rheumatoid arthritis.

Degenerative Arthritis

Symptoms and Signs. Degenerative arthritis causes pain localized to the involved joint persisting both day and night. The pain is aggravated by weight-bearing and worsens as the day progresses. The pain is relieved by rest. Signs include joint synovitis, decreased range of motion, deformity (including subluxation), and crepitation with motion. Radiography reveals hypertrophic changes about the articular margins such as beaking, osteophytes, sclerosis, and cysts.

Treatment. Osteoarthritis or degenerative joint disease of the foot is initially treated nonsurgically by splinting of affected joints, soft orthotics, and well-made running shoes. Alternatively, the foot can be splinted by wearing a shoe with a stiff shank and a rocker- bottom sole (see Fig. 80-27). Push-off is limited. Foam, leather, and other materials are used to make removable shoe inserts, which increase shock absorption. An NSAID can reduce inflammation and pain. The standard dose of ibuprofen is 600 mg t.i.d. with meals for 2 to 3 weeks. If the pain persists, another NSAID is worth trying. If still unsuccessful, additional NSAIDs are probably going to be ineffective. Other medical therapies are discussed elsewhere (Chapter 27, Chapter 83, and Chapter 84).

When pain persists despite conservative treatment, several operative options are available. Bony osteophytes, which decrease motion and cause impingement pain at the ankle and the MP joint of the big toe, can be excised. Diffuse involvement of those joints not responding to conservative treatment requires arthrodesis (16). If the joint is fused in a plantigrade position, pain can be relieved and function restored. Fusing joints in the foot may cause arthritic changes in adjacent joints, which must compensate for the loss of motion.

Inflammatory Arthritis

Symptoms and Signs. Inflammatory arthritis is characterized by exquisite pain localized to involved joints. It is accompanied by stiffness after sitting or rest and is aggravated by inactivity. Some relief is achieved with heat, splinting, and limitation of the range of motion. Associated signs include increased warmth, joint effusion, capsular thickening about the joint, increased laxity, and progressive subluxation, particularly about the ankle, subtalar, and MP joints. Motion is progressively lost.

Inflammatory joint disease of the foot produces joint laxity and osteoporosis. Specific deformity includes hindfoot valgus, pronation of the midfoot, supination of the forefoot, and clawing of the small toes, leading to metatarsalgia.

Treatment. In addition to medical treatment of the underlying inflammatory disease, comfort and function can be improved by accommodative shoes providing support and extra room for the toes (see Chapter 27). Surgery relieves deformities predisposing to pressure problems and can be used to restore the foot to a plantigrade position. Ankle fusion, triple arthrodeses, and midfoot fusion are all helpful, with few complications. Prominent metatarsal heads cause intractable keratoses and metatarsalgia.

Pes Cavus

In pes cavus, the longitudinal arch of the foot is accentuated (Fig. 80-31). The deformity may be congenital or secondary to a neurologic disorder. The metatarsal heads are lowered in relation to the hind part of the foot, with consequent exaggeration of the longitudinal arch. The soft tissues in the sole are abnormally short and eventually the bones themselves alter their shape, perpetuating the deformity. Clawing of the toes, hyperextended at the MP joints and flexed at IP joints, is often seen. The toes become functionless and cannot bear their share of weight-bearing. The metatarsal heads have increased load because of distal migration of the plantar pad, loss of contact of the toes on the ground, and pressure on the IP joints of the toes from the shoe forcing the metatarsal heads down.

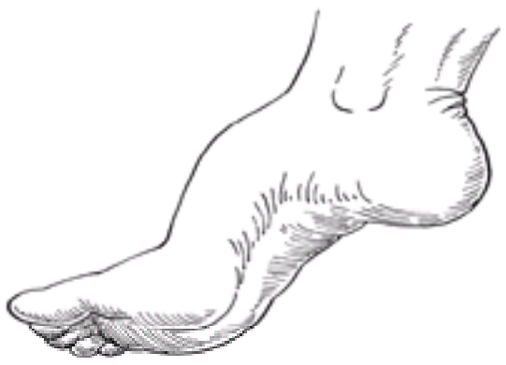


Figure 80-31. Pes cavus: The high arched foot is rigid. This limits shock absorption so that weight-bearing forces become concentrated on the metatarsal heads and the heel. Underlying neurologic disease should be considered in such patients.

In many patients, specific treatment is not required. Mild symptoms can often be relieved using a sponge rubber pad beneath the metatarsal heads to distribute load. A wide–toe box shoe will prevent rubbing of the toes and prevent overload of the metatarsal heads. If symptoms are severe, surgery is required.

Pain in the Hindfoot

Plantar Fasciitis

Etiology and Pathophysiology. Pain under the heel is often caused by a plantar fasciitis. Plantar fasciitis is secondary to pain at the insertion of the plantar fascia into the calcaneus. The pain is increased by weight-bearing and relieved by rest. Typically, the pain is worse after the first few steps in the morning or after rest (16). The condition can be part of a more widespread inflammatory condition, such as Reiter's disease (25). It is common in occupations entailing excessive standing or walking, especially when the individual is unaccustomed to such activity. It is more common in pronated feet. Men are more susceptible than are women. A bony prominence or spur can develop at the attachment of the plantar fascia to the calcaneus, although this is often found on radiographs of normal feet.

Symptoms and Signs. Moderate to severe pain and tenderness beneath the anterior portion of the heel, often radiating into the sole of the foot, is the presenting complaint. Although trauma may be the cause, in most cases the onset is insidious. Examination reveals a point of exquisite deep tenderness at the anteromedial area of the calcaneus, the point of attachment of the plantar fascia (see Fig. 80-22C).

Diagnosis and Treatment. Diagnosis is made through the history and physical examination. Radiographs are often normal. Other conditions or theories as to the etiology of plantar fasciitis include infracalcaneal bursitis under the fascial attachment, atraumatic periostitis, and entrapment of the calcaneal branch of the tibial nerve.

Initial treatment consists of preventing hyperpronation by well-constructed shoes with a medial arch support. Alternatively, a sponge rubber cushion with its center removed can be used under the heel. Pain is usually effectively relieved by NSAIDs. Ice and stretching exercises will also benefit the patient. Night splints are used in more resistant cases or when night pain is a significant feature. If the pain is persistent and severe, injection of a mixture of a local anesthetic and steroid can be considered. The injection can be made through the pedal pad or from the medial or lateral approach into the site of maximum tenderness. No more than three injections are used, because injection of steroids can cause secondary rupture of the plantar fascia, complicated often by flatfoot deformity and increased lateral foot pain due to overload of the calcaneo cuboid joint.

If these treatments are ineffective, a walking cast is necessary for 6 weeks. Release of the plantar fascia is sometimes necessary for chronic cases, but generally this condition responds to nonsurgical treatment (40).

Tarsal Coalition

Pathophysiology and Symptoms and Signs. Congenital fibrous union is a fusion between the bones of the hindfoot. In teenagers, the coalition can become painful as the coalition ossifies and forms a nonunion. If the coalition completely ossifies or if it never ossifies, it will not be painful. Later, the coalition can lead to arthritis of the surrounding joints. Overall, tarsal coalition is a relatively rare cause of subtalar pain.

Diagnosis and Treatment. History of pain and lack of subtalar motion in a young patient is diagnostic. Treatment consists of diminishing subtalar motion by the use of supportive shoes and a medial arch insert to provide increased shock absorption. This treatment alone may allow the partial fusion to unite like a fracture. Most patients usually respond to these measures (41,42). Surgery involves fusing the area of fibrous coalition or taking down the coalition when the joint surfaces are compatible with normal movement.

Heel Pad Deficiency

Etiology and Pathophysiology

Generalized pain over the entire calcaneal fat pad (painful heel pad) occurs when the heel pad is deficient or subjected to unusual stress. The heel pad is made of fat and elastic fibrous tissue contained within fibrous septa. Normally this tissue acts as a shock absorber. Its elasticity decreases with age, causing increased contact pressure and pain.

Symptoms and Signs

The pain of a deficient heel pad is localized over the entire calcaneal pad. If untreated, secondary scar formation and calcification will result. Acute stress on the pad can rupture or strain the compartments and cause temporary loss of compressibility and cause symptoms.

Diagnosis and Treatment

Diagnosis is made through the history, physical examination, and results of imaging (see Table 80-5). The pain is effectively controlled by NSAIDs; if severe, however, infiltration of 5 mL of a dilute solution of a long-acting local anesthetic (e.g., 0.25% bupivacaine) relieves pain for 8 to 10 hours. Steroids should not be injected because they will result in further atrophy of the pad. Definitive treatment of the condition involves addition of a shock-absorbing insert to the shoe and ensuring that the heel is supported by a firm center.

Tarsal Tunnel Syndrome

Etiology and Pathophysiology

Entrapment of the medial and lateral plantar nerves within the tarsal tunnel can cause pain, paresthesia, and weakness of the intrinsic flexors of the foot (27). The posterior tibial nerve passes deep to soleus and ends by dividing into the medial and lateral plantar deep to the flexor retinaculum behind the medial malleolus. The flexor retinaculum is a strong fibrous band extending from the medial malleolus to the calcaneus. It forms the roof of the tarsal tunnel, the walls being formed by the posterior margin of the tibia and the lateral side of the calcaneus and talus. The tibial nerve can become trapped within the tunnel. Any space-occupying lesion, such as tumor or synovial hypertrophy, can compress the nerve within the tunnel. Subsequent edema and scar formation will limit blood supply to the nerve and inhibit the full elongation (uncoiling) of the nerve between joint movements. Stretching of the nerve by flatfoot deformity can cause tension within the nerve at the tarsal tunnel. In

late cases, axonal or wallerian degeneration may ensue (see Chapter 19 and Chapter 77 for details).

Symptoms and Signs

The pain is nocturnal and paresthetic or burning in nature and may be associated with numbness (27). The symptoms can be felt when the patient is standing or reclining. If both plantar nerves are involved, the symptoms extend over the plantar surface of the foot and the dorsum of the distal part of the toes. Sometimes the medial calcaneal branch of the tibia becomes entrapped as it perforates the flexor retinaculum. Numbness is distributed to the heel and medial side of the sole of the foot. Tenderness can usually be elicited over the nerve behind the medial malleolus, and a positive Tinel's sign can be elicited by tapping the nerve at that site.

Diagnosis and Treatment

Entrapment is a diagnostic challenge. Because the condition can coexist with peripheral neuropathies it is necessary to decide whether the pain and other symptoms and signs are caused by the neuropathy itself or by tarsal tunnel compression. Electromyographic and nerve conduction velocity studies can be helpful.

An attempt should be made to treat the condition conservatively. Injection of local anesthetic and steroids into the tarsal tunnel can be helpful, as can NSAIDs. Transcutaneous electrical nerve stimulation should also be tried. If the patient experiences lancinating pain, tricyclic antidepressants or anticonvulsants should be tried (see Chapter 85 and Chapter 86).

If the symptoms persist after a few weeks of conservative management, surgical decompression is justified. In severe flatfoot, the symptoms may more relate to stretching of the nerve around the medial malleolus rather than compression itself. In this scenario, augmentation of the arch may be more appropriate than nerve release. The proximal ridge of the abductor hallucis, often a site of compression, is divided to release the tunnel. Varicose veins and ganglions are frequent sources of compression within the tunnel. These patients should be checked to see that their foot is not hyperpronating, because this increases tension on the plantar nerves and aggravates symptoms.

Painful Conditions of the Midfoot

Medial Arch Strain

Medial arch strain can occur in normal feet from prolonged standing on hard surfaces, particularly when the foot is not well supported. Treatment consists of activity modification and wearing of shoes supporting the heel and arch and providing shock absorption. Flatfoot should be supported by arch supports or orthotics to decrease the medial arch strain.

Lisfranc's Joint Instability

Etiology and Symptoms and Signs. A twisting midfoot injury, such as a severe inversion or a forefoot plantar flexion, can lead to injury of Lisfranc's (metatarsal cuneiform) joint. Excessive pain and swelling in the midfoot suggest the diagnosis. Palpation reveals tenderness of the affected joints.

Diagnosis. The history and findings of the physical examination lead to the diagnosis. Whereas Lisfranc's fractures are detectable by radiography, joint subluxations and sprains are difficult to demonstrate by this method. Stress radiographs taken with the foot plantar flexed and inverted may be required.

Treatment. When recognized early, support of the foot either by a cast or a well-fitted shoe promotes healing of the ligaments. If seen 3 to 4 months later, a chronic condition can have developed that might require selective fusion of the painful joints, particularly the metatarsal cuneiform joints. Overweight patients usually have the poorest results, particularly with conservative treatment (15).

Posterior Tibial Tendon Insufficiency

Etiology and Pathophysiology. The posterior tibial tendon is the main dynamic support of the medial arch. If the tendon is disrupted such as occurs with fracture of an accessory navicular, or injured, the arch eventually collapses. A tight heel cord aggravates the situation by holding the heel in valgus when sufficient subtalar motion exists. The tendon can be torn, sprained, or stretched with eversion-type injuries (32). Over time, the foot assumes a pronated posture that is asymmetric to the opposite foot. The patient cannot rise up on that foot or invert the heel. Rheumatoid arthritis can lead to silent rupture.

Symptoms and Signs. Posterior tibial tendon insufficiency causes progressive flatfoot deformity with overload of the midfoot. The patient experiences persistent dull aching pain associated with tenderness, and occasionally swelling is present. Eventually the patient experiences difficulty in standing and walking.

Diagnosis and Treatment. Diagnosis is made through the history and physical examination and by the results of special tests (see Table 80-5), including ultrasound and standing plain radiography. Early treatment consists of wearing supportive shoes to correct and control pronation. Later, when the condition has been established and collapse has already started, augmentation of the posterior tibial tendon helps to restore dynamic support of the arch. As a flatfoot results in posterior tibial tendon overload some form of augmentation of the arch may be required to reduce the stress on the repaired tendon. Procedures such as calcaneal osteotomy, lateral column lengthening, talonavicular fusion, or subtalar fusion may be performed. Augmentation or repair is accomplished using the flexor digitorum longus or extensor hallucis longus. In cases of severe deformity or when degenerative changes have occurred in the midfoot, a triple arthrodesis may be required.

Ganglion

Etiology and Symptoms and Signs. A ganglion is a mucus-filled cyst that usually arises from a joint or tendon sheath. The condition is particularly uncomfortable in the foot because of shoe pressure. Motion of the foot during weight-bearing tends to pump fluid into the ganglion. The condition causes mild tenderness on palpation that is aggravated by pressure and ambulating.

Treatment. Painless ganglions can be left alone. Nonsurgical treatment is often unsuccessful for painful ganglions. Aspiration and installation of steroids sometimes help, but in Lippert's experience (22) these are rarely successful. Definitive treatment requires excision of the ganglion down to its origin. The neck of the ganglion can be tied off or excised completely so that the ball valve effect is eliminated. Patients should be protected in a walking cast for 10 to 14 days to allow the soft tissues to heal and the source of the ganglion to be obliterated by scar.

Painful Disorders of the Forefoot

Stress Fracture

Sedentary individuals and those who begin a new activity that requires running or prolonged walking may develop a stress fracture (march fracture) in the neck of the metatarsal bones. Although any bone of the foot can be involved, stress fracture of the second metatarsal occurs as a consequence of running or dancing on hard surfaces. Sometimes bone scans are necessary for the diagnosis, although radiographic changes are usually evident approximately 10 to 14 days after fracture. Treatment consists of the use of a walking cast until healing occurs, which may require 4 to 6 weeks. If the cast is removed too soon, the stress fracture tends to become chronic and more difficult to treat. In some patients, stress fractures may occur because of abnormal loading of the forefoot. In these cases, when conservative treatment fails, procedures to reconstruct the forefoot may be considered.

Metatarsalgia. Metatarsalgia refers to pain under the heads of the metatarsals owing to excessive load. Metatarsalgia is common in rheumatoid arthritis. In this case, excessive mobility in the medial column leads to loss of support of the first ray. Dislocation of the MP joints displaces the plantar pad distally, prevents the toes from reaching the ground, and causes the toe box of the shoe to increase pressure on the metatarsal heads. Usually, the first metatarsal carries two-sixths of the body weight and the others one-sixth each (7). If the first metatarsal fails to carry weight, the second metatarsal carries three-sixths, or one-half, of the body weight. Excessive load leads to stress fracture, dislocation of the plantar plate, and claw toe deformity.

Etiology and Pathophysiology. In a pronated or splayed foot, the balance of weight-bearing is upset. The transverse arch is depressed, and greater weight is borne on

the second, third, and fourth metatarsal heads. The interosseous ligaments that support the arch are stretched, permitting the forefoot to broaden and splay out (7).

The condition is more common in cavus and rheumatoid feet, in which claw toes have pushed the metatarsal heads downward and displaced the protective padding distally. Women who wear high-heeled shoes are more prone to metatarsalgia as a result of the position of the foot, which concentrates the weight-bearing forces on the metatarsal heads. Congenital traits, such as a long first metatarsal or hypermobile first ray, may increase the risk of metatarsalgia.

Symptoms and Signs. Initially patients experience tenderness of the metatarsal head, which has been described as “walking with a pebble in the shoe.” A callus may be found under the second or third metatarsal head, which itself is painful and causes further irritation by increasing the weight-bearing on the metatarsal head. The tenderness is aggravated when the examiner squeezes the metatarsal head between the thumb and index finger. The examiner should compress each metatarsal head individually and must not compress the tissues between the heads (ligaments and interdigital nerves), because this could cause pain and tenderness and confuse the diagnosis.

In some cases, excessive load occurs under the first metatarsal head. This can occur in patients with a cavus foot or after fracture and malunion of a metatarsal. Excessive load may occur if the second metatarsal is too dorsiflexed, or the first is too plantarflexed.

Diagnosis and Treatment. The diagnosis is made through the history and careful physical examination and by the results of plain radiography and bone scanning (see Table 80-5). Most individuals obtain relief with the use of a metatarsal pad placed in the shoe or as a removable insert (see Fig. 80-26). These devices redistribute the weight-bearing forces away from the metatarsal heads into the arch region. Occasionally, patients present with metatarsalgia under one or two heads secondary to a previous fracture or to some other structural abnormality. Selective padding is usually effective. When an intractable keratosis occurs under one of the metatarsal heads and does not respond to padding, shaving of the callus may effect relief. If these measures do not work, pressure can be reduced by performing an osteotomy of the metatarsal shaft or by excising the condyles of the metatarsal head. The goal of surgery is to equalize weight-bearing under the metatarsal heads. Failure to accomplish this results in a painful transfer keratosis (16).

Painful Conditions of the Great Toe

Hallux Valgus

Etiology and Pathophysiology. Hallux valgus describes the lateral deviation of the great toe at the MP joint. Patients often notice the medial prominence of the first metatarsal head, known as a *bunion*. Hallux valgus is more common in women, especially those past middle age. Although the underlying cause can be congenital (metatarsus primus varus), ill-fitting shoes with a narrow toe may cause progression (43).

Lateral deviation of the big toe is the most obvious feature of the deformity. On standing plain radiographs, the gap between the head of the first and second metatarsals is unduly wide. Secondary and associated changes are numerous. These include the development of a bursa over the medial aspect of the great toe, which can be painful. Some patients also develop secondary arthritic changes at the MP joint (Fig. 80-32). The sesamoids are laterally displaced from under the metatarsal heads and can cause painful sesamoiditis. In other patients, second metatarsal overload and second metatarsalgia may be the primary complaint, and secondary claw toe deformity may develop. Other patients have symptoms more related to the associated flatfoot deformity causing arch and lateral column pain and posterior tibial tendonitis.

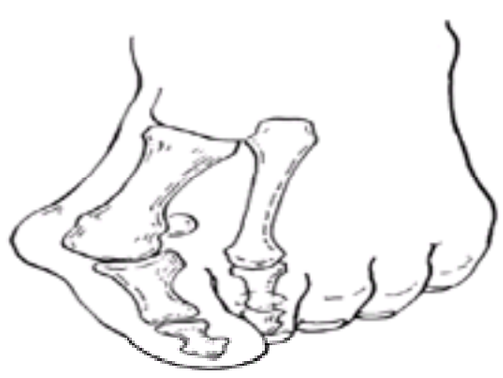


Figure 80-32. Hallux valgus. See text for details.

Symptoms and Signs. Early symptoms may arise from tenderness over the bunion from pressure against the shoe, and the patient encounters difficulty in obtaining comfortable footwear. Additional symptoms later arise from osteoarthritis of the MP joint and from flattening of the transverse arch (anterior flatfoot), which is a common associated deformity. On examination, the deformity is obvious and the skin over the prominent joint is hard, red, and tender. In late stages, the forefoot is often flat and splayed and the toes can be severely clawed.

Treatment. Nonsurgical treatment consists of wearing extra-wide shoes and arch supports to prevent pronation. Walking with the foot pronated causes an increased valgus stress on the toe, stretching out the medial capsule. Surgery is performed when nonsurgical measures fail. Surgery is tailored to address the symptoms. Subluxed painful sesamoids with a low intermetatarsal angle can be addressed by a distal osteotomy. The deformity must be flexible, because a distal soft tissue release cannot be performed during a distal osteotomy procedure as the blood supply to the bone will be disrupted. More severe deformities can be addressed by a proximal metatarsal osteotomy or first tarsometatarsal fusion. Occasionally, a first MP joint fusion is required. Contractures around the metatarsal head must be released to reposition the first metatarsal head close to its neighbor. Treatment is usually successful in relieving the pain and deformity provided that the first metatarsal is not excessively shortened or elevated. Some recurrence of the deformity is typical but is not associated with recurrence of pain.

Hallux Rigidus

Etiology and Pathophysiology. Hallux rigidus is osteoarthritis of the first MP joint characterized by lack of joint motion and pain, particularly at push-off (Fig. 80-33). The cause may be multifactorial and include congenital factors, improper shoes (especially those causing hyperextension of the joint), abnormal gait, obesity, and trauma as contributing factors (44).

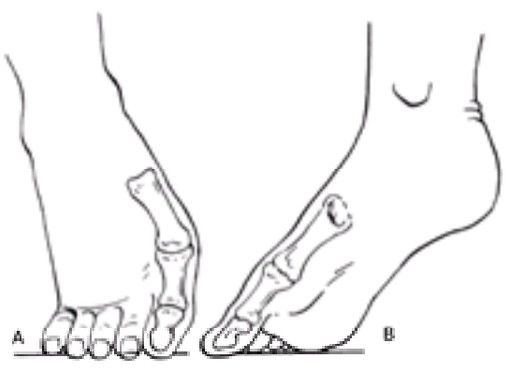


Figure 80-33. Hallux rigidus. **A:** Anterior view. **B:** Medial view. Arthritis of the metatarsophalangeal joint reduces motion, especially in dorsiflexion. Push-off is painful.

Symptoms and Signs. Almost all patients present with symptoms of pain and restriction of motion in the first MP joint. These are usually of gradual onset and patients often give a history that indicates no obvious cause (30). During the initial phase, the motion most severely restricted is dorsiflexion while plantar flexion can be unaffected. Later, more global restriction of motion occurs. Palpation usually elicits considerable tenderness, and any forceful motion, especially dorsiflexion, causes pain. These patients have a particularly difficult time finding any shoe that allows more comfortable walking.

Diagnosis and Treatment. The diagnosis is made through the history and physical and radiographic examination (see Table 80-5). Nonsurgical treatment consists of splinting the joint through the use of a stiff-soled shoe with a rocker-bottom sole (see Fig. 80-27). Frequently, these measures and the use of NSAIDs are all that is required. Operative treatment consists of improving the range of motion by excising osteophytes and freeing up the sesamoid complex. At least 30 to 40 degrees of dorsiflexion at surgery are required for pain relief. Advanced changes in the joint require MP fusion with the toe in 20 to 30 degrees of dorsiflexion. The best position is determined by having patients stand in their shoes and then taking a lateral radiograph. Silastic spacers are no longer indicated.

Hypermobility of the First Ray

Hypermobility of the first ray leads to diminished weight-bearing on the first ray, resulting in pain and intractable keratosis under the head of the second metatarsal (45). Treatment consists of transferring more weight to the first ray. This can be accomplished by having the patient use a shoe insert that is built up selectively under the first metatarsal head. In some cases, fusing the first MP joint is required to increase the weight-bearing capability of the first ray.

Intractable Keratosis

Intractable keratosis refers to hard calluses located under one or more of the metatarsal heads and often associated with aching pain. These are a skin response to excessive weight-bearing on the metatarsal heads. Despite conscientious attempts of the patient to reduce the thickness of these lesions by paring and grinding, daily weight-bearing forces encourage the formation of deeply penetrating indurated lesions. When local measures fail, the pressure on the metatarsal head must be reduced surgically. These options are described above; care must be taken to avoid uneven weight-bearing forces that could transfer the keratoses to adjacent metatarsal heads (46).

Sesamoiditis

Sesamoiditis, which must be distinguished from metatarsalgia, is an inflammation involving the sesamoid–metatarsal head complex. The presenting picture is one of localized swelling and pain aggravated by dorsiflexion of the MP joint. Sesamoiditis can be confused with first metatarsal overload, particularly in patients with cavus feet.

Treatment consists of eliminating weight from the area until the inflammatory reaction subsides. A walking cast is often necessary in addition to the use of NSAIDs. Because sesamoids are weight-bearing bones, they should be preserved unless all other treatment options have been unsuccessful.

Gout

Acute gouty arthritis of the first MP joint causes severe pain. Antiinflammatories help to control the overall reaction, and splinting the toe in a bunion shoe allows the patient to walk. The diagnosis is established by aspirating the joint to test for uric acid crystals and by determining the serum uric acid level. The condition usually responds to treatment measures within 24 hours. Surgery is rarely indicated unless advanced degenerative changes have taken place, in which case the treatment for hallux rigidus applies.

Painful Disorders of the Small Toes

Interdigital Neuroma

Interdigital neuroma, also known as *Morton's neuroma* and *Morton's metatarsalgia*, is characterized typically by metatarsal pain combined with radiating and lancinating pain in the third and fourth toes (47). Morton's neuroma can be hard to distinguish from metatarsalgia.

Etiology and Pathophysiology. The pain and characteristic neurologic symptoms and signs are caused by the neuroma, which is a fibrous thickening of the digital nerve of the cleft between the third and fourth metatarsals just proximal to where the nerve divides into its terminal digital branches. The neuroma takes the form of a fusiform swelling, usually approximately 1 cm long, that surrounds the nerve as it lies in the space between the heads of the third and fourth metatarsals. The cause of the fibrous thickening is uncertain.

Symptoms and Signs. This condition involves middle-aged women more often than younger women and men. The condition is characterized by pain in the forefoot on standing or walking. The pain starts in the metatarsal region and radiates forward into the contiguous side of the second and third or third and fourth toes or to the fourth toe alone. Like neuralgia in general, the pain is sharp, burning, and piercing in character and is often associated with bouts of lancinating pain. Patients often state that they can relieve the pain by taking the shoe off and squeezing or manipulating the forefoot (47). Moving the metatarsal head from side to side and applying pressure to the sole of the foot between the third and fourth metatarsal heads or second and third metatarsal heads elicits pain and is often associated with a clicking sound.

Diagnosis and Treatment. Interdigital neuroma is often diagnosed but inadequately resected. Patients should be followed to ensure that the symptoms are consistent and also that any conservative measures used are not related to discomfort.

Conservative measures include wearing shoes with extra-wide toe boxes, pads between the metatarsal heads to separate the involved toes, and metatarsal pads to relieve pressure on the metatarsal heads. Steroids injected into the web space are sometimes helpful, but injury to the affected digital nerve from the injection can aggravate the condition. If the patient does not respond to nonsurgical measures, surgical excision may be performed. Failure rate of surgery is approximately 20% and may relate to inaccurate diagnosis (16,47).

Hammertoes and Claw Toes

Hammertoes and claw toes are deformities caused by a combination of neurologic imbalance, anatomic predisposition, activity level, and shoe wear. They cause painful corns and callosities and interfere with their shared weight-bearing distribution on the metatarsal heads (Fig. 80-34). Often, the pain is localized in the metatarsal head region on the plantar aspect. Metatarsal overload and plantar plate rupture may be the cause of the deformity. Distal migration of the plantar pad is often seen, exposing the metatarsal head to greater peak forces. The shoe forces the toe and metatarsal head down, increasing the metatarsalgia. Conservative treatment includes the use of metatarsal pads and shoes with extra depth boxes to relieve pressure toe points. An intractable keratosis may develop underneath the metatarsal head of the involved toe.

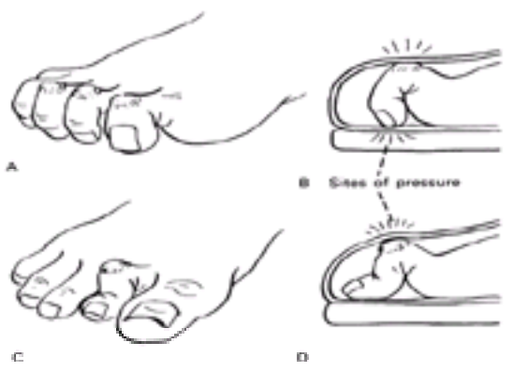


Figure 80-34. Typical small toe deformities. Claw toe **(A,B)** and hammertoe **(C,D)** deformities often cause corns and calluses with standard footwear. Extra deep shoes avoid these problems.

If conservative treatment fails, surgery may benefit the patient. The toe is straightened and held reduced. This may require flexor to extensor tendon transfer, IP joint excisions or IP joint fusion, extensor tendon release, and for dislocated toes, MP joint exploration. The toe is stabilized with an intramedullary pin for approximately 3 weeks while tissue healing takes place. The toe is straight, and the calluses resolve. The plantar pad is reduced under the metatarsal head, reducing the metatarsalgia.

Soft Corns

Soft corns occur between toes. *Soft* refers to a tendency to macerate in the moist interdigital environment. Soft corns are a result of poor foot hygiene and should be managed conservatively.

Hard Corns

Hard corns occur over the IP joints of hammertoes and claw toes, or on the dorsum of the fifth toe. The underlying deformity is treated.

Overlapping Toes

Overlapping toes cause intractable corns, either from floor contact or impingement against the shoe. Whereas conservative measures described for hammertoes and claw toes should be considered, this condition often requires surgical correction of the deformity. The approach is the same as that used for hammertoes and claw toes.

Ingrown Toenails

An ingrown toenail can be exquisitely painful, particularly when aggravated by pressure from the shoe (Fig. 80-35). Causes include improper nail trimming (cutting the nails back at the nail margins), or abnormal nail growth. Preventive measures consist of proper nail trimming and wearing shoes with an adequate toe box.

Figure 80-35. Ingrown toenail is often caused by improper nail cutting techniques or by wearing ill-fitting footwear that creates pressure against the lateral nail fold producing exquisite pain and tenderness.

Later stages may require cotton packing underneath the nail. This pushes the nail fold away and prevents the tip of the nail from irritating the nail fold. Once chronic, surgery may be required. A simple medial or lateral border nail plate resection decompresses the area of inflammation and allows the tissues to heal. Often a new nail grows in without problems in the absence of nail bed deformity. In some cases, a complete nail bed excision and matrixectomy are required (48).

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CHAPTER 81

Nonspecific Treatment Effects

Judith A. Turner

An understanding of the role of nonspecific effects in patient-provider interactions can help clinicians improve the outcomes and satisfaction of their patients. This chapter summarizes the findings from studies of placebo or nonspecific treatment effects that are relevant for clinicians who treat patients with pain problems. Knowledge of this literature may also help clinicians to evaluate critically the literature on various pain treatments to make informed decisions in treatment planning.

A number of factors may influence patient outcomes after any treatment for pain (Table 81-1). These factors fall into three general categories. The first category includes *specific effects of the treatment*, attributable solely to the characteristic content or process of the therapy. The second category includes *natural history and regression to the mean*. Most acute and some chronic pain problems improve or even resolve completely, regardless of treatment. Headache and low back pain are two examples of conditions that for many individuals recur episodically with periods of no or mild pain between episodes. Patients with chronic conditions typically have fluctuating symptoms and seek medical care (and enroll in research studies) when symptoms are at their worst. Thus, the next change is likely to be an improvement. When a group of patients with extreme scores on symptom measures is selected for study or treatment, over time the average scores in the group will decrease due to fluctuations toward more typical values. This tendency is known as *regression to the mean* (1). Apparent improvement may also reflect measurement error or random variation in patient symptoms over time (1). Clinicians and patients alike may mistakenly attribute a decrease in a patient's symptoms to a treatment when, in fact, the change is simply a fluctuation in a cycle of waxing and waning symptoms. The third category includes *nonspecific effects of treatment*—that is, change due to factors not specific to the particular drug or therapy. These include physician attention, interest, and concern in a healing setting; patient and physician expectations of treatment effects; the reputation, expense, and impressiveness of the treatment; and characteristics of the setting that influence patients to report improvement. The term *placebo effect* is often used synonymously with *nonspecific effects*.

1. Specific treatment effects
2. Natural history, regression to the mean
3. Nonspecific treatment effects (placebo effects)

TABLE 81-1. Factors that influence patient outcomes

The word *placebo* was first used in the English language in the fourteenth century as the name given to vespers sung for the dead (2). The first line of these vespers was the Latin version of a psalm (translated, “I shall walk before the Lord in the land of the living”). Apparently because of a translation error, “I shall walk” became *placebo* (“I shall please”) (2). Because these vespers were sung for a substantial fee, the term “placebo” had a negative connotation. The word appeared in Hooper's *Medical Dictionary* in 1811, defined as “any medicine adopted to please rather than to benefit the patient” (3). In the past 30 years, many definitions of placebo have been advanced. A useful definition was proposed by Brody (4): an intervention designed to simulate medical therapy but that is not believed to be a specific therapy for the target condition, or an inefficacious treatment believed efficacious at the time of use. Brody (4) further defines *placebo effect* as a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiologic property. Thus, a placebo effect can occur with any treatment, not just with a placebo. A *placebo response*, in contrast, refers to any change in a patient's behavior or condition after the administration of a placebo (5). These distinctions are not always made in the literature, however.

The following sections summarize what is currently known concerning placebo response rates, the pharmacologic and other characteristics of placebo responses (including magnitude and duration), nocebo effects, factors that influence nonspecific effects, and explanations that have been proposed for placebo effects. Finally, the implications of this literature for researchers and clinicians are discussed.

PLACEBO RESPONSE RATES

A common misconception is that approximately one-third of patients will show a placebo response in any clinical trial. This figure is based on Beecher's (6) classic article, a review of 15 studies (seven of which were Beecher's) of patients with a variety of conditions (postoperative pain, cough, angina pectoris, headache, drug-induced mood changes, seasickness, anxiety and tension, and the common cold). Beecher (6) reported that symptoms were “satisfactorily relieved” by a placebo in 35% of patients on average across these studies. However, it is important to note that the placebo response rate ranged from 15% to 58% across the studies. Since Beecher's review, placebo response rates have been observed to vary widely, often greatly exceeding 35%. Since Beecher's review, placebo responses have been observed in other settings and for other conditions [e.g., acute postoperative pain (7), peptic ulcers (8), angina pectoris (9,10), temporomandibular disorders (11)]. Roberts et al. (12) reviewed uncontrolled studies of medical and surgical treatments that were originally believed efficacious but later abandoned because they were found to be no better than placebo. On average, 70% of 7,000 patients included in the studies reviewed had excellent or good outcomes (12). Some studies reported success rates of 100%. Another review of 31 randomized trials found that, on average, 48% of patients showed healing of peptic ulcers, based on endoscopy, after treatment with only a placebo (8). In some of these studies, the rate was as high as 90%.

Even patients with a long history of chronic pain show clinically and statistically significant improvement with placebo. For example, Deyo et al. (13,14) found that, despite the chronicity of their pain (average duration of 4 years), back pain patients' scores on measures of pain severity, pain frequency, and functional status improved on average 20% to 40% after sham transcutaneous electrical nerve stimulation plus hot packs.

NONSPECIFIC EFFECTS OF SURGERY

Beecher (15) emphasized that surgery could evoke a placebo effect and urged caution in interpreting the results of new operations. Two classic studies (9,10) conducted in the 1950s demonstrated substantial and sustained improvement in angina pectoris after sham surgery (skin incision alone). These double-blind randomized trials compared a procedure believed at the time to help angina pectoris (internal mammary artery ligation) with skin incision alone (with vessel exposure but no ligation). In one study, 6 months after the operation, 63% of the ligated patients and 56% of the patients who had skin incision only were substantially improved (9). In the other study, all patients who had skin incision only reported greater than 50% improvement during the subsequent year (10). Benefits were not limited to decreased pain; they also included reduction in nitroglycerin use and increased exercise tolerance.

Improvement in pain after spine surgery may be due in part to some combination of natural history and nonspecific effects. A review of long-term outcomes for 2,504 patients undergoing diskectomies for lumbar disk disease found that, among patients who had no disk herniation (negative surgical exploration), 37% had complete relief of sciatica and 43% had complete relief of back pain (16). Given the lack of known therapeutic effects of surgical exploration of the spine, these outcomes appear to be due to nonspecific effects and/or natural history. The success rates that have been reported for operations for painful lumbar spine disorders are similar to success rates reported for discredited therapies for other conditions. Across 74 studies of surgery for lumbar spinal stenosis, an average of 64% of patients had good or excellent outcomes at long-term follow-ups (17). Similarly, across 47 studies of lumbar spinal fusion, 68% of patients had good or excellent results at long-term follow-ups (18). The lack of randomized controlled trials makes it impossible to draw conclusions concerning the extent to which the outcomes of these operations are due to specific surgery effects, nonspecific effects, or natural history. The weak association between radiologic findings and symptoms (19,20,21,22,23 and 24), and between technical success of surgery (e.g., solid fusion) and symptom improvement (25,26), also suggests the possibility that improvement after back surgery may to some extent be attributable to factors such as natural history and patients' and surgeons' expectations of improvement.

In sum, rates of good patient outcomes after medical and surgical treatments that have no specific therapeutic effects for painful conditions vary considerably across studies but, on average, are strikingly high. This makes obvious the need for studies that compare the short- and long-term clinical outcomes of treatments and procedures believed to relieve pain with those of placebo or control therapies. Although case series reports may provide some useful information, such as rates of specific complications, they cannot provide information concerning whether the outcomes are due to natural history, specific therapy effects, or nonspecific effects.

CHARACTERISTICS OF PLACEBO RESPONSES

Placebos have been demonstrated to have in common with active medications time-effect curves and peak effects, cumulative effects (greater effects with repeated administrations), and carryover effects after cessation of treatment (27). Furthermore, when a placebo is administered to people with pain after they have received an analgesic drug, the pain-relieving effect of the placebo is proportional to that of the drug that preceded it (28). Dose-response effects have also been demonstrated—for example, one study found that two placebo capsules produced more pronounced effects than one (29).

Nonspecific effects of treatments are not always positive; adverse effects have been demonstrated to occur after the administration of inactive pills or procedures. It is well known that placebos are associated with side effects. The most common are drowsiness, headaches, nervousness, insomnia, nausea, and constipation (30). A review of 109 double-blind drug trials found that, overall, 19% of healthy volunteers reported adverse events during placebo administration (31). Complaints were most frequent after repeated dosing and in elderly subjects. The type of side effect varied according to the therapeutic drug it was being compared with in the drug trial. Sham treatments can also worsen preexisting symptoms. For example, in a double-blind study of a magnetic device purported to relieve pain, 13 of 58 patients with pain discontinued treatment after one or two treatments because their pain was worse (32). Six months later, three of these patients believed the treatment made their pain permanently worse.

The duration of response to placebos has not been well studied. Fedele et al. (33) found a gradual decrease in the effectiveness of placebo treatment of dysmenorrhea over three consecutive menstrual cycles. However, patients with angina pectoris in the placebo arm of a double-blind randomized trial had a 77% reduction in anginal attacks after 6 months on placebo (34), and some patients with rheumatoid arthritis who were given placebos reported moderate to marked improvement for as long as 20 months (35). Patients with painful diabetic neuropathy reported a decrease in pain intensity over the first 3 weeks they received a placebo but then showed a partial return toward baseline levels during weeks 4 to 6 (36). In one of the studies of sham surgery for angina pectoris, clinically significant improvement in angina symptoms was maintained for up to 1 year (10). Of course, the extent to which these responses reflected natural history/regression to the mean versus placebo effects cannot be determined. It is likely that the magnitude and duration of placebo responses will vary with varying characteristics of patients, conditions, treatments, providers, measures, and settings. These are discussed in later sections of this chapter.

NOCEBO EFFECTS

The nocebo effect has been defined as the causation of sickness (or death) by expectations of sickness (or death) and by associated emotional states (37). For example, pain can be produced in normal subjects by the power of suggestion. Headaches were reported by 70% of college students told that a (nonexistent) electric current was passing through their heads (38). This study was later replicated by a different group of researchers, who also found that the subjects' pain ratings increased when they believed the electrical current had been increased (39). Hahn (37) distinguishes nocebo effects from placebo side effects, which occur when expectations of healing produce symptoms. Hahn (37) also points out that the act of giving a patient a diagnosis may have a placebo or a nocebo effect, and that failure to give the patient a diagnosis may have a nocebo effect.

One general practitioner randomly assigned his patients with symptoms but no abnormal signs, in whom no definite diagnosis could be made, to a positive or a negative encounter with him (40). In the positive encounter, patients were given a diagnosis and told they would be better in a few days. In the negative encounter, the doctor told patients he was not certain what was the matter with them. Two weeks later, 64% of the positive encounter group, but only 39% of the negative encounter group, reported that they had gotten better (a statistically significant difference). The author speculated that these minor illnesses would be expected to resolve spontaneously by 2 weeks in the majority of patients and that the 61% nonimprovement rate in the negative encounter group reflected adverse effects of the encounter. Another study also suggests that diagnostic testing may have a placebo effect and/or that not testing may have a nocebo effect. Patients thought to have noncardiac chest pain of unclear etiology were assigned randomly to diagnostic testing or no testing (41). Patients not tested were more than twice as likely to report short-term disability. Other examples of nocebo effects are presented in the next section of this chapter.

FACTORS THAT INFLUENCE NONSPECIFIC EFFECTS

Patient Factors

No personality, demographic, or other patient characteristics have been shown consistently to predict placebo responses (42). Specifically, placebo effects have not been found to relate consistently to age, gender, ethnicity, educational level, intelligence, locus of control, extraversion, introversion, neuroticism, or suggestibility (42). In fact, individuals who have a placebo response in one situation may not show a placebo response in a different situation (43,44). For example, one study found that positive responses to a placebo given for labor pain were not correlated significantly with the responses to a placebo given to the same women in the postpartum period (44).

The patient factors that have been shown to influence nonspecific effects are listed in Table 81-2. Patients' positive attitudes toward the provider and toward the treatment have been shown to predict improvement in studies of psychiatric outpatients treated with placebo, psychotropic drugs, or psychotherapy (42). There is also some evidence that highly anxious subjects may show the greatest placebo responses (42).

1. Positive attitudes toward provider, treatment
2. Anxiety
3. Expectations of effects
4. Treatment adherence

TABLE 81-2. Patient factors that influence nonspecific effects

Patient expectations of treatment effects have been shown to influence their responses, at least in some situations. For example, when subjects in one study were given a pill containing only a magnet to measure stomach contractions, the contractions increased, decreased, or did not change according to the effects they were told the pill would cause (45). In a study of asthmatic patients, isotonic saline produced increases or decreases in airway resistance according to what patients were told to expect (46). Furthermore, when patients were given a true bronchodilator, its effects were about twice as great if patients were told it would produce this effect than if they were told it would produce the opposite effect. A later study (47) also demonstrated both nocebo and placebo responses in asthmatic patients, according to their expectations. When patients believed they were inhaling an irritant chemical, which was in fact water, they showed a bronchoconstrictive response. This nocebo effect was shown in the same study to be *abolished* by a placebo. When subjects inhaled an inactive substance they thought was a powerful new drug *before* inhaling the water solution they thought was an irritant, they had no bronchoconstriction in response to the irritant. In yet another study (48), after subjects drank a beverage they believed was caffeinated coffee but in fact was decaffeinated, motor skill task performance was either enhanced or impaired according to what effects they were told the beverage would have.

Expectations of adverse events have been shown repeatedly to be associated with the subsequent occurrence of such adverse events. An extreme example of this is voodoo death, death that can occur in some cultures by unknown mechanisms, believed to be due to the belief of the victim that death is imminent (49). In Western culture today, the belief that one is susceptible to heart attacks has been shown to be a risk factor itself for coronary death. Analysis of the Framingham study data (50) revealed that among middle- aged female homemakers free of coronary disease, those who believed they were more likely than others to develop heart disease were 3.7 times more likely to have a myocardial infarction (MI) in the next 20 years, even after controlling for commonly recognized cardiac risk factors.

Symptoms may also occur when an individual becomes aware of symptoms in others and believes that he or she may also be vulnerable to the condition. A well-recognized form of this phenomenon is *mass hysteria*. Kerckhoff and Back (51) carefully examined the spread of such a sociogenic illness, the 1962 “June Bug” outbreak in a Montana mill. Sixty-two of 965 workers were affected, fainting or complaining of pain, nausea, or disorientation. All of those affected worked in dressmaking departments. Persons affected were 62% more likely to have worked overtime at least two or three times a week, 2.2 times more likely to be sole breadwinners, 5.6 times more likely to be divorced, and 30% more likely to have a child younger than age 6. These facts strongly implicate the role of physical and emotional stress in such conditions.

Other studies have also demonstrated the ability of expectations to produce symptoms. After being told that a medicine administered through a skin patch would induce seizures within 30 seconds, 77% of psychogenic seizure patients showed seizure behavior when the patch, which actually contained only alcohol, was applied (52). Symptoms included nonresponsiveness, generalized violent thrashing, and uncoordinated movements. Nineteen percent of the patients reported auras and 44% showed postictal confusion or sleepiness, or both. A double-blind study designed to evaluate a controversial method of food allergy testing compared the effect of injecting the food substances with the effect of injecting a saline solution (53). Twenty-seven percent of patients given the food substance injection and 24% of those given saline experienced symptoms of nose itching, watering or burning eyes, plugged ears, tight or scratchy throat, nausea, dizziness, sleepiness, and depression.

Another factor demonstrated to be associated with nonspecific treatment effects is treatment adherence. Patients who adhere closely to a prescribed regimen may have better outcomes than those who do not, even when taking a placebo. This observation was first made in a double-blind randomized trial that compared the efficacy of a lipid-lowering drug with placebo on mortality in men who had survived an acute MI (54). Although the lipid-lowering drug was no better than placebo in reducing 5-year mortality, men who adhered closely to the prescribed regimen (i.e., who took 80% or more of the capsules) had a marked reduction in mortality compared with poor adherers (i.e., who took less than 80% of the capsules). Surprisingly, this reduction in mortality was similar in the placebo and lipid-lowering drug groups. Even after controlling for 40 known or suspected coronary risk factors, the placebo noncompliers had a 5-year mortality rate 57% higher than that of the placebo compliers.

The effects of adherence on mortality after MI were further explored in data from the Beta Blocker Heart Attack trial (55). This multicenter randomized double-blind trial compared propranolol with placebo in men surviving an acute MI. Men with poor adherence—that is, who took 75% or less of the placebo or active medication—were 2.6 times more likely to have died within a year after their MI. As in the Coronary Drug Project, poor adherers had an increased risk of death whether they were on placebo or active medication. The association between poor adherence and mortality was not accounted for by measures of the severity of MI, sociodemographic features, smoking, or psychological characteristics.

Yet another study (56) found that the association between medication adherence and mortality after MI is also present in women. In this study, 602 women were assigned randomly to propranolol or placebo 5 to 21 days after an MI. Fourteen percent of the poor adherers but only 6% of the good adherers to placebo or propranolol died within the next 2 years. The effect of adherence on mortality remained undiminished after adjustment for treatment group (placebo versus propranolol), age, severity of MI, and other clinical and sociodemographic variables. The mortality rate was approximately twice as great for poor adherers as for good adherers in the propranolol group and approximately three times as great for poor adherers in the placebo group.

Adherence has also been shown to be associated with clinical outcomes in conditions other than heart disease. For example, a randomized clinical trial (57) of oral antibiotic prophylaxis in patients with cancer receiving chemotherapy showed that fever or infection occurred in 22% of patients who received oral antibiotics and 27% of patients on placebo, but those with excellent adherence had a lower incidence of fever and infections, regardless of whether they received antibiotics or placebo.

What explains this association between adherence and outcome? Gallagher et al. (56) suggest several possibilities. First, adherence to a medical regimen, whether active medication or placebo, may be associated with other favorable health practices or social circumstances related to outcomes but not measured in these studies. Second, baseline health status that is better in some ways not measured in these studies may facilitate both better outcomes and better adherence. Finally, adherence may be one manifestation of prognostically favorable patient characteristics, reflecting an individual's ability to make lifestyle changes that limit disease progression.

Provider Factors

Table 81-3 lists provider factors that have been found to influence nonspecific effects. The provider's warmth, friendliness, interest, sympathy, empathy, prestige, and positive attitude toward the patient and toward the treatment are associated with positive effects of placebos as well as of active treatments (42). The importance of provider expectations was illustrated in a study of a new antihypertensive drug believed at the time to be more effective than existing drugs (58). In the middle of this double-blind study, partners of the enthusiastic physician administering the drug broke the code. Without telling him which pills were the placebo and which were the drug, they told him that the drug, although effective, appeared similar to existing drugs. Although less enthusiastic, they decided to complete the study. The difference between the drug and placebo was maintained, but there was an immediate, marked increase in the blood pressures of patients in both groups.

1. Warmth, friendliness, interest, sympathy, empathy, positive attitude toward patient
2. Prestige
3. Expectations of treatment effectiveness

TABLE 81-3. Provider factors that influence nonspecific effects

In a double-blind study of dental extractions (59), placebo responses were compared for patients in two groups. In the first group, the clinicians knew they would administer either a narcotic analgesic, a placebo, or a narcotic antagonist. In the other group, the clinicians knew they would administer only a placebo or a narcotic antagonist. Placebo patients in the first group reported significantly less pain associated with the dental extraction than did placebo patients in the second group. Because the two placebo groups differed only in the clinicians' knowledge of the range of possible treatments, this knowledge appears to have resulted in subtle behaviors that influenced patient responses.

A study of patients undergoing a procedure for the treatment of chronic pain found that the treating physicians' expectations of pain relief from the procedure, but not the patients', predicted actual pain relief from the procedure (60). These findings indicate that patient expectations of pain relief do not always predict actual pain relief. It is likely that the physicians could predict patient pain relief in this study because of their prior experience with the procedure, and it is also possible the physicians somehow subtly communicated their expectations to patients during the procedure and this influenced patient response.

HOW ARE PLACEBO EFFECTS EXPLAINED?

Several explanations have been proposed for placebo effects, as listed in Table 81-4.

1. Decreased anxiety
2. Learning
3. Expectations
4. Endorphins

TABLE 81-4. Explanations for placebo effects

Decreased Anxiety

Stress and anxiety adversely affect several physiologic processes and increase symptom reporting. There is some evidence that placebos may be most effective for highly anxious subjects, and placebo effects are often attributed to reduction in anxiety and suffering (61). Although placebos have been shown to decrease anticipatory anxiety (62), it is not clear whether anxiety reduction is a cause of the placebo effect or a component of it (63).

Learning

A treatment may have a positive effect because of its association with effective treatments the patient has had before (i.e., a learned or conditioned response). Neutral stimuli such as syringes, health care professionals, medical equipment, and hospitals can function as conditioned or discriminative stimuli for the alleviation of symptoms if they have been associated with powerful unconditioned stimuli (e.g., analgesic medication) that relieve symptoms (64). In support of this learning model are the findings that when placebos are given after active analgesic medications, the analgesic effect of the placebo is proportional to that of the active medication (28). Animal studies have demonstrated that after one or more injections of a drug, the physiologic effects of the drug can be elicited by an injection of saline (65,66). Experiments have demonstrated that placebo responses can be conditioned (67), and one study found the direct experience of conditioning to be more powerful than expectancy formed through verbal persuasion (68).

Crossover study designs present a good opportunity to study conditioned responses to placebos because one group of patients receives the placebo without prior drug exposure and another group takes placebo after drug exposure. A study of patients with mild to moderate essential hypertension tested the conditioning model prediction that the placebo response would be greater after drug exposure than before (69). After a 1-week baseline of no treatment, patients were randomly assigned to one of three groups. The first group of patients received placebo for 1 week, followed by 50 mg of atenolol daily for 1 week, followed by no treatment for 1 week. The second group of patients received atenolol for 1 week, followed by placebo for 1 week, followed by no treatment for 1 week. The third group received atenolol for 1 week, followed by nothing for 2 weeks. This last group was included to show any residual drug effects that might persist after the atenolol was stopped.

Averaging the mean arterial pressures of each patient during the last 4 days of each week and subtracting those values from the average mean arterial pressures over the last 4 days of the no-treatment baseline period gave a measure of the antihypertensive response of each patient for each week. There were no differences between the blood pressure changes of patients taking placebo *before* atenolol and those of patients taking nothing. In contrast, *after* atenolol treatment, patients taking placebo maintained an antihypertensive response, whereas those taking nothing after atenolol showed a return toward baseline. This demonstrates that the placebo response was more than a residual drug effect. This study is also one of a number that have demonstrated that placebo responses are not limited to subjective variables such as pain, but also include physiologic parameters.

Expectations

It has been argued that the effect of a conditioning procedure on placebo responses is mediated by expectancy (70). Expectations of pain relief with a treatment may result from prior classic conditioning or from other types of learning and have been hypothesized to mediate placebo analgesia (71). An implication of this is that drug expectancies may potentiate drug effects (70,72). A patient's expectation that a treatment will relieve his or her pain may reduce his or her anxiety and concerns and cause him or her to notice small improvements, to disregard negative events, and to interpret ambiguous stimuli favorably (73). Changes in patients' appraisals and expectancies may also result in behavior changes that lead to improved outcomes. For example, a patient with back pain may resume functional activities that he or she had avoided due to fear of pain or harm.

Endorphin Effects

Levine et al. (74) reported that high doses of naloxone, an opiate antagonist, abolished the placebo reduction of pain after wisdom tooth extraction, suggesting that

placebo responses might be mediated by endogenous opiate release in the central nervous system. However, subsequent studies have yielded contradictory results (75,76). At present, the role of endogenous opiate processes in placebo responses remains unclear.

Summary

Currently, there exists considerable controversy about placebo effects. At one extreme, it has been argued that “the extent and frequency of placebo effects as published in most of the literature are gross exaggerations” (77). Kienle and Kiene (77) assert that apparent placebo effects can be explained by a variety of factors, including the natural history of the disease, regression to the mean, concomitant treatments, methodologic flaws, and subject and observer biases. Clearly, studies designed to test these explanations are needed to understand the nature and characteristics of nonspecific effects in different pain therapies for different conditions.

RESEARCH IMPLICATIONS

Drugs, medical treatments, surgery, biofeedback, psychotherapy, and even diagnostic tests can have nonspecific effects that influence patient outcomes (41,64). Only randomized controlled trials can establish that a treatment results in greater improvement than would occur due to the natural history of the condition and nonspecific effects. Random assignment of subjects to treatment and control conditions is necessary to reduce systematic bias in group membership, which may lead to differential improvement due to differences in subject characteristics rather than in the treatment. However, even in randomized controlled trials, clinicians and subjects know there is a control and an experimental treatment, and outcomes may be influenced by their expectancies of outcomes with each treatment and beliefs about which treatment the subject received. If either or both can guess (e.g., by side effects) which treatment the subject has received or if one treatment is more credible, this may bias the study results. To the extent that the subject or clinician believes a treatment may be ineffective, the power of nonspecific effects will be reduced or underestimated.

The ideal randomized controlled trial is double-blind. However, even under “double-blind” conditions, subjects, clinicians, and evaluators often can distinguish at better-than-chance rates between active medication and placebo, and clinicians often can distinguish between different active medications (78,79 and 80). In addition, research has demonstrated that so-called blind evaluators of subject outcomes are biased in their ratings by their beliefs about what group the subject was in (81) and that subjects' guesses about what drug they are on are associated with their drug reactions and outcomes (82).

Therefore, the control treatment should be as similar as possible to, and as credible as, the active treatment. Visit frequency, contact, support, and side effects should be equivalent in the control and active therapy conditions. Although it can be difficult to create credible placebo controls, creative sham treatments have been devised (e.g., sham transcutaneous electrical nerve stimulation units, misplaced needling as a control for acupuncture, subtherapeutic weight as a control for traction, massage as a control for spinal manipulation). Trials in which control treatments mimic the active therapy typically have found less advantage of the active treatment over the control than have trials with obviously different types of therapy or with inert placebo controls (83,84).

Both a completely untreated group and a placebo-treated group are necessary to distinguish between nonspecific effects and the effects of the passage of time in a trial, although these may not be feasible in many situations. In studies of individuals with chronic pain, long baselines with multiple measures of pain before treatment can reveal changes in the absence of treatment and thereby help to estimate the magnitude of regression to the mean as a source of within-patient change (85,86).

Ethical and practical factors make it difficult to conduct surgery trials with sham controls. Randomized trials that compare alternative surgical procedures or surgery versus credible alternative nonsurgical therapies may be feasible and may yield useful information in many situations. For example, two prospective, randomized studies compared spine surgery with and without instrumentation in terms of clinical and technical outcomes and complications (87,88).

However, a prospective, randomized, placebo-controlled trial of knee surgery (89) demonstrates the feasibility and value of a placebo surgery trial. In this small pilot study, 10 patients with chronic osteoarthritic knee pain who gave full informed consent were randomized to three operations—arthroscopic lavage, a standard arthroscopic debridement, and a placebo arthroscopy. Each patient was taken to the operating room, and the randomization envelope was opened to reveal which procedure the patient was to receive. Patients undergoing placebo arthroscopy were prepared, draped, examined, and injected with local anesthetic in the same manner as the other two groups. Three stab wounds were made in the skin with a scalpel, but no instruments were placed into the knee. The knee was manipulated, instruments were requested and passed, saline was splashed, and a standard arthroscopic debridement was simulated as closely as possible in case the patient was not totally unaware during the procedure. One-half to 1 hour was spent performing the placebo surgery—the same amount of time as the other two operations.

At each postoperative visit, the patients and examining physician were questioned as to which procedure they believed the patient had received. The patients and physician were never able to guess the procedure correctly more often than would be explained by chance. Follow-up assessments were conducted by an orthopedic surgeon blinded to the procedure the patient received. At 6 weeks and 6 months after surgery, 80% of patients who received the placebo surgery reported believing the operation was worthwhile. At 6 months after surgery, all three treatment groups reported improved pain, with the average pain relief 3.8 on a 0 to 10 scale. Four of the five placebo surgery patients indicated they were satisfied with the surgery and said they would recommend it to family and friends, and the fifth patient was neutral.

In addition to providing information about the efficacy and effectiveness of a specific therapy, randomized controlled trials can also increase knowledge about nonspecific effects by including no-treatment and placebo/sham treatment conditions. The understanding of placebo effects will be advanced by studies designed to examine the factors other than specific treatment actions that influence patient outcomes. These include natural history, regression to the mean, patient expectations and beliefs, provider expectations and beliefs, characteristics of the treatment situation that influence patients and providers to behave in certain ways (e.g., to report improvement), conditioning and other types of learning, and psychophysiologic states of the patient such as anxiety and relaxation.

Finally, despite the important information that double-blind trials can provide, it should be noted that the effects of drugs in double-blind trials may not necessarily be the same as in actual clinical settings. In double-blind studies, subjects are aware that they may receive a placebo. In contrast, patients treated by drugs or other therapies in a clinical setting are not told the therapy may be a placebo and thus have a different cognitive set than subjects in a research study. The psychological (nonspecific) and pharmacologic or other specific, active effects of a drug or other therapy may be additive or they may be interactive (72). An active treatment effect in a clinical setting may be potentiated by the patient's expectations of improvement. A double-blind placebo-controlled study may find less effect for an active treatment than would be seen in an unblinded clinical setting.

CLINICAL IMPLICATIONS

Nonspecific effects accompany any treatment and, in fact, can be found with any provider-patient interaction. These effects can be quite strong and can lead patients and providers to mistakenly assume improvement is due to the specific effects of the treatment. Nonspecific effects may be strongest when the patient is anxious, the clinician is perceived as having great expertise, the patient and clinician believe the treatment is powerful, and the treatment is impressive and expensive. The demonstration of the role of learning in placebo responses suggests that past treatment responses may influence a patient's responses to subsequent treatments in a positive or negative manner, depending on the prior history.

The literature on placebo effects suggests several ways clinicians may be able to harness the power of nonspecific effects to improve the outcomes and satisfaction of their patients, as listed in Table 81-5. These include showing genuine warmth, interest, and concern and conveying “realistic optimism” about the patient's prognosis and treatments prescribed. In addition, visible signs of the clinician's expertise (e.g., diplomas, board certifications) and an air of confidence can help increase a patient's confidence in the clinician. Finally, eliciting and addressing the patient's concerns and goals for the visit, performing a physical examination, and providing a diagnosis and prognosis may have positive effects by increasing the patient's confidence that his or her symptoms have been diagnosed accurately and decreasing the patient's worries and fears.

1. Convey genuine warmth, interest, and concern.
2. Convey "realistic optimism" about treatments you prescribe.
3. Display diplomas, board certifications, and so forth where patients will see them.
4. Convey an air of confidence (but not arrogance).
5. Elicit and address patient worries, concerns, and goals.
6. Let the patient know you have reviewed previous medical records/tests and conduct a thorough history and physical examination, so the patient believes you have sufficient knowledge to make an accurate diagnosis.
7. Provide a diagnosis and realistic prognosis to the extent possible.

TABLE 81-5. Suggestions for harnessing the power of nonspecific effects

Given the current limits in most clinical settings on the amount of time available for patient visits, it can be quite challenging to accomplish all of the suggestions in the previous paragraph in addition to the other necessary components of the visit. However, visits can be structured so as to allow practitioners to harness the power of nonspecific effects while obtaining the information necessary to make clinical decisions. Asking the patient about his or her primary goal for the visit and primary worries and concerns at the beginning of the visit, and addressing these in the visit, can be very helpful and may actually save time (e.g., because the patient doesn't then bring up a major concern at the very end of the visit or because the patient feels confident in his or her ability to safely self-manage the problem and thus is less likely to make unnecessary return visits). Health care providers may also find that telling the patient what they are doing and why while conducting a physical examination results in increased patient understanding of their condition as well as reassurance that their symptoms are being evaluated thoroughly.

It can be useful to inquire as to what the patient has found helpful in managing his or her present symptoms recently or in the past and to encourage the patient to continue to use these strategies to manage pain. The practitioner may also suggest additional pain management strategies other patients have found useful and convey to the patient that such self-management strategies can be very effective. Handouts about specific syndromes (e.g., low back pain, headache), including information about their prevalence, about what percentage of patients improve over various periods of time (e.g., within 1 week, 1 month, 3 months, 1 year), and about effective self-management strategies, can be given to patients to take home and read. Such handouts may also include information to help guide patients in making decisions about whether and when they should return to their health care provider (e.g., “red flags” indicating a potentially serious problem that should be evaluated). The visit may be ended with one or more specific treatment recommendations (if appropriate), information concerning the likely time course of the patient's symptoms, and a plan for when the patient should return or call.

It is not valid to use a placebo to assess whether a patient's pain or disease is “real,” and it is a mistake to dismiss the complaints of patients who show a placebo response. To purposefully deceive a patient by prescribing a placebo may be argued to be unethical and may entail several risks, including patients' reacting negatively if they discover the truth; side effects; patients' becoming more worried, concerned, and pessimistic if they fail to improve (73); and increased risk of not improving with subsequent treatments.

CONCLUSION

Patients' pain problems and psychological and physical dysfunction are influenced importantly not only by physiologic processes but also by environmental and cultural factors, learning, and patient beliefs and expectations related to their pain. Changes in pain over time reflect complex interactions between physiologic processes and cognitive-behavioral and environmental factors. Nonspecific effects, natural history, and regression to the mean can influence patient outcomes in all pain treatment situations and must be distinguished from specific effects when examining the efficacy of medical and surgical treatments. It cannot be assumed that a response rate greater than one-third implies that a treatment is better than placebo. The extent to which patient outcomes after a medical or surgical treatment reflect nonspecific effects, regression to the mean, natural history, or specific treatment effects is unclear in the absence of randomized controlled trials with outcomes assessed by persons who are unaware of what treatment the patient received. Finally, aspects of the clinician-patient interaction can have powerful positive or negative effects on patient outcomes.

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CHAPTER 82

*Clinical Trials**

Richard A. Deyo

Controversies abound in the clinical management of pain, and there are enormous geographic variations in care. Lumbar spine surgery rates vary fivefold among developed countries, with rates in the United States being highest and rates in the United Kingdom being among the lowest (1). Within the United States, rates of surgery for spinal stenosis vary more than fourfold among states, from less than 30 per 100,000 older adults in Rhode Island to 132 per 100,000 in Utah (2). In smaller geographic areas, variations become more striking. Within Washington State, county back surgery rates vary more than sevenfold, even after excluding the smallest counties (3).

Another problem in pain management is a series of fads in treatment that have been eventually discredited but that enjoyed widespread use, with substantial costs and side effects, before they were found ineffective. Examples include sacroiliac joint fusion for the treatment of low back pain, coccygectomy for coccydynia, bed rest and traction for back pain, and many others (4). Internal mammary artery ligation was once practiced for treating angina pectoris, and gastric freezing for duodenal ulcers (5). Such ineffective treatments drain resources from more useful interventions, have side effects, and eventually damage professional credibility.

Finally, we are faced with the affront of rising disability rates for chronic painful syndromes, despite steady improvements in the ergonomics of work tasks and technological advances in medicine. Rates of work disability due to back pain rose steadily during the 1980s (6) and claims data demonstrate that carpal tunnel syndrome and low back pain predict longer duration and cost of claims than other medical conditions (7). Thus, despite impressive gains in our understanding of the molecular and cellular origins of pain, there is an important gap in translating this knowledge into effective clinical management. One reason may be the limited quality of clinical trials of innovative treatments, with widespread use of inadequate research designs that lead to conflicting and confusing results. Biostatistical and epidemiologic methods make it possible to substantially improve this situation, but many of these principles are not widely appreciated.

CASE SERIES PARADIGM

Historically, much of pain treatment research consisted simply of case series in which treatment was applied to a group of patients, and the proportion who improved was reported. This remains a popular research design, but is vulnerable to many pitfalls.

First, many case series are retrospectively reported. After 30 or 100 patients have been treated, the clinician looks back at his or her experience and tries to summarize the characteristics, treatments, and outcomes of the patients studied. Unfortunately, in this retrospective approach, there is often incomplete baseline information on patient characteristics. For example, factors such as age, sex, previous surgery, disability compensation, neurological deficits, and pain duration are thought to have a major influence on the outcomes of back surgery. However, in a systematic review of outcome studies on surgery for spinal stenosis, 74 relevant articles were found, but less than 10% mentioned all these patient characteristics (8).

A second problem with the retrospective case series is that there is no blinding of patient, therapist, or outcome assessor to the nature of the treatment provided. This allows important unconscious biases to creep into the assessments. Most of us would not trust outcomes rated by a surgeon evaluating his or her own patients, and yet this is the norm in much of the literature.

By definition, case series do not include control groups for comparison. The assumption seems to be that patients with painful conditions, and especially chronic pain, will not improve unless effective treatment is given. However, there are many reasons why patients improve in the face of ineffective therapy, some of which are listed in Table 82-1. First, the natural history of many painful conditions is to improve spontaneously. This may be true even for patients with long-standing pain, who sometimes improve for unclear reasons. For acute conditions such as acute low back pain, rapid improvement is the norm. Second are placebo effects, which are not well understood but are consistently underestimated. Several factors may mediate placebo effects, including patient expectations, learning and conditioning from previous treatments, reduction of anxiety, and endorphin effects (5).

Natural history of a condition to improve
Placebo effects
Regression to the mean
Nonspecific effects: concern, conviction, enthusiasm, attention

TABLE 82-1. Why patients may improve with ineffective therapy

Another poorly appreciated factor is “regression to the mean.” This term was coined by statisticians who observed that in a group of patients who are assembled because of the extreme nature of some clinical condition, there is a tendency for the condition to return to some average level that is less severe over time. This is a result of random fluctuations more than a steady trajectory of improvement. For example, Figure 82-1 shows what we often assume to be the course of chronic pain problems, with a steady level of severity that falls after successful intervention. However, the second panel is more likely to represent the true natural history, with good days and bad days, and fluctuations being the norm (8). Patients seek us out when their symptoms are most extreme, and we might easily be misled by assessing outcomes at some subsequent time when random fluctuations have returned their symptoms toward a more average level. As Sartwell et al. pointed out, “the term chronic has a tendency to conjure up ideas of stability and unchangeability . . . it is changeability and variation, not stability, that is in fact the dominant characteristic of most long-lived conditions” (9).

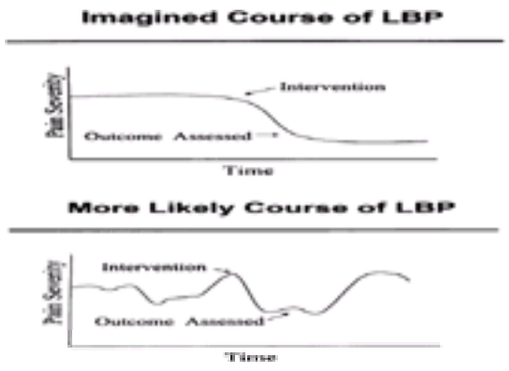

Figure 82-1. Hypothetical course of chronic low back pain (LBP). (From Deyo RA. Practice variations, treatment fads, rising disability. Do we need a new clinical research paradigm? *Spine* 1993;18:2153–2162, with permission.)

Finally, a host of nonspecific effects play an important role in patient improvement. The concern, conviction, enthusiasm, and attention of a therapist, a researcher, and a clinical staff may all have desirable effects. Table 82-2 shows a potential consequence of these factors, using data from a clinical trial of patients with chronic low back pain (8). The 31 patients in Table 82-2 had had back pain an average of 4 years. They were given a clinical intervention that resulted in 20% to 44% improvements in pain frequency, severity, and function, all of which were highly statistically significant. However, this seemingly effective treatment for chronic pain was a sham transcutaneous electrical nerve stimulation (TENS) unit, along with hot packs twice a week. This was the control arm of a randomized trial, and illustrates the substantial improvements that may occur among those with long-standing pain who receive ineffective treatments.

Outcome measure	Score improvement: Baseline to 1-mo follow-up	*p* Value
Overall function (SIP)	32%	.002
Physical function	44%	.001
Pain severity (VAS)	33%	.006
Pain frequency (5-point scale)	20%	.000

SIP, Sickness Impact Profile; VAS, visual analog scale.

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TABLE 82-2. Therapeutic trial for patients with chronic low back pain: mean duration of 4 years, n = 31

CONTROL GROUPS: AN IMPROVEMENT OVER THE CASE SERIES

Given the variety of factors that may produce improvement with ineffective therapy, it is incumbent on investigators to have a comparison group of subjects, who might experience all the same reasons for improvement as a treatment group but who do not receive the active therapy. An investigator would want to reproduce many of the causes for improvement that are listed in Table 82-1 among such a control group. With this goal in mind, the appropriate comparison group is unlikely to be one that receives no care at all. Patients in such a group would not experience placebo effects or the nonspecific effects of clinical concern and enthusiasm. Thus, a preferable control group would be one that receives other credible, appropriate care that does not include the specific treatment under study. This might consist of "usual care" supplemented by a placebo of some sort. The placebo must be as credible and seemingly likely to help as the active therapy. This is the reason for providing inactive pills in the control groups of drug trials, but even for nondrug treatments, credible therapy should be provided. Examples include the use of sham TENS units in trials of TENS, the use of subtherapeutic weight in trials of traction, "misplaced needling" as a control for acupuncture, or even educational brochures that create the sense of some additional intervention and concern but that may have no effect on patient outcomes (10).

An implication of these considerations is that a "waiting list" control group is not adequate because these patients experience none of the placebo or nonspecific effects of the intervention group. Similarly, it would be unwise to choose as a control group patients who did not have adequate insurance coverage for the treatment being provided because insurance coverage is related to important sociodemographic characteristics. Patients with the best insurance are typically those with the highest salaries and the greatest incentive to improve, whereas those with less insurance coverage are likely to be those with lower incomes, less satisfying jobs, and less motivation to improve. Another convenient but misguided control group would be patients who were intended to receive a particular treatment but for some reason were not compliant. A striking example of the flaw in this line of reasoning is apparent from large-scale drug trials in which patients in the placebo arm were examined for their compliance with tablets. In a study of cholesterol-lowering therapy, control patients were divided among those who took more than 80% of their placebo tablets and those who took less than 80% (11). Even after adjusting for 40 coronary risk factors, there were enormous differences in mortality between the compliant and noncompliant groups. Patients who were compliant with their placebos had a 5-year mortality of only 16%, whereas those who were not compliant had a 5-year mortality rate of 26% (p = .000000007) (11). It seems unlikely that such a striking difference in a hard outcome such as mortality was entirely due to placebo effects, and it was probably related to important differences between the groups that were not apparent in either their compliance behavior or their coronary risk factors. These may have included other health habits, behaviors, attitudes toward risk, and occupations. Thus, noncompliant patients are often strikingly different from compliant patients, and we cannot assume that any differences in outcome are related only to treatment effects.

What about finding a control group in which patients are well matched to the treatment patients on a number of characteristics? As the cholesterol-lowering placebo study suggests, with its adjustment for 40 different risk factors, this procedure may not capture the important differences between two groups of patients. In fact, Table 82-3 shows how one might assemble two groups of objects that are well matched on five different characteristics and yet literally be comparing apples and oranges (8).Table 82-4 shows actual data for a comparison of outcomes of two groups of Medicare patients who underwent low back surgery. They were well matched on diagnosis (all had spinal stenosis), gender, age, insurance (all Medicare), and surgical procedure (all had a laminectomy without fusion). Despite being well matched on these five characteristics, the likelihood of reoperations differed almost fourfold between the two groups. Differences of this magnitude might easily be attributed to some dramatic advantage of the treatment used in group A. However, these groups were intentionally assembled in such a way that group A was composed of African-American patients who had not had prior surgery, and group B was composed of white patients with prior surgery (8). These two characteristics, which might easily have been overlooked and unmeasured, accounted entirely for the difference in reoperation rates.

	Apples	Oranges
Shape	Round	Round
Source	Tree	Tree
Edible?	Yes	Yes
Size	Handheld	Handheld
Weight	½ lb.	½ lb.

Reprinted from Deyo RA. Practice variations, treatment fads, rising disability. Do we need a new clinical research paradigm? Spine 1993;18:2153–2162, with permission.

TABLE 82-3. Why not find "matching" controls?

	Group A (n = 252)	Group B (n = 141)	Significance
% Women	57%	55%	NS
Mean age	71	72	NS
% Fusion	0	0	NS
4-Year reoperations	4%	15%	<.0005

NS, not significant.

Reprinted from Deyo RA. Practice variations, treatment fads, rising disability: Do we need a new clinical research paradigm? Spine 1991;16:2153–2162, with permission.

TABLE 82-4. Two cohorts of Medicare patients with laminectomy for stenosis(1985)

If waiting lists, patients with insufficient insurance coverage, noncompliant patients, or carefully matched patients make poor control groups, is there a better solution? Fortunately, the concept of random allocation provides an ideal method of establishing a comparison group that is likely to be similar in nearly all respects to an intervention group.

RANDOMIZED ALLOCATION TREATMENT AND CONTROL GROUPS

The term *randomized trial* has become familiar among clinicians and yet is often misunderstood. Some assume that a randomized trial is one in which patients are randomly selected from a population of interest. However, just the opposite may be true. Patients may be highly selected from a group of potential candidates based on specific characteristics that make the study treatment safe and likely to succeed. Randomization does not refer to the selection of patients, but rather the patients' allocation to the treatment or the control group.

Why is randomization such a desirable way of creating a control group? It is attractive because many of the biases described previously with other types of control groups are largely eliminated. With random allocation, we may not even know the important prognostic factors, but they will be equally distributed (given a fair randomization and enough patients) between the treatment and control groups.

Some investigators have quantified the magnitude of bias that occurs when randomization is not used in trial design by looking at the maldistribution of known baseline prognostic factors and the magnitude of apparent treatment effects. One such study, shown in Table 82-5, compared blinded randomization (in which investigators could not know into which group the next patient would fall) with unblinded randomization (in which the investigators could know into which group the next patient would fall) and with nonrandom allocation of controls (12). The investigators examined a series of treatments for acute myocardial infarction, and as the table shows, demonstrated that maldistribution of prognostic factors was least with blinded randomization and greatest with nonrandom allocation of treatment and controls. Similarly, the likelihood of finding a substantial improvement in case fatality rate rose dramatically, from just 9% of trials with blinded randomization up to almost 60% of trials with nonrandom allocation. This observation suggests that using nonrandomly allocated controls is nearly a sure way of getting a positive result.

Allocation method	Prognostic maldistribution (%)	Difference found in case-fatality (%)
Blinded randomization	14	9
Unblinded randomization	27	24
Nonrandomized	58	58

Data from Chalmers T, Celano P, Sacks HS, Smith J. Bias in treatment assignment in controlled clinical trials. *N Engl J Med* 1983;309:1358–1361; reprinted from Deyo RA. Practice variations, treatment fads, rising disability: Do we need a new clinical research paradigm? Spine 1991;16:2153–2162, with permission.

TABLE 82-5. Bias in studies of myocardial infarction

The importance of randomized designs for pain treatments was further illustrated in a systematic review of TENS therapy for postoperative pain. The investigators found 17 randomized trials of efficacy and 15 of these showed no benefit. In contrast, among 19 nonrandomized studies, 17 had a substantial positive treatment effect. The authors concluded that nonrandomized trials overestimate pain-relieving effects and may lead to the wrong conclusions (13).

Thus, the best way to reduce bias in comparisons between a treatment and some alternative is to randomize patients and to ensure that the investigators are blind to which group the next patient will enter. Why is the blinding of allocation so important? Although this question has not been well studied, we can imagine a variety of reasons. If the investigator has a bias as to which treatment group is more effective—even a subconscious bias—he or she may approach the next subject differently if the intended study group is already known. This may affect the way in which a clinical trial is presented to a patient, the enthusiasm with which consent is sought, or the rigor with which eligibility criteria are applied. In one dramatic local example, patients were assigned to treatment arms according to their hospital numbers. The residents involved in the study actually manipulated the assignment of hospital numbers as patients were registered in the emergency room.

There is sometimes confusion about what constitutes randomization. Randomization requires using a list of random numbers that may be published or determined by a computer program, so each successive subject has an equal likelihood of being assigned to each treatment arm. Alternating assignment is not the same as randomization because it is absolutely systematic rather than random and creates the potential biases noted previously from unblinded randomization. Similarly, assigning patients without conscious bias, or haphazardly, is not the same as random allocation. Using hospital numbers, date of birth, or day of the week is not the same as randomization. The rigorous randomized study will report how the random sequence was determined and how investigators were blinded to the assignment of sequential patients.

For certain interventions, it may be undesirable or unfeasible to randomly allocate individual patients to a treatment or a control group. For example, if one were testing a guideline that involved changes in clinic organization and changes in management by nurses or other ancillary staff, it might be extremely difficult to ensure that all involved gave one particular approach to some patients and not to others. Furthermore, individual physicians would have difficulty treating certain patients according to a guideline and others not according to the guideline. In such a circumstance, one might wish to allocate clusters of patients, such as entire clinics, to intervention or control arms. Similarly, one might randomly allocate hospitals or physicians, with all of their patients, to intervention or control conditions. In these designs, in which entire clusters of patients are randomly allocated to one approach or the other, specific statistical methods are needed that account for the similarities among patients of a single physician or facility. Analytic techniques for such studies have been well described (14) and appropriate computer software is increasingly accessible.

The relatively rapid advances in other fields of medicine, such as oncology and cardiology, occur because a succession of large randomized trials, typically implemented in multiple centers, result in cumulative knowledge. Such trials are still the exception rather than the rule in pain treatment, perhaps in part because of lower research funding for nonfatal conditions. Nonetheless, other fields suggest a model for research that might be emulated by the pain community.

What outcomes should be measured in a clinical trial? In traditional clinical trials, investigators often seek the most objective possible outcomes for evaluation, such

as joint range of motion, spinal fluid endorphins, or dynamometer measures of muscle strength. Although the search for objective outcome measures is laudable, pain is inherently a subjective phenomenon and one that may correlate only modestly with these physiologic measures. For example, Table 82-6 illustrates several examples of reported dissociations between physiologic measures and pain or functioning (15).

• Biofeedback reduces paraspinal electromyography activity but not pain.
• Tricyclic antidepressants relieve pain and depression but do not alter cerebrospinal fluid beta-endorphin levels or paraspinous electromyography activity.
• Statements of pain severity correlate poorly with medication use, health care use, and activity level.
• Reduced spinal mobility may be associated with improvement in pain and disability or lower risk of pain.
• Muscle function does not predict 10-year incidence of back symptoms.
• Correlations between lumbar spine mobility and modified Oswestry questionnaire are only .04–.17 (absolute value).
• In a clinical trial of rigid corset, improvements in symptoms with activity were observed but not in spine mobility or straight-leg raising.
Reprinted from Deyo RA. Measuring the functional status of patients with low back pain. Arch Phys Med Rehabil 1988;69:1044–1053, with permission.

TABLE 82-6. Examples of dissociations between various outcome measures

Ultimately, some researchers have argued that the essence of “hard” data is their reproducibility under the same circumstances (16). Thus, reproducibility may actually be more important than who makes the measurement, whether it is preservable or whether it is numerical. Happily, many subjective phenomena can be measured in reproducible fashion. A good example is the use of visual analog pain scales and other ordinal rating scales for quantifying pain. However, most investigators would want to go beyond the self- report of pain to actually examine patients' behavior and function in their daily lives. Again, daily functioning may correlate poorly with basic physiologic measures and should therefore be measured directly rather than inferred (15). Performance measures such as a series of timed tasks or an “obstacle course” may have the attraction of seeming objectivity, and yet performance on such physical tasks is highly influenced by motivation, mood, setting, financial incentives, and other nonphysical attributes of the patient and his or her environment. Self-report measures of health status or functional status are quite reproducible and are increasingly incorporated into clinical trials of pain therapy. Examples include the Sickness Impact Profile (17,18) and the shorter SF-36 (19), as well as condition-specific scales such as the Roland Disability Scale for patients with back pain (20), the Arthritis Impact Measurement Scale (21), the Seattle Angina Questionnaire (22), and many others.

Work status is often used as an outcome measure for chronic pain treatment because of its clear relevance to both patients and to society. However, it has a number of drawbacks as an outcome measure, most important of which is that it is influenced by many nonmedical factors. For example, studies have demonstrated that the likelihood of return to work in the face of a painful medical condition depends importantly on job satisfaction, relationships with fellow employees and supervisors, regional unemployment rates, the presence of another breadwinner in the family, closeness to retirement age, and physical job demands. Similarly, the duration of pain-related disability is strongly associated with the patient's educational status, income (23), and the generosity of disability benefits. For many members of our society, including students, housewives, and retired persons, return to employment is simply not available as an indicator of outcome. Thus, although this measure of outcome is important in many settings, it should be interpreted in light of these many potentially confounding factors.

OTHER ISSUES IN THE DESIGN OF CLINICAL TRIALS

Table 82-7 lists several criteria that have been proposed for critical readers to evaluate studies of treatment efficacy (24,25). Although these were designed as guides for critical readers, they also create a departure point for clinical investigators. A similar but lengthier and more detailed set of criteria for evaluating clinical trials has been proposed by the back subgroup of the Cochrane Collaboration, an international effort to systematically review clinical trials of treatments for all medical conditions (26). The list of criteria in Table 82-7 begins with random allocation, which was discussed in detail previously.

Are the results of the study valid?
Primary guides
Was the assignment of patients to treatments randomized?
Were all patients who entered the trial properly accounted for and attributed at its conclusion?
Was follow-up complete?
Were patients analyzed in the groups to which they were randomized?
Secondary guides
Were patients, health workers, and study personnel “blind” to treatment?
Were the groups similar at the start of the trial?
Aside from the experimental intervention, were the groups treated equally?
What were the results?
How large was the treatment effect?
How precise was the estimate of the treatment effect?
Will the results help me in caring for my patients?
Can the results be applied to my patient care?
Were all clinically important outcomes considered?
Are the likely treatment benefits worth the potential harms and costs?
Reprinted from Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? JAMA 1993;270:2598–2601, with permission.

TABLE 82-7. Readers' guides for an article about therapy

Complete Follow-Up

The second item in the list in Table 82-7 concerns completeness of follow-up for patients who entered the trial. Investigators should follow up on every patient who enters the study because those who drop out may be systematically different from patients who remain in the study. For example, disgruntled patients who have failed to improve may drop out of a trial, leaving an obvious bias in favor of the new treatment. On the other hand, patients with dramatic improvements may drop out because they are so much better they see no need for continued medical contact. Dropouts from clinical studies often differ systematically from those who remain with regard to their baseline characteristics.

In highly mobile societies, such as the United States, obtaining complete follow-up can be difficult. Strategies for maximizing follow-up include gathering multiple telephone numbers at the time of enrollment for the patient, relatives, and friends; excluding patients who are planning to move in the near future; excluding patients who have no telephone; multiple mailings of questionnaires; financial incentives to return data; using the briefest possible follow-up questionnaires; and even use of the Worldwide Web to track patients through public records.

A useful rule of thumb is that at least 85% of patients who enter a trial should be included at the end of the study. One way to ensure that the results are robust in the face of dropouts is to do a “worst-case analysis,” in which one assumes that all dropouts from the treatment group failed to improve, whereas all dropouts from the comparison group improved substantially. If this worst- case analysis does not change the conclusion, one can be confident in the findings (24).

As suggested in Table 82-7, it is also important that patients be analyzed in the groups to which they were randomized, regardless of whether they received the intended treatment (e.g., because of poor compliance). We have seen the hazards of assuming that patients who are noncompliant are otherwise the same as compliant patients. Indeed, patients who do not receive the intended therapy may be systematically different from those who do, and the only way to avoid a biased comparison is to keep patients for analytic purposes in the group to which they were assigned.

Blinding

It is common to talk about “double-blind” trials, but the term is sometimes used ambiguously. Typically, it is meant to imply that the patient is unaware whether he or she is receiving active treatment or a placebo, and the therapist is also unaware. In some cases, it may be impossible to “blind” patients or therapists, as in trials of surgical treatments or some rehabilitation interventions. However, there is a third party that may be blinded, an independent assessor of outcomes. Maintaining such

a blinded assessor should be feasible, even when it is impossible to blind patients and therapists.

As noted in the discussion of control groups, creativity can sometimes produce credible placebo or alternative treatments that at least help to maintain blinding. In many situations, it may be feasible and desirable to test the success of blinding at the end of a study. This has been done in clinical trials such as one examining beta blockers after heart attacks (in which reduced pulse and blood pressure tended to reveal the active treatment group) (27) and in studies of TENS for low back pain (in which sham treatment fails to produce the same sensation as active therapy) (28). In both of these examples, patients and physicians were able to guess better than random chance whether individual patients were in the treatment or control group, and yet the magnitude of blinding failure was sufficiently modest that the results could be presented with some confidence. The importance of blinding is that it helps to create similar expectations on the part of patients and similar enthusiasm by the therapists. Furthermore, it ensures that the same level of attention and concern is provided to both a treatment and a control group.

In trials of drug therapy, crossover designs have commonly been used because they help to reduce the effects of interpatient variability in baseline and outcome measures. For many pain treatments, however, such designs may be undesirable because they would preclude blinding. For example, a crossover study from sham TENS to true TENS, or from subtherapeutic weight to therapeutic weight with traction, or from mild exercise to strenuous exercise would almost certainly preclude patient blinding. Because of loss of blinding, a host of analytic problems (29), and the potential for improvement due to natural history, crossover trials may be undesirable for many types of pain therapy.

Baseline Similarity of Study Groups

Randomization usually provides the best way to produce groups with equivalent prognoses. However, randomization may not always work, and investigators should present a comparison of baseline characteristics of patients in the treatment and control groups. In a randomized trial, any observed differences are chance occurrences but may still be sufficiently large to compromise the validity of the study. When this occurs, investigators can adjust for baseline differences using statistical techniques, although this cannot adjust for differences in unmeasured prognostic characteristics.

Were Groups Treated Equally Except for the Experimental Treatment?

Sometimes patients in a treatment group are given multiple interventions, and yet the authors or readers are tempted to ascribe the results to a single feature of the treatment. For example, a patient who receives a sclerosant injection into the spinal ligaments along with corticosteroids and spinal manipulation might be said to have improved because of the sclerosant therapy, and yet much of the observed improvement might be due to the cotreatments (30). Thus, it is important that any cotreatments be given to the control group as well (31).

Furthermore, multiple treatments for chronic painful conditions are common. Many patients obtain over-the-counter pain medications; visit multiple physicians; or seek alternative forms of therapy such as chiropractic care, acupuncture, or massage. In outpatient trials, it may be difficult to prevent patients from obtaining such cotreatments, and it may simply be necessary to inquire about these “cointerventions” and ensure that they are roughly equivalent between two groups. Alternatively, investigators may make strenuous efforts to ensure that patients do not receive certain types of cointerventions. Even the nature of follow-up should be consistent between study groups. If one group has closer follow-up, for example, more adverse events might be reported, or treatment might be given more intensively. Furthermore, increased contact with a caring clinician can have important nonspecific effects, as noted previously.

Reporting the Results

In some studies, actual outcome measurements are not reported, and only the *p* values for the significance of results are provided. However, this gives a reader no idea what the magnitude of treatment effects may have been. In a very large trial, a trivial difference between groups may achieve statistical significance even though the difference is too small to be clinically relevant. On the other hand, in a very small trial, a large treatment effect might fail to achieve statistical significance because of the small numbers. Thus, the magnitude of treatment effect is somewhat independent of statistical significance, and must be reported. An ideal way to present the results is to give the actual estimate of success rates or mean scores along with 95% confidence limits, which allow the reader to see the range of results that would be consistent with the study findings. The 95% confidence limits are closely related to *p* values, but give readers a better understanding of the potential range of effects compatible with the data. Ultimately, a *p* value tells us how precise an estimate of treatment effect is, but not its magnitude.

Generalizability of Results

Although a clinical trial may be internally valid, it may not be applicable to other patients. Thus, it is important that patients and treatments be adequately described for a reader to know whether they would be likely to apply to his or her own situation.

Sometimes, subgroup analyses are used to examine clinically relevant groups of patients, and results are found to differ among subgroups. There is a great risk that subgroup analyses may be overinterpreted and may simply represent chance effects. Confidence in such subgroup analyses is enhanced if the treatment effects are large, were unlikely to have occurred by chance, occurred in an analysis that was specified before the study began, were found in one of very few subgroup analyses, and were replicated in other studies (25).

Another issue in judging generalizability concerns the outcomes that were measured. As we saw previously, improvements in physiologic end points do not necessarily translate into improvements in pain, functioning, or employment status, and if these latter phenomena are important, they should be measured directly.

Benefits Versus Harms and Costs

Sometimes, even effective treatments may not be widely implemented because of a high risk of complications or exorbitant costs. Although many clinical trials will not have the resources to perform formal cost-effectiveness analyses, it is important to account for the risks of the treatments being compared as well as their benefits.

NEW DIRECTIONS IN CLINICAL TRIALS

An important principle in most clinical trials is to assemble groups of patients who are relatively homogeneous in their expected prognoses and responses to treatment. For many painful conditions, this is difficult because of diagnostic ambiguity and the lack of precise classification systems. For example, clinicians and investigators often have different criteria for defining spinal segmental instability, carpal tunnel syndrome, whiplash, thoracic outlet syndrome, and many others. Thus, rather than simply attaching a diagnostic label to a group of patients, it may often be preferable to provide detailed clinical descriptions that would allow a reader to decide if the subjects meet his or her own criteria for the condition under study and whether they resemble his or her own patients. Similarly, in situations for which good prognostic data are available, one may wish to stratify patients entering a clinical trial so that the prognosis within strata is more homogeneous. For example, one might choose in a trial of back surgery to group patients with and without previous back surgery and examine the outcomes separately. One might choose to examine patients with and without disability compensation separately. This strategy is called *prognostic stratification* and may disclose patterns of treatment efficacy that would otherwise not be apparent. It amounts to specifying subgroup analyses in advance but may also influence recruitment strategies to ensure adequate numbers in key subgroups.

Some investigators may wish to consider the use of factorial research designs. With a factorial design, patients are simultaneously randomized to receive or not receive two different treatments. Thus, for example, one might simultaneously be allocated to receive study drug A versus a placebo and to receive exercise program A or exercise program B. Such factorial designs have important efficiencies if the dropout rate is low. If there is no statistical interaction between the two treatments (in this example drug therapy and exercise therapy) then one has an unbiased assessment of the effect of each treatment. Such designs might be useful in studying combinations of therapy such as an analgesic plus a muscle relaxant, drug therapy plus physical therapy, and other clinically relevant combinations. Indeed, this may be the best way to evaluate the multimodal therapy that is widely advocated for the treatment of chronic pain. If there is no synergy between treatments, the investigator essentially has two trials for the price of one. If there is synergy, there is no other way to identify this effect. Factorial designs introduce analytical complexities that are avoided in simple parallel designs, but in some circumstances, the benefits may outweigh the disadvantages (32,33).

Greater standardization of outcome measurement would represent an important advance in studying pain treatment. At present, individual investigators often choose unique and sometimes idiosyncratic measures of outcome that are difficult to compare with other studies. The lack of standardization of outcome measurements makes it difficult to compare individual studies, to synthesize results in the form of metaanalysis, and to interpret the results. The last occurs because readers may have little sense of the clinical relevance of a given percentage change or point change on a particular pain or functional scale. Efforts to provide some core

standardized measures across multiple trials would alleviate this problem, and such core instruments have been proposed for trials of back pain therapy (34). In addition, organizations such as the American Academy of Orthopaedic Surgeons have proposed batteries of outcome measures for a variety of musculoskeletal conditions, and such efforts may help to bring about greater uniformity of measurement. The advantage of a brief set of core instruments would be that there is greater comparability among trials but still flexibility for individual investigators to add specific measures that might be most relevant or important for their studies.

Many interventions for chronic pain require large numbers of patients to observe effects that may be relatively small yet clinically relevant. Enrollment of an adequate number of patients is nearly a ubiquitous problem for prospective studies, and this could be alleviated by the use of multicenter trials. Multicenter trials require both greater funding and greater organizational efforts than single-site studies but may be the only way to feasibly obtain answers to important questions. Not only do multicenter trials offer the advantage of more rapidly accruing adequate numbers of patients, but they also enhance the likelihood that results will be generalizeable at the end of a trial because the treatment has already been tested in different settings.

For clinicians, the results of rigorous randomized trials may become more accessible through the efforts of the Cochrane collaboration. This is an international effort to systematically review and where possible combine the results of multiple randomized clinical trials and make the results available on the Worldwide Web. Although this effort is relatively young, the database is rapidly building, and many of the literature syntheses are also being published in conventional journals.

CONCLUSION

Despite the rapid growth of research literature on the treatment of pain, there remain wide variations in care, a proliferation of unorthodox treatments, and a succession of fads that are often demonstrated to be ineffective when well-designed studies are performed. Disability due to painful conditions is increasing, and there is only a limited professional consensus on optimal approaches to many painful conditions. The disappointing pace of progress in this area may be partly the result of few comprehensive theories that would guide treatment innovations. However, an equally important factor may be the methodologic inadequacy of clinical trials that are necessary to evaluate innovations before introduction to clinical care. Flaws in research design jeopardize not only the internal validity of research results, but also their generalizability to other populations. Greater attention to scientific principles in the design of clinical research should accelerate progress in this area, lead to more consistent clinical practices, and improve patient care.

*Supported in part by Grant #HS-08194, from the Agency for Health Care Policy and Research.

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CHAPTER 83

Systemic Nonopioid Analgesics

H. Richard Miyoshi

The nonopioid analgesics discussed in this section include both that large group of chemically unrelated compounds generally known as *nonsteroidal antiinflammatory drugs* (NSAIDs) and some newer nonopioid analgesics with novel mechanisms of action that may fill the void left by opioids and NSAIDs. In addition, this chapter looks at some new areas of exploration that may lead to other kinds of nonopioid analgesics. Use of NSAIDs for specific pain syndromes is also discussed in Parts III and IV of this text.

GENERAL PRINCIPLES OF NONSTEROIDAL ANTIINFLAMMATORY DRUG PHARMACOLOGY: PROSTAGLANDINS AND CYCLOOXYGENASE

NSAIDs have myriad central and peripheral effects, many of which appear to be mediated by inhibition of prostaglandin (PG) synthesis. Investigations in the central nervous system (CNS) into the activity of inflammatory cells, release of enzymes and oxygen- derived free radicals, and other mechanisms are beginning to reveal NSAID effects that are independent of PG synthesis, but these are not yet well characterized (1,2 and 3).

It was about a quarter of a century ago that John Vane proposed that inhibition of PG biosynthesis was the mechanism of action of aspirinlike drugs (4). It was later found that the mechanism involved specifically the enzyme PG endoperoxide synthetase, now more commonly known as *cyclooxygenase* (COX) (5). This insight led to the development of the first generation of nonaspirin antiinflammatory drugs. In the early 1990s, COX was discovered to have two isoforms with different functions and distributions in the body, leading to a new way of looking at NSAID activity and new avenues for drug development.

PGs are a class of physiologically active, lipid-soluble compounds synthesized from arachidonic acid, a 20-carbon unsaturated fatty acid. These short-lived molecules are not stored and are synthesized in response to specific stimuli. They are essential to the regulation and normal physiology of, among other things, the gastric mucosa, renal blood flow, and smooth muscle in bronchioles. PGs are also a part of the inflammatory response. PGE_2 has been identified as a critical factor in the swelling and pain associated with inflammatory states. It also may regulate the effect of histamine and other mediators on nerve endings. Additionally, another closely related compound, thromboxane A_2, is an important factor in platelet aggregation, whereas prostacyclin (PGI_2) is important in disaggregation. This is just one of many examples of physiologic systems that are regulated by the opposition of two different prostanoids, of which one (in this case, thromboxane) could be considered pathologic and the other (in this case, PGI_2) could be considered homeostatic (6).

Synthesis of PG and thromboxane begins when phospholipase A_2 releases arachidonic acid from cell membranes (Fig. 83-1). Arachidonic acid can go through a number of metabolic pathways, yielding a number of biologically active compounds known as *eicosanoids*, which are derived from C20 fatty acids (eicosanoic acids). Included in this group are products of the lipoxygenase pathway such as the lipoxins, hydroperoxytetraenoic acids, hydroxytetraenoic acids, and leukotrienes, which are important in asthma. The COX pathway produces the prostanoids derived from prostanoic acid, which include the PGs, thromboxanes, and PGI_2. COX itself catalyzes two reactions. First, it acts as a cyclooxygenase, combining arachidonic acid with two oxygen atoms to produce PGG_2. Next, it acts as a peroxidase, reducing PGG_2 to PGH_2. A variety of synthases then convert PGH_2 to other PGs with a variety of specific functions (7).

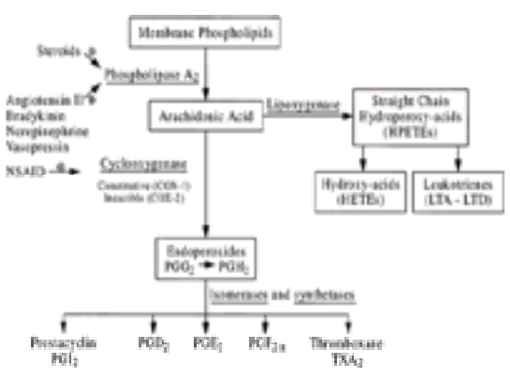

Figure 83-1. Biosynthesis of eicosanoids from arachidonic acid. (NSAID, nonsteroidal antiinflammatory drug; PG, prostaglandin.)

NSAIDs achieve many of their effects by inhibiting COX. As is discussed in more detail below, this includes many of their therapeutic effects, as they decrease PG synthesis at sites of inflammation, but it also includes many of their adverse side effects, as they also decrease PG synthesis needed for proper functioning of the kidney, gut mucosa, and smooth muscle. One of the more important developments in NSAID pharmacology is the discovery in the last decade that these two sets of effects are largely mediated by two different isoforms of COX. In general, COX-1 is the constitutive enzyme that produces PG needed for homeostasis, for example, in the kidney, gut mucosa, platelets, and endothelium, whereas COX-2 is inducible and produces PG as part of the inflammatory process. This division of function is not perfect; COX-2 plays a homeostatic role in some systems, such as the renal medulla and uterus (8), whereas COX-1 may produce some PGs that contribute to inflammation (9). However, the overall separation may make it possible to develop drugs that would produce most of the antiinflammatory effects of NSAIDs by selectively inhibiting COX-2, with many fewer of the side effects that current NSAIDs cause by also inhibiting COX-1 (10).

The two isoforms can be differentiated in a number of ways, but a simple biochemical way is to compare their sensitivity to the reference compound, aspirin. Aspirin inhibits the cyclooxygenase activity but not the peroxidase activity of COX-1. It affects COX-2 quite differently, converting it from a cyclooxygenase to a 15R-lipoxygenase. The two isoforms are also quite different in their distribution and mode of activation. COX-1, the “housekeeping” or constitutive form of the enzyme, is widely expressed in healthy tissue and appears to be localized in the endoplasmic reticulum. It produces PG needed for normal cell activity in response to stimulation by circulating hormones. Its concentration is relatively stable, but can increase two- to fourfold in response to hormones or growth factors (11). COX-2, the inducible isoform, is expressed in endothelial cells, macrophages, synovial fibroblasts, mast cells, chondrocytes, and osteoblasts after tissue trauma (12). It also has some constitutive expression in neurons and gastric mucosa (13). It is present at very low levels in other healthy tissue but increases more than 20-fold during inflammation (9,14). COX-2's highest concentrations are in the nuclear envelope, but it can also be found in endoplasmic reticulum and in the nucleus during cellular growth, replication, and differentiation. Cytokines, endotoxins, growth factors, and reactive oxygen molecules all may induce COX-2 gene expression (15). Conversely, the glucocorticoids and the cytokines that inhibit inflammation suppress expression of the COX-2 gene (10).

Another important area of investigation is the relationship between COX and nitric oxide (NO) (Fig. 83-2). Both COX and nitric oxide synthase (NOS) have constitutive and inducible isoforms. The constitutive isoforms regulate a number of homeostatic processes. The inducible isoforms, COX-2 and inducible NOS, are both either proinflammatory or yield proinflammatory compounds. The induction of both is inhibited by antiinflammatory steroids, raising the question of whether their encoding genes are in the same family. It appears that NO activates COX-2, increasing production of PGE_2 (16). In fact, NO appears to be an important modulator of COX activity, playing a significant role in regulating the extent of the inflammatory process. Numerous compounds that affect COX-2 or inducible NOS or both are being studied as potential antiinflammatory agents, with promising results (17,18).

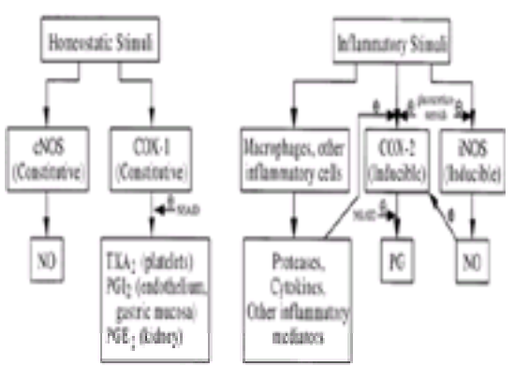

Figure 83-2. A proposed model of the interactions between nitric oxide (NO) and cyclooxygenase (COX) pathways. (NOS, nitric oxide synthase; NSAID, nonsteroidal antiinflammatory drug; PG, prostaglandin; TXA_2, thromboxane A_2.)

PHARMACOLOGY OF SPECIFIC NONSTEROIDAL ANTIINFLAMMATORY DRUG EFFECTS

Analgesia and Antiinflammation

The best understood aspect of the analgesic effect of NSAIDs is their impact on inflammation. Inflammation is the normal response of tissue to injury. It includes enzyme activation, mediator release, extravasation of fluid, cell migration, and tissue breakdown and repair. Many other products of COX are involved, but PGE_2 is the main eicosanoid found in inflammatory conditions and is an essential factor in producing both inflammation and pain. It stimulates nociceptors, either directly or, more likely, by upregulating their sensitivity to other algogenic agents such as bradykinin, which is released when cell membranes are ruptured (19). NSAIDs thus relieve inflammatory hyperalgesia in part by inhibiting COX-2 in inflamed tissues, thereby blocking formation of PGE_2. PGI_2 also causes hyperalgesia in animal models and is detected in inflammatory tissue at concentrations comparable to PGE_2. However, the hyperalgesia caused by PGI_2 is immediate and short-lived, in contrast to the slow onset and long duration of that caused by PGE_2 (20).

The full analgesic effects of NSAIDs probably go well beyond their effects on inflammation to involve a wide array of peripheral and central actions. Some other areas of peripheral action under investigation are lipoxygenase inhibition and a number of non-PG inhibitory actions. With respect to central actions of NSAIDs, the precise role of PG in normal and pathologic central functions is not yet clear (19). However, there is extensive evidence of the importance of COX and PG in central pain mechanisms.

PG, PGD_2, and PGE_2 receptors and PGD and PGE synthases have been found in numerous regions of the brain. The lack of specific antagonists for E, D, F, and I series PG to date has limited the elucidation of their exact function in the CNS. However, it has been shown that PG may increase the excitability of neurons receiving ongoing afferent input. They may achieve this by facilitating the release of excitatory neurotransmitters, by decreasing presynaptic bulbospinal inhibition, or by reducing neuronal membrane stability (21).

COX-1 and COX-2 also appear to play important roles in the CNS. COX-1 is distributed in neurons throughout the brain but is most abundant in the forebrain. Low levels of COX-2 immunoreactivity and COX-2 messenger RNA have also been detected in the forebrain. Forebrain PG may be involved in complex integrative functions, such as the control of the autonomic nervous system and sensory processing (22). Evidence is accumulating that COX-2 is closely involved in the brain's self-modulating response to afferent inputs and that NSAIDs may therefore influence that response. Patterns of COX-2 immunoreactivity seem to show that it is induced in certain groups of neurons in response to natural excitatory synaptic activity. COX2 has also been identified as a neuronal immediate early gene—that is, a gene whose expression can be rapidly induced with synaptic activity in the brain (23). COX2 appears to be involved as an immediate early gene in the development of certain long-lasting changes in neuronal responsiveness that result from brief noxious afferent input (24). Basal levels of COX2 expression have been found to be dependent on activation of the *N*-methyl-d- aspartate–type glutamate receptors that have been found to mediate neuronal plasticity in response to neuronal activation. Arachidonic acid, the substrate of COX, is also generated in brain in response to activation of glutamate receptors in the long-term potentiation model of neuronal plasticity (24).

Antipyresis

The full mechanism of the antipyretic action of NSAIDs is still in question. There are PGs in the hypothalamus. Endogenous, fever-producing PGE_2 is thought to originate from COX-2 induced by lipopolysaccharide or interleukin-1 in endothelial cells lining the cerebral blood vessels (25).

Sodium Retention and Hyponatremia

NSAIDs may cause mild sodium retention in 10% to 25% of patients. Several mechanisms for this effect have been suggested, including direct tubular and indirect vascular effects. NSAID-induced sodium retention tends to be much more severe in patients with edema due to such conditions as congestive heart failure, cirrhosis of the liver, and nephrotic syndrome. Using NSAIDs in these conditions or in cases of renal insufficiency can also lead to resistance to the natriuretic effects of diuretics, including loop diuretics (26).

PGE_2 and other PGs oppose urinary concentration mechanisms in the kidney. Consequently, NSAID reduction of PG synthesis may result in excessive urinary concentration and thus water retention and hyponatremia. This is usually not clinically significant, but it may become a problem in patients at risk for hyponatremia because of edema-causing disorders or other reasons (26).

Renal Failure

Under normal conditions, the rate of PG synthesis in the kidney is very low, so that inhibition of renal vasoactive PG by NSAIDs does not significantly affect renal hemodynamics or function (27). However, in states of renal hypoperfusion, vasodilator PGs serve an important role in the maintenance of glomerular filtration rate by means of their effects on renal arterioles. The use of NSAIDs in patients with renal hypoperfusion may lead to vasoconstriction of both afferent and efferent arterioles as well as mesangial contraction, significantly reducing glomerular filtration rate. Renal hypoperfusion may be due to overall volume depletion [induced by diuretics, gastrointestinal (GI) fluid losses, or hemorrhage, for example], to sepsis, or to intravascular volume depletion (e.g., that caused by the edema of congestive heart failure, cirrhosis of the liver, or nephrotic syndrome). Vasoconstrictive acute renal failure is the most commonly seen form of nephrotoxicity associated with NSAIDs and is frequently reversible when the drug is stopped and volume is replenished (26).

Much less frequently seen with NSAID use are renal parenchymal diseases including acute interstitial nephritis, often associated with nephrotic syndrome, and chronic progressive renal disease with or without renal papillary necrosis. These conditions are relatively infrequent but are more often seen in the elderly.

NSAIDs should be used with caution in patients at risk for hypoperfusion or who have decreased renal reserves (Fig. 83-3).

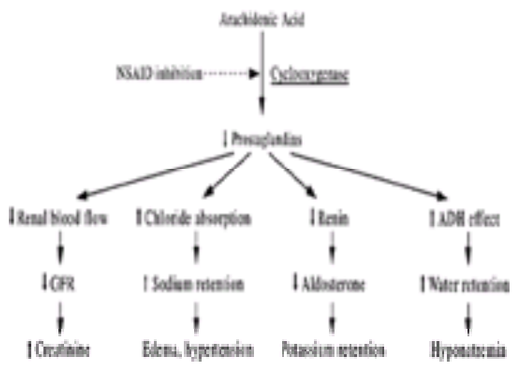

Figure 83-3. Cascade of renal effects of nonsteroidal antiinflammatory drugs (NSAIDs). (ADH, antidiuretic hormone; GFR, glomerular filtration rate.)

Vascular Tone

Prostanoids are known to regulate vascular tone. They modulate the vasoconstrictor and antinatriuretic effects of pressor hormones, especially the renin-angiotensin system. PGE_2 and PGI_2 have antihypertensive activity. PGH_2 and thromboxane A_2 have hypertensive activity (28). In the periphery, PGE_2 is a potent vasodilator. In arterioles there seems to be a tonal equilibrium between prostanoids, which dilate cerebral arterioles, and leukotrienes, which cause constriction (24). The effects of NSAIDs on vascular tone are therefore not simple, since the blocking of the arachidonic pathway decreases synthesis of all these modulators. However, except as outlined above in the setting of the hypoperfused kidney, the effects of NSAIDs on this balance are rarely clinically significant.

Intolerance/Sensitivity

The term *aspirin allergy* has fallen by the wayside. *Aspirin sensitivity* and *aspirin intolerance* are the terms current in the literature.

There are two different types of aspirin sensitivities that are most important. One is the urticaria-angioedema type, which is most commonly seen in patients with chronic urticaria and which has an overall incidence of 3.8%. The other is the bronchospastic type, with bronchospasm often occurring in a triad with severe rhinitis and nasal polyps (polyps being present approximately 50% of the time). Approximately 19% of asthma patients have this type of aspirin sensitivity. In asthma patients with nasal polyps and pansinusitis, the incidence goes up to 40% (29). Consequently, the traditional triad is now sometimes expanded to a tetrad of asthma, rhinitis, nasal polyps, and sinusitis (30).

The mechanism for both types of aspirin sensitivities is related not to an immunologic response mediated by IgE, but probably to the inhibition of COX and the consequent shunting of arachidonic acid metabolism to other pathways. The most important of these appears to be the 5-lipoxygenase pathway, with increased production of leukotrienes (LTB_4, LTC_4, LTD_4, LTE_4) resulting in bronchospasm, increased mucosal permeability and secretions, and neutrophil influx into the tissue (30).

There is cross-sensitivity with all the potent NSAIDs. Severe manifestations, up to and including anaphylaxis, have occurred with the use of some of these agents, so a careful history of sensitivity to aspirin and the aspirin sensitivity tetrad must be ascertained before NSAIDs are prescribed.

Compounds with weak COX activity, on the other hand, are usually tolerated by aspirin-intolerant patients. Acetaminophen, which generally produces only weak inhibition of COX, has been implicated in hypersensitivity reactions in only a small percentage of patients and may be seen as a reasonable alternative to NSAID in aspirin-sensitive patients (31). However, with a sufficiently large dose, a threshold may be reached and the risk of hypersensitivity reactions may increase (32).

Gastric Irritation

Gastric toxicity remains the most common morbidity of the NSAIDs and the major limitation to the use of these drugs in pain and inflammation. Most of the GI effects of NSAIDs are relatively manageable, but complications such as bleeding and perforation may occur and be life-threatening.

Gastric cytoprotection involves multiple mechanisms including adequate mucosal blood flow, epithelial cell renewal, surface active phospholipids, mucus production, bicarbonate secretion, and mediators including PGs, sulfhydryls, interleukin-1, and neuropeptides. Damage caused by NSAIDs probably involves many, if not all, of these mechanisms (33,34).

It has been demonstrated that the local effects of NSAIDs are important factors in gastric irritation and may be additive to the systemic effect of the inhibition of PG synthesis. First, NSAIDs are lipid-soluble, weak organic acids. They are unionized at the low pH of the gastric lumen. In the unionized state they easily penetrate the hydrophilic lipid-protective layer and enter the superficial lining cells of the mucosa. At the higher pH of the intracellular environment the compounds ionize, becoming trapped in the cell (ion trapping). The higher concentration of compound in the cell changes the permeability of the cell membrane, allowing increased influx of hydrogen ions into the cell and resulting tissue damage.

A second form of topical damage is mediated primarily by damage to mitochondria, with uncoupling of oxidative phosphorylation and decreased adenosine

triphosphate formation that results in loss of tight junction integrity, allowing backflow of pepsin and acid through the decreasing protective layer of mucus (34).

These local effects are compounded by NSAID inhibition of COX-1 constitutive synthesis of PGE_2 and PGI_2. In the stomach, these hormones normally act to protect the mucosa by reducing gastric acid secretion, exerting direct vasodilator action on the mucosa, and stimulating the secretion of mucus as a protective physical barrier and the secretion of duodenal bicarbonate to help neutralize excess acid. PGI_2 is also important in inhibiting adhesion between neutrophils and vascular endothelium, which may also be important in the genesis of mucosal injury. NSAIDs suppress the production of both PGE_2 and PGI_2 (33). Aspirin may also suppress the production of NO, which is also an inhibitor of adherence (35). The selective COX-2 inhibitors that are now available may produce less of these systemic aspects of NSAID GI toxicity. There are also drugs either on the market or in trials that are lipoxygenase inhibitors, PG/NSAID combinations (misoprostol/diclofenac), or NO-releasing/NSAID combinations (nitrofenac), all intended to provide adequate antiinflammatory activity with less GI toxicity than traditional NSAIDs (36,37). Aside from new drugs and drug combinations, the use of protectants (sucralfate), PGE analogs (misoprostol), H2 blockers (e.g., ranitidine), and proton pump inhibitors (omeprazole and others) is still helpful in preventing and treating NSAID-induced ulcers (38).

The question of whether gastric irritation caused by NSAIDs creates an avenue for infection by *Helicobacter pylori*, or conversely whether NSAIDs may decrease injury to gastric mucosa by *H. pylori* because of their antiinflammatory effects, has been extensively debated. Currently, the evidence does not seem to support an important relationship between NSAID use and *H. pylori* infection (39).

Anticoagulation

NSAIDs can interfere with platelet function by several mechanisms involving COX. Platelets are the prototype of cells that unequivocally contain COX-1 (9). COX is also found in endothelium. The PG and thromboxane produced in platelets serve both platelet-activating and platelet-inhibiting functions. PGI_2 is of particular interest because it prevents platelet aggregation but not adherence to the endothelium and is therefore important to minor endothelial injury healing (40). PGI_2 and NO produced in endothelium in response to the presence of activated platelets are platelet inhibitors and vasodilators. NSAIDs interfere with the synthesis of all these activating and inhibitory COX-1 products. However, in most cases, the overall clinical effect of NSAIDs is to inhibit coagulation by inhibiting production of thromboxane A_2.

Aspirin is the only NSAID that is used therapeutically for its antiplatelet effects. For most of the NSAIDs, the antiplatelet effect is transitory because it is concentration-dependent; when the serum drug level and thus the level of COX-1 inhibition drop below a threshold point, the antiplatelet effect is nil. With aspirin, however, the antiplatelet effect lasts for the life of the platelet after aspirin exposure, because aspirin irreversibly acetylates platelet and megakaryocyte COX and platelets are unable to synthesize new enzyme.

The net antiplatelet effect of NSAIDs may be useful in some patients who are vulnerable to thrombotic events, but it also creates a risk of excessive bleeding. Regular use of aspirin increases fecal blood loss and the risk of overt GI hemorrhage, especially in the elderly. With respect to perioperative bleeding, studies of NSAID effects have had conflicting results. In many cases, the potential effect on bleeding may be insignificant or outweighed by the risks involved in discontinuing the NSAID before surgery and allowing time for platelets to recover (at least a week for aspirin; hours to days for other NSAIDs). The risks of excessive bleeding are increased in patients with coagulopathies; patients who use alcohol, other anticoagulants, or zidovudine; or patients undergoing surgeries in which even small amounts of excessive bleeding may be harmful, but those risks should be considered carefully in all patients for whom regular NSAIDs are being prescribed (41).

Hepatic Dysfunction

Symptomatic hepatic effects attributable to therapeutic use of most NSAIDs are extremely rare and usually mild (42). There is no clearly established explanation for why some compounds are more hepatotoxic than others. It is possible that some compounds undergo oxidation, probably to the phenylic ring structure, yielding highly reactive metabolites. Compounds that cause mild hepatic damage, such as diclofenac and bromfenac, may produce some reactive epoxides during biotransformation (43). Some caution must be used in prescribing them to those with a history of hepatic dysfunction. NSAID overdose can lead to frank liver failure, especially with phenacetin and acetaminophen.

Uricosuria

Most NSAIDs increase the urinary excretion of urate and many, such as the salicylates, have been used to treat acute and chronic gout. This effect is dose-dependent, with low doses actually inhibiting urate excretion and high doses being necessary for gout treatment.

Central Nervous System Effects

Many NSAIDs cause CNS side effects, including headache, dizziness, and confusion. These can be severe enough to cause patients, especially the elderly, to discontinue treatment. The issue of memory loss with NSAIDs is still being debated. In one study, high-dose NSAID therapy was associated with a decline in longitudinal memory (44). Another study showed an inverse relationship between NSAID use and cognitive decline (45). NSAID use in Alzheimer-type and other dementias is an area that is just beginning to be studied. Some epidemiologic studies have shown a lower-than-expected prevalence or delayed onset of Alzheimer's disease in patients taking NSAIDs. The mechanism may involve COX-2–mediated suppression of microglial activity (46).

There have been reports of depression and paranoia with NSAID use. The mechanism and frequency of these adverse reactions have not been elucidated, but these reports indicate a need for caution in patients with psychiatric or substance abuse disorders.

Effects on Parturition

The inhibition of myometrial contractions during pregnancy depends on an equilibrium among a number of different inhibitors, which may include progesterone, PGI_2, relaxin, parathyroid-related peptide, and NO. Uterine responsiveness during pregnancy is controlled by estrogen and other uterotrophins during early stages and by uterotonins like oxytocin and PGs in later stages. The balance of these compounds may also be important at term, so that if one or more is withdrawn prematurely there may be a predisposition to premature delivery (47). The importance of PG in parturition is suggested by the increase in COX-2–mediated PG production in amniotic fluid at the approach of term, before the appearance of myometrial contractions. COX inhibitors are used to suppress myometrial contractility, thus delaying labor (48).

The closure of the ductus arteriosus is mediated by inhibition of PG synthesis. The constriction and ultimate closure of the ductus arteriosus can be accomplished by the use of potent NSAIDs, indomethacin being the most commonly used (49). With the advent of the COX-2 inhibitors, it may be possible to delay premature labor and close the ductus arteriosus with fewer side effects.

Effects on Dysmenorrhea and Menorrhagia

Primary dysmenorrhea is largely caused by endometrial PG. The endometrium and menstrual fluid of women with primary dysmenorrhea contain significantly higher levels of PG than those of women free of this condition. Three mechanisms have been identified by which PGs cause this type of pain. First, abnormal production of endometrial PG causes abnormal uterine contractility, which may be painful in itself. Second, this abnormal uterine activity can cause decreased uterine blood flow with resulting painful ischemia. Third, the cyclic endoperoxides that are intermediates in PG synthesis, along with relative increases in PGE_2, increase the responsiveness of pain fibers to such stimuli as movement or pressure, bradykinin, or histamine (50).

Most NSAIDs are significantly better than placebo at treating the pain of primary dysmenorrhea. This is at least in part the result of suppression of endometrial PG synthesis, as shown by the close correlation between reductions in pain and reductions in the concentration of PG in menstrual fluid. However, in this as in other types of pain, some of the analgesic effect may be the result of central mechanisms (50).

Menorrhagia is also in some cases the result of abnormal PG production. Specifically, some women with menorrhagia have been found to have elevated levels of PGI_2 metabolites compared to unaffected women. Since PGI_2 is a vasodilator that relaxes uterine smooth muscle and inhibits platelet aggregation, it is easy to see how abnormally elevated PGI_2 levels could contribute to menorrhagia. Studies have shown that women with menorrhagia may lose as much as 30% to 50% less blood

when they are treated with NSAIDs, such as ibuprofen, naproxen, or mefenamic acid, compared to treatment with placebo (50).

Prevention of Cancer

A number of studies have indicated a connection between NSAID use and decreased risk of colorectal cancers (51,52). The use of NSAIDs as a preventative measure for colorectal cancer is being studied and seems promising, but the appropriate dose and duration are still in question (53). COX has also been shown to be induced by polycyclic aromatic hydrocarbons, which thereby accelerate their own COX-mediated oxidation to more potently oncogenic compounds (54). COX-2 inhibitors may ultimately have a role in cancer prevention and treatment. Evidence is also accumulating that PGs produced by COX-2 are important to the growth and survival of many malignancies. PGs are known to affect mitogenesis, cellular adhesion, and apoptosis. There is evidence that some PGs enhance immunosuppressive effects of tumor cells. Some cancers, including cancers of the head and neck, breast, lung, and colon, form more PGs than normal tissues (55). A connection has been made between the activity of COX-2 and the development of colorectal cancer (53). The overexpression of COX-2 is associated with a resistance to apoptosis, and in one study this resistance was reversed by sulindac (56). If the risk of cancer may be increased by chronic inflammation via overexpression of COX-2, then the risk may be diminished by the use of prophylactic COX-2 inhibitors. With the advent of the selective COX-2 inhibitors, the use of NSAIDs in the treatment of cancers may turn out to be safe and effective.

PHARMACOKINETICS AND PHARMACODYNAMICS

Absorption

All NSAIDs and acetaminophen are readily absorbed from the upper intestinal tract and are generally given as oral preparations. Some absorption can also occur from the stomach, particularly if the pH is low. These drugs are also absorbed through any mucous membrane, so acetaminophen, aspirin, and many other NSAIDs can be given in suppository form, although this is done primarily with acetaminophen and aspirin for their antipyretic effect. The plasma concentration after oral administration reflects adequate oral dosage within 30 minutes and reaches a peak in approximately 2 hours. It gradually declines thereafter, depending on the half-life of the agent.

Physiochemical Properties

The NSAIDs are generally extensively plasma protein–bound (90% to 99%). The binding to other proteins and tissues varies between compounds. The exception is acetaminophen, which is only approximately 20% bound. NSAIDs are highly metabolized in the liver, with the exception of azapropazone and nabumetone, which are only 40% metabolized. Metabolism of NSAIDs in some cases serves to activate and in others to inactivate the compound and usually consists of hepatic conjugation to sulfuric or glucuronic compounds that return to the plasma. Small amounts of drug can be conjugated in other body tissues as well, but these amounts are insignificant. Most of the NSAIDs are acidic compounds. A few, such as azapropazone, are amphiprotic, having two ionizable sites.

Another property of interest is the chirality of some compounds, mostly the propionic acid derivatives or “profens,” ketorolac and etodolac. These compounds have a chiral center. Although they are used as racemates, the absorption, distribution, metabolic conjugation, and ultimate elimination of these molecules are stereospecific. In each case, the S-enantiomer is a much more potent COX inhibitor than the R-enantiomer. Conversion of the inactive R-enantiomer to the active S-enantiomer occurs unidirectionally *in vivo*, with the extent of the conversion varying between drugs and individuals. This may be part of the reason why the plasma concentrations of the profens (except naproxen, which is formulated as a pure active S-enantiomer) do not correlate well with effect, since both enantiomers are lumped together in ordinary measurements of serum concentration (57).

Distribution

Most NSAIDs and acetaminophen are rapidly (although unevenly) distributed throughout all body tissues by passive processes. The more lipid-soluble drugs have more CNS effects, both positive and negative. Because they are highly plasma protein–bound, the plasma concentrations are much higher than in other tissues. With ionization constants (pK_a) of most of the drugs being in the range of 3 to 5, pH is important to distribution (19,58).

One area of distribution that is of particular interest is the synovial fluid. The effective therapy of inflammatory conditions depends on getting the active form of drug (active metabolite, free fraction, or active enantiomer) to the tissue being targeted. In the case of arthritis, the target is the joint and the data show that NSAIDs seem to act primarily by inhibiting COX-2 in the synovial fluid. The synovial expression of COX-2 is different among inflammatory diseases with differing degrees of synovial inflammation (59). Uptake of NSAIDs into the synovial fluid occurs by a process of limited diffusion, which is affected by a number of physical and chemical properties (60). The half-life of NSAIDs in the synovial fluid parallels that in plasma.

Time Course of Effects

The relative time course of NSAID effects does not always follow the same curve as relative half-life. One possible explanation for this phenomenon is that different agents have different modes of COX inhibition.

A number of NSAIDs are reversible competitive inhibitors of both isoforms of COX (e.g., ibuprofen). A few are irreversible competitive inhibitors that covalently modify the enzyme (e.g., aspirin). For a third category, the course of action is more complex. These NSAIDs (e.g., flurbiprofen and indomethacin) are time-dependent inhibitors of COX-1 and COX-2 that show an apparent slow increase in the potency of inhibition over time. It appears that they initially form a reversible enzyme-inhibitor complex that subsequently becomes a less reversible complex, probably due to a change in conformation. There have been reports that some of the COX-2–selective compounds may be selective because of differences in the time-dependence of the inhibitor-enzyme complexes they form with COX-1 and COX-2. They may be weak competitive inhibitors of COX-1 and slow time-dependent inhibitors of COX-2. What this means clinically needs more study (61).

Excretion

All nonopioid analgesics are excreted primarily in the urine, both in free and in conjugated form. The relative concentrations of the free and conjugated forms vary with the pH of the urine, with higher concentrations of the more acidic form being found in alkalinized urine. Small amounts of these drugs are also found in the bile and thus pass into the intestine to be excreted in the feces.

CLASSIFICATION OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

A number of different classification schemes for NSAIDs have been suggested based on various clinical and pharmacologic features. One is to classify them according to their ability to inhibit COX-1 or COX-2, either in absolute terms or as a ratio between the two. Various attempts to create such a classification have yielded very different absolute measurements of inhibitory power, but similar results when rank-ordering the drugs according to their COX-2/COX-1 ratios. However, there are still too many variables for this classification scheme to be consistent enough to be useful (62).

Another potential way of classifying NSAIDs is by their mode of inhibition, as discussed previously under Time Course of Effects. Classification by serum half-life is of limited value because of the lack of correspondence between serum half-life and effect half-life. Classification according to acidity of the compound, which influences absorption, distribution, and side effects, is also not very helpful because so few of the NSAIDs are nonacidic at this time.

Chemical classification (Table 83-1), old-fashioned as it may be, remains the most useful way of sorting these drugs into groups with similar clinical properties and is used to organize the following discussion of individual drugs.

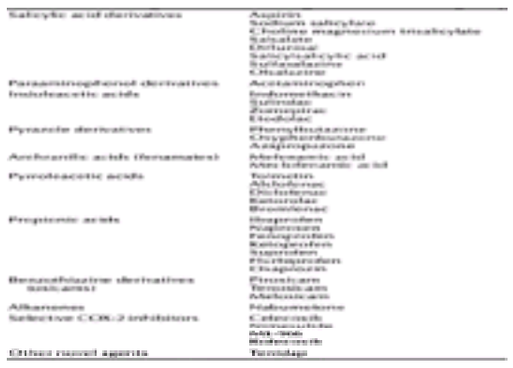

TABLE 83-1. Classification of nonsteroidal antiinflammatory drugs

PHARMACOLOGY OF INDIVIDUAL DRUGS

Salicylates

Aspirin

Aspirin is reviewed in detail here as the prototypic salicylate, but individual characteristics of other drugs of this class are also discussed. Table 83-2 and Table 83-3 outline their classification, pharmacokinetics, pharmacology, and adverse effects.

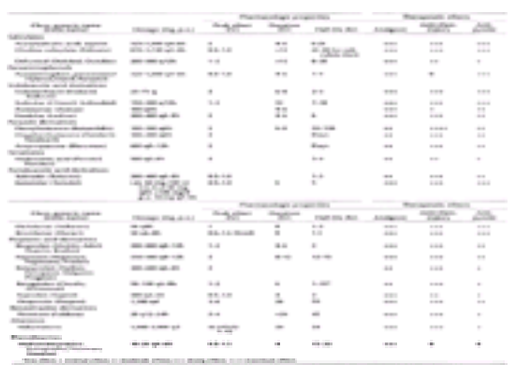

TABLE 83-2. Nonopioid (nonnarcotic) analgesics: classification, pharmacokinetics, and pharmacology of nonopioid analgesics

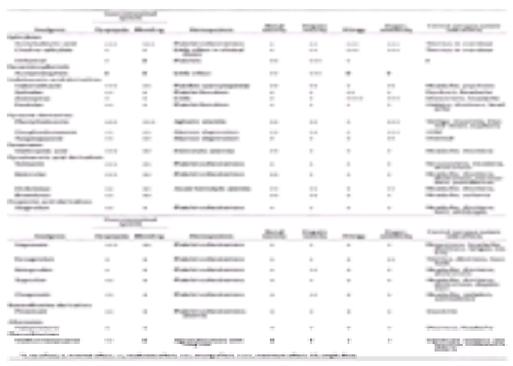

TABLE 83-3. Nonopioid (nonnarcotic) analgesics: adverse (toxic) and other physiologic effects of nonopioid analgesics

Pharmacology. Aspirin is probably the most widely used analgesic. It has strong antipyretic and antiinflammatory properties in addition to its analgesic effects. Aspirin covalently acetylates the active site of COX, irreversibly inhibiting the enzyme. Its clinical effects are all probably based on central and peripheral inhibition of PG production. The analgesic effect is primarily a peripheral effect, although a central action has been hypothesized, possibly in the hypothalamus.

Analgesia is most effective for mild to moderate pain arising from integumental structures rather than from the viscera. Aspirin is effective in relieving moderate to severe bone pain. It is also commonly used for its platelet-inhibiting effects to reduce the risk of myocardial infarction and stroke.

Aspirin is absorbed rapidly from the stomach and upper small intestine when taken orally, with peak plasma levels being reached in approximately 2 hours. It is approximately 70% converted to salicylate in approximately 30 minutes. The rate of absorption depends on multiple factors, including disintegration time and dissolution rate of tablets and pH of the surface of the mucosa. The dissolution time is the rate-limiting step in the process and is the target for different preparations. Rectal absorption is slower and is variable depending on retention time.

This compound is distributed throughout most body tissues by a passive pH-dependent process. It is bound to plasma proteins, especially albumin. This may be a cause for concern in hypoalbuminemic states such as those seen in rheumatoid arthritis. Its interactions with other highly bound medications are variable.

Metabolism occurs primarily in the liver, and excretion is through the urine and feces in conjugated forms. The plasma half-life for aspirin is approximately 15 minutes. For salicylate, one of its metabolites, the plasma half-life is 2 to 3 hours for low doses and up to 30 hours for high doses (63). Changes in urinary pH result in profound changes in excretion. The higher the pH, the greater the excretion rate (64).

Side Effects. The primary side effects of salicylate ingestion are epigastric distress, nausea, and vomiting. All salicylates can produce GI hemorrhage, exacerbation of peptic ulcer disease, and erosive gastritis. Chronic aspirin ingestion can produce iron deficiency anemia through blood loss from the GI tract. GI problems are usually dose-related but can be seen as a hypersensitivity response at low doses. Self-limiting and reversible changes of liver function can occur with high doses of aspirin (38). Bleeding time is prolonged with even small doses, and a single dose of aspirin can double the bleeding time for up to 1 week. Aspirin should therefore be avoided in patients with liver damage, hypoprothrombinemia, vitamin K deficiency, or hemophilia.

Salicylate intoxication is marked by CNS disturbances and significant alterations in acid–base balance and can be fatal.

Another complication of aspirin therapy is the hypersensitivity response, which was discussed in more detail previously. Briefly, it is more common in adults than in children, and a previous history of hypersensitivity to other chemicals or the tetrad of asthma, rhinitis, nasal polyps, and sinusitis are warning signs. An acute anaphylactoid response, which can be fatal, can also be seen with small doses of aspirin.

The use of salicylates in viral syndromes has been epidemiologically associated with Reye's syndrome, a two-phase illness that occurs predominantly in children and

adolescents. The first phase is a viral illness, most frequently influenza or chickenpox, which includes fever, vomiting, general malaise, or upper respiratory symptoms. At 3 to 5 days from onset of the viral illness, there is onset of vomiting and a change in neurologic state, probably caused by cerebral edema and hepatic dysfunction with a resulting increase in ammonia levels. Encephalopathy may persist for 1 to 4 days with a slow return to premorbid neurologic function over a number of weeks. It is not clear whether salicylates cause Reye's syndrome and, if so, by what mechanism, but it has been proposed that these drugs may act together with certain viruses to damage mitochondria in susceptible individuals. It has been suggested that after a viral illness, individuals who have a preexisting genetic or metabolic defect in metabolism may experience a higher than usual concentration of calcium in the mitochondria, which with the addition of salicylates could set the proposed reaction into motion. This reaction has been called *mitochondrial permeability transition* and is thought to involve mitochondrial swelling, depolarization, and the uncoupling of oxidative phosphorylation (65).

Aspirin is probably the most nephrotoxic of the NSAIDs. The nephrotoxicity of phenacetin/aspirin combinations, which was at one time attributed to phenacetin, may well have been due to aspirin. The combination of other analgesics with aspirin may synergistically exacerbate aspirin's nephrotoxicity (12). Such combinations should be used with caution, if at all.

Choline Magnesium Trisalicylate

Choline magnesium trisalicylate is a mixture of choline salicylate and magnesium salicylate. Its analgesic, antipyretic, and antiinflammatory properties are similar to those of aspirin. It does have some different properties, however, that can make it preferable to the more commonly used aspirin. It is water-soluble and thus is available in both tablet and liquid forms, making it more convenient for pediatric use. It has a much longer half-life than aspirin and can be prescribed on a once- to twice-daily basis, resulting in better compliance with the therapeutic course.

At therapeutic doses, choline magnesium trisalicylate does not demonstrate significant inhibition of platelet aggregation and can be used in circumstances in which the bleeding potential of aspirin is a problem (e.g., in patients with a bleeding diathesis or who are in the perioperative period). Because it is water-soluble, it causes significantly less irritation of the gastric mucosa, so it is often tolerated by those in whom gastric irritation precludes aspirin use.

Diflunisal

Diflunisal is a difluorophenyl derivative of salicylic acid marketed primarily as an analgesic. It is not a clinically useful antipyretic, probably because it does not cross into the CNS (66). It has an 8- to 12-hour half-life, but it also shows a gradual increase in drug levels over time with continued use. This means that dosing is necessary only twice a day but that a loading dose is necessary to reach effective plasma concentrations.

Diflunisal is less irritating to the GI tract than aspirin and also has much less effect on platelet aggregation, its effects being readily reversible on discontinuation of the medication. A potentially life-threatening hypersensitivity reaction has been reported, with fever, chills, and rash followed by progression to multiple organ involvement. This reaction has not been seen with other salicylates (67).

Paraaminophenol Derivatives

Acetanilid, a parent compound of paraaminophenol derivatives, was introduced as an antipyretic in 1886. Derivatives were synthesized because of its toxicity, and phenacetin was ultimately introduced as an analgesic-antipyretic. Acetaminophen (paracetamol) was identified as phenacetin's active metabolite in humans, and it is now the most common derivative of paraaminophenol in use. Phenacetin was removed from the market because of the high correlation found between its use and nephrotoxic effects.

Acetaminophen (Paracetamol)

Pharmacology. Acetaminophen (like phenacetin) has analgesic and antipyretic effects similar to those of aspirin. Acetaminophen appears to act as a PG synthesis inhibitor, but it seems that its effect is more pronounced centrally than peripherally (68). Perhaps this is why it is more specifically antipyretic than antiinflammatory, but it also suggests that the analgesic activity of all NSAIDs may be related to central activity as well as to peripheral antiinflammatory effects.

Absorption from the stomach is minor. Most of the drug is absorbed by passive diffusion in the small intestine, making the rate of absorption dependent on the rate of gastric emptying. Acetaminophen's plasma half-life is approximately 2 hours.

This mild systemic analgesic is often combined with weak opioids in compounds for the relief of mild to moderate pain. It is recommended as an antipyretic and can be used for those sensitive to aspirin and for children and adolescents, in whom Reye syndrome is associated with aspirin treatment for fever.

Side Effects. Toxic effects are rarely seen in individuals who adhere to recommended therapeutic doses, which are limited to a maximum of 4 g per day. When phenacetin was available, toxic effects from therapeutic doses appeared in individuals who could not metabolize the compound to acetaminophen.

The major toxicity of acetaminophen is on overdose, especially acute overdose (>;10 to 15 g). Nephrotoxicity, thrombocytopenia, and hepatic toxicity are the primary toxic side effects of acute or chronic overdose of phenacetin or acetaminophen. Methemoglobinemia and hemolytic anemia, although common with high doses of phenacetin, are rarely seen with acetaminophen.

The mechanism for damage by acetaminophen is through a highly reactive metabolite that normally is inactivated by glutathione. Overdoses of acetaminophen deplete glutathione stores, allowing the metabolite to accumulate and bind covalently to cell constituents. In severe cases, the result may be acute hepatic necrosis, which can progress to fulminant liver failure (69).

The combination of aspirin and phenacetin was once thought to be the cause of analgesic nephropathy, and there has been concern that acetaminophen could have similar toxicity (69). However, studies have shown that acetaminophen is unlikely to contribute to analgesic nephropathy. Aspirin and the salicylates, on the other hand, are more clearly nephrotoxic (70). Combinations of aspirin with acetaminophen or other analgesics may act synergistically to increase this potential toxicity (71). Since such combinations have not shown any advantage over either drug alone, they should be avoided.

Indoleacetic Acid Derivatives

Indoleacetic acid derivatives were synthesized after a search for drugs with antiinflammatory properties. The initial product was indomethacin, introduced to clinical care in 1963 specifically for the treatment of rheumatoid arthritis. Other compounds with less toxicity than indomethacin have been found, and it is likely that this group of compounds will yield more useful medications in the future (72).

Indomethacin

Pharmacology. Indomethacin has prominent analgesic, antiinflammatory, and antipyretic properties, similar to those of aspirin. Because it is one of the most potent inhibitors of COX, it is used primarily for its antiinflammatory properties in the treatment of rheumatologic disease. Additionally, after aspirin it is one of the analgesic drugs of choice for the initial treatment of pain associated with metastatic disease of bone (73). It is also a uricosuric and is used to treat acute gout. Once control of target symptoms has been attained with indomethacin, a less toxic NSAID should usually be substituted.

Side Effects. A high incidence of untoward side effects has been noted with the use of indomethacin (67), and approximately 20% of patients are intolerant of this medication. GI complaints, including nausea, anorexia, and abdominal pain, are common. Ulceration can occur anywhere in the upper GI tract, with perforation and hemorrhage. Acute pancreatitis has been reported, and rarely, fatal hepatitis and jaundice have been seen (74). Indomethacin can cause sodium and water retention; it also antagonizes the effects of diuretics and the antihypertensive effects of propranolol (70). It can produce severe headache and has also been implicated in the production of depression, psychosis, hallucinations, and suicide. Bone marrow depression and, rarely, aplastic anemia can occur with long-term administration. A hypersensitivity reaction similar to that noted with aspirin can occur, and some cross- sensitivity can be present. Because of the severity of some of these side effects it is recommended that indomethacin be used as tolerated over a limited period (e.g., 2 weeks) and that other less toxic compounds be substituted when the pain,

inflammatory process, or both, are under control.

Sulindac

Sulindac is closely related to indomethacin and was produced as an alternative with less toxic side effects (52). It is used primarily for the treatment of rheumatologic problems.

Sulindac is a prodrug (i.e., an inactive chemical that is metabolized to an active compound). Its sulfide metabolite is a potent inhibitor of COX. This probably accounts for sulindac's low rate of GI side effects, because the active drug does not appear in the GI tract.

Toxic effects are nevertheless primarily GI but are not severe and are restricted mostly to abdominal pain, nausea, and constipation. Drowsiness, dizziness, and headache can also occur. Skin rash and pruritus have also been reported. Some cross-sensitivity to aspirin can occur, with possible similar manifestations.

The best evidence linking an NSAID with liver disease is with sulindac. There are a number of reports in which hepatitis was seen on rechallenge, suggesting some sort of causal relationship (75).

Zomepirac

Zomepirac was produced from the indoleacetic acid molecule and is primarily an analgesic agent (72). It has antiinflammatory and antipyretic properties, but these, especially the former, are not pronounced; the antiinflammatory effects are far weaker than in other compounds of this class.

Zomepirac displays a low tendency to produce GI and hemopoietic side effects. It has been discontinued in North America, however, because of a relatively high incidence of fatal allergic responses associated with its use.

Etodolac

Etodolac is a chiral NSAID marketed as the racemate. It and its acylglucuronide metabolite are well distributed into synovial fluid (76). Etodolac appears to inhibit COX-1 and COX-2 equally well. It also inhibits the formation of bradykinin, which may add to its activity as an analgesic. It is used in rheumatoid arthritis, osteoarthritis, tendonitis, and bursitis as an analgesic and antiinflammatory. It has been used long term (>1 year) with few problems. It is a uricosuric and also has been used in acute gout (52).

Etodolac is well tolerated and causes less GI irritation and ulceration than a number of other compounds. This may be because of a minimal effect on PGE_2 and PGI_2 in gastric mucosa (62).

Pyrazole Derivatives

Pyrazole derivatives were originally introduced as antipyretics in the late nineteenth century. They were then found to have analgesic and antiinflammatory properties and came to be used for these as well. The two most common forms, antipyrine and aminopyrine, were used extensively and appeared in many over-the-counter medications until it was discovered that aminopyrine caused severe bone marrow toxicity. In 1938, aminopyrine was prohibited for use in the United States. Pyrazole derivatives interfere with PG synthesis by inhibiting COX, and this appears to be the basis for their antipyretic, analgesic, and antiinflammatory effects. They also induce hepatic microsomal enzyme systems and thus increase biotransformation of many other drugs.

Phenylbutazone

The introduction of phenylbutazone was somewhat accidental. It is a congener of antipyrine and aminopyrine and was used originally as a solubilizing agent for aminopyrine. When these compounds were withdrawn from clinical use, a search for pharmacologic relatives yielded phenylbutazone as a possible therapeutic agent.

Phenylbutazone has analgesic, antiinflammatory, and antipyretic properties. In addition to inhibiting the synthesis of PG, it inhibits the synthesis of mucopolysaccharide sulfates in cartilage and uncouples oxidative phosphorylation. All of these actions probably contribute to its antiinflammatory, antipyretic, and analgesic effects. It is more effective than aspirin as an antiinflammatory agent but less effective as an analgesic. It is used only for short-term acute gouty arthritis, active rheumatoid arthritis, active ankylosing spondylitis, and acute attacks of osteoarthritis of hips and knees where there is no other option. It should not be used when other less toxic agents are available (67).

Phenylbutazone has a short half-life and requires multiple daily dosing.

Although its primary untoward effects are GI, CNS effects are seen in a small number of individuals. The most important adverse effects are primary or activated ulcer disease, serum-sickness-type hypersensitivity, hepatitis, nephritis, and various forms of bone marrow depression, which can lead to aplastic anemia and agranulocytosis. These toxic reactions are more often seen in elderly individuals, and thus phenylbutazone should not be used in this population. Approximately 60% of the patients who develop hepatic injury from phenylbutazone do so within 6 weeks. Phenylbutazone should therefore be used only in the unusual case in which no other alternative is available, and only for the shortest possible time to minimize the risk of hepatic injury.

Oxyphenbutazone

Oxyphenbutazone is a metabolite of phenylbutazone and is primarily an antiinflammatory, but it can be used for its analgesic and antipyretic effects. It is more highly protein-bound than its parent compound and has a plasma half-life of up to several days. This gives it some possible advantages in that effective serum concentrations can easily be maintained.

Oxyphenbutazone tends to produce less gastric irritation than phenylbutazone and is more readily tolerated by some individuals.

Azapropazone

Azapropazone is another derivative of phenylbutazone and has similar activity. Its pharmacokinetics are similar to those of phenylbutazone but unlike the parent compound it is not extensively metabolized. It is excreted unchanged in the urine at a rate of 60% to 70%. It is used primarily for the treatment of rheumatic conditions, not as an analgesic. It has a potent uricosuric effect, so it is useful for treating acute gout.

Azapropazone has significantly fewer side effects than phenylbutazone and has low toxicity. The overall incidence of untoward reactions is probably lower than 10%. No cases of agranulocytosis have been reported to be associated with its use.

Anthranilic Acids (Fenamates)

The fenamates were discovered in the continual search for “a better aspirin.” The amine analog of salicylic acid and anthranilic acid was investigated, and a number of compounds derived from it were studied as analgesics, antiinflammatory agents, and antipyretics. Because of the toxicity of most of these compounds, few are now available for clinical use.

Mefenamic Acid

Mefenamic acid is a COX inhibitor. It may also act as a PGE_2-receptor antagonist, as it competes for PG-receptor binding sites *in vitro* (68). It has been proposed for use primarily for its analgesic properties in rheumatic diseases, but it can also reduce pain in soft tissue injuries, other painful musculoskeletal conditions, and

dysmenorrhea (77). However, due to toxicity it is rarely if ever indicated for these conditions.

In addition to a significant number of GI adverse effects, isolated cases of hemolytic anemia that might be of autoimmune origin have been reported with the use of mefenamic acid. In view of its toxicity and the fact that this drug offers no advantage over other available agents, it should not be used.

Pyrroleacetic Acid Derivatives

In the search for a molecule that would maintain antiinflammatory and analgesic efficacy with fewer side effects than current agents, elaboration on pyrroleacetic acid resulted in the discovery of tolmetin sodium in the mid-1970s and other compounds subsequently (78). However, as with most other families of compounds produced to date, clinical effectiveness in this class came only with the usual side effects and toxicity.

Tolmetin

Tolmetin has antiinflammatory effects somewhere between those of aspirin and phenylbutazone (78). It is structurally related to zomepirac. It also appears to interfere with the PG cascade to produce its antiinflammatory effects. It has good antipyretic and analgesic actions, although it is not primarily prescribed as an analgesic. Its main use as an antiinflammatory agent has been for rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Overall, in clinically effective doses, the incidence of side effects is slightly lower than with aspirin and significantly lower than with phenylbutazone. Peripheral edema, sodium retention and hypertension have occurred. Each 200-mg tablet of tolmetin contains 0.8 mEq of sodium, a fact that should be considered in patients who require strict sodium restriction.

Alclofenac

Alclofenac is a new compound that is similar to tolmetin but is slightly less effective in terms of its antiinflammatory effects. It is not presently available in North America.

Diclofenac

Pharmacology. Diclofenac is a potent nonselective inhibitor of COX, but it does have a favorable ratio of COX-2 to COX-1 inhibition and so may provide antiinflammatory effects with less toxicity (79). It also may reduce the migration of leukocytes into sites of inflammation by causing them to shed l-selectin, an adhesion receptor involved in the initial binding of leukocytes to activated endothelium. Aspirin, indomethacin, and ketoprofen also appear to share this property (80). This may be another reason for the wide range of variability in NSAID effectiveness.

The bioavailability of diclofenac is 60% lower than many other NSAIDs due to significant presystemic elimination (81).

Diclofenac is commonly used for osteoarthritis, rheumatoid arthritis, and gout. It is also used in an ophthalmologic preparation for cataract surgery to maintain pupillary dilatation (82).

Side Effects. GI side effects are the most common ones reported. Elevation of hepatic aminotransferases occurs in approximately 15% of users and is usually reversible. There have been a number of case reports of hepatitis from diclofenac. In two cases, rechallenge led to hepatotoxicity. It is still not clear that diclofenac is more hepatotoxic than other NSAIDs, but the recommendation is that aminotransferases be evaluated during the first 8 weeks and that the drug be discontinued if abnormal levels persist or if there are any signs of overt liver injury. Impaired clearance of a metabolite may be the problem (75).

Ketorolac

See Table 83-4 for dosage guidelines for ketorolac.

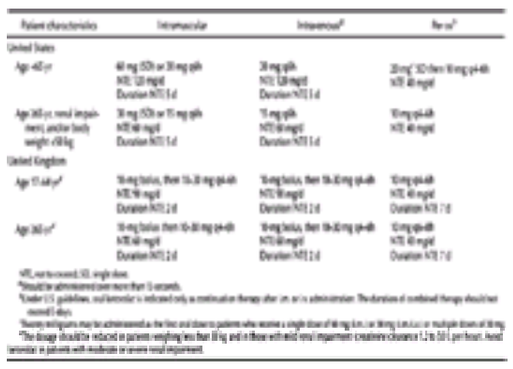

TABLE 83-4. Ketorolac dosage guidelines for the United States and United Kingdom

Pharmacology. Ketorolac is a potent analgesic, but its antiinflammatory activity is only moderate. However, because potential toxicity limits ketorolac to short-term use, actions other than analgesia are less important. Ketorolac may cause analgesia through some central opioid-related effect, the release of endogenous opioids, a modulatory effect on opioid receptors, or altered opioid kinetics. Another theory is that it influences NO, which in turn is thought to have an effect on COX (83).

Ketorolac's primary use is as an analgesic for mild to moderately severe acute pain states. The analgesia from ketorolac is delayed but lasts longer than that of the standard opioids. Combining it with opioids can allow opioid doses to be reduced by 25% to 50%, thus reducing opioid side effects. Ketorolac has been used for renal colic, migraine, sickle cell crisis, postoperative pain, and gynecologic surgery.

Ketorolac is available as a tromethamine salt, which enhances its aqueous solubility and makes it one of the few NSAIDs available in parenteral as well as oral forms. It also has antiinflammatory activity topically and is available as an ophthalmic preparation.

Maximum plasma concentrations are reached 30 to 60 minutes after intramuscular, subcutaneous, rectal, or oral administration. The half-life is approximately 5 hours in normal subjects and increases in the aged and renally impaired up to 6 to 7 and 9 to 10 hours, respectively.

Side Effects. The long-term use of ketorolac is not recommended because of an increased risk of adverse effects. The largest number of reported adverse effects are GI and hematologic. GI ulceration occurs most often in stomach and duodenum but colonic ulcers have also been found, suggesting a systemic effect. A postmarketing study of GI and operative-site bleeding found a correlation between risk of bleeding, age, drug dosage, and duration of therapy. There have also been cases of reversible nephropathy after even short-term parenteral treatment.

Bromfenac

Bromfenac is a phenylacetic acid derivative related to diclofenac. It was approved by the U.S. Food and Drug Administration in 1997 and is indicated for short-term management of pain, usually less than 10 days. It is a potent analgesic with rapid onset (30 minutes) and duration of action of approximately 8 hours. The compound has been studied against ketorolac, naproxen, and acetaminophen/oxycodone combinations and has shown efficacy.

The side-effect profile is equivalent to other drugs in the class, with GI upset and headache being the most common. It also carries a warning about severe hepatic

reactions, usually in patients taking the drug for longer than 1 month (84). It was removed from the market in mid-1998 due to liver toxicity.

Propionic Acid Derivatives

The search for new aspirinlike compounds has been most successful among compounds of the propionic acid family, which offer advantages over many older antiinflammatory analgesic compounds. In fact, some of these agents, such as ibuprofen and suprofen, are now marketed primarily as analgesics. They were introduced in the early 1970s, and newer compounds of the group continue to appear. This causes some difficulty for the practitioner because heavy promotion by pharmaceutical firms makes it difficult to identify which drugs are more beneficial than other nonopioid analgesics.

Propionic acid derivatives all have effective antiinflammatory, analgesic, and antipyretic activity. They all act by inhibiting COX and interfering with PG synthesis, although with widely varying potency from one agent to another. As would be expected, they produce GI side effects, cause GI erosion, alter platelet function, and produce prolonged bleeding times.

The compounds in this class, along with ketorolac and etodolac, are chiral drugs. Although marketed as racemic mixtures, there are differences in the activity and pharmacokinetics of different isomers. The NSAIDs in which this has been primarily studied are the two arylpropionic acids and ketorolac (85). Stereoselectivity has been shown to occur in conjugation reactions and in elimination. A unidirectional stereospecific inversion of inactive R-enantiomer to the active S-enantiomer occurs *in vivo* and is variable. The amount of conversion depends on drug and interpatient differences (7,20,85).

Ibuprofen

Ibuprofen is the most widely used of this class of compounds. It is now available as an over-the-counter preparation in North America (e.g., Nuprin, Datril, Advil) and as a suspension (e.g., Pedia-Profen). Ibuprofen is rapidly absorbed from the upper GI tract and is also available in suppository form as it is well absorbed rectally, although at a slower rate. It is 99% plasma protein–bound and passes slowly through the synovium, the site of greatest importance in the treatment of rheumatologic diseases. It is used equally as an analgesic and antiinflammatory and, although not advertised as such, also has antipyretic properties (67).

Ibuprofen has been approved for cautious administration in people with peptic ulcer disease, but its use is not advised when active untreated ulcers are present. A low incidence of other side effects is associated with its use.

Naproxen

Naproxen is readily absorbed from the GI tract when taken either orally or rectally. Uptake is rapid, but absorption of orally administered drug can be slowed by concomitant ingestion of food, aluminum hydroxide, or magnesium oxide or increased by ingestion of sodium bicarbonate. Naproxen has a long half-life in plasma of 12 to 15 hours; this is a factor in its popularity because it can be given two times a day.

Naproxen is somewhat more toxic than ibuprofen, having more GI and CNS effects. The CNS uptake of the drug is good enough that it is one of the first-line NSAIDs in migraine. There are rare reports of clinical liver disease. In the cases in which jaundice occurred, resolution was rapid and complete (75).

Fenoprofen

Fenoprofen is more often used for rheumatologic problems than as an analgesic (86). It is extremely well tolerated as compared to other nonopioid analgesics.

Ketoprofen

Ketoprofen is used primarily as an antiinflammatory agent in the treatment of rheumatic disease. Like some other NSAIDs, it may affect adhesion molecules and bradykinin (64). The primary side effect is GI disturbance, which occurs in approximately 15% of patients, causing discontinuation in approximately 5%.

Suprofen

Suprofen is the first of the propionic acid derivatives to be presented primarily as an analgesic, although it shares antiinflammatory and antipyretic properties with other compounds of its class (87). Its use has been associated with flank pain thought to be caused by uricosuric activity, and the oral drug was consequently removed from the North American market. The ophthalmologic preparation used for inhibition of intraoperative miosis is available in the United States (29).

Flurbiprofen

Flurbiprofen is one of the most potent of this NSAID class. It has been marketed most heavily for such unusual indications as periodontal disease, in which it (and other NSAIDs) have been found to reduce bone loss (88). Like suprofen and diclofenac, it is also marketed as an ophthalmic solution for prophylactic inhibition or reduction of intraoperative miosis. PG and other substances (substance P) appear to mediate contraction of the pupillary sphincter in response to surgical manipulation. This type of miosis is independent of the cholinergic receptors, and flurbiprofen does not interfere with the miotic effect of acetylcholine when this is administered to induce desired miosis intraoperatively (89).

Oxaprozin

Oxaprozin has a half-life of approximately 55 hours, making it the only propionic acid derivative that can be given once daily. It is well absorbed orally, with peak concentrations in 3 to 6 hours, which may be a disadvantage in acute pain. It has saturable protein binding, which may give it an advantage over other long half-life NSAIDs (e.g., piroxicam) in that it may be less likely to accumulate. It is also a uricosuric (16).

It is used for treatment of many painful inflammatory conditions such as osteoarthritis, rheumatoid arthritis, gouty arthritis, and other acute and chronic conditions such as tendonitis and bursitis (67).

Oxaprozin is well tolerated. The most frequently reported side effects are GI and mild CNS effects.

Benzothiazine Derivatives (Oxicams)

The benzothiazine derivatives are the latest class of chemical compounds to be studied for their combined analgesic, antiinflammatory, and antipyretic effects. They were introduced to the North American market in 1982 (90).

Piroxicam

Piroxicam is one of the oldest and most studied of the oxicams. It is used as a standard in numerous studies. Its long half-life and its relative COX-1 specificity make it theoretically not an ideal drug for short-term patients with other risk factors for toxicity.

Piroxicam is completely absorbed when given orally, and concomitant ingestion of food and antacids does not affect absorption. It is used primarily for arthritis and acute musculoskeletal injuries because of its combined analgesic and antiinflammatory effects. It has the advantage of a long half-life (50 hours), permitting once- or twice-daily dosing for improved compliance.

Up to 40% of patients experience GI side effects. These are severe enough to cause discontinuation of the drug in only approximately 10% of patients.

Tenoxicam

Tenoxicam is a derivative of the oxicam class. It has been studied in acute and chronic rheumatic diseases for analgesia and antiinflammatory activity. It affects leukocyte function and may affect oxygen radicals.

It is completely absorbed in 1.0 to 2.6 hours, which can be delayed to 4 to 6 hours by food, and has an elimination half-life of 60 to 75 hours. The long half-life is an advantage in chronic conditions, allowing once-daily dosing. It is one of the least lipophilic of the NSAIDs, which may decrease its risk of side effects in certain tissues such as CNS, fat, and skin. It has good penetration into synovial fluid, which may be the site for its activity in chronic inflammatory diseases.

Tenoxicam is comparable to piroxicam with respect to effectiveness and side effect profile. It is not marketed in the United States at this time.

Meloxicam

Meloxicam is a selective COX-2 inhibitor, with some COX-1 activity. At this time it is in late phase III trials and is not available in the United States. After oral dosing, the half-life of meloxicam is approximately 20 hours and its time to maximum concentration is 5 to 6 hours. There is also a parenteral form. Meloxicam is metabolized in the liver and the metabolites are excreted in urine and bile.

This drug has been studied in rheumatic diseases and found to be as effective as the NSAIDs to which it was compared (piroxicam, diclofenac, and naproxen) (91). These same studies showed that meloxicam, compared to a group of standard NSAIDs, caused fewer GI and renal side effects (92).

Alkanones: Nabumetone

Nabumetone is a member of another new class of NSAIDs, the alkones. It is a nonacidic prodrug that weakly inhibits COX. The metabolite 6-methoxy-2-naphthylacetic acid (6-MNA) is a potent inhibitor of COX. It is not known which COX 6-MNA inhibits in humans, but there is some evidence in animals that it might be COX-2–specific.

Because nabumetone is then metabolized into inactive metabolites that are excreted in the urine, there is no biliary excretion and no enterohepatic recycling. This fact, along with nabumetone's status as a nonacid prodrug, gives it a lower propensity for causing GI side effects. This has been borne out in a number of studies comparing it to naproxen and ibuprofen (93).

Nabumetone's reported side effects are still most commonly GI, but they are minor, usually involving abdominal pain, dyspepsia, diarrhea, and flatulence. Although there are GI side effects reported at comparable levels to diclofenac, ibuprofen, naproxen, and sulindac, there is little evidence to show that there is much GI toxicity (94).

Selective Cyclooxygenase-2 Inhibitors

Celecoxib

A number of new compounds are undergoing trials. Celecoxib is a nonacidic tricyclic selective COX-2 inhibitor that shows promise in rheumatoid conditions and pain. It has recently been released in the United States, as has Rofecoxib, a drug with similar characteristics.

Nimesulide

Nimesulide is a sulfonamide compound once thought to have a novel mechanism that is now believed to be weak inhibition of COX- 2. It may have other novel mechanisms including oxygen radical scavenging and inhibition of oxidative metabolism by neutrophils, plus effects on tumor necrosis factor-a and platelet activating factor. Nimesulide has a pK_a value of 6.5, which is an important factor for its favorable GI tolerability. It has been used for a number of years in Italy and is as effective as a number of reference agents (e.g., peroxicam, diclofenac, and etodolac) for a number of acute and chronic inflammatory conditions. It also has fewer reports than other NSAIDs of problems with cross-reactivity with aspirin or in patients with asthma (95). It is not marketed in the United States at this time.

Another compound is Rofecoxib, a long-half-life selective COX-2 inhibitor that is undergoing trials in osteoarthritis with good results and few side effects. It also crosses the blood–brain barrier, so it is of interest in Alzheimer's disease. It is also being studied for possible effects on colon cancer (96). It was released in the U.S. in 1999 and is indicated for osteoarthritis, acute pain, and dysmenorrhea. COX-2 inhibitors seem to reduce GI and platelet side effects, but renal toxicity remains a problem.

Other mechanisms are being tested, such as combined COX-2 and 5-lipoxygenase inhibitors (97).

Other Novel Agents: Tenidap

Tenidap is a new drug with a novel dual mechanism of action: It modulates the production and activity of some proinflammatory cytokines and inhibits COX. Its place in rheumatic diseases may include treatment *and* disease modification (2). It has a side effect profile consistent with other COX inhibitors, mainly GI and some renal effects. It can cause a reversible proteinuria that is probably due to the compound's inhibition of tubular function rather than to tubular or glomerular damage (98).

The use of tenidap and other disease-modifying antirheumatic drugs is likely to increase in the future, producing new information that may enable us to treat pain and inflammation more successfully and with much less toxic drugs.

The dramatic increase in information about mechanisms of nociception (Chapter 3) **[[AU: 6]]** is likely to lead to new drugs with higher specificity of action and, it is hoped, fewer side effects.

ACKNOWLEDGMENTS

The author wishes to acknowledge Dr. Stephen H. Butler and Dr. Constantino Benedetti, authors of the chapter covering this topic in the previous edition, some of whose text has been retained in this edition. The author also wishes to acknowledge Dr. Susan Woyna for her assistance in the editing of this chapter.

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CHAPTER 84

Systemic Opioid Analgesics

H. Richard Miyoshi and Susan G. Leckband

This chapter discusses the pharmacology and some aspects of the clinical application of systemic opioid analgesics, which include opioid agonists, agonist-antagonists, and combination drugs used in pain control. For many decades, these drugs, given alone or as part of a multimodal program, have been the most frequently used method of pain control. The reason for their popularity and widespread use is that in most countries of the world they are readily available and inexpensive, and, when properly administered, provide effective pain relief (1,2,3,4,5,6,7 and 8). Recently, great advances have been made in our knowledge of pain and its mechanisms and of the pharmacokinetics, pharmacodynamics, and general pharmacology of systemic opioids. This has been accompanied by a marked improvement in older delivery systems and the use of novel new ones.

These advantages and recent advances in formulations and delivery systems usually permit the selection of an optimal drug, dose, and route for providing pain relief. However, this is often not done. Bonica indicated in the previous edition that most patients with acute pain, cancer pain, and chronic nonmalignant pain were not provided with adequate relief. Although this probably happens less often today, it continues to occur because students of medicine, nursing, dentistry, and other health professions responsible for providing care to patients in pain are still not appropriately trained in the clinical pharmacology and appropriate use of these drugs. Consequently, many practitioners underestimate the dosage range and overestimate the duration of action of systemic analgesics and have irrational fears of producing addiction, physical dependence, and respiratory depression.

This chapter provides some of the information that clinicians need to optimally use opioids. We present an overview of the pharmacology and clinical application of systemic opioids in three major sections: (a) basic considerations, which includes a review of the general principles of pharmacokinetics and pharmacodynamics and their application to the opioids, (b) pharmacology of specific opioids, and (c) finding a new consensus. Relevant information is also presented in Chapter 3, Chapter 4 and Chapter 5, Chapter 9, Chapter 10, Chapter 36, and Chapter 103.

BASIC CONSIDERATIONS

General Pharmacologic Principles

Pharmacology refers to all available information about a drug, including its history, source, production, and physical and chemical properties as a chemical or compound, as well as its interaction with the recipient organism (usually humans) with regard to absorption, distribution, biotransformation, excretion, biochemical and biological effects, mechanism of action, and therapeutic effects and uses. *Pharmacokinetics* is the study of drug disposition in the body over time, including absorption, distribution, biotransformation, and elimination. *Pharmacodynamics* is the study of the relationship between the concentration of drug at the site of action and the biologic or physiologic response.

Pharmacokinetics

Absorption. Absorption refers to the rate and extent that a drug leaves the site of administration. A drug must cross at least one membrane to get to the site of action. A number of physical factors govern this process, including the drug's molecular size and shape, solubility, and ionization constant and the relative lipid solubility of its ionized and unionized forms, on the one hand, and the physicochemical properties of the membranes it must cross, on the other. The best drugs from an absorption standpoint are small, lipid-soluble, neutral molecules, which can cross membranes with some ease.

The pK_a of a drug is the pH at which 50% of the drug is in the ionized form. Its value is derived from the Henderson-Hasselbach equation. The pK_a indicates how much unionized drug versus ionized drug will be present in a specific medium, such as the acidic medium of the stomach.

Among oral agents, aqueous solutions are the best absorbed, followed by oily solutions, suspensions, and oral solids. A factor affecting absorption of oral solids is the rate of dissolution. For example, a tablet with a slow dissolution rate will be absorbed more slowly than a capsule of the same compound, as gelatin capsules dissolve relatively quickly.

For injectables, the rate of absorption is related to concentration. A high concentration of drug in a small volume of solute leads to faster absorption, and a low concentration of drug in a large volume leads to slower absorption. The same can be said for the oral route—again, the higher the concentration of the compound at the site of absorption, the faster the compound is absorbed. Rates of absorption can therefore be controlled to some extent by changing concentration.

Modification of the surface area and perfusion of the absorption site can influence drug levels at the site of action. Measures as simple as the application of massage or heat to the area of absorption can increase perfusion. Conversely, vasoconstriction due to drugs, shock, or some other disease-related factor can decrease perfusion and may profoundly affect absorption. The surface area for absorption is also important. The pulmonary alveolar epithelium, the intestinal mucosa, and the skin are large areas that have been used.

Routes of Administration. The importance of knowing the choices in route of administration cannot be overestimated. Knowing the advantages and disadvantages of each route along with the availability of routes for each drug gives the clinician a wide range of options (Table 84-1).

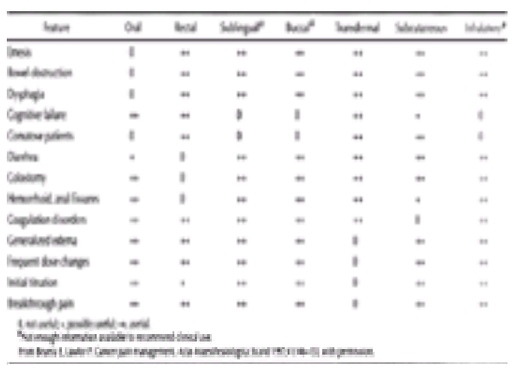

TABLE 84-1. Potential applications for various routes of opioid administration

Oral administration is the most common route. It is convenient, is usually cost-effective, and, for the most part, is the safest route. The disadvantages are slower and more variable onset of effect compared with parenteral routes. However, slow transit and variable absorption in the gut have also been used to therapeutic advantage. The oral route is the only route in which drug formulation can reliably control the distribution, metabolism, and excretion of a drug. For example, compounds that irritate the stomach, such as aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs), are available in enteric formulations designed not to dissolve until reaching the small intestine. A number of more complicated strategies have also been used to control or at least modify the rate of dissolution. In one common approach, the drug (initially morphine but more lately oxycodone and hydromorphone) is absorbed onto a hydrophilic polymer, which is then embedded in some form of matrix (wax or higher-molecular-weight aliphatic alcohols). Polymer and matrix are then ground up and compressed into solid dosage forms (tablets). After the tablet is administered the gastric fluid dissolves the tablet surface and hydrates the hydrophilic polymer, which turns into a gel. The rate of release is the rate of diffusion of the dissolved drug through the gel layer at the surface of the tablet. This is a function of the type of hydrophilic polymer, the type of hydrophilic matrix, or the ratio of the two.

A second approach to modifying absorption is to create a pellet that has an inert core onto which the drug is applied, which is then covered by a polymer coat of a specific thickness and porosity. Once the pellet gets to the gastrointestinal tract, the fluid diffuses through the outer coat to dissolve the drug. The combination of the type of inert core and the composition and thickness of the polymer coat regulates the rate of dissolution. A third approach uses a suspension in which the drug (most commonly morphine) is attached to small bead of ion exchange resin. This dosage form is ideal for those who cannot swallow pills or may need a “sprinkle” preparation (9).

Subcutaneous administration, initially used for multiple bolus injections, now is used for infusions and patient-controlled analgesia (PCA). Compared with the oral route, it obviates the need for normal gastrointestinal function and is somewhat faster for some analgesics. This route has variable uptake times. The more water-soluble the drug, the more prompt the absorption. In depot or repository forms (insoluble suspensions), the absorption is slower and more controlled. In edematous tissue, absorption may be erratic due to poor perfusion. Some of the limitations of the subcutaneous route are the need for small volumes and possible pain or necrosis at the site of injection.

Intramuscular (IM) administration is less variable for most compounds but again absorption is not rapid. It has the same advantages as the subcutaneous route, but larger volumes, oily vehicles, and some slightly more irritating drugs can be used.

Intravenous (IV) administration gives the most immediate effect with bolus administration and also makes it easy to maintain a steady state using continuous infusion. Unfortunately, the immediacy of effect can also be a disadvantage, and means that most drugs should be injected slowly. IV drugs must be water soluble. Large-molecular-weight proteins and peptides that would be poorly absorbed through a membrane can be delivered to sites of drug action readily via IV administration. The ability to dilute irritating drugs and give large volumes over time are additional advantages over other routes.

Rectal administration is often used for patients who have gastrointestinal upset, vomiting, or other reasons to avoid oral intake. The bioavailability of rectally administered drugs has shown a great deal of interindividual variation. For instance, for morphine the bioavailability was found to be approximately 53 ± 18%. Notably, availability of oral morphine is only approximately 37%, suggesting that at least for this drug, rectal administration allows partial avoidance of first-pass metabolism. Medications absorbed well by the upper part of the gastrointestinal tract are also absorbed well rectally. Passive diffusion appears to be the main absorption mechanism (10).

Sublingual administration is another option for patients with gastrointestinal upset who need to avoid or may not be able to obtain injections. There are also advantages and disadvantages to this route. Drugs given by the sublingual route enter the systemic circulation through the mucosa of the mouth and bypass hepatic first-pass metabolism. The proportion of drug absorbed is dependent on the drug's pK_a, the partition coefficient of the nonionized form, lipid solubility, molecular weight, rate of diffusion from the mouth, and, not least of all, the pH of the mouth (10). The best sublingual drug is therefore one that is not ionized at the pH of the mouth and has moderate lipid solubility. Morphine given sublingually has been used for many years but the data for its use by this route are equivocal (11). A newer, related delivery system is oral transmucosal fentanyl citrate, in which fentanyl in a candy mixture is shaped into a lozenge on a stick. The uptake from this oral transmucosal system is a combination of absorption directly through the oral mucosa and gastrointestinal absorption of drug swallowed in saliva (12,13).

Intranasal administration is another novel route. The surface area of the nasal cavity is relatively large (180 cm^2) and highly perfused. The best agents for intranasal administration usually have low molecular weights and are lipid soluble. Bypassing of first pass metabolism and a relative potency similar to the IV route are two of the advantages of the intranasal route. The best use of intranasal opioids may be in the treatment of breakthrough pain. A number of compounds have been tried, including butorphanol, oxycodone, meperidine, a number of the fentanyls, and diamorphine (14,15 and 16).

In *direct instillations*, a catheter is placed in the epidural or subarachnoid space to permit delivery of a restricted amount of drug directly to the nociceptive system, primarily at the spinal cord level (17,18). Central catheter placement near the periaqueductal gray is also used for opioid administration (19).

The *transdermal route* is currently being used in two forms: passive (conventional) systems and active (iontophoretic) systems. The variables that are most important in dermal delivery systems have to do with the permeability of the stratum corneum and include skin temperature, placement site, integrity of the skin, age, and ethnicity (20).

The passive system transfers the drug (e.g., fentanyl) from a reservoir with sufficiently high concentration gradient to the skin. The transferred drug establishes a secondary reservoir within the skin layers, which then releases the drug at a uniform rate for up to 72 hours. There are two phases to the absorption of the drug: a rapid skin absorption phase and then a plateau phase, when there is a sustained release for the duration of the placement. A problem with the passive system is that the plateau is fairly constant, but there is substantial interpatient variability in peak concentration. After the patch is on 48 to 72 hours, the patch is removed and the absorption continues from the secondary skin depot. The apparent terminal half-life is 16 to 25 hours, which means that after the patch is removed there will be drug on board for a considerable amount of time.

The active (iontophoretic) transdermal fentanyl system was developed to overcome the stratum corneum's inherent resistance to absorption of drugs. The system consists of a skin delivery electrode, a skin current returning electrode, and an electric power source. With the application of an electric field, charged components of drug are propelled through the skin. It appears that iontophoresis could be used to deliver clinically significant doses of other similar drugs. The advantage over the passive system is that the terminal half-life appears to be shorter. More research into this route is in progress (21).

Bioavailability. Absolute bioavailability refers to the fraction of a given dose of drug that reaches the general circulation as compared with the same dose given IV. *Relative bioavailability* compares the absolute bioavailability of two different dosage forms. *Physiologic bioavailability* is a measure of the effect of the administered drug.

Bioavailability is also affected by such factors as the form of administration (e.g., tablet or liquid) and the site (e.g., oral or IM). The rate of absorption from the site of administration (e.g., full stomach or empty stomach) is important. Plasma protein binding can also influence bioavailability and varies with differences in plasma protein levels because of diet, disease states, and hepatic function (22,23). There are also variables at the manufacturing level. Biologic nonequivalence has been seen with ostensibly equivalent drug preparations from different companies (24).

Distribution. Volume of distribution refers to the extent to which a drug is distributed within the body at a given time. It is defined as the amount of drug in the body divided by the plasma concentration. There are three main compartments for distribution: the vascular compartment (the bloodstream), which accounts for approximately 5% of body weight; the extracellular compartment, which is approximately 15% of body weight; and the intracellular compartment, which is approximately 30% of body weight. Large molecules and highly bound compounds usually stay in the vascular compartment. Hydrophilic compounds are distributed in both vascular and extracellular compartments. Highly lipid-soluble compounds are distributed in all three compartments. The volume of distribution might be greater than the volume of body fluids for some drugs at steady state, but for others (e.g., those that are highly plasma protein bound), it can be close to the plasma volume.

After drugs are absorbed or injected into the circulation, they are distributed throughout various areas of the body, including the compartment of their site of action. Activity is based on the concentration of the drug at the site of action and is influenced by distribution to the various body compartments. Distribution occurs in two separate phases: an early phase through the bloodstream to highly perfused organs such as the heart, liver, kidney, and brain, which is related directly to cardiac output and regional flow; and a second phase of slow diffusion into less well-perfused areas, such as the viscera, skin, muscle, fat, and bone. For some drugs, pharmacokinetic data allow this slow phase to be split further, and various artificial volumes of distribution have been defined (25). Obviously, differences in

distribution speed to various compartments greatly affect onset of drug activity, depending on the compartment where the site of action lies. A highly diffusible drug that acts on a highly perfused organ will have the most rapid effect.

In plasma, only the unbound and nonionized portion of the drug, the diffusible fraction, is free to leave the vasculature. The diffusible fraction determines the initial concentration gradient and therefore the rate of diffusion. The other factor in determining the rate of movement of the drug from plasma to tissues is lipid solubility.

The two major plasma proteins that bind drugs are albumin for acidic drugs and a_1-glycoprotein for basic drugs. Highly bound drugs have a low diffusible fraction, low volume of distribution, and little access to cellular sites of action. The metabolism and excretion of drugs, either directly or in metabolized forms, are also limited by high plasma protein binding.

Lipid solubility has various effects on distribution. Lipid-insoluble drugs do not cross tissue barriers readily and have a small volume of distribution but, more important, have limited access to sites of action. Highly lipid-soluble drugs diffuse rapidly to potential sites of action and then rapidly distribute out to other tissue, such as muscle. They can also accumulate in body fat, which can ultimately make a short-acting, lipid-soluble drug into a long-acting one by filling the fat store, leaving biotransformation and excretion as the only ways to terminate drug action.

In the normal system the pH of drugs is not usually a major factor in distribution, because the pH difference between intracellular and extracellular compartments is small (7.0 versus 7.4).

Mathematical models of drug distribution based on data from pharmacokinetic studies have made it easier to predict appropriate prescribing practices (26). These models have also explained some puzzling redistribution patterns within the body, suggested unrecognized sites of action, and explained some peculiarities observed with prolonged administration. As they are refined, these models will add more to our understanding of pharmacokinetics and facilitate improved patient care (27,28 and 29).

Biotransformation. Biotransformation refers to the structural change of a drug through enzymatic transformation in various organs of the body. For most drugs, the lipid solubility needed for passage through membranes is also a hindrance to elimination. The body must take these lipid-soluble compounds and biotransform them into polar hydrophilic compounds for them to be eliminated. This also terminates their activity. The enzymes that do this are present in the body to metabolize endogenous compounds. The fact that they metabolize drugs and other xenobiotics is coincidental. Biotransformation occurs primarily in the liver; to a lesser extent in the kidney; and to a slight degree in other organs such as skin, gastrointestinal tract, gastrointestinal flora, lung, brain, and placenta.

Biotransformation involves a number of different processes. *Functionalization reactions*, also known as *phase I reactions*, either add or expose a functional group on a molecule that can then either be excreted or react with endogenous compounds to form a water-soluble conjugate. Functionalization reactions may involve oxidation, reduction, hydrolysis, and hydration as well as isomerization. These reactions usually terminate a drug's pharmacologic activity, except in the case of pro-drugs, which need the reaction to form the active compound.

Conjugative reactions, also known as *phase II reactions*, create a covalent linkage between a functional group on the compound and another group such as glucuronic acid, sulfate, glutathione, amino acids, and acetate, among others, using a diverse group of enzymes. *Glucuronide synthesis* is the main conjugation reaction in the detoxification process. The glucuronide compounds are generally inactive and are easily excreted. Other conjugation reactions produce acetylated compounds, glycines, and sulfates, but to a lesser extent. Again, these compounds are inactive and are readily excreted, primarily in the urine but also in the feces through the biliary system. A few conjugated compounds, however, are active—for example, the M6-glucuronide of morphine, which is more potent than the parent compound.

Hydrolysis is the process that deactivates esters and amides (e.g., local anesthetics). *Reduction* detoxification has two pathways, one for azo compounds (RN = NR') and another for nitro compounds (RNO_2).

Oxidative reactions are more varied and include dealkylation, aliphatic and aromatic hydroxylation, *N*-oxidation, *N*-hydroxylation, sulfoxide formation, deamination, and desulfuration.

The mixed-function oxidation system, also known as the *cytochrome P-450 enzyme family*, is probably the major catalyst of drug biotransformation. These heme-containing, monooxygenase enzymes are found in smooth endoplasmic reticulum of such diverse tissues as liver, kidney, lung, and intestine. They catalyze a variety of reactions, both oxidative and reductive in nature involving myriad substrates. The P-450 mixed-function oxidases differ slightly from each other with respect to molecular weight, carbon-monoxide– binding spectra, electrophoretic and immunologic properties, and catalytic activities toward different drugs. The name comes from the spectral absorbance maximum produced at or near 450 nm when carbon monoxide binds to the enzyme in its reduced state.

The enzymes of this “gene superfamily” have been categorized into 12 families, four of which are involved in the metabolism of drugs. The nomenclature is as follows. The generic label CYP (for “cytochrome P”) is followed by the number of the subfamily, a letter for the specific enzyme, and a final numeral denoting the numeric order in which the enzyme was discovered. The most important isoenzymes with respect to drug-drug interactions are CYP1A2, CYP2D6, and CYP3A3/4. These enzymes all have powerful oxidizing capacity, low and overlapping substrate specificities, and low substrate affinities. They have various rates of activity depending on genetic factors (genetic polymorphisms) and on the influence of other compounds or chemicals in the system that can induce or inhibit enzyme synthesis and activity. These influences and the resulting effects of one drug on the metabolism of another are the subjects of intense current interest and a rapidly growing literature (30,31 and 32) (Table 84-2A and Table 84-2B).

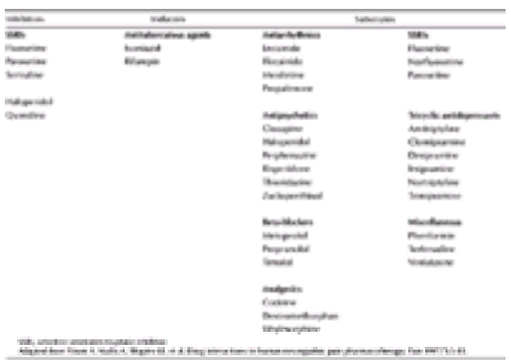

TABLE 84-2A. Partial list of CYP2D6 inhibitors, inducers, and substrates

TABLE 84-2B. Partial list of CYP3A3/4 inhibitors, inducers, and substrates

Elimination. Drugs are eliminated either primarily as polar compounds or primarily unchanged. Many drugs are excreted unchanged (e.g., some inhalation anesthetics). Elimination of polar compounds is primarily through renal excretion by glomerular filtration and active tubular secretion. Many drug metabolites formed in the liver are added to bile and excreted by the gastrointestinal tract, although usually these metabolites are found in the bloodstream and urine as well. Minor sites of elimination include sweat, tears, saliva, and breast milk. Excretion in breast milk can be problematic due to the risk of causing unwanted pharmacologic activity in the infant.

Clearance. Clearance is simply defined as the rate of elimination by all routes divided by the concentration of the drug, usually in blood or plasma. It is an important factor in selecting the doses and times of administration necessary to reach a steady state. Changes in renal or hepatic function, or both, can significantly change clearance. Variations in clearance may require modifying the dose, dosing interval, or both. Clearance is not much affected by changes in drug concentration at the range of clinical concentrations. This means that in clinical settings a constant fraction of drug is eliminated per unit of time, making it relatively easy to calculate dosage changes necessitated by clearance variations.

Half-Life. The half-life of a drug is the time it takes for plasma concentration to decrease by 50%. It serves as a measure of how rapidly drug concentration changes. It is a derived parameter that is inversely related to clearance and is directly related to the volume of distribution at steady state. For most drugs, terminal half-life serves as a useful measure of how rapidly drug concentration changes and how rapidly effects will dissipate. Terminal half-life is not as helpful in IV drugs that have intricate multicompartment pharmacokinetics, such as the fentanyl family of opioids. In these drugs, the rate at which concentration decreases and effects dissipate is determined not only by terminal half-life but also by the whole course of the infusion, because distribution into various compartments changes as the infusion continues. The concept of “context-sensitive half-time,” the time required for a 50% decrease in drug concentration after a particular infusion course, has been developed to take account of these complexities. Context-sensitive half-time is determined using computer modeling based on known pharmacokinetic parameters (33,34).

Steady State. A steady-state level of a drug occurs when the drug has accumulated in the body compartment under consideration, so that relatively little change in concentration is seen over time. This concentration plateau depends on the rates of administration and clearance from the phase in which it is active. Thus, when the rate of administration to a compartment equals the rate of clearance from a compartment a steady state is reached. The rate of decrease from a steady state depends on the half-life of the drug.

For example, the accumulation of nitrous oxide has a fast phase (3.5-minute half-life) and a slow phase (30-minute half-life). The rapid rise in its arterial concentration occurs during the fast phase because redistribution is minimal, but true steady state is prolonged because the terminal phase of accumulation depends on many factors. For clinical purposes a steady state is said to be reached after five to six half-lives (i.e., 96.9% and 98.4% of maximum concentration, respectively). For nitrous oxide this would be approximately 3 × 5, or 15 minutes.

Diazepam, on the other hand, has a redistribution half-life of 1 hour and a terminal half-life of 30 hours. Accumulation is slower and a steady state would not be reached for 506 hours with continuous infusion (analogous to breathing nitrous oxide). It is therefore given in bolus, and a steady state is not necessary or desirable for its clinical effectiveness.

Pharmacodynamics

Mechanisms of Drug Action

Receptor Binding. Most drugs act by binding to cell proteins, including receptors, enzymes, and proteins involved in transport processes. Receptors are proteins that bind drugs and initiate a response. There are many different types of drug receptors and many different mechanisms of receptor action. Receptors may activate G-proteins, open ion channels, or alter gene expression by binding DNA. Opioids act primarily on receptors, as described in more detail below. Drugs that act on receptors may function as agonists, triggering a response from the receptor, or as antagonists, blocking the activity of an agonist; antagonists may be competitive or noncompetitive.

Enzyme Inhibition. Enzymes are another common site of drug action; these drugs bind to enzymes and inhibit their activity. NSAIDs, for example, act by inhibiting cyclooxygenase, again as described in more detail in Chapter 83. Enzyme inhibitors may be either reversible (e.g., ibuprofen) or irreversible (e.g., aspirin).

Obviously, the structure and physiochemistry of a specific drug are the important determinants of its binding activity. Changes in molecular structure can increase potency but also tend to increase toxicity. Sophisticated techniques are increasingly allowing specific structural alterations to reach desired functional effects.

Other Mechanisms. There are mechanisms for drug activity other than protein binding. Some drugs interact with ions to produce an effect (e.g., antacids). Others are substituted by the body for cellular substrates, thus changing cell function. Others act by somewhat ill-defined physiochemical mechanisms that are not specifically related to structure.

Analgesia and Equianalgesia. The analgesic effect of a drug is the pain relief it induces. Equianalgesia is a way of comparing the analgesic effects of drugs with different structures. It indicates that the same degree of pain relief is obtained from two specified medications at the specified doses. For example, morphine, 10 mg IM, is equianalgesic to meperidine, 75 mg IM. This clinical usage of the terms “analgesia” and “equianalgesia” is appropriate only for opioids and is not based on the determination of an altered response to a noxious stimulus, as in the International Association for the Study of Pain (IASP) definition.

Potency. Potency refers to the intensity of effect for a given dose of drug. It is an estimate of the absolute concentration of a drug needed to produce a response. For therapeutic applications potency is stated in dosage units.

Therapeutic Index. The therapeutic index is an indication of the safety of a given drug, and is the median effective dose (TD_{50}:ED_{50}).

Relative Toxicity Ratio. The relative toxicity ratio is a comparison of the toxic effects of two drugs with the same desired clinical effect. For example, if pentobarbital and phenobarbital are given for seizure control, the toxicity ratio with respect to respiratory depression is 10:3 because phenobarbital has approximately a threefold advantage over pentobarbital as an antiseizure drug but an equal sedating effect.

Drug-Drug Interaction. Every time more than one drug is used there is a chance for a drug-drug interaction. With the addition of each additional drug the chance of an interaction increases. Any aspect of a drug's pharmacokinetics may be affected by drug interactions, including its absorption, biotransformation, and elimination. The pharmacodynamics of a drug can also be altered independent of changes in pharmacokinetics. The most important drug-drug interactions to be aware of are those affecting potentially toxic drugs with narrow therapeutic indices (32).

Drugs can interact with each other to produce potentiation or additive effects. *Potentiation* is said to occur when the net effect of two drugs used together is greater than the sum of their individual effects, as when an opioid analgesic is given with a nonopioid analgesic. *Additive effects* are said to occur when the net effect of two drugs used together is equal to the sum of their original effects. *Antipotentiation* occurs when the net effect of two drugs used together is less than the sum of their individual effects, as when an NSAID is given with another NSAID.

Clinical Pharmacology and Pharmacokinetics

Relation between Dose and Effect. As the tissue involved is exposed to increasing concentrations of drug, there is an increase in the number of receptors occupied, up to a point of saturation. After this concentration of maximal response there is usually no increase in effect and an increase in side effects. The drug concentration needed for a specific response has a wide range. This is why the concentration-response curve is usually converted to a log concentration-response curve, giving us the familiar sigmoid dose-response curve. Do not expect a simple relationship to exist between dose and effect, especially in a large population in whom individual differences in response further complicate the issue. The effective dose, side effects, and toxicity of drugs vary widely among patients with similar clinical problems. In one study of postoperative pain, a four- to fivefold difference in requirements for opioids was seen after major laparotomies (35).

Dosing of Drugs. The way in which a drug is administered—by a single dose, by an intermittent dose, or by continuous dosing—is determined by the clinical pharmacology of the drug and by the clinical situation for which it is used. A *loading dose* is an initial large bolus given to produce a rapid increase in the therapeutic blood level of a drug. A *maintenance dose* is the amount of drug necessary to maintain a steady state when given intermittently or by continuous infusion.

To take just a few examples, a single dose of an analgesic with a long half-life is appropriate for a relatively short pain experience. The use of methadone by IV bolus intraoperatively has been proposed to provide postoperative pain relief (36). For some procedures, such as herniorrhaphy, the long half-life of methadone (24 to 36 hours) can provide most of the postoperative analgesia with a single large dose so that NSAIDs might be all that are necessary for pain relief beyond its effective duration. Intermittent dosing with opioids of intermediate half-lives (e.g., morphine or meperidine) is commonly used for the relief of longer-lasting postoperative pain, as with a thoracotomy.

Continuous dosing by IV drip allows blood concentration closer to a steady state to be controlled and is especially appropriate for drugs with a short half-life. There has been some interest in this method for relieving postoperative pain using fentanyl or sufentanil (37). Postoperative pain management is discussed in Chapter 41.

Therapeutic Monitoring. For effective analgesia, the dose of a given drug must be matched to the requirements of a given patient and the timing must be such that blood levels remain at or above the minimum effective analgesic concentration (MEAC) for that patient. The balance must be maintained while the patient is monitored for overdose and significant side effects. Unfortunately, these real complexities are usually ignored and analgesics often are given by rote without consideration for the volume of distribution; for individual variations in absorption, metabolism, and clearance; or for the patient's clinical state.

Remarkable and rapid advances have been made in several fields pertinent to the treatment of pain. More information is available about the physiology of pain and its psychological effects on the individual, the interaction of pain and the personality, and emotional and psychological reactions and their modification by social and environmental factors. Knowledge of the pharmacology, pharmacokinetics, and toxicology of the rapidly expanding number of analgesics is becoming increasingly sophisticated and complex. Despite all this, treatment of pain is often inadequate, and medications used for pain relief can be a source of abuse. This can lead to the development of tolerance and physical dependence fostered unwittingly by both the patient and treating physician or can lead the patient to develop side effects, some of which are potentially lethal. Therefore, in approaching the control of pain, a few simple guidelines must be followed.

- *Evaluation of pain*. The source and cause of pain and its severity should be analyzed not only from a nociceptive viewpoint but also from a psychological-behavioral perspective.
- *Use of optimal drug and optimal dose*. The most appropriate medication for the problem should be selected for each individual patient in an optimal dosage.

  There is an optimal drug for each patient but no particular drug that is optimal for all patients. Morphine is used as a reference point. Other mu opioids may have faster onset, longer duration of action, or better tolerance for a particular patient, but none has more analgesic effect.

  Optimal dosage is the minimum amount of a drug repeated at appropriate intervals to give the desired therapeutic effect with a minimum of side effects. Appropriate monitoring of the patient by personal observation, and in some cases by blood studies, is necessary to follow compliance with dosage regimens, to assess the therapeutic effects, and to identify untoward side effects or toxicity of the medications prescribed. The effect of the first few doses is critically important to observe so that an accurate estimate of maintenance dose and dosing time can be made. Meticulous pharmacokinetic calculations and frequent measurement of blood levels would be ideal but are not practical in most institutions at present. Instead, clinical response is the primary consideration.

  In the hospital, monitoring is the primary responsibility of the nurses and physicians. In some cases, especially with the terminally ill who are treated at home, the family might have to be responsible for monitoring the patient. This requires the family to be conversant with the medication and its pharmacology as well as to be in close communication with treating physicians and nurses to optimize care. If the appropriate drug is given in the wrong dose and at the wrong interval, the health care system has failed. Unfortunately, this can be the case when analgesia is desired, and lack of careful therapeutic monitoring is usually the cause.

  The interaction of the drug and patient is highly dynamic. For example, pathologic alterations of hepatic or renal function, or both, can drastically decrease the metabolism and excretion of morphine to the extent that a previously appropriate analgesic dose can lead to drug accumulations and cause serious toxicity.
- *Type of pain.* As discussed repeatedly in this book, it is important to distinguish between nociceptive pain and neuropathic pain. It is also necessary to determine whether pain is acute, is associated with cancer, or is a chronic nonmalignant pain when choosing a therapeutic approach involving systemic analgesics. Generally the approaches to the treatment of acute pain problems and pain associated with cancer are somewhat similar, whereas the therapeutic approach to chronic nonmalignant pain is quite different. Opioid analgesics in adequate doses, given at appropriate intervals, as a continuous infusion, or as an infusion with a PCA unit, constitute the primary approach to most acute pain problems and to most pain associated with cancer. Opioids are generally not recommended as initial therapy for chronic continuous pain, but if properly prescribed, they can be useful in chronic recurrent or cyclical pain states of nonneoplastic origin. The whole issue of opioid treatment of chronic nonmalignant pain is one of the most debated areas of pain management. Other chapters discuss particular pain states and their individualized treatment in detail.

Clinical Pharmacokinetics and Pharmacodynamics of Opioids

After IV injection or absorption into the vascular system, an opioid must leave the plasma, diffuse into the tissues [primarily the central nervous system (CNS)], and reach the receptors to trigger its pharmacologic action. For rapid access to the CNS, an opioid must have both high diffusible fraction in plasma (unless the drug is directly instilled) and a high lipid solubility. Lipid solubility is an especially important property of intraspinal opioids, influencing their onset and duration of action, diffusion, and side effects (see Chapter 103).

The product of the diffusible fraction and the lipid solubility of an opioid is known as the *diffusion potential* into the CNS. The ratio of the diffusion potential of an opioid compared with that of morphine is called the *lipid diffusion index*. Thus, the lipid diffusion index of morphine equals 1, of meperidine equals 14, and of fentanyl equals 160.

After an IV bolus of fentanyl, this opioid enters the brain rapidly because of its high diffusion potential. As the plasma concentration falls as a result of removal of the drug by tissues and biotransformation, the gradient reverses and fentanyl leaves the brain equally rapidly. Meperidine follows the same process of forward and then reverse transfer to and from the brain, but more slowly because of its lower diffusion potential. Morphine has the lowest diffusion potential of all the common opioids, resulting in a slow dynamic interaction between plasma and CNS drug concentrations. First, there is a considerable delay between IV morphine injection and development of maximal brain concentration (and onset of maximal effect). Second, morphine leaves plasma so slowly that biotransformation or elimination lowers plasma concentration and further decreases the “driving concentration” during the onset period, causing a further reduction in its rate of diffusion into the CNS. Because of its low lipid solubility, however, less drug is nonspecifically bound by brain lipids and less is needed in the CNS to exert the same effects. Finally, once morphine has penetrated the CNS tissue, the diffusion back to the plasma is also slow. In 1979 Nishitateno et al. (38) elegantly demonstrated that the plasma concentration of morphine does not parallel the brain concentration of the drug. Instead, the brain concentration remains at higher levels compared with the decreasing plasma concentration over time (38).

Once a specific plasma concentration of opioid has been reached, the final effect is not equal for every individual. This varied response is best illustrated by considering the wide range that exists among patients with regard to the MEAC for each specific opioid. The MEAC is the minimal plasma level of an opioid that can control severe pain in a particular patient. For example, a patient with a plasma concentration of meperidine (pethidine) of 410 ng per mL might still experience severe pain, obtaining relief from pain when the concentration reaches 460 ng per mL. This is the MEAC for meperidine for that patient (39). Although the MEAC is fairly consistent for each individual patient [Mather et al. (40) found at most a twofold intrasubject variation], a great intersubject variation has been noted. Austin and colleagues (39) found that, in six patients, the intersubject MEAC varied from 270 to 700 ng per mL for meperidine, whereas Tamsen et al. (41) found a similar variation, ranging from 94 to 754 ng per mL. In practical terms, this represents an eightfold intersubject difference in meperidine requirements, confirming empiric clinical observations of a seven- to eightfold difference in opioid requirements. Morphine has a mean MEAC of 16 ng per mL, with a range of 6 to 33 ng per mL (42). Optimal control of pain is achieved by maintaining the plasma concentration of the opioid at a constant value just above the patient's own MEAC for that drug. All this underscores the necessity of individualizing opioid dosage according patient response.

Recent Advances in Opioid Pharmacology

Prompted by the introduction of the Melzack and Wall (43) gate theory of pain more than two decades ago, by the International Association for the Study of Pain, and

by many others, including the second edition of this text, exciting new results in pain research have made the pharmacology of pain treatment progressively more sophisticated. Knowledge of the neurophysiology and biochemistry of pain transmission and modulation systems (44,45 and 46), of drug receptors and their influences within these systems, and of changes in these systems produced by acute and chronic pain is continually increasing (13). More information is available about drugs long used for analgesia and about promising new drugs designed to be more specific for pain modulation. Drug delivery itself is becoming more specific with regard to the agents being administered and to the problems for which they are being given. A few of the areas where advancements are occurring are surveyed here.

Clinical Trials. As proposed by Beecher (47) and Houde (48), among others, controlled clinical trials with and without placebo are now comparing newer drugs of the opioid and nonopioid classes not only to placebos but also to standards of their class, such as morphine for the opioids and aspirin for the nonopioids. This has led to a reevaluation of the effectiveness of some older drugs as well as to the availability of new drugs. Close scrutiny of analgesic effects, side effects, and toxic effects in such trials in both humans and animals (49) has resulted in safer and more effective clinical care. The Oxford Pain Relief Unit has established a database that reviews all of the randomized trials from 1950 to 1990 (50). The data from this pool have been augmented by the efforts of the newly formed Cochrane Collaboration, the role of which is "to collaborate with others to build, maintain, and disseminate a database of systematic, up to date reviews of randomized controlled trials of healthcare" (51). With these impressive efforts to organize the masses of available data, we may be able to guide patients toward more effective treatments and away from unproven, ineffective and possibly harmful treatments.

Pain Measurement. Combined with the methodology of controlled clinical trials, newer techniques of pain measurement, both objective and subjective, have allowed more accurate evaluation of the effectiveness of analgesic medications in animals, in normal human subjects (52), and in those suffering from acute or chronic pain (49). There has been increasing interest in the psychology of pain as well, with recognition that pharmacology is only one component of effective pain treatment. Pain measurement is still in its infancy despite advances in the field, and a "pain thermometer" has yet to be found that could allow accurate objective measurement of pain and suffering.

Analytic Techniques. Analytic chemistry is another area where advances continue. Minute quantities of chemicals (including analgesics) in blood and in many other body fluids and tissues can be analyzed (49,52). Drug monitoring of analgesics is mostly used to evaluate suspected toxicity, but the same analytical tests could be used for therapeutic monitoring. There are multiple tests of different orders of complexity, from simple color spot tests, colorimetric tests, enzymatic methods, and immunoassays to thin layer and gas chromatography, high-performance liquid chromatography, and automated high-performance liquid chromatography (53). The *in vivo* release of neurotransmitters and its modification by different drugs in animal models can now be monitored (54). New imaging techniques (e.g., positron emission tomography, magnetic resonance imaging) allow the metabolism of the human brain to be observed and recorded and expand the prospects for more specific pain research in the future.

Pharmacokinetic Studies. The increasing accuracy of analytic chemical methods now allows the pharmacokinetics of opioids and nonopioids in tissue compartments of the body to be followed—for example, in plasma and in target structures such as the nervous and integumentary systems. This allows prediction of dose and correct dosing interval for these drugs so that adequate blood and tissue levels can be maintained for better pain control. These techniques are becoming more available and promise to be a future supplement to clinical monitoring. Analytic studies have also shown wide variations among patients with regard to plasma drug concentration (37,39,40,55,56,57,58,59 and 60). These results are still not widely enough known, however, so that many physicians still use fixed routine doses and intervals of dosing in patients with both acute and chronic pain, frequently resulting in inadequate analgesia.

Opioid Effects and Mechanisms

This section reviews that aspect of opioid pharmacology relating to opioid actions and their mechanisms, including analgesia and other common effects both desired and undesired. Opioids have pharmacologic effects on almost every organ and function in the human body (61). Some of these effects are beneficial, and some are not. The most important targets are the CNS and the gastrointestinal system, but the cardiovascular, pulmonary, genitourinary, and immune systems are all directly affected.

Site and Mechanism of Analgesia. Unlike the NSAIDs, which have a ceiling effect for analgesia, opioids act in a dose-dependent manner and usually can control all intensities of pain with increasing doses up to the induction of surgical anesthesia. The major drawbacks are the side effects, which increase proportionately with dose. Therapeutic analgesic doses of opioids control dull, prolonged, aching pain better than sharp colicky pain. At high doses (e.g., 2 to 3 mg morphine per kg body weight), however, they induce profound analgesia, with obliteration of autonomic responses, to the most intense nociceptive stimuli.

Systemic opioids induce analgesia at several levels of the CNS (62). In the spinal cord, they impair or inhibit the transmission of nociceptive input from the periphery to the CNS in a dose-related manner. In the basal ganglia, opioids activate a descending inhibitory system that modulates peripheral nociceptive input at the spinal cord level. In the limbic system, opioids alter the emotional response to pain, making it much more bearable (63).

Although great advances have been made in understanding the opioid system, our knowledge is far from complete, and a detailed and clear understanding of the intrinsic mechanism of action of opioids is still lacking. Several factors hinder the elucidation of this mechanism:

- The multiplicity of opioid substances, each of which interacts with more than one site on the macromolecules that form the opiate receptors (64,65).
- The ability of one substance to act as an agonist in one animal tissue and as an antagonist in another, adding further confusion (66). Certain compounds (tramadol) may act on a multitude of receptors both opioid and nonopioid in nature.
- The difficulty of finding agonists and antagonists that are receptor-specific. Naloxone, for instance, is a mu antagonist at low concentrations (up to 15 nM), but at higher concentrations antagonizes sigma and kappa (64).
- The discovery that animal tissues can transform the nonpeptide, nonmorphinan reticuline to morphine and codeine and that these substances are present in animals, although at levels so low that physiologic significance is unclear. There is some speculation that these peripheral opioid binding sites may have some role in the immune system (28,29,67,68 and 69).

Despite these difficulties, we now have a great deal of information regarding this complex system. Opioid agonists, either exogenous or endogenous, produce analgesia and other central effects by dynamically binding to specific receptors in the encephalon and spinal cord. Opioid binding can either stimulate or depress different neuronal populations. For instance, in most animal species, opioids stimulate the Edinger-Westphal nucleus of the oculomotor nerve to produce miosis and stimulate the chemoreceptor trigger zone in the area postrema to decrease the threshold of nausea and vomiting, whereas they depress the respiratory centers.

Evidence indicates that the descending antinociceptive system, activated mainly by opioids in the periaqueductal gray of the brainstem, requires a much lower concentration of these drugs to produce analgesia than the analgesia elicited strictly by the activation of the receptors of the substantia gelatinosa of the spinal cord (17). Therefore, opioids at low cerebrospinal fluid concentrations, such as those obtainable after oral, IM, or IV administration, act mostly through the descending antinociceptive system. After intraspinal administration, in which high cerebrospinal fluid concentrations are produced, the activation of opioid receptors in the substantia gelatinosa constitutes the major mechanism of analgesia (17).

Several opiate receptors are now known, each with more or less different functions and drug affinities (Table 84-3 and Table 84-4) (46,61,64,65,70). Five receptors have been identified: mu, kappa, delta, sigma, and epsilon (64,65,70). They are G-protein–linked receptors, which have been reviewed and are further explained in Chapter 3 and many other texts (71). Briefly, mu receptors (m_1, m_2) mediate supraspinal analgesia (spinal, in animals), euphoria, respiratory depression, and physical dependence. Kappa receptors (k_1 to k_4) mediate spinal analgesia, miosis, dysphoria, and sedation. Delta receptors (d_1, d_2) may mediate spinal analgesia, show little or no cross-tolerance with mu agonists, and when partially activated by a subanalgesic dose of delta agonists, greatly potentiate morphine analgesia.

TABLE 84-3. Opioid activity and selectivity by receptor type

TABLE 84-4. Opioid receptors and clinical effects

Sigma receptors mediate dysphoria, hallucinations, and stimulation of respiratory and vasomotor centers. Findings suggest that sigma receptor agonists, which include ketamine and phencyclidine (PCP, “angel dust”), are potent agonists of excitatory transmitters at the spinal cord level and are not reversed by naloxone. These characteristics suggest that the sigma receptor might not belong to the opiate receptor family but to the phencyclidine receptor family (70,72). The identity and existence of the epsilon receptor are also in question. Research is ongoing but is hampered by the lack of a currently available selective epsilon receptor ligand (73). Another receptor is called the *ORL-1* (opioid-receptor–like). It does not bind to conventional ligands but may have something to do with analgesia or hyperalgesia. Its opioid peptide, nociceptin/orphanin FQ, may have inhibitory activity at the cellular level (74,75). More research is needed to clarify its part in analgesia. There is also evidence for an M-6-glucuronide receptor (76,77 and 78).

Other Central Nervous System Effects

Limbic System. The detailed neural mechanisms by which opioids produce euphoria and tranquility or dysphoria are not completely clear (79). The study of reward systems and their role in addiction to opioids and other drugs has revealed layer after layer of complexity. Briefly, our current knowledge indicates that the mesolimbic system is the center of the reward system, with dopamine being the primary neurotransmitter involved. There seems to be a dual modulation of the mesolimbic dopamine system by mu and kappa receptors, which may be the key to the neurochemical mechanism of morphine and other mu agonist reward effects. Opioid-induced euphoria has been attributed to mu and possibly delta receptor activation. The production of dysphoria has been attributed to sigma and kappa receptors or a balance between mu and kappa receptors, but this is still uncertain (80,81). The model depends on the counterbalancing between “yin and yang,” the mu (and perhaps delta) versus the kappa agonists. These same mechanisms may be responsible for the reward and addictive properties of cocaine, amphetamine, and alcohol, as well as of opioid analgesics (82,83).

Hypothalamus and Pituitary. The hypothalamus is involved in the maintenance of body temperature and contains autonomic centers that control sympathetic and parasympathetic systems. A single dose of morphine slightly lowers body temperature in humans, whereas the chronic use of high-dose opioids seems to increase body temperature. In general, opioids decrease the response of the hypothalamus to afferent stimulation and reduce the stress response. This is apparently an indirect effect because the response of the hypothalamus to electrical stimulation is not altered by the administration of opioids.

The administration of opioids in the usual therapeutic dose causes a slight decrease in pituitary hormone levels. The acute administration of large doses of opioids is followed by a decrease in the concentration of luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, and b-endorphins. This is due to decreased release of gonadotropin-releasing hormone and corticotropin-releasing factor from the hypothalamus (72). Tolerance soon develops, however, and patients receiving opioids chronically are found to have normal concentrations of circulating cortisol, luteinizing hormone, and testosterone (72).

The systemic administration of the opioid antagonist naloxone affects the release of several hypophyseal hormones. It increases the concentrations of luteinizing hormone and follicle-stimulating hormone, whereas it decreases those of prolactin and growth hormone. It may be that endogenous opioid peptides have a role in regulating secretion of some pituitary hormones (84).

Interpretation of the effect of opioids on antidiuretic hormone is controversial. Some studies have shown that the plasma concentration of this hormone increases with opioid administration and decreases with naloxone (85). Other authors, however, believe that opioid-associated diuresis is caused by hemodynamic or renal effects and not by alterations of antidiuretic hormone concentration in the plasma (72).

Brainstem and Medullary Centers

RESPIRATORY DEPRESSION. Opioids, in particular the mu receptor agonists but also kappa and sigma receptor agonists, have a direct effect on the respiratory centers of the pontine and bulbar brainstem. This is noticeable even at therapeutic doses of morphine and increases progressively with higher doses.

The effect of opioids on respiration is multifaceted. They depress both respiratory rate and tidal volume and, as a consequence, decrease minute ventilation. The major effect is a decrease in responsiveness of the medullary respiratory centers to carbon dioxide tension. Pain counteracts some of this depression. If the opioid is titrated to achieve adequate pain relief, clinically significant respiratory depression usually does not occur because pain is a powerful respiratory stimulant and counteracts the opioid-induced depression. On the other hand, this complication may occur if the drug is given in excessive doses or if adequate doses are administered too frequently. For example, severe depression can develop in debilitated patients who are given methadone too often, with consequent rapid buildup of plasma levels and perhaps accumulation of metabolites that are not analgesic but that still depress medullary centers. Sudden deterioration of hepatic or renal function that decreases the elimination of an opioid may also cause it to accumulate. PCA is one way to minimize such problems, as the patient will be able to titrate pain relief and side effects.

Another setting in which the risk of respiratory depression or even arrest increases is when a patient on opioid therapy undergoes a neurosurgical operation or nerve block that abruptly eliminates the pain and its respiratory stimulating effects. It is especially important to watch such patients closely during and after these procedures (86). Again, use of PCA will reduce this risk.

Other patients at risk may be those with sleep apnea syndrome or who depend on intercostal accessory muscle activity as with chronic obstructive pulmonary disease, morbid obesity, or postabdominal surgery, because for these patients rib cage breathing, which may be impaired by opiates, may be more important than diaphragmatic breathing (87).

Mild respiratory depression can be reversed by reducing the drug dosage, whereas moderate or severe depression should be treated with naloxone doses of 0.1 to 0.4 mg IV. Because naloxone is a fast but short-acting agent, repeated administration or an IV drip is usually necessary in patients taking long-acting opioids to prevent severe respiratory depression or arrest from recurring. For patients who have been on chronic opioid therapy, it is important to administer the naloxone slowly, because not doing so could precipitate severe withdrawal symptoms. Physicians should also be aware that naloxone has, on rare occasions, produced severe pulmonary edema (88).

COUGH SUPPRESSION. Opioids also cause depression of the cough reflex, probably via direct suppression of the cough center in the medulla. There appears to be no direct correlation between the cough-suppressant activity of an opioid and its respiratory depressant effect. In fact, opioids have been developed that effectively suppress cough without significantly impairing ventilation (87). Probably the most widely used opioid for this purpose is codeine. For some patients, the suppression of this reflex may be deleterious, due to a decrease in the clearance of sputum and secretions. All opioids should be avoided during asthma attacks because of possible histamine release, respiratory depression, and drying of secretions, a combination of effects that can be catastrophic.

NAUSEA AND VOMITING. Nausea and vomiting are common and highly disliked side effects of opioid therapy. Patients will often refuse these analgesics if emesis is not treated.

The physiology of nausea and vomiting is quite complex. The chemoreceptor trigger zone for emesis is located in the area postrema of the medulla. The vomiting center is also in the medulla, inside the blood–brain barrier. The vomiting center receives input from the gut, the cerebral cortex, and the vestibular system, as well as from the chemoreceptor trigger zone. All these inputs affect nausea and vomiting. Opioids cause direct stimulation of the chemoreceptor zone that causes emesis. This effect is potentiated by vestibular stimulation (hence, ambulatory patients suffer more emesis than supine patients); it is antagonized by certain substances with potent dopamine blocking effects (e.g., chlorpromazine, droperidol).

These complexities, plus a considerable degree of interdrug variability in individual patients, make the treatment of this common side effect something of an art. However, nausea and vomiting can usually be prevented or effectively treated. Nausea can be prevented by the concomitant use of hydroxyzine, by giving a reduced dose of opioids (89), or by the concomitant use of prochlorperazine or haloperidol. Transdermal scopolamine (Transderm Scop), commonly used to prevent emesis associated with motion sickness, is also an effective treatment.

If the patient is vomiting, the antiemetic drug should be given IM, rectally, or transdermally. In such cases it may also be desirable to switch to rectal administration of opioids. Morphine and dihydromorphinone are available in suppository form. In patients for whom opioids are prescribed for home care, it is often advisable to issue a week's supply of an antiemetic drug to be used prophylactically to avoid nausea and vomiting.

SEDATION. Excessive sedation, drowsiness, confusion, dizziness, and unsteadiness can develop during the first few days of opioid therapy but usually clear in 3 to 5 days. Persistent sedation and drowsiness can be ameliorated, either by reducing the dose of opioid but increasing the frequency of administration to ensure sustained analgesia, or by the concomitant use of amphetamines for relatively short- term therapy and for patients with terminal cancer or perhaps with nonmalignant chronic pain states (90).

There has been concern over the possible impairment of cognitive and psychomotor performance by psychotropic drugs. The effect of short- and long-term opioids has been reviewed (91). The results were reassuring. If the patients on opioids show any impairment, it is a function of slowed response, not impairment of accuracy. People on stable doses of opioids for extended periods of time, whether for treatment of cancer pain or heroin-abuse treatment, show little or no impairment, suggesting some kind of tolerance or habituation occurs (92,93).

RIGIDITY. High doses of opioids injected IV at a rapid rate can induce muscular rigidity associated with a decrease in chest compliance that could progress to the inability to ventilate. This occurs not only in humans but also in rats and other experimental animals. The precise mechanism of this effect is not known, but it is probably caused by the interaction of opioids with receptors located in the substantia nigra and striatum (94). Although there is no convincing evidence that one drug is worse than another, highly lipid-soluble drugs (e.g., alfentanil, remifentanil), which develop a fast equilibrium between blood and brain after rapid bolus administration, are the ones most likely to produce this phenomenon (77). Opioids also have some association with other types of tonic-clonic movements or myoclonus.

CONVULSIONS. Some opioids can cause convulsions of several different types. Morphine, methadone, and d-propoxyphene, when given in high doses, cause convulsions that are reversible with naloxone. For this reason, and except for normeperidine (norpethidine) because there is little if any evidence that opioids cause electroencephalographic changes in generalized cortical activity in humans (95), these “seizures” are not likely to be epileptic and may be more closely related to opioid-induced rigidity. Meperidine, its metabolite normeperidine, and thebaine produce multifocal myoclonic convulsions that are not reversed by naloxone but sometimes (although not always) respond to anticonvulsive agents (96). In humans, fortunately, opioids induce convulsions and seizures at doses that are much higher than those required for analgesia.

PRURITUS. Opioid-related pruritus mostly occurs with intraspinal opioids and is usually limited to the face and torso (97). Its mechanism is not known but it appears to be centrally mediated. It can be controlled by small, carefully titrated doses of naloxone or nalbuphine (98,99,100 and 101). Because nalbuphine is a mu antagonist-kappa agonist, pruritus may be mu-mediated. Many endogenous compounds may be involved. Histamine, prostaglandins, tachykinins (substance P), opioid peptides, serotonin, interleukins, or a combination of these compounds have all been strongly implicated (102).

Peripheral Effects. Different opioids act on various organ systems in similar ways but with different intensities (Table 84-5). Clinical trials have shown that potent opioids, administered in equianalgesic doses to the general population, produce a similar statistical incidence and degree of effects. Depending on the particular circumstance, these may be either welcomed or undesired. However, certain patients experience one or more of these effects to a greater degree than the general population and may show different susceptibility to different opioids. Thus, all patients receiving opioid therapy should be closely monitored for adverse side effects and complications, and if side effects are particularly intense, other opioids should be tried at equianalgesic doses.

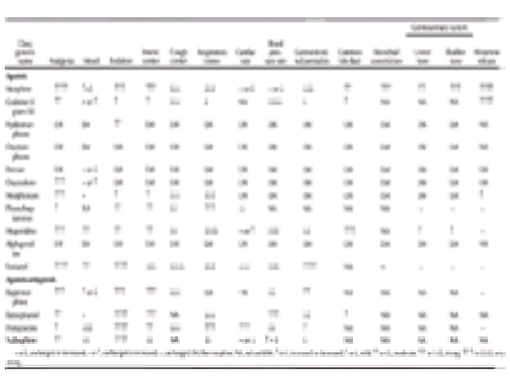

TABLE 84-5. Systemic pharmacologic and toxicologic effects of common opioids

Cardiovascular System. Therapeutic doses of opioids do not have a significant effect on the myocardium of healthy individuals. In patients with coronary heart disease, however, therapeutic doses of morphine cause a decrease in oxygen consumption, cardiac work, left ventricular pressure, and diastolic pressure (72). Large doses of opioids are therefore used to induce anesthesia in cardiac cripples.

Hypotension due to histamine release can be problematic after large doses of morphine (103). Histamine-blocking agents only partially reverse this hypotension, but it is completely reversed by naloxone. Fentanyl analogs sufentanil, alfentanil, and remifentanil do not release histamine. Histamine release can also cause dilatation of cutaneous blood vessels, with resultant flushing and sweating, mostly of the face and trunk.

Morphine and morphinelike opioids, such as fentanyl and its analogs, have a vasodilating effect on peripheral arterioles and veins. Morphine should be used with caution in hypovolemic patients because it can aggravate hypotension or even induce hypovolemic shock. The hypotension caused by opioids can be treated with IV fluids and, if need be, a-adrenergic agonists. Equally important, morphine should be used with great care in patients with cor pulmonale because sudden death has been reported (72).

The minor cardiovascular effects observed with opioids may be due to stimulation and depression of different parts of the CNS involved with cardiovascular regulation. During shock caused by sepsis, hypovolemia, or spinal cord injury, the administration of opioids worsens the clinical picture, whereas large doses of naloxone may lead to improvement (72). Fentanyl and its analogs reduce heart rate and can cause bradycardia if used in conjunction with vagal-stimulating procedures such as laryngoscopy. This lowering of heart rate can be advantageous in procedures in which lower heart rate improves the balance between oxygen supply and demand. Meperidine, on the other hand, increases heart rate with its anticholinergic activity. Cardiovascular stimulation can also be seen with the agonist-antagonists (pentazocine, nalorphine) and on occasion with fentanyl analogs.

Pulmonary System. It has been reported that high doses of meperidine or morphine can cause constriction of the bronchi. This is rarely seen with usual analgesic doses. During an asthma attack, opioids should not be used because their depressive action on the respiratory center, release of histamine, drying of secretions, and decrease of the cough reflex might worsen the clinical picture by decreasing respiratory drive and increasing airway resistance. Pulmonary edema is a potential complication that usually occurs only with opioid intoxication. In one series of cases, patients developed pulmonary edema while being treated for cancer pain. These cases usually involved high doses with rapid dose escalation (93).

Gastrointestinal System

MOTILITY. Opioids have a generalized depressant effect on gastrointestinal motility (72,104). They reduce longitudinal peristalsis and increase sphincter tone. Constipation is the predictable result. Along with nausea, this is one of the opioids' most common and troublesome side effects. The prophylaxis of constipation needs to be considered as soon as an opioid is initiated. Chronic constipation can be more difficult to treat than the pain itself.

STOMACH. Opioids slightly decrease secretion of hydrochloric acid, increase antral tone, and decrease gastric motility, resulting in increased time for gastric emptying (up to 12 hours) and consequent poor absorption of other oral medication. Slowed gastric emptying also creates increased risk of esophageal reflux.

SMALL INTESTINE. Digestion of food in the small intestine is decreased, along with biliary and pancreatic secretion. Smooth muscle tone increases and propulsive peristaltic contractions decrease markedly. Even though the amplitude of rhythmic, segmental contractions is enhanced, they are nonpropulsive. The duodenum is more affected by opioids than the ileum. More water is absorbed and the viscosity of the chyme is increased because of the prolonged time that chyme is in the small intestine.

LARGE INTESTINE. Propulsive contractions of the colon are greatly diminished or completely abolished by opioids. The mechanism of action seems to be both at the level of the gastrointestinal tract and at the level of the CNS. Tone can increase to the point of spasm, further delaying the transit of the gastrointestinal contents. The feces lose a considerable amount of water and become dry and compacted, which causes constipation that may progress to frank bowel obstruction. Tolerance to the constipating effect of opioids does not develop to a great extent, and most patients on chronic opioid therapy suffer from constipation. It cannot be too strongly recommended that initiation of opioids be accompanied by a bowel care regimen that may include extra fluids, stool softeners, or cathartics.

BILIARY TRACT. Therapeutic doses of opioids cause increased biliary tract pressure. This is thought to be due to either constriction or spasm of the sphincter of Oddi and can last 2 to 12 hours after administration of a therapeutic dose. This increase in pressure can cause epigastric distress, which can be relieved by small amounts of naloxone (105); smooth muscle relaxants such as nitroglycerin, 0.6 mg sublingually; or amyl nitrate.

The effects of opioids on the sphincter of Oddi are complex and early study results were inconsistent. With the use of endoscopic retrograde cholangiopancreatography the studies are more reproducible (105). Equianalgesic doses of fentanyl, meperidine, morphine, and pentazocine increase the pressure in the common bile duct 99%, 61%, 53%, and 15%, respectively, above baseline (106). Other opioids, mixed agonist-antagonists, partial agonists, and other agents (tramadol) have been tested. The best alternatives to meperidine, the traditional favorite, seem to be buprenorphine (partial agonist), nalbuphine (agonist-antagonist), and, with some reservations, tramadol.

Genitourinary Tract

URETER AND BLADDER. Opioids tend to increase the tone and amplitude of contraction of the ureter, but this response varies in humans (107). They can also produce urinary urgency by increasing the tone of the detrusor muscle of the urinary bladder. Increased tone of the sphincter vesicae may make urination difficult to the point of requiring catheterization, after even therapeutic doses of morphine. This has been observed particularly in a large percentage of male patients receiving intraspinal opioids (97). Naloxone antagonizes this action. Tolerance also develops to opioid effects on the bladder.

UTERUS. Therapeutic doses of opioids decrease uterine contractions and can prolong labor (108). Large doses of opioids should not be used during labor, not only because of this effect on the mother, but also because they can cross the placenta and reach the CNS of the fetus. Their effects can persist in the neonate, who is particularly sensitive to the respiratory depressant effect of opioids. Uterine hyperactivity, however, is decreased by morphine, which tends to return contractility to normal. In this particular situation the duration of labor and delivery can be shortened by morphine.

Immune System. There is some evidence that the opioid receptors expressed by immune cells are similar to or even the same as the neuronal subtypes, mostly mu, delta, and kappa. There may also be novel opioid receptors (mu_3) and/or binding sites on immune cells that are selective for morphine (109). Delta agonists appear to function in an autocrine/paracrine manner. Kappa receptors are present on a number of peripheral and central cells involved in host defense, and kappa agonists modulate both cellular and humoral immune responses. Some research has shown that opioids can act as cytokines to regulate a number of functions of both granulocytes and mononuclear cells. The opioid peptides, a-endorphin and enkephalins, appear to be able to function as endocrine hormones when secreted into the systemic circulation and may mediate the influence of the CNS on the peripheral cells that provide host defense and immunity.

Morphine alters a number of mature immunocompetent cells that are involved in cell-mediated and humoral immune responses. It also influences the differentiation of pluripotent stem cells into myeloid and lymphoid cell lines. It reduces or halts thymocyte proliferation in response to interleukin-2 or mitogens across the entire T-cell line.

There may be important differences between autoregulation of the immune system by endogenous opioids as part of a complex system involving numerous signal molecules and cell types, and immune modulation by exogenous opioids. The immunomodulating effects of opioid drugs may have clinical importance. There is evidence that opiate addicts have increased rates of lymphadenopathy, infectious complications, and cancer consistent with a degree of opiate-induced immunosuppression. There is also evidence that in some circumstances morphine may enhance human immunodeficiency virus expression. Further study is needed to allow the risks of opioid drug–induced immunosuppression to be minimized and any potential therapeutic applications to be identified and put to use (109,110 and 111).

Tolerance and Dependence

Tolerance. Tolerance is a normal pharmacologic response to chronic opioid therapy. It is defined as reduction of response to a drug after repeated administration or the need for a higher dose to maintain the same effect. Tolerance develops at different rates for various effects. For example, tolerance to the analgesic and euphoric effects of morphine develops much more rapidly than tolerance to its constipating effects. Tolerance to analgesia also seems to develop more slowly with PCA than with continuous infusion, for reasons that are still not clear.

One of the reasons for the development of tolerance may be pharmacokinetic, involving changes in distribution of the drug or changes in its rate of metabolism due to enzyme induction. There may also be a pharmacodynamic change, such as a change in receptor density or a change in the relative numbers of multiple receptors. Tolerance may also involve opioid receptor desensitization (71). Some interesting new data have come out of research on morphine suggesting that *N*-methyl-d-aspartate (NMDA) receptors and nitric oxide receptors are required for the induction and maintenance of tolerance (112,113 and 114). Other studies suggest

the delta and kappa receptors have a specific role in the development of tolerance.

The earliest sign of tolerance is the patient's complaint that the duration or degree of analgesia, or both, has decreased, although no increase is seen in the nociceptive input. This is usually treated by increasing the frequency or dose of the drug, or both. Alternatively, because cross-tolerance among opioids is not complete, switching to an alternative opioid often results in adequate pain relief. The mechanism for this is not at all clear but may have to do with the differential receptor occupancies of each drug. The alternative opioid is given in equianalgesic doses; the patient is carefully monitored; and the dose, time interval, or both are either increased or reduced according to individual needs.

Physical Dependence. Physical dependence is another physiologic response to the pharmacologic effects of chronic opioid use. It is defined as the potential for an abstinence syndrome after abrupt discontinuation, precipitous dose reduction, or administration of a specific antagonist (115). The abstinence syndrome consists of yawning, lacrimation, frequent sneezing, agitation, tremor, insomnia, fever, tachycardia, and other signs of hyperexcitability of the sympathetic nervous system. The rule of thumb is that for each drug the abstinence syndrome is the opposite of the effect (usually peripheral) of the original drug. The time of onset and the characteristics of the abstinence syndrome vary, usually depending on the half-life of the drug. It can be prevented by slowly tapering the dose of the opioid at a rate of 15% to 20% daily, and it can be effectively treated by reinstituting the drug in doses of approximately 25% to 40% of the previous daily dose (86).

Addiction and Pseudoaddiction. Physical dependence on opioids is pharmacologic and, like the development of tolerance, does not in itself constitute addiction (116). Addiction is a behavioral pattern of drug use characterized by an overwhelming involvement with compulsive drug use, use of the drug for effects other than pain relief despite adverse consequences, and/or preoccupation with acquisition of the drug. Unlike mere physical dependence, addiction is associated with a high tendency to relapse after withdrawal (117).

Fear of addiction has been an important factor in the underdosing of opioids in patients with severe pain, but opioid addiction rarely occurs in patients receiving opioids for medical purposes. In a study of nearly 40,000 hospitalized medical patients who were monitored for psychological dependence, Porter and Jick (118) found that among the nearly 12,000 patients who received one or more doses of opioids, only four cases of psychological dependence were documented in patients who had no previous history of addiction. In another study of cancer patients receiving chronic opioid therapy, Kanner and Foley (119) found that drug abuse and psychological dependence did not occur in this population. Moreover, in patients with severe pain caused by recurrent or metastatic advanced cancer who are likely to require opioid therapy until death, addiction and physical dependence should not be considered as reasons to not give opioids in adequate doses. Patients with cancer pain who are to be managed with opioids should be given ample doses for effective pain relief for as long as necessary.

Pseudoaddiction to opioids is an iatrogenic syndrome of behavioral changes, similar to those seen with idiopathic opioid addiction, that can develop as a direct result of inadequate pain management (120). Uncontrolled pain of malignant or nonmalignant origin can cause perfectly responsible patients to engage in inventive behavior that may appear demanding or even sociopathic, simply because their pain relief regimen does not provide adequate analgesia. Many of these patients are mislabeled as “drug-seeking” or “antisocial types” until they are questioned appropriately by a clinician who knows what questions to ask. The best way to avoid such unnecessary rifts in the therapeutic alliance is to be sure that the pain management regimen is adequate, closely monitored, and frequently adjusted to compensate for changes in the patient's needs. The patient's reports of pain should be acknowledged and validated. The backbone of the medication regimen should be adequate, scheduled (*not* pain-contingent) doses, with additional drug available for breakthrough pain, and adjustments to the scheduled doses if breakthrough pain is frequently occurring.

Despite current efforts to improve clinicians' understanding of effective pain management, in many if not most communities there is still a great deal of opiophobia. Opiophobia is the syndrome of failure to administer adequate opioid analgesics because of the fear of producing addiction or toxicity. The etiology of opiophobia is multifactorial: Peer pressure (provider and patient), regulatory agency pressure (real or perceived), and lack of education on opioids and the fundamentals of pain management all contribute to its persistence. Lower socioeconomic groups, younger patients, and other minority populations are particularly likely to be its targets; these patients frequently receive lower doses of opioids but higher levels of scrutiny (121). All of these factors contribute to the underuse of these relatively simple and very effective medications, due to no fault of the patients.

PHARMACOLOGY OF SPECIFIC OPIOIDS

Classification of Opioids

There are several ways to classify the opioids. One system subdivides them into weak opioids with low addiction potential and stronger opioids with higher addiction potential. Another system considers opioids for their agonist, partial agonist, and agonist- antagonist activities. Opioids can also be divided into naturally occurring, semisynthetic, and synthetic groups. The weak/strong dichotomy is easy but not that helpful, so the latter two classification systems are discussed here (Table 84-6).

TABLE 84-6. Two classification systems for opioids

The naturally occurring opioids are the alkaloids of opium and comprise two chemical classes. Those of one class contain the three-ringed phenanthrene nucleus and include morphine, codeine, and thebaine. The other class consists of the benzylisoquinoline alkaloids, which lack any analgesic activity; examples of this group are papaverine and noscapine. The semisynthetic opioids are obtained by simple modification of a naturally occurring alkaloid. For instance, heroin is derived from morphine and etorphine is derived from thebaine. Synthetic opioids contain the phenanthrene nucleus of morphine but are completely synthesized. The synthetic opioids are further subdivided into several groups based on their chemical structure (e.g., morphinans, phenylheptylamines, phenylpiperidines).

The most useful opioids are described in some detail in this section. Table 84-7 contains summary data for comparison. Again, because of great intersubject variability, the dosages indicated after each drug are only given for orientation and represent the average dose required to control moderate to severe pain in adult patients. In the clinical setting the dose for each individual must be titrated with regard to amount and frequency for adequate pain control.

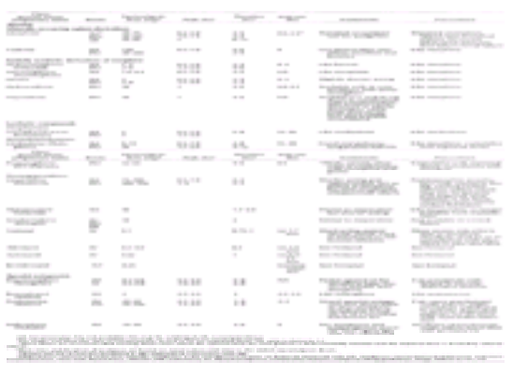

TABLE 84-7. Pharmacokinetic and pharmacodynamic data of common opioid analgesics used for pain

Pharmacology of Individual Opioids

Agonist Opioids

An agonist drug creates its pharmacologic effects by binding to and activating stereospecific receptors. Agonist opioids include morphine, codeine, meperidine, dihydromorphinone, and methadone, among others. Naturally occurring agonists are described first, followed by semisynthetic and synthetic agents.

Naturally Occurring Opium Alkaloids

Morphine. Morphine is the reference standard for all the potent opioid analgesics. The effects and side effects of mu opioids are as for morphine. Despite our long familiarity with morphine, many details of its pharmacology and pharmacokinetics remain unresolved. There are still some unanswered questions about its physiochemical nature—for example, its relative lipophilicity and whether that explains its relatively rapid onset of effects (122).

Morphine is metabolized in the liver and possibly also in the brain and kidneys. There are two major metabolites, morphine-3-glucuronide and morphine-6-glucuronide, which are mainly eliminated in urine and bile. It appears that although glucuronides are normally thought to be inactive, morphine-6-glucuronide is actually more potent than the parent compound. Morphine-3-glucuronide may have a part in the side effects of morphine. In patients with impaired renal function the accumulation of these metabolites becomes important, causing first increased effect and then, as more drug accumulates, toxic effects (123).

Among clinically used opioids, morphine gives the clinician the most options for effective routes of administration. It can be instilled directly via intrathecal and epidural routes. It has also been used for cancer pain using the intracerebroventricular route. When rapid onset is important, IM and subcutaneous administration, with their peak plasma levels at 20 minutes, provide alternatives to IV administration (124). There are also a number of protocols for using morphine either IV or subcutaneously for both continuous infusion and PCA (see Chapter 36, Chapter 41, Chapter 42 and Chapter 43, Chapter 103). Morphine is absorbed from all mucous membranes, allowing sublingual, buccal, and rectal administration, but not from intact skin. Oral absorption takes place in the small intestine and is virtually complete. There are myriad oral preparations, from oral solution and immediate-release tablets to the multiple sustained- release preparations that allow dosing once to three times daily rather than every 3 to 5 hours.

The controlled-release preparations of morphine offer great advantages for long-term therapy in patients with terminal cancer pain and noncancer pain because they provide constant plasma levels for long periods of time. There are controlled-release tablets, capsules, suspensions, and suppositories. The preparations are not necessarily bioequivalent, but with some minor dose adjustment, equal analgesia can be obtained across a number of controlled-release options (9). The outcome will be smoother, more consistent pain relief for long-term therapy, regardless of the diagnosis.

Side effects associated with the use of morphine are those common to all the opioids. Tolerance and physical dependence develop when morphine is given for a period of several weeks to months.

Codeine. Except for aspirin, codeine is probably the most widely used analgesic—and the most commonly used prescription opioid—in the world. Codeine's major disadvantage is its lack of effectiveness in treating severe pain, and stronger opioids must be used in such cases. Codeine has a low affinity for opioid receptors and so produces a lower incidence and degree of physical dependence than most other opioids. The analgesic effect of codeine is due to its conversion to morphine. Approximately 10% of administered codeine is demethylated to form morphine. Codeine has strong antitussive effects that are mediated by codeine's active metabolites depressing the cough reflex in the medulla. There may also be distinct receptors that bind codeine itself.

Codeine has a high oral-to-parenteral potency ratio, both as an analgesic and as a respiratory depressant: 60 mg of codeine given IM or subcutaneously is equivalent to 180 mg orally. This is thought to be due to less first pass metabolism in the liver with parenteral administration. Only levorphanol, oxycodone, and methadone have a similarly high oral-to-parenteral potency ratio. Codeine's half-life ranges from 2 to 4 hours, with analgesia lasting 3 to 6 hours.

Genetic differences in P-450 enzymes are known; some patients may not be able to convert codeine to morphine, and this drug could therefore have no analgesic properties for such individuals. Codeine is a CYP2D6 enzyme substrate and a minor CYP3A3/4 enzyme substrate. Codeine's analgesic effects, as well as side effects, may be decreased with concomitant use of enzyme inhibitors such as quinidine, cimetidine, phenothiazines, haloperidol, ritonavir, and some of the selective serotonin reuptake inhibitors (SSRIs). Its analgesic effects are increased with cigarette smoking, probably due to enzyme induction.

Even with little renal elimination (5% to 17%) and apparently unaltered disposition of orally administered codeine in renal failure, two cases of codeine-induced narcosis in patients with renal failure have been reported, as well as one case of respiratory arrest precipitated by codeine in a child with chronic renal failure (125,126 and 127). Decrease the dose by 25% in patients with creatinine clearance of 10 to 50 mL per min and 50% in patients with clearance of less than 10 mL per minute. Codeine is available in the United States in oral, subcutaneous, IM, and IV formulations.

Partially Synthetic Morphine Derivatives

Dihydromorphinone (Hydromorphone). Hydromorphone (Dilaudid) is a semisynthetic derivative of morphine that is approximately six to eight times as potent. The most agreed-upon conversion is that 1.5 mg of hydromorphone is equianalgesic to 10 mg of morphine. It is easily absorbed by the gastrointestinal tract and is thus effective after oral and rectal administration. It can also be used parenterally and intraspinally. Due to its high solubility, it is particularly useful subcutaneously (128,129). Hydromorphone is hydrophilic; when given epidurally, its long half-life resembles that of epidural morphine, and its short latency of analgesia is similar to meperidine's (130). A controlled-release hydromorphone, available in some countries, has been shown to be as effective administered every 12 hours as immediate-release hydromorphone administered every 4 hours (131).

Dihydrohydroxymorphinone (Oxymorphone). Oxymorphone is a congener of morphine with a substitution of a ketone group at the C-6 position, conferring a more rapid onset of effect, greater potency, and slightly longer duration of action than morphine (132). Oxymorphone has a short half-life, but due to slow dissociation from its receptor sites it has a prolonged duration of action that correlates poorly with its plasma concentration. It is approximately seven to 10 times as potent as morphine, with a high affinity for mu receptors. Oxymorphone is less likely to produce histamine release than morphine (128,133). It is available in the United States in injectable and rectal formulations (Numorphan).

Diacetylmorphine. Diacetylmorphine, or heroin, is rapidly hydrolyzed to 6-monoacetylmorphine (6-MAM) and further hydrolyzed to morphine (134,135). Both heroin and 6-MAM are more lipid soluble than morphine and enter the CNS more readily. However, it is hypothesized that 6-MAM and morphine are the moieties responsible for heroin's pharmacologic actions. Due to its high lipid solubility, IM heroin has a faster onset of action but a shorter duration of action than morphine and is twice as potent as morphine.

Heroin is not available for clinical use in the United States. There are campaigns to make it available, but with the marketing of high potency hydromorphone, the need for it becomes less urgent. It is used in other parts of the world, however, especially for the treatment of terminal cancer pain, although several studies have failed to show an advantage for this drug over other opioids used at equipotent dosages (136,137,138,139 and 140). Parenteral heroin is not superior to morphine in terms of analgesia, effects on mood, or side effects (134,138). Heroin is seldom given orally; after oral administration, only morphine, not heroin or 6-MAM, can be measured in blood (128,134).

Dihydrohydroxycodeinone (Oxycodone). Oxycodone is a derivative of thebaine but can also be made by modifying morphine. It is a potent mu agonist with analgesic potency almost equivalent to that of morphine when given parenterally and is nearly 10 times as potent as codeine when given orally (141). Oxycodone is reported to have fewer side effects than morphine; morphine caused more nausea in a double-blind, crossover study (142). It is metabolized by *N*- and *O*-demethylation and

conjugation, catalyzed by CYP2D6 (143). At least part of its analgesic action appears to be mediated by active metabolites (141). Oxycodone is available as a single-entity formulation or with aspirin or acetaminophen as a fixed-dose combination. The dose limitation of the combination is based on toxicity of the nonopioid analgesics when used in high dose. Oxycodone has a half-life of 2 to 3 hours, with a duration of action between 4 to 5 hours. A controlled-release product is also available (Oxycontin) (144).

Dihydrocodeine. Dihydrocodeine has analgesic and antitussive efficacy. It has also been used in maintenance programs for those addicted to opioids (145). It is available in tablet form in both regular-release and controlled-release formulations and is also available for parenteral administration.

There are reports of significant interindividual differences in dosage requirements with this drug (145). This may in part be due to its metabolism. Dihydrocodeine is *O*-demethylated to dihydromorphine, catalyzed by CYP2D6, and *N*-demethylated to nordihydrocodeine, predominantly catalyzed by CYP3A (145,146). In other opioids that are dealkylated (i.e., codeine, hydrocodone, and oxycodone), the metabolite has a higher affinity for the mu receptor and is usually more active than the parent compound (145). Approximately 7% of the population of whites are poor metabolizers via the CYP2D6 pathway. This means some patients will achieve only suboptimal pain relief with these drugs even when taking a standard therapeutic dose.

Dihydrocodeine also shows altered kinetics in renal failure patients. One study reported a delayed peak, greater area under the curve, and still-detectable urine levels after one dose in the majority of such patients receiving dihydrocodeine (147). Dihydrocodeine-induced narcosis in an anuric patient undergoing hemodialysis has also been reported (148).

Synthetic Compounds. Synthetic opioids include morphinans, phenylheptylamines, and phenylpiperidines.

Levorphanol. Only the *l*-isomer of levorphanol has analgesic effect. The *d*-isomer, dextromethorphan, is devoid of analgesic actions but has antitussive activity. Levorphanol's analgesic effects are similar to those of morphine, but there are reports of less nausea and vomiting with levorphanol. Levorphanol is typically given subcutaneously, but may also be given by slow IV infusion, IM, or orally. Levorphanol is less effective when given orally, but its oral-to-parenteral potency ratio is relatively high and comparable to codeine and oxycodone.

Levorphanol is slowly metabolized, with a half-life of 12 to 16 hours, but its duration of analgesia is shorter, ranging from 4 to 6 hours, slightly longer than that seen with morphine. Due to its slow metabolism and the discrepancy between plasma half-life and duration of analgesia, repeat dosing can lead to drug accumulation. Levorphanol acts primarily through the mu receptors but does have some effect at kappa $_3$ and delta, as evidenced by the lack of complete cross-tolerance between morphine and levorphanol. Due to its effect on multiple opiate receptors, levorphanol is often used as a second-line agent after morphine or in patients tolerant to morphine (128).

Methadone. Methadone is a synthetic opioid that is slightly more potent but less dependence-producing than morphine. Methadone produces less euphoria and less sedation than many other opioids. The central mechanism of action is similar to that of morphine. It is well absorbed when taken orally, so it is of little advantage to administer it parenterally. The subcutaneous route of administration is not recommended due to local skin toxicity (149).

Methadone has a long and unpredictable half-life, ranging from 13 to more than 100 hours, and consequently a longer duration of action than any of the aforementioned opioids, making it ideal for long-term administration. It is commonly used in addiction rehabilitation programs and is useful in managing pain problems that require prolonged opioid treatment. Its longer duration of action is mainly due to extensive plasma-protein binding (150). There may also be other mechanisms, such as renal ion trapping, that add to the half-life of this weakly basic molecule. To reach steady state, however, it must be administered for several days, so during the first 2 to 3 days of use, doses should be given every 4 to 6 hours and thereafter every 6, 12, and even 24 hours. The convenience of extended dosing intervals must be balanced against greater likelihood of peak-related side effects with larger doses.

Oral doses of 5 to 10 mg every 6 to 8 hours are often prescribed. Doses of up to 20 to 30 mg every 4 hours have been given without ill effects, however, in terminal cancer patients and other individuals with high degrees of tolerance. Due to the large interindividual variations in pharmacokinetics, the range of dosage and frequency varies according to the severity of the pain and the patient's tolerance (151,152).

Methadone has proven efficacy in the management of terminal cancer patients with pain, and it has been given for up to 2 years in such cases without any significant incidence of abuse. Less clear are indications for its long-term use in chronic nonmalignant pain problems; in general, long-term opioid administration should be avoided in such cases. However, patients with chronic pain with cyclic variations of intensity and severe time-limited bouts of pain, such as low back pain, can certainly be treated with methadone (or with any other long-acting opioid) on a recurrent basis.

Levo-Alpha-Acetylmethadol. Levo-Alpha-acetylmethadol (LAAM) is a congener of methadone used in the United States only in government-designated maintenance programs for the treatment of opiate dependence. It is effective for heroin addiction presumably because of its protracted duration of action; a single dose of LAAM can be given every 72 hours (153). LAAM is slowly converted to active metabolites and therefore has a slow onset of action. Dosages range from 10 to 140 mg three times a week.

Propoxyphene. Propoxyphene is available as either propoxyphene hydrochloride or propoxyphene napsylate. Sixty-five mg of propoxyphene hydrochloride is equivalent to 100 mg of propoxyphene napsylate. Propoxyphene is structurally related to methadone. It binds primarily to mu receptors but is less selective than morphine, as evidenced by incomplete cross-tolerance between propoxyphene and morphine (72). Only the *d*-isomer has analgesic activity. Several clinical trials have shown that 90 to 120 mg of propoxyphene is equipotent to 60 mg of codeine, and doses of 60 mg are no more effective than 600 mg of aspirin. Doses of 32 mg or lower are no more efficacious than placebo (154). Propoxyphene is often compounded with other medications, such as aspirin or acetaminophen. From clinical experience propoxyphene appears to have an abuse potential but it is not certain whether this is physiologic or psychological. Unless the drug has been used at high dosages, such as 800 to 1,200 mg per day, it is not clear that withdrawal reactions ensue after abrupt cessation of the drug. Thus, propoxyphene appears to be less effective as an analgesic than codeine and to have enjoyed some popularity because of supposedly lower dependence potential, a property not observed in practice. Its higher cost should also discourage clinicians from prescribing it as a codeine substitute.

Propoxyphene has an onset of action of one-half to 1 hour, with peak effects seen at 1 to 2 hours and a duration lasting 4 to 6 hours. Its half-life is 6 to 12 hours, longer than that of codeine; however, propoxyphene is metabolized to norpropoxyphene, an active metabolite with a half-life of 30 to 34 hours that can accumulate. Very high doses of propoxyphene can cause respiratory depression, CNS depression, and convulsions. Delusions, hallucinations, confusion, cardiotoxicity, and pulmonary edema have also been noted (155). Naloxone antagonizes propoxyphene-induced respiratory depression, convulsions, and some cardiotoxic effects.

Meperidine. Meperidine (pethidine) is a synthetic phenylpiperidine opioid analgesic often used interchangeably with morphine. At equianalgesic doses, meperidine produces less smooth muscle contraction and causes less constipation and urinary retention than morphine, probably due to its greater ability to enter the CNS (72). Meperidine is absorbed by the gastrointestinal tract, but the oral dose is approximately 50% less effective than when given IM (72). Meperidine's absorption after IM administration may vary as much as 50% or more even when administered at the same site (39,156). Given IM, meperidine does not significantly affect heart rate, but IV use frequently causes a marked increase in heart rate (72). Given during labor, meperidine may increase the frequency, duration, and amplitude of uterine contractions but does not interfere with normal postpartum contraction or involution of the uterus and does not increase the incidence of postpartum hemorrhage (157). Meperidine produces less respiratory depression in the newborn than does an equianalgesic dose of morphine or methadone.

Meperidine is *N*-demethylated to meperidinic acid and normeperidine. The latter is an active metabolite with one-half the potency as an analgesic but twice the potency as a proconvulsant compared with the parent compound (158). Chronic dosing can lead to accumulation of the metabolite, which can result in CNS irritability (mood changes, anxiety, tremor, multifocal myoclonus, and occasionally seizures) (159). The ratio of normeperidine to meperidine in the plasma is higher in patients with renal failure (160). Naloxone does not reverse meperidine-induced seizures and is to be used with caution in patients receiving meperidine long term due to possible precipitation of seizures by blocking the depressant action of meperidine but allowing the convulsant activity of normeperidine to emerge (161). Meperidine is relatively contraindicated for the management of chronic cancer pain because of these potential complications (128).

Meperidine is involved in some clinically significant drug interactions. Concomitant use of meperidine with a monoamine oxidase inhibitor may cause severe respiratory depression, delirium, hyperpyrexia, convulsions, and death. This interaction has not been observed with other opioids (162,163 and 164). Tricyclic antidepressants and chlorpromazine may increase the respiratory depressant effects of meperidine. Phenobarbital and phenytoin increase the systemic clearance and decrease the oral bioavailability of meperidine, causing an increase in the concentration of normeperidine in the plasma.

Alphaprodine. Alphaprodine is another derivative of phenylpiperidine and is similar to meperidine but approximately twice as potent as an analgesic, with an even shorter duration of action. Alphaprodine analgesia lasts 1 to 2 hours, whereas meperidine's lasts 2 to 4 hours (158). The shorter duration of action is due to the smaller volume of distribution and higher plasma clearance for alphaprodine (158). In comparison with other opioid analgesics, both fentanyl and alphaprodine are shorter acting than meperidine and fentanyl is shorter acting than alphaprodine (144). Due to the short duration of action, it has been used frequently for analgesia during the early phases of labor when epidural block is not available to the patient. It is no longer available in the United States.

Ketobemidone. Ketobemidone is structurally related to meperidine. It is not available for use in the United States and is currently considered a schedule I narcotic. In other parts of the world, it is available in two formulations: ketobemidone and ketobemidone in combination with the spasmolytic A29 (*N,N*-dimethyl-3,3-diphenyl-1-methylallylamine chloride) (165,166). Data have demonstrated that ketobemidone, like methadone and dextropropoxyphene, is a weak noncompetitive NMDA-receptor antagonist, in addition to being an opioid receptor agonist (167,168). NMDA receptors are thought to be involved in the development and maintenance of neuropathic pain. Ebert et al. suggest that there is “a presumed opioid-insensitive component,” involved in neuropathic pain, and this component can apparently be blocked by NMDA-receptor antagonists (168). In an animal model equivalent to neuropathic pain in humans, the NMDA-receptor antagonist component of ketobemidone contributed to its pharmacologic effect (168,169). It is unknown at this time if these findings apply to humans.

Ketobemidone can be administered parenterally, orally, or rectally. The pharmacokinetic parameters and equianalgesic dose are roughly equivalent to morphine's. Ketobemidone undergoes extensive first-pass metabolism to norketobemidone, which has five times more potency at NMDA receptors than the parent compound (170). Norketobemidone is readily conjugated and eliminated even at high doses. This may give ketobemidone an advantage over meperidine, although perhaps not other opioids, in renal failure (171).

Fentanyl. Fentanyl, the first of the 4-anilinopiperidine class, is a chemical congener of the reversed ester of meperidine. Unlike morphine, it has high lipid solubility, which facilitates its transfer across the blood–brain barrier (172). Fentanyl is metabolized primarily in the liver to phenylacetic acid, norfentanyl, and small amounts of pharmacologically active *p*-hydroxyl (phenethyl) fentanyl (172). Like all other highly lipid-soluble drugs (with the exception of remifentanil) its elimination half-life is influenced by the duration of prior administration, which determines the extent of fat sequestration. In steady state, the elimination half-life is usually 7 to 12 hours (172).

Fentanyl is 75 to 100 times as potent as morphine (173). Its low molecular weight and high lipophilicity make it a good candidate for transdermal administration (174). The transdermal systems are designed to release fentanyl at a nearly constant rate along a concentration gradient from patch to skin. Typically, fentanyl is detected in the blood 2 hours after the initial transdermal patch application, but considerable delays from 17 to 48 hours have occurred that have been attributed to depot accumulation of the drug within the skin before diffusion into systemic circulation (172). Skin temperature may also play a role in fentanyl absorption. An elevation in body temperature up to 40°C may increase the absorption rate by one-third (172).

Transdermal fentanyl gives the same degree of pain control as morphine but is associated with significantly less constipation, nausea, and daytime drowsiness (173,174). The incidence of constipation has been shown to be reduced 50% to 66% after patients switch from oral morphine to transdermal fentanyl (172,173,175). This may be due to the difference between the concentrations required to achieve analgesia and those required to elicit a reduction in intestinal activity (172). Other side effects seen with fentanyl are typical of those seen with other opioids. An unusual side effect reported in approximately 3% of patients is mild to moderate itching and transient erythema; however, this is thought to be due to the plastic patch or adhesive rather than the drug itself (172,176,177). Rarely, an opioid withdrawal syndrome is seen when switching patients from sustained release morphine to transdermal fentanyl, which is attributable to physical rather than psychological dependency (172). Symptoms may be managed with short-acting oral morphine rescue doses. Transdermal fentanyl is contraindicated in patients with acute postoperative pain.

Fentanyl is also formulated as a lozenge for oral transmucosal administration. Transmucosal fentanyl was compared with oral hydromorphone in pediatric patients for burn care and was found to have similar efficacy (178). Transmucosal fentanyl offers an alternative route of opioid administration when IV administration is unavailable or undesirable (178).

Alfentanil. Alfentanil is a congener of fentanyl. It is approximately 10 times less potent than fentanyl but has a more rapid analgesic effect, shorter time to peak effect, shorter distribution, and shorter elimination half-life than fentanyl or sufentanil. The volume of distribution and total body clearance with alfentanil are smaller than with fentanyl and sufentanil, giving it a shorter half-life after bolus. The extremely high proportion of nonionized molecules of alfentanil result in a very short onset and peak effect because most of the drug can pass the blood–brain barrier. Alfentanil is slightly more lipophilic than fentanyl and is indicated for incremental injections, continuous infusions, and anesthetic induction. Because its formulation is preservative-free, it may be used intrathecally and epidurally. Alfentanil may be given intraspinally, due to its high lipophilicity. As with fentanyl, the dosage of alfentanil should be titrated to effect and based on ideal body weight rather than actual weight.

Alfentanil is predominantly metabolized by CYP3A3/4. Erythromycin can inhibit the oxidizing activity of this enzyme system and decrease the clearance of alfentanil by 50%. Cimetidine may also prolong opioid action by decreasing hepatic metabolism. Halothane can induce the activity of microsomal enzymes and has been reported to decrease the analgesic activity of alfentanil. Propofol inhibits the oxidative enzymatic degradation of both alfentanil and sufentanil (179).

Sufentanil. Sufentanil, a thienyl derivative of fentanyl, is five to 10 times more potent than fentanyl, with an affinity for opioid receptors 30 times greater than fentanyl's (180). Sufentanil has a volume of distribution, distribution half-life, and elimination half-life between those of fentanyl and alfentanil (181). Sufentanil and fentanyl are 50% protein bound, compared with 33% of alfentanil. It is likely that sufentanil's shorter elimination half-life is due to higher hepatic metabolization and reduced volume of distribution compared with fentanyl. Sufentanil has a somewhat faster onset of action and a shorter duration of respiratory depression than fentanyl (180). It has higher lipid solubility than fentanyl, alfentanil, and possibly remifentanil (181). After long-term administration, as with other highly lipid-soluble drugs, the elimination half-life is prolonged and is a function of the duration of administration.

Sufentanil should be dosed based on ideal, rather than actual, body weight.

Remifentanil. Remifentanil, GI-87084B, is an esterase-metabolized opioid of the 4-anilidopiperidine class (182,183). Remifentanil is unique in its rapid hydrolysis by nonspecific esterases in blood and tissues (182,183 and 184). It is not hydrolyzed by pseudocholinesterase, acetylcholinesterase, or carbonic anhydrase (182). Clearance should be unaffected by cholinesterase inhibition. The hydrolytic activity in blood is associated with red blood cells rather than plasma constituents, although plasma protein binding protects the drug from rapid hydrolysis (182).

Pharmacokinetic comparisons between remifentanil and alfentanil show that, although the volume of distribution at steady state is similar, remifentanil's clearance is significantly greater, at approximately 3 L per minute (182,183). There is a low interindividual variability in clearance when the ideal body weight is used in dosing calculations (182,185). This suggests that the relationship between infusion rates and blood concentrations will be more predictable than for other opioids (185). Remifentanil's pharmacokinetics are unaltered in renal failure and severe liver disease but are influenced by age (182). Bolus doses should be halved and infusion rates decreased to one-third in the elderly (182,185).

Despite remifentanil's rapid clearance, infusion rates should be titrated according to clinical response. Remifentanil has a distribution half-life of approximately 2 to 4 minutes and an elimination half-life of 10 to 20 minutes (186). The rapid onset of effects and rapid approach to steady state often allow bolus doses to be omitted; however, there is a rapid offset of effects as well (186). The interruption of an infusion will result in the offset of effects within 5 to 10 minutes. The rapid offset of effects permits the use of an opioid-based anesthetic technique and allows for early extubation but requires that there be adequate early postoperative analgesia orders in place (182,186).

Remifentanil is currently available for IV use. It is not for intrathecal or epidural administration due to the presence of glycine in the formulation. Glycine is an acidic buffer used to facilitate the preparation of remifentanil by providing a visible product after lyophilization, but when given intrathecally or epidurally, it causes motor impairment, perhaps through inhibition of spinal motor neurons.

Remifentanil is no more efficacious than other opioids in the piperidine family. Its potential advantages and disadvantages are due directly to its unique pharmacokinetic profile (182).

Agonist Combination Products

A number of products are available combining an antipyretic-analgesic, such as aspirin or acetaminophen, and an opiate agonist, such as codeine, hydrocodone, dihydrocodeine, opium, oxycodone, meperidine, or propoxyphene. Often other substances are added to aid in pain relief, such as caffeine, promethazine, belladonna, or butalbital. The combination of an antipyretic-analgesic and an opiate agonist often provides more analgesia than a single agent, allowing a lower dose of both agents to give adequate pain relief with minimum side effects (187). Opiates such as codeine and hydrocodone are weak mu agonists and therefore not indicated for chronic, severe pain.

These combination agents are sometimes considered pharmacologically “dirty,” but they provide a reasonable way to treat mild to moderate pain inexpensively and easily. They serve a need and conform to the spirit of the World Health Organization ladder (188).

Hydrocodone. Hydrocodone is available only as a combination product with acetaminophen or aspirin. It is important to note that the acetaminophen amount varies, ranging from 167 mg for the elixir to 750 mg for Vicodin ES, so care must be used when dosing in order not to exceed the maximum recommended amount of eight tablets per day for hydrocodone, 2.5, 5, or 7.5 mg, with acetaminophen, 500 mg, per tablet, or five tablets per day for hydrocodone, 7.5 mg, with acetaminophen, 750 mg, per tablet.

In comparison with codeine, 30 mg, combined with acetaminophen, 300 mg, hydrocodone, 5 mg, with acetaminophen, 500 mg, gave significantly more pain relief and a slightly longer duration of action, but this may be due to the acetaminophen content (187). One double-blind study showed a comparable degree of analgesia between codeine, 60 mg, and hydrocodone, 10 mg, and a superior degree of analgesia compared with placebo (189). Single doses of 500 mg to 650 mg of acetaminophen show more efficacy in relieving pain than 300 mg (190).

Hydrocodone is metabolized by CYP2D6 to an active metabolite, hydromorphone (dihydromorphinone) (191). Hydrocodone displays relatively weak mu receptor binding. Hydromorphone shows stronger mu receptor binding and may mediate hydrocodone's pharmacologic effects (192).

Agonist-Antagonist Derivatives

There is some confusion about the agonist-antagonist label. These compounds are kappa and mu receptor partial agonists. Their pharmacology once again relies on the opposing effects of mu and kappa (81). Agonist-antagonist opioids are less efficacious than the pure mu agonists but can produce analgesia with less respiratory depression and have a lower abuse potential. A ceiling effect on respiratory depression as well as on analgesia has been noted with this class of opioids. In an attempt to identify drugs with high analgesic activity and low incidence of side effects, several drugs with agonist-antagonist activity or with partial agonist activity have been introduced to clinical practice.

Buprenorphine. Buprenorphine is a highly lipophilic, semisynthetic derivative of thebaine and is a member of the C-bridged oripavine series (193). It is a potent partial agonist at the mu receptor and appears to be a kappa antagonist (72,194,195). Buprenorphine is approximately 30 times more potent than morphine when given IM. It is easily absorbed from the oral mucosa, and a sublingual preparation is used in most parts of the world (196). Buprenorphine produces its analgesic effect 45 to 60 minutes after parenteral administration. Its duration of action varies from 3 to 14 hours after a single dose. Data from more than 9,000 patients indicate that the mean duration of action is a little over 8 hours (193). The side effects are similar to those of morphine, but euphoria seems to be less frequent, whereas sedation is more evident (193). Buprenorphine is 96% protein bound (72).

Buprenorphine exhibits a bell-shaped dose-response curve for analgesia, gastrointestinal motility, and respiratory depression in some animal studies (193,197,198). The bell-shaped dose-response curve is unique in that, with increasing doses, antinociceptive effects are reduced to almost zero.

Chronic pain patients have been given sublingual buprenorphine for several months without the need to increase the dosage, indicating that the development of tolerance to its analgesic effect might be slower than with other opioids (199). Some patients chose to discontinue the drug because of side effects, especially sedation and nausea, rather than failure to obtain analgesia. Abrupt withdrawal of buprenorphine in dependent patients causes a mild to moderate abstinence syndrome that is much less severe than after morphine withdrawal (200). The abstinence syndrome is delayed in onset for 2 days to 2 weeks after drug discontinuation, peaks at approximately 2 weeks, and lasts for more than 1 week (72). Patients using other opioids should not be abruptly switched to buprenorphine because this could precipitate an abstinence syndrome.

The side effects of buprenorphine are mostly sedation, nausea and vomiting, constipation, diaphoresis, and some respiratory depression. Naloxone is ineffective in reversing serious respiratory depression induced by buprenorphine, suggesting that it dissociates slowly from opioid receptors (72,193,194 and 195).

From a study of deaths from buprenorphine in France, it was concluded that IV injection of crushed tablets, concomitant intake of psychotropics (especially benzodiazepines), and high formulation dosages are risk factors for fatality (194,201). Respiratory and cardiovascular collapse has been reported in a patient who received therapeutic dosages of buprenorphine and diazepam (202). There is a case report of severe postoperative respiratory depression following IM ketorolac after epidural buprenorphine (203).

Buprenorphine is *N*-dealkylated by CYB3A3/4. Protease inhibitors, ritonavir, indinavir, and saquinavir inhibit the metabolism of buprenorphine and methadone, which can lead to accumulation (204).

Butorphanol. Butorphanol is a morphinan congener, 14-hydroxymorphinan, with a profile of action similar to pentazocine's (72,205) but with greater analgesic efficacy and fewer side effects. Like pentazocine, butorphanol exhibits a “ceiling” for inducing respiratory depression; dosages of butorphanol of greater than 2 mg do not result in a corresponding increase in respiratory depression (72,206). Increasing dosages of butorphanol do increase the duration of respiratory depression (206). Butorphanol is also similar to pentazocine in its ability to produce a significant increase in pulmonary arterial pressure, increase in cardiac workload, and decrease in systemic arterial pressure (72,206,207).

The principal actions of butorphanol result from its agonist activity at kappa receptors and antagonist activity at mu $_1$ receptors (206). Butorphanol has also been reported to be a partial agonist at sigma receptors (208). Parenterally, butorphanol, 2 to 3 mg, is approximately equal to morphine, 10 mg, in producing respiratory depression and analgesia, with onset, peak, and duration of action similar to morphine (72). Its parenteral use is associated with significant sedation even though patients remain responsive (72). It produces approximately 50% less nausea and vomiting than morphine, and side effects such as constipation and urinary retention are less frequent after chronic administration than with morphine if used at therapeutic doses.

Butorphanol undergoes significant hepatic first-pass metabolism when orally administered, with a bioavailability ranging from 5% to 17% (206). Due to this extensive metabolism, butorphanol has been formulated for IV, IM, and transnasal administration (206). These three routes of administration result in similar plasma concentration-time curves, with no first-pass metabolism associated with IV, IM, or transnasal administration (206). Noninvasive transnasal administration of butorphanol results in rapid absorption with an onset of analgesia within 15 minutes, peak plasma concentrations within 30 to 60 minutes, and elimination half- life ranging from 4.7 to 5.8 hours; elimination half-life is increased in the elderly and in patients with impaired renal function (206).

Adverse effects associated with transnasal use are related to the duration of use and include nasal/sinus congestion, nasal irritation, rhinitis, pharyngitis, upper respiratory infection, tinnitus, and epistaxis (206). Psychotomimetic effects, such as hallucinations and dysphoria, are usually seen in less than 1% of patients with injectable and transnasal butorphanol (206). A case report of psychosis with visual hallucinations has been reported with butorphanol, 1 mg IV (209).

Nalbuphine. Nalbuphine is an analgesic derivative of the agonist oxymorphone and the antagonist naloxone and is a kappa agonist and mu antagonist (16,210,211). Mu-mediated effects such as respiratory depression, constipation, nausea and vomiting, and abuse potential are less frequent or less severe than with other opioids. However, the kappa-mediated analgesia produced by nalbuphine is less than that produced by pure mu agonists, so nalbuphine is not recommended for severe pain. Kappa receptor activity also produces its own set of side effects, including sedation, dysphoria, and diuresis (184). Euphoria is observed after administration of 8 mg of nalbuphine IM. Dysphoria and psychotomimetic reactions are not problematic until 70 mg have been given. A primary side effect is sedation, which is similar to that induced by butorphanol.

The analgesic effect after IM administration appears after 45 to 60 minutes and has a duration of action slightly longer than that of morphine. The plasma half-life of nalbuphine is approximately 5 hours. It is metabolized mainly in the liver. Tolerance and physical dependence have been described. Because nalbuphine is a mu antagonist it can precipitate an abstinence syndrome in patients taking large doses of morphine over time; therefore, these patients should not be switched to nalbuphine abruptly. Nalbuphine has been studied for use in the treatment of morphine side effects, especially itching (100,101).

Pentazocine. Pentazocine is a benzomorphinan derivative that is a weak competitive antagonist at the mu receptor and agonist at the kappa $_1$ and possibly kappa$_3$ receptors (72,206,212). A single IM or subcutaneous dose of 30 to 60 mg produces analgesia similar to 10 mg of parenteral morphine but with an overall shorter duration of action; however, its analgesic activity is weak and unpredictable (72,195). Pentazocine, 35 mg, given orally gave analgesia equivalent or less than equivalent to 600 mg aspirin (195,213,214 and 215). Its half-life is 2 to 3 hours and its IM-to-oral relative potency ratio is 1 to 3 (128). The respiratory-depressant effect of pentazocine plateaus at doses greater than 30 mg (128).

Pentazocine is associated with a high incidence of adverse psychotomimetic effects, such as hallucinations, dysphoria, euphoria, and depersonalization, which are dose-related and more prevalent in long-term use (72,128,195). Pentazocine is not recommended in the management of patients with chronic cancer pain and is relatively contraindicated in patients with cardiac dysfunction due to its propensity to increase left ventricular end diastolic pressure, systemic vascular resistance, left ventricular work, and systemic and pulmonary artery pressure, causing increased cardiac workload (128,195,216). Pentazocine causes less elevation of intrabiliary pressure than does morphine but significantly more than does buprenorphine (72,195). Pentazocine passes the placental barrier but reportedly less than does meperidine (72). Like meperidine, it may increase uterine activity and shorten the first stage of labor (195). Vomiting with nausea is less commonly seen with pentazocine than with morphine (72,195).

When given to postaddicts, pentazocine, 40 mg IV or subcutaneously, produces morphinelike effects, but doses of 60 mg produce nalorphinelike effects of nervousness and loss of energy (72). Pentazocine may precipitate withdrawal symptoms in patients dependent on morphine due to its antagonist action at the mu receptor (72).

To discourage the use of tablets as a source of injectable pentazocine, they are formulated with naloxone, which is rapidly destroyed in the liver after oral consumption but will produce aversive effects when used parenterally in subjects dependent on opioids (72). Prior to the addition of naloxone, oral preparations of pentazocine (Talwin, “Ts”) and tripelennamine (PBZ, “Blues”;), an H $_1$- blocking antihistamine, were commonly used IV as a substitute for heroin, but frequent use resulted in pulmonary artery occlusion from the cellulose and talc tablet binders.

Dezocine. Dezocine is a bridged aminotetralin with mixed opioid agonist/antagonist properties (217). Dezocine displays a 10-fold greater affinity for mu than delta receptors, which may modify the mu response, and a 40-fold greater affinity for mu than kappa receptors (217). On a milligram-per-milligram basis, dezocine is at least as potent an analgesic as morphine and exhibits a similar duration of action (217). The anesthetic-sparing effects of dezocine in animals are much greater than those of older agonist/ antagonist opioids such as butorphanol and nalbuphine and approach those of morphine and fentanyl (217). As with other agonists/ antagonists, there is a ceiling effect for analgesia, but there are some reports that dezocine exhibits a higher ceiling than other drugs in that class. Successive IV doses of dezocine, 0.15 mg per kg, produced a ceiling of analgesia at 0.30 mg per kg, with further doses failing to increase the level of analgesia (217). There is also a ceiling effect for dezocine-induced respiratory depression. In single analgesic doses, dezocine is a slightly more potent respiratory depressant than morphine (217).

Dezocine is equipotent with morphine in producing opiatelike effects, including euphoria, unlike other agonist/antagonists such as nalbuphine, pentazocine, and cyclazocine, which produce signs and symptoms readily distinguishable from those of morphine. However, multiple dosing of dezocine does not result in either tolerance or limiting adverse effects.

Dezocine exhibits a large volume of distribution and a very high total body clearance. It is *O*-glucuronidated to dezocine glucuronide and dezocine sulfate (217).

Meptazinol. Meptazinol is a centrally acting analgesic belonging to the hexahydroazepine series (195). Structurally it is similar to the opiates, with actions resembling those of the mixed opioid agonist/antagonists, but it has many properties that are not typical of opiates, in particular low incidence of respiratory depression, constipation, and miosis (195,218). Meptazinol does exhibit a high propensity for causing nausea and vomiting (184). Meptazinol combines selective mu$_1$ receptor antagonism with cholinomimetic activity (184,218,219). Studies in various pain states show characteristics of analgesia of meptazinol comparable to those seen with equianalgesic doses of pentazocine, meperidine, or a combination of dextropropoxyphene and acetaminophen (paracetamol) (220). Meptazinol has a faster onset of action and a shorter duration of action than morphine, buprenorphine, and pentazocine (220).

Animal studies have revealed an antiarrhythmic effect of meptazinol (220,221,222 and 223). It has been suggested that meptazinol might have beneficial effects in hemorrhagic and endotoxic shock (219,224,225). In some patients, it has produced significant changes in blood pressure, cardiac output, mean arterial pressure, heart rate, and rate/pressure product during anesthesia (220). Improved ventricular performance has also been reported in some patients (220). Meptazinol may improve the myocardial oxygen demand/supply ratio by combining a negative chronotropic effect with an ability to decrease afterload (220,226).

Peak plasma concentrations occur within 0.5 to 2 hours (220). The bioavailability of meptazinol is low due to extensive first- pass hepatic metabolism to inactive metabolites (220). The elimination half-life of meptazinol in adults averages 2 hours but is extended in the elderly (219). The plasma half-life in the neonate is similar, at approximately 3 hours (219). In comparison, the half-life of meperidine in the neonate is approximately eight times that in the adult (219,227).

Propiram. Like ketobemidone, propiram is a schedule I substance in the United States. Propiram displays partial agonist activity; it can both suppress and precipitate abstinence symptoms. It has specific affinity for mu receptors, and is one-seventh to one-tenth as potent as morphine as an agonist and approximately one–two hundredth as potent as nalorphine as an antagonist (228). Propiram is inactive at sigma receptors (228). Propiram shows less psychotomimetic effect and exhibits lower physical dependence and abuse potential than pure mu agonists. It displays a faster onset but similar duration of action compared with meperidine, pentazocine, and possibly codeine. Propiram has an onset of action of one-half hour, a duration of action of approximately 4 hours, and an elimination half-life of 5 to 7 hours (228). When administered parenterally, it produces a degree of respiratory depression similar to morphine, 10 mg (228).

Nonopioid Centrally Acting Analgesics

Tramadol. Tramadol hydrochloride is a centrally acting synthetic analgesic with a modest affinity for mu receptors and a weak affinity for kappa and delta receptors (229). Tramadol is approximately 10-fold less potent in binding the mu receptor than is codeine (229,230). Tramadol's effectiveness as an analgesic appears to have multiple mechanisms of action beyond the binding of opioid receptors; it also inhibits serotonin and norepinephrine reuptake and enhances neuronal serotonin release, which may potentiate descending inhibitory pain pathways (184,185,229,230). Tramadol is a racemate, possessing both positive and negative enantiomers (185,229,230). The positive enantiomer has a higher affinity for mu receptors and is a more potent inhibitor of serotonin reuptake (185,229,230). The negative enantiomer is a more potent inhibitor of norepinephrine reuptake (185,229,230).

With reduced interactions with mu receptors, tramadol is less likely to produce significant tolerance, physical dependence, and abuse (230,231) than opioids. Postoperative tramadol caused significantly less respiratory depression and sedation than morphine, but the incidence of nausea, vomiting, and dizziness was not significantly different (220). Adverse events correlate with dose and have been reported in 15.3% of patients.

An increased incidence of seizures has been reported in patients receiving tramadol (185). It has been suggested that the occurrence of convulsions may be increased with doses of tramadol above the recommended dosing range of 400 mg per day, but seizures have also been reported at doses within the recommended range (232). Tramadol should be used with caution in patients taking other medications that decrease the seizure threshold (e.g., tricyclic compounds, neuroleptics) or in conditions with a recognized risk for seizures (e.g., epilepsy, head injury) (232). Tramadol should not be used in combination with the monoamine oxidase inhibitors, tranylcypromine, or phenelzine (232). Tramadol is contraindicated during anesthesia due to an increased rate of intraoperative recall (184).

Tramadol is demethylated and conjugated to an active metabolite, (+)- *O*-desmethyltramadol (+)(M1) by CYP2D6 (229,232). (+)(M1) is up to sixfold more potent than its parent compound and binds to opioid receptors up to 200-fold more; however, it is weaker at inhibiting monoamine oxidase (229). The contribution of (+)(M1) to analgesia and potential opioidlike abuse is unknown (229). Quinidine will inhibit the metabolism of tramadol to (+)(M1), thereby increasing tramadol serum levels and reducing (+)(M1) serum levels (232). However, it produced little change in tramadol analgesia in one study, despite (+)(M1) serum reductions by one-third to

one-fourth the levels of placebo-control subjects (229).

Concomitant use of tramadol with enzyme inducers such as carbamazepine has been reported to reduce tramadol's half-life by 33% to 50%. The total daily dose of tramadol may need to be increased to achieve the same level of analgesia when using this drug with carbamazepine. Conversely, tramadol's half-life has been reported to increase 20% to 25% when used concurrently with cimetidine, an enzyme inhibitor; therefore, dose reduction may be required. Dose reductions are required in patients older than 75 years of age and in patients with renal or hepatic impairment.

Opioid Antagonists

In 1915 Pohl produced the first opioid antagonist by making a minor change in the structure of the codeine molecule (97). Minor changes in other opioid agonists have produced substances that bind to one or more opioid receptors and have no pharmacologic effect. These can displace or, more probably, replace an opioid agonist from the receptor, reducing or abolishing the pharmacologic effect of the opioid agonist in a dose-dependent fashion. Naloxone and naltrexone show a relative lack of intrinsic agonistic properties and are safe and efficacious in reversing opioid-induced respiratory and CNS depression. Their predecessors, levallorphan and nalorphine, are not pure antagonists and can induce respiratory depression (188).

Naloxone. Naloxone is a synthetic *N*-allyl derivative of oxymorphone. It acts by antagonizing the actions of opioids and has few effects unless opiate agonists are administered (72). It is a relatively pure competitive antagonist with clinically insignificant intrinsic agonist activity. Subcutaneous doses of up to 24 mg of naloxone produce only slight drowsiness (72,188). It is often used to reverse the respiratory depression induced by an overdose of opioids; however, it has also been used for the diagnosis of physical dependence, and it has been studied for use in the treatment of shock, stroke, and spinal cord and brain trauma (72,233,234,235,236,237,238 and 239).

Naloxone is administered parenterally, as oral doses are almost completely metabolized by the liver before reaching the systemic circulation. Naloxone is metabolized primarily by conjugation with glucuronic acid (72). It is administered IV at a dose of 1 to 5 mg per kg. The effect is rapid and the respiratory depression is promptly corrected. IV naloxone, carefully titrated, is often used after administration of intraspinal opioids to abolish unwanted side effects such as pruritus, urinary retention, nausea, and vomiting without significantly affecting the analgesia (see Chapter 103). Naloxone is a short-acting medication (30 to 45 minutes) and supplemental doses may be needed in patients with respiratory depression induced by long-acting opioids. IM injections of twice the initial IV dose can provide therapeutic plasma levels of longer duration (239). Alternatively, a continuous infusion of 5 mg per kg per hour of naloxone can be used for long-term treatment of respiratory depression, such as that induced by a high dose of intraspinal opioid.

Rapid injection of IV naloxone can cause nausea and vomiting, which can be mostly prevented by giving the therapeutic dose over 2 or 3 minutes. Cardiovascular stimulation has occurred after administration of opioid antagonists. Tachycardia, hypertension, pulmonary edema, and cardiac dysrhythmia up to ventricular fibrillation have occurred after the administration of naloxone. These effects are attributed to a sudden increase in sympathetic nervous system activity.

Naltrexone. Naltrexone is a cyclopropyl derivative of oxymorphone, structurally similar to naloxone and nalorphine (240). It is much more efficacious orally than naloxone. Its duration of action is approximately 24 hours, with a peak plasma concentration reached within 1 to 2 hours. Naltrexone is twice as potent as naloxone in morphine-dependent subjects (240). Naltrexone is metabolized to 6-naltrexol, which is a weaker antagonist than its parent compound but has a longer half-life. Naltrexone has a half-life of up to 10 hours, with almost no accumulation in long-term use. Similar to naloxone, naltrexone produces negligible opioid agonist effects. High doses were reported to cause mild dysphoria in one study but have caused no subjective effects in several other studies (240).

Cholecystokinin. The duodenal mucosa secretes an octapeptide, cholecystokinin, which increases the contractility of the gallbladder and relaxes the sphincter of Oddi. Evidence suggests that cholecystokinin release is controlled selectively by delta receptors and occurs in response to the activation of spinal cord receptors by morphine (114). When administered directly into the CNS, it antagonizes the analgesic effect of opioids. It has been suggested that cholecystokinin might be an endogenous opioid antagonist. This hypothesis is further substantiated by the fact that proglumide, a cholecystokinin antagonist, potentiates opioid analgesia in animals (241).

FINDING A NEW CONSENSUS

The detailed pharmacology of the opioids is complex. In addition to all the individual and environmental factors that can affect each aspect of pharmacokinetics, opioid pharmacodynamics include activity at many interacting levels. Multiple parts of the CNS, multiple receptor types, and multiple intracellular processes, from G-protein–mediated signal transduction to nitric oxide, are all involved and all influence each other in ways we have hardly begun to understand.

From a clinical point of view, matters are somewhat simpler: To treat pain rationally you just need to know a few things about the pain and the patient. Is the pain neuropathic or nociceptive? Is it acute, chronic, or chronically intermittent? What caused it? What are the patient's age, sex, renal and hepatic function, and history of opioid use? With the answers to these and a few other similar questions, the clinician can make a rational choice of drug and treatment strategy, drawing on the growing body of clinical research and experience described in the remainder of this text.

These choices will ideally be based on an assessment of risks and benefits. For example, morphine is the standard by which all other systemic opioids are measured. No one has succeeded in identifying any compound that is a more effective analgesic. Another agent is chosen when that agent has some advantage over morphine—less risk of nausea, perhaps, or faster onset of action—that is not outweighed by other drawbacks. In pharmacology, risks and side effects are never eliminated. They are just traded off. Vigilance in monitoring; repeated reassessment of the patient and the pain; and a willingness to change agents, doses, or routes when indicated are the affordable price of good clinical care.

The biggest obstacles to rational opioid use are not complicated pharmacology or lack of good drugs, but bias and lack of education. The most common reasons for inadequate treatment of pain are probably fear of respiratory depression, fear of causing tolerance and addiction, and fear of increased regulatory scrutiny. As discussed previously, respiratory depression is rarely a clinical problem (and in the comfort care of the terminally ill it probably should not even be considered a major risk). New research into kappa agonists may make it even less anxiety provoking in the future. Tolerance is a practically inevitable physiologic response that is usually easily managed—in the treatment setting by increasing doses or changing agents and in the discontinuation setting by the use of reasonable tapering protocols. In the future, NMDA antagonists may decrease the incidence of tolerance and potentiate analgesia (242), and nitric oxide synthase inhibitors plus or minus NMDA antagonists may be able to attenuate or block the opioid withdrawal syndrome (243). Addiction is another danger more feared than real; it rarely develops in the medical treatment of pain. The treatment of pain in addicts is a difficult problem that often elicits punitive responses from otherwise compassionate clinicians. It is not for the faint of heart, but with a well-thought-out interdisciplinary plan based on specific contracts with the patient, the experienced pain clinician can treat an addict's pain safely and adequately without exacerbating the addictive illness. Doing so is not “giving in.”

In short, “opiophobia” is still among us. Fortunately, regulatory agencies are slowly moving toward more humane pain treatment. The Agency for Health Care Policy and Research in the United States and the World Health Organization are continuing to fine tune their guidelines in the direction of humane and adequate treatment of pain. Input from the American Pain Society is also helping to bring consistency in adequate pain treatment closer to reality (244). On a more local and economic level, the trend toward using patient satisfaction surveys as a guidepost in clinical planning is forcing private hospitals and publicly funded academic institutions to find more effective pain treatments. This progress toward a more rational, humane consensus on pain management philosophy in the clinical community, along with advances in pharmacology and new routes of administration for pain medications, makes the future of pain treatment promising.

ACKNOWLEDGMENTS

The authors wish to acknowledge Dr. Stephen H. Butler and Dr. Constantino Benedetti, authors of the chapter covering this topic in the previous edition, some of whose text has been retained in this edition. The authors also wish to acknowledge Dr. Susan Woyna for her assistance in the editing of this chapter.

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CHAPTER 85

Antidepressants, Muscle Relaxants, and N-*Methyl-*D*-Aspartate Receptor Antagonists*

Mitchell B. Max and Ian H. Gilron

This chapter discusses the use of selected antidepressants, muscle relaxants, and *N*-methyl-d-aspartate (NMDA) antagonists for reducing pain. This particular grouping reflects the organization of previous editions, in which antidepressants, muscle relaxants, antianxiety agents, and neuroleptic drugs were presented under the heading of *psychotropic drugs*. We prefer to drop that term because research in animals and patients has shown that antidepressants and muscle relaxants can relieve pain in patients with normal mood by mechanisms having little to do with emotional processes. Neuroleptic agents are not addressed as a class because, with the exception of methotrimeprazine, a strongly sedative phenothiazine occasionally used to treat cancer patients who cannot tolerate the respiratory or gastrointestinal side effects of opioids (see Chapter 36), there is little evidence supporting their analgesic efficacy. The following pages focus on the pharmacologic principles of pain treatment; the diagnosis and treatment of emotional disorders associated with chronic pain are discussed in Chapter 26.

ANTIDEPRESSANTS

Apart from the opioids and the acetaminophen–nonsteroidal antiinflammatory drug group of analgesics, antidepressants are probably the most commonly prescribed class of drugs for the treatment of chronic pain. Their use for pain was first described by Lance and Curran (1), who carried out a placebo-controlled trial showing that amitriptyline reduced the severity of tension headache, and by Woodforde et al. (2), who described amitriptyline's apparently beneficial effect in a case series of patients with postherpetic neuralgia. These authors differed in their opinions of the relative importance of antidepressant and specific antinociceptive effects; Lance and Curran thought a vasodilator action, not a mood effect, accounted for benefit, whereas Woodforde et al. favored an antidepressant action. Taub and Collins (3) reported their clinical experience that a combination of amitriptyline and fluphenazine appeared to benefit patients with neuropathic pain, whereas amitriptyline alone had little effect. Watson et al. (4) carried out a placebo-controlled trial of amitriptyline that showed benefit in patients with postherpetic neuralgia who were free of depression or other psychiatric disorder. This study both undercut the rationale for Taub and Collins' antidepressant-phenothiazine combinations and provided support for the new hypothesis that potentiation of serotonin (5-HT) and norepinephrine (NE) pathways descending from brainstem to spinal cord might relieve pain (5).

Clinical Efficacy of Antidepressant Drugs for Pain Treatment

Benefit Varies According to Source of Pain

Tricyclic antidepressants, including amitriptyline, imipramine, nortriptyline, desipramine, clomipramine, and doxepin, block the reuptake of NE, 5-HT, or both at spinal dorsal horn synapses, potentially leading to increased inhibition of pain (see Chapter 4). One might expect that such an effect would reduce most types of chronic pain, but the pattern of results from more than 75 published controlled clinical trials shows a highly variable effect depending on the type of pain studied. Most of the published studies were reviewed in a formal metaanalysis by Onghena and Van Houdenhove (6) and a qualitative systematic review by Magni (7). Their conclusions, which have been confirmed by a smaller number of studies in the 1990s, are summarized in Table 85-1. The diagnostic categories are listed in order of decreasing effect size calculated by Onghena and Van Houdenhove. The effect size is the ratio of the mean reduction in pain determined in the study (relative to placebo) divided by the standard deviation of the pain reduction; it therefore reflects the certainty that some favorable effect occurred rather than the actual magnitude of the pain reduction. In this table and in the rest of the section, pain reduction is the only outcome variable discussed, because the published studies of antidepressants provide few data about changes in patients' physical functioning, return to work, and health care consumption.

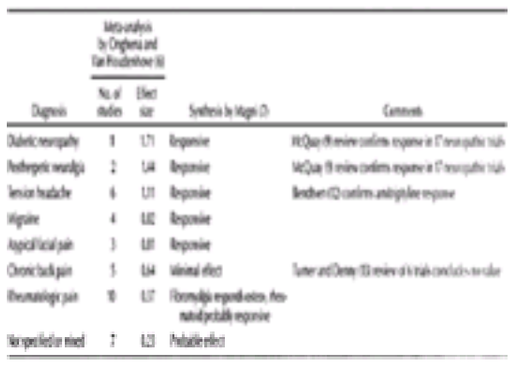

TABLE 85-1. Review of antidepressant analgesia

As of 1998, studies in diabetic neuropathy and postherpetic neuralgia offer the most convincing evidence for benefit. Only three of the 16 published studies relating to painful diabetic neuropathy and postherpetic neuralgia were included in the Onghena and Van Houdenhove metaanalysis (6), but subsequent reviews that include the more recent studies (8,9) confirm the top ranking of neuropathic pain. McQuay et al. (9), whose data summary (10) appears in Figure 85-1, calculated that approximately one in three patients obtains at least 50% relief from a tricyclic antidepressant above any placebo effects, an effect similar to that derived from their metaanalysis of the analgesic effects of anticonvulsants (11).

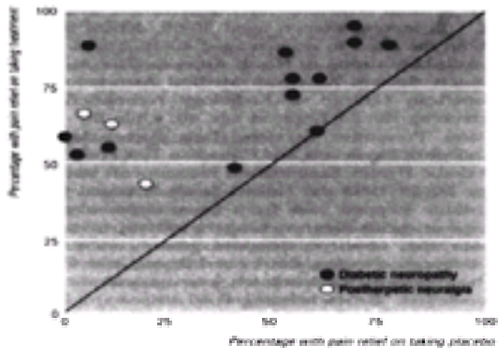

Figure 85-1. Effectiveness of tricyclic antidepressants in double-blind, placebo-controlled trials in diabetic neuropathy and postherpetic neuralgia. Each trial is represented by a data point. The percentage of patients in the trial with at least 50% reduction in pain on the antidepressant is plotted against the percentage with 50% reduction in pain on placebo. All except one of the points are above the diagonal line (zero-effect line) illustrating that antidepressants were superior to placebo in almost all the studies. (From McQuay HJ, RA Moore. Antidepressants and chronic pain. *BMJ* 1997;314:763–764, with permission.)

There is also relatively convincing evidence for the efficacy of tricyclic antidepressants in preventing tension and migraine headaches (see Table 85-1). The robust effects of amitriptyline in tension headache (but not of the selective 5-HT-reuptake blocker citalopram) were reconfirmed by Bendtsen et al. (12). Three studies suggested benefit of tricyclics in atypical facial pain. The finding of little clinical benefit of tricyclics in low back pain has been reinforced by another metaanalysis by Turner and Denny (13) and by a new study by Atkinson et al. (14) showing that nortriptyline, titrated to a plasma concentration of 50 to 150 ng per mL reduced pain by only approximately 10% relative to placebo, a benefit largely due to a strong effect in the subgroup of patients with definite nerve root injury and radicular pain. Results in rheumatologic pain differ according to diagnosis: Fibromyalgia has responded to low-dose amitriptyline in several studies, whereas results in osteo- and rheumatoid arthritis have been less impressive (7). Klein (15) reviewed five controlled trials of tricyclic antidepressants in irritable bowel syndrome and nonulcer dyspepsia and concluded that there was little evidence for efficacy.

In view of the widely differing results in various disease conditions and the paucity of controlled trials in any conditions apart from neuropathic pain, one must be cautious in making generalizations across disease conditions about the finer points of drug choice and prescribing. It may be useful to specifically examine the trials in neuropathic pain, because this is the disease category in which the largest number of trials has been done. Three groups, in Toronto, Odense, and Bethesda, have carried out the majority of these trials, using similar patient populations and methods, and have arrived at similar results.

In 15 of 16 studies of diabetic neuropathy and postherpetic neuralgia (see Fig. 85-1), at least one tricyclic antidepressant relieved pain significantly better than a placebo. The result was strengthened in many of these studies by demonstration of superiority to an “active placebo,” which mimicked antidepressant side effects (16,17,18 and 19) to another antidepressant (20,21 and 22) or to another active drug (23). This is important because patients' perceptions of side effects might bias them toward reporting pain relief, potentially imputing spurious efficacy to a drug with prominent side effects if compared only to an inert placebo.

Many of these neuropathic pain studies showed that a significant analgesic effect remained even when depressed patients were excluded from the analysis (17,19,24). Each of the research groups has prospectively assessed a number of different subtypes of pain and discomfort, expecting that antidepressants might relieve one type more than others, but no such selective effect was apparent. The antidepressants in these studies relieved brief, lancinating pains as well as constant pains (4,16,17) and allodynia as well as spontaneous pain (16,21). No differences have been discerned among the relief afforded various qualities of steady pain, such as burning, aching, sharp, or pressing pain (19,23), or between pain, paresthesia, and dysesthesia (24). The methodologic features of these studies make the positive results more convincing and are missing from many of the studies in other disease conditions.

Although the large majority of neuropathic pain trials were carried out in patients with either diabetic neuropathy or postherpetic neuralgia, single reports suggest that amitriptyline is superior to placebo in a poststroke central neuropathic pain (25) and a mixed group of nondiabetic peripheral neuropathies (26). However, in two trials in patients with human immunodeficiency virus–related painful neuropathies (27,28), amitriptyline's effect was small and did not significantly surpass placebo.

Which Neurochemical Actions of Antidepressants Correlate with Pain Relief?

Many of the controlled trials in neuropathic pain have examined whether relatively selective blockers of NE or 5-HT retain the pain-relieving effects of the mixed reuptake blockers amitriptyline and imipramine. Sindrup et al. (24) have shown that the time course of imipramine analgesia is consistent with the hypothesis that pain relief is mediated by blockade of monoamine reuptake. Careful preliminary studies of each patient's metabolic rate for imipramine allowed a high fixed dose to be given, rather than the cautious titration used by most investigators. Figure 85-2 shows that reductions in pain and other symptoms approached maximum values after 4 days of treatment, roughly paralleling the expected plasma drug concentrations.

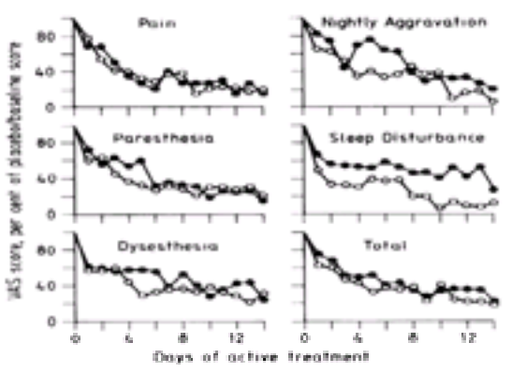

Figure 85-2. Onset of action of imipramine (*open circles*) and paroxetine (*filled circles*) in a study of patients with painful diabetic neuropathy. Both treatments were superior to placebo (not shown). Near-maximal reduction of pain (upper left) is evident as early as 4 to 6 days after beginning treatment with a fixed dose of imipramine determined by a prior dose-finding period. The time course of onset of pain relief parallels the expected time course of plasma antidepressant concentrations. These results are consistent with the hypothesis that a rapidly occurring drug effect, such as acute blockade of monoamine reuptake, directly mediates pain relief. (VAS, visual analog scale.) (From Sindrup SH, Gram LF, Brosen K, et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990;42:135–144, with permission.)

Several caveats must be raised about the assumptions of the selective monoamine reuptake blocker studies. First, because the concentrations of various antidepressants in human brain tissue and, in particular, at the relevant receptors, are not known, it is uncertain whether selective or complete blockade of central neural mechanisms is attained. As Richelson (29) has pointed out, explanations of comparative effects of antidepressants based on affinity constants are on firm ground only for peripheral tissues, where plasma drug concentrations are relevant. The use of radiolabeled NE- and 5-HT–receptor ligands in future brain imaging studies may allow direct assessment of effects of antidepressants at central monoaminergic synapses. A second caveat is that even if some of these drugs selectively affect reuptake of NE or 5-HT, the consequences do not remain confined to that monoamine system. In studies of depressed patients, Potter et al. (30) found that zimelidine and desipramine, selective blockers of 5-HT and NE reuptake, respectively, each produced similar alterations in the levels of CSF metabolites of both 5-HT and NE.

Taken as a whole, studies by the Bethesda, Odense, and Toronto groups suggest that the relatively “dirty” tricyclics, amitriptyline and imipramine, which block reuptake of both NE and 5-HT and also block H1, adrenergic, and cholinergic receptors, have the greatest efficacy, exceeding the relatively specific NE-reuptake blockers desipramine and maprotiline. Evidence supporting specific serotonin-reuptake inhibitors is the least impressive at the moment, although paroxetine and

citalopram relieved diabetic neuropathy in one study each (24,31).

After placebo-controlled studies of desipramine in both diabetic neuropathy (18) and postherpetic neuralgia (16) that showed analgesic effects similar in magnitude to those previously described with amitriptyline, the Bethesda group carried out a crossover comparison of amitriptyline (mean dose, 105 mg per day) to desipramine (111 mg per day) in 38 patients with diabetic neuropathy (19). To evaluate the efficacy of selective serotonin-reuptake blockade, they compared fluoxetine, 40 mg, to a benztropine active placebo in 46 diabetics in a comparison run concurrently with the amitriptyline-desipramine study. Figure 85-3 shows that amitriptyline and desipramine were each effective. The difference between the two drugs was not statistically significant. In contrast, fluoxetine was not significantly more effective than a placebo. The modest trend toward a fluoxetine effect apparent in Figure 85-3 disappeared when the 13 depressed patients were excluded from the analysis. There was no suggestion of an analgesic effect in patients with relatively high or low plasma concentrations of fluoxetine or its metabolite, norfluoxetine.

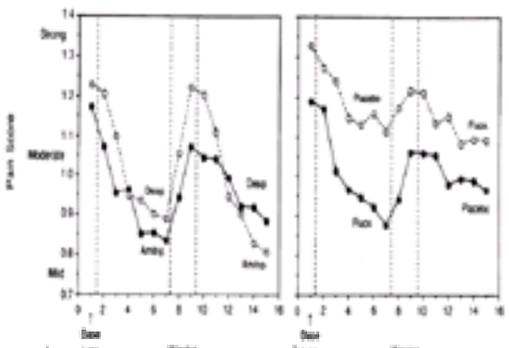

Figure 85-3. Intensity of pain caused by diabetic neuropathy during treatment with amitriptyline (*Amitrip.*) and desipramine (*Desip.*) in 38 patients **(A)** and during treatment with fluoxetine and placebo in 46 patients **(B)**. The mean weekly values of the descriptors of pain intensity are plotted; three of the actual descriptors used in the diary are shown in their equivalent positions on the ordinate. Each curve represents a single group receiving sequential treatments. The central vertical lines distinguish the two 6-week treatment periods from the intervening 2-week washout period. There was no statistically significant difference between the effects of amitriptyline and desipramine, but both were significantly more effective than placebo in the subgroup of patients who were randomized among all four possible treatments. There was no significant difference between the effects of fluoxetine (*Fluox.*) and placebo, and the modest trend favoring fluoxetine was due entirely to the data from the 13 depressed patients. (From Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992;326:1250–1256, with permission.)

This finding is consistent with Watson and Evans' (20) report from Toronto that the specific serotonin-reuptake blocker zimelidine was ineffective in patients with postherpetic neuralgia who responded to amitriptyline. It is possible that serotonin-reuptake blockade alone has a weak pain-relieving effect but enhances the pain-relieving effects of NE-reuptake blockade. This hypothesis would explain the trend toward greater effectiveness of amitriptyline, which inhibits 5-HT reuptake more strongly than does desipramine. Watson et al. (21) reported the similar result in postherpetic neuralgia that the selective NE-reuptake blocker maprotiline was less effective than amitriptyline.

Sindrup and his colleagues at Odense University (31) have reported results that agree in many respects with those of the other groups. Figure 85-4 combines the results from a number of their studies in patients with diabetic neuropathy. As reported by the other groups, the tricyclic antidepressants with “balanced inhibition” of 5-HT and NE reuptake, imipramine and clomipramine, appeared to be the most effective agents, and the selective NE-reuptake blocker desipramine was also effective (19,20 and 21). Mianserin, a nontricyclic antidepressant that does not block reuptake of either monoamine, did not relieve pain, also consistent with the monoamine hypothesis. Mianserin has strong antihistamine effects, suggesting that H1-receptor antagonism is not sufficient to relieve neuropathic pain. The difference between the groups' findings is that Sindrup et al. found that two different selective serotonin-reuptake inhibitors (SSRIs), paroxetine and citalopram, had at least some analgesic effects in groups of 20 and 15 patients, respectively. This contrasts with the flatly negative results in the 61 patients who were given fluoxetine or zimelidine by the other two groups. There were no obvious differences between the populations of diabetic neuropathy patients studied by Sindrup et al. (31) and Max (19), and the spectrum of receptor actions of fluoxetine, paroxetine, and citalopram is quite similar. Larger studies should be conducted to try to confirm the results of the Odense group. If the SSRIs produce some analgesia, albeit less than the mixed blockers, they will offer improved treatment for patients with fragile medical conditions, because these drugs cause no postural hypotension, cholinergic blockade, or heart block.

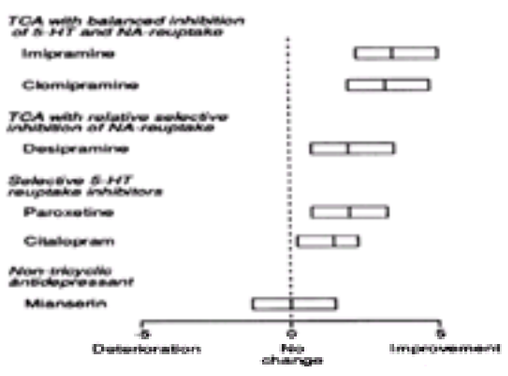

Figure 85-4. Effectiveness of various antidepressants on symptoms of diabetic neuropathy. Medians (*vertical lines*) and 95% confidence intervals (*boxes*) describe the differences between different antidepressants and placebo as measured by physician scoring of symptoms of pain and discomfort on a 0 to 10 scale. Data are drawn from a number of the studies by Sindrup et al. As in the studies by Max et al. (see Fig. 85-1) and Watson et al., a selective norepinephrine (*NE*)-reuptake inhibitor was effective, and drugs that inhibit both NE and serotonin (*5-HT*) reuptake appeared even more effective. The results shown here differ from findings of the latter two investigators in that the specific 5-HT-reuptake inhibitors, paroxetine and citalopram, showed a statistically significant analgesic effect. TCA, tricyclic antidepressant. (From Sindrup SH, Bjerre U, Dejgaard A, et al. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther* 1992;52:547–552, with permission.)

Several studies have also found that SSRIs were unimpressive in other conditions previously shown to respond to tricyclics. In a crossover study of 34 patients with tension-type headache, Bendtsen et al. (12) reported that amitriptyline, 75 mg per day, reduced the duration and frequency of headache pain by approximately 30%, whereas citalopram, 20 mg per day, had no significant effect. Norregaard et al. (32) reported no effect of citalopram, 20 or 40 mg per day, in fibromyalgia. In contrast, Rani et al. (33) reported that fluoxetine, 20 mg per day, was superior to placebo and similar to amitriptyline, 25 mg per day, in a small group of patients with a mixture of rheumatologic disorders, mostly low back pain and osteoarthritis.

Concentration-Response Relationship for Antidepressant-Mediated Analgesia

There have been few prospective dose-response studies of antidepressants for chronic pain. McQuay et al. (34) compared doses of 25, 50, and 75 mg per day of amitriptyline in a randomized, blinded crossover study in a group of patients with mixed chronic pain diagnoses. The 75-mg-per-day amitriptyline dose significantly surpassed 25 mg per day, which they had previously shown to be better than placebo (35), as had Sharav et al. (36) in facial pain and Goldenberg et al. (37) in fibromyalgia.

Sindrup et al. (38) studied imipramine in 15 patients with painful diabetic neuropathy (Fig. 85-5). Based on preliminary characterization of patients' imipramine metabolism, the investigators chose a series of doses between 25 and 350 mg per day that would ensure a maximum plasma concentration of imipramine and desipramine well above 400 nM per L (or approximately 120 ng per mL). Most patients received an ascending series of doses with 1 week of treatment at each dose;

dose reductions were included at various points in seven of 15 patients. In Figure 85-5A, patients' visual analog scores for pain are plotted against plasma tricyclic concentration; each line represents one patient. Figure 85-5B shows the cumulative number of patients who reached at least 95% of their maximal pain relief at a given plasma concentration. Most patients appeared to get optimal relief at or below 400 nM per L, a plasma concentration that required imipramine doses of 125 to 350 mg per day. Because of the great variability in both pharmacokinetics and the plasma tricyclic concentrations needed to obtain optimal response, Sindrup et al. (38) cautioned that one should not discontinue treatment because of an inadequate response to a standard dose such as 100 mg per day. Sharav et al. (36) prospectively compared high (mean dose, 129 mg per day) and low (23 mg per day) amitriptyline doses to placebo in a patients with facial pain of muscular or neuropathic etiology and reported a trend toward superiority of the higher dose that did not reach statistical significance. Watson (39) had reported seven cases of a “therapeutic window” for amitriptyline analgesia—that is, patients reporting pain relief that disappeared with further dose increase and reappeared with dose reduction. No other reports have confirmed this, however.

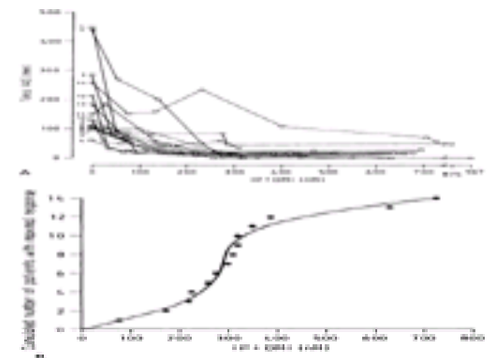

Figure 85-5. A prospective study of the imipramine (*IP*) concentration-response relationship in patients with painful diabetic neuropathy. **A:**Total neuropathy symptom scores (maximum possible score = 600) are plotted against plasma concentrations of IP plus its active metabolite desipramine (*DMI*). Each line represents a single patient, numbered 1 to 14 to the right of the *y* axis, and each circle represents IP treatment for 1 week at that particular dose level. Pain and other neuropathic symptoms declined progressively with higher plasma drug concentrations. **B:** Solid circles represent the cumulated number of patients experiencing more than 95% of maximal response [total visual analog scale (VAS) score at baseline – total VAS score during treatment] at or above various plasma concentrations of IP and DMI. Plasma concentrations higher than 400 nmol were sufficient to produce near-maximal responses in most patients. (From Sindrup SH, Gram LF, Skjold T, et al. Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. *Clin Pharmacol Ther* 1990;47:509–515, with permission.)

Many other authors have attempted to correlate antidepressant dose and plasma concentrations with effects in studies in which each patient's dose was individually titrated based on pain relief, but no clear associations have been consistently replicated (40). Compared to prospective studies in which the dose or plasma concentration is randomized to several different levels, individual titration designs are very inefficient in elucidating the relationship of pain relief to dose, because dose is a dependent variable. For example, even if there were an underlying positive dose-response relationship in the population, this fact might be obscured because patients who obtain significant relief might have their titration stopped at a low dose, whereas patients who continue to have large amounts of pain would usually be pushed up to high doses.

Genetic Variability in Metabolism of Tricyclic Antidepressants and Dose-Concentration Relationships

A crucial issue to bear in mind is that there is extraordinary variation in plasma concentrations among patients receiving the same dose because of genetic polymorphism in CYP2D6, the cytochrome P450 enzyme that oxidizes and inactivates all of the tricyclic antidepressants (41,42 and 43). Seven percent to 10% of Caucasians and 1% of Asians have mutations in both copies of the 2D6 gene. Such patients get drug levels more than tenfold higher than average and are termed *poor metabolizers*. Most patients (*extensive metabolizers*) have two normal copies of the gene, but many patients have intermediate levels of metabolism due to mutations of one gene or minimally disruptive mutations of both genes, and occasional patients (*ultra-rapid metabolizers*) have multiple copies of intact genes. Some commonly prescribed drugs, including fluoxetine, paroxetine, and quinidine, powerfully inhibit the function of the 2D6 enzyme, converting extensive metabolizers into poor metabolizers, leading to as much as a tenfold elevation of levels of tricyclics and other drugs metabolized by the 2D6 enzyme, including dextromethorphan, mexiletine, and a variety of other antiarrhythmics, antipsychotics, b-adrenergic blockers, and other drugs (42). Figure 85-6 shows the amount of increase in plasma desipramine levels produced by the addition of various SSRIs in a number of published studies (44). Fluoxetine and paroxetine have powerful effects that could cause serious toxicity in patients concurrently treated with tricyclics, but other SSRIs such as sertraline, citalopram, fluvoxamine, and venlafaxine have smaller effects that would less often be clinically significant. Fluoxetine is unique among the antidepressants in that 2D6 inhibition may persist for 1 month after fluoxetine is stopped because of the 7- to 15-day elimination half-life of the active metabolite norfluoxetine. Antidepressants are involved in several other drug-drug interactions that may be important for practice. For example, the SSRI fluvoxamine inhibits several other cytochrome P450 enzymes, including 3A3/4, which can lead to moderate elevations in plasma levels of carbamazepine and benzodiazepines, and 1A2, leading to higher levels of theophylline.

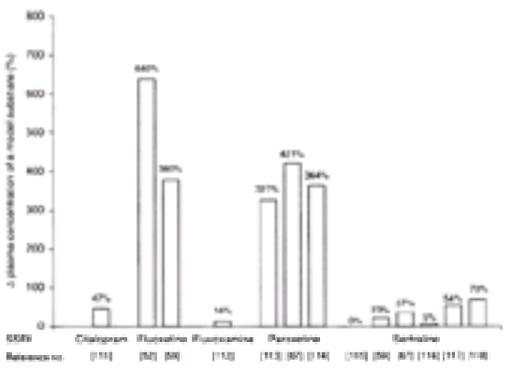

Figure 85-6. Mean increases in plasma desipramine or imipramine concentrations caused by the addition of various selective serotonin-reuptake inhibitors (*SSRIs*). Data from 13 published studies are summarized. Fluoxetine and paroxetine are powerful inhibitors of the cytochrome P450 2D6 enzyme and cause large elevations of plasma concentrations of tricyclic antidepressants. Citalopram, fluvoxamine, and sertraline are less likely to cause clinically significant elevations in tricyclic metabolism. [From Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis of pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997;32(Suppl 1):1–21, with permission.]

The variability in antidepressant metabolism has two implications for practice. First, the clinician must be familiar with the important drug interactions caused by antidepressants (41,42,44) and monitor patients closely when adding antidepressants to drugs likely to have metabolic interactions. Second, dose titration of these drugs must be individualized. Low starting doses of tricyclics (10 to 25 mg per day) are warranted to avoid serious toxicity in poor metabolizers, but one can fail to produce benefit in some patients who are extensive or ultra-rapid metabolizers unless one verifies, by checking a blood level, that clinically meaningful plasma concentrations have been achieved (e.g., at least 50 to 100 ng per mL for the commonly used tricyclic compounds).

Mechanisms of Clinical Pain Relief Produced by Antidepressants

Blockade of Norepinephrine and Serotonin Reuptake

As discussed above, the monoamine hypothesis has driven much of the clinical research with antidepressants, and the hypothesis that an increase of NE, and to a lesser extent 5-HT, is responsible for analgesia is consistent with most of the data. In animals, a variety of interventions that enhance spinal NE or 5-HT function reduce pain (45). The onset of clinical pain relief within a few days (see Fig. 85-2) is consistent with the monoamine reuptake hypothesis and differs from the delayed

response of major depression (46,47). Although the small number of studies in neuropathic pain with various SSRIs differ somewhat on whether these drugs produce modest or negligible analgesia, all of the studies agree that mixed NE/5-HT-reuptake blockers such as amitriptyline or imipramine are superior to more selective compounds, whereas mianserin, an antidepressant that does not block monoamine reuptake, was ineffective in diabetic neuropathy (22).

We believe that the monoamine hypothesis is still the most appealing explanation for antidepressant analgesia. If true, mixed NE/ 5-HT-reuptake blockers (e.g., venlafaxine), which lack many of the cardiovascular side effects of the tricyclics, should be useful clinical agents, but controlled studies with these agents have not been completed at the time of this writing.

Blockade of Sodium Channels

All of the tricyclic antidepressants block neuronal and cardiac sodium channels, and several groups have proposed that peripheral nerve sodium channel blockade is the main mechanism for analgesia (48,49). An appealing feature of this hypothesis is that neuropathic pain conditions appear to be the most sensitive to tricyclics, and these pains are thought to be mediated in large part by ectopic discharges in injured nerve sprouts and dorsal root ganglion cells that decrease with sodium channel blockers such as lidocaine (50).

This hypothesis faces several challenges, however. First, the differential effectiveness of various antidepressants needs to be explained. For example, fluoxetine was ineffective in treating diabetic neuropathy pain (19) and an animal model of neuropathic pain (48) but blocked neuronal sodium channels almost as effectively as drugs known to be effective in neuropathic pain, such as amitriptyline and desipramine (49). Second, the effectiveness of tricyclics in conditions such as headache and fibromyalgia needs to be explained in terms of sodium channel blockade. Ptacek (51) has speculated that common migraine may be caused by mutations in sodium, calcium, or other ion channels causing neuronal hyperexcitability, but there is no evidence for this as yet, let alone any evidence linking fibromyalgia or tension-type headache to abnormal sodium channel activity.

The sodium channel hypothesis for antidepressant analgesia generates some important predictions. One might expect that combinations of an antidepressant with another drug working through sodium channel blockade, such as mexiletine or carbamazepine, would be mechanistically redundant. Such combinations would not be clinically advantageous unless the combination reduced some toxicity of the components of the combination unrelated to sodium channel blockade. Also, one would expect other blockers of sodium channels that did not block monoamine reuptake to share the clinical effectiveness of antidepressants.

Antagonism of NMDA Glutamate Receptors

Eisenach and Gebhart (52) have shown that intrathecal amitriptyline produces analgesia that is mediated in part via blockade of NMDA receptors. This finding is not clinically relevant to systemic treatment with tricyclics, however, as the tissue concentrations reached with oral administration are several orders of magnitude lower than those achieved in the spinal cord with intrathecal administration. One can calculate from the affinity of amitriptyline for brain NMDA receptors (52) that clinically achieved concentrations would not block a substantial proportion of NMDA receptors.

Sympathetic Blockade

Esler (53) reported that intravenous injection of desipramine, 25 mg, reduced sympathetic efferent activity by approximately 90%. This may contribute to pain relief in patients with sympathetically maintained pain.

Effects on Visceral Nerve Fibers

Su and Gebhart (54) have reported that systemic administration of imipramine, desipramine, or clomipramine reduced by up to 80% the discharge of mechanosensitive afferents in response to noxious distension of the rat colon. This effect occurred after the central connections of the nerves had been severed and in the presence of antagonists of NE and 5-HT receptors. The authors speculated that this effect might be mediated by an action on the peripheral nerve receptor, perhaps involving peripheral opioid receptors and calcium channels. Despite this powerful effect in animal models of visceral pain, clinical investigators have been unimpressed with antidepressants in irritable bowel syndrome (15).

Effects on Mood

Although a major thrust of recent clinical research with antidepressants has been to establish analgesic effects distinct from effects on mood, experienced clinicians know that depressed patients with pain suffer less when their depression has been treated.

Adverse Effects of Antidepressant Drugs

Cardiovascular Effects

The most serious toxicities of tricyclic antidepressants occur in the cardiovascular system: postural hypotension, heart block, and arrhythmias. Postural hypotension is mediated through blockade of a-adrenergic receptors. It may occur in any age group but is most serious in elderly patients in whom syncope and falls are liable to lead to serious trauma. Ray et al. (55) reviewed a series of 1,400 patients with hip fracture and controls and estimated that prescribing tricyclic antidepressants or benzodiazepines to patients over the age of 65 triples the risk of hip fracture. This risk of antidepressant-related injury is increased even more in patients with volume depletion or congestive heart failure or patients who are receiving concurrent treatment with vasodilators. Nortriptyline and, to a lesser degree, doxepin probably have a lower incidence of postural hypotension compared to amitriptyline, desipramine, imipramine, and clomipramine (Table 85-2), which are equivalent in this regard (56).

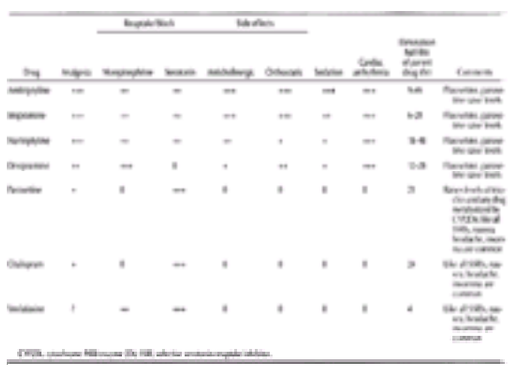

TABLE 85-2. Antidepressants commonly used to treat chronic pain

The tricyclics slow conduction throughout the heart and may be hazardous in patients with preexisting cardiac conduction disease, particularly bundle branch block (QRS >110 milliseconds) (56). A new concern has emerged following the finding in several large studies that chronic treatment of patients with ischemic heart disease with quinidine or moricizine increased the incidence of sudden death by stimulating the occurrence of complex ventricular arrhythmias. The cardiac electrophysiologic effects of tricyclic antidepressants are quite similar to quinidine and moricizine. One study has confirmed that treatment of depressed patients with ischemic heart disease with nortriptyline led to potentially dangerous sinus tachycardia or complex arrhythmias in 18% of patients, compared to only 2% of patients treated with paroxetine (57). There may even be a risk of treating elderly patients without obvious cardiac ischemia with tricyclic antidepressants, as silent ischemic events are common in this group. The SSRIs are free of all of these cardiovascular side effects, but unfortunately, they do not appear to be very effective for chronic pain. We hope that venlafaxinelike drugs will be more effective.

Five cases of desipramine-associated sudden death in children 8 to 12 years old were reported several years ago (58), raising the issue of whether desipramine or

tricyclic antidepressants in general are dangerous to children. Although extensive studies have revealed no more than minor changes in electrocardiography and pulse rate with desipramine or other tricyclics, experts recommend additional precautions when treating children with tricyclics, including taking an electrocardiogram before drug treatment, periodically during dose escalation, and after plasma drug concentrations to avoid overdose in slow metabolizers.

Sedation

Sedation, probably produced by blockade of H1 receptors, can be either a dose-limiting toxicity or a boon to patients with insomnia. Amitriptyline, imipramine, and doxepin are quite sedative, whereas nortriptyline is minimally sedative, and desipramine and the SSRIs often produce insomnia. Sedative effects usually decline after several weeks of treatment. As the half-lives of all of the tricyclics and SSRIs approximate 24 hours, one can time the administration of single or divided dose schedules to optimize the impact of sedative effects.

Anticholinergic Effects

Amitriptyline, imipramine, and doxepin produce strong anticholinergic effects, causing patients to complain of dry mouth, constipation, and urinary retention. Nortriptyline and desipramine are mildly anticholinergic, whereas the SSRIs lack these effects.

Weight Gain

Patients frequently report increased appetite and weight gain while on tricyclic antidepressants. Some clinicians feel that amitriptyline is a particular offender in this regard, but there are no controlled comparisons of the tricyclics. In contrast, the SSRIs cause anorexia and mild degrees of weight loss.

Sexual Dysfunction

The tricyclic antidepressants and SSRIs have all been reported to delay or prevent orgasm in both sexes (59). Studies of clomipramine, paroxetine, and fluoxetine have shown that this effect may prove beneficial in patients with premature ejaculation. This is thought to be due to enhanced 5-HT activity at central 5-HT $_2$ receptors that inhibit ejaculation. If these side effects interfere with sexual activity, the dose may be reduced, or intercourse should be timed to coincide with trough levels of drug.

Psychiatric Complications

Tricyclic antidepressants may trigger manic episodes in patients with bipolar disease. The major psychiatric risk of tricyclic treatment, however, is suicide; the many cardiovascular effects of tricyclics often lead to a lethal outcome of overdose. Psychiatric consultation should be considered before treating patients with severe depression, bipolar disease, or otherwise complicated psychiatric history.

Withdrawal Syndromes

Abrupt or gradual discontinuation of tricyclic antidepressants may trigger a number of symptoms, including nausea, vomiting, headache, malaise, sleep disturbance, akathisia, or paradoxical behavioral activation resulting in hypomanic symptoms (60). Withdrawal phenomena most commonly begin 24 to 48 hours after the last dose and may last up to 1 month.

When fluoxetine was introduced into general use, the lack of withdrawal symptoms led many clinicians to assume that other SSRIs would share that advantage. Experience with newer SSRIs has led to the conclusion, however, that it is only the long half-life of fluoxetine (2 to 4 days) and its active metabolite norfluoxetine (7 to 15 days) that minimizes withdrawal symptoms. All of the other SSRIs, with elimination half-lives near 24 hours, have been reported to cause symptoms such as dizziness, lethargy, paresthesias, nausea, vivid dreams, irritability, and depressed mood.

For both classes of antidepressants, withdrawal symptoms can be minimized by tapering the dose gradually and by raising the dose should symptoms be troublesome. In patients who develop unexplained symptoms during long-term antidepressant treatment, clinicians should consider the possibility that they have missed several doses, bringing on acute withdrawal.

Serotonin Syndrome

Combinations of antidepressants with certain other drugs may precipitate a “serotonin overload syndrome” characterized by myoclonus, hyperreflexia, tremor, increased muscle tone, fever, shivering, sweating, diarrhea, delirium, or coma (61,62 and 63). It is usually reversible if the responsible drugs are discontinued, but deaths have been reported. The most common precipitant has been combinations of monoamine reuptake inhibitors with SSRIs, tricyclics, venlafaxine, tryptophan, dextromethorphan, or serotonergic weight-loss agents such as fenfluramine or dexfenfluramine, but other combinations of drugs on this list, such as SSRIs plus tryptophan, dextromethorphan, or weight-loss agents have also triggered the syndrome.

Combinations of Antidepressants with Other Analgesic Drugs

Most analgesic clinical research to date has focused on the effects of single drugs and on the search to create substitutes with similar efficacy and fewer side effects. This search has met with limited success. In published clinical trials, a variety of different classes of drugs including antidepressants, gabapentin, mexiletine, opioids, and clonidine have rarely reduced chronic pain more than 20% to 25% relative to placebo, and as outlined above, antidepressants with narrower spectra of effects at receptors may be less effective or totally ineffective. Clinical researchers in other disease areas have successfully dealt with the same problem by developing combinations of drugs with additive or supra-additive therapeutic effects but differing side effects.

There have been very few rigorous studies of combinations of antidepressants with other analgesics. The only controlled study of the combination of an antidepressant with a phenothiazine showed no augmentation of pain relief when flupentixol, 3 mg per day, was added to amitriptyline in patients with idiopathic pain disorders (64). We advise against the use of antidepressant-phenothiazine combinations, particularly in view of the risk of tardive dyskinesia from the phenothiazine. Goldenberg et al. (37) compared the effects of amitriptyline plus naproxen to either drug alone or a placebo in patients with fibromyalgia and found little or no effect of naproxen alone or in combination. A number of animal studies have demonstrated augmentation of opioid analgesia by tricyclic antidepressants (65). Levine et al. (66) and Gordon et al. (67) have reported that pretreatment with 1 week of desipramine, 50 to 75 mg per day, augments postoperative morphine analgesia, but these studies did not examine whether analgesia was increased more than side effects or whether there was a pharmacokinetic interaction; other studies have failed to show augmentation of opioid analgesia by tricyclics (68,69). Studies of other drugs in combination with antidepressants would be of obvious interest. However, the design of these studies will be quite challenging, and investigators will need to take great care in characterizing their patient populations, assessing side effects as well as pain relief, and manipulating and monitoring plasma drug concentrations.

Treatment Recommendations

Choice of Antidepressant versus Other Classes of Drugs

In neuropathic pain, there is strong evidence for the efficacy of tricyclic antidepressants, but other drugs including gabapentin, opioids, and carbamazepine may provide similar degrees of relief. Choice of drug will depend on the ability of the patient to tolerate side effects of the various drugs and the urgency of the need for pain relief. In a patient with severe cancer-related neuropathic pain, for example, opioids may be the drug of first choice. In patients with ischemic heart disease or orthostatic hypotension, gabapentin would be preferable, as it is free of cardiovascular side effects. In the patient with insomnia or depression, the sedative and antidepressant effects of tricyclics would provide additional value. In headache, fibromyalgia, and atypical facial pain, tricyclics are considered first- line treatments.

Choice of Antidepressant

Table 85-2 compares the analgesic efficacy and side effects of antidepressants commonly considered in the treatment of pain. Broad-spectrum drugs such as amitriptyline, imipramine, and nortriptyline appear to have greater efficacy than selective NE- reuptake blockers or SSRIs. Although nortriptyline has been less

extensively studied in chronic pain than amitriptyline or imipramine, this is our drug of first choice because it blocks reuptake of both NE and 5-HT, causes little sedation, and causes less postural hypotension and fewer anticholinergic effects than the other broad-spectrum tricyclics. In a large clinical series and a controlled clinical trial in patients with postherpetic neuralgia, Watson and colleagues (70,71) showed virtually identical response rates of nortriptyline and amitriptyline. Desipramine is an alternative in patients who are unable to tolerate nortriptyline.

There are few positive controlled studies on which to base a recommendation of nontricyclic antidepressants. The two studies suggesting effectiveness of paroxetine and citalopram in diabetic neuropathy pain may favor the choice of these drugs for neuropathic pain, but there are few pharmacodynamic differences between these drugs and fluoxetine or sertraline. Similarly, a single study supports the use of mianserin in chronic gastrointestinal pain (72). If the monoamine hypothesis is accurate, venlafaxine may be an excellent analgesic drug, but there are no published controlled trials.

Dosing Regimens

1. Before starting tricyclic antidepressants, take a careful cardiovascular history and perform a baseline electrocardiogram. Consider whether other drugs the patient is taking affect the cytochrome P450 2D6 enzyme (examples include paroxetine, fluoxetine, and quinidine) or might potentiate orthostatic hypotension (diuretics, antihypertensives, nitrates).
2. Begin treatment with a dose of 25 mg per day in patients under 50 years of age or 10 mg per day in patients over 50. Give doses of sedative tricyclics at bedtime. If insomnia occurs, give the drug once in the morning or in divided doses.
3. Raise the dose by an increment similar to the starting dose every 3 to 4 days until the patient reports troublesome side effects, achieves satisfactory pain relief, or reaches a dose of 100 to 125 mg per day. (If treating major depression, higher doses are indicated. See Chapter 26.)
4. If no relief is achieved at 100 to 125 mg per day, determine the plasma level approximately 24 hours after the last dose. If this level is below the range of 50 to 100 ng per mL (for amitriptyline or imipramine, take the sum of the parent drug and its respective active metabolite, nortriptyline or desipramine), the patient may either be a rapid metabolizer or be poorly compliant. Consider raising the dose.

MUSCLE RELAXANTS

Nociception from muscle may play a role in several pain syndromes including tension-type headache (73), myofascial disorders (74), low back pain (75), acute musculoskeletal injury (76), and central nervous system (CNS) disorders associated with chronic spasticity (77). This section covers the heterogeneous group of skeletal muscle relaxant drugs (Table 85-3) that inhibit muscle tone and are often used in the treatment of these and other disorders (77,78,79,80 and 81). It is not always clear in these disorders that muscle is the primary source of pain or that these drugs work solely by relaxing muscles, but we think there is sufficient evidence to retain the rubric of “skeletal muscle relaxants” for now. The clinical information presented focuses on the management of acute muscle spasm because of the lack of rigorous data on the prevalence or response to treatment of chronic muscle spasm. This discussion does not include depolarizing or nondepolarizing muscle relaxants (e.g., succinylcholine, pancuronium), which are primarily used for paralysis during surgical anesthesia. Table 85-3 shows the pharmacologic classification and main indications for skeletal muscle relaxants.

Primary indication	Pharmacologic classification	Example (proprietary name)
Acute muscle spasm	Antihistamine	Orphenadrine (Norflex)
	Benzazole derivative	Chlorzoxazone (Parafon)
	Benzodiazepine	Diazepam (Valium)
	Carbamate esters	Methocarbamol (Robaxin)
		Carisoprodol (Soma)
	Methylpropanediamine derivative	Tolperisone (not marketed in North America) (Pratzel et al. [33])
	Tricyclic derivative	Cyclobenzaprine (Flexeril)
Chronic central nervous system spasticity	α-Adrenergic agonist	Tizanidine (Zanaflex)
	Benzodiazepine	Diazepam (Valium)
	GABA derivative	Baclofen (Lioresal)
	Peripherally acting	Dantrolene (Dantrium)
Fibromyalgia	Tricyclic derivative	Cyclobenzaprine (Flexeril)
Nocturnal leg cramps	Peripherally acting	Quinine (Quinamm)

TABLE 85-3. Classification of skeletal muscle relaxants

History of Skeletal Muscle Relaxants

Phenoxypropanediol (Antodyne), the prototypical skeletal muscle relaxant, was discovered in 1910 (82) followed by its derivative 3-*o*-toloxypropanediol (mephenesin) in 1946; mephenesin was shown to produce ascending paralysis in animals without sedation (83). Although mephenesin's short duration of action made its use in clinical practice extremely limited, experimental models used to study its effects have advanced our understanding of neural modulation of muscle tone (next section) leading to the development of a diverse group of skeletal muscle relaxants such as methocarbamol, cyclobenzaprine, baclofen, and tizanidine (82,84).

Neuromuscular Physiology

Segmental and Supraspinal Regulation of Muscle Tone

Figure 85-7 schematizes the neural regulation of muscle tone and possible sites of action of skeletal muscle relaxants (85,86 and 87). Skeletal muscles contain among their muscle fibers fusiform sensory muscle spindles (also called *intrafusal fibers*) that signal changes in muscle length. These sensory structures lie in parallel with ordinary (extrafusal) muscle fibers that normally contract to move or stabilize one or more joints.

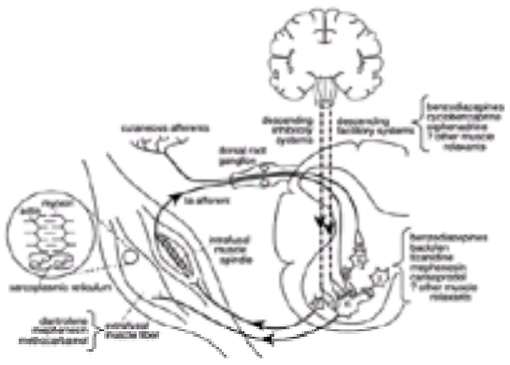

Figure 85-7. Neural regulation of muscle tone: possible sites of action of skeletal muscle relaxants. See text for details. (+, excitatory effect; –, inhibitory effect; a, alpha-motoneuron; Ca^{2+}, calcium ion; E, excitatory interneuron; g, gamma-motoneuron; I, inhibitory interneuron.)

Segmental Monosynaptic Reflex

When a muscle is stretched, the fibers in its muscle spindles also stretch, causing an increase in the frequency of neural discharges carried by Ia afferent nerve fibers. These Ia fibers enter and traverse the dorsal horn and terminate on alpha-motoneurons in the ventral horn, producing excitatory postsynaptic potentials, which promote contraction of the muscle from which the muscle spindle originated. Conversely, *decreases* in muscle length silence Ia nerve fiber activity, which results in a

decrease in muscle contraction. Therefore, the afferent activity from the muscle spindles serves as a negative feedback on changes in joint position.

On the efferent side, muscle spindles are innervated by small gamma-motoneurons that originate in the ventral horn of the spinal cord and travel together with the alpha-motoneurons that innervate extrafusal muscle fibers. These gamma-motoneurons (like alpha- motoneurons) release acetylcholine, which adjusts the sensitivity of the spindle such that it can regulate muscle tension over a wide range of muscle lengths. The adjustment of spindle sensitivity by gamma-motoneurons may be illustrated by explaining how an individual can carry a heavy pail of water. If we start by imagining the pail being carried with a relatively straight arm extending down from the shoulder, both intrafusal spindles and extrafusal muscle fibers in the biceps muscle are in a relative state of stretch. This stretch increases the input from Ia afferent fibers to promote biceps muscle contraction and thus maintain the pail in a steady position. If the individual wishes to flex the elbow and continue to carry the pail in this flexed position, he or she will generate a pattern of efferent motor impulses from alpha- and gamma-motoneurons that contract the extrafusal fibers and intrafusal fibers, respectively, of the biceps. The internal contraction of the biceps muscle spindle maintains tension on the Ia afferent receptor, which then fires to maintain the contraction of the extrafusal biceps fibers to keep the joint flexed. Without this increase in tension in the biceps muscle spindle, flexion of the elbow would result in decreased tension in the biceps muscle spindles, decreased Ia afferent activity, and difficulty keeping the arm in the desired degree of flexion.

Polysynaptic Reflexes

In the spinal cord, a complex network of excitatory and inhibitory interneurons mediates motor reflexes in response to deep and cutaneous stimulation. Such reflexes mediate ipsilateral flexion and contralateral extension in response to noxious stimuli to coordinate a protective or escape response. For example, after noxious stimulation of the left foot of an animal, ipsilateral flexion withdraws this foot from the stimulus and contralateral extension helps the animal escape from the stimulus. Impulses from cutaneous afferents travel through the dorsal horn of the spinal cord and terminate on excitatory interneurons, which in turn terminate on presynaptic terminals of the intrafusal Ia fiber to further promote its excitatory effect on the ventral horn alpha-motoneuron.

Supraspinal Regulation

Early electrophysiologic studies have identified inhibitory centers in the bulbar reticular formation (88) and facilitatory centers from several brain regions (89) that further regulate both corticospinal and reflex muscle activity. Alterations in both of these systems by “spasticity-producing” CNS diseases as well as by skeletal muscle relaxants may exert an important effect on the above described reflexes and on regular corticospinal muscle activity.

Neurotransmission in the Spinal Cord

Excitatory neurotransmitters proposed to play a major role in the modulation of movement in the spinal cord include excitatory amino acids such as glutamate and aspartate as well as neuropeptides such as substance P. These transmitters are released from the terminals of primary afferent fibers to mediate the above-mentioned reflexes as well as from excitatory interneurons to enhance motor tone at the spinal level (77). The major inhibitory spinal neurotransmitters are glycine and gamma-aminobutyric acid (GABA). Glycine is thought to be released by inhibitory interneurons, and GABA (from both supraspinal and interneuronal inputs) is thought to play a major role in presynaptic inhibition of motor neurons in the spinal cord (77). In addition to these inhibitory transmitters, supraspinal descending monoaminergic systems release the transmitters noradrenaline, dopamine, and 5-HT, which facilitate locomotion and reflex activity.

Pathophysiologic Mechanisms of Spasticity and Muscle Spasm

Disease or dysfunction of the above regulatory components of muscle tone may lead to acute reflex muscle spasm or chronic spasticity whose pathophysiology is poorly understood. In the case of spasticity (sometimes called *upper motor neuron syndrome*), lesions of descending pathways such as the corticospinal, vestibulospinal, or reticulospinal tracts may result in either excessive excitation or diminished inhibition of alpha-motoneurons at the spinal segmental level (85). In the case of acute muscle spasm, a peripheral injury or noxious stimulus may result in a reflex increase in muscle tone, either by the activation of segmental polysynaptic reflexes (described above), thus producing hyperexcitability of alpha- or gamma-motoneurons, or by the supraspinal activation of descending facilitatory systems that increase segmental muscle tone (90).

Sites and Mechanisms of Action

Site of Action

Skeletal muscle relaxants have been observed to act at several CNS sites important in the regulation of muscle tone. Due to this diversity of action, the relative importance of drug action at each of these sites remains unclear. Early studies suggested that the skeletal muscle relaxant mephenesin acted on excitatory spinal interneurons since it effectively inhibited polysynaptic reflex contractions while leaving monosynaptic reflexes unaffected (91). However, further studies of mephenesin demonstrated an effect on monosynaptic systems as well (92), and other studies showed that mephenesin and methocarbamol prolong the refractory period of skeletal muscle by a direct action on skeletal muscle fibers (93). Dantrolene, which is distinct in its mode of action from most other skeletal muscle relaxants, acts peripherally on skeletal muscle by inhibiting the release of calcium ions from the sarcoplasmic reticulum (77). Finally, it has been observed that higher doses of diazepam are needed to effectively suppress polysynaptic reflexes in animals after spinal transection in comparison with spinally intact animals (94). The interpretation of this finding has been that diazepam inhibits polysynaptic reflexes, in part, by acting in the brainstem to suppress a descending facilitatory system.

Neurotransmitter Mechanisms

Very little has been described about the effects of skeletal muscle relaxants such as cyclobenzaprine, methocarbamol, carisoprodol, and chlorzoxazone on neurotransmission. However, benzodiazepines such as diazepam are known to act by potentiating the postsynaptic effects of GABA in the CNS (85). Baclofen (parachlorophenyl GABA) is a lipophilic derivative of GABA that binds to $GABA_B$ but not to $GABA_A$ receptors and may exert its effect, in part, by inhibiting the evoked release of excitatory amino acids (e.g., glutamate) and substance P (77). Tizanidine, a newer antispasticity agent, is an a_2-adrenergic receptor agonist that may also act by decreasing spinal excitatory amino acid release (95).

Clinical Information

Evidence for Efficacy

Benzodiazepines. In addition to trials of benzodiazepines in conditions of muscle spasm (see Other Muscle Relaxants, later in this chapter), a general discussion about the use of benzodiazepines in pain management is warranted. In 1994, Dellemijn and Fields reviewed several controversies surrounding the use of benzodiazepines in the treatment of chronic pain. Although evidence exists to suggest that benzodiazepines may alleviate situational anxiety and thus be useful analgesic adjuvants in the setting of acute pain (96), their clinical utility in chronic pain management is somewhat controversial. In conditions where anxiety and muscle spasm potentiate each other, benzodiazepines may improve these two symptoms and interrupt this vicious cycle. However, benzodiazepines may worsen depression, which may further aggravate pain (97). Although controlled trials support the efficacy of benzodiazepines in certain disorders such as chronic tension headache (1,98) and temporomandibular joint dysfunction (99), benzodiazepines have been ineffective in controlled trials of postherpetic neuralgia (24) and other chronic nonmalignant pain syndromes (100).

Other Muscle Relaxants. In 1997, van Tulder et al. (101) conducted a systematic review of randomized controlled trials of common interventions used in the treatment of low back pain. Based on detailed trial assessment criteria including those of study population, interventions, treatment effect, and data presentation and analysis, this review identified 14 trials of muscle relaxants, eight of which were scored as high quality (i.e., greater than 50/100 on a methodologic assessment score). All five high-quality trials comparing muscle relaxants to a placebo reported a significant reduction in pain intensity with the muscle relaxant in comparison with placebo (102,103,104,105 and 106). Two of the three high-quality trials that compared different types of muscle relaxants showed no difference in pain intensity between those compared (107,108). Based on this analysis, it was concluded that there is strong evidence (i.e., multiple relevant, high-quality randomized controlled trials) that muscle relaxants are more effective than placebo for acute low back pain and that there is strong evidence that different types of muscle relaxants are equally efficacious for acute low back pain (101). Some of the studies showing subjective clinical improvement of low back pain also demonstrated that the muscle relaxant studied successfully decreased objective measures of muscle spasm (102,105,106). This evidence demonstrates that muscle relaxants actually alleviate reflex muscle spasm, which likely contributes to their pain-relieving effects.

The evidence of efficacy of muscle relaxants in the treatment of low back pain provides the rationale for using these drugs for other conditions such as cervical (109) and temporomandibular disorders (90,110). However, direct evidence of efficacy in these conditions is equivocal (111,112 and 113). Two clinical studies by Basmajian have looked at the clinical and electromyographic effects of muscle relaxants in the treatment of cervical muscle spasm (111,114). A double-blind comparative study of cyclobenzaprine, diazepam, and placebo included only ten patients being treated for neck spasm and showed that cyclobenzaprine produced significant clinical improvement in neck spasms compared to diazepam and placebo (111). Furthermore, the improvement noted with cyclobenzaprine was correlated with an augmentation of myoelectric activity measured by electromyography. A subsequent study comparing diazepam and phenobarbital to placebo in 40 patients with reflex cervical muscle spasm failed to show any clinical analgesic effects with either drug despite significant myoelectric augmentation (seen previously with improved clinical effects of cyclobenzaprine) with diazepam (114). This negative result was partially explained by the likelihood that in many cases pain was originating from other nonmuscular structures and thus was unaffected by pharmacologic muscle relaxation. Two other studies evaluating muscle relaxants in the treatment of temporomandibular dysfunction fail to support their efficacy in this condition. In 1960, Schwartz et al. (112) reported on a double-blind placebo-controlled study of carisoprodol in 34 patients with temporomandibular dysfunction syndrome showing no benefit with carisoprodol over placebo. A similar study of carisoprodol in 60 temporomandibular dysfunction patients by Gallardo et al. (113) failed to show any beneficial clinical effects. Again, these negative results may partially be explained by the heterogeneity of disease mechanisms, some of which give rise to pain of a nonmuscular origin. Table 85-4 shows several high-quality controlled trials of muscle relaxants in the treatment of acute back pain, neck pain, and orofacial pain.

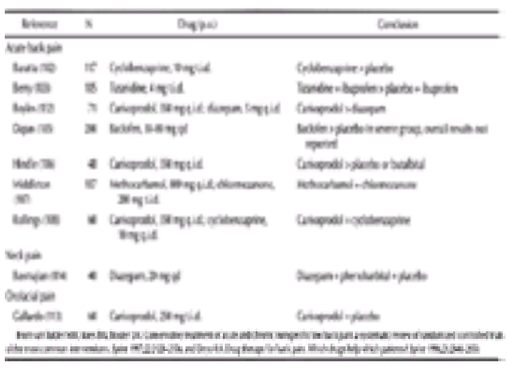

TABLE 85-4. Randomized controlled trials of skeletal muscle relaxants

Evidence for efficacy has been demonstrated for the muscle relaxants baclofen, dantrolene, and tizanidine in the treatment of spasticity secondary to upper motor neuron or spinal disorders (77,85,95). However, due to limited clinical evidence in the treatment of acute muscle spasm, these agents are not indicated for this use (115). Of relevance to the analgesic effects of centrally acting muscle relaxants, intrathecally administered baclofen, in addition to its effects on central spasticity (116), has been evaluated in a few small studies for analgesic effects in the treatment of pain related to central spasticity (117,118 and 119). Two small (n = 7 to 14) studies have demonstrated brief analgesia following acute intrathecal baclofen administration to patients with chronic neuropathic pain related to spinal cord injury (118,119). However, Loubser and Akman (117) studied *chronic* intrathecal baclofen administration in 16 patients with central spasticity and showed that although this resulted in a significant decrease in spasticity-related musculoskeletal pain, there was no change in neuropathic pain symptoms.

Indications

Table 85-5 outlines commonly used drugs that are indicated for the treatment of painful skeletal muscle spasm. Other muscle relaxant agents discussed in detail elsewhere (120,121) include chlorphenesin carbamate (Maolate), metaxalone (Skelaxin), and quinine (Quinamm). In addition to skeletal muscle spasm, cyclobenzaprine (Flexeril) is also indicated for the treatment of fibromyalgia (122).

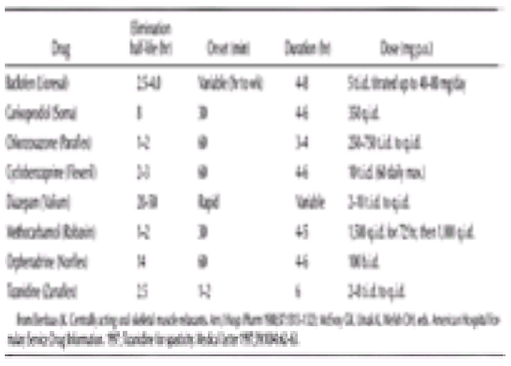

TABLE 85-5. Clinical pharmacology of commonly used skeletal muscle relaxants

Contraindications

Health professionals should consult individual drug product information prior to prescribing or recommending any of these medications. All drugs are contraindicated in patients with a known history of specific drug hypersensitivity. Carisoprodol (Soma), a muscle relaxant that becomes metabolized to the sedative anxiolytic drug meprobamate (Miltown), is contraindicated in patients with a history of acute intermittent porphyria or with a history of hypersensitivity to meprobamate. As a tricyclic antidepressant derivative, cyclobenzaprine (Flexeril) shares the toxic potential of these agents and is contraindicated in patients with hyperthyroidism, congestive heart failure, ischemic heart disease, cardiac arrhythmias, heart block, or other cardiac conduction disorders and in those at risk of a suicidal overdose. Also, cyclobenzaprine is contraindicated in patients receiving monoamine oxidase inhibitors and should not be used within 14 days after discontinuation of any of these agents (115).

Precautions

As all of these skeletal muscle relaxants are CNS depressants, caution should be used when administering these drugs concomitantly with other CNS depressants, including alcohol, so as to avoid additive depressant effects. Also, patients should be instructed that skeletal muscle relaxants may impair ability to perform hazardous activities requiring mental alertness or physical coordination such as operating machinery or driving a motor vehicle. Of relevance to other tricyclic compounds and other antidepressants, it should be noted that the cytochrome P450 2D6 enzyme isoform plays only a minor role in the metabolism of the tricyclic derivative cyclobenzaprine and thus should not be much of a concern regarding its clinical use (123). Skeletal muscle relaxants with anticholinergic adverse effects such as cyclobenzaprine and orphenadrine should be used with caution in conditions where these effects are undesirable such as urinary retention, angle-closure glaucoma, increased intraocular pressure, or concomitant administration of other anticholinergic drugs. Finally, due to the lack of established safety, skeletal muscle relaxants should not be used during pregnancy or lactation or in pediatric age groups unless the potential benefits outweigh the possible risks (115).

Techniques of Administration

Table 85-5 shows the recommended dose, elimination half-life, onset, and duration of action of several commonly used and orally administered skeletal muscle relaxants (120,121). Although these drugs all come in oral preparations, diazepam, methocarbamol, and orphenadrine are also prepared and approved for parenteral (intravenous or intramuscular) administration. Some of these drugs are also prepared and approved as drug combinations with other analgesics including

carisoprodol [with acetylsalicyclic acid (ASA) or with ASA/codeine], methocarbamol (with ASA or with acetaminophen), and orphenadrine (with ASA/caffeine) (115).

Complications

Adverse Effects

The most frequent adverse effects of benzodiazepines and other skeletal muscle relaxants are related to CNS depression and include drowsiness, dizziness, lightheadedness, and fatigue (120,124). Cyclobenzaprine and orphenadrine also produce anticholinergic adverse effects such as dry mouth, blurry vision, urinary retention, and constipation (115). Chlorzoxazone has been associated with a limited number of cases of serious hepatic toxicity presenting with abnormal liver function tests, cholestasis, and hepatic necrosis following 1 to 5 months of administration (125). This risk of liver toxicity might be worse with acetaminophen combinations (e.g., Parafon Forte). Given the similar efficacy of different muscle relaxants, the risk of hepatic toxicity with chlorzoxazone makes it an unfavorable choice.

Abuse Potential and Dependence

Benzodiazepines and other skeletal muscle relaxants have the potential for abuse (126,127). Preston et al. (128) conducted a behavioral study in adult male volunteers to evaluate the abuse potential of methocarbamol in comparison with lorazepam and placebo. Results from this study suggest that methocarbamol has some abuse potential at supratherapeutic doses that is less than that of lorazepam and is limited by dose-related side effects. Discontinuation of benzodiazepines after chronic use has been reported in several cases to produce a withdrawal syndrome characterized by autonomic hyperactivity resulting in tremulousness, sweating, insomnia, tachycardia, mild systolic hypertension, and rarely seizures (129). Carisoprodol (Soma), whose active metabolite is meprobamate, is thought to carry with it a risk of meprobamate dependence (130). Abrupt discontinuation of carisoprodol following chronic use (several days) at 100 mg per kg has been reported to result in mild withdrawal symptoms such as abdominal cramps, insomnia, chills, headache, and nausea (115). Furthermore, psychological dependence has been reported, albeit rarely, with chronic carisoprodol administration.

Conclusions

Skeletal muscle relaxants are a diverse group of pharmacologic agents that decrease skeletal muscle tone by promoting the inhibition of certain supraspinal and spinal motor neurons and, in some cases, through direct action on skeletal muscle. Strong evidence exists for the efficacy of skeletal muscle relaxants in the treatment of muscle spasm associated with acute low back pain as well as for the similar efficacy of different muscle relaxant agents in treating this condition. Carisoprodol is our first choice because of the several high-quality controlled trials showing superiority to placebo or other muscle relaxants and its favorable safety profile over several decades on the market. More research is necessary to demonstrate the efficacy of these agents in the treatment of other disorders such as tension headache, neck pain, and temporomandibular dysfunction. The most prominent and clinically relevant adverse effects of skeletal muscle relaxants are those related to dose-dependent, reversible CNS depression. The abuse potential of these drugs is a relative contraindication to use for periods longer than several weeks. Other than for short-term use in the treatment of acute muscle spasm, there is little evidence of a favorable risk-benefit profile to support the general use of benzodiazepines as adjuvant analgesics in chronic pain management.

ANTAGONISTS OF THE *N*-METHYL-D-ASPARTATE GLUTAMATE RECEPTOR

As discussed in Chapter 4, animal studies have shown that many of the plastic changes that pain causes in the CNS are mediated by glutamate receptors, which are classified into NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid/kainate, and metabotropic subclasses. A small number of controlled trials with NMDA-receptor antagonists have suggested efficacy in various chronic pain conditions. Because of the limited data from controlled studies of chronic dosing, we think it is premature to recommend the use of these drugs at this writing. However, because clinicians are already using NMDA antagonists in patients with refractory pain, we briefly discuss the clinical pharmacology of ketamine and dextromethorphan, the two NMDA-receptor antagonists for which multiple controlled trials suggest analgesic efficacy.

Ketamine

Ketamine has been used as an anesthetic agent for more than 3 decades (133), but interest in chronic administration for pain was only recently kindled by the recognition that at subanesthetic doses, its primary effect is blockade of the phencyclidine site in the ion channel associated with the NMDA receptor (134). A series of placebo-controlled trials [references in Stubhaug and Breivik (135)] have shown that brief infusions of ketamine reduce pain caused by postherpetic neuralgia, chronic trauma, amputation, spinal cord injury, fibromyalgia, surgery, and a variety of types of experimental pain and hyperalgesia, but at doses that often cause sedation and dissociative reactions. In surgical settings, anesthesiologists often coadminister benzodiazepines with ketamine to ameliorate or prevent recall of psychotomimetic reactions, but Krystal et al. (136) have shown that lorazepam worsens the sedative, attention-impairing, and amnestic effects of intravenous ketamine and only partially reverses ketamine-induced psychosis at doses that do not produce sleep.

Chronic subcutaneous infusion of ketamine appeared effective in several patients with postherpetic neuralgia (137), but subcutaneous induration prevented chronic treatment. Several case reports (138,139 and 140) describe benefit from chronic oral administration of ketamine—either the intravenous preparation is dissolved in juice or an oral suspension can be used. Doses were titrated to effect in each patient and ranged between 50 and 60 mg p.o. four to six times per day.

The pharmacokinetic profile of oral ketamine differs from intravenous ketamine in humans in that there is a prominent first-pass effect; the liver metabolizes more than 80% of the ingested drug to the active metabolite norketamine. There is little information about the long-term toxicity of oral ketamine. Case reports of possible serious toxicity describe hepatic damage (141), gastric ulcer (138), and memory impairment (142). In view of these concerns, chronic ketamine should only be given when standard measures have failed, under close medical supervision.

Dextromethorphan

Dextromethorphan, widely available as an over-the-counter cough remedy, has recently been recognized to block the ion channel associated with the NMDA receptor as does its primary metabolite, dextrorphan (143,144). Dextromethorphan is also an agonist at sigma-1 receptors and an antagonist at the transporter for FHT reuptake (61) and at ion-gated calcium channels (145). Steinberg et al. (146) measured dextromethorphan concentrations in brain tissue of neurosurgical patients pretreated with the drug. By comparing these with brain tissue levels affording neuroprotection in animal models of ischemia, they concluded that adequate blockade of NMDA receptors requires doses several times higher than the maximum antitussive dose of 120 mg per day.

Two randomized clinical trials (147,148) showed that chronic treatment with dextromethorphan at an average dose of 400 mg per day reduced pain in 31 patients with diabetic neuropathy to about 80% of the intensity reported by placebo-treated patients, a degree of pain relief approximating that shown in other studies of tricyclic antidepressants, mexiletine, and gabapentin. Side effects at this dose include dizziness, fatigue, and confusion, which were prominent during upward dose titration but mild after a maintenance dose was found. Patients with postherpetic neuralgia did not report pain relief in either study. A previous study (149) had not shown any analgesic effect at 81 mg per day.

Like the tricyclic antidepressants, dextromethorphan is primarily metabolized by the cytochrome P450 2D6 enzyme, whose multiple alleles cause great variability in drug concentrations achieved in different patients. Capon et al. (150) reported the median elimination half-life to be 2.4 hours in extensive metabolizers and 19.1 hours in poor metabolizers. In order to get uniformly high dextromethorphan plasma levels (and to solve the difficulty in obtaining a high-dose preparation of pure dextromethorphan) several groups have administered quinidine, 50 to 75 mg twice daily, along with dextromethorphan. This drug powerfully inhibits the 2D6 enzyme, converting extensive metabolizers to poor metabolizers and increasing plasma dextromethorphan by 20-fold (151). We would urge caution in using this drug combination for several reasons: (a) Quinidine has its own toxicities, including potentiation of cardiac arrhythmias and allergic reactions, although the doses sufficient to block 2D6 activity (50 to 75 mg twice daily) are much lower than the doses generally used to treat cardiac arrhythmias; (b) blood concentrations of any other drug metabolized by 2D6 will also rise precipitously, including tricyclic antidepressants, mexiletine, antipsychotics, and b-adrenergic blockers (42,43); and (c) the blockade of metabolism will greatly lower plasma and CNS levels of the active metabolite dextrorphan. It is possible that dextrorphan played an important role in the pain relief reported in the treatment of diabetic neuropathy with high-dose dextromethorphan (147). If so, these results would not carry over into treatment with a low-dose dextromethorphan-quinidine combination.

Because dextromethorphan increases the amount of 5-HT at central synapses, it may cause the potentially fatal serotonin syndrome when combined with other

serotonergic drugs, including paroxetine, fluoxetine, and monoamine oxidase inhibitors (61,62 and 63). Case reports have suggested that dextromethorphan may trigger mania in patients with bipolar affective disorder (152).

Other *N*-Methyl-D-Aspartate Receptor Antagonists

A single paper reports that a single intravenous infusion of amantadine temporarily reduced chronic postsurgical neuropathic pain (153). There are no chronic treatment studies with the commonly available oral form of this medication. Memantine, another NMDA channel blocker commonly used in Germany for the treatment of Parkinson's disease and Alzheimer's disease, is under study in acquired immunodeficiency syndrome–related neuropathy, diabetic neuropathy, and postherpetic neuralgia.

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CHAPTER 86

Anticonvulsants and Local Anesthetic Drugs

Michael C. Rowbotham and Karin L. Petersen

Anticonvulsants and local anesthetic drugs have been used for decades to treat chronic pain. Sufficient basic and clinical scientific evidence has accrued to firmly establish anticonvulsants and local anesthetic drugs as specialized analgesics. Neither class of drug has clearly established analgesic efficacy for musculoskeletal, nociceptive, or idiopathic pain. However, both classes can dramatically relieve neuropathic pain.

Research in animals with experimental nerve injury and humans with chronic neuropathic pain has highlighted one clinically important mechanism for the production of neuropathic pain: ectopic impulse generation by damaged, dysfunctional primary sensory neurons and their axons. This abnormal, ectopic discharge can be suppressed by anticonvulsants and local anesthetics with sodium channel blocking effect at concentrations orders of magnitude lower than needed to block the propagation of action potentials in normal nerves (1,2). Because the process of ectopic impulse generation is far more sensitive to sodium channel blockade than is normal impulse conduction, these drugs can be given systemically or regionally without fatal toxicity from failure of normal nerve conduction. Anticonvulsants that do not block sodium channels, such as gabapentin, are also highly effective analgesic agents. Discerning the neuronal basis for the analgesic effect of these drugs has been the subject of much research.

In this chapter, anticonvulsants and systemic local anesthetics are discussed in the context of current concepts of the pathophysiology of neuropathic pain. First, the mechanisms behind neuropathic pain and ectopic neuronal activity are summarized, and the mechanisms by which membrane stabilizing drugs suppress ectopic firing are reviewed: (a) Na-channel blockade and (b) non–Na-channel blockade. Then, the clinical literature relating to their use and efficacy in the treatment of neuropathic pain is reviewed. Finally, the currently available anticonvulsants and systemic local anesthetic drugs are reviewed.

NEUROPATHIC PAIN AND ECTOPIC NEURONAL ACTIVITY

In teased axon recordings from dorsal roots in rats and rabbits with chronic nerve injury, Wall and Gutnick (3) and Kirk (4) demonstrated an increased level of ongoing discharge in afferent A and C fibers compared to normal intact dorsal root and dorsal root just after acute nerve section. Subsequent studies identified two principal sources of this activity: the nerve injury site (e.g., neuroma or nerve compression zone) (5,6; reviewed in 7) and the associated dorsal root ganglia (DRG) (8,9 and 10). In addition to spontaneous firing, ectopic discharge at both of these locations can be produced by gentle tapping and by a range of chemical stimuli. In contrast to the nerve injury site, the DRG have not yet been investigated as a potential source of ectopic firing in humans despite the strong experimental evidence in animals.

Ectopic neuronal activity contributes to pain in three ways. First, abnormal afferent barrages that propagate into the central nervous system (CNS) directly will elicit paraesthesias, dysesthesias, and pain. For example, continuous discharge in C fibers produces continuous sensations of burning pain, and intermittent spontaneous bursts in A-d or A-b fibers produce lancinating dysesthesias or paresthesias. Second, ectopic sites are abnormally likely to generate action potentials (single or prolonged bursts of neuronal activity) spontaneously and in response to gentle mechanical stimulation, sympathetic efferent activity, and circulating catecholamines. Third, abnormally increased afferent input via nociceptors can trigger and maintain “central sensitization.” Central neurons become sensitized in response to a brief but intense barrage of nociceptor input or sustained low-level nociceptor input (11). Once central neurons are sensitized, even innocuous mechanoreceptor stimulation from an area around the nerve injury is perceived as painful (12,13 and 14). This effect of ectopic firing in neuropathic pain is best illustrated under conditions in which a well-localized focus of abnormal neuronal discharge can be identified. Sheen and Chung (15), for example, severed the spinal nerve of DRG L-5 and L-6 in rats, creating a focus of ectopic discharge in the L-5 and L-6 neuromas and DRG. The result was behavioral signs of ongoing pain, presumably due to the ectopic firing, and allodynia in the hindlimb skin served by the neighboring L-4 root that was presumed to be due to central sensitization triggered by the ectopic firing. Blocking central propagation of the abnormal ectopic discharge by secondarily cutting the L-5 and L-6 dorsal roots eliminated the ongoing pain and normalized sensation in the L-4 territory.

Confirmatory evidence in humans has been gathered using the method of percutaneous microneurographic recording from single nerve fibers (16). Microneurography allows a direct comparison of neural discharge and sensation. A small number of such studies in patients with neuropathic pain have appeared (17,18,19,20 and 21). Spontaneous and evoked discharges were strikingly correlated with neuropathic paresthesias and pain. As reported by Cline and colleagues (17), patients who complained of burning pain and hyperalgesia had spontaneous activity in unmyelinated primary afferents. Nystrom and Hagbarth (19) documented ongoing discharge in the peroneal nerve in a lower extremity amputee. Their patient had ongoing phantom foot pain that was augmented by percussion of the neuroma. Each percussion elicited an intense burst of spike activity, mostly in slowly conducting axons. Local anesthetic block of the neuroma eliminated percussion-evoked neuronal activity and pain. In a patient with radicular pain after surgery for disk herniation, straight-leg lifting (Lasegue's sign) produced dysesthesias referred to the foot as well as ectopic impulse bursts in the sural nerve, the intensity of which waxed and waned in close correlation with the abnormal sensation (18).

There is some clinical evidence that large areas of touch-evoked allodynia are due to a state of central sensitization maintained by ectopic impulse generation from the area of most severe neuropathic pain. Rowbotham and Fields (22) reported dramatic shrinkage of the area of allodynia with local anesthetic skin infiltration of just the area of maximum pain in a small series of patients with postherpetic neuralgia. Gracely et al. (23) reported a patient whose painful scar near the knee was surrounded by touch-evoked allodynia extending up the thigh and down the calf. Local anesthetic block of the scar eliminated the extended allodynia as well as the scar pain for the duration of the block. The interpretation offered was that noxious input originating in the scar triggered a spinal central sensitization state that amplified, and rendered painful, A-b touch input from the thigh and calf. More difficult to explain are those rare patients in whom a brief infusion of systemic lidocaine will reproducibly relieve neuropathic pain for days or weeks.

CONTRIBUTION OF NA^+ CHANNEL BLOCKADE TO PAIN RELIEF

Na^+ channels are membrane proteins found in all nerve cells. Among many functions, Na^+ channels constitute a major component of the impulse-generating machinery. Impulse propagation along axons is critically dependent on the functioning of Na^+ channels. The development of ectopic hyperexcitability is thought to be due to remodeling of the local electrical properties of the axon membrane via changes in Na^+ channel distribution (7). The principal underlying mechanism appears to be the accumulation of excess voltage-sensitive Na^+ channels in terminal swellings of axonal sprouts in the region of injury and in patches of demyelination (24).

Research suggests that there may be ten or more different Na^+ channel subtypes. Na^+ channels are classified as tetrodotoxin (TTX)-sensitive or TTX-resistant based on the response to TTX, an extremely potent selective Na^+ channel blocker. TTX inhibits neuronal activity in animal neuropathic pain models by blocking

TTX-sensitive Na^+ channels in the injured nerve but also blocks TTX sensitive Na^+ channels throughout the nervous system. A TTX-resistant Na^+ channel named *PN3* (or alpha-SNS) has been identified. In contrast to previously identified Na^+ channels, PN3 is located only in the PNS on small neurons in the DRG (25). The PN3 Na^+ channel is suggested to be of specific importance to pain transmission. Experimental nerve damage leads to changes in PN3 expression in the DRG (26,27 and 28). Using immunolabeling, migration of PN3 Na^+ channels from the DRG to C and A-d fibers has been demonstrated, implying that ectopic neural activity after nerve injury may be due to a dynamic redistribution of pain-specific Na^+ channels. Developing an analgesic agent specifically targeting the PN3 Na^+ channel has potentially important implications, since clinical use of nonselective Na^+ channel blockers are limited by systemic side effects presumed due to actions on cardiac and CNS Na^+ channels.

A variety of anticonvulsant and local anesthetic drugs that suppress abnormal discharge originating at nerve injury sites and associated DRG act on Na^+ channels (29). These include the anticonvulsants carbamazepine, phenytoin, and lamotrigine (30,31); the antiarrhythmics mexiletine and tocainide (32); and lidocainelike local anesthetics (33). Each of these prevents the generation of spontaneous ectopic impulses at much lower concentrations than are required to block normal impulse propagation. Abram and Yaksh (34) compared the effect of systemic lidocaine in three rat pain models: the formalin test (which uses a chemical stimulus to produce a two-phase nociceptive response), partial ligation of the sciatic nerve (which produces neuropathic hyperalgesia), and normal paw withdrawal to noxious heat. Doses of lidocaine that markedly reduce neuropathic hyperalgesia leave the withdrawal latency to noxious heat in the normally innervated paw and both phases of the formalin unaffected. Higher doses of lidocaine reduce only the second phase of the formalin test, which is thought to be due, in part, to the development of central sensitization. In a study of rat sciatic neuromas by Chabal and colleagues (32), lidocaine, mexiletine, and tocainide abolished spontaneous activity and markedly suppressed the ability of gentle mechanical stimulation to evoke abnormal activity. Other studies in animal models of neuropathic pain demonstrate that systemic lidocaine sometimes relieves cutaneous hypersensitivity for a longer time than would be expected from the serum half-life of the drug (35). In sum, these results suggest the following rank ordering of lidocaine effects on pain: (a) Low plasma levels suppress ectopic impulse generation in chronically injured peripheral nerve; (b) higher levels suppress central sensitization and central neuronal hyperexcitability; (c) high levels have general analgesic effects; (d) very high levels are associated with seizure activity, cardiac arrhythmias, and cardiovascular collapse; and (e) supralethal systemic levels block normal axonal impulse conduction.

ANALGESIC EFFECTS INDEPENDENT OF NA^+ CHANNEL BLOCKADE

Some anticonvulsant drugs are highly effective in controlling pain but seem to do so without blocking Na^+ channels. Proposed mechanisms of analgesic actions for non-Na^+ channel blocking drugs revolve around effects on sensitized central neurons, such as direct or indirect inhibition of the release of excitatory amino acids, blockade of neuronal calcium channels, and augmentation of CNS inhibitory pathways via increasing GABA-ergic transmission.

The best example of an effective non-Na^+ channel blocking anticonvulsant is gabapentin, a lipophilic GABA analog. Two large multicenter clinical trials of gabapentin for neuropathic pain demonstrated efficacy (36,37). Gabapentin does not reduce acute nociceptive pain (38,39). However, gabapentin does reduce signs of central sensitization in animals after experimentally induced hyperalgesia and may do so by reducing the sensitization of dorsal horn sensory neurons (39,40 and 41). Furthermore, it has been demonstrated in animal models that gabapentin reduces hyperalgesia following experimental nerve injury (38,42). Despite intensive study, the basis for gabapentin analgesia remains uncertain. Gabapentin was developed as an analog to the neurotransmitter GABA but has since been shown not to interact with either $GABA_A$ or $GABA_B$ receptors [for review, see Taylor et al. (41)]. Since gabapentin is excreted unmetabolized, active metabolites cannot explain the analgesic effect in humans. GABA-ergic function could be potentiated without direct interaction with GABA sites by increasing the concentration of GABA in neuronal tissue through release of GABA from nerve terminals (43), enzyme effects, or decreased GABA breakdown (for review, see 41 and 44). Another possible mechanism is mobilization of intracellular GABA via gabapentin-sensitive transporters. However, the best evidence to date comes from studies rank-ordering effects of gabapentin and related drugs on a specific gabapentin-binding protein found in brain and spinal cord. The binding site, called a $_2$d, is a subunit of an N-type voltage-gated calcium channel found in high density in the cerebral cortex, superficial dorsal horn, cerebellum, and hippocampus (38,41,45). Studies in spinal cord dorsal horn preparations have found that gabapentin binding is primarily postsynaptic and is resistant to neonatal capsaicin treatment and rhizotomy. GABA itself has no activity at this binding site, but gabapentin analogs that bind to the a $_2$d-subunit do appear to have analgesic activity. At this time, it is not certain which, if any, of the suggested mechanisms may be relevant to the analgesic efficacy of gabapentin.

CLINICAL USE OF LOCAL ANESTHETICS, ANTIARRHYTHMICS, AND ANTICONVULSANTS IN TREATMENT OF CHRONIC PAIN

Systemic administration of local anesthetics for analgesia has a long history (46). Beginning in the 1930s, procaine and later lidocaine have been given systemically for a broad variety of painful conditions. More recently, analgesia from systemic local anesthetic administration has been established through prospective controlled studies in patients with painful diabetic neuropathy (47,48 and 49) and postherpetic neuralgia (50). In two large uncontrolled series, systemic local anesthetics were most often effective for patients with pain due to peripheral nerve injury (51,52). In contrast, the effect of systemic local anesthetic in acute nociceptive pain is less consistent. Cassuto et al. (53) reported significant analgesic efficacy for intravenous lidocaine in postoperative pain and Jonsson et al. (54) reported its efficacy for burn pain. However, other controlled studies have reported systemic local anesthetics to have minimal or no analgesic effectiveness for postoperative pain. The effect of lidocaine on human experimental pain models is modest (55,56). Other diagnostic groups for whom excellent responses to systemic local anesthetic administration have been reported anecdotally include cranial neuralgias, multiple sclerosis, adiposis dolorosa (57), cancer pain, thalamic pain, and arachnoiditis (1,58,59).

Currently, lidocaine infusions are used to either further explore the nature of the pain (55) or to predict response to an oral antiarrhythmic or anticonvulsant agent that also blocks sodium channels (60,61). Mexiletine is the only oral antiarrhythmic agent studied prospectively for comparative response after intravenous lidocaine in neuropathic pain patients.

Anticonvulsants are a broad category tied together only by their ability to suppress epileptic seizures. Anticonvulsants came into general use by neurologists for a variety of painful conditions once carbamazepine was demonstrated to have dramatic efficacy in the treatment of trigeminal neuralgia (62,63,64,65,66,67 and 68). Clinical experience suggests that they are most effective in conditions in which the pain has a lancinating component (i.e., a neuropathic quality) (69,70). This point has not been examined quantitatively, however, and the efficacy of anticonvulsant drugs such as valproic acid and gabapentin in migraine prophylaxis (65) is noteworthy. In addition, gabapentin has been used anecdotally for a broad range of chronic pain states extending well beyond peripheral neuropathic pain and headache to include atypical facial pain, complex regional pain syndromes, fibromyalgia, and central pain.

CHOOSING A DRUG

Table 86-1 lists usual doses, common side effects, and general precautions regarding the specific oral drugs reviewed in this chapter. For further detail on specific drugs, see the *Physicians' Desk Reference* (71) and reviews of epilepsy therapy by Brodie and Dichter (72) and Dichter and Brodie (73). For newer drugs, such as gabapentin and topiramate, reports of unusual adverse events are largely limited to patients with refractory seizures on multidrug regimens. Of the oral medications currently available, there is no specific rank-order validated by prospective, blinded, comparative studies of patients with chronic pain. Carbamazepine and gabapentin would appear to be the first choice drugs, followed by mexiletine and valproic acid. The other anticonvulsant, antiarrhythmic, and local anesthetic drugs described here are used primarily for treatment of neuropathic pain and have not been studied in large-scale, prospective controlled trials. Carbamazepine has been the traditional first-line anticonvulsant agent and is the only one the U.S. Food and Drug Administration has approved for management of pain (trigeminal neuralgia). The overall side effect profile of carbamazepine and the need for close monitoring of hematologic function are substantial drawbacks that make many pain clinicians reluctant to use this drug. At the present time in the United States, it appears that gabapentin is the anticonvulsant agent used most often for chronic pain. However, carbamazepine and gabapentin have very different mechanisms of action. Nonresponse to one agent probably has no predictive value for response to the other. For a patient with trigeminal neuralgia, the first choice will likely remain carbamazepine until proven otherwise. For all other chronic pain conditions, gabapentin is probably the first choice anticonvulsant because of demonstrated efficacy in large controlled clinical trials (postherpetic neuralgia, diabetic neuropathy, and migraine prophylaxis), anecdotal evidence for efficacy in a variety of other chronic pain states, ease of use, and its relatively benign adverse event profile. Dosing of most pain patients can be managed on clinical criteria alone. Blood levels are useful for monitoring compliance and toxicity. It is noteworthy that for carbamazepine up to 100% circadian variation in plasma levels have been demonstrated making interpretation of plasma levels difficult (74). Furthermore, published recommendation of plasma levels refers to seizure control, not pain control.

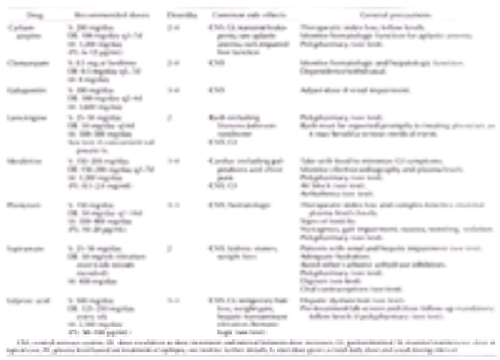

TABLE 86-1. Recommended total daily doses, number of daily doses, common side effects, and general precautions regarding the specific oral drugs reviewed in this chapter

Carbamazepine

Carbamazepine is the first-line drug for the treatment of trigeminal neuralgia and is the only anticonvulsant the U.S. Food and Drug Administration has approved for treatment of any neuropathic pain disorder. The primary mechanism of action underlying pain relief from carbamazepine is thought to be sodium channel blockade. In animal studies, carbamazepine reduces polysynaptic responses and posttetanic potentiation. Carbamazepine has not been thoroughly studied using current animal models of acute and chronic pain, but older studies showed a reduction in pain in cats subjected to repetitive infraorbital nerve stimulation. Like the local anesthetics lidocaine, mexiletine, and tocainide, carbamazepine reduces spontaneous activity in experimental neuromas (30). Controlled clinical trials with carbamazepine have produced mixed results. Success has been documented in trigeminal neuralgia and diabetic neuropathy but not in postherpetic neuralgia and central pain (69,75,76,77 and 78). Many other studies with carbamazepine in a variety of neuropathic pain disorders indicate efficacy but are small or uncontrolled, or both.

Side effects of sedation and unsteadiness can be prominent with carbamazepine, so therapy is best initiated with a very low dose of 100 mg twice daily. The dose should be increased in 100-mg increments every 7 days until either satisfactory relief is obtained or intolerance/toxicity appears. Only occasionally do total daily doses exceed 1,200 mg (divided t.i.d. or q.i.d.). For most patients, therapeutic plasma concentrations are between 6 and 12 mg per mL, although the occasional patient may require higher levels for stable pain control. In particular, trigeminal neuralgia patients may have exacerbations of pain requiring brief periods of higher than usual doses for control. Because of individual variation in the pharmacokinetics of carbamazepine and the fact that signs of toxicity appear near the upper end of the therapeutic range of plasma concentrations, it is important to carefully adjust the dose when initiating long-term therapy. Dose-related side effects include rash, fatigue, sedation, ataxia, vertigo, and blurred vision. Nausea and vomiting are also common. Rarely, rash may lead to erythema multiforme or Stevens-Johnson syndrome. A mild leukopenia occurs in approximately 10% of patients and persists in a quarter of these. Because of rare cases of irreversible aplastic anemia, approximately 1 in 15,000 persons exposed, regular monitoring of hematologic function is strongly recommended. Combinations of carbamazepine with other anticonvulsants, selective serotonin-reuptake inhibitor antidepressants, and oral contraceptives need careful monitoring because carbamazepine will affect blood levels of other drugs and vice versa.

Clonazepam

Clonazepam should be considered as a third-line drug for neuropathic pain. Unlike the other anticonvulsants reviewed here, clonazepam is structurally and pharmacologically related to the benzodiazepine family. There is only limited evidence for pain relief with other benzodiazepines (79) and strong evidence that benzodiazepines such as diazepam are not analgesic even when administered intravenously for up to 6 hours at a time (80). Max and coworkers (81) studied lorazepam, another benzodiazepine with anticonvulsant properties, in a double-blind crossover comparison with amitriptyline and placebo in patients with postherpetic neuralgia. Lorazepam was ineffective compared to amitriptyline. Other benzodiazepines with anticonvulsant activity, such as diazepam and lorazepam, have been specifically investigated in blinded clinical trials for neuropathic pain and found ineffective. The antiepileptic mechanism for clonazepam, although uncertain, is presumed to involve potentiation of inhibitory GABA neurotransmission. Reduction in pain intensity with clonazepam may be due to its antianxiety and antispasticity effects rather than to its anticonvulsant effect. Successful treatment of a variety of cranial neuralgias with clonazepam has been reported in uncontrolled studies that include a total of 46 trigeminal neuralgia patients and a small number suffering from sphenopalatine ganglion neuralgia, malignant skull base neuralgia, glossopharyngeal neuralgia, cluster headache, and phantom limb pain (82,83,84 and 85). Effective daily doses ranged from 3 to 8 mg.

The initial dose of clonazepam is usually 0.5 mg taken at bedtime. The dose is then titrated to effect by adding 0.5 mg every 5 to 7 days in a divided daily dose, two to four times per day. The maximum dose recommended for the treatment of epilepsy is 20 mg per day, but pain relief or intolerable side effects, usually sedation, should be apparent at doses below 8 mg per day. Clonazepam's elimination half-life is 18 to 39 hours. Catabolism is by first-order kinetics. Being a CNS depressant, acute toxicity of clonazepam may include confusion, somnolence, hypotension, and even coma. Patients should be warned that their ability to perform hazardous activities, such as driving, may be impaired. Transiently elevated serum aminotransferase and alkaline phosphatase, anemia, leukopenia, thrombocytopenia, and eosinophilia have all been reported. Periodic complete blood counts, platelet count, and liver function tests should be performed. Clonazepam should be discontinued with a gradual taper, as abrupt stoppage may result in severe withdrawal symptoms, including seizures. Because clonazepam is a benzodiazepine, patients with a history of substance abuse or alcoholism should be warned and monitored closely for signs of psychological dependence.

Gabapentin

The popularity of gabapentin for pain, likely exceeding that of all other anticonvulsants, appears to be due to ease of monitoring, a relatively low incidence of serious adverse events, and a perception of efficacy. Gabapentin was approved for marketing in the United States in 1995 as adjunctive therapy in the treatment of seizures.

Because of its apparently benign side effect profile and relative lack of drug interactions, gabapentin is currently entering widespread use for pain management. In some pain centers, gabapentin is being used as first-line therapy for all types of chronic pain. Several case reports and open-label clinical trials have reported analgesic efficacy of gabapentin in a variety of painful conditions (86,87). In a large retrospective review of charts, Rosenberg et al. (88) reported an analgesic effect of gabapentin in neuropathic pain, but not in low back pain. Two large, multicenter, double-blind, placebo-controlled clinical trials have demonstrated that gabapentin reduced pain from diabetic neuropathy (36) and postherpetic neuralgia (37). In another large study, gabapentin was reported effective for migraine prophylaxis (89).

Dosage recommendations for adults are a starting dose of 300 mg per day, increasing in 300-mg-per-day increments as tolerated up to total doses of 2,400 to 3,600 mg per day. Since gabapentin is absorbed via saturable active transport mechanism, four times daily dosing will produce higher blood levels than three times daily dosing. Because of the short half-life, doses should not be given more than 12 hours apart and discontinuation of the drug should be spread over 1 week (or longer). The dose must be adjusted in patients with renal failure, but no adjustment is necessary in patients with hepatic disorders because the drug is excreted unmetabolized. The most common side effects are related to CNS depression, such as dizziness, ataxia, and somnolence. Unlike carbamazepine, clinical trials do not indicate routine monitoring of clinical laboratory parameters is necessary for safe use of gabapentin, and gabapentin can be administered in addition to other antiepileptic drugs without concern of the serum concentration of gabapentin or other antiepileptics. Acute oral overdoses of up to 49 g have been reported without fatality.

Lamotrigine

Lamotrigine was approved for use as an add-on anticonvulsant in the treatment of partial seizures. Lamotrigine is similar to phenytoin and carbamazepine in blocking voltage-dependent sodium channels (90). Like other anticonvulsants suppressing ectopic impulse activity, central release of the excitatory transmitters glutamate and aspartate is reduced by suppressing abnormal peripheral input (91).

Animal data have demonstrated an analgesic effect of lamotrigine (38,92). In a study of postoperative pain, 200-mg single doses of lamotrigine reduced both postoperative pain and analgesic requirements (93). Large single doses of lamotrigine (300 mg) modestly suppressed pain during cold-pressor testing compared to placebo, but the effect was less than that observed with phenytoin and dihydrocodeine (94). So far, one double-blind, placebo-controlled study of the analgesic effect of lamotrigine has been published. In this small study, lamotrigine as an add-on therapy reduced daily pain in trigeminal neuralgia (95). Similar results have been

found in open trials of diabetic neuropathy (96) and trigeminal neuralgia (97). Furthermore, there are anecdotal reports of efficacy in both peripheral and central neuropathic pain conditions (98,99). In a placebo-controlled, double-blind trial, lamotrigine did not reduce migraine frequency (100).

Starting doses depend on other drugs being used concurrently, but standard recommendations suggest 50 mg per day for 2 weeks, then escalating to 100 mg per day, divided b.i.d. The dose can be escalated by 50 mg per day every 7 to 14 days to the usual maintenance dose of 300 to 500 mg per day, divided b.i.d. Lamotrigine is well absorbed from the gastrointestinal (GI) tract, with peak plasma levels in 1.5 to 5.0 hours. It is metabolized by glucuronidation and has a single-dose half-life of 24 hours. Unlike gabapentin, there are significant interactions of lamotrigine with other anticonvulsants. Concurrent use of carbamazepine and lamotrigine increases carbamazepine levels and can produce clinical toxicity. Valproate concentrations are decreased and lamotrigine half-life more than doubles when lamotrigine is used concurrently with valproic acid. Concurrent use of lamotrigine with phenobarbital, phenytoin, or primidone leads to shortening of the lamotrigine half-life because of induction of hepatic glucuronidation enzymes. Patients on concurrent valproate therapy require slower titration and should start on 25 mg every other day for 2 weeks, then 25 mg daily for 2 weeks, and then the dose can be escalated with 25 to 50 mg per day every 1 to 2 weeks to a maintenance dose of 100 to 150 mg per day, divided b.i.d.

Rash is the most common adverse effect, with up to 10% developing rash and 1 in 1,000 patients developing Stevens-Johnson syndrome (101). The incidence of rash is higher with fast dose escalation and when patients are on concurrent valproate. When lamotrigine treatment is started, the patients should be instructed that (a) rash may occur, (b) that it may herald a serious medical event, and (c) should rash occur, it must be reported promptly to their physician. Other adverse effects include dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting.

Lidocaine (Intravenous)

Administration of lidocaine, and its predecessor procaine, by the intravenous route has been reported since the 1940s (46) to produce dramatic pain relief in some patients. Although pain relief lasting several days to weeks is reported in rare cases, patients should be warned that even when significant analgesia is reported, pain typically returns to baseline within 1 to 2 hours. The abrupt return of pain in some patients may be interpreted as a pain exacerbation above baseline severity. The protocol used at the University of California, San Francisco, Pain Management Center is to administer lidocaine intravenously at a dose of 5 mg per kg over 45 minutes, without a bolus. In patients with normal hepatic function, end-infusion blood levels are approximately 1 to 3 mg per mL, the low antiarrhythmic range for lidocaine. The infusion may be continued at the same rate for an additional 15 to 30 minutes if pain relief is incomplete. Side effects are mild, and cardiovascular changes are minimal. Alternative methods of delivering lidocaine intravenously may be used. For instance, Marchettini (55) successfully used a 60-second injection of 1.5 mg per kg as a test procedure. Others have used computer-controlled infusion pump systems to target and maintain stable plasma lidocaine concentrations (102,103).

After an intravenous bolus of 50 to 100 mg, lidocaine antiarrhythmic effects begin in 45 to 90 seconds and last 10 to 20 minutes. The terminal phase half-life of lidocaine is 1.5 to 2.0 hours. Approximately 90% of an intravenous lidocaine dose is rapidly metabolized by the liver. Although serious adverse effects are uncommon with the administration of parenteral lidocaine, continuous electrocardiographic, heart rate, and blood pressure monitoring is required, and resuscitative equipment must be immediately available. The procedure should be used with caution in patients with hepatic insufficiency, sinus bradycardia, and incomplete heart block. An increase in ventricular rate may occur in patients with atrial fibrillation. If an arrhythmia develops or prolongation of the PR interval or the QRS complex occurs, the infusion should be discontinued. Intravenous lidocaine is contraindicated in patients with known hypersensitivity to amide-type local anesthetics, Adams-Stokes syndrome, and severe heart block. The most common side effects, albeit transient and dose-dependent, are associated with intravenous lidocaine's CNS effects. These adverse effects include drowsiness, dizziness, tremulousness, euphoria, blurring of vision, paresthesias, and dysarthria. In the doses normally used, lidocaine is an anticonvulsant. At high blood levels, usually exceeding 10 mg per mL, lidocaine may cause seizures. If a patient is concurrently taking another local anesthetic antiarrhythmic, adverse effects could appear earlier in the infusion. Cimetidine and propranolol each may diminish the systemic clearance of lidocaine, resulting in higher plasma lidocaine levels.

Although there is good evidence that intravenous lidocaine reduces pain in a variety of disorders, its usefulness in chronic pain management remains unclear (51,52). In a few patients, relief from each administration is sufficiently long lasting that they prefer periodic intravenous lidocaine to daily oral medications. The response to intravenous lidocaine partially predicts response to oral local anesthetics for arrhythmia control (104). The evidence that the lidocaine infusion test is useful in predicting response to analogous oral medications is limited to one small, blinded prospective study (61). In that study, subjects received random-order, double-blind infusions of lidocaine, 2 mg per kg and 5 mg per kg, followed by 4 weeks of open-label mexiletine, up to 1,200 mg per day. Although the response to mexiletine was significantly correlated with the overall response to the two doses of lidocaine, some lidocaine nonresponders responded to mexiletine. Finally, a lidocaine infusion may serve as a control for systemic spread of lidocaine following a successful regional nerve block. Because many nerve blocks produce very high blood levels of local anesthetic for a brief period, equivalent pain relief from a systemic lidocaine infusion suggests that the nerve block relieved pain due to systemic spread of the lidocaine.

Mexiletine

Structurally similar to lidocaine, mexiletine is a local anesthetic and a class IB antiarrhythmic. A randomized, double-blind, placebo-controlled crossover study by Dejgard et al. (47) showed that mexiletine significantly reduced pain, dysesthesias, and paresthesias in patients with chronic painful diabetic neuropathy. A second blinded study showed mexiletine to be especially beneficial in those diabetic neuropathy patients with pain descriptors of stabbing, burning, heat, and formication (49). An intermediate dose of 450 mg per day was felt best overall. In open-label trials, mexiletine has been reported effective for a variety of painful neuropathies, poststroke pain, multiple sclerosis pain, and phantom pain (105,106).

The initial dose is 150 mg or 200 mg once per day with food. The dose is then increased as tolerated by one capsule every 3 to 7 days up to a ceiling of 1,200 mg total per day, divided into three to four doses. Electrocardiography and plasma levels should be monitored closely at the higher doses. Mexiletine plasma levels peak in 2 to 3 hours. The elimination half-life is 10 to 12 hours, but in patients with abnormal liver function it may exceed 25 hours. Therapeutic plasma levels for antiarrhythmic effects range from 0.5 to 2.0 mg per mL. Plasma levels of mexiletine may be reduced with concomitant therapy with phenytoin, rifampin, and phenobarbital; cimetidine therapy may result in elevated mexiletine levels. Mexiletine is contraindicated in patients with preexisting second- or third-degree atrioventricular blockade, but patients with first-degree atrioventricular block may be treated safely. Hypotension and bradycardia may occur with overdosage. Mexiletine may worsen arrhythmias, but uncommonly affects less serious arrhythmias, such as frequent premature beats and nonsustained ventricular tachycardia. In less than 10% of patients, mexiletine may cause palpitations and chest pain. In controlled studies, upper GI distress occurs in 40%, and tremor, lightheadedness, and incoordination each occur in about 10%. GI effects can be reduced by taking the medication with meals, an antacid, or Carafate. Ataxia and seizures are reported to occur in 2 of 1,000 patients. Dose-limiting sedation and dysequilibrium appear to be less of a problem than with carbamazepine.

Other Oral Local Anesthetic Antiarrhythmics: Tocainide and Flecainide

Flecainide may be worth considering as an alternative therapy for neuropathic pain (107) if the use of mexiletine is limited by side effects. The use of mexiletine is, however, much more extensive for pain management. A third oral local anesthetic– type antiarrhythmic, tocainide, had accumulated evidence for efficacy in animal studies and in a double-blind clinical trial in trigeminal neuralgia (108). However, its use has been severely restricted because of a higher than expected incidence of aplastic anemia, exceeding that for carbamazepine.

Phenytoin

Phenytoin was the first anticonvulsant to be specifically used in pain management, but it is now rarely used. Uncontrolled studies totaling 49 patients reported phenytoin to be effective in the treatment of trigeminal neuralgia (109). Double-blind, placebo- controlled studies have demonstrated analgesia with phenytoin in diabetic neuropathy (110) and Fabry's disease (a small fiber neuropathy) (111), although a small trial by Saudek et al. (112) failed to demonstrate analgesia in diabetic neuropathy. Phenytoin is available for parenteral administration and can be used in patients who are having severe and frequent attacks of trigeminal neuralgia (113). In such patients, intravenous administration of phenytoin may provide immediate relief. There are no studies comparing parenteral phenytoin and lidocaine to determine which would be more useful in stabilizing uncontrolled trigeminal neuralgia.

Therapy is usually initiated as 150 mg per day (dosed t.i.d.), and maximum daily doses rarely exceed 450 mg per day. Phenytoin has complex kinetics. Because phenytoin progressively interferes with its own disposition, it is easy to precipitate toxicity with even small increases in dose. Signs of toxicity include nystagmus, gait impairment, nausea and vomiting, and sedation. Cardiac conduction effects at very high blood levels can be life threatening. Coadministration of other drugs can

affect the plasma levels of phenytoin and result in neurotoxicity. Furthermore, phenytoin can induce the metabolism of other antiepileptic drugs.

Topiramate

Topiramate has been used for seizure disorders since 1996, but there are no published clinical trials on the effect of topiramate as an analgesic agent. Topiramate is a carbonic anhydrase inhibitor and has been shown to reduce neuronal activity by voltage- dependent blockade of Na^+ channels, enhancement of GABA at $GABA_A$ receptors, and antagonism of the kainate subtype of the glutamate receptors. Based on the mechanism of action, some analgesic efficacy seems probable, and topiramate is occasionally used in the treatment of chronic pain.

Treatment should be initiated with 25 to 50 mg per day followed by weekly titration of 50 mg to effective analgesic dose. A period of up to 6 weeks to reach maximal tolerated dose is recommended. Doses for pain equivalent to treatment of seizure disorders, 400 mg per day divided in two doses, appears logical. Clinical trials for epilepsy have used daily doses ranging from 200 to 1,000 mg (114,115). Monitoring of plasma concentrations is not mandatory. In patients with renal impairment, one-half of the usual dose is recommended, and in patients with hepatic impairment, topiramate should be administered with caution as clearance could be decreased. Tapering should be done gradually to minimize the potential of increased seizure frequency. Psychomotor slowing, somnolence, and fatigue are prominent, and patient acceptance is better with slow dose-titration regimens. Adequate hydration is recommended, since 1.5% of subjects in clinical trials developed kidney stones. For obvious reasons, other carbonic anhydrase inhibitors should not be administered concomitantly. Topiramate also has the unusual side effect of producing weight loss in a significant proportion of patients. This differentiates the topiramate from nearly all other medications used for pain control. In clinical trials, subjects lost an average of 1.7% to 7.2% body weight depending on dose. Weight loss peaked after 15 to 18 months of therapy with partial return to pretreatment weight thereafter (Ortho-McNeil Pharmaceutical Co., *unpublished data*, 1996). Topiramate has been shown to affect the serum levels of coadministered antiepileptic drugs, and therefore, with polypharmacy, monitoring of serum levels of coadministered drugs as well as of topiramate is required. Administration of topiramate to patients receiving digoxin requires careful monitoring of serum digoxin levels, since topiramate may reduce serum digoxin levels. Furthermore, the efficacy of oral contraceptives may be compromised by topiramate administration.

Valproic Acid

Valproic acid and divalproex sodium are structurally unrelated to any of the other anticonvulsants. Valproic acid is most often prescribed as divalproex sodium (Depakote), an equal combination of valproic acid and sodium valproate. Its analgesic mechanism of action is unknown, but valproic acid is known to increase GABA-ergic neurotransmission and increase brain GABA. Furthermore, excitatory amino acids in brain are reduced by valproic acid (116).

Valproic acid has proved useful in the prophylaxis of migraine in controlled clinical trials (for review, see 117). Limited data exist for the analgesic efficacy of valproate for neuropathic pain and other types of nonheadache pain. One study found no effect of valproate in central pain compared to placebo (118) (only amitriptyline has been reported effective for this condition). In an open- label study, Peiris et al. (119) reported partial or complete control of trigeminal neuralgia in nine of 20 patients with valproic acid in doses of up to 1,200 mg per day. No plasma level therapeutic range has been established for pain control with valproic acid. Similar to the treatment of seizures, the starting dose for the treatment of pain is 250 mg twice per day and the dose is gradually titrated to effect, with a recommended maximal dose in migraine prophylaxis at 1,000 mg per day. Valproate should not be administered to patients with hepatic dysfunction and should be discontinued if signs of dysfunction appear. Side effects and potentially serious toxicity have greatly limited the use of valproic acid for chronic pain. The combination of sedation, GI side effects, hair loss (usually reversible), abnormal liver function tests, potentially fatal hepatotoxicity, inhibition of platelet aggregation, and numerous other potential hematologic and nonhematologic effects makes pretreatment screening and close follow-up mandatory. When concomitant therapy is initiated, clinical status and plasma concentrations should be carefully monitored because changes in metabolization may affect the serum concentration of antiepileptics with polytherapy.

FUTURE DEVELOPMENT OF ANTICONVULSANTS AND LOCAL ANESTHETIC DRUGS

The dose-limiting side effects involved in the systemic use of Na^+ channel blockers include sedation, ataxia, vertigo, blurred vision, nausea, and vomiting. All are CNS effects. It is very often dizziness and loss of alertness that limit titrating to higher, and possibly more effective, analgesic doses. Another potential approach to avoiding dose-limiting CNS toxicity would be to produce a carbamazepine or lidocainelike agent in a form that preserves membrane-stabilizing properties of the parent drug but does not cross the blood–brain barrier. No such drug exists at present. Pharmacologic agents that block Na^+ channels by binding to the extracellular mouth of the channel are known and used widely in basic neuroscience research (e.g., TTX and saxitoxin). They differ from the local anesthetics and anticonvulsants, however, in that their potency does not depend on the firing rate of the neuron (i.e., they are not use-dependent blockers), but are highly toxic substances. Finally, mention should be made of the likelihood that the ectopic neural activity underlying neuropathic pain may be due to a dynamic redistribution of pain-specific Na^+ channels, Na^+ channel molecules subtly different from those present in low threshold afferents and those present in the heart and the brain. This difference might permit the creation of novel Na^+ channel blockers that selectively target and silence nociceptors. The success of drugs acting by mechanisms other than sodium channel blockade, most notably gabapentin, indicates much future potential for analgesic/anticonvulsant drugs.

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CHAPTER 87

Topical Medications

Bradley S. Galer

BASIC INFORMATION

Topical medications (Table 87-1) are applied directly on the painful body area, where they penetrate the skin. A topical medication's site of activity is in the peripheral tissues, including soft tissue and peripheral nerve, directly underlying the site of application. Topical drugs, formulated as a gel, cream, liquid, or patch, should not produce any clinically significant systemic drug concentration.

	Topical	Transdermal
Application site	Skin: directly on painful skin	Skin: distant from painful region
Site of activity	Peripherally (soft tissue, nerve)	Systemically
Serum drug concentration	Insignificant	Necessary
Systemic side effects	No	Yes
Titration needed	No	Yes
Drug-drug interaction	No	Yes

TABLE 87-1. Topical versus transdermal drug delivery

Transdermal medications, on the other hand, are also applied directly to the skin, but the site of drug application can be distant from the area of pain (currently available transdermal drugs include fentanyl and clonidine). Transdermal drugs' sites of activity are not local but via a systemic effect. The medication of transdermal delivery systems is typically contained in a pooled reservoir within a patch, which is designed to push drug directly into the bloodstream. Therefore, unlike topical medication patches, a transdermal patch cannot be cut into different sizes.

Therefore, the key difference between topical and transdermal drug delivery systems is that a topical medication does not result in any clinically meaningful blood levels, whereas a transdermal drug must result in clinically effective serum concentrations for its clinical effect.

History

Applying medicinal substances directly on the skin is likely one of the oldest routes of administration. Ancient cultures ground herbs and plants into pastes for medical uses, including the treatment of pain. Over the past century, many tonics, gels, salves, and lotions have been sold as over-the-counter remedies for pain, although most have little to no scientific study to back their claims (e.g., “snake oils”). Many of these older topical medicinal products may in fact act only as counterirritants—that is, they produce a mild to moderate noxious stimulus that then suppresses the perception of the pain.

Only in the past few decades has the pharmaceutical industry begun to develop topical drugs for the treatment of pain with the aim of producing products with proven efficacy. However, even at the time of this writing, the commercial availability of topical pain medication with controlled clinical trial evidence of efficacy remains sparse. Yet, much development and clinical trial study are currently under way, with the promise of safe and effective topical drugs for the treatment of many acute and chronic painful conditions.

Theoretical Bases

Mechanisms of Action

Because topical drugs, by definition, must act locally on dysfunctional or damaged soft tissues or peripheral nerves, all abnormal pathophysiologic events within the periphery that generate or maintain pain are potential targets for these medications. In acute pain syndromes and arthritic conditions, topical drugs may play a role in reducing the inflammatory response and concurrent sensitization of nociceptors. In chronic neuropathic pain, abnormal neuronal activity generated by abnormal impulse generation secondary to upregulated sodium channels or a-adrenergic receptors is a potential target, as is the ongoing neurogenic inflammatory response.

Clinical Advantages

Theoretically, topical drugs' activity should be solely at a site of pain generation, unlike oral and other systemic drugs that first need to enter the bloodstream before they arrive at the necessary site of action. Therefore, because topical drugs do not result in any clinically significant serum levels, adverse reactions are limited to those produced by local reaction, such as allergy or skin rash. Most of the currently prescribed oral and transdermal medications for pain, both acute and chronic, are hampered by their systemic side effects. With nontopical agents, it is most often necessary to titrate the dosage to effect, either pain relief or intolerable side effect; unfortunately, the latter often occurs resulting in an aborted drug trial and the patient still suffering from pain.

Another advantage to topical agents is their lack of drug-drug interactions, again due to their lack of systemic activity. The potential for drug-drug interactions is common in many patients with chronic painful conditions, such as the elderly with arthritis or postherpetic neuralgia (PHN), and those suffering from painful neuropathies, such as diabetic and human immunodeficiency virus (HIV) patients.

When treating chronic pain conditions, treatment with oral agents requires slowly titrating the dose until either significant pain relief or intolerable side effects are reported by the patient—a time-consuming procedure that may take weeks or even months. The time to a noted effect with topical agents, on the other hand, usually is on the order of days. Thus, yet another advantage to topical drugs is the significant amount of time saved with no need to titrate the dose over several weeks or

more.

An additional important advantage of topical drugs is their ease of use. Patients either need to apply a liquid, cream, or gel several times a day or, with some preparations, apply a patch once or twice a day.

Clinical Information

Indicated Pain Conditions. Clinical conditions associated with pain in which a topical agent may have potential efficacy include both acute and chronic pain states. Acute pain conditions suitable for topical pharmacotherapeutic intervention include acute soft tissue injuries (e.g., sprains, strains, and contusions), postsurgical pain, and acute herpes zoster (shingles). Chronic nonmalignant pain states appropriate for topical drug treatment include arthritic conditions and chronic peripheral neuropathic pain conditions, such as PHN, diabetic polyneuropathy, HIV neuropathy, idiopathic neuropathy, complex regional pain syndromes, stump pain, and other neuroma pains.

Medication Classes. Currently only a few agents are commercially available for the treatment of pain, including nonsteroidal antiinflammatory agents, capsaicin, and local anesthetic agents. However, several new topical drugs—using different topical formulations, with a new active medication ingredient, or both—are actively being investigated (at the time of this writing), and it is hoped that they will prove efficacious in the not too distant future for the treatment of a variety of acute and chronic pain conditions.

Several different topical formulations may be available within the same medication class, which may differ significantly with regard to efficacy and side effect profile. Such different topical drugs in the same class may differ in several clinically significant ways, including (a) the actual active medication being delivered; (b) the topical vehicle formulation's ingredients, which affect skin penetration and drug delivery; and (c) the application form in which the drug is available, such as liquid, gel, salve, or patch/ plaster. Each of these three factors has vastly important relevance with regard to the topical drug's efficacy and adverse events (Table 87-2).

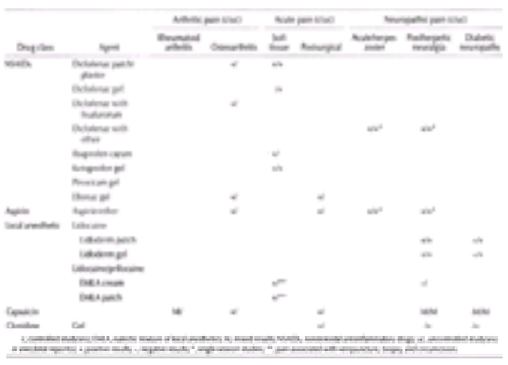

TABLE 87-2. Controlled and uncontrolled studies assessing the efficacy of topical drugs for the treatment of pain

DRUGS

Nonsteroidal Antiinflammatory Drugs

Of all of the drug classes, the nonsteroidal antiinflammatory drug (NSAID) class has the most studied and currently available different topical drug formulations that are commercially available or under investigation. Many different NSAIDs with vastly different vehicle formulations have been assessed in mostly acute pain syndromes and arthritic conditions.

Mechanism of Action

NSAIDs traditionally have been thought to have their primary mechanism of analgesic activity in the periphery, specifically via their inhibition of prostaglandin synthesis. However, a dissociation between the degree of pain relief of certain NSAIDs and their actual antiinflammatory effects suggests other important analgesic mechanisms of activity (1), including other peripheral effects, such as inhibition of the lipoxygenase pathway, inhibition of excitatory amino acids, and effects on G protein–mediated signal transduction (2).

Topical NSAIDs may also have direct effects on damaged and dysfunctional peripheral nerves. Topical NSAIDs theoretically could reduce primary afferent sensitization occurring as part of a localized abnormal neurogenic inflammatory response (3). An animal study of rabbit corneal nerve injury reported a significant reduction of abnormal neural activity and mechanosensitivity after application of topical diclofenac (4).

Clinical Trial Data

Acute Pain. Topical NSAID treatment has been studied for several clinical conditions associated with acute pain, including minor sports injury pain, postsurgical pain, and ophthalmic pain. A multicenter, randomized, double-blind, placebo-controlled study of acute sports injury pain found significant reductions of pain over a 2-week period with a diclofenac patch/plaster (5). An open-label study observed a 60% reduction in pain with this diclofenac patch/plaster in traumatic sport and overload injuries (6). Similar controlled studies in acute soft tissue injuries revealed significant reductions in pain over the first 48 hours with an ibuprofen cream (7) and over 7 days with ketoprofen gel (8). An open-label uncontrolled study comparing several different topical gels for acute soft tissue injury pain observed that diclofenac gel and ketoprofen gel were similar in efficacy, whereas piroxicam gel was less effective (9).

A double-blind comparative study assessed piroxicam gel applied preoperatively to patients undergoing an inguinal repair, local anesthetic inguinal block, and no treatment and reported that both the topical NSAID gel and the nerve block similarly reduced pain scores, time to first analgesic, and total opiate consumption as compared to the no-treatment group (10). Double- blind controlled studies have assessed topical NSAIDs for the treatment of acute pain associated with traumatic corneal abrasions and found significant reductions in pain (10,11 and 12). A study has also reported significant pain reduction with topical diclofenac treatment for postoperative pain associated with phototherapeutic keratectomy (13).

Arthritic Pain. A large randomized, multicenter, double-blind, 4-week study compared topical eltenac gel with oral diclofenac and placebo in patients with osteoarthritis of the knee and found that both active treatments were significantly better than placebo in reducing pain only in patients with severe symptoms, but that the number of gastrointestinal adverse reactions were three times higher in the oral NSAID group as compared to the topical NSAID group (14). Controlled studies demonstrated efficacy of a topical diclofenac in hyaluronan for the treatment of osteoarthritis (15,16 and 17). Placebo-controlled studies have reported significant reductions in pain with topical diclofenac plaster (patch) in patients with osteoarthritis of the knee (18), and inflammatory peri- and extraarticular rheumatologic diseases (19). After several days of diclofenac plaster application in patients with monolateral knee joint effusion, low levels of diclofenac were measurable in the synovial fluid without producing elevated serum levels (20). An open-label uncontrolled study reported topical flurbiprofen patches provided significantly better pain control as compared to oral diclofenac with significantly fewer gastrointestinal side effects after 2 weeks of treatment in patients with “soft-tissue rheumatism” (21).

Neuropathic Pain. A single-session, double-blind, cross-over study reported significant pain reduction for the treatment of both acute herpes zoster and PHN with a topical diclofenac/diethyl ether mixture with no significant side effects (22). This same study reported that an indomethacin/diethyl ether topical mixture was not superior to placebo in a single-session protocol. Another single- session study observed significant pain reduction in patients suffering from PHN with hydrous stupes (topical patches) containing indomethacin, ketoprofen, or flurbiprofen (23). However, no long-term efficacy studies with topical NSAIDs have been published for the treatment of either acute herpes zoster or PHN. No studies have assessed the use of topical NSAIDs for other peripheral neuropathic pain conditions.

Aspirin

Although no commercially produced form of topical aspirin is available at the time of this writing, several studies have reported the results of compounded formulations of topical aspirin for the treatment of pain associated with herpes zoster.

Mechanism of Action

Like the topical NSAIDs, topical aspirin may alleviate pain by affecting the inflammatory response and, at least theoretically, in neuropathic pain states by reducing neurogenic inflammation.

Neuropathic Pain

A double-blind, placebo-controlled, single-session clinical trial demonstrated statistically significant pain relief in patients with acute herpes zoster and PHN after application of a topical aspirin/diethyl mixture (24). In addition, several open-label studies have described pain reduction in PHN using topical mixtures of aspirin and chloroform or diethyl ether (25,26). No controlled study has assessed the long-term benefits and side effects with topical aspirin formulations.

Local Anesthetics

Over the past decade, two commercially produced forms of topical local anesthetics have extensively undergone the rigors of placebo-controlled clinical trials testing, Lidoderm gel and patches and EMLA (eutectic mixture of local anesthetics, 2.5% lidocaine and 2.5% prilocaine) cream and patch. To date, both products have proven efficacy for different clinical pain states, Lidoderm for peripheral neuropathic pains and EMLA for acute pains associated with invasive procedures, such as venipuncture. Other topical formulations of local anesthetics have also been reported for the treatment of acute pain states.

Mechanism of Action

Local anesthetic drugs applied topically are thought to provide pain relief by reducing ectopic discharges in superficial somatic nerves, which are damaged and dysfunctional in neuropathic pain states and are normally active in acute injuries, such as venipuncture. It is not necessary to produce a total anesthesia of the skin to produce clinically significant pain relief in chronic neuropathic pain states. Animal models of neuropathic pain have shown significant reductions in the abnormal tonic, evoked, and ectopic activity in damaged peripheral nerve with local anesthetic concentrations dramatically below that which blocks impulse conduction (27,28). In addition, a topical patch, such as the Lidoderm patch, has been shown to have an added benefit of protecting allodynic skin from direct mechanical stimulation and thereby of reducing an allodynic patient's pain (29,30).

Neuropathic Pain

A large multicenter, placebo-controlled, double-blind study reported significant pain relief with 4 weeks of lidocaine patch (Lidoderm) use in patients with long-standing PHN and mechanical allodynia (30). Another controlled trial in PHN, using an enriched enrollment crossover design, demonstrated that long-term lidocaine patch users (mean duration of patch use was 3.3 years; mean duration of PHN 7.3 years) preferred the lidocaine patch to the placebo patch, 78% versus 9% (p <.001) (31). In addition, several double-blind, placebo-controlled, single-session studies have reported Lidoderm, both the gel and patch formulations, to be effective in significantly reducing the pain of PHN without any significant side effects (32,33 and 34). Lidocaine serum levels after use of this gel and the patch formulation are an order of magnitude below antiarrhythmic serum levels and are thus very safe, even in patients with cardiac conditions (29,30,33).

A randomized controlled trial of topical lidocaine gel and patches for the treatment of painful diabetic neuropathy showed clinically significant reductions in pain with both the active and placebo treatments in the vast majority of subjects but no statistical difference between the two treatments (Galer BS, Gianis A, *unpublished results,*1988). Of interest, the vast majority of subjects in this study continue to use the lidocaine patch or gel in a compassionate use protocol with clinically meaningful reductions in pain, even if they responded to the placebo treatment in the controlled study. Anecdotal evidence also suggests this drug may be useful for the treatment of other peripheral neuropathic pains, such as idiopathic polyneuropathy, painful mononeuropathy, stump pain, reflex sympathetic dystrophy, and painful HIV neuropathy (35,36).

Long-term efficacy appears to be maintained for this new topical lidocaine preparation. PHN and diabetic neuropathy patients who have applied Lidoderm for several years report continued pain relief, with some patients noticing a decrease in the size of the painful region and others needing to apply the topical medication less and less frequently. No significant acute or chronic side effects have been observed.

The other commercially available formulation of topical local anesthetic, EMLA, has failed to demonstrate efficacy superior to placebo (37).

Acute Pain

Controlled studies have reported EMLA cream applied under an occlusive dressing for 60 minutes reduces pain associated with venipuncture (38,39), intramuscular saline injections (40), spinal needle insertion (41), excisional biopsy or curettage with electrosurgery of cutaneous lesions (42), and pain from circumcision in neonates (43). A patch impregnated with EMLA was also shown to reduce pain associated with a skin biopsy in children (44) and venipuncture pain in adults (45).

A controlled comparative study of volunteers undergoing intravenous catheterization reported that liposome-encapsulated tetracaine provided more effective pain relief than EMLA cream after 60 minutes' application time, although the tetracaine also caused more erythema than the EMLA (46). Topical proparacaine was shown in a double-blind study to reduce the pain after photorefractive keratectomy (47). A double-blind study reported equally effective pain reduction with the use of topical bupivacaine- adrenaline-cocaine and topical tetracaine-adrenaline-cocaine mixtures for pain associated with wound suturing (48). A double-blind study assessed the efficacy of topical local anesthetics for pain associated with suturing lacerations in children and concluded that topical prilocaine-phenylephrine plus tetracaine-phenylephrine (tetraphen) was as effective as topical tetracaine-adrenaline-cocaine (49).

Capsaicin

Mechanism of Action

Capsaicin is an over-the-counter drug composed of an extract of chili peppers. It has been postulated that capsaicin selectively stimulates and then depletes substance P from nociceptive primary afferents and thus may produce pain relief in certain chronic pain states. However, this physiologic activity has not been definitively proved to be the mechanism of action of currently available capsaicin products. An animal study of experimental polyarthritis has noted that pretreatment with capsaicin significantly attenuated joint swelling and radiologic and histologic measures of arthritic changes, suggesting that capsaicin may directly suppress inflammation (50). Moreover, capsaicin produces a counterirritant effect in a majority of patients by causing a mild to severe burning on application, which may also be a potential therapeutic pain mechanism. (Because of this commonly occurring burning on application, placebo-controlled trials of capsaicin should be interpreted with caution since both subject and researcher are unblinded when this occurs.)

Neuropathic Pain

Topical capsaicin has been studied in PHN and painful diabetic neuropathy with mixed results. In PHN, several studies have reported reductions in pain (51,52,53 and 54), whereas others have not (54). Similarly, controlled studies in painful diabetic neuropathy have also resulted in both negative and positive findings. A randomized controlled trial of 0.075% capsaicin in painful diabetic neuropathy showed no benefit (55). Another controlled study using 0.075% capsaicin in painful diabetic neuropathy reported improvement in pain with capsaicin, although an intent-to-treat analysis was not performed (56). A controlled trial using an active placebo (a topical substance that also produced burning on application but had no pain-relieving capabilities) reported no difference between capsaicin and this active placebo in patients with a variety of painful polyneuropathies (57). One small controlled study reported topical capsaicin reduced the pain of postmastectomy syndrome (58).

Unfortunately, currently available formulations of capsaicin have been disappointing clinically as an analgesic agent for all neuropathic pains (59). Currently, most

authorities rarely prescribe the drug for the treatment of neuropathic pain due to its overall poor efficacy and the high proportion of patients who complain of a worsening of their pain with drug application.

Arthritis Pain

Two controlled studies have demonstrated efficacy and safety for the use of topical capsaicin in the treatment of arthritis pain. A small double-blind, placebo-controlled study concluded that capsaicin significantly reduced hand pain from osteoarthritis but not pain from rheumatoid arthritis (60). However, a large double-blind study of arthritic knee pain reported significant pain relief in both rheumatoid arthritis and osteoarthritis, with more relief reported by rheumatoid arthritis subjects (61).

Clonidine

At the time of writing, no topical clonidine product is commercially available. However, a new formulation of a topical clonidine gel is being studied for a variety of neuropathic pain states.

Mechanism of Action

Clonidine is an a_2-adrenergic partial agonist. Alpha-2 receptors are autoreceptors located on the sympathetic nerves' terminals, which when activated inhibit their release of norepinephrine. Several lines of evidence suggest an abnormal adrenergic sensitivity in peripheral neuropathic pain states. For instance, locally infused adrenaline results in a worsening of pain and allodynia patients with reflex sympathetic dystrophy (62) and PHN (63). In addition, animal models of peripheral neuropathic pain have shown that injured neurons are sensitive to adrenergic activity, that is, an increase in ectopic impulse generation occurs in response to sympathetic agonists and to activation of postganglionic sympathetic efferent axons (64). Moreover, this adrenosensitivity appears to be an inherent property of the injured somatic peripheral nerve (65). Thus, application of clonidine topically may reduce release of norepinephrine from sympathetic nerve terminals, thereby alleviating the abnormal ectopic firing resulting from the dysfunctional nerve's adrenosensitivity, and, at least theoretically, result in clinically meaningful reductions in pain and allodynia.

Neuropathic Pains

No controlled studies have been performed using a topical form of clonidine, at the time of this writing. However, uncontrolled pilot studies have been performed assessing different concentrations of this new formulation of topical clonidine gel for the treatment of PHN, complex regional pain syndrome type I, and painful diabetic neuropathy. These open-label studies have observed improvement in pain and hyperalgesia in some patients (66). Controlled trials with topical clonidine gel are being planned.

One uncontrolled case series assessed the efficacy of transdermal clonidine patch (Catapres) in four patients with “sympathetically maintained pain” and two with “sympathetically independent pain” (67). This series observed that the patients with sympathetically maintained pain obtained complete relief of hyperalgesia only in the localized skin region under the patch but no change in the spontaneous ongoing pain, whereas no pain relief at all was noted by the two patients with sympathetically independent pain.

CONCLUSIONS

Theoretically, topical drugs have many clinically relevant advantages over other pharmacotherapeutic drug delivery systems, such as oral, transdermal, and intrathecally delivered drugs. By applying a drug directly to the skin, where it penetrates and acts directly at a site of pain generation without the need for systemic activity or invasive procedure, topical medications have the promise of producing pain relief with few side effects and little risk and cost. In the past, the question plaguing topical drug delivery has been whether clinically meaningful degrees of pain relief can be achieved with topical administration. Controlled clinical trials have demonstrated efficacy for a variety of topical drugs and topical formulations, such as NSAIDs' treatment of acute soft tissue injury and arthritis and topical local anesthetics' treatment of chronic peripheral neuropathic pains and acute pain associated with invasive procedures. The future looks bright for topical drug delivery, with many newer topical agents being studied for the treatment of both acute and chronic pain conditions. Because of their efficacy, safety, quick time of onset, and ease of use, topical medications should be considered first-line agents for the treatment of many pain states.

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CHAPTER 88

Operant or Contingency Therapies

Wilbert E. Fordyce

This chapter concerns the use of contingency management (CM) procedures in the treatment of chronic pain. It builds on the overlapping topics discussed in Chapter 25, Chapter 89, and Chapter 109. *Contingency management* refers to a set of methods for helping patients and practitioners to change behavior. Although the terms *contingency management* and *operant conditioning* are essentially interchangeable, the former term fits more closely the focus of this chapter. CM is a method not for treating pain per se but rather for helping patients to modify pain behaviors and related activities or actions. CM can also be viewed as a method for rehabilitating pain patients by increasing functional performance in daily life. More detailed accounts of these concepts and procedures can be found in Fordyce (1), Sanders (2), and Baer (3).

A conceptual perspective underlying CM has been described by Brady (4, p. 31) as follows:

> . . . health related processes interact in profound and enduring ways with environmental circumstances and behavioral activities. . . . Conceptually, the roots of this behavioral perspective . . . can be identified with the fundamentals of environmentalism, which has two main features. The first of these is that knowledge comes from experience rather than from innate ideas, divine revelation, or any other obscure source. And the second holds that action is governed primarily by consequences rather than by instinct, reason, will, cognitions, beliefs, attitudes, or any of the myriad explanatory fictions that appear to have been created out of whole cloth by the magic of the human language.

This perspective is more extreme than the viewpoints I have expressed in Chapter 25; it is also narrower than that used elsewhere in this text.

This chapter presents principles of CM technology and then describes a format for its use. The applied elements address the use of behavioral principles in exercise and reactivation, managing analgesics and interpersonal interactions regarding pain and well behaviors.

OVERVIEW AND RELATION TO OTHER METHODS

Optimal treatment of chronic pain is a multimodal process. No single, narrowly based intervention is likely to bring about comprehensive and lasting change in long-established pain problems. This holds true whether the therapy involves surgery, medication, or such noninvasive modalities as ultrasound, traction, massage, CM, or cognitive-behavioral methods, the last two of which are somewhat complementary (see Chapter 89). The application of CM techniques to the modification of pain behavior and other associated behaviors should almost always be done in conjunction with other modalities. In particular, the effects of these procedures can be enhanced by addressing the profound misunderstandings patients often have about the nature of pain, the healing process, and the adverse effects of disuse and prolonged use of analgesics. The importance of responses of the world to pain behaviors makes it worthwhile to change these behaviors.

There is a synergistic relationship between CM methods and didactic or teaching methods. In chronic soft-tissue injury pain and some other pain problems, the symptom, pain behavior, often has become the problem: disability. CM is a technology that may be used to help change pain behavior—that is, change disability. The behaviors targeted for change are themselves influenced by anticipations. Anticipations can be viewed as meanings attached by patients to cues or stimuli encountered (i.e., the events expected to follow the cues or stimuli perceived). A patient anticipating adverse or painful consequences when using a body part or assuming a particular position is more likely to display pain behaviors, either before the action is undertaken to forestall anticipated pain and suffering or shortly thereafter. Thus, any intervention that helps to influence anticipations is relevant.

Information about pain, healing, and the effects of disuse is likely to influence what a patient anticipates. Information by itself, however, is rarely an effective way to change established behaviors. If it were, providing chronic pain patients with brochures or other materials that explain clearly the rapid nature of the healing process, the adverse effects of disuse, and how properly designed motion can promote healing would suffice to modify most pain behavior patterns. Of course, such an approach does not work any more than providing inveterate smokers with information about the adverse effects of smoking results in cessation of smoking. Relevant information can, however, promote a readiness to undertake treatment and reactivation (see Chapter 94).

Pain behaviors relating to body action are best altered by exercising and increasing activity. Cognitive components, including information, may facilitate change of pain behaviors but, in the case of chronic pain, are unlikely to be sufficient. Conversely, effectiveness of CM methods may be lessened considerably if a patient's readiness to participate is hampered by anticipating adverse consequences to becoming reactivated.

CM involves the use of environmental consequences in a studied way to help a person to modify behavior. It involves analyzing which environmental consequences support the strength or weakness of the behavior of interest and then changing those consequences to others that will support a different pattern of behavior. Cognitive-behavioral methods, while implicitly and often explicitly using systematic environmental contingencies as part of its treatment strategy, attach more focus on helping to modify patients' perceptions or labeling of sensations and, as a result, the behaviors to which they lead. Both approaches strive to make clear to patients and families that hurt and harm are not the same and that, once healing time has passed, using painful body parts is an important way to make them better. As noted, this is accomplished by providing information but also, more important, by providing for learning by doing.

CM and cognitive-behavioral methods clearly overlap and are sometimes indistinguishable. The labeling of sensations and perceptions and guided ways of seeking to change those has a particular relevance to recent onset or acute pain. A focus on environmental contingencies becomes more important in chronic pain.

TERMINOLOGY AND PRINCIPLES

The intent here is to describe methods by which CM can be applied to modification of pain behaviors. This is not an exhaustive review of CM technology. The level of detail provided should, however, be sufficient to permit clinical applications.

Three interlocking tenets form the foundation of CM. More complete accounts of what follows can be found in references 1, 2, and 5.

1. *Behavior* refers to specific actions or movements—not general classes of behavior and not thoughts or feelings;
2. Behavior is sensitive to consequences. Therefore, the rate or strength of a behavior tends to increase when followed by positive reinforcement or to decrease when followed by negative consequences or the absence of positive reinforcement.
3. There are no inherently reinforcing or nonreinforcing consequences. Reinforcing or nonreinforcing properties are defined by the particular past experience of the

person.

Behavior

Behavior refers to a specific action or pattern of activity elicited by a discrete stimulus or by a stimulus constellation such as cues present in a specific social setting. Behavior sequences occur or cease in response to environmental cues, which indicate the time and place of reinforcement, punishment, or extinction (absence of reinforcement) contingencies. Behaviors are considered strong if they occur frequently and weak if they are infrequent.

Specificity is essential in describing behaviors to be changed. For example, acting honestly is a general behavior; answering a particular question truthfully is specific. In the context of clinical pain, to say that a patient manifests pain behaviors is broad and vague. Limping, avoiding flexing forward, and asking for analgesics are specific behaviors that can be targeted for change.

One should first identify which specific behaviors are occurring excessively (e.g., reclining, taking medications, limping), too infrequently (e.g., walking, working, gardening), or not at all. Noting that a patient is “not moving enough” is too general. Noting that a patient walks less than 500 feet per day, avoids flexing forward, or is taking analgesics six or more times per day is more specific. (For more detailed discussion of behavior, see Chapter 25.)

Reinforcement

Definitions of what is or is not reinforcing for a person are empiric and circular. A reinforcing consequence is one that, when programmed to occur rapidly, contingent on, and systematically after the behavior of interest, increases the rate of the behavior it follows. Conversely, rate of a behavior is decreased by arranging that it no longer is followed by the consequence previously reinforcing it or by effectively reinforcing a behavior incompatible with it. Limping or grimacing, if followed systematically by special attention, sanctioned rest, or provision of analgesics, is likely to strengthen or increase in frequency. Limping or grimacing in relation to a healed injury if no longer followed systematically by those consequences is likely to diminish in strength or frequency of occurrence.

The strength of a behavior also tends to diminish if effective reinforcement becomes contingent on occurrence of a behavior incompatible with the one to be reduced. The difference between this approach and that of withdrawing reinforcement is illustrated by two very different methods for reducing excessive reclining in a deactivated pain patient. Suppose, for example, that a spouse tends to provide special supportive attention when the patient reclines at a time when, were there no pain problem, he or she would be active. Whatever the intent of the attention, the spouse is probably positively reinforcing reclining and that behavior may become more persistent. One method for applying CM-based methods for changing behavior—in this case, reclining—is to help the spouse to avoid being especially attentive when adverse reclining is occurring. If the spouse is an influential person to the patient, adverse reclining is likely to diminish. There is a different and often better way to go. It is usually easier to increase or accelerate a behavior than to decrease or decelerate it. Therefore, focusing on increasing walking, a behavior incompatible with reclining, may be more effective. The practitioner should see to it that positive reinforcement becomes contingent on walking. Walking is likely to increase and, conversely, reclining to decrease. A pain behavior is being reduced and reactivation is being facilitated.

Selection of Reinforcers

What consequences are likely to be reinforcing? This is determined not by some preordained state of affairs but by the particular history or experience of the person. Money, for example, is not always reinforcing to everyone or to an individual in every situation.

There is a straightforward answer to selection or determination of reinforcers that usually works and that one may program as consequences to help change behavior. Observation of what a person does frequently points to what is reinforcing. This is the Premack principle (6), the essence of which is that high strength behaviors may be used to reinforce low strength behaviors. By the nature of things, what a person does frequently is likely to occur because the activity is reinforcing. Similarly, what a person does infrequently is likely not to be reinforcing and may even be aversive. For a person who often reclines, rest is quite probably a potentially effective reinforcer. For a restless person, one who tends to keep moving, activity is likely to be reinforcing and rest aversive.

In treatment settings, rest, attention, and time out from aversive activities are all likely to be effective reinforcers and have the further advantage of being readily available and logistically simple to program. An example will illustrate application of the Premack principle. Let us assume that a given chronic low back pain patient reclines often and almost always avoids vigorous activity. We shall suppose that neuroanatomic or pathophysiologic reasons for not undertaking reactivation are no longer sufficient to warrant deactivation. For that patient, rest is likely to be reinforcing, perhaps also attention or pain behavior-contingent social regard. In addition, exercise or vigorous walking is, in his or her present deactivated state, probably aversive. Sanctioned time out from those activities is therefore also likely to be highly reinforcing. A detailed format for putting these circumstances together to promote reactivation is set forth later in this chapter.

Scheduling of Reinforcement

To be effective, reinforcement must occur promptly and be contingent on completion of the behavior it is designed to reinforce. For example, therapist approval withheld until the end of an hour-long physical therapy session is usually too long a delay. Patient performance should be closely monitored during early treatment sessions, and therapist response should be expeditiously expressed. Later, as progress occurs, therapists may be able to ease the level of monitoring and promptness of reinforcement.

Reinforcing each occurrence of a target behavior is known as *continuous reinforcement*; reinforcing only some occurrences of the behavior is known as *intermittent reinforcement*. Continuous reinforcement, although rarely fully attainable, is useful in early stages of a conditioning process to help “jump-start” the behavior.

Reducing the frequency of reinforcement is desirable and usually logistically necessary (1,5,7). Continuous reinforcement tends to lead to satiation and ultimate reduction in strength of the target behavior to the point of extinction. Intermittent reinforcement is more durable. The ratio between occurrence of the behavior and a reinforcing consequence should diminish as the behavior strengthens. This tends to occur in the natural order of events. For example, reinforcing an early and small number of repetitions of an exercise by therapist approval and attention yields a relatively high ratio of consequence to behavior. As numbers of repetitions increase with treatment, therapist response now occurs at a lower ratio of consequence to behavior. The ultimate goal is to provide the opportunity for naturally occurring reinforcing events in the patient's environment to begin to take over as consequences to help maintain treatment gains (7). Therapist fading of reinforcement frequency is an important prelude to that.

Units of Behavior (Movement Cycles)

What are the units of behavior to be measured? The basic unit is known as a *movement cycle*. A movement cycle is completed when the person is in a position to repeat it. In an exercise such as forward flexing, the movement cycle is to flex forward and then return to the upright position. In walking, it is moving one and then the other foot forward. Unless the person is beginning an exercise from an extremely reduced activity level, simple repetitions of an exercise will suffice (e.g., six pelvic tilts, four laps walked). The extremely deactivated patient may require a finer mesh of movement units or cycles in the initial stages of reactivation. Walking laps, for example, may begin with single steps between parallel bars or laps in the bars. As progress occurs, walking quotas can be shifted to meters walked outside the bars.

Punishment

Punishment is virtually never a desirable or effective way to help a person to change behavior for many reasons. There are ethical and moral principles involved. In addition, punishment, if severe enough, tends not to reduce behavior but to displace it in time and space only to occur on another occasion or in another place. The treatment relationship and readiness of the patient to respond to therapist direction and approval are compromised by punishment. A punishing therapist is likely soon to become an aversive stimulus, someone to be avoided or ignored.

Treatment Relationship

CM methods are not a substitute for a treatment relationship. The treatment relationship, including full informed consent and agreement as to objectives, is a prerequisite of all behavior change methods. During treatment, therapists should behave in ways that encourage undertaking some behaviors patients believe or fear will be harmful or, at the least, painful. Patients who are not confident that compliance with therapist instructions and directions will lead to beneficial effects likely will

fare poorly in treatment unless therapist encouragement and support prepare them to make the initial efforts. Because patients are initially unlikely to know that beneficial effects will follow treatment effort, they must view their therapists positively and have trust in them. Establishing patient trust and confidence in the therapist is at the core of treatment.

TREATMENT

Exercise

To take into account pain-related and other medical considerations and to bring to bear expertise regarding physical exercises, such exercises should be prescribed by an appropriately competent person. Most exercises occur in standard exercise facilities. The exercise of walking may require use of a different space.

Two commonly used exercises illustrate how to proceed: pelvic tilts and riding a fixed bicycle. First, the game plan should be explained fully and patient consent to proceed obtained. This explanation should describe determination of baselines, establishing quotas, and quota incrementing, as described below and listed in Table 88-1.

Baselines
Quotas
Quota incrementing
Quota failure

TABLE 88-1. Operant aspects of exercise

Baseline

Ask the patient to do pelvic tilts continuously “until pain, weakness, or fatigue cause you to want to stop. You decide when to stop.” Count and record number of repetitions, or in the case of riding the bicycle, distance ridden, for two to four trials separated by 30 minutes or more of rest, but more typically across 2 to 3 days. The average number of repetitions can be used as baseline. Always measure performance in numbers of repetitions or distance, never in time units.

Quotas

After baseline is defined, the assignment for each session is number of repetitions to be performed without interruption, as will have been explained at the outset of treatment. That is, rest or pause after each exercise assignment is contingent on achieving the quota.

Set an initial quota of approximately two-thirds or three-fourths of the number of repetitions—or distance ridden—averaged during baseline trials. The guiding principle is that initial quotas should be sufficiently below baseline levels to ensure success in early trials. This arranges that rest or time out from activity—which presently is probably aversive—becomes contingent on performance of the targeted behavior, namely, exercise.

Quota Incrementing. Quota incrementing is a therapist judgment call, but the incrementing plan should be determined after baselines have been defined and not on the basis of patient performance each session. It should be based on clinical judgment as to likelihood the patient can perform and adjusted further by number of therapy sessions available and by the anticipated therapy ceiling goal. For example, given a 4-week, once-daily session (20 sessions), if the baseline is nine and a reasonable end point is 25 repetitions, an increment schedule of one per session, starting with an initial quota of six, is usually adequate and reaches 25 one day early. If the therapist is confident of a more rapid incrementing rate, the schedule in the above example might be two each session. In the case of bicycle riding, the quota is distance ridden (e.g., in miles or tenths of a mile). Quotas should never exceed the therapist's reasonable expectation of the patient's ability to achieve but should be at the highest level commensurate with the therapist's confidence regarding achievement.

The working-to-quota mode provides the reinforcer of rest or time out from activity, enhanced further by therapist support and approval. It also illustrates applying the incompatible-response strategy. Reclining is decreased by increased activity level. In the example, time out from aversive activity as provided by the working-to-quota system and therapist response to performance serve as reinforcement. These may be augmented by patient awareness of progress. Having patients keep graphs recording performance is a way of enhancing this, although signs of progress are not always a potent reinforcement. The quota incrementing process should have been explained fully at the outset of the exercise program.

Quota Failure. Repeated failure to achieve quotas, assuming they have been reasonably set and there is no biomedical reason for failed performance, usually means the patient is more reinforced by rest or nonperformance than by progress. That in turn usually means that the situation to which the patient is destined to return has aversive qualities sufficient to deter success at treatment. There is no defensible reason for continuing treatment unless quotas begin to be achieved. Failures, except for an occasional lapse that is corrected by achieving the next quota, should be discussed in a forthright manner with the patient. If he or she cannot explain the failure(s) in acceptably logical terms, three options should be offered:

1. Terminate the program immediately.
2. Arrange a brief pause (e.g., one to three sessions) in incrementing rate, holding at the present level and then resuming the increment schedule with program continuation contingent on performance.
3. Continue with the increment schedule with continuation of the program contingent on meeting quotas.

It is important that patient performance be monitored rigorously. Failed quotas across several exercises or for several sessions require prompt intervention.

Speed Walking

Speed walking is an additional tool for helping to bring about reactivation and the maintenance of appropriate activity levels (Table 88-2). It is vitally important that a thorough medical clearance to engage in the speed walking program be obtained before proceeding. Conceptually, speed walking is an application of use of an incompatible response to diminish deactivation. It also can be thought of cognitively as seeking to establish patient self-perception as that of being a vigorous person, a condition somewhat incompatible with being disabled. An incidental but not infrequent by-product of speed walking is the reduction or elimination of limping, guarding, or knee-buckling during ambulation. Knee-buckling is sometimes observed to have become established as a conditioned form of guarding or protecting oneself from anticipated pain or weakness when the need to do so may have diminished or disappeared because of healing. Engaging in gradually incrementing speed in walking can be an effective method for overcoming that.

Course
Target speeds
Baseline pace
Graph results
Speed walking quota
Quota failures

TABLE 88-2. Speed walking

The objectives of the speed walking component to reactivation should be discussed thoroughly at the outset. Specifically, it should be made clear that the intent is not to establish a habit of walking rapidly; it is to help to learn by doing that it is safe to move with vigor. Achieving this will also demonstrate to family members and other interested persons that vigorous movement is a safe and effective way to further health and activity level, thereby favorably influencing their readiness to support return to normal activity levels. Target speeds should be indicated along with instruction not to strive to exceed those speeds beyond an incidental second or two.

1. Lay out a measured course (e.g., 50 meters per lap).
2. Target speeds (i.e., seconds elapsed during lap trials) should be identified. Unless there are specific medical or anatomic contraindications, 18 to 20 seconds for men and 20 to 22 seconds for women have been observed to be appropriate target speeds. The gender difference relates to typical leg length differences.

   It has also been observed that patients may compete with each other or with themselves to the point at which they begin attempting laps at a near-reckless pace. The objectives of speed walking will have been achieved by reaching the target speeds noted. Further reductions in elapsed time serve no good purpose and may expose the patient to some risk.
3. Instruct the patient to walk one lap at whatever pace he or she chooses. Explain further that the program objective will be to help him or her to walk a 50-meter lap in 18 to 20 seconds if male; 20 to 22 seconds if female. Time the lap, and repeat the process for two to three trials to establish a baseline of elapsed seconds. If target speeds occur during baseline trials, speed walking may be abandoned as unnecessary.
4. Prepare a graph with the ordinate in seconds extending from zero to whatever amount slightly exceeds baseline elapsed times. The abscissa should be of trials or treatment sessions. Draw a straight but diagonal quota line on the graph from 2 to 3 seconds above the highest baseline elapsed time to the target speed level (i.e., 20 or 22 seconds) at the point of anticipated number of speed walking sessions in the program for that patient. If more than one speed walking session is planned per day, the abscissa can be defined in terms of days of treatment.
5. Each speed walking trial should have a speed quota. That quota is defined as the number of elapsed seconds which, when recorded on the graph, reaches the highest possible point *beneath* the sloping line.
6. Quota failures at speed walking should be dealt with essentially as described above in relation to other exercises. That is, first reassess neuroanatomic and neurophysiologic factors to ensure those are not barriers to performance. Second, discuss with the patient why quota failures are occurring. If it is an incidental or capricious lapse, the program should continue as graphed with perhaps one or two repeat trials to achieve the quota. If there are repeated failures, program termination should be considered. Elimination of the speed walking component to treatment is a less desirable alternative.

Behavioral Management of Analgesics

This section is not concerned with decisions about whether to prescribe analgesics and, if so, which ones. It is concerned with using CM technology to reduce dependence or habituation (1,8,9). The methods described here are not needed for chronic pain patients presenting with little or no analgesic consumption.

Pain-related medications have often been prescribed on an as-needed basis. For recent onset and time-limited pain problems, the as-needed regimen is appropriate. Chronic pain is a different matter. Protracted use of narcotics can induce psychological or physiologic dependence, or both. CM methods are a straightforward way of dealing with this issue (Table 88-3). The procedure has come to be known as the *pain cocktail*. That is a method, not a commodity (1). Full description of the pain cocktail procedure should be provided and patient consent to proceed obtained.

1. Identify risk
2. Observe baseline consumption
3. Prepare initial pain cocktail
4. Deliver on time-contingent basis
5. Taper active ingredients
6. Discontinue when only vehicle
7. Open disclosure at all times

TABLE 88-3. Drug profile

1. Patients who are impaired by excessive opioid and sedative-hypnotic drug intake will almost certainly require an inpatient phase of treatment until medication ingestion has been significantly reduced, because it is essential to have close monitoring and control over access to drugs when they are inappropriately used. The patient is then instructed to take whatever analgesics are desired for 24 hours.
2. Determined by observation, not patient report, the type, frequency, and amount taken in a 24-hour period can be recorded. This may be repeated for a second or even third day, although this is infrequently required. The point is to determine what the patient presently requires or consumes. The 24-hour ingestion amount and average interval between is the baseline.
3. Prepare the initial pain cocktail. This consists of substituting an equivalent amount of methadone to the opioids that the patient has been taking, plus a color- and taste-masking vehicle—cherry syrup usually serves well—to total 10 mL (9). Other medications can be dealt with in a similar fashion by substituting a long-acting equivalent for short-acting drugs and then tapering.
4. Deliver the pain cocktail on a time-contingent basis around the clock. The interval should not be greater than observed baseline time intervals. An every 4 or 6 hours' schedule is common.
5. To diminish cognitive disarray from toxicity, reduce the active ingredient in the cocktail by 15% to 20% per day until the sensorium clears. When that point is reached, readjust the fading schedule to 20% a week. If no toxicity is demonstrated, the initial fading schedule can be 15% to 20% a week.
6. When the active ingredients have reached zero, indicate this to the patient and offer the option of discontinuing the cocktail or of continuing it for a few days before stopping.
7. Full and open disclosure of current levels of analgesics in the pain cocktail should be given to all patients who request it. This rarely proves to be any encumbrance to the fading program.

Social Reinforcement

Treatment Staff

The objectives here are twofold: to focus staff attention, responsiveness, and support on patient performance toward restoration of function and to minimize the extent to which professional staff actions are contingent on pain behaviors. To be nonresponsive is not to ignore a patient. It is to avoid letting approving behaviors occur.

Professionals interacting with the patient should be alert to encourage each increment in performance. Lavish praise and the like are usually inappropriate and ineffective. Straightforward acknowledgment of performance, given in positive tones, is helpful.

Patient expressions of pain behaviors should be responded to minimally. One does not ignore the patient. For example, maintain eye contact but let one's voice and facial expression remain neutral—not negative, but matter of fact.

Patient failures to achieve an exercise quota can be responded to in the same way. It often assists in putting the responsibility back where it belongs by adding the question “What do you think it means?”

Family

Family and significant others in the patient's social milieu will have evolved patterns of responding to pain behavior (1,10). These may be empathetic and socially supportive, neutral, or punitive and aversive. Family responsiveness often plays a role in helping to maintain a pain problem by pain behavior–contingent responses. It is essential, therefore, that initial evaluation of patients includes interviews with spouse or significant other to determine what if any problems may exist in this regard and to help set the stage for remediation.

Problems in patient–social milieu interactions regarding pain behaviors usually evolve because such responsiveness has become contingent on pain behaviors. It is a variation of “the squeaky wheel gets the grease.” Another form of environmental response to pain behaviors is admonishment of the patient to avoid activities that they feel might worsen the pain problem. In effect, they are punishing well behavior. These problems should be addressed. One or more meetings with spouse or significant other and a professional staff person usually suffice. The problem should be explained, and methods of remediation should be communicated as set forth above in regard to professional staff responsiveness.

Sometimes key persons in the milieu have developed resentment toward patient limitations in function and accompanying pain behaviors. This can be a complicated matter, reflecting long-standing relationship difficulties between patient and the other person(s). Sometimes aversive responsiveness to pain behaviors actually serves as reinforcement to those behaviors. The critical ramifications of these negatively toned interactions need to be studied by appropriately prepared professionals. If the problem is judged not to be entangled with long-standing relationship issues, it may suffice to have two to three meetings with the key person(s) to assist him or her in learning to focus on positive attainments by the patient, while becoming essentially nonresponsive to pain behaviors, as described above.

CM principles as described in this chapter are the foundation of multidisciplinary pain management and have been proven to be useful in the treatment of patients with chronic pain. Many other treatment strategies, both psychological and medical, also play an important role. Not all clinical psychology training programs provide adequate instruction in this form of therapy, whose principles must also be applied by physical and occupational therapists, nurses, and physicians.

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CHAPTER 89

Cognitive-Behavioral Therapy for Chronic Pain

Judith A. Turner and Joan M. Romano

BASIC CONSIDERATIONS

History and Theoretical Basis

Behavioral therapies, emphasizing the promotion of adaptive behavior through the application of principles derived from learning theory, began to be developed in the 1950s (1,2). In contrast to psychodynamic psychotherapy, which seeks to change underlying personality processes presumed to cause maladaptive behaviors, behavioral therapies aim to modify maladaptive behaviors directly through the application of techniques based on learning theory principles (3). Maladaptive behaviors are assumed to be, to a considerable degree, acquired through learning experiences and to be modifiable through exposure to new learning experiences. Specific maladaptive behaviors and factors maintaining them are identified at treatment onset; specific, clearly defined treatment goals are set; and treatment is generally focused on the present and time-limited. Examples of behavioral therapies include systematic desensitization, assertiveness and social skills training, and operant conditioning. Fordyce (4) was a pioneer in the application of behavioral treatment approaches to chronic pain, which before the 1970s had been viewed generally as a strictly biomedical problem (see Chapter 25 and Chapter 88).

During the 1960s and 1970s, the importance of cognitive processes in emotional and behavioral problems gained increased attention. Cognitive processes (thoughts, attributions, beliefs, appraisals) were recognized as mediators of individuals' emotional and behavioral responses to environmental events. Rational-emotive therapy (5) was developed from a theory that assumes that emotional distress arises from faulty or irrational patterns of thinking. In rational-emotive therapy, the therapist assists the patient in determining external events and the associated thought patterns and underlying beliefs that give rise to negative emotions and then in altering irrational beliefs and thought patterns. Beck and his colleagues (6,7) developed a cognitive therapy that specifically targeted depression. This active, time-limited, structured therapy involves techniques designed to identify, reality test, and correct negative distortions in patients' views of themselves and their experiences. This therapy has been adapted for use with anxiety, anger, and other problems.

Cognitive-behavioral therapy (CBT) refers to an approach that combines cognitive therapy techniques with behavioral techniques such as relaxation training and assertiveness training. Meichenbaum (8) and others (9) emphasize a coping skills model— that is, teaching patients a variety of methods that can be applied across problems and situations. The reader interested in an overview of the historical development of cognitive theory and CBT in the field of psychotherapy should review Mahoney and Arnkoff (10).

Paralleling this increase in interest on the part of behavioral scientists in the cognitive aspects of behavior and behavior change has been increased recognition of the role that cognitive, affective, and behavioral factors play in the experience of pain. With this recognition has come an appreciation of the importance of examining the influences of psychological factors on an individual's pain experience and behavioral responses to pain and the potential for decreasing pain, suffering, and disability through cognitive and behavioral techniques. The rationale for applying CBT strategies to chronic pain problems is that learning new cognitive and behavioral responses to pain and to factors that can influence pain, such as stress, can give the individual a sense of control over pain; decrease negative emotions, thoughts, and beliefs related to the pain; decrease maladaptive behaviors; and increase adaptive behaviors. This, in turn, may reduce pain, suffering, and disability. These cognitive-behavioral techniques are typically incorporated as part of a broader comprehensive pain management approach.

Advantages and Disadvantages

The advantages of cognitive-behavioral techniques include their applicability to a broad range of clinical problems and pain syndromes and the fact that they have been proven efficacious in relatively brief group and individual treatment formats (e.g., six to 12 sessions), making them appealing in the current health care climate emphasizing low-cost, cost-effective, evidence-based treatments. One disadvantage is that CBT requires active patient participation and home practice. Not all patients are willing to expend the time and effort necessary to realize benefits. Another consideration is that specialized training is required to conduct CBT (e.g., graduate training in clinical psychology), and professionals skilled in the use of these methods may not be available in all settings. However, some highly structured CBT protocols can even be delivered by trained lay leaders (11).

CLINICAL CONSIDERATIONS

Indications and Contraindications

Any individual with a persistent pain problem potentially may benefit from CBT. The exact techniques applied are guided by the nature of the individual patient's problems. For example, a patient who tends to have many negatively distorted thoughts (e.g., “This pain is awful, and it will never get any better. I can't stand it—it is overwhelming.”) may benefit greatly from cognitive restructuring techniques (learning to identify and modify negatively distorted thoughts). A patient who tends to respond to stress with increased anxiety, muscle tension, and pain may benefit from learning a variety of stress management and relaxation techniques.

Several factors are likely to influence treatment success, particularly in chronic pain problems, and are worthy of empiric investigation. Patients who are not interested in CBT even after receiving information concerning the rationale for such an approach and what the therapy involves or who present for treatment only because they felt pressured to by an agency, such as a workers' compensation organization, or by a family member or physician, may be particularly challenging. However, such patients may become receptive to CBT if their physicians provide information and encouragement and if a working alliance between patient and CBT therapist is established so that the patient comes to perceive the therapy to be of potential benefit to him or her. Also, willingness to comply with and participate fully in a psychological treatment is likely to be minimal in patients who are convinced they have an organically based problem not influenced significantly by psychological factors. Attitudes of family members are also very important. Spouses who believe patients' pain is caused totally by biomedical factors and that psychological treatments are not relevant are unlikely to support treatment efforts and may undermine patient progress. Finally, the availability of personal, social, and environmental resources that can support treatment gains may well be critical in determining the long-term outcome.

Data are generally unavailable on particular factors that would predict positive or negative response to CBT for pain. In chronic pain problems complicated by factors such as chemical dependency, deactivation, compensation or litigation issues, or potent environmental reinforcers of pain behaviors, CBT alone may be insufficient to produce the desired patient outcomes. However, it may be useful as part of a more comprehensive multimodal treatment program that addresses a variety of important influences on the patient's pain and disability (see Chapter 11, Chapter 18, and Chapter 109).

Techniques

Although cognitive-behavioral therapies vary in goals and techniques, they share certain fundamental characteristics, including (a) the assumption that an individual's feelings and behaviors are influenced greatly by his or her thoughts (cognitions); (b) an emphasis on using active, structured techniques aimed at teaching patients

how to identify, monitor, and change maladaptive thoughts, feelings, and behaviors; (c) a focus on helping patients acquire skills in applying such techniques on their own to a variety of life problems; (d) a collaborative approach to therapy, in which the patient and therapist work as a team to help the patient learn and apply skills that are most relevant to the patient's unique situation; and (e) a relatively brief course of therapy.

The cognitive-behavioral therapist works from the premise that patients must be actively involved in learning to manage their own problems, including pain. Patients must have a clear rationale for the use of cognitive-behavioral techniques in dealing with their pain and be receptive to trying them. Many patients, understandably, are focused on obtaining a medical cure for their pain and fail to see the relevance of psychological approaches. Furthermore, some patients may interpret a referral to a psychologist as an indication that the physician believes their pain is “all in their head.” Patients may be provided several illustrations of ways CBT can be beneficial. One is that stress, which can stem from chronic pain and associated problems, as well as from other sources, can result in increased muscle tension, which in turn can produce increased pain. This serves as a rationale for relaxation and stress management training. Similarly, chronic pain can also be associated with feelings of anger or anxiety, which may also increase muscle tension and pain. It is helpful to emphasize to patients that the existence of such relationships does not imply that the sole cause of the patient's pain is stress or tension, but only that such processes can increase pain and suffering. It can also be stated to patients that chronic pain typically causes disruption in a number of important areas, including vocational functioning, marital and family relationships, and social and leisure activities. Such negative changes can in turn result in depression and anxiety, increased time available to focus on and worry about the pain, and decreased ability to cope with or tolerate the pain.

A simplified explanation of gate-control theory (12), emphasizing the importance of cognitive-evaluative and motivational-affective processes in the pain experience, can be very useful. It is important that patients recognize that pain is a subjective experience influenced by thoughts and feelings, as well as by nociceptive input. Many patients with chronic pain have never been told that an increase in their pain does not necessarily indicate that physical damage is occurring. Learning this, and being reassured that increased pain as they become more active does not indicate physical harm, can be extremely helpful in decreasing patients' activity avoidance and fear of movement. Patients also learn in CBT that, by recognizing and modifying maladaptive responses, regardless of the physical modalities being used to treat the pain and its organic causes, they can learn to better manage their pain and decrease suffering.

Cognitive-behavioral treatments are more likely to be successful if certain guidelines are followed (13,14):

- Organizing and presenting information in logical categories (e.g., diagnosis, treatment, expected results)
- Providing details of the treatment both verbally and in written form
- Tailoring instructions for each patient
- Presenting information gradually to avoid overwhelming patients
- Emphasizing the “how” rather than the “why” of treatment
- Assessing patients' understanding by asking them to describe what they will do after the session
- Providing a method by which patients can assess their performance of homework assignments
- Including patients' families in the treatment program
- Following up with patients to make sure they remember and understand the techniques
- Identifying obstacles to use of techniques and ways to overcome those obstacles

Two major types of CBT are cognitive restructuring and coping skills training. Each is described briefly in Table 89-1. Cognitive restructuring procedures and coping skills training overlap considerably; in practice, they reflect different emphases rather than completely different therapeutic modalities.

Type	Description	Example
Cognitive restructuring	Patients are taught to monitor and evaluate negative thoughts and to generate more accurate and adaptive cognitions.	A chronic pain patient who responds to increased pain by thinking, “I can't take this anymore” is taught to examine such thoughts and develop more accurate and adaptive ones; for example, “Is it really true that I can't deal with this? No, it may be difficult, but I've endured it before and can again.”
Coping skills training	Patients are provided a rationale for the use of techniques and then taught various skills for managing pain and stress.	
Relaxation		Physical and/or mental relaxation methods
Imagery		Imagining pleasant scenes
Coping self-statements		“Relax.” “I can cope.” “I can do something about my pain.” “It's not the end of the world.”

TABLE 89-1. Major types of cognitive-behavioral therapies

Cognitive Restructuring

Cognitive restructuring techniques, typified by rational-emotive therapy (5) and cognitive therapy (6), are used to teach patients to identify and modify maladaptive, negatively distorted thoughts that can lead to negative feelings such as depression, anxiety, and anger. Patients learn to examine objectively whether such thoughts are accurate and justified by evidence and to substitute more adaptive, evidence-based cognitions for negatively distorted thoughts. The term *restructuring* does not imply a literal change in any internal structure or process. However, it does serve to indicate that what is being learned is a method for examining and modifying one's thoughts about experiences and events that can be generalized across a number of situations. A somewhat similar approach, use of coping self-statements, is discussed in a later section, Adaptive Coping Self-Statements.

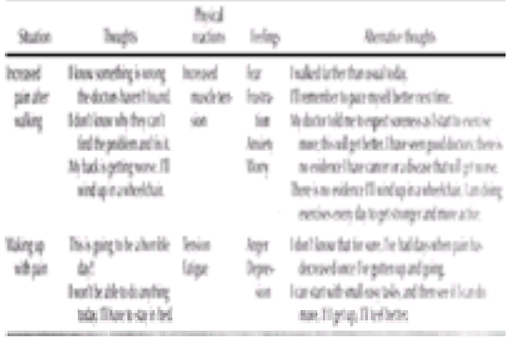
In using cognitive-behavioral techniques with chronic pain patients, establishing a plausible rationale for these interventions is critical, as many of these patients tend to reject psychological approaches to their problems. A simplified explanation of the gate-control theory of pain provides an excellent way to begin introducing the notion that psychological as well as physiologic factors may play a role in determining how pain is experienced. This concept can be made personally relevant to patients if the therapist helps them to identify factors that increase or decrease their experience of pain, discussing these in terms of opening or closing the “pain gate.” These factors may be classified as physical, emotional, and cognitive, as shown in Table 89-2.

Type of influence	Opens gate	Closes gate
Physical	Overexertion Muscle tension	Muscle relaxation Heat or ice Medication
Emotional	Anxiety Depression Anger	Happiness Mental relaxation
Cognitive	Worry Increased attention to pain Catastrophizing	Attention focus on something other than pain Coping self-statements

TABLE 89-2. Examples of influences on the pain gate

The next step in engaging a patient in CBT is helping him or her to recognize that emotional responses to pain are greatly influenced by one's thoughts. It can be helpful to delineate the components of a stressful situation through the use of a worksheet such as the one shown in Table 89-3. The therapist should emphasize that although we often cannot control or avoid distressing life events, we almost always can exert some control over how much suffering and life disruption such events

produce. Once patients understand these connections between thoughts and feelings, they are trained to identify their negative “automatic thoughts,” evaluate the accuracy of these thoughts, think of possible alternative appraisals, and counter negative thoughts with more positive or realistic cognitions. For example, suppose a patient experiences increased pain after walking some distance (the event) and then thinks to himself, “I know something is wrong that the doctors haven't found. This is going to get worse and I'll wind up in a wheelchair.” The usual consequences of such cognitions are anxiety, fear, and worry, and the patient may respond by avoiding activity. The consequences will be much less negative, however, if the patient thinks, “I walked much farther than usual today. I'll remember to pace myself better next time. My doctor told me to expect some soreness as I start to exercise more. It doesn't mean that I will wind up in a wheelchair. I am doing exercises every day so I can become stronger and more active.”



Situation	Thoughts	Physical reactions	Feelings	Alternative thoughts
Increased pain after walking	I know something is wrong. The doctors haven't found it. I don't know why they can't find the problem and fix it. My back is getting worse. I'll wind up in a wheelchair.	Increased muscle tension	Fear Frustration Anger Anxiety Worry	I walked farther than usual today. I'll remember to pace myself better next time. My doctor told me to expect soreness as I start to exercise more. She will get better. I have seen good doctors. There is no evidence I have cancer or a disease that is getting worse. There is no evidence I'll wind up in a wheelchair. I am doing exercises every day to get stronger and more active.
Waking up with pain	This is going to be a horrible day! I won't be able to do anything today. I'll have to stay in bed.	Tension Fatigue	Anger Depression	I don't know that for sure. I've had days when pain has decreased once I've gotten up and going. I can start with small easy tasks, and then see if I can do more. If I get up, I'll feel better.

TABLE 89-3. Template for identifying and countering negative thoughts

As a second example of this model, suppose that a patient has increased pain on awakening one day. Negative cognitions (e.g., “This is going to be a horrible day! I won't be able to do anything today. I'll have to stay in bed.”) are likely to result in anger and depression. On the other hand, the patient is likely to feel much less angry and depressed if he or she thinks, “I don't know that for sure. I've had days when pain has decreased once I've gotten up and going. I can start with small easy tasks, and then see if I can do more. If I get up, I'll feel better.”

Many chronic pain patients find it very difficult to recognize their negative automatic thoughts in response to increased pain or stress, and a number of sessions may be needed to develop this skill. It is often helpful to have patients “relive” a recent situation in which there was much pain, stress, anxiety, or depression, relating step by step what happened, how they were feeling, and what they were thinking. Patients typically need much help in fully describing their thoughts and feelings. They may say they simply felt anxious and had only one thought in a particular situation, when careful questioning may reveal several important additional feelings and thoughts. Each feeling described should be explainable by at least one thought. For example, if a patient says she felt angry in a certain situation but can give no thoughts that would lead to feelings of anger, the therapist should help the patient to reconstruct what thought was associated with that feeling. Similarly, if a patient describes a thought (e.g., “That was unfair.”) that would be associated with anger in most people but does not list that feeling, the therapist might point out that most people would feel angry if they thought that, and ask if the patient might not have had some negative emotional reaction at that time.

Between sessions, it is extremely useful to have patients record their thoughts and feelings during or immediately after situations in which they experience increased pain or stress. These records can be used during the following therapy session to provide examples for continued learning and practice of skills. It is important that patients learn to distinguish events, thoughts, and feelings. Many patients at first incorrectly record thoughts as events or feelings, feelings as thoughts, and so forth.

Only when patients can readily identify automatic thoughts and feelings should the therapist move on to instructing them in evaluating the accuracy of negative thoughts and generating alternative thoughts. In this process, the therapist and patient work together to examine whether negative thoughts are realistic and whether there may be other possible interpretations of the event or situation. The goal is not to persuade patients that their thinking is wrong but to help them examine the extent to which their negative thoughts are supported by evidence. For example, if a patient's thought is “I can't do anything any more because of this pain,” the therapist might ask, “Is it true that you can't do anything? Is there anything you can do despite the pain?” The therapist and patient might then go on to list what the patient is able to do, as well as what the patient can no longer do. They might also discuss the importance of activities that the patient cannot do and whether there are any ways the patient might be able to accomplish some of these activities despite the pain. Finally, the patient and therapist might design a homework assignment to test the patient's thoughts and assumptions and provide additional information for further discussion. As therapy progresses, core assumptions underlying negative thinking patterns may emerge, such as self-worth's being equated with ability to do certain types of work or activities. Addressing these core assumptions and themes with the techniques described here is an important component of CBT.

To summarize, the therapist aims to teach patients how to identify negative distorted thoughts, examine the accuracy of these thoughts, and generate more realistic and more adaptive ones. Thus, the focus is not on solving a particular problem but rather on learning a cognitive skill for dealing with negative thoughts and emotions. The goal is not to eliminate negative emotions, which are recognized to be a normal part of life, but rather to reduce the intensity of negative emotions that result from distorted cognitions about events and situations.

Coping Skills Treatments

Coping skills therapies aim to help patients develop a repertoire of skills for managing pain and stress. Although these skills often include cognitive restructuring, they also encompass other techniques, such as relaxation and distraction. Of the various specific coping procedures that have been taught in therapeutic situations, relaxation, imagery, and the generation of positive coping self-statements seem to be the most commonly used.

Relaxation and Imagery Techniques. A wide variety of relaxation methods exist; none has been proven more consistently effective than others when applied to chronic pain problems (see Chapter 92). It is often useful to teach patients several methods, so that patients may select the approach they find most useful. Daily practice of relaxation over several weeks appears to be necessary for realization of maximum benefits. Techniques that many patients with chronic pain find useful include progressively tensing and then relaxing major muscle groups (15), imagery (13), and deep breathing (13).

As with instruction in any cognitive or behavioral technique, the therapist should explain to patients why and how the procedure helps relieve stress, tension, and pain and emphasize the necessity of regular practice to develop skills and realize maximum benefits. Patients can be told that pain and other physical and psychological stressors often result in increased autonomic and emotional arousal and muscle tension. Muscle tension tends to spread to adjacent muscle groups and has the effect of further increasing pain. To illustrate this fact patients may be instructed to clench their fists and observe the impact on other muscles in their arms, shoulders, and jaws. The therapist then explains that relaxation is a very effective means of reducing the muscle tension, autonomic arousal, and negative emotional responses that make pain worse, thus breaking up a vicious cycle.

Relaxation and imagery methods are also helpful in diverting attention from pain, improving sleep (often disrupted in chronic pain syndromes), and giving patients a sense of control over pain. Furthermore, patients learn to monitor muscle tension in their bodies and to decrease tension before it mounts. Mentioning the effective use of relaxation and breathing techniques for labor pain may help enhance the credibility of this technique for patients.

Relaxation must be taught over a number of sessions—in our experience, at least six—for a patient to become proficient in its application. Ideally the patient and therapist meet once or twice a week, and the patient practices relaxation daily at home between sessions. An audiotape may be given to patients to use for home practice. The therapist observes the patient during the sessions to see how relaxed the patient is able to become and what body areas he or she has difficulty relaxing. During each session, some time should be spent discussing problems the patient has had in doing the home practice and in generating possible solutions. Typical problems include not being able to find time to practice and experiencing distracting thoughts while attempting to relax.

In our experience, there is no “right” protocol that patients must follow to relax fully; rather, the therapist and each patient should work together to develop a method tailored to the individual. After patients become proficient at being able to relax in a quiet, comfortable place, training can focus on generalizing relaxation skills to other settings and positions. The ultimate goal is for each patient to be able to achieve relaxation, without having to tense muscles, in any situation. As training

progresses, patients should find that they automatically notice tense muscles in daily situations and respond by relaxing.

Many techniques are helpful for enhancing relaxation: saying a word such as “calm” or “relax” silently to oneself, focusing on a pleasant image, and listening to music. Mental imagery can be used with muscle relaxation techniques as a procedure for decreasing pain. Again, numerous types of imagery have been described (16). Pain can be imagined as an object (e.g., a tight band) that can be manipulated to decrease discomfort, or the patient can imagine being in a pleasant place such as a meadow or a beach, to give just two examples. It is very important that the patient find an image that is highly involving, if possible using multiple (visual, auditory, tactile) senses. For example, if the image of walking on a beach is used, patients may be asked to imagine the colors of the sea, sand, and sky; the sounds of waves and birds; and the feelings of the warm sun and sand. Many patients are best able to work with images of actual situations they have experienced.

Adaptive Coping Self-Statements. The use of adaptive self-statements is another coping skill frequently taught. This involves teaching patients to cope with increased pain or stress by thinking adaptive thoughts (*self-statements*). Examples of coping statements are “I can deal with this,” “Focus on relaxing,” and “This tension is a cue to use my coping skills.” Although this technique is similar to the cognitive restructuring approaches described already, less emphasis is placed on acquiring a general method of examining and modifying cognitive processes than on learning a set of particular coping self-statements to be used in situations of pain and stress.

These techniques may be useful in coping with flare-ups or increases in pain associated with medical procedures or treatments. The patient may be given the rationale that anxiety and tension can increase discomfort and that the level of anxiety experienced is strongly influenced by what one says to oneself about the experience. Examples are useful in illustrating these points. Most patients can understand that certain thoughts (e.g., “I can't take this”; “This is unbearable.”) produce increased anxiety and focus on pain and suffering. A useful way to decrease this anxiety and tension is to respond to negative thoughts by substituting or countering with thoughts emphasizing the patient's ability to cope. Once the rationale has been established and the method demonstrated, it is useful to have the patient rehearse these techniques when imagining him- or herself in the painful situation. The patient is instructed to recognize the natural reactions of anxiety, muscular tension, and negative thoughts (e.g., “This is horrible”; “I can't stand this.”) and to then counter these thoughts with more positive ones (e.g., “This won't last long. I can handle it. Just relax.”).

Coping statements may be used in four different phases of coping with pain (13). In the first phase—preparing for the pain—such statements as “Think about what you can do to deal with this. Worrying will not help.” are used. In the second phase—confronting and handling the sensations—such statements as “Use the tension as a cue to relax. I can think of something pleasant.” are helpful as the pain begins to increase. The third phase—critical moments—involves feelings of intense pain or beliefs that one cannot deal with the pain. Statements such as “Just focus on a strategy for dealing with the pain. I can handle each moment as it comes with breathing and relaxation. I'll get through this.” are helpful in countering negative thoughts about one's ability to cope. In the final phase—reflections on how one did—the patient praises him- or herself for coping with the pain with statements such as “I handled that pretty well.” Patients may find it useful to keep a list of coping self-statements that they have found useful (e.g., “I can cope,” “Take some deep breaths and relax.”) on a card in their wallets.

Group Therapy. Group CBT is often an important component of pain treatment programs (see Chapter 109). Groups have the obvious advantage over individual sessions of enabling one therapist to work simultaneously with a number of patients. Another advantage of groups is that patients benefit from contact with and support and encouragement from others with similar experiences and problems. They may be more receptive to feedback and suggestions from other patients in the group than from the therapist. The group format also enables patients to role-play with a number of different people and observe others' role-playing.

Such sessions may be considered “psychoeducational” in nature. That is, educational approaches such as structured content and didactic teaching are combined with psychological techniques such as role-playing to teach coping skills that the patient can apply to current and future personal and interpersonal problems (17). Many groups start by providing information to patients about their pain condition (e.g., education about arthritis, temporomandibular disorders, low back pain, or complex regional pain syndromes). This may include current understanding about causes, role of diagnostic tests, various treatment options and the pros and cons of each, and what is known about the prognosis and natural history of the condition. The therapist may then go on to discuss the biopsychosocial model, the role cognitions and emotions play in pain, and the interrelationships among stress, tension, and pain. This may be tied into gate-control theory (12), and asking patients to generate a list of factors that “open” (e.g., tension, anxiety, worry, fear) and “close” (e.g., relaxation, attention diversion) the gate usually helps make these concepts more concrete and relevant to patients (see Table 89-2). Greater patient belief that such relationships are important in their pain problem and that the techniques to be taught can help them cope more effectively with stress and pain will create greater patient receptivity to therapy. Thus, it is important to cover these issues thoroughly with patients in the first few sessions. Visual aids, videos, and reading materials can help supplement the didactic content of the group.

Information provision alone may be insufficient to produce changes in patient behaviors and functional status (18,19 and 20). Thus, CBT groups include cognitive and behavioral techniques, in addition to education, to increase the likelihood of patient behavior change resulting in improved physical and psychosocial functioning. Typically, each patient develops specific individualized goals for behavior change as part of group CBT treatment. This could include goals such as increased physical activity (e.g., increasing daily walking time) or increased social or recreational activity (e.g., increased family recreation).

Group CBT typically consists of six to twelve 1- to 2-hour sessions, usually once a week for outpatients or once a day for patients in an inpatient or day treatment pain program. Sessions can cover diverse topics, such as stress management training, communication and assertiveness skills training, problem solving, cognitive restructuring techniques, sleep hygiene, coping with pain flare-ups, maintenance of gains and relapse prevention, conflict resolution, and anger management. Although the exact topics may vary according to the particular patient population and the total time available, the emphasis of all such sessions is on increasing the patient's sense that he or she can decrease pain, distress, disability, and other negative effects of pain by learning and using the techniques taught.

Size of groups may vary, but it is ideal to have at least six patients and no more than 10 patients in a group. The format is structured, with time allowed for education and skills instruction, practice, and rehearsal. It is also helpful, but not always possible, to include only patients with the same pain problem (e.g., low back pain or headaches) in a group, so that the group can receive education and other problem-specific content relevant to all members. Ideally, all patients in the group will be able to comprehend, read, and write the language in which the group is conducted, but it is possible to include patients without these skills by involving an interpreter or providing other special assistance. It is essential to screen patients before enrolling them in group CBT. Patients must be willing and able to attend the groups and receptive to taking an active role themselves in managing their pain. Patients who wish only to find a medical cure for their pain or who are quite angry or hostile may undermine other group members' progress and are not appropriate for group CBT.

Factors Affecting Treatment Outcomes

Compliance with Homework Assignments. There is evidence that the patients who most frequently use the cognitive-behavioral skills taught in CBT are those with the best long-term outcomes (21,22). Homework is usually required of patients in cognitive-behavioral treatment. This may consist of recording pain and mood ratings, recording thoughts and feelings in different situations, and practicing new techniques and behaviors. Noncompliance with such assignments frequently occurs. Therapists can use the following strategies to enhance compliance:

- Enlist the patient as a collaborator in setting up the assignment, incorporating his or her goals, suggestions, and feedback in designing the assignment, rather than giving the patient a standard, predetermined assignment.
- Start out with a very simple, easy assignment that the therapist and patient feel confident the patient can do; then progress gradually to more difficult and complex assignments.
- Suggest that the patient enlist the assistance of a spouse or family member. For example, the patient could ask his or her spouse to help prevent interruptions during his or her relaxation practice.
- Make sure the patient understands the homework assignment (what is to be done and the rationale) and believes it to be useful.
- Ask the patient what problems he or she anticipates might interfere with successfully completing the assignment, then generate ways of coping with such problems.
- Reinforce completion of homework assignments by attention and interest. If an assignment is not completed, work with the patient to understand why. Did the patient forget? Did the assignment seem too difficult? Once the reasons for not completing the assignment are understood, assignments may be modified to enhance the chances of successful completion in the future.

Maintenance of Gains and Preparing for Setbacks. An important component of treatment with all patients with chronic pain is discussion of ways to maintain the gains made in treatment and ways to cope with future setbacks or pain flare-ups. Several things may be done before setbacks occur to minimize the probability of their occurring and their negative impact. At the beginning of treatment, discussing the patient's expectations of treatment, what it can and cannot do, and the time frame for change is very important. Many patients have unrealistic hopes for rapid, complete pain relief, but they may not disclose these beliefs. Throughout treatment, the

therapist should work with the patient to identify obstacles and high-risk situations that might interfere with his or her practice and application of coping skills.

The therapist should tell patients, early in treatment, that setbacks (e.g., decreased rate of progress, periods of increased pain or depression) are quite likely to occur, both during and after treatment. Patients should be assured that setbacks during treatment can be very useful in providing information as well as an opportunity to practice newly learned coping skills. The therapist should encourage patients to share their negative thoughts about the treatment and to discuss setbacks, so that the reasons for them and various ways of handling them can be explored. One useful approach is to first review with patients their responses to increased pain before entering treatment in terms of their behaviors, emotions, thoughts, and physiologic reactions. These responses may include lying down; feeling depressed, anxious, and angry; thinking, “I can't stand this” or “I'll never get better”; and tensing up. These reactions may then be discussed in light of what patients have learned in the program about gate-control theory. These responses are likely to “open the pain gate” and thus contribute to the perpetuation of disability and pain. Although they are common and understandable responses to increased pain, they are not constructive coping strategies. A more adaptive coping plan consists of two components: ways to prepare for pain flare-ups and coping strategies to use at times of increased pain.

Patients may be best prepared to deal with flare-ups if they maintain realistic expectations regarding their occurrence. This means having neither an unrealistic belief that pain will never recur (which may set the patient up for severe disappointment and discouragement if a setback occurs) nor an overly pessimistic view that pain cannot be modified and the patient is unable to do anything to cope with it (which can lead to depression and failure to use techniques that have been taught). Advance preparation also involves keeping skills in stress management, communication, relaxation, exercise, and stretching well practiced. Skills that have not been used for some time are unlikely to work well in a crisis. As part of treatment, the therapist and patient should develop a list of red flags for setbacks—that is, situations or symptoms that in the past have been associated with increased pain or stress and indications that the patient is no longer engaging in practices that promote adaptive functioning (e.g., regular exercise, good sleep habits, application of stress management and communication skills). A specific plan of action for responding to such red flags should be written out. A typical plan includes coping self-statements (e.g., “I can cope with this,” “This is a good opportunity to use my skills.”), a relaxation exercise, and coping activities to engage in (e.g., taking a walk, stretching, working on a hobby), as well as a reevaluation of the patient's plan for maintaining adaptive behaviors such as exercise and stress management. It is useful to have the patient rehearse specific plans for dealing with pain flare-ups and other setbacks during CBT.

Keefe, Beaupré, and Gil (23) have described the application of Marlatt and Gordon's (24) four-step relapse prevention method to patients with chronic pain. The first step involves stopping and paying attention to the cues that a setback is occurring. The second step is to keep calm, using relaxation or other strategies. The third is to review the situation leading to the setback. The fourth is to make an immediate plan for implementing coping. The therapist and patient role-play how the patient might cope with setbacks.

Therapist Characteristics. Although many of the procedures described in this chapter appear relatively straightforward, therapists must be trained in their appropriate application. Typically, CBT therapists are doctorate-level clinical psychologists with postdoctoral training in pain management. Complex issues often arise during treatment, requiring considerable skill on the part of the therapist. These may include symptoms of major psychopathology, significant marital or family distress, issues related to workers' compensation and disability compensation systems, and persistent somatic focus and resistance to the use of psychological techniques. Whether or not such issues are salient, the importance of therapist style characteristics cannot be overemphasized. As with any psychotherapy, therapist warmth, empathy, respect for the patient, and attentiveness to the patient's goals and needs are important to the success of the treatment.

Results

Cognitive-behavioral strategies have been applied to a number of different chronic pain problems, including low back pain (25,26,27 and 28), headache (29), fibromyalgia (30,31 and 32), osteoarthritis (33,34), rheumatoid arthritis (RA) (35,36,37,38,39,40 and 41), ankylosing spondylitis (21), and temporomandibular disorders (42,43,44,45 and 46). Most multidisciplinary pain treatment programs incorporate cognitive-behavioral methods in addition to physical therapy and other modalities (see Chapter 109). A number of controlled trials have demonstrated the efficacy of CBTs in improving pain, depression, and physical disability in a variety of pain conditions [see reviews (47,48)].

Turner (49) conducted a metaanalysis of 14 randomized trials of cognitive and behavioral treatments for chronic low back pain published before April 1994. Compared with control conditions (waiting list or attention control group), cognitive-behavioral treatments were superior on posttreatment self-report measures of pain intensity, pain behavior, and functional disability, but not observed pain behavior or depression. However, most of the subjects in these studies were community volunteers, and, in general, they were not very depressed and did not show many pain behaviors before treatment. Thus there was little room for improvement on these dimensions. Studies that compared cognitive-behavioral treatments with control conditions at follow-ups were not available.

Turner (49) found six studies that compared cognitive or behavioral treatments with another treatment, such as physical therapy or standard medical care, for low back pain. In this metaanalysis, cognitive-behavioral treatments were found not to differ significantly from other treatments at either posttreatment or follow-up assessments on measures of pain, pain behavior, functional disability, and depression, although there was a trend toward a statistically significant posttreatment effect size in favor of CBT on a self-report measure of disability (the Sickness Impact Profile). Because only two to three studies used any one outcome measure and sample sizes were small, more studies are needed to resolve the question of the efficacy of CBT relative to other treatments for chronic low back pain problems.

Scheer et al. (50) reviewed randomized clinical trials of CBT interventions for subacute and chronic low back pain that assessed return to work and were published between 1975 and 1993. They found eight articles describing five studies that included or emphasized CBT for chronic lower back pain. They concluded that the data did not support the effectiveness of cognitive-behavioral strategies in affecting vocationally relevant outcomes, but that the majority of studies had significant methodologic limitations.

The Division of Clinical Psychology of the American Psychological Association published a list of empirically validated psychological treatments for various disorders, and this list included CBT for chronic pain (51). A National Institutes of Health Technology Assessment Conference Statement (52) concluded that there was moderate empirical support for the efficacy of CBT for chronic pain and that there was strong evidence for the efficacy of relaxation techniques and multimodal treatments for chronic pain problems. Also according to this statement, the data are not sufficient to conclude that one cognitive or behavioral technique is usually more effective than another for a given condition, although, for an individual patient, one approach may be more appropriate than another. The panel concluded that additional efficacy, effectiveness, and cost-effectiveness studies are needed, as are innovative methods of introducing psychosocial treatments into health care curricula and practice.

In a comprehensive review, Compas et al. (47) concluded that the literature supported the efficacy of CBT for rheumatic diseases. Compas et al. (47) found five studies that compared CBT to both attention control and standard medical treatments for rheumatic diseases. All five studies reported improvements in psychological functioning and three found significant pain reductions in patients who received CBT. One of the studies that failed to show overall improvements in pain (39) did find significant pain reduction at long-term follow-up in CBT participants who had shown high adherence to the practice of CBT techniques. The only study that found no improvement in outcome after CBT (53) used a sample of RA patients who had very active disease and demonstrated significant increases in measures of disease activity over the course of the study.

Compas et al. (47) also concluded that CBT was more effective than waiting list or education control conditions for patients with rheumatic diseases. In a study of ankylosing spondylitis patients, CBT was significantly more effective than a waiting-list control in reducing pain, anxiety, and psychophysiologic symptoms (21). In a study of RA patients, compared to an education control condition, CBT produced significant decreases in pain and joint inflammation (38).

Compas et al. (47) also reviewed the literature on CBT for chronic low back pain and for migraine headaches. They concluded that CBT was more effective than a waiting-list control in improving pain, activity level, and psychological functioning in patients with chronic low back pain. For migraine headache, however, they found no evidence that cognitive therapy or CBT enhances the benefits of biofeedback and relaxation training.

In a study examining the process of change in patients participating in a multidisciplinary pain treatment program, Jensen, Turner, and Romano (54) found that improved patient functioning was associated with changes in patient pain-related beliefs and cognitive coping strategy use, consistent with a cognitive-behavioral model. Some studies (26,27,42), but not all, have found continued improvement on outcome measures after the end of CBT for up to 1 year, perhaps as a result of patient application of skills learned in CBT.

Several investigators have examined whether involving family members enhances the efficacy of CBT. Radojevic et al. (40) randomly assigned 65 RA patients to four group treatment conditions: (a) CBT with family support, (b) CBT alone, (c) education with family support, and (d) a no-treatment control condition. Subjects in the

CBT with family support group attended the sessions with a family member. Patients were trained in cognitive pain coping and relaxation techniques, and the patient and family member were taught methods for prompting and reinforcing the use of learned pain control skills. Patients in the CBT alone condition received the same skills training, but no family member was involved. The CBT with family support condition was superior to all other conditions in reducing joint swelling at posttreatment. Both CBT conditions were effective in reducing joint pain at follow-up.

Keefe et al. (55) evaluated the efficacy of a spouse-assisted CBT intervention in managing osteoarthritic pain. Patients with osteoarthritic knee pain were randomly assigned to one of three conditions: (a) spouse-assisted CBT, (b) conventional CBT, or (c) an arthritis education/spouse support control condition. Patients in the spouse-assisted CBT condition attended sessions with their spouses in which they were trained in pain coping skills and in couples' skills (communication skills, behavioral rehearsal, problem solving, and maintenance training). At posttreatment, patients in the spouse-assisted CBT condition had lower levels of pain, psychological disability, and pain behavior and higher scores on measures of coping efforts, marital adjustment, and self-efficacy than did patients in the education-support control condition. These differences were statistically significant. Although there were no significant differences between spouse- assisted CBT and conventional CBT, there was a consistent pattern for patients in the spouse-assisted CBT condition to have the best outcome, conventional CBT the next best outcome, and education-support the poorest outcome.

Complications

Adverse effects of cognitive-behavioral therapies appear to be rare but have been reported. For example, some patients describe increased anxiety associated with the use of relaxation (56). However, because these treatments carry few if any serious risks, chronic pain patients who fail to respond initially to a particular technique may be given trials of other cognitive-behavioral strategies. Increased empiric study of these methods will provide data for specifying when these techniques are most appropriate and likely to be effective.

CONCLUSIONS

CBT is now considered an empirically validated treatment for chronic pain problems. Since the last edition of this book, substantial scientific evidence for the efficacy of CBT for diverse chronic pain problems has come from randomized clinical trials. However, it should be noted that CBT interventions are multimodal treatment packages that combine education about pain with training in a variety of cognitive and behavioral coping skills. There are few data concerning which components are necessary, sufficient, or most important. Furthermore, many experts have called attention to the need to match patients to treatments (45,47,57). For example, patients with greater physical and psychosocial dysfunction may require longer, more intensive, and more individualized treatments. Continued research may lead to the development of guidelines to assist clinicians in selecting the most cost-effective treatments for individual patients.

CBT has been largely applied to, and studied in, patients with long-standing chronic pain. Several investigators have suggested the potential value of providing CBT interventions to patients early in the course of their pain problem (42,49,57). Early intervention has the potential to increase patients' confidence that they can self-manage many symptoms, reduce unnecessary health care utilization, and decrease physical and psychological dysfunction.

This chapter has provided an overview of the rationale for the use of CBT with patients with chronic pain as well as a description of specific types of such interventions. Although the techniques may appear straightforward and easy to use, clinical acumen and experience are necessary for their successful application. Considerable patient investment in learning and applying the skills taught is important in producing a positive outcome, and this may be a barrier to their use with some patients. Nonetheless, there is now strong evidence that such interventions can be a very valuable treatment modality for many patients with chronic pain problems.

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CHAPTER 90

Biofeedback Therapy for Chronic Pain Disorders

John G. Arena and Edward B. Blanchard

Biofeedback for chronic pain disorders is a biopsychosocial technique that has been in existence since the seminal work in 1970 of Budzynski, Stoyva, and Adler (1) with tension headache patients. The most concise definition of biofeedback is probably that of Olton and Noonberg (2, p. 4), who characterized it as “any technique which increases the ability of a person to control voluntarily physiological activities by providing information about those activities.” In reality, the process of clinical biofeedback training generally involves the use of a machine—now usually a computer—that allows a therapist to monitor the patient's bodily responses (generally surface muscle tension or surface skin temperature). Information concerning the patient' s physiologic responses are then relayed back to the patient, generally either through an auditory modality (a tone that increases or decreases on, for example, muscle tension increasing or decreasing), a visual modality (now usually a computer screen where, e.g., surface skin temperature is graphed on a second-by-second basis during each minute), or both. Through this physiologic feedback, patients learn how to control their bodily responses through mental activity. Figure 90-1 illustrates visual feedback provided through the use of a computer screen for a migraineur receiving hand surface temperature biofeedback.

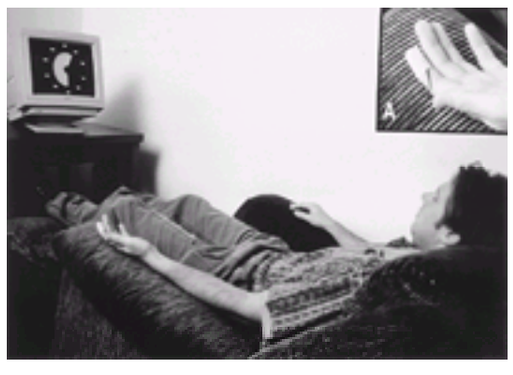

Figure 90-1. Visual feedback given through the use of a computer screen for a migraineur receiving hand surface temperature biofeedback. Inset A contains a close-up of the subject' s hand with the thermistor attached.

Two general theories underlie the use of biofeedback for most chronic pain disorders. The first is a direct psychophysiologic theory, which attributes the etiology or maintenance, or both, of the pain disorder to predominantly physical pathology that is corrected by biofeedback training. For example, it has traditionally been assumed that tension headache is caused by sustained contraction of skeletal muscles in the forehead, neck, and shoulder regions. Through the use of biofeedback, the patient learns to decrease muscle tension levels, leading to a decrease in headache activity. The second theory is predominantly psychological and postulates a relationship between situational stress and chronic pain (3). Through the use of biofeedback, the patient learns to decrease physiologic responses such as muscle tension levels or sympathetic nervous system activity, thereby leading to a decrease in overall stress levels, that, in turn, brings about a reduction in pain. Most clinicians subscribe to both theories, depending on the assessment of the individual patient.

Since the previous edition of this book (4), the literature on the use of biofeedback for pain disorders has grown exponentially. Every reference to biofeedback for pain management cannot be included in this chapter. We provide a review of the current literature for each of the major pain disorders for which biofeedback has been used, reviewing primarily the work published since the prior edition of this textbook and arriving at conclusions about efficacy that are consonant with contemporary research and clinical application.

Although biofeedback has been used for a wide variety of pain disorders, chronic headaches—both tension and vascular (migrainous) headache—have received the most attention in the literature. The quality of the published studies (i.e., controlled evaluations of efficacy) are highest for the treatment of headache. The use of biofeedback training for both tension headache and migraine headache has been endorsed by the Association for Applied Psychophysiology and Biofeedback and by the American Association for the Study of Headache. The American Psychological and Psychiatric Associations and the National Institutes of Health (5) have also provided endorsement for the use of biofeedback for these types of headaches in the context of comprehensive medical, psychological, and psychiatric care.

In view of these considerations, we devote a large portion of this chapter to biofeedback treatment of headache (see Chapter 48), with the remainder devoted to numerous other pain problems for which biofeedback has been used—predominantly lower back pain (LBP) and myofascial pain dysfunction (MPD) syndrome. Wherever possible, references to comprehensive reviews are included (6).

BIOFEEDBACK TREATMENT OF CHRONIC HEADACHE

Tension (Muscle Contraction) Headache

The phenomenology and pathophysiology of tension (muscle contraction) headache are described in Chapter 48 and are not repeated here.

Frontal Electromyographic Biofeedback

The initial report on biofeedback treatment for tension headache (1) described the procedure for frontal electromyographic (EMG) biofeedback, the standard paradigm to this day. It is important to note that the term *EMG* refers to surface electromyography, which uses noninvasive (surface) electrodes, is painless, and involves the pattern of many motor action potentials. In contrast, EMG when used as a diagnostic procedure involves invasive needle electrodes, looks at a single motor action potential, and is often quite painful.

The standard EMG biofeedback procedure for tension headache involves measuring the muscle tension in the forehead by placing electrodes approximately 2.5 cm over each eyebrow and another (ground) electrode in the center of the forehead. The signal is then electronically processed to provide the patient with information on changes in the electrical activity of the muscles on a moment-by-moment basis. Through this feedback, the patient learns how to relax the musculature of the face and scalp and how to detect early symptoms of increased muscle tension. For EMG biofeedback, the feedback signal is generally auditory and may consist of a tone that varies in pitch, a series of clicks that vary in frequency, or a similar system.

Before the electrodes are attached, the skin surface may be cleaned with a mild abrasive, followed by swabbing the forehead with an alcohol preparation. To insure

against infection, only disposable EMG electrodes with adhesive collars are used.

Treatment sessions usually last 30 to 50 minutes with 15 to 40 minutes of each session devoted to the actual feedback training. In our research (and in our clinical work), we have typically used the following format for biofeedback training sessions:

1. Attachment of electrodes and initial adaptation: 10 minutes.
2. In-session baseline, during which patients are asked to sit quietly with their eyes closed: 5 minutes.
3. Self-control 1, during which patients are asked to attempt to decrease their forehead muscle tension levels in the absence of the feedback signal: 3 minutes.
4. Feedback training, with the feedback signal available: 20 minutes.
5. Self-control 2, during which patients are asked to continue to decrease their forehead muscle tension levels in the absence of the feedback signal: 3 minutes.

The two self-control conditions are included to determine whether generalization of the biofeedback response has occurred. Generalization involves preparing the patient to, or determining whether the patient can, carry the learning that may have occurred during the biofeedback session into the“real world.” If the patient can decrease muscle tension without any feedback before the biofeedback condition (self-control 1 condition), then the clinician can assume that between-session generalization has occurred. If the patient can decrease muscle tension without any feedback following the biofeedback condition (self-control 2 condition), then the clinician can assume that within-session generalization has occurred.

There are other methods clinicians use to train for generalization of the biofeedback response. For example, in an attempt to make the office biofeedback training simulate real world situations, many clinicians initially train patients on a recliner; then, once they have mastered the rudiments of biofeedback in this extremely comfortable chair, they progress to, sequentially, a less comfortable office chair (with arms), an uncomfortable office chair (without arms), and, lastly, the standing position. Finally, giving the patient homework assignments to practice the biofeedback response in the real world is a routine way of preparing him or her for generalization.

It is important to note that clinicians vary tremendously in their biofeedback procedures, depending on personal style, training, and the type of patient seen. For example, the biofeedback portion of the session may be decreased significantly in length for patients who have poor concentration abilities or expanded if the patient has had a breakthrough in learning the biofeedback response in the latter minutes of the biofeedback session. Other clinicians choose not to include self-control conditions or choose to vary the length of the adaptation and baseline periods.

Although there is a large body of research on the use of EMG biofeedback alone as a treatment for tension-type headache, in clinical practice some form of relaxation training, usually an abbreviated version of Jacobson' s progressive muscle relaxation (see Chapter 92), is routinely added as an adjunct to the biofeedback treatment. It is common clinical practice to give the patient an audiocassette of the relaxation induction to guide home practice. Patients are asked to practice the relaxation on a daily basis.

The direct experimental comparisons of frontal EMG biofeedback and relaxation training have usually shown no advantage for one over the other. A sequential comparison by Blanchard and colleagues (7) showed a significant advantage for combining the two modalities over either one alone.

Published reports have used from five to 16 treatment sessions. We recommend planning at least ten to 12 sessions on a once- or twice-weekly basis. Some of our patients have required as many as 24 sessions.

Electrode Placement

Although the vast majority of published reports use the forehead or frontal electrode placement, there is some controversy about this point. This is perhaps because the Task Force Report of the Biofeedback Society of America, in their influential position paper on tension headache (8), strongly implied that frontal placement was the gold standard for biofeedback with tension headache sufferers, making no mention of other site placements. In the standard placement, the active electrodes are centered above each eye, approximately 2.5 cm above the eyebrow. A ground electrode is typically placed midway between them, as illustrated in Figure 90-2. With this very wide placement, muscle activity is detected not only in the forehead, but probably also from the rest of the face, scalp, and neck, down to the clavicle (9).

Figure 90-2. Frontal electromyographic electrode placement.

Some writers (10,11) have advocated attaching electrodes to other sites, such as the back of the neck or temporalis area, especially if the patient localizes his or her pain there. However, three of the four studies that compared biofeedback training from different sites between subjects found no advantage of one cite over the other (12,13 and 14). Arena and his colleagues (15) have published the only systematic comparison of a trapezius (neck and shoulder region) versus frontal EMG biofeedback training regimen with tension headache patients. They found clinically significant (50% or greater) decreases in overall headache activity in 50% of subjects in the frontal biofeedback group versus 100% in the trapezius biofeedback group. The trapezius biofeedback group was more effective in obtaining significant clinical improvement than the frontal biofeedback group. Thus, there is some limited support for the use of an upper trapezius electrode placement with tension headache patients. Figure 90-3 illustrates the upper trapezius electrode site placement.

Figure 90-3. Upper trapezius electromyographic electrode placement.

Outcome Results

A convenient way of reporting outcome is the average proportion or fraction of a sample of tension-type headache patients who achieve a clinically significant reduction in headache activity, as documented by the daily headache diary. For EMG biofeedback, this value ranges from 45% to 60% (16). When EMG biofeedback and relaxation are combined, the average improves to 70% to 75% (7).

Vascular Headache

There are two different forms of vascular headaches: migraine headache and cluster headache. More detail on these diagnoses and their treatment is provided in Chapter 48 and is not repeated here.

Biofeedback has not proved to be especially useful with cluster headache. In the largest case series, Blanchard and colleagues (17) reported that only two of 11 (18%) patients showed even modest improvements (some headaches less severe, some cluster bouts shortened, a few headaches aborted) over a 30-month follow-up after a 22-session regimen of relaxation training and thermal biofeedback.

Two related but somewhat different vascular headache populations have been the objects of an extensive research literature: those with only migraine headache, both with and without aura, and those who suffer from both migraine and tension-type headaches. The latter have been less studied.

Thermal Biofeedback

The initial systematic report on the thermal biofeedback treatment of migraine headache by Sargent and colleagues (18) described successful results when patients were taught to warm their hands with the assistance of biofeedback. Their treatment protocol, and many that have followed, included training in a meditative, self-instructional form of relaxation known as *autogenic training* (19).

Treatment sessions routinely follow the same temporal format described earlier for frontal EMG biofeedback. A temperature- sensitive probe, usually a thermistor, is attached to a fingertip (usually the ventral surface of the index finger of the nondominant hand) with care being exercised not to create a tourniquet or inhibit circulation to this phalange. The feedback signal can be auditory or visual. When patients are allowed to sample both, approximately 80% choose a visual display.

The patient should be in a relaxed position with care taken to keep the thermistor away from chair arm surfaces or other body surfaces. The room should be 72° to 75°F. It is very difficult for the patient to learn and emit the response in a cold room.

Patients are told that they must relax and *allow* their hands to become warm, rather than trying to force them to become warm. Effortful striving seems to hamper learning. Passive volition seems to work best. The autogenic phrases related to relaxation, heaviness, and warmth are taught at early sessions as one strategy.

The feedback portion of a session should be 15 to 20 minutes. From eight to 16 sessions have been described. We find a majority of patients begin to show good volitional control by about the seventh or eighth session. Some clinicians advocate training patients to a certain hand temperature criterion, 95°F or more. Patients are asked to practice regularly at home with electronic home trainers (cost of $50 and up) or simple alcohol-in-glass thermometers (approximately $1).

The mechanism by which thermal biofeedback benefits migraine headaches is unclear (20). It probably involves a diminution of peripheral sympathetic activity. Regular practice seems to have a prophylactic effect.

Outcome Results—Migraine

For patients with pure migraine headache, thermal biofeedback (with or without adjunctive autogenic training) leads to clinically significant improvement in 40% to 55% of cases (5,7,16). A systematic course of relaxation training seems to help. In one study, cognitive therapy added to the thermal biofeedback and relaxation did not improve outcome on a group basis (21).

Thermal biofeedback has been shown to be especially helpful with pediatric migraine headache (youth ages 8 to 17). In this population, success rates are usually in the 65% to 75% range. A quantitative review by Hermann and colleagues (22) showed thermal biofeedback to be on a par with the best prophylactic medication. Treatment sessions should be shorter overall with the younger population.

Outcome Results—Combined Migraine and Tension-Type Headache

For patients with both kinds of the primary benign headache disorders (migraine and tension-type), the results with thermal biofeedback alone (or with autogenic training) are a bit lower, averaging 30% to 45% success (5,16). Relaxation training alone leads to 20% to 25% success. The best outcomes have resulted from the combination of thermal biofeedback and relaxation training (again some form of progressive muscle relaxation) (7,16). Results show 50% to 55% success rates. Thus, we recommend a combination of the two treatments for these headache patients.

BIOFEEDBACK TRAINING FOR LOW BACK PAIN

LBP is a complex clinical pain syndrome that is frequently treated with a number of modalities (see Chapter 76). Estimates are that 13 million Americans are permanently disabled as a result of chronic LBP (23). Only EMG biofeedback has been used with this population, and the training procedures are similar to those described for tension headache. Figure 90-4 illustrates a bilateral paraspinal EMG biofeedback placement.

Figure 90-4. Paraspinal electromyographic electrode placement.

A number of theories concern the relationship between muscle tension and chronic LBP (24,25). These can be broken down into two major models:

1. The biomechanical theory, in which the EMG levels of the paraspinal muscles of the back are lower than normal, or there is a left-right asymmetry in the back, in which case the EMG activity on one side of the back musculature is abnormally lower or higher than the other side. This is presumed to be due to some mechanical or physical pathology, including tumor or infection, trauma, abnormal gait, or poor posture (2).
2. The stress-causality or psychosocial stressor theory, in which back pain is presumed to be due to increased paraspinal muscle activity caused by ineffective stress coping skills (25).

There is limited evidence to support either of these two theories (24,25 and 26). With LBP patients, biofeedback has been used as a general relaxation and stress reduction technique, as well as to specifically correct muscle tension abnormalities. Typically, paraspinal electrode placements have been used, but a number of

studies use forehead placements.

Although biofeedback is used extensively in comprehensive pain treatment programs (see Chapter 11), only a few studies have examined the efficacy of biofeedback alone in the treatment of back pain. We review here only those studies that have used biofeedback as the primary mode of treatment. For an in-depth, although somewhat dated, review of biofeedback for chronic LBP, see Sherman and Arena (27).

Previously, we detailed the methodologic limitations of many of the biofeedback studies in the treatment of LBP (27). These include small sample sizes; failure to describe the instrumentation and biofeedback procedures sufficiently to allow replication of the research; and the lack of clearly defined LBP diagnostic categories (many studies simply combine all subjects into a single diagnostic group), explicit inclusion and exclusion criteria (many studies combine both chronic and acute subjects), adequate control groups, pain diaries, and multiple outcome measures. The first section of Table 90-1 outlines the research conducted on LBP since the previous version of this chapter (28,29,30,31 and 32). Wherever possible, the overall percentage of improvement in the biofeedback condition is given; if this is not available, the percentage of subjects who achieved clinical improvement (arbitrarily defined by the authors as 50% or greater reduction in pain levels) is presented. As can be seen from this table, only three LBP biofeedback studies with a sample size of 15 or greater have been published since the prior version of this chapter.

TABLE 90-1. Biofeedback for chronic lower back pain (LBP)

Bush, Ditto, and Feuerstein (28) randomly assigned 66 LBP subjects to one of three groups: paraspinal biofeedback, psychological placebo, or wait list control. Regardless of treatment, all groups showed significant reductions in pain, anxiety, depression, and EMG following treatment and at 3-month follow-up. This well-designed study suffers primarily from a lack of clearly defined diagnostic groups—subjects simply had a“diagnosis of LBP without major physical findings” (pp. 309, 310)—and from reporting no usable outcome data, as numeric data such as pre- and post-treatment means on pain measures were not given.

Stukey, Jacobs, and Goldfarb (32) randomly assigned 24 chronic LBP subjects into one of three treatment conditions: EMG biofeedback (upper trapezius and paraspinal), relaxation training, or placebo. They found that relaxation therapy was superior to EMG biofeedback and placebo in decreasing mean reported pain intensity levels following a function test during which a physical therapist evaluated eight movements the patient performed. They also found relaxation, in comparison to the other groups, to decrease significantly upper trapezius levels, increase activities of daily living (as rated by a physical therapist), and increase subjective relaxation ratings. Unfortunately, this study suffered from some serious methodologic limitations. First, and most important, there are no clinically relevant measures of pain outcome, such as a pain diary recorded over some length of time. Instead, the pain outcome measure is a single snapshot in time. Second, chronic back pain sufferers with multiple diagnoses were combined, and there is no way for the reader to determine whether diagnoses were evenly distributed among the three groups. Finally, there were no measures of medication reduction, and eight subjects per group limits the generalizability of the study' s results.

Newton-John, Spence, and Schotte (30) assigned 44 chronic well-functioning LBP subjects to a cognitive-behavior therapy, EMG biofeedback to the erector spinae muscles, or wait list control group. At posttreatment, significant improvements in pain intensity, perceived level of disability, and adaptive beliefs about pain and levels of depression were found for both active treatment groups but not the wait list controls. The two treatment groups did not significantly differ from each other. Results were maintained or improved at 6-month follow-up. This, also, is a well-designed study that suffers only from a lack of clearly defined diagnostic groups—subjects simply had a diagnosis of“non-malignant lower back pain” (p. 692).

Several studies since the last edition of this chapter have examined the efficacy of EMG biofeedback in patients with multiple pain sites or have used heterogeneous populations (e.g., a mixture of patients with localized low back, upper back, neck, or shoulder pain). The second portion of Table 90-1 outlines these studies (33,34,35 and 36). Two of these studies are clearly superior to the others and deserve special mention.

Flor and Birbaumer (35) had 78 subjects who suffered from chronic musculoskeletal pain (57 low back and 21 temporomandibular joint dysfunction) randomly assigned into one of three groups: EMG biofeedback to the site of the pain (“back or jaw”), cognitive-behavior therapy, or conservative medical treatment. Results at posttreatment showed reductions in pain levels for all three groups, with only the reduction for the biofeedback group being statistically significant. At both 6- and 24-month follow-up, the EMG biofeedback group was significantly superior to both the cognitive-behavior therapy and conservative medical treatment groups on such measures as emotional distress and pain-related use of the health care system. On pain severity, it was superior to the cognitive-behavior therapy group at 6-month follow-up and superior at both 6- and 24-month follow-up to the conservative medical treatment group. Unfortunately, no separate results for LBP versus temporomandibular joint pain were provided, and even within the LBP subjects there was a mixture of various etiologies and diagnoses. This study is important, however, because it demonstrated that biofeedback was superior to“the best presently available medical interventions” (p. 655).

Spence and colleagues (36) randomly assigned 45 patients with chronic neck, shoulder, and upper extremity pain into one of four groups: EMG biofeedback to various muscle sites, relaxation therapy, combination therapy, or a wait list control. Immediately following treatment, subjects in the three active treatment groups showed significantly lower pain levels in comparison to the wait list controls. At 6-month follow-up, pain measures continued to decline and there were no differences between the three active treatment groups. This is a well-designed study that does not suffer from any significant methodologic limitation, other than separate results for the various diagnoses not being presented.

As we have previously concluded (4,27), biofeedback appears to hold promise as a clinically useful technique in the treatment of patients with back pain. Although we believe that optimal clinical improvement is clearly obtained when biofeedback is used within the context of a comprehensive, multidisciplinary pain management program [see Turk and Okifuji (37) for an excellent review of the advantages of such pain programs], the cumulative weight of the evidence, from studies outlined in both this and an earlier version of this chapter, suggest that EMG biofeedback is likely to be helpful, as a single therapy, in the treatment of musculoskeletal LBP.

However, many of the concerns that we have previously outlined (4,27) remain valid. First, only two studies have directly compared biofeedback to relaxation therapy, and both of these studies were significantly flawed so as to limit definitive conclusions. Direct comparisons of biofeedback to relaxation therapy are clearly needed. Second, although more studies are including follow-ups, longer (at least 1 year) and larger-scale (at least 50 per group) follow-up studies are required. Third, evaluations of treatments based on diagnosis (i.e., the cause of the pain) should be conducted. Fourth, comparisons of various biofeedback treatment procedures, such as paraspinal versus frontal electrode placement, or training while supine versus training while standing, are necessary. Finally, further evaluations of patient characteristics predictive of outcome, such as sex, race, chronicity, psychopathology, and psychophysiologic reactivity, are needed.

BIOFEEDBACK TREATMENT OF MYOFASCIAL PAIN DYSFUNCTION SYNDROME

MPD syndrome, also known as *temporomandibular joint syndrome*, is considered a subtype of craniomandibular dysfunction that is caused by hyperactivity of the masticatory muscles (see Chapter 49). It is characterized by diffuse pain in the muscles of mastication, mastication muscle tenderness, and joint sounds and limitations. Although disagreement exists as to the cause of the hyperactivity (e.g., occlusal problems vs. psychological stress), several researchers have examined the use of EMG biofeedback as a treatment, which can provide relief by teaching patients to relax the muscles of the jaw. Consistent with the logic of this approach, the most common electrode placement is on the masseter muscle (Fig. 90-5), although frontal muscle placements have also been used. Excellent overviews of the treatment of MPD syndrome are available (38,39).

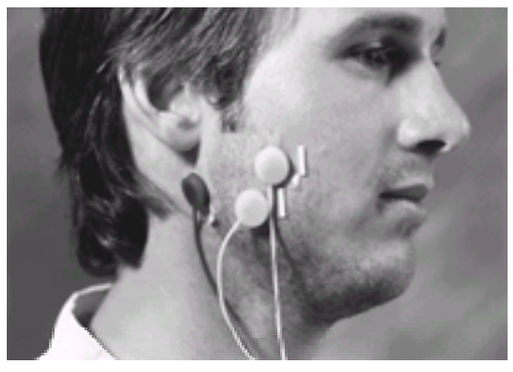

Figure 90-5. Masseter electromyographic electrode placement.

A summary of the literature on biofeedback therapy for MPD syndrome published since the last edition of this chapter is presented in Table 90-2 (40,41,42,43,44,45,46,47 and 48). Wherever possible, the percentage of improvement in the biofeedback conditions is given; if this is not available, the percentage of subjects who achieved clinical improvement (arbitrarily defined by the authors as 50% or greater reduction in pain levels) is presented.

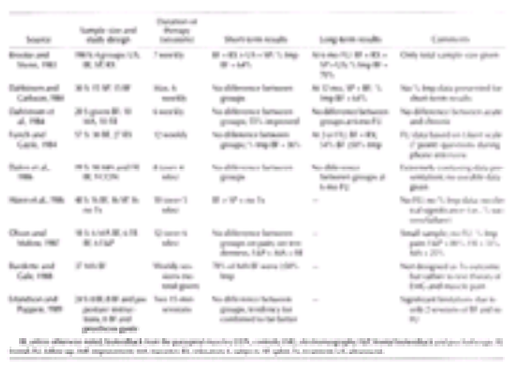

TABLE 90-2. Biofeedback for myofascial pain dysfunction syndrome

Two studies (40,41) compared biofeedback to a no-treatment control group. Using a combination of frontal and masseter biofeedback, Dalen and his colleagues (40) found no differences in pain between the control and biofeedback groups, both immediately after treatment and at 6-month follow-up, with both groups reported to improve significantly. This study, however, is significantly flawed, with no usable outcome data being presented, making it impossible to judge the actual percentages of improvement in both groups. In addition, no explanation was given as to why the no-treatment control group improved. The second study (41) found masseter biofeedback to be significantly better than no treatment, but, like the Dalen study (40), no usable outcome data were presented and, in addition, no follow-up was conducted.

Two studies (42,43) directly compared masseter biofeedback to relaxation therapy. Unfortunately, the relaxation procedure was not described at all in the Brooke and Stenn (42) study and only briefly described as a cognitive-type (i.e., focus on muscles and let them go) procedure in the other (43). Both studies at follow-up, however, found no difference between the two procedures.

Only two studies (44,45) have directly compared masseter and frontal biofeedback, finding no differences in outcome between the two placements. As in the headache literature (49,50 and 51), there was no relationship between ability to control one' s muscle tension and degree of improvement from biofeedback (40,41,46,47). Studies that have combined biofeedback with other treatments (45,48), although flawed, have found tendencies for the combined treatment to be superior to biofeedback alone. Studies that have compared biofeedback to more traditional medical procedures, such as occlusal splints, have found biofeedback to be equal or superior to the traditional medical intervention (41,42,44,48).

Finally, three glaring observations stand out regarding Table 90-2. First, although the majority of the studies have significant limitations, when taken as a whole they appear to be quite impressive in support of the efficacy of EMG biofeedback for MPD syndrome. Second, the four most recent studies all failed to provide any follow-up, but, when follow-up was presented, short-term results were sustained or improved. Finally, and most troubling, no MPD syndrome study of biofeedback as a treatment in and of itself has been published since 1989. Given these earlier positive results, this observation is somewhat perplexing.

The studies presented in Table 90-2, taken in conjunction with the studies detailed in the previous edition of this chapter, strongly suggest that EMG biofeedback is a clinically useful technique in the treatment of MPD syndrome. Biofeedback appears to produce improvement in a significant number of patients and is at least as effective as traditional dental treatments such as occlusal splint therapy.

Deficiencies in the research on biofeedback treatment for MPD syndrome are similar to those discussed in the section on LBP. Large-scale outcome studies, comparing (a) masseter versus frontal versus temporalis placement sites, (b) biofeedback versus relaxation, (c) biofeedback versus traditional dental strategies, and (d) biofeedback in conjunction with other treatments versus traditional dental strategies. The latter approach has been used by Turk and his colleagues (52,53 and 54) in a number of methodologically elegant studies. In these studies, not included in Table 90-2 due to the lack of a biofeedback-only condition, various combinations of biofeedback, stress management training, and intraoral appliances are used, with results showing strong support for combined treatments. Finally, lack of long-term follow-ups, or for that matter, any follow-up at all, is a serious limitation that needs to be corrected. Four of the nine studies reviewed had no follow-up, and three of the five that did contain follow-up were for only 6 months.

BIOFEEDBACK TREATMENT OF OTHER CHRONIC PAIN DISORDERS

Biofeedback has been used with numerous other chronic pain syndromes—so many, in fact, that we cannot hope to review all of them here. Rather, we summarize what we feel are the most interesting areas for clinicians and researchers, including most areas for which a substantial literature exists, as well as some areas for which, although promising, there is a paucity of treatment studies.

The thermal biofeedback treatment of Raynaud' s disease has a well-documented efficacy, with most studies showing a reduction in vasospastic attacks of 80% or more [see (55) for an excellent review of this literature]. Similarly, the work from Blanchard' s laboratory on irritable bowel syndrome [see (56) for a review] has repeatedly demonstrated the effectiveness of a treatment package that includes thermal biofeedback.

Along a similar vein, the biofeedback literature on treatment of constipation pain, especially in children, is both impressive and growing. Here, three studies particularly stand out. Benninga and colleagues (57) gave 29 children who suffered from constipation and encopresis an average of five sessions of EMG biofeedback of the external anal sphincter. At 6 weeks, 55% were symptom-free. Another group of investigators (58) placed 13 children who suffered from constipation into a standard medical care group, while another group of 13 children were placed in an EMG biofeedback (of the external anal sphincter—one to six sessions) plus standard medical care group. At 16-month follow-up, all children were significantly improved, with the biofeedback plus standard medical care group significantly more improved than the standard medical care only group.

One large-scale study, however, does not support the efficacy of EMG biofeedback for constipation pain. In a procedure similar to Cox et al. (58), Van der Plas and colleagues (59) placed 94 children who suffered from constipation into a standard medical care group, while another group of 98 children were placed in a

five-session EMG biofeedback (of the external anal sphincter) plus standard medical care group. At 18-month follow-up, over one-half the children in both groups were significantly improved, with no significant difference between the two groups. In spite of this large-scale study suggesting no advantage to the inclusion of EMG biofeedback to conventional medical care, we believe there is sufficient evidence to conclude that EMG biofeedback is a useful technique in treating the pain of both adult and childhood constipation, especially when the patient has proven refractory to standard medical care.

In addition to constipation pain, a growing body of evidence now exists in the colorectal literature for the efficacy of biofeedback for pain, especially for intractable rectal pain (60,61,62,63 and 64), with one study showing a 75% decrease in pain levels and 88% of patients no longer requiring pain medications (64). One interesting study (60) demonstrated that the use of EMG biofeedback reduces additional surgery for solitary rectal ulcer by 73%.

An extremely interesting and well-designed initial study using EMG biofeedback for the treatment of vulvar vestibulitis was conducted by Glazer and his colleagues (65). Vulvar vestibulitis causes extreme pain in the vulva and pain during sexual intercourse. In this study, 33 women with vulvar vestibulitis were given a portable EMG biofeedback unit and instructions on how to conduct daily, at-home biofeedback-assisted pelvic floor muscle rehabilitation exercises. After an average of 16 weeks of training, pain decreased in an average of 83% and 79% of patients resumed intercourse. It appears that large-scale, controlled EMG biofeedback studies would now be appropriate in the treatment of this painful gynecologic condition.

Fibromyalgia is a type of nonarticular, noninflammatory rheumatism that is characterized by diffuse pain, sleep disturbance, tenderness, and functional impairment. A number of studies have examined the efficacy of EMG biofeedback in the treatment of fibromyalgia (66,67,68,69 and 70), all concluding that EMG biofeedback is useful in reducing fibromyalgic pain (see Chapter 30). Given the relatively promising results, it appears that, here too, large-scale, controlled EMG biofeedback studies would now be appropriate.

Finally, thermal biofeedback has been shown to have some usefulness in reducing the pain of reflex sympathetic dystrophy (see Chapter 20) (71,72). For example, Grunert and his colleagues (71) found that a combination of thermal biofeedback, relaxation therapy, and supportive psychotherapy significantly reduced reflex sympathetic dystrophy pain by 48%. These results were maintained at 1-year follow-up, with 14 of 20 patients returning to work. For any clinician working with such extremely refractory pain patients, these results are indeed persuasive. Once again, it appears that large-scale, controlled studies need to be conducted.

CONCLUSIONS

Biofeedback has been demonstrated to be a useful clinical tool in the treatment of a variety of chronic pain states. Headache and LBP have been the best studied, probably because of their prevalence. Further research should be undertaken to identify patient factors that predict the successful use of this treatment strategy. Applications to other types of chronic pain should also be tested in a rigorous fashion. The technology required to use biofeedback is of low cost; there are few, if any, complications of this treatment; and it is applicable to patients with many diagnoses. Biofeedback deserves a more generalized usage in the treatment of chronic pain.

ACKNOWLEDGMENTS

This chapter was supported by a Department of Veterans Affairs MERIT-Review awarded to John Arena and a National Institutes of Health Grant (NS-33072) awarded to Edward Blanchard. John Arena gratefully acknowledges the assistance of Glenda Bruno, R.N., M.S., and, especially, Gayle S. Rozantine, Ph.D., in the preparation of this chapter.

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CHAPTER 91

Hypnosis

Joseph Barber

It is both dramatic and compelling to observe the tranquil face of a patient undergoing a painful medical procedure with no anesthetic except the patient's ability to dissociate from pain. It is equally poignant to observe a patient's relief from the pain of an injury or disease—relief created not by analgesic medications, but by the psychological capacity to dissociate from pain and suffering. One wonders how this can be possible. There has been so much nonsense written about hypnosis and so many unwarranted claims that it may be difficult for the reader to have a receptive mind. In this chapter, I include information gained from rigorous laboratory and clinical research and I have not included claims or allegations that are not supported by such evidence.

Hypnosis is a condition characterized by a markedly increased receptivity to suggestion, resulting in the possibility for dramatic modification of perception and memory. Price and Barrell (1) have identified five elements common to the hypnotic experience:

- Feeling of well-being
- Absorbed and sustained focus of attention
- Absence of judging, monitoring, and censoring
- Lack of orientation toward time, location, and sense of self
- Experience of one's own responses as automatic

Note that nothing in this description suggests that a patient has been rendered powerless by the hypnotic condition. The integrity of personality and character remains unchanged. An individual who is ordinarily vulnerable to the influence of others will continue to be vulnerable in the hypnotic circumstance. Similarly, an individual who is not ordinarily vulnerable to influence will continue to be invulnerable while hypnotized. For this reason, the effective clinician remains mindful of the need to support and encourage a hypnotized patient, to engage the patient's motivation for relief. Although apparently miracle cures occur often enough to maintain the superstitious illusion of hypnotic power, it is not likely that a clinician can successfully suggest to a hypnotized patient that his or her symptoms will suddenly vanish. Rather, hypnotic suggestions can be used as psychological leverage to enhance the effectiveness of a clinical intervention. In the therapeutic examples offered later in the chapter, the reader will notice that the clinician's acknowledgment of the patient's complexity—for instance, his or her pessimism, skepticism or unrealistic expectation, and, especially, of the pain's meaning to the patient—is reflected in the subtlety and complexity of the suggestions.

With the advent of contemporary anesthetics, of course, hypnotic analgesia is seldom needed in the operating room. However, the patient with chronic or recurrent acute pain who has not responded to curative or palliative intervention may benefit from the appropriate application of hypnotic techniques for pain management.

The first objective when introducing the domain of hypnosis is to acknowledge the healthy skepticism of the reader. Laboratory and clinical research has highlighted the value of hypnotic procedures as both primary and adjunctive clinical interventions. This chapter focuses on how these interventions, as well as interventions involving nonhypnotic suggestion, can be used in the clinical management of acute or chronic pain, and is organized in three parts: (a) basic considerations, including a brief historical overview of hypnosis and suggestion and current theoretical explanations of the action of this intervention; (b)technical considerations, with brief discussion of patient selection issues and of the most common hypnotic techniques used; and (c) clinical applications, including a brief summary of results obtained in various acute and recurrent pain conditions.

For more detailed accounts of how to apply hypnotic techniques and of the relevant supporting research, the reader may refer to Barber (2), Barber and Adrian (3), Fromm and Nash (4), Hilgard and Hilgard (5), Hilgard and LeBaron (6), Lynn and Rhue (7), and Price (8).

BASIC CONSIDERATIONS

History

Hypnosis is a troublesome word, because popular accounts nearly always convey wrong-headed ideas, many of which involve claims of powerful influence and magical effect. A persistent image associated with hypnosis is that of a man with a penetrating gaze mysteriously compelling someone (usually an attractive young woman) to behave in dramatically uncharacteristic ways. This impression has its roots in the early history of hypnosis, which, unfortunately, was often an amalgam of mysticism, magic, and hokum. Although the eighteenth-century physician Franz Anton Mesmer (1734–1815) initiated the development of what has become the domain of clinical hypnosis, his theory of action was a mistaken one (that it involved the transfer of magnetic fluid from the clinician to the patient), and his fascination with the drama of the process was a distraction from its psychological essence.

The Societé Royale in Paris created the Franklin Commission, a panel of eminent scientists chaired by Benjamin Franklin, to investigate experimentally Mesmer's claims of magnetism. The investigative work of the commission was historic for two reasons: It was perhaps the first instance of formal psychological experimentation, and the experimental results ultimately led to the concepts of hypnosis and suggestion.

The subsequent development of the theory and practice of hypnosis in the nineteenth century was primarily focused on its medical application, most notably pain relief, but in 1843, the English physician James Braid documented the importance of the psychological responsiveness of the patient (in contrast to the power of the hypnotist, a myth that exists even today). He observed how a suggested idea could dramatically alter the patient's experience. Braid coined the term *hypnotism*. This was an unfortunate choice, since it connotes a condition of sleep, although the hypnotic experience is not associated with sleep; rather, it is a state of deep absorption in a suggested experience.

In 1850, James Esdaile (9), an English surgeon working in India, successfully used hypnotic methods to induce anesthesia for a series of major surgical cases. This practical development was met with disbelief but also hope, since it meant the end to the routine agony (and associated morbidity) of surgery. Since Esdaile's report, there have been numerous accounts of surgery performed with hypnotic suggestion as the only anesthetic. Almost simultaneous with these initial reports of hypnoanesthesia, however, was the announcement of the successful use of chloroform in the operating room, which led to a waning of interest in the use of hypnoanesthesia.

Toward the end of the nineteenth century, and into the early years of the twentieth century, the focus of clinicians interested in hypnotic phenomena was its

psychiatric application in the treatment of hysteria and dissociation. Except for reports of the use of hypnotic methods in battlefield hospitals, there were no significant developments in the use of hypnotic methods for the relief of pain until the late 1950s, with the work of Ernest and Josephine Hilgard.

After securing his reputation as a premier scholar of human learning Ernest Hilgard established the Hypnosis Laboratory at Stanford University in 1957. For the next 3 decades, that laboratory was a fountainhead of hypnosis research, including especially the investigation of hypnotic analgesia (5,6,10,11,12,13,14,15,16 and 17). At the same time, Martin Orne (18,19), directing the Unit for Experimental Psychiatry at the University of Pennsylvania, also began to conduct hypnosis research, including the investigation of hypnotic analgesia. These pioneering efforts were the basis for subsequent research that has led to the richness of theory and research informing our contemporary understanding of hypnotic analgesia.

Theoretical Bases: Anatomy, Physiology, and Psychology

Because hypnosis is often mistakenly thought of as a magical or occult phenomenon, it is worth remembering that hypnotic phenomena are, in fact, psychological in nature and fundamentally explicable by psychological theory and principles. As Kihlstrom (20) reminds us, “Nothing about hypnosis changes the way the mind works.” How, then, are we to understand phenomena that cut across the spectrum of experience, including amnesia, analgesia, and hallucination? Although there remains the challenge of explaining hypnotic phenomena within a single, integrated psychological theory, over the past 20 years, two primary explanatory schema have risen to prominence: Ernest Hilgard's neodissociation theory, with variations suggested by Bowers (21,22 and 23), Kihlstrom (20,24), and Woody (25,26), and variants of a sociocognitive theory that is primarily the work of Theodore Barber (27), Coe and Sarbin (28), Spanos (29), Kirsch (30,31), and Lynn (7).

Neodissociation Theory

Dissociation theory dates from the late nineteenth century and offers an account of various psychopathologies, most notably hysterical disorders, and provides the essential concept of “a division between two streams of consciousness . . . with only one of these streams accessible” to conscious awareness (20, p. 187). Hypnotic suggestion is effective in both the alteration of symptoms (e.g., sensory alterations, such as blindness, deafness, and anesthesias, as well as motor symptoms, such as paralysis and mutism) of hysterical patients as well as in the creation of similar symptoms among normal human subjects. Consequently, there seems to be a logical connection between dissociative processes and hypnotic processes. Building on the dissociation theory proposed by psychiatrist Pierre Janet (32) nearly a century earlier, Ernest Hilgard offered a neodissociation interpretation of hypnotic analgesia (14). The neodissociation perspective reflects the recognition that some behaviors are not consciously intended, initiated, or controlled. “Dissociated control” (21,33) in everyday life is particularly well revealed in various mental lapses but is the basis for hypnotic responsiveness as well: “Such dissociated control of thought and behavior depends on a hierarchical model of mind, which assumes . . . that different cognitive control systems can operate in relative independence of each other” (22, p. 135).

The neodissociation model proposes that the hypnotic process creates a temporary functional separation between certain cognitive control structures, resulting in the corollary separation of awareness. For example, Hilgard suggests that a hypnotized patient comfortably undergoing a painful procedure is able to do so because of the separation—the dissociation—between the cognitive structure(s) responsible for the appreciation of pain and the central control structure(s) responsible for the individual's conscious awareness. Because a central feature of all hypnotic phenomena is the felt sense of automaticity—that the thought or behavior occurs without effort or, perhaps, even of intention—Hilgard's explanation applies to all hypnotic phenomena, not only hypnotic analgesia. Moreover, his explanation also accounts for nonhypnotic dissociative processes. Recent brain imaging research (34) has yielded evidence for the alteration in brain activity that correlates with hypnotic analgesia and has been interpreted as evidence for the neodissociation model (8).

Sociocognitive Theories

It is well known that social psychological variables affect individual psychological variables in a variety of circumstances. Orne's classic research (35,36) demonstrated that hypnotic experience is not immune from the effects of social variables such as attention of the clinician, the environment, and past experiences. This recognition of the relevance of social psychology to the understanding of hypnotic processes has led some to propose that social variables are *primarily* relevant to this understanding (29). Spanos writes, “Thus, from my perspective, successful hypnotic responding to suggestions . . . reflects goal-directed actions by subjects who, in coordinated fashion, generate experiences and enact behaviors in order to meet what they tacitly understand to be the requirements of the test situation” (p. 325).

Variations of contemporary sociocognitive theory of hypnotic processes have been described by Spanos (29), Kirsch (30), and Kirsch and Lynn (31). Both the neodissociation theory of divided consciousness and sociocognitive theories focus on mechanisms that create alterations in awareness, but whereas neodissociation theories emphasize a temporary splitting (dissociating) of consciousness, sociocognitive theorists emphasize ordinary conscious processes; these do not include perceptions and cognitions that are out of ordinary awareness. Kirsch (30), for instance, theorizes that it is an individual's belief and expectation that determines the hypnotic experience: “Typical hypnotic responses can easily be altered by providing subjects with expectancy-altering information” (p. 451).

The sociocognitive view suggests, for example, that an individual's expectation of analgesia may be self-confirming, so that it is the anticipation itself that reduces the pain.

No one theory has fully accounted for the range of hypnotic phenomena, and all contemporary theories are necessarily tentative. It is likely that any successful theory that emerges will take into account social processes as well as an individual's psychological processes. Both the sociocognitive and neodissociation models each contribute to our understanding of hypnotic processes. However, the neodissociation perspective is supported by a substantial accumulation of data from both basic and clinical research (6,12,13,15,19,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44 and 45). It is particularly clear from this research that hypnotic experience is commonly experienced as automatic and involuntary—and that lack of awareness of certain thoughts or behaviors is central to the experience—a finding that contradicts a central tenet of sociocognitive theory, which is that hypnotized individuals are experiencing no more than what they expect and intend to experience. The neodissociation perspective appears to offer the most parsimonious psychological explanation of hypnotic analgesia and has sufficient empirical support to warrant both our tentative confidence and further exploration (8,25,26,46,47).

Psychophysical and Neurophysiologic Investigations

Psychophysical and neurophysiologic evidence also supports the neodissociation perspective. In reviewing this evidence, Price (8,48) has identified three components that underlie the processes suggested by Hilgard: (a) selective reduction of the affective dimension of pain, (b) reductions in sensory pain by mechanisms that divert pain from conscious awareness once nociceptive information has reached higher centers, and (c) inhibition of pain signals at the spinal level.

Kiernan et al. (40) demonstrated the dissociative quality of hypnotic analgesia and were the first to suggest the role of inhibitory spinal mechanisms in hypnotic analgesia, identifying specific spinal afferent activity associated with hypnotic analgesia. Rainville et al. (43) investigated cerebral blood flow changes that varied with onset and offset of hypnotic analgesia, and reported that their “results provide a new description of the neurobiological basis of hypnosis by demonstrating a specific pattern of cerebral activation underlying the multiple cognitive processes involved in this intervention.” Rainville et al. (34) have extended these findings, offering further evidence for the neurophysiologic correlates of hypnotic analgesia. This evidence constitutes yet more support for the neodissociation model.

Evidence for endorphin involvement in analgesia, including acupuncture analgesia (49), led to the hypothesis of a similar role in hypnotic analgesia. Several investigations, however, have not supported this hypothesis (49,50,51 and 52). In fact, no evidence has been developed to associate particular neurotransmitters with hypnotic analgesia. Sternbach (53), for example, did not find evidence to support his hypothesis for the involvement of acetylcholines in hypnotic analgesia.

TECHNICAL CONSIDERATIONS

Hypnotic Responsiveness

Scientific observation of hypnotic phenomena over the past 200 years has differed on several counts, but one observation most investigators agree on is that—as with all psychological variables—there are individual differences in response. It is well known that, as with any treatment, patients differ in the degree to which they respond to hypnotic treatment (5,6). “Who can be hypnotized?” is a commonly asked question. The question particularly relevant to the clinician considering its use with a patient is, “Under what conditions can hypnotic methods be used to reduce a particular patient's suffering?”

Research has explored this question and determined that variables such as age, intelligence, and personality do not predict hypnotic responsiveness (5). The only

personality trait that has been shown to significantly correlate with responsiveness is imaginative absorption—an individual's capacity to have a temporary experience of believing in imaginary perceptions (54).

Experimental investigations intended to identify predictors of hypnotic responsiveness (also referred to variably as *hypnotic susceptibility* and *hypnotizability*) have yielded differing results. In the typical study, hypnotic responsiveness is measured by reference to an individual's performance on a standardized test. Such a test creates the opportunity to respond to a hypnotic induction and to several suggestions for classic hypnotic behaviors (e.g., analgesia, amnesia, and hallucination). The number of behaviors the individual demonstrates then becomes the numeric measure of hypnotic responsiveness. Hilgard and Morgan (15), for example, demonstrated that the correlation between such measures and an individual's ability to hypnotically reduce experimental pain is significant ($r = 0.50$); this accounts for only 25% of the variance. However, they also reported that 44% of individuals whose responsiveness scores were low were able to reduce their pain by 10% or more.

> This means that the relation between reduction and hypnotic responsiveness is probabilistic, with a greater probability of successful pain reduction for those highly responsive to hypnotic suggestions. The data do not mean that those unresponsive to hypnotic suggestion as measured by the scales, have no possibility of help through suggestion. (5, p. 68)

A preponderance of laboratory evidence clearly supports the idea that hypnotic responsiveness is a relatively stable trait and that only a minority of individuals can achieve clinically significant hypnotic analgesia (5,6,10,11,13). However, the issue is not as clear as this may suggest, for there is also evidence that there may be other variables that determine clinical effectiveness of hypnotic treatment (55,56,57,58,59,60,61 and 62). We can infer from these investigations that variables inherent in the clinical context (including the clinician-patient relationship and the patient's felt need for relief) may engender responsiveness to hypnotic treatment in individuals whose responsiveness scores are measurably low. The laboratory research of Gfeller et al. (61) in particular confirmed the clinical lore that the clinical relationship is a primary determinant of responsiveness.

Gfeller and his colleagues (61) compared a low-interpersonal-training treatment with a treatment designed to augment rapport with the trainer and diminish resistance to responding. Following the intervention, 50% of previously unresponsive subjects tested as being highly responsive to hypnotic suggestion. Practice-alone control subjects' performance was stable across testing. The importance of rapport was demonstrated by rapport ratings paralleling group differences in hypnotic responding.

One explanation for the disparity in research findings, at least with respect to the analgesic capacity of those individuals with low responsiveness to hypnotic suggestion, might be that those with high responsiveness are better able to reduce the sensory-discriminative component of pain, whereas those with low responsiveness are sufficiently able to reduce the motivational-affective component (62). For example, it may be that low responders are not capable of dissociating from the sensory-discriminative component but are able to reinterpret the experience, thereby reducing the motivational-affective component. If these two components are not independently measured, it is entirely possible that some patients' measures reflect the sensory component, whereas others' reflect the affective component. This distinction may be particularly salient between the hypnosis laboratory (where pain measures tend to emphasize the sensory component by asking how intense the sensation is) and the clinic (where pain measures tend to emphasize the affective component, since it is suffering that brings the patient to the clinic).

It is also worth considering that reporting bias may well play a role in the discrepancy between findings in the laboratory and the clinic (see Chapter 24). In general, the clinical literature reports hypnotic suggestion to be more effective as an analgesic than one would predict from the experimental reports. Part of the explanation for this discrepancy may be found in the difference in motivation between laboratory subjects and clinical patients. Experimental subjects are significantly less motivated to experience a hypnotic effect than are patients who are seeking relief from suffering. There are also significant differences in the behavior (and motivation) of experimenters and clinicians. Experimental protocols usually require rigid adherence to a well-operationalized, standardized induction and set of suggestions. Rarely is the purpose of an experiment the search for optimum hypnotic effect. However, that is precisely what is involved in the clinical situation. Effective clinical use of hypnotic suggestion requires an individualized approach. Rarely is a standardized set of procedures followed, and the clinician, normally focused only on doing what is effective, may vary or repeat procedures until success is obtained. Although this may lead to successful clinical outcomes, it is usually impossible to assess the causal link between treatment and results (see Chapter 81).

Moreover, as Diamond (60) suggests, the relationship between the clinician and patient is a powerful determiner of the hypnotic effect (or any clinical effect). The relationship between an experimenter and subject is significantly less personal (sometimes the hypnotic induction is even conveyed by a tape recorder) than the well-developed, intimate, and more potent relationship of a concerned clinician and a patient in pain. Whatever the explanation for the disparity of reported hypnotic effect between experimental and clinical contexts, it is clear that clinical success with hypnotic suggestion requires innovative, personalized, clinically sophisticated procedures. It is difficult to compare such procedures with well-controlled experimental procedures. So, for the moment, the complex question of hypnotic responsiveness remains an open one.

Advantages and Disadvantages

The therapeutic goals in the treatment of acute or recurrent pain are the reduction of suffering and return to good function. Hypnotic methods may be suitable to both goals. The primary advantage of hypnotic intervention is that, in a given case, it may be effective when no other treatments have been. It is less invasive than medical pain management interventions, and it does not produce side effects, such as somnolence or motor retardation, as opioid medications may. Moreover, because suggestions can include those that encourage a healthy outlook and expectation for recovery, the clinician may expect that, in addition to analgesic effects, successful hypnotic intervention will also facilitate the patient's development of an optimistic and salutary outlook.

Unlike other pain management interventions that are done to the patient, hypnotic methods require the active psychological engagement with and involvement of the patient. So, in the case of a patient who may be ambivalent about achieving symptom reduction (as in the case of a patient for whom there are financial disincentives for rehabilitation), this ambivalence may result in only intermittent or temporary response or in a lack of treatment responsiveness altogether. Adequate evaluation before treatment will identify such ambivalence, and treatment plans can be guided by this information.

A distinct advantage of hypnotic methods of pain management is the potential for long-term effectiveness. In this connection, the importance of using posthypnotic suggestions is discussed later, under Extending Relief.

CLINICAL APPLICATIONS

Indications and Contraindications

A patient who suffers acute, recurrent, or chronic pain may be a likely candidate for hypnotic treatment if the following contraindications are not present:

- Disincentive for relief (e.g., financial or social reward for continued suffering)
- Intellectual impairment (characterized by an inability to attend and to learn)
- Psychological impairment (characterized by blurring of psychological boundaries, poor reality orientation, severe depression)

Because hypnotic treatment can cause radical alterations in cognitions and behavior—with a concomitant experience of nonvolitionality—concern is sometimes expressed that hypnotic techniques can be harmful. Much effort has been made to settle the question of whether hypnosis can cause an individual to behave in ways that would be harmful. Even though there has been no reliable documentation of an instance of harm coming to an individual as a result of clinical hypnotic intervention, this concern is often raised because of the occasionally harmful consequences of the antics performed by subjects of nightclub hypnotists. Whereas the behavior demonstrated in such acts can be explained without reference to hypnosis (e.g., group pressure and compliance with demand characteristics), there is still reason to believe that the psychological changes that can be produced by hypnotic intervention are sufficiently powerful to warrant its use only by trained clinicians. Hypnotic treatments, like any other clinical tool, can be misapplied, resulting in harm. This is a good reason to carefully train clinicians; it is not, however, a good reason to avoid the use of effective clinical tools.

Hypnotic methods can be harmful when

- The clinician does not have an adequate understanding of the patient's psychological needs and capacities. However, adequate training can prepare the clinician to respond appropriately to the patient.
- The patient's capacity for coping with deep absorption in fantasy, or with intense emotional contact with the clinician, is insufficient. However, the clinician can be prepared for this by adequate evaluation before treatment, through the use of both standard clinical interview and formal assessment instruments, such as

the Minnesota Multiphasic Personality Inventory-2, the Symptom Check List 90, and perhaps one of the depression inventories (e.g., the Beck Depression inventory), which can inform the clinician about the patient's psychological health. The Tellegen Absorption Scale allows the clinician to infer how readily the patient may respond to hypnotic intervention, since this requires imaginative absorption.

The experience of being hypnotized is generally innocuous and often pleasant. Yet, hypnotic treatment should only be undertaken by someone with sufficient clinical skills, including knowledge of psychological phenomena and psychopathology. Because hypnotic techniques can be applied across several areas of clinical expertise, it might be a temptation for a clinician trained in one area to use hypnotherapy to treat a patient whose problem would otherwise lie outside the clinician's training. For example, a psychologist may be well trained to treat a patient's pain, if the patient has already had an adequate medical evaluation and the psychologist is mindful of the medical aspects of the patient's condition. It would not be appropriate for the psychologist to treat a patient's pain without proper medical collaboration. Similarly, a gynecologist may be properly trained to hypnotically treat a patient's pelvic pain, but it would be inappropriate to treat the patient's psychosexual dysfunction with hypnotherapy. If the patient's pelvic pain is associated with psychological factors, it is best for the gynecologist to refer the case to someone with appropriate psychological training. One should only treat a problem one is trained to treat. If one is also trained in the use of hypnotic methods for such a problem, those methods will probably enhance the treatment. Training in hypnotic methods, alone, however, is not an alternative for adequate clinical training in general.

Techniques

Since hypnotic treatment requires the patient's cooperation and responsiveness, it is helpful for the clinician to observe how the patient responds. For example, ordinary suggestions made to a patient about sitting comfortably provide an important opportunity to observe how the patient responds. For example, how literal or confluent is the response? How at ease is the patient? This is not a hypnotic response, but it may offer a clue to subsequent responses. Moreover, this reminds us that suggestions alone—in the absence of a hypnotic experience—can substantially augment clinical effectiveness, through promoting patient comfort and confidence, and by promoting healthy expectations.

The manner in which the clinician introduces the topic of hypnotic treatment to the patient may either augment or diminish the patient's subsequent responses. The word *hypnosis* tends to have such unhelpful connotations for most people, and it probably does not convey an accurate idea of the treatment intended by the clinician. So it may be most helpful to discuss the treatment without reference to the word *hypnosis.* Rather, the treatment can be described in more operational terms, thus obviating the use of the word altogether. The intention is not to obfuscate or deceive, but, rather, to communicate clearly. Of course, if the patient uses the word *hypnosis*, the best response probably requires use of the word, as well. If a patient has had prior experience with hypnotic treatment—especially if the experience was satisfying—this experience can be used.

Following are some examples of what might be said to introduce the topic of hypnotic treatment, using operational terms:

- “You probably know that the relationship between mind and body is a powerful one. Would you like me to show you how to use the power of your imagination to help you feel better?”
- “Let's use your ability to fantasize, now, to help you feel better.”
- “Mental imagery can be very helpful in retraining your nervous system so that the nerves that carry the useless information about your pain will do so less and less in the future.”
- “Your ability to become deeply absorbed by your imagination can be really helpful to you now. Will you close your eyes right now, and take a very deep, very relaxing breath, so you can begin to notice how really relaxed your mind can become?”

Each example is intended to convey to the patient that he or she possesses the means to increase comfort. The clinician who uses such “nonhypnotic” language to introduce hypnotic treatment should remember subsequently to use language that is consistent with this introduction.

The three fundamental elements of hypnotic treatment are induction, therapeutic suggestions, and suggestions to end the hypnotic experience.

Induction

Hypnotic induction is the facilitation of the patient's alteration in consciousness from ordinary wakefulness to a state of imaginative absorption that supports the acceptance of clinical suggestions. The goal of the induction is to engage the patient's capacity to dissociate. Although there are a few classic induction techniques, in truth, the clinician is free to create whatever induction will most readily facilitate the patient's experience of trust, security, and interest in what the clinician is saying. Instruction in the technique of induction is well beyond the scope of this chapter. However, the literature is replete with such instruction (2,3,5,6,5364,65,66,67,68,69 and 70). In the context of this chapter, however, we can explore the ideas that make up an effective hypnotic induction.

Because hypnotic treatment requires the active involvement of the patient's imagination, the first goal of the clinician about to embark on hypnotic induction is that of engaging the patient's interested attention. It may be that the clinical context itself—and the patient's wish to be relieved of suffering—will be sufficiently interesting.

The second goal is to help the patient to focus his or her attention—to reduce the range of attention—and then to direct that attention inward, at which point the patient's imagination can begin to emerge as the agent of the ensuing hypnotic process. (At this point, suggesting that the patient close his or her eyes has the virtue of both eliciting a cooperative, voluntary response from the patient as well as eliminating visual sources of distraction—and offering another opportunity to observe how the patient responds to a suggestion.)

The final goal of the induction process is that of dissociation. Dissociation distinguishes the hypnotic experience from the nonhypnotic. Many adults and most children are able to develop a hypnotic experience with little or no facilitation by the clinician (6,70,71 and 72). In such cases, the clinician can function best by acting as a guide.

The following is an example of a hypnotic induction. It has been abbreviated for purposes of highlighting the essential suggestions (which, in practice, may often be repeated for emphasis).

1. Engaging the patient's interest and attention: “Are you ready to begin learning how to use your imagination to see if you can feel better?”
2. Focusing attention and turning it inward: “Close your eyes and take a very deep, very comfortable breath and, now, hold it . . . hold it. . . . That's fine. Now, let it all the way out, and just notice how easily can feel yourself sink down into a place of very deep quiet and relaxation.”
3. Dissociation: “As you become more and more aware that each breath contributes to a greater sense of comfort and ease, you might have already noticed that the sounds around you . . . all the sounds you can hear . . . are sounds that can become more and more a part of your experience of comfort and relaxation . . . with nothing to bother you, and nothing to disturb you.”

Therapeutic Suggestions

Once the patient is experiencing dissociation, suggestions can be offered to reach the therapeutic goal. Posthypnotic suggestions are discussed later in the chapter, but it is at this stage of treatment that they may be communicated. It is helpful to the clinician to know if the patient is responding to suggestions. Since the analgesic response takes place only in the patient's imagination and is essentially invisible to the clinician, suggestions for other, overt behaviors may be helpful, simply to assess the patient's responsiveness. Examples of therapeutic suggestions are given later in the chapter.

Suggestions to End the Hypnotic Experience

Once therapeutic suggestions, including posthypnotic ones, have been given, the hypnotic experience can be brought to an end. (In the case of immobile patients, e.g., patients in a burn ward, this may not be necessary.) Normally, the clinician suggests that the patient will, after the experience, feel alert, rested, curious about the outcome, and so on. For example, “So now, I'd like you to take one or two very deep, very refreshing, very energizing breaths. As you open your eyes, notice how easy it is for you to so quickly feel alert and refreshed. Almost like waking from a very refreshing nap.”

Strategies for Creating Hypnotic Analgesia

Just as there is an almost limitless range for creating a hypnotic induction, so, too, the patient's capacity for developing hypnotic analgesia may be accessed by a variety of suggestive strategies. When developing the treatment plan and considering which strategy to use, the clinician should be clear about the goal. In an acute context, for example, the goal may be simply to facilitate the patient's comfort during the acute period. In the context of treating recurrent pain, however, the clinician might keep in mind that the goal is to facilitate a reduction of suffering on the part of the patient with a concomitant return to good function (except, of course, in the case of patients with terminal illness). So, although the clinician may elect to follow one of the classic strategies described that follow, optimal effectiveness may depend on creativeness guided by the clinician's understanding of the patient's individual needs (e.g., autonomy or dependence, firmness or gentleness, clarity or ambiguity). For instance, does the patient feel more at ease if the clinician relates as an equal partner in the treatment or as an authority? Does the patient respond more readily if the intervention is approached as skills training or as an experience of altered consciousness? To what extent is the patient ambivalent about experiencing a reduction in pain? What consequences might the clinician expect if the patient feels less pain and suffering? Should the reduction in pain be suggested to be immediate or to occur at a later time? These are a few of the many questions the clinician will consider during the ongoing observation and growing understanding of the patient.

Acute Pain

For the immobile patient—one undergoing a painful procedure, is status postoperative, or is incapacitated by disease or injury—activity and full orientation to the environment are not important. Suggestions for dissociation from severe pain (and, too, from the unpleasantness of the circumstance), and can yield substantial levels of comfort (73,74). Since the clinical purpose here is to reduce the patient's suffering, the nature of the pain is irrelevant. What is crucial is the patient's understanding and expectation about pain. In other words, the meaning of the pain is what distinguishes the intervention from one patient to the next. Patients suffering from postoperative pain, postburn pain, dental pain, labor pain, and acute pain from other medical procedures may all benefit from hypnotic intervention. For more detailed instruction in the treatment of acute pain, the reader is referred to descriptions of treatment of labor pain (74), postburn pain (75), dental pain (56,76), and pain from medical procedures (77).

Here is an example of a suggestion intended to produce such dissociation for a postoperative patient:

> You don't have to stay here in bed, conscious of all the work, all the noise, that goes on here in the hospital. Would you enjoy a kind of vacation from this room?
>
> Wouldn't it be pleasant to imagine gently floating through the window and out into the beautiful blue sky of this sun-filled day? And to just float on, to wherever you'd like to be? Almost like living a favorite daydream . . . just enjoying going wherever you'd like to go, being wherever you'd like to be, leaving your body here in the room to be taken care of. Your mind, your imagination, can take you far away, if you'd like, to a holiday from discomfort, a holiday from boredom, to really enjoy yourself.

Chronic Pain Syndromes

Because hypnotic processes take place at the highest level of neural organization, the nature, quality, and location of pain are not essential determinants of success (as it would be, e.g., with a local anesthetic acting on peripheral nerves). That is, there is no strategy unique to treatment of osteoarthritic pain of the knee rather than the elbow, or of causalgic pain of the arm or of the leg, or of neuropathy of the face or of the foot. Hypnotic treatment can be effectively applied to any pain syndrome, so long as pain relief is in the patient's interest.

What is relevant about the choosing strategies for treating various pain syndromes is the phenomenology of the pain. That is, how the patient experiences the pain and what the pain means to the patient are crucial to effective treatment. Does the pain worsen with activity (as might be the case with, e.g., osteoarthritis)? Does the pain worsen with certain mood states? Is the patient's life threatened by the pain? Is the patient's sense of self threatened by the pain? Does the pain remind the patient of the trauma that caused the pain? Does the patient think someone else is responsible for causing the pain (as might be the case with a patient injured by a drunk driver)? If so, does the patient feel victimized by the injury or illness? Does the pain mean to the patient that life can no longer be happy, satisfying, or meaningful? Does the pain mean that the patient can no longer enjoy certain activities? Does the pain mean that the patient expects increasing disability and death? Will the patient receive compensation only so long as there is pain? The answer to these questions will guide the clinician's interventions.

Interim Strategies

Ordinarily, the patient suffering recurring pain has had prior experiences of treatment failure, so the clinician may find it helpful to use temporary interventions to accommodate the patient's pessimistic expectation and belief about pain relief. Once the patient has experienced what may be initially implausible—that is, the modulation of intransigent pain—more ambitious clinical goals may then be set. The following are examples of some initial treatment strategies.

Sensory Substitution. Just as one's imagination can alter the perceived intensity of pain, so it can also alter the perceived sensory quality, resulting in a reinterpretation of sensations that may be more tolerable. A sensation of intolerable burning, for instance, can be substituted by a sensation of cold. The substituted sensation does not necessarily have to be pleasant, but only more tolerable than the original sensation. Substituting a sensation is probably not the ultimate clinical goal, but it has the following advantages:

- The patient knows the pain is still present (e.g., so the cancer patient can be assured that the persisting cancer will continue to receive proper medical attention) and can monitor its progress, thus retaining a sense of control over the condition (78).
- The substitute sensation is not particularly pleasant, so its presence may seem more plausible to the patient than a pleasurable sensation.
- Because the patient does not lose financial and social incentives (because the pain still persists), this interim strategy may be a means for negotiating with the patient further treatment goals that might involve the loss of some or all such incentives.

The following is an example of suggestions for sensory substitution:

> Those sharp sensations in your shoulder, the ones you describe as “like a knife blade,” are very likely to begin to feel peculiarly different in a little while. I'm not sure exactly how they will begin to feel. It might seem, at first as if the sharpness just becomes more and more dull . . . as if the sensation is less deep, maybe. Or, maybe you have already begun to notice that the steadiness of the sensations has begun to change . . . as if they seem to come in waves now . . . strange, not altogether pleasant waves of dull pressure.

Displacement of Pain. Displacement of pain from one area of the body to another is yet another example of a perceived modulation. It can be useful both to render an intolerable pain more tolerable as well as to embolden a patient to experience fuller relief. Displacement may be particularly appropriate when the pain is well localized and primarily intolerable because of its location. Midline pain, for instance, is less tolerable than pain located more peripherally.

> You have probably already noticed that the pain moves, sometimes, just a little, sometimes surprisingly . . . and you might begin to notice, as I talk with you, that the movement seems to become more noticeable . . . and that it moves in an almost circular way, like an outward spiral. Spiraling outward, always spiraling outward, sometimes so slowly it's almost as if it isn't happening. If you pay attention to that movement, though, you might notice that the feeling seems to be moving out of the center of your belly, spiraling ever outward; almost as if it's reaching, reaching . . . so curious, so odd, yet farther and farther from the center of your belly.

Diminution of Intensity or Affect. Most of us have had the experience of being able, by using our imagination, to modulate a perceptual experience. Sometimes we feel a change in the intensity of the perception, and sometimes we notice a change in how we feel about the perception, and sometimes our experience is that both components have changed.

The hypnotic experience makes it possible for an individual to modulate the perception of pain, sometimes only a little, and sometimes to a dramatic degree. Here is an example of a suggestion that might be made to a patient to reduce the sensory component of pain:

> You remember that you have rated the intensity of the painful feeling as a “7.” Picture in your mind an image of that “7.” Do you see it? That's fine. The number you see is the number you feel. And the number you feel is going to become smaller and smaller. Now, notice, as you watch that “7” very closely,

watch how it begins to change. Notice how curiously the sharp angles of the “7” begin to soften, to become a gentle curve. . . . Tell me when you begin to first notice that the “7” has become a “6.”

[The patient has reported seeing the “6.”]

That's fine. . . . Now, as we continue, notice how the loop of the “6” begins to separate and, ever so slowly, becomes. . . . What number do you see now?

[The patient reports a “5.”]

That's fine. And tell me, now, do you feel the same or different than when we began?

This conversation can proceed, with the clinician continuing to guide the patient to an experience of continually lower intensity pain.

The same suggestions could focus on the affective component, rather than the sensory. In this case, reduction of the sensory component is not an issue. All that matters is that the sensations are not perceived to be unpleasant or bothersome, so that the patient does not suffer (independent of the intensity of sensation).

Examples of Strategies for Treating Chronic Pain Syndromes

Cancer Pain. Although some cancer patients experience pain of the disease itself, much of the pain associated with cancer is a result of clinical procedures (78). Such procedural pain can be treated as described previously, under Acute Pain.

The significant feature of cancer pain that requires the clinician's awareness is the meaning of the pain to the patient. Cancer pain threatens the patient's sense of safety and security. Some patients report feeling a particular dread of “being eaten” by the cancer. The pain of cancer may be both as much a source of anxiety and fear as it is actual sensory pain. As with treatment of other syndromes, the treatment of the pain associated with cancer requires that hypnotic suggestions encompass the patient's own sense of the pain. For instance, does the patient equate pain with death? Does the patient have a vivid sense that the cancer is consuming him or her? Sometimes, patients are reluctant to become fully unaware of the pain of cancer because they experience it as a way to monitor the progress of the disease. The clinician will be more effective if it is clear how the patient experiences his or her pain.

Headache. Although the etiology of headache is complex and varied (see Chapter 48), I simplify the problem for purposes of this chapter by collapsing the many headache categories to the following few, which encompass most of the headaches likely to be treated by hypnotic methods: migraine headache, muscular tension headache, cluster headache, and posttraumatic headache.

Headache pain is often less easy for a patient to tolerate than pain located elsewhere because it seems so central to awareness. It may be helpful, then, to “co-opt” the pain by incorporating it into the suggestions for hypnotic induction—so that the patient does not have to struggle to resist the pain to pay attention to the clinician. Here is an example of suggestions that might be used when employing such a strategy:

As you listen to the sound of my voice, notice that the sensations of aching [or pressure or whatever the patient experiences] can be almost at the very center of your awareness. You can hear my voice and pay attention to those sensations. As you do, nothing else seems to matter. Everything else just fades away. You hear my voice, you understand my words, you feel the sensations in your head, and nothing else matters.

And notice how curiously those sensations seem to change as I speak. You might notice that they seem to fade, momentarily, with each word. Or you might notice that they seem to move, almost in a spiral, each time I speak. I don't know exactly how you'll notice those sensations change, but I hope you can be interested and curious to notice. . . .

Also, it may be helpful to treat the patient when the headache is not present, using posthypnotic suggestions to intervene when the pain subsequently recurs (see Posthypnotic Suggestion, later in this chapter). This is a crucial factor when treating migraine pain. Ordinarily, the pain of a migraine is sufficiently debilitating that a patient cannot tolerate hypnotic treatment during a migraine episode. Migraines are treated most effectively by posthypnotic treatment. When a patient is not in pain, hypnotic suggestions may use prodromal signs as posthypnotic cues that then result in the posthypnotic experience of aborting the headache before it begins. This strategy, in modified form, is also effective for patients whose migraines are not accompanied by an aura. A more detailed exploration of this procedure can be found elsewhere (2).

Neuropathic Pain. The pain of facial neuropathy or of the various peripheral neuropathies can be approached in a number of ways, using the principles above. Here is an example of suggestions that might be given to a patient with facial neuropathic pain:

It is so curious that those painful feelings in your face are going to begin to change. I'd like you to be particularly alert to the ways they feel different in the future. For instance, you might notice that, the instant you feel the sensation of electricity just below your eye, in the very next instant it will feel more like a strange sort of touching sensation . . . almost as if someone is moving a feather across your face.

Or, you might notice that the painful sensation seems to “want to start,” but just can't get started. As if those feelings are becoming weaker and weaker. And soon it will be very difficult to feel them at all.

Or, you might notice that you have learned a kind of control over the painful feelings in your face. The next time you feel one, you can take a very deep breath, hold it for a moment, and then, as you let it all the way out, you notice that you are also letting the pain all the way out . . . almost as if you are breathing it out. And you can continue to breathe it out, with every breath, so that you feel better and better. And you can enjoy discovering just how much difference you can make to how well you feel.

Musculoskeletal Pain. The most effective treatment of recurring musculoskeletal pain is likely to be a combination of antiinflammatory medication, physical therapy, and strengthening exercise. Except for the relief of acute pain, and perhaps to facilitate the patient's compliance with nonhypnotic treatment, it may be that there is no appropriate role for hypnotic treatment of musculoskeletal pain.

Phantom Limb Pain. Phantom limb pain can be particularly vexing, to both patient and clinician alike, both because its etiology remains mysterious and its treatment variably successful. Hypnotic treatment may contribute to the patient's pain relief, especially if, in addition to suggestions for analgesia, suggestions are also focused on the patient's sense of loss and how to accommodate to the loss—to make peace—with respect to the amputation. It can be especially effective to help the patient experience the phantom limb as comfortable (e.g., the limb is no longer twisted or crushed or otherwise in pain). Subsequently, suggestions may be given for lessening of any awareness of the limb.

Extending Pain Relief

Just as the temporary relief of a local anesthetic is likely not to be a satisfactory clinical result for the patient with recurring pain, so the relief a patient may feel during the hypnotic treatment is also not sufficient. Once temporary relief has been achieved, then, it becomes necessary to extend the duration further, so the patient may feel more comfortable at work, at play, while awake, and while asleep.

Posthypnotic Suggestion. The unique and significant role played by posthypnotic suggestions in the effective management of pain has been explored in greater detail elsewhere (5). In this chapter, I describe the utility of posthypnotic suggestions and offer a model for their use to extend hypnotic pain relief, for it is through the application of posthypnotic suggestions that the practical and clinically meaningful relief of pain is most readily accomplished.

Although we await a satisfactory theory of action of posthypnotic analgesia, the following is an explanatory schema that serves as a first attempt (79):

1. Hypnotic suggestions (and their subsequent repetition) result in the dissociation of noxious perceptions, reducing the sensory and/or affective components of pain.

2. Over time, this analgesia results in neural reorganization (80) so that pain responses are replaced by new, nonpainful responses that are developed in response to painful stimuli so they no longer produce suffering.
3. The hypnotic effect is greatly facilitated by the clinical relationship.

As every clinician knows, the reality of the therapeutic enterprise does not break down neatly into the principles described above. However, in formulating treatment from those principles—of promoting a trusting therapeutic relationship and an openness to new learning—two components may be identified: The simultaneous communication to the patient of certain ideas and the use of posthypnotic suggestion. These ideas include the following:

- An initial empathic joining with the patient's hopelessness while suggesting a paradoxic hopefulness
- An extension of the patient's usual experience of being controlled by the onset of pain by suggesting the subsequent reduction of pain will also be out of the patient's control.

An example might be as follows:

> You've had such frustration, you must find it almost impossible to believe that anything can help your pain. It must be very hard to believe that I can help you. So it can be a very interesting, maybe very pleasing surprise when you begin to notice that you really are feeling better.

The attitude that seems to be helpful in supporting therapeutic effect is similar to that associated with 12-step programs: Abandon your inflexible belief in total personal control and relinquish your usual attitude of either unreasonable hopelessness or hopefulness.

Occasional subsequent reversals in the course of the patient's life (e.g., emotional trauma, reinjury, progression of disease) can markedly reduce the patient's continued pain relief. However, if subsequent treatment takes into account the meaning of the reversals, improvement may once again be reestablished.

Patients who successfully experience significant pain reduction tend to focus on those experiences and to minimize occasional failures, partly by incorporating the clinician's own optimism and partly by virtue of their own optimistic qualities. This optimism is supported by clinical success, which is why effective hypnotic treatment usually progresses stepwise, built initially on occasional noticeable differences in the pain, yet also acknowledging the patient's experience of not being able to reduce the pain.

Posthypnotic suggestion for analgesia uses the patient's fear of being unable to control the pain, and yet of wishing that pain would be relieved. The clinician hopes that this attitude will facilitate the development of a therapeutic relationship that capitalizes on the patient's pleasant early memories of being well cared for and needs for nurturing, thereby empowering the clinical intervention. Although suggestions must necessarily be highly idiosyncratic, responding to the patient's needs and expectations, the following may serve to illustrate suggestions:

> I wonder if you'll feel surprised, later today. . . . I don't know what time, later today, of course . . . maybe at 10 of 4 . . . or maybe at 4 of 10. . . . I really don't know what time it will be . . . that you will have the opportunity to suddenly notice that you're feeling better than you expected to feel.
>
> I don't know, though . . . it might not actually be the time on the clock . . . maybe it will have to do with what you are doing at the time . . . maybe you'll be turning the pages of a magazine . . . or sipping from a cup . . . or turning to catch a glimpse of color going by. . . . I don't know what you'll be doing later today when you have the opportunity to suddenly notice that you're feeling better than you expected to feel.

Self-Hypnotic Management. Another means for extending the duration of relief is by teaching the patient how to use self-hypnotic techniques. Self-hypnosis requires the patient to take the initiative to take time out from his or her day, to settle in comfortably, and to provide suggestions for inducing the hypnotic experience, followed by therapeutic suggestions. Most patients seem able to learn self-hypnotic techniques, although, as with most processes of personal development, this may involve complications. A patient's interest in learning self-hypnotic techniques and willingness to use them provide a valuable index of his or her motivation for actively participating in recovery, as well as a means of assessing broader psychological issues, such as attitude toward pain and readiness for self-care. If not effectively assessed, these attitudes may become an obstacle to therapeutic success.

It is sometimes the case that, even when experiencing hypnotic analgesia, some patients are resistant to initiating and maintaining such treatment for themselves. A common issue that emerges when such resistance is addressed is the patient's preference for being taken care of by the clinician, rather than initiating self-care. Most people enjoy being nurtured and cared for by someone else, and hypnotic treatment is likely to evoke this preference. The pleasure of being nurtured can be threatened by what may be perceived as the demand for self-care. Exploration of a patient's reluctance to use self-hypnosis may reveal that

- Although hypnotic analgesia is a relief, self-hypnotic training and treatment may feel emotionally empty and, therefore, aversive.
- Hypnotic treatment may recall a patient's earlier experiences of nurturing and care, so self-hypnotic training may feel like abandonment.
- Hypnotic treatment feels virtually effortless, but self-hypnotic treatment may feel unpleasantly effortful.

A patient's experience of self-hypnotic training as both effortful as well as abandonment by the clinician may be sufficient to lead to avoidance of learning self-hypnotic techniques. When a patient's motivation for learning self-hypnosis has been established, however, a number of techniques are available (81). A simple technique involves the use of a posthypnotic suggestion. For example, the clinician might say

> Whenever you want to feel this kind of comfort and well-being, all you have to do is sit back in a chair, a sofa, or a bed and take a very deep, very satisfying breath . . . and hold it, hold it. Then, as you let it all the way out, these feelings of comfort and well-being automatically come washing over you, just like water in a hot tub, with nothing to bother you and nothing to disturb you.

Self-hypnotic methods involve learning a skill; as with other skills, competence improves with practice. Sometimes it is helpful to make an audiotape for the patient to use at home as a practice aid, although it is also helpful to emphasize to the patient that the development of this skill (and the consequently increased duration of pain relief) requires a substantial commitment of time and effort.

As a patient's improving condition permits greater independence from treatment, less frequent treatment is necessary. At this point, clinical follow-up becomes increasingly important. Sometimes, substantial time passes during which a patient successfully maintains pain relief. Then, for a variety of reasons, he or she may find such pain management difficult. At such times, a “booster” treatment may be all that is necessary to return the patient to independent functioning. It may also be useful to help the patient identify the antecedents to the present difficulty in using self-hypnosis, so future coping will be more effective. Sometimes, of course, with a worsening medical condition, more intensive treatment may become necessary.

Results

Self-Reported Pain

Hypnotic treatment can be expected to reduce a patient's subjective report (and experience) of pain and suffering. Use of a Visual Analogue Scale simplifies the patient's task of reliably reporting both the sensory-discriminative and the affective-motivational components of pain. There is tremendous variation in both the latency and degree of reported pain relief. Some patients report relief following the first treatment, whereas others do not report relief until undergoing several treatments. Similarly, the duration of relief may be initially highly variable. The clinician can help the patient to tolerate this initial variability to capitalize on the improvement it represents, and to develop more stable and durable pain relief.

Functional Status

The clinician's interventions need to be focused on rehabilitation since this, not merely analgesia, is the clinical goal. Patients successfully treated for acute recurrent and chronic pain can be expected to return to good function, subject to the physical limitations of their condition.

Return to Work

If a patient's pain is substantially reduced by hypnotic intervention, the patient can be expected to return to work. Symptomatic relief is unlikely in patients for whom the opportunity to return to work is unappealing. Patients whose coping strategies include self-hypnotic skills learn to integrate them into their daily work lives.

Complications

Hypnotic methods are not without risks that, although rare, may include complications as the result of accelerated transference, acting out, disorientation, hysterical manifestations (e.g., paralysis), and memory contamination (82). As is evident from this list, these risks are more likely to be associated with the use of hypnotic methods in psychotherapy and less likely in the context of pain management.

If the therapeutic goals are not aligned with the patient's perceived self-interest, then complications are likely to arise from any treatment, including hypnotic treatment. Although there is no evidence that the hypnotic experience is itself harmful, if the patient is severely depressed, psychotic, or pathologically irresponsible, complications to hypnotic treatment may arise (82). An adequate medical and psychological evaluation will be likely to alert the clinician to potential complications, and adequate clinical training will prepare the clinician who confronts such complications (83).

CONCLUSIONS

Hypnotic intervention can be effective for the palliative treatment of a wide range of acute and recurring painful conditions. Medical treatment of pain is evolving with an increasing understanding of the role of psychological processes in pain modulation. Hypnotic treatment is also evolving, and with a greater emphasis on active participation by the patient, primarily through greater utilization of self- and posthypnotic strategies (8,79,81). As research and clinical techniques develop further, the unscientific attitudes identified with the earlier history of hypnosis should become increasingly rare, and clinical effectiveness will become increasingly common.

ACKNOWLEDGMENTS

The author is grateful to these colleagues for their generous criticism of various drafts of this chapter: Nicholas Covino, Ph.D.; Fred Frankel, M.B.Ch.B., D.P.M.; Irving Kirsch, Ph.D.; Sam LeBaron, M.D., Ph.D.; Mary Pepping, Ph.D.; Mark Scott Smith, M.D.; and Erik Woody, Ph.D.

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CHAPTER 92

*Relaxation and Imagery Techniques**

Karen L. Syrjala

Relaxation with imagery (R&I) is one of the most widely used methods for nonpharmacologic relief of pain. A form of R&I is nearly always a component of multidimensional chronic pain treatment. R&I also is effective with acute and cancer pain problems, as discussed in Chapter 9 and Chapter 36.

Numerous techniques and terms are used within the rubric of R&I, including progressive muscle (tense-release) relaxation, autogenic relaxation, imagery, visualization, and meditation. Although it is possible to describe separately the relaxation method and the imagery method, in practice, nearly all relaxation incorporates a form of imaging, whereas nearly all imagery begins with a form of relaxation. Consequently, the clinician needs to understand and be able to use both components. Relaxation is used to pull focus away from pain and to induce a physical state of decreased muscle tension, as well as decreased autonomic and affective arousal. In theory, this state is inconsistent with the usual pain experience and, in itself, may reduce pain perception. Imagery provides a directly competing cognitive focus, which can block perception of pain during total concentration on imagery. After imagery is completed, pain reduction may continue through a shift in cognitive interpretation of nociceptive signals or through more direct neurochemical mechanisms. Both relaxation and imagery disrupt the pain-dysfunction feedback loop by increasing patient focus on feelings of well-being, thereby decreasing the focus on pain, as well as the tension, anxiety, depression, and inactivity related to pain.

As is described in this chapter, R&I has been shown to be effective in the treatment of chronic low back pain, cancer pain, rheumatoid arthritis, childbirth, and acutely painful procedures. Headache and temporomandibular disorder (TMD) pain have been treated successfully with relaxation alone or combined with imagery. This chapter first considers some basic information, including a historical perspective of R&I techniques, theoretical bases including physiologic effects, and advantages and disadvantages of the methods. I then detail clinical methods and efficacy, as well as possible complications that a clinician should be prepared to manage. For further details on the application of specific approaches, the reader is referred to several books with useful information for professionals (1,2,3,4 and 5). In addition, Bernstein and Borkovec (6) have written a manual for training professionals in progressive relaxation. For reviews of research or practice of R&I, see articles by Fernandez and Turk (7), Keefe and Caldwell (8), McCaffrey and Beebe (9), the NIH Technology Assessment Panel (10), Syrjala and Abrams (11), Syrjala and Roth-Roemer (12), Turner and Romano (13), Vessey and Carlson (14), and Wallace (15).

With the increased public attention to self-help and alternative therapies, bookstores are full of books and audiotapes instructing patients in how to use imagery on their own. With a review of these, clinicians will find several that they can recommend for patient use, along with professional care, in treatment of specific pain problems. As an example, Davis et al. (16) have a relaxation workbook designed for patient use. *Books and audiotapes should not be considered adequate treatment alone. Most patients require initial professional assistance to adapt methods to their individual needs* (17,18). *Tapes alone can bias patients against trying R&I with a professional, since they believe "it doesn't work for me."*

BASIC INFORMATION

History

Relaxation was in use by the 1930s as a technique for reducing tension and anxiety. Progressive muscle relaxation (PMR) was introduced by Jacobson (1), who found that by extensive practice with systematic tensing and releasing of muscle groups, anxious patients could learn to discriminate the resulting sensations and produce an experience of deep relaxation. Wolpe (19) modified the procedure into a program that could be completed in six 20-minute training sessions with twice-daily home practice. He then incorporated relaxation into his systematic desensitization therapy for phobias, reasoning that relaxation would provide a response incompatible with fear. The relaxed state was paired with gradual exposure to the feared stimulus. The patient first imagined the exposure while relaxing and then actually confronted the feared object in real life. This method of treatment for phobias is still used today.

Autogenic training (AT) originated with a Berlin psychiatrist, Johannes H. Schultz, and was popularized in North America by Luthe (20). AT does not require tensing of muscles but instead consists of turning attention to each muscle group in turn, suggesting sensations of heaviness and warmth. After progression through the muscle groups, attention is turned to slowing the heart rate, developing a regular respiration pattern, and finally regulating the viscera and cooling the forehead. The objective of AT is autonomic regulation as well as muscle relaxation. In its passive concentration, AT resembles meditation. In its content it incorporates the use of imagery, although these images are limited and intentionally repetitive.

Benson (2) has described the relaxation response as a form of meditation without the religious or lifestyle connotations of transcendental meditation, Zen, or yoga. In the two most tested meditation strategies, the relaxation response and mindfulness meditation, patients are taught awareness in the moment, without judgment. Procedures vary, but awareness can focus on breathing, a phrase, or on a detached observation (for extended details of how to implement meditation, see references 3,5, and 21).

Although relaxation began as a treatment for anxiety, from the time that behavioral psychologists began working with pain patients, R&I techniques have been a key element of standard treatment (4). A sequential combination of PMR and AT is most frequently taught, with deep breathing and guided imagery often incorporated. Although not technically included in any of the original versions of relaxation already mentioned, deep breathing can be the first step toward helping patients focus attention before proceeding with further relaxation. Guided imagery serves as a distraction technique and, more important, as an effective means of introducing alternative thoughts, images, or ways to perceive pain. As such, the imagery component can be critical to the success of relaxation as a pain relief tool (7).

Theoretical Bases

The mechanisms through which R&I reduces pain are still under debate, except for consensus on the obvious mechanisms of tension relief and altered sympathetic arousal (10). Little is known about brain physiologic changes in response to relaxation, but more is known about peripheral physiologic change. Even brief PMR training has produced significant reductions in heart rate, respiratory rate, and electromyographic (EMG) forearm muscle tension (22). Furthermore, during relaxation, physiologic changes have been greater than those observed during hypnosis for systems not under voluntary control (e.g., heart rate and tonic muscle tension). Other documented physiologic responses to relaxation include decreases in oxygen consumption, blood pressure, and serum lactic acid levels; increases in skin resistance; and alterations in blood flow (23). Investigators have found that plasma norepinephrine levels either increase or do not change after relaxation (24). It has been hypothesized that these peripheral changes, which indicate a decreased arousal of the sympathetic nervous system, are related to decreased end-organ responsiveness to norepinephrine (23).

Reduced sympathetic activity after relaxation does not fully explain the pain reductions found in a substantial number of conditions (13,25,26 and 27). In tension headaches and TMD pain, the reduction in reported pain may be due, at least in part, to muscle relaxation effects and decreased sympathetic arousal, although not all studies have shown this. Altered blood flow may account for some of the effect with migraine headache. Other physiologic and cortical processes almost certainly are involved in accomplishing the pain relief reported with imagery in some acute and chronic pain conditions.

Measured brain responses to relaxation include increased electroencephalogram alpha and theta waves (23), but research has confirmed few other brain activity changes. One theory holds that relaxation and meditation result in a shift in hemispheric dominance, with greater activation of centers in the right hemisphere, although this is unproven (23). Another hypothesis speculates that pain relief is a function of changes in catecholamines, endorphins, or other neurochemical systems (10). Some data suggest that a spinal–thalamic–frontal cortex–anterior cingulate pathway influences subjective response to pain, whereas a spinal–thalamic–somatosensory cortex pathway influences pain sensation. Pain signals may be modulated through a descending pathway that involves the periaqueductal gray. At the dorsal spinal cord, serotonin and norepinephrine appear to play important roles in sensory modulation. Although these mechanisms have been hypothesized for some time, they remain difficult to test.

Advantages

R&I has three primary advantages over the similar but more complex techniques of biofeedback and hypnosis (see Chapter 90 and Chapter 91): (a) Patients can be trained in the use of the skills with relative ease; (b) no special equipment or extensive training of the therapist is required; and (c) patients readily accept R&I techniques, whereas they are more likely to reject hypnosis (28).

Although it can be difficult to predict who will benefit from R&I, the lack of serious complications and the relative ease and low cost with which it can be tried make this a method with minimal risks. Unlike the practice of hypnosis, R&I is essentially a skill that can be learned; it does not depend to any extent on the responsiveness of the patient. If a patient is unable to visualize images, PMR can be taught with potential benefit, and methods can be adapted to the particular capabilities and preferences of a patient. Thus, the flexibility within the method leaves room for adaptation to a wide variety of styles or needs. Expectations of patients tend to be more realistic than for hypnosis, which tends to evoke a wish for a ”magic cure,” higher expectations, and higher levels of fear of loss of control.

Disadvantages

R&I requires the participation of the patient. To optimize benefit, patients must practice outside the trainer's office. Although self-control is one of its appeals to patients, lack of practice is one of the greatest problems in its use. Further disadvantages follow as corollaries to R&I's advantages. These include the lack of implied magic cure that can be hoped for with either a medical intervention or hypnosis. Ease of use and lack of cost can be associated in patients' minds with lower expected efficacy. The effects of R&I may not be immediately apparent but can accumulate over time, thus requiring not only practice but also patience. R&I are subjective experiences not unlike pain; as such, their effects can be difficult to measure and confidence in their benefits may be low. Finally, for most conditions, R&I is not, alone, an adequate treatment for pain, but must be considered a complementary method used in combination with appropriate medical treatment.

CLINICAL INFORMATION

Indications

Indications for treating pain vary with the type of pain and the condition of the patient. Relaxation is recommended for any patient for whom tension is a significant cause of pain or for whom tension and fear may be augmenting the pain problem. In acute pain situations such as childbirth, trauma, or procedural pain, R&I may be combined with medication and other distraction strategies that decrease a focus on discomfort and speed the passage of time. Relaxation is clearly indicated in the treatment of tension, migraine, and cluster headaches and in TMD pain. In other chronic conditions and in cancer pain, clinical trials have indicated that R&I and meditation reduce pain (11,18,26,29). With the limitations of time in the current medical practice environment, R&I is most strongly recommended for patients who have chronic conditions that cannot be adequately relieved with medical intervention alone. In addition, patients will benefit from R&I training if they must regularly repeat acutely painful situations because fear and phobias can increase over time with exposure to these stimuli.

Contraindications

Contraindications are few and usually relate more to the mental status and characteristics of the patient than to the pain condition itself. Pain or sedation that prevents a patient from focusing attention, or a delirium that disrupts cognition, needs to be treated with other methods until concentration is possible. Then, briefer images with a short relaxation component can permit participation by a patient who otherwise could not sustain the mental effort needed for more extended training. Sometimes these patients feel ease of intense discomfort by combining images with physical massage or pressure on a part of the body (shoulder, hand, lower arm or calf muscles) that is not in pain. Of course, clinicians must be cautious and should consider having someone else in the room if they decide that physical touch with imagery is needed to help a patient with pain that cannot be relieved with medical methods alone.

Certainly religious objections, intense fear of loss of control, or resistance to trying the method for any reason should be respected. Skepticism is not a reason to withhold treatment if the patient is willing to give the technique a valid try—clinicians can encourage a healthy skepticism and empirical testing attitude. Similarly, patients who ask for biological explanations for why mental strategies might work usually respond well to information about physiologic mechanisms behind R&I. These patients also may do best with PMR in the beginning because this helps to enhance awareness of physical changes that occur as the body relaxes. The same is true for patients who seem out of touch with their bodies and unaware of tension or for patients who are action-oriented ”doers not thinkers.”

Intense anxiety or preoccupation that prohibits focus on imagery must be attended to pharmacologically or with discussion before beginning R&I. Because anxiety can increase during imagery, the clinician should assess a highly anxious patient and ensure that emotional expression is tolerable. Usually these patients need to express thoughts and feelings first. Then the clinician can reevaluate the patient's ability to focus. Ability to engage in a discussion of places that the patient enjoys should indicate adequate ability to participate in imagery.

Two additional circumstances can complicate the use of R&I: One is the patient who is feeling very out of control; the other is the patient who has a strong need to be in control. For patients who feel completely out of control of their experience and environment, a clinician can appropriately take charge of the situation and let patients know the clinician is going to ensure their safety while there. Clinicians need to convey to patients that the situation is manageable and the pain can be relieved. If these messages seem to reassure and calm the patient, the clinician should be able to move into imagery. For patients who give indications that they must be in control, clinicians will want to assess whether these patients might respond best to permissive, indirect imagery versus more structured PMR methods. PMR helps in this situation because patients can be told exactly what steps the clinician will take. Generally patients feel safest with PMR because it is clear that patients control their own responses. Alternatively, if imagery is used, the clinician can encourage patients to select as many features as possible and can incorporate options and permission to have other thoughts or experiences during the imagery. Another strategy is to have patients tell the clinician what they see, feel, hear, and do in their imagery, with the clinician asking questions rather than leading the imagery process.

Techniques

Preparation of the Patient

Relaxation may be learned and practiced by virtually anyone. The techniques can be taught by those who have had relatively limited training, but clinicians should be aware of and prepared to handle possible complications. Before relaxation training begins, the clinician should explain to pain patients the rationale for the particular procedure being used. Many patients view relaxation as irrelevant to their pain problem or even as an indication that the doctor thinks the pain is ”just tension” or ”all in my head.” Most patients are helped in their disbelief by a brief discussion of the gate control theory of pain, hypothesized neuroendocrine effects, and the feedback loop between pain and tension or fear. Patients can also be told that relaxation training is harmless and, if nothing else, will leave the patient feeling relaxed. The clinician can then suggest that the procedure be tried as an ”experiment,” with nothing to lose. This approach is preferable to promising patients dramatic pain relief because this rarely occurs initially. Patients also need to understand that R&I is a skill, like learning to read. Benefits take time to reach their peak, and daily home practice is necessary to become adept at the procedure and to maintain benefits. Audiotapes can be helpful in supporting home practice.

To prevent surprises and help patients feel secure, clinicians should describe the basic steps involved in the technique and estimate the length of time required to

complete the procedure. Although increased comfort can be achieved in as little as 5 minutes, deep relaxation requires at least 20 minutes for new practitioners and may continue for up to 45 minutes. Patients can be advised that they will likely be most comfortable with their eyes closed, although this is not mandatory, and that they are free to move at any time to make themselves more comfortable. Use of a reclining chair with a headrest is desirable, or patients can sit on the floor or a regular chair. They should not lie on a bed, unless the goal is rest for a sleep-deprived patient in pain. Lying on a bed tends to evoke falling asleep rather than completing the imagery. Unplugging the phone and minimizing other noises or disruptions are helpful. In hospital rooms this is not always possible. So it is helpful to add a statement such as ”and just allow any sounds around you to fade to the distance, part of the background that adds to your feeling of being in a different place, a place all your own right now.” Surprisingly, after imagery patients often indicate that they were unaware of any sounds or disruptions even though they may seem intrusive to the clinician.

Training Procedures

Deep breathing is the most rapidly learned of the relaxation techniques. Very little training is needed to obtain benefits. For patients in intense acute pain, deep breathing may be the most that they can accomplish. Controlled breathing also can be quite effective in capturing and holding a very distressed patient's attention and may be the first step toward using imagery to further distract the patient from the distress of the moment. I am aware of no reports on the usefulness of deep breathing in isolation from other strategies for pain control, although it is a component of many relaxation procedures that have been researched. One component that is often not stressed but can be quite valuable in relieving pain is making a sound while breathing, usually just emphasizing the sound of air leaving the lungs and mouth. Variations on this method are commonly used in childbirth preparation (30). Typical instructions for deep breathing are given in Table 92-1.

TABLE 92-1. Instructions for deep breathing [a]

PMR is the most routine of the techniques. Because it requires the patient to tense and release muscle groups, it provides the most feedback to the clinician (as well as the patient) on the participation of the patient. The tense-release format provides momentum from which the patient can achieve relaxation well below usual levels of tension relief. Before implementing this technique with a patient, the clinical investigator is urged to read the manual by Bernstein and Borkovec (6).

Autogenic relaxation is similar to PMR in that it progresses through the body, focusing attention on relaxing each area of the body in turn. Autogenics, however, does not require tensing muscles first. The focus is on imagining a feeling of warmth and heaviness in each area. Imagery may be inserted after completion of the relaxation phase or may be combined with the relaxation phrases. This technique is useful with patients who are quite fatigued and in general discomfort. The imagery component may relate only to feelings of warmth, heaviness, and sensations that accompany relaxation or may be augmented at length depending on the will and interest of patient and clinician.

Incorporating imagery into relaxation can greatly enhance efficacy as a pain relief tool (7,18,31). Imagery also increases the enjoyment of patients and therefore the likelihood that they will use the technique. Activating all the senses in the mind creates distraction as well as hypnosislike experiences of comfort, well-being, and mastery of a problem. For instance, patients can be asked to choose a place where they have felt most at ease or joyful, at a time when they were pain free. As patients recapture the familiar experience of a place with sight, sound, taste, smell, and touch, they also recapture the feelings of comfort. Clinicians can then suggest to patients that by imagining themselves in that place, patients can once again be comfortable and in control of how they feel. The content of images can vary greatly, from going to pleasant places to modifying the pain experience directly (11,32). More success in using imagery may be achieved by patients with greater ability to generate images and those who have a greater capacity to experience images as if they are real (33,34). Patients without these abilities may respond more to the relaxation component of R&I. Choice of images may be the most important factor in the success of imagery. Pain reduction is greater when patients can choose their images and when they make statements to themselves in the imagery that they are able to tolerate or modify the pain (34). Pleasantness may be more important to encouraging use of the imagery than in enhancing its effect on pain (35).

An alternative imagery strategy is more akin to meditation. This approach involves focusing on the pain rather than away from it and on picturing details of the pain location (36). There is some indication that for more extreme, unremitting types of pain such as with terminal cancer, focusing on the pain rather than away from it is more effective in achieving pain reduction (37). Table 92- 2 lists of some of the more commonly used imagery strategies for pain control. These can be incorporated into imagery of going to a favorite place or can be combined with deep breathing.

TABLE 92-2. Imagery options for pain controlstrategies

In execution, meditation most resembles deep breathing. Instead of focusing sequentially on each part of the body, meditation requires a cultivated ”detached observation” (3,5). Two similar approaches to meditation have been useful in medical settings. One involves repeating a phrase or word to oneself and is referred to as the *relaxation response* (2); the other is called *mindfulness meditation* (5,21). Mindfulness meditation is similar to the imagery approaches that transform painful sensation (36). Attention is focused not on changing pain perception but on insight developed from distinguishing all sensations as they occur moment by moment. Thoughts about pain are observed from the position of a neutral observer. Although relaxation response training is easy to implement, few data exist on its effectiveness as a pain reduction method. Mindfulness meditation has been shown to reduce pain in chronically ill patients (21,26). An experienced clinician is recommended as a trainer. Instructions for using the relaxation response and instructions for mindfulness meditation are detailed thoroughly in the Kabat-Zinn book (5).

Results

Comparisons have been made between R&I strategies and hypnosis or biofeedback, as well as between different relaxation techniques. Numerous studies have also tested packages of cognitive-behavioral skills training that have included a form of R&I. Each of these interventions, including hypnosis, biofeedback, and

cognitive-behavioral packages, elicits similar physiologic responses and subjective reductions in pain when compared with no treatment (13,18,23,25,27,31,38). In general, research results indicate that R&I demonstrates greater effect size than other strategies alone and that packages of cognitive-behavioral skills are not always superior to R&I alone (7,8,38). Hypnosis, biofeedback, and audiotaped relaxation are less effective than live PMR in achieving reductions in sympathetic arousal (22,39). An exception may be frontalis EMG levels, which have shown greater reductions with autogenic relaxation than with tense-release relaxation, although both approaches produce some decrease in EMG (40). This may be of some interest to clinicians choosing between relaxation techniques for the treatment of tension headache.

Much of the research on the effectiveness of relaxation alone for pain reduction has been conducted with tension headache patients. In general, the results of these studies suggest that relaxation is effective and that benefits are maintained at follow-up (13). Relaxation training alone appears to be a reasonable first step for headache sufferers, with the addition of biofeedback for those patients who are unsuccessful with relaxation alone (41). Similarly, research with TMD pain patients suggests that many can be treated successfully with relaxation alone, although some may benefit from the addition of biofeedback (42). With other conditions, relaxation is best implemented in combination with imagery. The next sections discuss efficacy of a single method of R&I within specific conditions, as this is how most clinical trials of the methods are tested.

Chronic Conditions

R&I is most often used as one element in a set of cognitive-behavioral treatments for chronic pain, rather than as an independent pain control technique. Research indicates that R&I can contribute to reduced pain levels, reduced medication use in a number of chronic conditions, and reduced disability, although the role of R&I versus other cognitive methods is not yet clear (27,38). The evidence for sustained improved function is less consistent but more often than not supports improvement in disability after treatment (27,38,43,44). Chapter 89, by Turner and Romano, presents a thorough review of the effectiveness of cognitive-behavioral strategies that usually include R&I.

Kabat-Zinn et al. (5,21,26) have used mindfulness meditation to successfully treat a variety of chronic problems, including pain located in the low back, neck, shoulder, arm, leg, face, head, chest, peripheral nerves, and multiple sites. Ten percent to 20% of patients refused to use this strategy for pain control. A majority (72%) of the patients who were willing to try were able to reduce their pain by 33% or more. In addition, improvement was noted in body image, activity, mood disturbance, and medication use. Compliance both during and after participation in the program was reported to be high. These results support the contention that meditation may have a generalized beneficial effect for chronic pain patients.

Headache. Tension headache research dominates the literature and generally reveals relaxation to be as effective or more effective than biofeedback (13,25,45,46). The same results have been found with migraine headache, although fewer studies are available. The most careful explorations into the relative roles of relaxation and biofeedback in relieving headache have been reported by Blanchard et al. (41,45,47) and Andrasik et al. (48) (see Chapter 90). In terms of both cost-effectiveness and success, the optimal therapy for tension, migraine, or mixed tension and migraine pain appears to be a two-step treatment beginning with PMR. For those patients who do not show substantial reduction in headache activity with PMR, the second step is instituted. For vascular headache patients, the second step is thermal biofeedback; for tension headache patients, frontalis EMG biofeedback is the second step. Blanchard et al. (49) found that with this two-step therapy 73% of tension headache patients and 52% of vascular headache patients were much improved. All groups improved with relaxation, with the tension headache patients improving the most. Among those patients who received biofeedback, the vascular headache patients responded most favorably.

Philips and Hunter (50) tested the effects of PMR versus PMR with calming imagery for tension headache patients. The two groups showed similar improvements in pain. The authors suggested that the addition of imagery produced a larger improvement in pain based on several outcome measures even though no individual measure showed significantly superior effects.

The superiority or equivalence of relaxation and biofeedback has not been supported by all research. LaCroix et al. (51), for instance, found that thermal biofeedback was superior to frontalis EMG feedback and relaxation for migraine patients, although all groups improved.

With regard to home practice, Andrasik et al. (48) reported that posttreatment practice was unrelated to maintenance of effects. It should be noted, however, that all patients in this study were provided with regular therapist visits.

Low Back Pain. Studies comparing relaxation with other techniques for low back pain indicate that relaxation is an effective treatment but that combining relaxation with other cognitive-behavioral strategies may be advantageous (see Chapter 89). Turner (29) compared PMR treatment with PMR plus additional cognitive-behavioral therapy or no treatment. The two treatment groups both reported reduced pain intensity and disability immediately after treatment and at 1.5- and 2-year follow-up. The cognitive-behavioral group, however, showed some superiority in maintaining treatment gains and in hours worked per week. A number of other studies by Turner et al. support the use of relaxation as one component of effective cognitive-behavioral treatment for chronic pain (13,27,29,38,54). McCauley et al. (52) compared PMR with hypnosis in the treatment of low back pain and found that both treatments were similarly effective and superior to a placebo EMG treatment. Sanders (53) compared single sessions of PMR, assertion training, reinforcement of activity, and ”functional pain-behavioral analysis training” in four low back pain patients. With the exception of functional analysis, each treatment differentially, but positively, affected medication use, pain ratings, and up time.

Additional research is needed on the relationship of component interventions to specific outcomes in the low back pain patient, even though these studies suggest that relaxation makes some contribution to favorable outcomes. In particular, research is needed that tests the efficacy of imagery combined with relaxation training for treatment of chronic conditions.

Temporomandibular Disorder Pain. The research on relaxation and cognitive-behavioral packages that include PMR for TMD pain supports the conclusion that relaxation is effective in reducing pain and is at least as successful as biofeedback, the most commonly compared treatment (54). Funch and Gale (42) reported that biofeedback and audiotaped relaxation training were equally effective in reducing TMD pain. Patients who were more successful with relaxation were generally younger, had experienced TMD pain for a shorter period of time, and reported other psychophysiologic disorders. Patients who were more successful with biofeedback tended to be older and married and had experienced pain for a longer period of time. The differential effect of relaxation and biofeedback with different patients also was found in a single-subject, multiple-baseline study by Moss et al. (55). In this study, relaxation with EMG feedback was most effective for three out of four patients tested. In the largest randomized controlled clinical treatment, Dworkin et al. (54) compared patients receiving usual treatment for TMD with patients receiving usual treatment plus a package of cognitive-behavioral skills that included relaxation training. The skills-trained group reported continued improvement over 12 months of follow-up and overall lower pain scores and a strong trend toward reduced pain interference with function.

Arthritis and Autoimmune Diseases. Evidence for the benefits of self-management strategies for coping with arthritis pain and dysfunction have been collecting over the last decade (56,57,58,59,60 and 61). As with other chronic pain clinical trials, benefits seem to continue or even to expand over time after treatment. Educational strategies that may or may not include relaxation exercises are widely used in arthritis and are cost-effective and pain relieving over and above the effect of medication treatment alone (8,58,62). Even more so than with low back pain and other chronic conditions, arthritis and autoimmune diseases are not treated with R&I alone, but rather with R&I as a component of educational and other cognitive skills training (8). Consequently, it is difficult to know to what extent R&I is an essential component of these techniques. There is no reason to believe that patients with arthritis pain or the patients with autoimmune diseases would respond differently than patients with other chronic illnesses such as low back pain or cancer, even though each disease has its own unique characteristics and therefore stressors to tax coping.

Cancer Pain. Cancer patients may experience acute treatment-related pain or chronic pain (see Chapter 35). The chronic pain may be stable (e.g., postmastectomy pain) or progressive (e.g., tumor invasion pain). Successful treatment depends to some extent on tailoring therapy to the type of pain. In clinical reports, relaxation with guided imagery, sometimes called *hypnosis*, is touted (63,64). However, there is little controlled research on the efficacy of R&I with adult cancer patients. As noted by Jay et al. (65), research on adult cancer patients has focused on chronic pain, whereas research on children with cancer has focused on acute procedural pain.

Spiegel and Bloom (66) provided group ”self-hypnosis” training to breast cancer patients and reported an additive analgesic effect of hypnosis, with smaller increases in pain and suffering over time. Syrjala et al. (31) provided three groups of bone marrow transplant patients with training in ”hypnosis,” cognitive-behavioral training including PMR, or support with no training. The group receiving hypnosis reported lower average levels of oral pain after chemoradiotherapy than the other two groups. In a second study, Syrjala and colleagues (18) tested R&I against three other groups: a standard treatment control, a supportive psychotherapy intervention, and a cognitive-behavioral package, which included R&I. Again, in this clinical trial R&I was the most effective treatment for pain, with cognitive-behavioral methods showing no mean additive effect over and above the R&I alone. There was an indication that some patients benefit from the cognitive-behavioral package who may

not have benefited from the R&I alone; however, power was not adequate to test this hypothesis. These data indicate a valuable role for imagery in helping cancer patients cope with pain and the need to individualize patient treatments.

Acute Conditions

Childbirth. Preparation for childbirth, which is now quite common, usually includes breathing exercises with a visual focus and sometimes includes formal relaxation training (see Chapter 71). As Tan (30) noted in his review, studies on the effectiveness of these strategies in reducing pain in childbirth are supportive but equivocal. Many of these studies do not include actual measures of pain levels in reporting favorable outcomes. Laboratory research has suggested that the attention-focusing component of preparation is more effective in reducing pain than is relaxation training (67) and that sensory transformation coping strategies are more effective than relaxation (68). Despite the equivocal data on pain reduction associated with childbirth preparation, the reduced distress resulting from such programs probably supports their continued use.

Acute Traumatic, Procedural, and Postoperative Pain. A number of sources confirm the benefits of relaxation training before various procedures and surgery. Only anecdotal evidence was found for the use of deep breathing, relaxation, and imagery during acute trauma, although hypnosis has been demonstrated effective during burn debridement (69). This is a difficult area to research because of the unpredictable availability of subjects and the wide variety of possible injuries. By and large, support for the use of these strategies in trauma situations must be extrapolated from research on other acute pain conditions.

Relaxation training before stressful procedures has been shown to be effective in reducing a number of measures of pain and distress. For example, patients trained in PMR and deep breathing before sigmoidoscopy rated themselves as less anxious and made fewer requests to stop the procedure than patients who were not trained in relaxation (70). Both relaxation and information have been reported to reduce heart rate and observer ratings of distress during endoscopy. Only relaxation also increased positive mood (71). Even greater effect was seen in a study of imagery/self-hypnosis during radiologic procedures. In this randomized clinical trial, patients receiving the active intervention reported less pain, used less analgesic medication, reported less anxiety, and had fewer procedural interruptions due to hemodynamic instability (72). In an interesting departure from using specialists to provide R&I to patients, Lang and colleagues (72,73) have trained radiology nurses and technicians to provide relaxation and imagery during painful procedures. Patients reported significantly lower pain scores, with a strong trend toward less drug use (73).

Laboratory and clinical studies have found that the effectiveness of relaxation training in acute situations may depend on the coping style of the patient. In the laboratory, it has been reported that patients who were more external in their ”locus of control” were better able to use relaxation training than were patients who were more internal—that is, saw themselves as the agent of control (74). During procedural discomfort, patients who reported that they preferred to avoid thinking about unpleasant things were helped more by relaxation than by information, whereas the reverse was true of the nonavoiders (71). In addition, patients who indicated that they were less independent benefited from both relaxation and information, whereas those who were more independent benefited from neither. Relaxation and information were not demonstrated to be harmful to patients who were not matched on intervention and coping style. Finally, with postoperative patients, Scott and Clum (75) found that brief relaxation training was profitable for those who had ”sensitizing” coping styles, but not for those who were avoiders. In sum, avoiders and ”external locus of control” patients may do particularly well with escape-oriented pleasant imagery, whereas other patients may respond well to all types of R&I.

Applications with Children

Research on the use of relaxation techniques with children is less extensive and well controlled than the research with adults. Lavigne et al. (76) and Vessey and Carlson (14) provide reviews of painful pediatric conditions and the interventions that have been successful. The terminology used in much of the published research is inconsistent. For example, treatments are interchangeably defined as active fantasy, guided imagery, breathing, hypnosis, relaxation, or imagery.

Children are generally able to participate in imagining as a distraction from pain or fantasy to modify the pain experience from approximately 5 years of age (14). Initially, imagery differs from play or active fantasy and storytelling only in its intention. I have found it particularly effective to use stuffed animals or soft puppets onto which the child can transfer the pain or the fear or anger that accompany pain. When left with the child, these toys become the transitional object with which the child can repeat the imagery when the clinician is not present. As children grow to adolescence, imagery and relaxation methods increasingly resemble those used with adults. However, adolescents and children are closer to fantasy than many adults and therefore require little or no time in relaxation and need to move to fantasy imagery more quickly. Adolescents respond well to imagery with themselves as heroes and the agents of change and success. Pain transformations can be included in these images of mastery.

In research with pediatric cancer patients, interventions have focused on procedure-related pain and distress (65,77,78 and 79). Effective treatments have included breathing and imagery, sometimes incorporated into a cognitive-behavioral package. Although numerous studies demonstrate that R&I can reduce distress related to procedures, and sometimes pain, increasingly we are seeing light sedation used for repeated invasive procedures such as lumbar punctures and bone marrow aspirations. Light sedation may be more effective than imagery at eliminating the distress and discomfort of these procedures, although relative risk, provider time requirements, and outcomes have not been formally studied.

A small number of case studies suggest that relaxation, particularly if coupled with imagery, can be effective in treating other pediatric pain problems. Distraction and breathing exercises have received some support as useful techniques for relieving pain during debridement for pediatric burn patients (76). Varni et al. (80) reported the successful use of relaxation and breathing to increase pain control in a 9-year-old with hemophilia. Unlike relaxation research with adults, which has focused on tension headache, pediatric research has focused on autogenic relaxation for migraine. This research clearly supports the use of autogenics for relief of migraine in younger populations (76).

Because children are usually easily engaged in active imagery, this component can be successfully introduced into most interventions with children in pain. Clinicians interested in the use of imagery are also referred to the literature on hypnosis, as many researchers using imagery with children commonly have termed their interventions ”hypnosis.”

Complications

Minor Problems

One of the advantages of relaxation techniques in comparison with more invasive therapies is the lack of lasting adverse side effects. Most complications are rare, are harmless, and can be handled with quick, matter-of-fact resolution of the problem. Muscle cramps can develop with PMR, in which case the patient can be asked to generate less tension in problem areas for shorter periods of time. If necessary, a pause can be taken while the patient massages cramped muscles. Unless the patient comments or appears uncomfortable, spasms should simply be ignored. Patients can be reassured that muscle spasms are common when people relax and occur in many people when they fall asleep. Movements are not uncommon but are generally not suggested unless they involve brief shifts to a more comfortable position. Talking and laughter usually stop if they are ignored. Alternatively, they can be casually acknowledged, such as ”and just notice that different feelings may come up and that's just fine, just a part of letting thoughts and feelings flow through your mind or body and away, leaving a feeling of being even more at ease.”

Because some patients experience intrusive thoughts as disruptive, they should be told ahead of time that such thoughts are to be expected. Suggest that as thoughts arise, they can be allowed to ”float through the mind, knowing that anything important will still remain later, but that right now there are no other things to focus on or to do but to let these normal thoughts just float away.”

If a patient falls asleep, the therapist might need to speak in a progressively louder voice until the patient is again awake. Patients who report falling asleep regularly during home practice should be instructed to practice earlier in the day and in a sitting position.

Problems Requiring Attention

Problems requiring the therapist to be more careful and attentive are infrequent. The more common difficulties and some solutions are described in Table 92-3. For certain patients, tension or pain can be localized in an area not sufficiently covered by the standard relaxation of body parts. TMD pain, as an example, benefits from exercises and relaxation targeted to that area (54). If residual tension remains, it is helpful to develop a tension or relaxation strategy that specifically targets the localized area. This might involve taking time after relaxing to go to any place in the body that continues to feel tight or uncomfortable, going to that place with the mind and watching while imagining breathing through that place in the body and noticing the changes in sensations. Sensory transformation imagery may be used to

expand on this experience.

TABLE 92-3. Problems and solutions encountered in clinical practice

Pain patients commonly have an initially greater awareness of the pain as attention is focused on internal states. In this case, patients can be instructed to observe the pain in a detached manner (similar to that just described previously). Usually the intensity will lessen. Alternatively, the clinician can move the patient's attention to another part of the body or to images away from the body.

Patients who have been particularly out of touch with body sensations can suddenly become aware of any number or type of strange, unfamiliar sensations while relaxing and focusing on the body. Patients might feel as though they are floating and disoriented to such an extent that they must open their eyes until they once again feel comfortable. If this sensation or others are frightening, the clinician will need to respond with reassurance. Other discomforting sensations can include tingling, nausea, lightheadedness, or a sense of losing control.

Patients who fear losing control require perhaps the greatest care in designing an appropriate intervention. These patients often respond initially to PMR because they are in control and the procedure feels most in their control. Telling them the process you plan to follow also helps to ease fears. Another strategy is to give these people choices of what they would like to try. With these patients, it is particularly important to include statements that they are in complete control of their experiences and what they choose to do, that at any time they can choose to change their experience or even to stop.

An increase in anxiety has been reported in some patients learning relaxation (81). In our experience, this occurs in approximately 2% of patients. Switching to a different relaxation (e.g., PMR) that more fully occupies the patient's attention may help reduce such anxiety. Discussion of the nature of the anxiety may reveal an alternative set of thoughts or images that can provide a more neutral focal point for the patient. Often patients feel some relief from expressing pent-up feelings. However, other patients may feel embarrassed or reluctant to try imagery again. This circumstance requires the use of clinical skills in deciding the best approach for each individual.

Sexual arousal can occur from the relaxation and perceived seduction of the setting. If treated matter of factly as similar to other normal intrusive thoughts, this usually resolves on its own (6).

Failure to practice relaxation strategies is by far the most common problem encountered in relaxation training. Clinicians can remind patients of other learning experiences, such as reading or biking, in which practice led to mastery. Discussion of changes in the home environment that would assist practice may also be helpful. Above all, clinicians must insist that practice is an important element of learning and using any relaxation technique successfully.

CONCLUSIONS

R&I techniques—including PMR, AT, deep breathing, imagery, and meditation—can be valuable in the treatment of both acute and chronic pain syndromes. The advantages of R&I include its relative cost-effectiveness and lack of lasting harmful side effects. Although the specific physiologic mechanisms through which R&I reduces pain have not been proven, relaxation reduces muscle tension, quiets the sympathetic nervous system, and provides a cognitive distraction from distress. R&I may also lead to neuroendocrine changes that inhibit pain perception.

For headache and TMD pain, relaxation appears to be the first treatment of choice, with biofeedback instituted for those patients who do not benefit from relaxation. For other chronic conditions, R&I may be as effective as biofeedback or any other packages of cognitive-behavioral skills. Furthermore, R&I is difficult to distinguish from hypnosis either in procedure or in effect. Similarly, with acute pain, R&I is as effective as other cognitive-behavioral approaches that have been studied.

There are no populations that should be excluded from using R&I, except for those with religious or other firm objections. Children and adults are equally adept at benefiting from the methods. Although R&I would rarely be used for painful conditions without considering appropriate medical treatments as well, R&I helps patients to be active participants in their health and should be considered whenever medical care alone is not adequate to alleviate pain.

The number of randomized, controlled clinical trials that demonstrate efficacy of R&I for many types of pain appear adequate to support a conclusion that this is an effective and cost-effective strategy for pain treatment. Challenges are to make this method less dependent on people with highly specialized expertise and to facilitate the incorporation of R&I into routine practice through training of nurses, technicians, and physicians providing front-line care. Other strategies are being tested that would combine video, printed, and audiotaped materials to patients who do not have access to experts or to provide these same types of materials through World Wide Web treatment groups. Matching patients to specific R&I techniques may also improve use. The survival of R&I as a pain strategy to combine with medical treatment may depend on these efforts to make R&I widely accessible. Another decade will tell whether R&I becomes a standard mode of treatment for those with pain or a rarely used relic from the self-help movement of the late twentieth century.

*This work was supported by grants from the National Cancer Institute (#63030, #68139, #78990) and the National Institute of Drug Abuse (#05513).

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CHAPTER 93

Psychotherapy in the Management of Chronic Pain

Eldon R. Tunks and Harold Merskey

Psychotherapy has been defined as any form of treatment for mental illness, behavioral maladaptations, and other problems assumed to be of an emotional nature in which a therapist deliberately establishes a professional relationship with a patient for the purposes of removing, modifying, or retarding existing symptoms, or attenuating or reversing disturbed patterns of behavior, and of promoting positive personality growth and development (1). The relationship between the therapist and patient is an essential component of psychotherapy and can be summed up as follows (2):

- The doctor or therapist is concerned with the emotional problems of the patient.
- The doctor or therapist is able to relinquish the doctor's traditional controlling role.
- The doctor or therapist has the capacity to reflect on the emotional interaction between the patient and himself or herself and the courage to comment on it to promote insight and change.

The material in this chapter is presented in two major sections: (a) Basic Considerations, including a brief overview of the effectiveness of various psychotherapies, indications for their use with chronic pain patients, and factors influencing their success, and (b) Clinical Applications. The latter section describes and evaluates the main types of psychotherapies used in the management of patients with chronic pain. These include supportive, dynamic, family, and group psychotherapy. More detailed discussion of these and other topics related to psychotherapy and pain can be found elsewhere (3,4 and 5).

BASIC CONSIDERATIONS

Efficacy of Psychotherapy

Although an extensive literature exists concerning psychotherapy, assessing the efficacy of psychotherapy has proven difficult because of the plethora of psychotherapies and theoretical models and variables within psychotherapeutic techniques that are difficult to measure. An extensive review of the methodologic and efficacy issues in psychotherapy noted that the problem of defining and measuring effectiveness in psychotherapy plagues all schools of psychological treatment, whether they be behavioral, dynamic, group, milieu, or any other type (6). What can be demonstrated is that different psychotherapies appear to be effective for different purposes and that psychotherapy is clearly better than no psychotherapy or placebo treatment (6). The most significant problems in evaluating psychotherapeutic efficacy relate to four major issues:

1. Outcome measures are usually not built into the therapeutic technique, with the exception of behavioral and cognitive- behavioral therapies.
2. The treatment relationship is fundamental and not easily quantified, either in its degree of formation or in its impact.
3. Therapeutic outcome often involves subjective variables, including improvement in sense of self, feeling understood, and resolution of previously unresolved conflicts. These are very difficult to measure and even more difficult to compare among patients or therapies.
4. Many therapies, including psychodynamic, supportive, client-centered, interpersonal, family, and group psychotherapies, depend on the formation and exploration of relationships. The psychotherapeutic relationship itself is a process that unfolds between two active participants, in response to the patient's unique circumstances, so that the course of treatment may follow very different patterns from one patient to another. Therapy often occurs over longer periods of time, during which many sources of variance, cointervention, and other supportive professional relationships are likely to affect the outcome. For these reasons, it is difficult to construct adequate scientific designs for research on psychotherapy.

Each of the two major types of psychological treatments—behavioral therapy and insight-oriented psychotherapy—deals with an essential part of the individual. Behavioral therapies focus on an individual's actions, including his or her adaptive and healthy behaviors as well as those that relate to illness and maintain distress. It is reasonable to believe that a change in behavior will affect the experience of self and of illness (see Chapter 89). On the other hand, insight psychotherapy may be preferred by persons who are experiencing subjective distress (e.g., anxiety, depression, insecurity, worry about troubled relationships) and by persons who are more introspective or who perceive themselves as psychologically “ill.” They may wish to explore these feelings, and, at times, may need to work specifically on their understanding of the “origins” of their conflicts, on emotional reactions that they find puzzling, on their place in interpersonal relationships, and on resolution of conflicts, all as springboards to making change.

To help patients in a compassionate way, the therapist must consider behavior, feelings, and thoughts. Therefore, neither the behavioral therapies nor the psychotherapies can stand completely on their own. Each is complementary to the whole business of helping, and, in fact, good psychotherapists and good behavioral therapists resemble each other in the essential attributes that make them effective, whatever their theoretical leaning (7,8 and 9).

Efficacy of Psychotherapies in Management of Chronic Pain

There is abundant literature establishing the efficacy of multimodal pain management programs and of cognitive-behavioral therapy combined with rehabilitation in chronic pain management (10,11,12 and 13) (see Chapter 109). There is far less quality literature on the subject of (nonbehavioral) psychotherapy for chronic pain.

Education for patients (e.g., Back School) remains an important part of most multimodal pain clinics. Numerous controlled studies have examined the efficacy of patient education as a specific modality with respect to reduced pain or improved function. The outcomes of these studies have been combined in several metaanalyses and systematic reviews. Bigos et al. (12) found that educating patients reduced the use of medical resources, reduced apprehensiveness, and sped recovery, but there was no strong evidence on which to judge the efficacy of Back Schools. DiFabio (14) found that multimodal programs including patient education showed the greatest efficacy for treatment of pain and physical impairment and for education and compliance outcomes, whereas Back School alone did not demonstrate significant effect sizes compared with their respective comparison treatments. Cohen et al. (15), in their systematic review, found that of four quality studies of group education for chronic low back pain, only one showed a positive short-term effect in improved pain intensity. Gross et al. (16) found that patient education with or without associated medical or physical therapy for neck pain patients did not significantly alter pain outcomes.

A few studies have attempted to compare various forms of individual psychotherapies with control treatments. Pilowsky and Barrow (17) compared four conditions: amitriptyline plus individual psychotherapy, amitriptyline plus supportive therapy, placebo plus psychotherapy, and placebo plus supportive therapy. Although antidepressant use was associated with reduced time in pain and increased productivity, psychotherapy was associated with increased pain and increased productivity. Another study by Pilowsky et al. (18) comparing amitriptyline and cognitive therapy versus amitriptyline and supportive therapy was statistically inconclusive because of sample size and other design problems, but the impression was that at follow-up the amitriptyline plus cognitive therapy group did better with respect to pain but not in productivity. A controlled study of psychodynamic therapy versus supportive listening for irritable bowel syndrome came to the conclusion that dynamic therapy was superior in terms of pain, abdominal symptoms, and the limiting effect on the patient's life due to bowel symptoms (19). During the year after

treatment, the group receiving psychotherapy had a significantly reduced number of outpatient visits to the gastroenterology clinic compared with the year before treatment.

Although not a study of pain patients, a large study reported by Elkin et al. (20) compared four treatment conditions for depressed patients: interpersonal psychotherapy, cognitive behavioral therapy, imipramine plus clinical management, and placebo plus clinical management. Significant differences were found only for the subgroup who were more severely depressed and functionally impaired. Antidepressant treatment was most effective in the more depressed and functionally impaired patients, and interpersonal therapy and cognitive therapy were similar in efficacy and did better for the less impaired than for the more impaired depressed patients. Given that many chronic pain sufferers also suffer depression and pain sufferers seek psychotherapy because of psychological distress, these results also have relevance for pain patients with depression (see Chapter 26).

Person-centered counseling (a form of supportive psychotherapy pioneered by Carl Rogers) has been studied in the format of a low-intensity telephone-based counseling intervention for patients with systemic lupus erythematosus or rheumatoid arthritis (21). Patients were randomized to usual care or person-centered counseling. At 4 months, systemic lupus erythematosus patients (but not rheumatoid arthritis patients) receiving the counseling had improved significantly more on arthritis impact measurement scale scores representing psychological dysfunction but not on scores of pain, physical disability, or total scores.

Although family or couple intervention for chronic pain patients has been extensively reviewed (22,23 and 24), controlled studies of efficacy are uncommon. The review by Guthrie suggested that couple therapy should be a fruitful avenue to explore in treatment of patients with chronic functional symptoms but that the strength of the evidence is still disappointingly small (25). Saarijarvi et al. (26,27) randomized chronic low back patients to couple therapy or control conditions. At 12 months' follow-up, improved marital communication and psychological distress of male patients were associated with the couple therapy, but the therapy versus control groups were not significantly different in measures of self-reported pain, disability, or use of medical services.

With the exception of multimodal and cognitive behavioral therapies, group therapy for chronic pain has not yet been the subject of controlled studies. There is one possibly relevant study by Kashner et al. (28), in which patients with somatization disorders were randomized to group therapy or to control (no group therapy) conditions. Group therapy patients improved more on measures of physical function and mental health compared with control patients. The more group sessions attended, the greater the benefit in mental and general health measures. The annual health care charges decreased significantly more in the group therapy patients.

Indications for Psychotherapy with Pain Patients

The use of psychotherapy with chronic pain patients must be considered carefully. A psychotherapeutic approach that may be quite suitable and helpful for neurotic outpatients in a psychiatry department may be totally inappropriate and unworkable with patients with chronic pain. One of the special features of pain patients is that they suffer from a subjective state, which has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, and often described in terms of such damage (29). Chronic pain is probably the outstanding example of such a subjective condition, which can result from physical causes, psychological causes, or both. In theory, any treatment that might improve the subjective state could be considered for a patient in pain, whatever the initial cause of the illness. In practice, psychotherapy for pain is indicated in the following situations and conditions:

- The patient believes that there is a connection between his or her pain and associated psychological disorder.
  One might assume that psychotherapy would be appropriate when much or all of the pain seems to follow from a psychological disorder and without a major physical contribution. Not many such cases, however, are susceptible to symptom relief through psychotherapy alone. Indeed, patients who suffer pain associated only with somatization usually turn out to be unreceptive to insight-oriented psychotherapy, and many patients with pain due to lesions become emotionally distressed and benefit from psychotherapy.
  However, when the patient believes that there is a connection between the pain and psychological disorder, it usually indicates a readiness to benefit from psychotherapy, regardless of whether there is also a painful lesion.
- Patients who suffer multiple problems of pain and also psychological distress concurrently may benefit more if psychotherapy is added to the treatment program.
  There is clear evidence that chronic pain patients who attend specialty clinics have a higher loading on psychosocial risk factors (e.g., litigation, emotional impairment, poor work history, interference with daily activity by the pain problem, an increased tendency to use health care resources) than others (30,31). In these patients, the medical disorder is not the sole issue; they also have significant problems of dissatisfaction and emotional maladjustment, for which psychotherapy is potentially relevant. Psychotherapy may not provide significant symptomatic relief for the pain itself, but it may aid the individual in adjusting his or her human relationships, improves peace of mind, and often improves treatment adherence. As a result goal achievement and morale improve.
  In many cases of serious depression, antidepressant medication is more effective than psychotherapy, although it often appears that the addition of psychotherapy increases the efficacy of antidepressant therapy, particularly in chronic or resistant depressions (see Chapter 26).
- Patients with prolonged and severe physical illness but without evidence of premorbid predisposition to psychological illness may develop emotional changes in response to suffering. For them, supportive psychotherapy can be a useful part of treatment (see Supportive Psychotherapy).
- For people who suffer psychosocial problems attendant on chronic pain, psychotherapy, behavior therapy, or both may enable them to alter interpersonal relationships and behaviors. When the aim is primarily to change subjective distress related to troubled relationships, conflicts, losses, or a disturbed sense of self, psychotherapy is the treatment of choice.

Factors Affecting Psychotherapeutic Outcome

In psychotherapy for people with chronic pain, the requisites for success include certain nonspecific factors found in any psychologically oriented therapy and other factors that specifically relate to treatment of the chronic pain condition.

General Factors

The general factors essential for success with any type of psychological therapy include the following:

- The therapist and patient must be in therapeutic contact.
- A consistent therapeutic rationale must unite patient and therapist.
- Mutually agreed-on therapeutic goals must be established.
- There is an agreed focus for treatment.
- Structured therapeutic exercises should provide opportunities for new learning.
- There must be active participation by a motivated patient.
- This active participation in the therapeutic exercises promotes successful experiences, leading to a sense of mastery.
- Opportunities for application of the new learning to problem areas are created.
- There is a therapeutic relationship that acts as the context for this process.

For additional discussion of these points, see references 7,8 and 9.

Patient's Readiness for Psychotherapy

This readiness is variously described as “motivation” or “engagement” and consists of the patient's ability to agree on a focus for change, to be able to demonstrate in practice the willingness to make efforts to change, to be open to considering psychological factors, and to be able to demonstrate the acquisition of insight during therapeutic encounters.

Patients need a realistic explanation of what is expected of them during psychotherapy, of the potential benefits to be gained, as well as of the things that may be difficult or require patience. Obviously, the patient must be able participate willingly, without feeling coerced. Informed consent not only protects the patient and therapist alike, but it also promotes adherence and motivation.

Factors Specific to Chronic Pain Patients

In dealing with chronic pain patients, the psychotherapist must be aware of several additional requisites for success:

- The need to consider not only the presenting chief complaint but also the context of the patient's problems, whether at home or at work.
- The need for an extra degree of tolerance for negative attitudes of patients who may not be at first “psychologically minded” or willing to look at the emotional factors in their difficulties.
- A greater need for flexibility in therapeutic methods.
- Recognizing the possible involvement with a multidisciplinary team while appreciating the perspectives and difficulties experienced by colleagues who are not psychiatrists or psychologists, in handling patients who have a combination of physical and psychological disorders.
- Willingness to assume a more active therapeutic stance as teacher and guide, rather than the traditional neutral stance of the psychotherapist.
- Recognizing the need for clearly defined, goal-oriented, and solution-oriented methods in therapy while enlisting the patient actively in defining goals for treatment and for change.

In terms of this last requirement, much can be learned from behaviorists. Their approach involves offering a clearly defined therapeutic program, offering a clear description of how progress will be measured, and placing responsibility on patients for measuring their own progress consistently toward that outcome. These principles, which are central to the behavioral therapies, are not at all inconsistent with dynamic psychotherapies and will be beneficial when included in all types of psychotherapeutic practice.

CLINICAL APPLICATIONS

In this section, we discuss the major psychotherapies that have been used in the clinical management of chronic pain patients. These are supportive, dynamic, family, and group psychotherapy.

Supportive Psychotherapy

The most important and widespread form of psychotherapy—supportive psychotherapy—is knowingly and unknowingly used by specialists in psychological methods and by other health professionals. The trusting relationship with a physician, therapist, or clergyperson is the paradigm of this approach, which extends into every nook and cranny of professional work. One example is the trust that patients develop for their favorite doctor (“My doctor listens and takes the time to explain things”). Another example is the reliance on a social worker for help in filling out an application for benefits, with reassurance and advice, which then leads to attachment to that professional and to the advice provided. At a minimal level, supportive psychotherapy gives a patient the feeling that there is another person who shares the patient's concerns, is sympathetic, and will be happy when the patient feels better or concerned when there are reverses. At the very least, supportive psychotherapy provides companionship for the lonely and empathy for the isolated.

The theoretical basis for supportive psychotherapy emphasizes reality and the possibility and importance of making choices. Notwithstanding pain and adverse circumstances, it is possible for a patient to reduce disability and to increase the sense of well-being by thinking through the problems, setting objectives, drawing on his or her skills, and obtaining aid and advice from others. It assumes that people in distress are more likely to be able to successfully confront their problems in this way if they experience a sense of support from a helper who also assists them in organizing a problem-solving response. Although this theory is not psychologically esoteric and the practice is within the competence of most health care workers, formal psychological training and experience improve one's ability to provide effective supportive therapy. It is a professional activity and much more than mere hand-holding because improved adjustment and not just maintenance of the status quo are expected. Principles to guide effective practice are given below.

Treatment Strategy

The style of the therapist is that of both teacher and “coach.” Sometimes the task is to listen and help patients achieve their own stated goals. At other times it is to provide information and advice. Therapeutic sessions are not rigidly prescribed but are offered while educating patients to be prepared to generate their own objectives. Sessions may last from 0.5 to 1 hour, at intervals of every few days to every few weeks, depending on the patient's need. Termination of therapy depends on several factors, including the end of formal pain clinic treatment, the resolution of certain important psychological or social problems, or the desire to “try it on one's own.”

Supportive psychotherapy should be inherent in the management of every patient in an organized pain therapy program. The provision of a “case manager,” the practice of comprehensive evaluation and discussion in which patients are made to feel that their total situation is being considered, and the development of a confiding relationship with patients all provide a climate of support and encouragement. The most important motivator for change is the opinion and attitude of someone who is respected and liked.

Competent supportive therapy provides more than the incidental benefits of concern, expectation of improvement, and resourceful management of problems. In its complete form, it begins with an assessment of the life situations and problems of the patient and the personality and strengths of the individual; it evaluates the manner in which this individual has in the past characteristically preserved his or her psychological integrity and responsibilities in the face of adversity; and it proceeds according to a clearly defined rationale aimed at restoring that patient's emotional equilibrium. The rationale in supportive psychotherapy is usually to support and facilitate styles of problem solving that previously were successful for the patient and to assist the patient in developing new coping methods where necessary. The primary objectives of supportive psychotherapy are to restore a sense of confidence and to assist the patient in reorganizing coping skills in the most adaptive and psychologically economical fashion.

Formulating a Supportive Psychotherapy Intervention

The following questions will serve as a practical guide to the clinician in conducting supportive therapy:

What is the current problem?

How does the patient describe the chief sources of distress or worry?

What are the current ways that the patient uses to try to cope with (or avoid) these problems?

What are the patient's emotional strengths, problem-solving skills, and resources (family, work, social network) currently available to the patient? Have medical impairments (e.g., head injury, major depression) diminished these strengths?

What needs to change to restore psychological equilibrium?

What previously successful coping patterns did the patient use before this problem occurred?

What main objectives will help to resolve the problem or improve the sense of control?

What are the first priorities in beginning to resolve the problem or in achieving the first measure of control?

What additional external or psychotherapeutic support, structure, or assistance will be needed to help the patient to do these things?

What is the “game plan” to work through this problem?

How can one establish a confiding and encouraging relationship in which the patient can discuss worries, attitudes, and progress?

What are the frequency and duration of meetings, and how should “emergencies” be handled?

What “road map” will guide the patient in setting priorities, organizing solutions, and working through the problems, day by day, in a way that the patient will perceive

as successful and not overwhelming?

How will this work be brought to completion?

What has the patient learned, and what skills have been developed?

How will the patient make the transition from relying on the therapist to developing his or her own support system?

Has the patient had an adequate chance to “say good-bye,” to avoid feelings of being abandoned or rejected?

Dynamic Psychotherapy

As with supportive psychotherapy, in dynamic psychotherapy, the relationship is seen as being the most crucial factor. It is the relationship with the therapist that provides a context for the corrective emotional experience. The theory for dynamic psychotherapy is more complex, is based on concepts drawn from various original psychoanalytic frameworks, and involves the reorganization of thoughts and feelings through insights gained in the psychotherapeutic relationship. Psychodynamic approaches assume that the patient's inner conscious and unconscious thoughts, conflicts, and defenses are determinants of behavior and adjustment. Some central concepts of dynamic psychotherapy include the following:

- Certain properties of the mind, such as drive, need for mastery, conscience, and sense of self, are subject to modification by “making the unconscious conscious”—that is, by gaining insight.
- Each individual acquires by experiences during maturation a repertoire of patterns of feeling, believing, and behaving. These patterns are fundamental to both healthy (adaptive) and also to neurotic (maladaptive) styles of adjustment and eventually characterize an individual's personality.
- Current patterns of feeling and behaving in response to ongoing problems reflect solutions to problems that the individual has learned in the past in the course of previous relationships.
- Psychological equilibrium depends on having the psychological energy and mental strategies to maintain stability and to control negative feelings and conflicts. This can be improved through a therapeutic relationship with a psychotherapist.

Further descriptions of the psychodynamic perspective with respect to chronic pain can be found elsewhere (4,5,32,33 and 34).

Dynamic psychotherapy alone is not an appropriate treatment for the majority of chronic pain sufferers, although one might get that impression from some classic papers that deal with pain from a psychodynamic viewpoint (32,33). Psychodynamic therapy, however, is likely to be beneficial, especially in the subjective aspects of adjustment, when combined with other appropriate pain management modalities (35). Patients for whom dynamic psychotherapy is preferred usually (a) suffer a sense of psychological discomfort, (b) experience distress with regard to their key relationships, (c) perceive themselves as having changed for the worse, (d) may be perplexed by their own impulses or feelings, (e) experience difficulties because they perpetuate in their current relationships conflicts that they previously experienced with significant others during their maturation, (f) or demonstrate barriers (“resistance”) to therapeutic progress because of hidden motives about which they lack insight.

Treatment Strategy

With chronic pain patients, dynamic psychotherapy is often, but not always, short term—perhaps five to 20 sessions—and is focused on a few specific psychological issues (although patients sometimes may prefer a much more thorough exploration of issues that trouble their lives). Sessions are usually an hour long and are held at regular intervals. Sessions could be as often as twice per week, but weekly or semimonthly sessions are most common. In the majority of cases, this method of psychotherapy is one of several approaches that are offered concurrently, including even other psychological therapies. Dynamic psychotherapy is not, for example, incompatible with behavior therapies, vocational counseling, or medical treatments for pain.

Although dynamic psychotherapy explores hidden feelings and motives, it is unlikely that this therapy would lead to finding a purely “psychological cause” for chronic pain. The real benefits are an improved sense of self, reduced feelings of perplexity or conflict about one's own feelings or impulses, and a more comfortable (less distorted) relationship with significant others. All of this can be very helpful toward an individual's ability to cope with persistent pain. Dynamic psychotherapy requires specific training and is usually conducted by psychologists or psychiatrists.

Family Therapy

Chronic pain is such a disruptive problem that it is prone to affect a patient's family and not just the pain sufferer. Accordingly, it is prudent to involve family members right from the beginning in pain treatment programs. In some cases, psychotherapy of the marital or family unit is indicated as part of chronic pain management because of the influence of the family on the chronic pain disability. The importance of the family perspective in chronic pain has been discussed in other reports (4,22,23 and 24).

The intent of family therapy is not merely to search for conflict (as some families initially fear) but rather to consider both the assets and liabilities in a family's function, in an effort to help the family organize its communication and problem solving in the most satisfactory way.

Some family factors are especially important in cases of chronic pain. These include the role of family members as agents of pain behavior reinforcement (36,37), the value placed by the family on illness-related communications, and the degree of stability with which the family has absorbed the sick role (38).

Common indications for family therapy might include one or more of the following:

- Illness in a family member results in disturbances in family function.
- There is reason to believe that family dynamics may contribute to or perpetuate the patient's problem.
- The family is overwhelmed by multiple problems, in addition to having a member with chronic pain.
- The identified patient is a child.
- There are indications that the family is sufficiently motivated for a family therapy approach.
- The family can be mobilized therapeutically to influence the pain behavior or disability.

Treatment Strategy

Whereas dynamic psychotherapy focuses on psychodynamic factors and formative past experiences in understanding the present, family therapy is oriented to the here-and-now, considers the whole family as “the patient,” and concentrates on communication more than on introspection. In addition, the therapist takes an active stance in style of interventions. Family therapy takes place over a fewer number of sessions than dynamic psychotherapy, focuses on group and communication dynamics, and is more intensive in demands on both patients and therapist. A course of family therapy with chronic pain patients commonly consists of three to 20 sessions, but five or six sessions probably is most typical.

Group Therapy

Numerous types of group therapies have been used in chronic pain management, including educational groups (e.g., Back School), marital couples' groups, therapeutic milieu (on an admission ward), groups aimed at teaching special skills such as relaxation or assertiveness, and cognitive-behavioral groups in pain clinics. Discussions of group approaches for chronic pain patients have been published elsewhere (4,39,40). Among the important advantages of group therapy are that it provides the following:

- Group therapy economizes therapist time by allowing several patients to be treated simultaneously.
- Group therapy allows for the therapeutic influence of one patient on another, including vicarious learning and the motivating effect of shared goals.
- Group therapy permits certain conflicts and problems to be played out in a “safe environment,” avoiding destructive consequences and permitting learning of

more adaptive responses.
- The peer group has the potential of causing patients to feel supported and understood.
- The group permits a forum for an educational component of therapy.

The theoretical rationale of this approach is that people recreate their interpersonal conflicts and demonstrate their assumptions when they are in the context of a group. The group has a modulating effect on the behavior of each member, which the therapist can influence therapeutically.

Group Techniques for Chronic Pain Patients

The published evidence does not support the efficacy of group or education approaches used in isolation in treatment of chronic pain (12,13,14,15 and 16). This does not mean that group approaches are of no avail, but it indicates that group approaches should be used in conjunction with other modalities or comprehensive pain management.

The common reasons for including pain patients in group therapy are to provide a vehicle for the educative component of pain management, to increase patients' awareness of key psychological factors in their problems and treatment, to promote informed and motivated participation, especially in the case of comprehensive or inpatient pain management programs, and to provide a “normalizing” effect of a peer group and modeling of healthier ways of coping.

The educational component can be geared to providing accurate information about pain management, teaching coping strategies through example and role-playing and by sharing of experiences between patients, improving appropriate assertiveness, practicing coping skills, improving communication skills, reducing the sense of isolation, and providing social reinforcement of healthier behavior (40).

Treatment Strategy

The following are general guidelines for conducting group therapy with chronic pain patients:

- To be effective and manageable, a group should consist of at least four and not more than approximately 12 members.
- Psychiatric patients and chronic pain patients should not be included in the same group.
- Patients should be interviewed before their inclusion in the group to ensure that there is adequate motivation for the group and that the patients have realistic expectations regarding the time commitment, their active participation, the readiness for the “give-and- take” that will likely occur in the group discussions, and the likely benefits that will accrue.
- Patients who are paranoid or suspicious (using “projection”), who have florid “borderline traits” (e.g., self-injury, dissociation, and distortion), or who have antisocial traits should not be included in group therapy.
- The group should be structured to be relevant to the problems of chronic pain patients. In group therapy with psychiatric patients, it might be acceptable for the therapist to give little information beyond the initial introduction and to concentrate instead on group dynamics as they appear spontaneously. In pain clinic practice, however, a didactic component usually is necessary to resolve misconceptions and fears about pain and to deal with practical issues related to living with chronic pain. Coping techniques for pain control (e.g., relaxation, cognitive techniques such as imagery or self-talk for pain control) are often helpful and may be included in some sessions (see Chapter 89).
- An explicit set of norms is expected. These typically include not abusing medication or alcohol, being on time, not skipping sessions, minimizing illness behavior, keeping therapy “in the room,” and not imposing on copatients between sessions. Patients who later on prove disruptive to the group, who are not respectful of the needs of other group members, and who are not able to change their behavior after accurate feedback from the group should not be allowed to continue.
- When group therapy is part of a multimodal pain management program, opportunities should be provided for group discussion of emotional and adjustment issues that arise in the course of the rest of the pain management program.
- Care must be taken to accommodate for the fact that some pain patients have limited sitting tolerance. Hence, sessions should not last more than 1 hour, and opportunities to change position or find a comfortable chair should be afforded. However, therapists should not tolerate dramatic illness behavior such as lying on the floor or groaning, avoiding group participation through dramatic pain behavior, or leaving the room.

Pain management programs (day care or inpatient) typically have daily group sessions for the duration of the treatment program, often 3 to 8 weeks (see Chapter 109). Outpatient program groups may meet less frequently but over a longer duration.

CONCLUSIONS

The psychological dimension is always important in cases of chronic pain; however, no one psychological method can possibly address the full spectrum of therapeutic need. A variety of psychotherapeutic methods ought to be available as an integral component of the pain management effort. A flexible approach, drawing on supportive psychotherapy; education methods; cognitive- behavioral techniques; and occasionally specialized methods, such as dynamic, family, and group therapies, will permit each patient's needs to be addressed appropriately. Various psychological pain management techniques are presented in the other chapters of this section.

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CHAPTER 94

Motivating the Pain Patient for Behavioral Change

Mark P. Jensen

Chronic pain rehabilitation, in contrast to cure, requires active patient involvement. After being evaluated by a pain clinician, chronic pain patients may be asked to increase, decrease, or maintain specific medications; initiate and maintain a program of regular exercise and activity; develop a plan for return to work; or learn and then regularly use specific pain management skills, such as relaxation or cognitive restructuring. Because so much of chronic pain rehabilitation depends on patient effort (self-management), patient motivation plays a vital role in chronic pain treatment.

When the clinician and patient agree on a course of treatment and the patient evidences a willingness to participate fully in this treatment, issues of patient motivation fade into the background. Treatment can proceed and both the patient and clinician can determine its effectiveness. However, problems arise when the clinician and the patient disagree on which intervention(s) to try next. For example, patients may hope for or expect “pain killers” or a surgery that will eliminate their pain, despite a clinician's reservations about either of these treatment options. Clinicians may believe that a course of active physical therapy or the development of a return-to-work plan will benefit the patient, whereas patients may not feel ready for either of these options “until the pain is taken care of.”

When clinicians and patients disagree about treatment, what can the clinician do? One option is to refuse to treat the patient and refer the patient back to his or her primary care provider or to another specialist. In this case, the patient misses an opportunity to try a treatment that the clinician believes will reduce the patient's pain and suffering. A second option is to insist that the patient try the recommended intervention despite the patient's reservations and resistance: “You must try this, it is your only option left.” This approach might work for some patients, especially when the treatment does not require sustained patient effort and is perceived as immediately helpful. Unfortunately, there are few chronic pain treatments that both (a) do not require sustained patient effort and (b) have immediate benefits (although the search for such a “magic bullet” goes on). A third option, and one that this chapter advocates, is for the clinician to spend time enlisting patient's motivation for and commitment to a treatment plan *before* offering treatment and then reinforcing and attending to motivation as treatment progresses.

This chapter is written for clinicians interested in learning more about this third option. The material is based largely on a set of therapeutic strategies developed by William Miller and his colleagues (1,2) that were designed to help individuals change addictive behaviors, and the interested reader is encouraged to read these sources for more detailed information about the motivational strategies described here.

The chapter has two major sections. In the first section, three key concepts underlying the use of motivational strategies are outlined. The second section reviews several specific clinician responses that (a) enhance patient motivation to consider new treatment approaches, (b) strengthen a commitment to a treatment plan, and (c) encourage continued participation in treatment and maintenance of any lifestyle changes made. Whenever possible, the discussions focus on how these concepts and strategies can be applied to behavior change, which is central to chronic pain rehabilitation.

KEY CONCEPTS OF MOTIVATIONAL STRATEGIES

For the pain clinician, three concepts about motivational approaches are especially important to understand. These include (a) viewing motivation as a probability of behavior change that can fluctuate considerably over time, (b) understanding the importance of the clinician's role for facilitating motivation to change, and (c) understanding behavior change as a multistage process. Each of these concepts is discussed in turn.

Motivation as a Probability

Traditionally, most clinicians have viewed motivation as something residing inside the patient. Lack of behavior change, or resistance to recommended treatment approaches, has been seen as an indication of a patient deficit in motivation: “This patient must not really want to get better if he or she refuses to accept my treatment plan.” An alternative view, and one that provides more hope that clinicians can influence patient motivation, is that motivation is “the probability that a person will enter into, continue, and adhere to a specific change strategy” (1). In this view, the probability that the patient will accept and adhere to treatment recommendations (e.g., “motivation”) depends, in large part, on the atmosphere in which treatment recommendations are made.

Creating an Atmosphere for Change

Pain clinicians sometimes take on the role of an expert to whom patients go to seek advice. In this role, the clinician, usually after a careful evaluation, gives the patient feedback and recommendations. The recommendations may include an offer of treatment (e.g., medication management, supervision of physical therapy, cognitive-behavioral therapy, skills training). The patient, in the role of a health care seeker, is expected to agree with the expert and then to follow through with the recommendations. As already discussed, this interaction often works when the patient agrees that the clinician's recommendations are sound and consistent with the patient's view of his or her pain. However, these roles work less well when the patient does not see how the treatment will help or believes that the treatment will make things worse. In this case the patient may feel that the evaluation was incomplete, that the clinician “did not listen to” or “does not understand” him or her, or that the clinician is incompetent. This can then create an adversarial relationship in which the clinician becomes frustrated with the patient for not accepting and following through with the treatment recommendations and the patient becomes frustrated with the clinician for his or her insensitivity or withholding a desired treatment that the patient believes could end his or her suffering. This scenario is not uncommon in chronic pain patient-clinician relationships.

An environment more conducive to change is one that recognizes patients' experiences, opinions, and feelings and communicates that recognition to the patient. Clinician responses that contribute to this environment differ markedly from the responses that would be expected from the traditional authoritative physician. They include, for example, asking open-ended questions, listening reflectively, affirming the patient, and summarizing (Table 94-1). The goal of these clinician responses is to create an atmosphere of trust and cooperation that helps set the stage for behavior change.

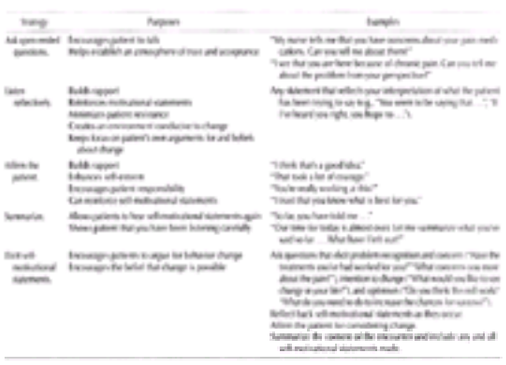

TABLE 94-1. Five strategies that enhance motivation to change

Rather than acting as an authority whose primary job it is to develop a list of treatment recommendations (at least in the initial encounter), motivational clinicians present themselves as coaches or teachers knowledgeable in a variety of pain self-management approaches. Clinicians concerned about motivation spend more time listening than they do talking, and much of what they say represents attempts to clarify and understand the patient's position. As described below, recommendations and advice, when made, are brief and are presented only when the patient has indicated a willingness to consider alternative approaches. Moreover, whenever possible, treatment recommendations are presented in the form of a "menu" of choices. A behavior change plan unique to the patient's own problem and situation is created in cooperation with the patient.

Although clinician responses that create an atmosphere of trust and cooperation help set the stage for behavior change, they would be ineffective without more specific responses that focus the patient's attention to the desirability of behavior change. Before these more specific responses can be described, a final concept needs to be explained: the concept of behavior change as a multistage process.

Behavior Change as a Multistage Process

Chronic pain patients usually see pain specialists because the strategies the patient is currently using to manage pain are not working. Although the patient may hope that the clinician will "find and fix" the problem, pain management ultimately depends more on what the patient does than on what is done to the patient. The primary purpose of motivational strategies is to increase the probability that the patient will engage in adaptive behavior change in the (near) future. That is, they will begin and fully participate in a specific treatment or try a new pain management approach. In order to facilitate this change, clinicians need to understand how change comes about. The most thorough model for behavior change has been developed by Prochaska and DiClemente (3), who have studied, in detail, the process of change from maladaptive (e.g., smoking) to adaptive (e.g., not smoking) health behaviors.

According to the model that Prochaska and DiClemente developed, adaptive behavior change involves five stages (Table 94-2). People who are not considering changing their behavior are in the *precontemplation* stage. Precontemplators see no need to change. They will show resistance when and if they feel coerced into changing some behavior that they do not view as a problem. Although precontemplator pain patients may suffer because of maladaptive coping strategies, they do not necessarily attribute their suffering to these maladaptive responses. Often, they blame their suffering on the pain itself. They may even view maladaptive responses (e.g., pain-contingent medication use and inactivity) as the "only" things that help. *Contemplation* is a stage in which a person acknowledges a need for change and may be considering making some change in the future. However, contemplators are not yet committed to change; they are in a constant state of weighing the pros and cons of altering their behavior. Contemplators might acknowledge that maladaptive coping responses create problems (e.g., side effects from medications, weakness, or perhaps even increased pain from inactivity) but may not see any other options for managing their pain. *Preparation* (also known as the *decision-making* or *determination* stage) involves both intent to make changes and taking some initial steps in the direction of change. Pain patients in the preparation stage express a willingness to try or learn a new approach to self-management of pain and problems associated with pain. Patients in the process of changing their behavior are in the *action* stage. Patients in the fifth stage, called *maintenance*, are making efforts to sustain the changes made in the action stage. Those unable to maintain the changes they have made are said to have relapsed. From this point, they may reenter the change cycle at any point (e.g., give up and become precontemplators or start right back in again at the action stage). People may, and often do, cycle through these stages several times before any change becomes permanent.

Stage	Description
Precontemplation	Patient sees no need to change current behavior.
	Patient will show resistance when asked or advised to change.
Contemplation	Patient feels ambivalent about change.
	Patient can identify both pros and cons of change.
Preparation	Patient has made the decision to try to change.
	Patient has made initial steps toward change.
Action	Patient is in the process of making concrete changes.
Maintenance	Patient is maintaining changes made in the action stage.

TABLE 94-2. Five stages of behavior change

There are some important characteristics about this stage model of change that influence how a clinician might think about and intervene with patients engaging in maladaptive pain coping behaviors, such as pain-contingent medication use, pain-contingent rest, or inactivity. First, the model predicts that people in different change stages should react differently to treatment, as a function of their change stage. For example, people in the preparation and action stages should be more likely than people in the precontemplation stage to benefit from treatments that require effort. Research supports this prediction, for both smoking cessation (4,5) and weight control treatment programs (6). One implication of this is *that not all patients are ready for treatments that require their own effort.* In fact, as described in more detail below, this model indicates that patients in different stages require different clinician responses to facilitate movement toward change.

SPECIFIC MOTIVATIONAL STRATEGIES

Given this background, we can now turn to the specific strategies that clinicians may use to create an atmosphere of change and develop a self-management plan that the patient can understand and accept. Motivational strategies can be organized into three types: those that generally enhance motivation for change and that should therefore be used for patients who are in the precontemplation or contemplation stages, those that strengthen the commitment for change and should be used in the preparation and action stages, and those that follow up on any treatment plan developed and that encourage maintenance of any changes made (1,2).

Strategies that Enhance Motivation for Behavior Change

Miller et al. (2) describe five specific strategies that can be used with patients in the precontemplation and contemplation stages to help guide them toward preparation and action. The first four, asking open-ended questions, listening reflectively, affirming the patient, and summarizing the interaction, all build rapport and contribute to an atmosphere for change. The fifth strategy, eliciting self-motivation statements, is unique to motivational approaches, and seeks to (a) support the patient's belief that change is possible and (b) encourage the patient to come up with his or her own reasons for change. Each of these strategies is described below and listed in Table 94-1.

Ask Open-Ended Questions

Open-ended questions are those that tend to elicit patients' concerns, ideas, and feelings. As such, they are an excellent strategy early in an encounter when the clinician seeks information about the patient's relationship with and commitment to the problem behavior. A good open-ended question is difficult to respond to with just a "yes" or "no." By encouraging the patient to express the problem in his or her own words, open-ended questions demonstrate that the clinician is interested in the patient's perspective on the problem. Two examples of open-ended questions are presented in Table 94-1.

In many cases, clinicians are limited to brief (e.g., 5- to 10-minute) encounters. Busy clinicians may therefore be concerned that asking open-ended questions would open a Pandora's box of (time-consuming) complaints, thereby turning a 10-minute encounter into an hour-long session. Some patients do require significant structure and limit setting to ensure that brief encounters remain brief. However, paradoxically, by initially giving patients a chance to air their primary concerns, patients may be more cooperative with the physician, increasing the efficiency of the encounter. Once patients feel heard they will feel less of a need to talk. They will also feel more understood and satisfied with the encounter. Moreover, knowledge of the patient's perspective of the problem may be helpful to enlist cooperation from the

patient for making the encounter even more efficient. For example, if time is starting to run out, the physician can say, “I'm sorry, but only 10 minutes were scheduled for your appointment today. To make sure we address [the important issue you raised earlier], I will need to ask you several questions and then discuss some treatment options with you. Is this alright, or would you rather make another appointment to do this?” The key here is not to use open-ended questions to encourage the patient to ramble for hours about anything that comes to the patient's mind. Rather, the clinician seeks to encourage the patient to communicate the primary problem(s) that need addressing from the patient's own perspective. Beginning the encounter with an open-ended question is an effective way for doing this.

Listen Reflectively

Reflective, or empathic, listening, as originally described by Rogers (7,8), provides a therapeutic environment that makes it easier for patients to consider making difficult behavior changes. This therapeutic strategy involves listening carefully to the patient and then reflecting back accurately what the patient has said. Reflective listening also acts to minimize patient resistance because it is more difficult to argue with someone seeking to understand you than with someone who is challenging you or lecturing you. Furthermore, and consistent with the goal of encouraging patients to convince themselves to engage in adaptive behaviors (see below), reflective listening keeps the patient talking and therefore increases the chances that the patient will say something that argues for behavior change.

Given the high volume of both verbal and nonverbal communication that can occur with every patient phrase, the clinician cannot hope to accurately reflect *everything* a patient says. Through careful selection of what to reflect back to the patient, reflective listening also may be used to emphasize and reinforce self-motivational statements (discussed further under Elicit Self-Motivational Statements).

Affirm the Patient

The clinician focusing on motivation seeks to affirm the patient at every opportunity. Affirmations, in the form of direct compliments and praise, are thought to provide a more positive environment for change by increasing rapport, enhancing patient self- esteem, encouraging patient responsibility, and reinforcing patient self-motivational statements (2). Affirming statements may be contrasted with reflective statements in that the former are sincere expressions of the *clinician's* positive responses to the patient (e.g., “I admire your courage”), whereas the latter consist of efforts to reflect the *patient's* concerns (e.g., “You really seem to be upset by this”).

Summarize

Toward the end of every patient encounter, even if that encounter was very brief, it is important to set aside a moment to summarize the basic content of the interaction. A summary serves an important opportunity for allowing patients to hear, yet again, any self-motivational statements they made during the encounter. However, it is also important to incorporate any concerns that the patient may have raised that indicate ambivalence about making a behavior change. This shows the patient that the clinician really listened.

A summary need not be lengthy. For example, after a 5-minute encounter that involved a patient's request for pain-contingent medications and a clinician's conclusion that complying with this request would not be helpful to the patient, the clinician could say

> “Even though we did not have much time to discuss treatment options for your pain, I think I have an initial understanding of the problem. You came today hoping that I would prescribe medications that you could take when you hurt as a way to ease the pain. I expressed some of my reservations about this approach. For example, despite using these in the past, you told me that the pain problem is not any better and in fact may be worse. You also expressed some worry about the effects of these medications on your concentration. I have found that patients do much better when they combine a taper of these medications with a regular exercise program. This is something that you seem willing to consider, although you still have some questions about how helpful this will be for you. Unfortunately, we did not have enough time today to address all your questions about this approach, and we agreed that I would see you again next week to discuss this option further.”

Elicit Self-Motivational Statements

Perhaps what sets the motivational strategies apart from other therapeutic approaches is the extent to which self-motivational statements are encouraged and reflected back to the patient. Self-motivational statements may be defined as arguments for behavior change (e.g., “It's time I did something about this”; “Okay, I'm ready to try something new”; “I can't go on like this anymore”). The strategies of asking open-ended questions, listening reflectively, affirming the patient, and summarizing, although basic to creating an atmosphere for change, would not effectively encourage change without a focus on eliciting self-motivational statements specifically.

The first step is to recognize self-motivational statements when they occur. Miller and Rollnick (1) describe four categories of self-motivational statements. Problem recognition statements indicate that the patient sees the problem behavior as having negative consequences (”I have gained weight mostly because of inactivity due to pain”; “Those pain killers make it so I can't work; you can't drive a truck and take those”). Expressions of concern indicate that the patient is upset or worried about his or her current situation (”I'm afraid I'm never going to get better”). Intention-to-change statements express an intention to make some change for the better or describe initial steps toward change (”I know I have to exercise”). Finally, statements that reflect optimism indicate that the patient believes he or she can be successful in making a positive change (”I think that if I take things a step at a time, I will be able to do this”). A primary goal of the clinician interested in a patient's motivation is to ask questions and make comments that elicit motivational statements like these and then (a) affirm the patient for making such statements (”That's a really good point; not all the people I work with recognize that”), (b) reflect these statements back throughout the interaction (e.g., during the session, “So you feel that . . .”), and (c) summarize them at least a third time at the end of the session.

Summary of Preliminary Strategies

The goal of the initial motivational strategies is to enhance motivation for behavior change—that is, to encourage movement from precontemplation to contemplation, and from contemplation to preparation. The strategies of asking open-ended questions, listening reflectively, affirming the patient, and summarizing all can be used to elicit and reinforce self-motivational statements. In this way, the clinician creates an environment in which the patient talks himself or herself into making positive behavior change. The assumption of this approach, supported by social science research, is that change will occur more rapidly when and if patients convince themselves that change is both necessary and possible than when clinicians try to convince patients of these things (9,10). These initial strategies should be used with precontemplators and contemplators until they enter, or are about to enter, the preparation and action stages. Rapid progression (e.g., within minutes) toward the preparation or action stages, as indicated by frequent self-motivational statements, suggests that the patient may be prepared to take action. At this point, the clinician should be ready to shift to the next set of strategies that strengthen commitment for behavior change. Slower progress suggests precontemplation and indicates that more time may be needed to enhance and build motivation for behavior change before the development of a treatment plan.

Strategies That Strengthen Commitment for Behavior Change

The timing of the switch from strategies that enhance or build motivation to change to strategies that elicit and strengthen a commitment to change is important. If the clinician switches strategies too early, the patient is likely to evidence resistance and progression to the action stage will be hindered. Fitting the motivational strategy to the patient, based on the stage of change, is essential to effective motivational enhancement. Six strategies that strengthen commitment to behavior change are listed in Table 94-3 and include the following: review of the consequences of behavior change, give advice, communicate free choice, develop a change plan, summarize, and ask for a commitment.

Strategy	Purposes	Examples
Review consequences of change.	Reminds patient that change has pros and cons. Allows patient to reinvent himself or herself of the reasons for changing.	"What do you think will happen if you were to . . . ?" "What are some of the benefits of changing?" "What are some of the costs of changing?"
Give advice.	Provides options. Influences action.	"I think you should . . . Does this make sense to you in your situation?" "Here are some options I think you should consider. Which of these makes the most sense to you?"
Communicate free choice.	Emphasizes that it is the patient's responsibility to decide on a plan. Encourages patient responsibility.	"How would you like to proceed?" "There are several ways we could go from here. What do you think?"
Develop a change plan.	Clarifies goals and change strategy. Fosters commitment to change.	"What, exactly, would you like to do at this point?" Consider using the change plan worksheet (see Fig. 94-1).
Summarize.	Allows patients to hear self-motivational statements again. Allows patients to hear and reaffirm change plan.	"Your major goals with this plan are to . . . and this will allow you to . . . Do I have that right?" "Let's review your plan to be sure I understand what you intended to do."
Ask for a commitment.	Clarifies patient's intent. Clarifies what patient is planning to do.	"Are you ready to commit yourself to doing this?"

TABLE 94-3. Six strategies that strengthen commitment to change

Review Consequences of Behavior Change

One effective way to strengthen commitment to change is to review with the patient the consequences of making the change versus not making the change. Most likely, the patient will realize that not making any changes means life as before. Such a life is unsatisfactory for many patients. An approach that elicits consequences of change is to ask the patient to review both the pros and cons of changing. More likely than not, much information about this would have already been reviewed earlier in the encounter or in previous encounters when self-motivational statements were elicited and discussed in detail with the patient. Patients may choose to list in two columns on a piece of paper the benefits and costs (or pros and cons) of different options. Such lists, as long as the contents are generated by patients and not "fed" to them by the clinician, and assuming that the benefits of behavior change outweigh the costs, should help strengthen the patient's motivation to change or maintain a behavior change plan.

For example, regular exercise should result in the patient's being more able to participate in activities that are important to him or her, such as child rearing, recreational activities, shopping, and household chores. On the other hand, documented improvement may lead to claim closure if a claims manager concludes that the patient now has enough strength and endurance to return to work. Both the positive and negative consequences of successful treatment should be acknowledged and discussed. However, as much as possible, discussions about the current and future *benefits* of the treatment plan should be emphasized and reiterated to enhance motivation before treatment and maintain motivation during treatment.

Give Advice

As patients with pain problems reach the preparation stage, they may ask for specific information and advice concerning how to proceed. One way to respond is to provide information based on personal experience or research and then ask a follow-up question concerning what the patient wishes to do. Whenever possible, offer a number of possible suggestions (a "menu") from which the patient might choose. This helps emphasize that it is the patient's responsibility to decide what specifically to do.

Giving advice can help increase motivation. However, some resistance to giving advice on the clinician's part may help to ensure that the patient is interested in hearing what is being suggested and not seeking to hear information with which he or she can argue. For example, a clinician might say, "I can tell you what I think might be best in your situation based on my experience with people who have problems like yours. However, I also believe that each person is different and that what is best for one person may not necessarily be best for another. That is why any decision about what you will do has to be up to you. I am here to support you in the development of a plan that *you* are interested in trying."

If the patient expresses the desire to know what you think might be best for him or her, especially after you communicate some resistance to providing advice, then short and clear advice statements are best (e.g., "I think you should maintain a regular exercise program"; or "I think you should give relaxation a trial. You might practice relaxation strategies 30 minutes a day for 1 month and then decide whether to continue."). In general, it is always a good idea to follow up any information and advice with questions that gauge the patient's response (e.g., "Does this make sense to you?" or "Do you have any questions about what I said?"). Such questions help to emphasize that it is the patient's responsibility to make a final decision as to what he or she is going to do next.

Communicate Free Choice

To maximize self-motivation and to facilitate the attribution of control to the patient, the clinician should provide frequent reminders of the patient's free choice in all aspects of his or her change plan. This can be difficult for some established pain treatment protocols that are not as successful when patients "pick and choose" which aspect and how much of the treatment they will do on any particular day. For example, in quota-based (i.e., non–pain-contingent as opposed to pain-contingent) reactivation programs, patients are asked to exercise to a specific and gradually increasing level (e.g., 10 minutes of aerobics or 12 partial sit-ups) every day no matter how good or bad the patient feels (11). Similarly, drug-tapering schedules are usually established ahead of time, and success is believed to depend in large part on patient adherence to the agreed-on tapering schedule. For treatments such as these that require a patient commitment to participating in the "whole" program, it is important to communicate the rationale behind the expectations and limitations of participation before offering the treatment to the patient. The patient's choice then becomes to participate or not participate in the treatment based on the established rules or requirements. However, to maximize motivation, it is important to provide as many treatment options for the patient as possible. Offering only a standard treatment plan for all patients would limit success. For example, in a quota-based exercise program, some choice can be provided regarding specific exercises ("Which activities are most important for you to become more able to tolerate?") or even the rate of increase ("If we go too slow, it may take too long to get where you need to be to feel better and do what you want to do. On the other hand, if we go too fast, meeting your quotas may be a challenge. Usually patients I see on an outpatient basis increase approximately 10% per week. What is most important is that you do increase a specific amount every week no matter how good or bad you feel. What rate of increase do you think makes sense for you given your goal of . . . ?").

Develop a Plan for Change

A primary goal of working with a patient in the preparation stage is to develop a behavior change plan to which patient can commit. Readiness to develop a plan may be initiated by the patient (e.g., "I'd like to get started on that exercise program we've been talking about"). It can also be effective for clinicians to raise the issue of plan development.

One strategy that the clinician might find useful to assist in the development of a plan for change is through the use of a change plan worksheet (CPW). This sheet can provide a structure for organizing the most important aspects of the patient's goals and reasons for making changes. It also provides the structure that may be used to develop a behavior change plan. The six questions addressed on the CPW are presented in Figure 94-1.


Change Plan Worksheet

The changes I want to make are: Date: _____

The most important reasons why I want to make these changes are:

The steps I plan to take in changing are:

The ways other people can help me are:
Person — Possible ways to help

I will know that my plan is working if:

Some things that could interfere with my plan are:

_____
Patient's Signature

Figure 94-1. Change plan worksheet. [Adapted from Miller WR, Zweben A, DiClemente CC, et al. *Motivational enhancement therapy manual: a clinical research guide*

for therapists treating individuals with alcohol abuse and dependence. (DHHS publication No. ADM 92-1894.) Rockville, MD: U.S. Government Printing Office, 1992.]

1. *"The changes I want to make are . . ."* Clear goals are important to effective behavior change plans. The goals should be identified by the patient as important. However, among individuals suffering from chronic benign pain, it would be wise to avoid listing "decrease pain" as a *primary* goal for several reasons. Although many patients identify this as a primary goal at the beginning of treatment, few adaptive behaviors that are in the patient's control have been shown to have a profound influence on chronic pain intensity in the short run. Moreover, two responses to pain that are thought by many clinicians to be maladaptive (pain-contingent use of opioid or sedative medications and pain-contingent rest) often have the short-term effect of decreasing pain experience. Thus, a primary goal of decreased pain, placed in a prominent position on the CPW, may actually work against long-term positive adaptation. Patients who insist on keeping pain reduction on the CPW (some may, and it is important to respect their ultimate choice) may be willing to consider "minimization of pain in the long run" as one of several goals. To the extent that the patient can identify goals over which he or she has some direct control (exercise, taking medications on a time-contingent bases and as prescribed, practicing adaptive pain coping strategies), there are more chances for success.
2. "*The most important reasons I want to make these changes are . . ."* Here is where the clinician or the patient can list the patient's review of the pros and cons of behavior change versus no behavior change. Be sure to emphasize those reasons for behavior change deemed most important to the patient. For example, some patients may want to exercise to have more endurance for playing with their grandchildren. Others may want to return to a particular job that requires a specific level of strength and endurance. Still others may be most motivated by a desire to lose weight. Identifying, discussing, and documenting how treatment adherence will make it more possible that the patient's own goals will be met will help enhance motivation.
3. "*The steps I plan to take in changing are . . ."* Under this heading, the ideas the patient has for making specific changes can be listed. Ideas initiated by the clinician may be included if the patient has endorsed these as his or her own. The more specific these plans are, the more helpful this section of the CPW will be to the patient. For example, stating "I will walk at a brisk pace for 2 minutes every day this week and increase by 2 minutes every week until I reach 20 minutes per day" is better than "I will try to walk some every day and try to do more each week." "I will practice relaxation every day for 1 hour for 1 month" is better than "I will try to relax more."
4. "*The ways other people can help me are . . ."* Pain clinicians have long recognized the importance of other people's responses to the patient as influencing patient functioning (11) (see Chapter 25). Discussing with the patient and someone close to the patient such as a spouse (if such a person is available) specific steps that the other person can take to assist the patient in making adaptive changes should increase the chances that such changes will actually occur.
5. "*I will know if my plan is working if . . .'* Because making adaptive changes to pain problems can be challenging, it is important to identify signposts that indicate the patient is moving in the right direction. Such signposts can act as potential reinforcers for the efforts made, even if the final goal has not yet been reached. Some goals—for example, reactivation— tend to result in *increased* pain and discomfort before the patient feels stronger. To the extent that such increase can be predicted, and even identified as a sign of progress (e.g., "Increased pain means that the muscles that need to be stronger are being challenged"), then the patient may be reassured rather than frightened. Specific signs of progress ("able to lift a bag of groceries," "able to drive for 15 minutes") toward the final goal ("able to grocery shop by myself") should also be included here.
6. "*Some things that could interfere with my plan are . . ."* To the extent that patients can identify specific problems they may encounter, and come up with plans for addressing these problems, then specific hurdles may be avoided altogether or at least more easily addressed.

Summarize

It is as important to summarize when strengthening a commitment to change as it was when building motivation to change. Patients have an opportunity to hear, yet again, their reasons for making change and their plan for change. The CPW, used by the clinician to keep track of the issues raised by the patient, may be used as a guide when summarizing. Changes offered by the patient during this summary should be incorporated into the CPW. The patient should get a copy of the CPW, and one should be included in his or her record.

Ask for a Commitment

The final strategy to use with patients when strengthening a commitment for behavior change is to ask them to commit to the plan they have outlined. Miller et al. (2) lists several issues worth exploring when obtaining a commitment. First, it is important to clarify what exactly the patient intends to do. This is a good time to review the CPW, beginning with the responses to the "steps I plan to take in changing are . . ." stem. Are the steps, as listed, actually what the patient intends to do? The other components of the CPW should also be reviewed at this time, including perceptions of the benefits of change and the costs of inaction and concerns about what might interfere with making the change and how to deal with these obstacles. After this review, simply ask the patient for a commitment to follow through with his or her plan: "Are you ready to commit yourself to this plan?" If so, then you can ask the patient to sign the CPW, give the patient a copy, and retain a copy for the patient's records.

If the patient does not feel ready to commit to a plan of action at this time, the clinician should ask the patient what he or she would like to do from here. Any pressure to "go ahead and try" some aspects of the plan (from the clinician) should be avoided. The patient may wish to think about the plan until the next visit or session. No patient should feel pushed into making a decision to change before he or she is feeling ready to do so, as this would likely result in more, rather than less, resistance to change in the long run.

Summary of Strategies That Strengthen a Commitment for Behavior Change

The strategies discussed above should be used with patients who are in the preparation or action stages. The primary purpose of these strategies is to develop a behavior change plan and obtain a commitment to this plan. The strategies that can help do this include the following: review consequences for behavior change, provide information and advice as requested, communicate free choice, assist the patient to develop a plan for change, summarize, and ask for a commitment. At this point, the patient should have a plan to make one or more specific behavior changes and should have expressed commitment to follow through on the plan. At the next encounter, interactions with the patient involve following up on the patient's efforts.

Follow-Through Strategies

Based on the premise that the most difficult obstacle to making adaptive behavior changes involves lack of motivation to change, and not a lack of information or skills, the first phases of motivational strategies might be considered the most difficult and challenging for the clinician. Once motivation to change has been developed and that motivation has been shaped into a clear plan of action and commitment to change, adaptive changes are more likely to occur. Follow-up and follow-through consist of only three basic strategies: reviewing progress, renewing motivation (if needed), and renewing commitment (if needed).

Reviewing Progress

The first thing to do in the follow-up session is to review the changes that have occurred, if any, since the last encounter. Review the specific commitment and plans made at the last encounter and explore the progress that was made toward the plan. Any and all approximations at progress should be praised. Although the occasional patient appears annoyed with praise (making it necessary for the clinician to provide alternative creative reinforcers), most people appreciate acknowledgment of and praise for their efforts. It is appropriate to express such praise in as dramatic a way as possible and for as long as the patient and encounter will tolerate.

Renew Motivation

An assessment of motivation to maintain change may include a review of the behavioral indicants of motivation (as reflected in what the patient has done since the last encounter), as well as the patient's responses to questions concerning reasons for making or maintaining changes. Any indications of a decrease in motivation to change can be met with the five strategies that enhance motivation described earlier (e.g., ask open-ended questions, listen reflectively, affirm the patient, summarize, elicit self-motivational statements).

Renew Commitment

Finally, the strategies used to strengthen a commitment for change (e.g., review consequences of behavior change, give advice, communicate free choice, develop a

plan for change) may be used to refine the CPW (if needed) and obtain a commitment to follow through on the new plan.

Problems with Motivational Strategies

Motivational enhancement strategies are not for everyone. Some clinicians are not comfortable with the basic approach of motivational strategies of encouraging patient choice and control over treatment. Some clinicians may not want to devote the time during encounters (which can sometimes be limited to no more than 5 minutes in some busy practices) eliciting patient concerns and providing treatment options and choices. For these clinicians, the strategies introduced in this chapter may be perceived as inefficient (1). Also, some patients may not want to be given choices and responsibility. These clinicians and patients may simply feel more comfortable with the more traditional clinician-patient roles that require the clinician to provide specific recommendations and expect the patient to follow through with those recommendations. Expecting all clinicians and patients to want to participate in the types of interactions described here is antithetical to the philosophy of the motivational approach.

What if motivational strategies do not work? Some clinicians may feel very comfortable with motivational strategies and may in fact already be using them to a large extent. Whether using these strategies for the first time or the thousandth time, they will not be effective for all patients in all situations. Most clinicians have worked with patients who continue to use maladaptive coping strategies for pain management *and* continue to refuse to consider alternative approaches. Some patients may appear motivated by what they say but show resistance through their (lack of) action. Such patients may become so annoyed with these motivational strategies and the lack of provision of what they see as more appropriate treatment(s) that they refuse to make or keep appointments. With such patients, I still seek to plant a seed of adaptive responding, even if only during a single encounter. For example, a clinician might say

> "In the little time we have had to get to know each other, I hope you understand that I respect your right to make all decisions about how you will handle this problem. You seem to be convinced that another surgery has the best chances of making you feel better, and surgery is not something that we offer. If at some time in the future you become interested in considering other approaches to managing your pain, I want you to know that we are here to help you do that."

A third problem concerning the application of motivational strategies to problems of pain management is the lack of controlled research specifying the relative adaptiveness of different pain coping responses. The motivational clinician seeks to encourage patients to avoid behaviors and coping responses that are maladaptive and and to use coping responses that are adaptive for that patient. Although there is little controversy regarding the need to change most of the problem behaviors to which motivational strategies have already been applied (e.g., smoking, problem drinking, heroin abuse, risk behaviors for contracting the human immunodeficiency virus), there remains controversy concerning the relative adaptiveness or maladaptiveness of specific behaviors related to pain problems. For example, although opioid medication use is strongly discouraged in some treatment programs (12), some clinicians believe that there is a place for opioid medications for some individuals suffering from chronic benign pain (13,14). Even physical exercise, which may be considered an essential component of multidisciplinary pain treatment (12), has not necessarily been shown to be important to short-term treatment effectiveness (15). Thus, clinicians do not always know which specific behaviors to discourage and which behaviors to encourage for a particular patient.

One reasonable approach to address this problem is to use motivation enhancement strategies to encourage behaviors that (a) are adaptive for most patients (in the experience of the clinician or based on the most recent research) and (b) the patient has not yet tried. Then, as the patient tries the new behavior or coping response, the clinician and patient can monitor changes in patient functioning to determine how helpful the new approach is.

CONCLUSIONS

The purpose of this chapter was to introduce pain clinicians to the motivational strategies outlined by Miller and his colleagues (1,2). These strategies have been applied to motivate individuals to change a number of specific problem behaviors, such as excessive drinking. They appear to translate well to the treatment of chronic pain problems, given the strong role that patient motivation plays in chronic pain treatment. Although the effectiveness of these strategies among chronic pain patients has not yet been tested empirically, support for their effectiveness for changing addictive behaviors is encouraging (1). Moreover, there is a growing interest in the applicability of motivational strategies for assisting individuals with chronic pain. For example, Kerns et al. (16) have published a measure of readiness to adopt a self-management approach to chronic pain based on Prochaska and DiClemente's (3) stages theory of change. This measure makes it now possible to test some basic hypotheses of the stage theory of change as it applies to change in chronic pain patients, so future research in this area can be anticipated.

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CHAPTER 95

Orthopedic Management of Pain

Michael J. Moskal and Frederick A. Matsen III

Pain is a personal experience that cannot be observed directly (1), yet it is a common complaint of patients presenting to physicians. Effective *orthopedic* management of pain suggests an underlying mechanical etiology of pain. Many patients, however, only consult a physician because of their fear that they might have cancer or some other serious disease (2), and for these patients, reassurance can be beneficial as the sole treatment of minor musculoskeletal disorders such as contusions or musculotendinous strains.

Nonoperative therapy is not synonymous with conservative management. In some cases, such as adhesive capsulitis, surgical capsular releases may be more conservative than a closed manipulation (3). Orthopedic treatment in the management of patients with pain can be divided into general modalities that diminish swelling and inflammation and specific modalities that restore the basic tenets of a well-functioning musculoskeletal system: motion, stability, strength, and smoothness. We present a concise discussion of the various modalities used and their underlying basis for diminishing mechanical pain. Broad and simple categories follow to provide a general understanding of the indications and treatment rationales for various orthopedic maladies.

GENERAL MODALITIES

RICE

RICE is the classic mnemonic that represents the general modalities used to treat pain after an injury: *r*est, *i*ce, *c*ompression, and *e*levation. Injury causes damage to the soft tissues, muscle, and bone. Damaged blood vessels cause bleeding as well as local release of various tissue factors, such as histamine and bradykinins, that result in edema, swelling, and pain. RICE can be used any time after an injury but seem to be most effective when instituted within the first 24 to 48 hours after an acute injury.

Rest

Rest for musculoskeletal disorders has been recommended for hundreds of years (2,4) and is one of the mainstays of orthopedic treatment. Orthopaedic *rest* does not necessarily mean complete inactivity or immobility but rather *relative rest*. Waddell and colleagues (5) reviewed 18 trials of either “bed rest” or advice to “stay active” in the treatment of low back pain. They found consistently that bed rest was not an effective treatment for acute low back pain, and in fact, it delayed recovery. Atlas and Volinn (6) found that patients with acute low back pain who received a recommendation for 2 days of bed rest had significantly fewer days of work absence than those who received a recommendation of 7 days. *Relative rest* implies reduction of activity and avoidance of strain for a limited period. For example, a contusion of the quadriceps muscle results in swelling and hematoma formation. Vigorous muscle contraction immediately after injury would result in increased bleeding and therefore swelling and pain. Fu et al. (7) have recommended that to reduce pain and hematoma formation cryotherapy should be coupled with at least 48 hours of rest in both exhaustive and nonexhaustive types of exercises. After bleeding has subsided, gentle range of motion exercises of the hip and knee allow healing but diminish muscle fiber contracture. Lengthy periods of immobilization can lead to arthrofibrosis, joint stiffness, muscle atrophy, and cartilaginous malnutrition.

Orthotic devices such as thermoplastic splints can provide protective support after a destabilizing injury to a joint. The purpose of a brace is to assist, restrict, or simulate function (8). For example, stenosing tenosynovitis of the thumb often responds favorably to immobilization of the carpometacarpal and metacarpophalangeal joints of the thumb using a forearm-based thumb spica splint. Mild strains to the medial collateral ligament of the knee are treated by applying a functional brace that allows knee flexion and extension, as in walking, but protects the ligament from valgus and varus (side to side) stresses. Slings provide comfort after clavicle fractures and shoulder dislocations, allowing the shoulder girdle muscles to rest. Slings can aid in elevation of the hand after trauma. Removable forearm-based wrist splints are useful to prevent wrist flexion at night and diminish symptoms associated with median nerve compression at the wrist or to rest the wrist extensors in lateral epicondylitis.

Rest, slings, and orthoses are used as part of a rehabilitation effort rather than the sole form of treatment. For example, chronic use of lumbar corsets for low back pain can lead to increased trunk and pelvic muscular weakness, which can further predispose the patient to future episodes of back pain. Rest need not be synonymous with inactivity; rather, it may indicate protected activity so that the natural reparative mechanisms can predominate.

Ice

The application of cold, or cryotherapy, may be effective for acute trauma and also repetitive microtrauma that is part of many vocational and athletic endeavors (7). Ice may diminish pain and swelling and improve function. Speer demonstrated that patients using a cryotherapy device after major shoulder surgery may use fewer narcotics and have less pain (9). Cryotherapy slows metabolism and promotes local vasoconstriction of blood vessels reducing bleeding, swelling, and pain (10,11). The duration of ice application is limited by its potential harmful effects, such as thermal injury to skin and subcutaneous nerves as well as rebound hyperemia after the cooling elements are removed (12).

Compression

Compression bandage wrapping has been widely used to diminish bleeding and swelling. Compression-type bandages have also been used to treat nonspecific joint pains in the ankle, knee, wrist, and elbow. Again, as part of a global program, compression may be effective in improving comfort. However, care should be taken if this modality is used. Increased pressures within a limb caused by unyielding external compression such as a cast can lead to increasing pain and, potentially, neurovascular compromise. Improper application can reduce lymphatic return of the extremity distal to where the bandage was applied, causing distal swelling. This is commonly seen after application of a compression wrap (or cast) to the wrist after an injury. Venous and lymphatic return can be impaired if the wrap is placed too tightly just proximal to the metacarpophalangeal joints. Finger swelling and diminished range of motion can ensue and diminish comfort and function.

The effects of compression bandaging have been reviewed: Thorsson and colleagues (13) found that maximal compression bandaging within 5 minutes of a contusion

to a thigh or calf muscle did not significantly reduce the size of hematoma or significantly shorten the time to complete subjective recovery compared to rest and elevation. Compression may have other effects; for example, McNair et al. (14) found that normal subjects wearing a knee sleeve had better knee proprioception. They concluded that alterations in proprioception as a result of bracing may be partly responsible for the improvement in knee injury statistics reported in some studies. Although compression bandaging seems to improve comfort and function, it may not alter swelling after an acute injury (15). Its use should be tempered by its possible harmful side effects.

Elevation

Elevation encourages lymphatic and venous return and can reduce local blood flow to a limb, helping to diminish swelling. The benefits of elevation are easily recalled, as nearly everyone has suffered injuries and the subsequent throbbing if that limb becomes dependent. Elevation is contraindicated in the presence of ischemia or impending compartmental syndrome (16).

Local Injections

Judicious use of local anesthetic combined with corticosteroids can be useful in reducing inflammation and subsequent pain that have not responded to other modalities such as rest, stretching exercises, or both. For example, stretching exercises are the mainstay of treatment for a stiff shoulder. However, pain may significantly limit the patient's ability to participate in therapy. An injection may be beneficial to diminish inflammation and pain so that physical therapy can be performed. Steroid injections provide symptomatic relief and, used alone, do not alter the disease process (17). The potential for impaired healing (18) should be balanced against the potential gains from the antiinflammatory response. Although the maximal number of injections has not been elucidated experimentally and every patient circumstance is unique, we try to limit a patient to one or two injections. If a patient does not respond to one injection, it is unlikely that further injections will be beneficial.

Pharmacologic Therapy

Nonsteroidal antiinflammatory medications reduce pain and may have a protective effect after muscle injury (see Chapter 83). The efficacy of nonsteroidal antiinflammatory medications in the enhancement of healing, pain relief, return of function, and protective effect has been called into question (19,20 and 21). Most studies look at only a single pharmacologic agent, and it may not be appropriate to make broad-based conclusions about the different types of nonsteroidal antiinflammatory medications. These studies do demonstrate that use of these medications may not be appropriate for all patients. Newer nonnarcotic and more traditional narcotic medications may be more beneficial to improve comfort as the patient recuperates after an injury or surgery (22).

Ultimately, it is important to remember that there is a complex interplay between pain and function and that medications are only part of treatment. Thus, while antiinflammatory medications seem to help to diminish musculoskeletal pain and improve return of function, their use should be carefully weighed against possible adverse drug interactions and systemic side effects, as well as the possible unfavorable effect on healing. Medications of all types are discussed in greater detail in Chapter 83, Chapter 84, Chapter 85, Chapter 86 and Chapter 87.

PHYSICAL THERAPY

Physical and occupational therapy play an integral role in orthopedic care and orthopedic management of pain. Stretching and strengthening programs may be curative in some clinical situations. Good communication between therapist and orthopedist should exist so that a particular treatment algorithm can be monitored and optimized. Various modalities used in physical therapy are discussed in greater detail in the remaining chapters in this section.

Stretching and Strengthening

Pain causes a reflex inhibition of musculotendinous contraction as well as purposeful avoidance of painful behavior. The cycle of pain and disuse can lead to weakness and stiffness. Weak quadriceps muscles can magnify patellar maltracking; shoulder stiffness is often painful and functionally debilitating. Moffroid (23) has shown that the lack of endurance of the trunk muscles is an important factor in low back pain. A complex interaction exists between pain and activity. For instance, simply walking can improve the overall comfort and function in elderly people with chronic musculoskeletal pain (24). Although it is clear that walking did not alter the underlying degenerative arthritis, it did lessen pain.

Therapists can guide patients as they progress through the rehabilitation process. This does not necessarily mean that a patient must attend frequent sessions with a therapist. Rather, we have found that many patients do well with patient-conducted home therapy programs. After an initial session with a physical therapist who demonstrates and explains the rehabilitative process, the patient conducts the exercises on his or her own time.

Thermal Therapy

After an acute injury has subsided, heat and cold can be combined to augment performance and diminish pain. As implied above, cryotherapy is useful for acute and microtraumatic overuse-type injuries. Heat seems to be beneficial in pain reduction in various arthritides as well as before initiation of exercises such as strengthening and stretching. Oosterveld and Rasker (25) reviewed the literature concerning the treatment of arthritis with locally applied heat or cold. The temperatures of the skin, superficial and deeper tissues, and joint cavities do change based on locally applied heat or cold. Most studies report beneficial effects of heat and cold on pain, joint stiffness, grip strength, and joint function. However, *in vitro*, higher temperatures increase the breakdown of cartilage and other tissues that contain collagen (25,26 and 27).

Iontophoresis, Ultrasound, and Phonophoresis

A therapist may apply an electric current to the skin and thereby transmit drugs such as corticosteroids through the skin using electrical potentials. Iontophoresis transmits drugs to the epidermis, dermis, and deeper tissues and is dependent on structural and physiochemical properties of the administered drug and the resultant change in skin permeability (28). Ultrasound uses high-frequency acoustic energy in fluid-based mediums to impart thermal and mechanical effects. Used as a thermal modality, ultrasound is purported to increase local blood flow and decrease pain from muscle spasms and contusions. Phonophoresis combines ultrasound therapy with a drug such as an antiinflammatory medication (29). Most information regarding the rationale for the use of physical agents in pain management is based on tradition, data extrapolated from basic science research, and uncontrolled clinical trials. Further research is needed to establish clinical efficacy and to determine treatment parameters for the physical agents used (30,31).

Electrical Stimulation

Electrical stimulation has been used for years as pain relief and as an adjunct to muscle rehabilitation (32); its use has increased since the 1970s (see Chapter 98). Transcutaneous electrical stimulation has been used to treat pain related to a variety of conditions including the musculoskeletal, nervous, and vascular systems. The physiologic mechanisms by which pain is affected are not defined; local neural blockade, branch block in the dorsal horn, and activation of a central inhibitory system have all been postulated (33).

MECHANICS OF JOINT PAIN

Most nontraumatic joint pain is associated with at least one of four mechanical problems: stiffness, instability, weakness, and roughness.

Stiffness

Joint stiffness can be insidious in onset, or it can arise after major trauma or surgery. Joint stiffness is tolerated to different degrees by the various joints in the body. For example, limited range of motion of the interphalangeal joint of the thumb is often well tolerated, whereas shoulder stiffness is painful and limits many activities of daily living. Flexion contractures that often accompany minor arthritic changes of the knee are often well tolerated in most activities during the day; however, sleeping at night may be especially difficult because the knee does not extend fully. Joint stiffness can alter overall body mechanics and lead to pain elsewhere, as in hip

stiffness and back pain.

Treatment for stiffness begins by delineating the underlying pathophysiology and functional limitations. Elbow stiffness is commonly posttraumatic in nature and can be classified as intrinsic (e.g., due to intraarticular fractures and adhesions) or extrinsic (e.g., due to muscle scarring or burns). A stiff elbow might not be painful. Most activities of daily living can be performed with minor extension and flexion losses. An elbow that is painless and functional may require no treatment at all. Shoulder stiffness (e.g., due to adhesive capsulitis, idiopathic capsular fibrosis and contracture) may be painful and functionally limiting. Treatment may include a patient-conducted global stretching program, manipulation, or surgical release. Patients with diabetes or endocrine disorders such as hypothyroidism are more likely to require surgical intervention for their stiff shoulder. After regional anesthesia or general anesthesia with muscle paralysis, shoulder range of motion is determined and the firmness of the end points is assessed. Closed manipulation can be useful, but surgical capsular release may be needed to increase motion.

Instability

Pain associated with an acute dislocation of a joint is easily understood. Hip dislocations occur after high-energy trauma such as a fall from a height or a motor vehicle accident; capsular tearing, articular surface damage, and muscle bleeding are painful. Instability and pain can be associated with subtler instabilities such as subluxations.

Closed reduction is usually sufficient to manage an acute dislocation. Analgesia or anesthesia is used to make the patient more comfortable and to encourage relaxation of muscles in spasm, thereby lessening the forces necessary to achieve reduction. Some joints cannot be reduced by closed manipulation due to soft tissue or bony interposition. For example, the volar plate of a finger metacarpophalangeal joint can become interposed in the joint after certain dislocations. Attempts at reduction often tighten the soft tissues and possibly increase joint damage. A surgical reduction can address both bony and soft tissues after a dislocation. Stability after reduction is typically tenuous, and a protected joint mobilization program is often needed. Ligament reconstruction may be needed to restore stability and function. Figure 95-1 illustrates rupture and repair of the acromioclavicular and coracoclavicular ligaments caused by a fall on the shoulder during an athletic activity.

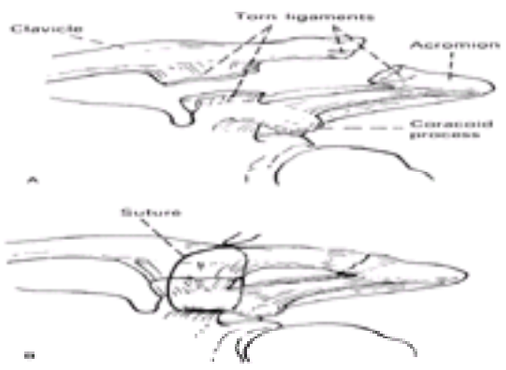

Figure 95-1. Ligament reconstruction. **A:** Third-degree acromioclavicular separation. In this injury, often sustained in landing on the shoulder after a fall while biking, skiing, playing football, or wrestling, the acromioclavicular and coracoclavicular ligaments can be torn. **B:** When substantial instability results, the torn ligaments are reconstructed by passing secure suture around the coracoid process and the clavicle. The bones are held in proximity while healing occurs.

Although not typically thought of in the context of stability, fractures can destabilize a limb, limiting its use. Proper alignment and stability after a fracture allow stable callous formation and healing. Malalignment can alter the forces on the joints above and below the fracture and therefore alter wear patterns and lead to pain. Closed manipulation after a fracture can restore alignment and stability (34,35). Good analgesia and muscle relaxation are essential components to minimize muscle spasm and achieve adequate reduction. Some fractures require surgical reduction followed by metallic fixation to enhance bony stability (Fig. 95-2). Stress fractures are multiple microfractures in a bone to due mechanical overloading that supersedes the body's normal reparative healing response. Stress fractures are commonly seen in the foot metatarsals after chronic rigorous activity, such as that experienced by military recruits in basic training. Decreased activity allows the fractures to heal as the body's healing response catches up. Regardless of treatment and fixation methods, the goals of fracture care are bony healing and restoration of function.

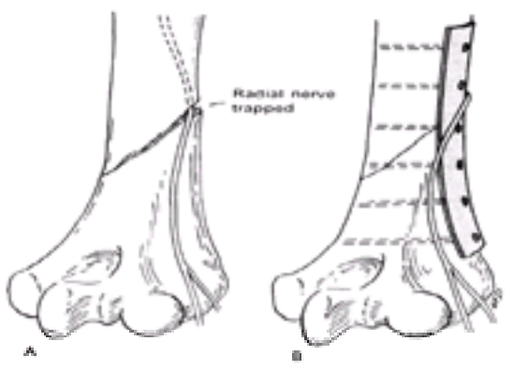

Figure 95-2. Open reduction and internal rotation of a distal humeral shaft fracture. Fractures of the distal humerus are not infrequently associated with radial nerve lesions. When the radial nerve is injured at the time of the fracture it is prudent to wait 6 to 12 weeks for nerve recovery. When the nerve is initially intact and then subsequently loses function during the process of reduction, however, it is possible that the nerve is trapped within the fracture **(A)**. If radial nerve function is acutely lost, open reduction and extraction of the nerve by internal fixation of the fracture, using a plate, is effective for protecting the nerve and permitting earlier return to function of the arm **(B)**.

Congenital, posttraumatic, or degenerative instabilities can be corrected in some situations by an osteotomy, or by cutting and realignment of the bone (35,36). For example, pediatric acetabular development of the hip joint requires concentric joint reaction forces and the biological plasticity of youth. Altered acetabular congruency with the femoral head due to either abnormal acetabular roof angles or femoral neck shaft angles can produce painful hip subluxations. In a child, an innominate osteotomy of the acetabulum and/or a varus osteotomy of the proximal femur can help to restore a more normal acetabulum configuration and hip joint stability, with return of comfort and function (37).

Weakness

Pain can reflexively diminish muscular power. Weakness itself does not necessarily cause pain. Rather, the causes and sequelae of weakness are often painful and have unique characteristics based on body location. Perry et al. (38) looked at postpolio patients with muscular weakness and noted that muscular substitutions for weak muscles placed increased demands on joints, ligaments, and muscles. They postulated that these increased abnormal forces might be responsible for pain and dysfunction. They suggested that treatment should consist of early identification of muscle overuse and ligamentous strain as well as lifestyle modification and bracing. Despite an intact muscular motor unit, strength and range of motion can be diminished due to tendinous pathology. Tendon function can be limited primarily by (a) diminished glide, (b) myotendinous unit contracture, and (c) rupture.

After an injury, such as surgery or a fracture in the area of tendons, bleeding can produce scar that limits tendon movement (glide). Active and passive range of motion is restricted, frequently causing pain at the limits of motion. For example, after phalangeal fracture, scar can form around the flexor and extensor tendons. If motion is ineffective in restoring normal flexibility and pull-through of the tendon, tenolysis might be required. In this procedure, the adhesions are sharply divided and the tendon is started on early motion to prevent restricting adhesions from reforming. If motion is limited in a particular position, the capsules of nearby joints may

contract in a shortened position, again limiting motion. In this case, the capsule would have to be released in addition to tenolysis.

Muscular contracture is often thought of as solely limiting power. Muscular contracture, however, can lead to pain and dysfunction in nearby anatomic locations. Ko et al. (39) found that patients with deltoid muscle contractures had a high prevalence of neck and shoulder girdle pain. After surgical release of the deltoid, pain in the neck and shoulder girdle resolved in 48 of 49 shoulders.

Partial or complete tendon ruptures can be painful as loads are applied to the tendon. Complete tendon ruptures can be treated by tendon repair, tendon advancement into bone, tendon grafting, and tenodesis. Patellar tendon ruptures can occur after a sudden eccentric (lengthening) force is applied across the knee joint, such as when a person missteps while walking over a curb. The large forces overcome the tensile strength of the tendon and it ruptures near the inferior pole of the patella or midtendon. Acutely, there is bleeding and an inflammatory response. Quadriceps muscle firing causes pain and cannot generate force to keep the knee straight. Tendon repair consists of direct repair for midsubstance tears, advancement into bone if the rupture is the patella or tendon grafting if there is major tendon loss or the muscle is chronically contracted and the tendon edges will not approximate. After the normal resting length of the muscle is restored and the local inflammatory response has subsided, comfort and function are restored. Finally, tenodesis can be used when it is difficult to restore normal tendon integrity; function can be at least partially restored by securing the ruptured end of the tendon. A classic example is tenodesis of the long head of the biceps to the proximal humerus after an intraarticular rupture.

Roughness

In general, roughness is the lack of smoothly gliding surfaces. The knee may be painful due to incongruous degenerated articular surfaces but also may be painful due to a torn meniscus that gets caught between the femur and tibia. The treatment of roughness is the restoration of smoothness. This restoration can range from a simple excision of a bony prominence to replacing the articular surfaces with artificial materials such as metal and plastic. In some situations decreasing the force across joints improves pain, whereas in others destruction is so severe that eliminating any motion, an arthrodesis, is the only surgical option.

In the forearm, bone from fracture callus can impede the movements of pronation and supination. A prominent olecranon process can prevent full extension of the elbow. Heterotopic bone in the forearm, about the hip, in the shoulder, or elsewhere can interfere with or prevent motion of the involved joint. Degenerative osteoarthritis of the knee frequently affects only the medial compartments. A high tibial osteotomy can realign the resulting varus configuration, shifting the load to the relatively unaffected lateral compartment. This type of reconstruction can restore comfort and function to the knee and avoid the potential problems of prosthetic arthroplasty (Fig. 95-3).

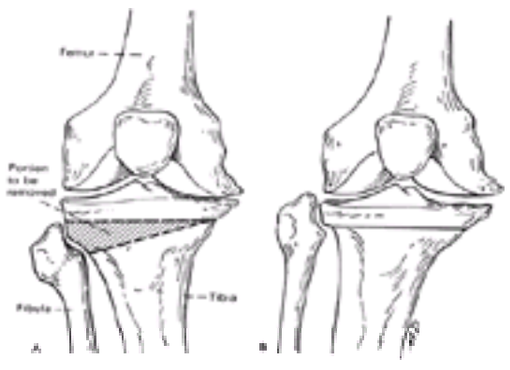

Figure 95-3. High tibial valgus osteotomy. **A:** Frequently, osteoarthritis selectively involves the medial compartment of the knee joint, which produces a progressive varus or bowlegged deformity of the leg in which the load is concentrated on the damaged medial side. A high tibial valgus osteotomy achieved by section of a laterally based wedge of the upper tibia can be a helpful therapeutic measure in this situation. **B:** When this wedge is removed and the dissection is closed, the varus deformity is eliminated and the load is transferred toward the relatively unscathed lateral compartment.

When damaged, menisci of the knee joint might require excision or repair. These menisci distribute forces across the knee and can be damaged by compressional or rotational loads across the knee, catching and tearing their substance. Torn and displaced meniscal fragments can cause pain and interfere with normal joint motion by catching between the femur and the tibia. Degenerative tears can also arise from wear and tear on the joint surface. Resection of the torn meniscus fragments can relieve the “catching” and pain but does not, however, restore normal function of the meniscus.

Arthrodesis, or joint fusion, is a common procedure for stopping the motion at a joint that has become destroyed, unstable, or both. For example, C-1 and C-2 vertebrae can become unstable because of rupture of the transverse ligament of the atlas in a patient with arthritis, jeopardizing the cervical cord at this level. Arthrodesis of these two vertebrae is the most effective way of preventing neurologic problems resulting from instability at this level. A shoulder that has become unstable from brachial plexus injury can be flail and render the rest of the upper extremity relatively useless (40). In such situations, function can be enhanced by fusing the humerus to the scapula in a position that favors use of the elbow, wrist, and hand (Fig. 95-4). Arthrodesis may be indicated for joints in which the functional loss is minimal yet pain relief is significant, as in arthritis of the distal interphalangeal joints.

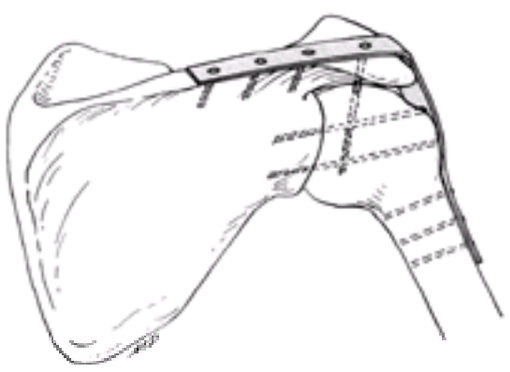

Figure 95-4. Arthrodesis of the shoulder joint. When the joint surface of the shoulder and the major muscles of the shoulder (the deltoid and rotator cuff) are substantially damaged beyond reconstruction or repair, comfort and some function can be restored by fusing the humeral head to the scapula. Here a contoured plate and screws are used to provide internal stability to the shoulder fusion. The shoulder is fused in a position that allows the hand to reach the front pocket, opposite axilla, and forehead. Motion is achieved by the scapulothoracic joint.

Biological arthroplasty procedures include resurfacing of the bone ends with fascia or dermis or a distraction-resection type of arthroplasty that allows the body to regenerate a new bearing surface. Resection arthroplasty is effective in certain circumstances, such as when the radiocapitellar joint is involved in rheumatoid arthritis of the elbow, where overall function is maintained. In an elbow with competent collateral ligaments, the radial head can be removed so that the rough surfaces of the capitellum and radial head do not articulate. The elbow remains stable due to the collateral ligaments and the articular surface of the ulnohumeral joint. Prosthetic arthroplasty involves the replacement of the damaged joint surfaces with Silastic or metal on polyethylene (41). Common examples include total arthroplasties of the hip, knee, shoulder, elbow, ankle, wrist, and fingers (Fig. 95-5). These new joint surfaces are anchored into position either by biological fixation (e.g., press fit, with or without tissue ingrowth) or by fixation enhancement with methylmethacrylate (bone cement). These procedures, by definition, eliminate the pain caused by rubbing of abnormal joint surfaces. Prosthetic arthroplasty is often of great benefit to the patient, but the procedure can fail because of infection, loosening, fracture, instability, or abnormal joint mechanics.

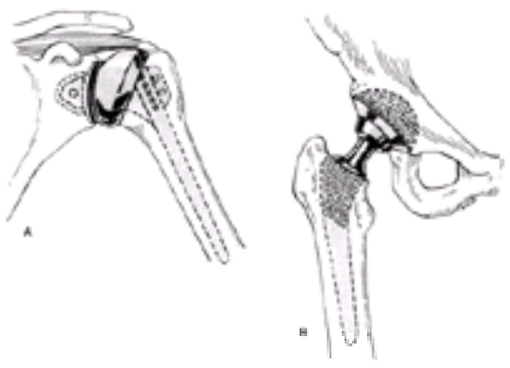

Figure 95-5. Joint replacement. **A:** Total shoulder arthroplasty. **B:** Total hip arthroplasty. In a shoulder replacement it is actually the articulating surfaces of the joints that are replaced. Stability and motion of the joint still depend on component position, joint reaction forces, and muscle integrity. Key elements in these procedures include accurate alignment of compartments, secure fixation of the components in the bone, and careful balancing of the ligaments and muscles about the joint.

Nonmechanical Pain

Pain unrelated to activity may be due to nerve dysfunction, trauma, or infection.

Neural Dysfunction

Neural function can be compromised by compression, stretching, scarring, or severance. In general, the return of function after an injury is affected by the specific nerve, age of the patient, and the location and type of injury. Recovery from an injury is improved if the patient is younger and the initial injury is less severe. For example, transection of the transverse carpal ligament for carpal tunnel decompression can result in diminished pain and improved grip strength and sensation. However, decompression of the median nerve at the wrist in an older patient with medical problems such as diabetes and longstanding compression may only halt the progression of further injury, and return of function is minimal. Spinal stenosis, narrowing of the spinal canal, or herniated disk may compress the spinal cord, a specific nerve root, or both. Disk excision does not beneficially alter the course of the degenerative process but is useful if significant pain or neurologic loss is present (37). Peripheral nerve compression syndromes are usually initially treated by behavioral modification such as splinting, local injections, and exercises as in thoracic outlet syndrome. If symptoms do not diminish with nonoperative treatment or if neural compromise is significant, progressive, or both, a surgical decompression such as section of the transverse carpal ligament in a carpal tunnel syndrome (Fig. 95-6) or ulnar nerve transfer for ulnar nerve compression at the elbow can be performed (42).

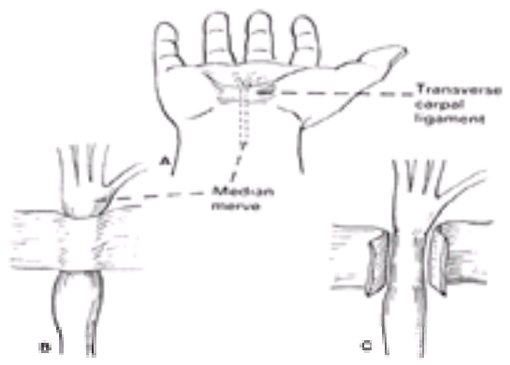

Figure 95-6. **A,B:** The median nerve is compressed at the wrist producing pain; hypesthesia in the thumb, index, and long fingers; and weakness of the thenar muscles. **C:** Symptoms can usually be ameliorated by section of the transverse carpal ligament.

Scar tissue is contractile in nature. Scarring about a nerve after an injury may produce pain and diminished function. Neurolysis removes scar from around the nerve. Patients should be carefully selected; surgery itself creates some bleeding and residual scar formation. Nerves that are divided can be repaired by direct suture repair, which attempts to align fascicles so that axons can regrow from the nerve cell body located proximal to the transection. Occasionally, cable grafts using nerves such as the sural nerve can be used to bridge segments of lost nerve.

Neoplasm and Infection

Benign, malignant, and metastatic bone lesions are painful due to a variety of reasons including chemicals produced by the tumor, structural instability, and local pressure. A more detailed discussion of this subject can be found elsewhere (17,18,19,20 and 21) and in the chapters on regional pain syndromes in this text (Chapter 46, Chapter 47, Chapter 48, Chapter 49, Chapter 50, Chapter 51, Chapter 52, Chapter 53, Chapter 54, Chapter 55, Chapter 56, Chapter 57, Chapter 58, Chapter 59, Chapter 60, Chapter 61, Chapter 62, Chapter 63, Chapter 64, Chapter 65, Chapter 66, Chapter 67, Chapter 68, Chapter 69, Chapter 70, Chapter 71, Chapter 72, Chapter 73, Chapter 74, Chapter 75, Chapter 76, Chapter 77, Chapter 78, Chapter 79 and Chapter 80). Surgery can diminish the “tumor load,” restore structural stability, and minimize compression due to space-occupying lesions. Surgical decompression can also help manage pain from infection.

Osteoid osteoma, a benign osteoblastic lesion with a typical well-demarcated nidus, undergoes intraosseous growth. Classically, the pain is worse at night and is temporarily relieved by aspirin. The tumor secretes prostaglandins and the aspirin may inhibit their formation. Although these tumors may eventually “burn out,” complete excision can result in the definitive elimination of the characteristic pain.

In osteomyelitis, systemically administered antibiotics cannot permeate the area of devitalized and devascularized bone, a sequestrum. Pain may be due to the local chemical milieu, compression of local structures, or structural instability. Generally, bone and purulent material must be completely excised to allow the body to eliminate the infection. If a substantial bony defect is present, stabilization may be required.

A benign bone tumor can cause pain due to its expansive growth characteristics or by destabilizing bone by replacing it with neoplastic cells. A large osteochondroma can cause local compression or roughness as surrounding tendons rub against it as its extraosseous expansion increases. Neoplasms such as giant cell tumors or fibrous dysplasia may weaken segments in bone and predispose to fracture. Giant cell tumors can be treated by removing all of the tumor tissue (43) and then filling the cavity with cancellous bone graft (44). Hopefully, the tumor will not recur and the bone graft will consolidate to restore bony integrity.

Chemotherapy and radiation therapy may be useful to kill neoplastic cells preferentially so that the tumor is more amenable to resection and/or to low the body to compensate to restore structural integrity. Combined chemotherapy and surgery have lowered the mortality rates in certain primary tumors (43,44). The incidence and prevalence of metastatic tumors are higher than those of primary tumors. Breast, prostate, thyroid, kidney, and lung cancers and other types of malignant tumors account for a large majority of tumors that metastasize to bone. Again, these tumors are painful because of structural compromise, chemical secretion, or local compression. The following are indications for orthopedic surgery in cases of skeletal metastasis (45): The tumor shows little or no sensitivity to radiotherapy or chemotherapy; the maximum dose of radiation has been applied and moderate to severe pain and instability are still present; pathologic fractures; and pain can be relieved and quality of life can be improved. Cancer pain management is discussed in detail in Chapter 35, Chapter 36 and Chapter 37.

Amputation

Indications for amputation of all or part of an extremity include malignant tumor, refractory infection, nonhealing ulcer, and untreatable ischemia (46). At times, amputation is indicated because of total loss of function of a part—for example, in a severe brachial plexus injury resulting in a flail arm below the shoulder. It is the paralysis of the limb, not the accompanying pain, that is the indication for amputation. Amputations usually heal, provided they are performed technically well and the flaps have adequate vascularity. Amputations are often not successful in the management of chronic pain (see Chapter 21).

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CHAPTER 96

Basic Concepts in Biomechanics and Musculoskeletal Rehabilitation

Stuart E. Willick, Stanley A. Herring, and Joel M. Press

The human body is like a marionette: The puppet itself is analogous to the bones and joints of the human body, and the strings that attach to the puppet are analogous to the muscles and tendons that move the human skeleton. The puppeteer provides the neural input to the doll's musculoskeletal system. For the marionette to work properly, several specific mechanical properties of the doll must be in optimal working order. First, the length and tension of the strings must be correct. Second, all parts of the puppet and the puppeteer must have adequate strength and endurance to impart movement to the doll and prevent fatigue and breakdown from occurring over the course of repeated performances. Third, and perhaps most important, the puppeteer must manipulate the strings in a smooth, coordinated manner so that the movements of the doll are smooth and lifelike.

Those who fabricate marionettes work very hard to ensure that the doll is finely tuned. The joints of the doll must have low enough friction to allow easy movement, yet must be stable enough to prevent limbs from undergoing excessive displacement during more dramatic scenes. The string lengths must be exact, so that the puppet appears symmetric and the joints are allowed full range of motion. The strings must also have enough tensile strength to preclude breakage, yet they must also have the proper amount of elasticity so that the doll's movements are smooth. Finally, the puppeteer must practice many hours to perfect each movement, scene, and performance.

For the clinician intent on maximizing a patient's musculoskeletal health, the mechanical properties of a marionette may serve as a simple model by which to view human biomechanical functioning. A comprehensive musculoskeletal rehabilitation program begins with restoring soft tissue range of motion and flexibility, just as the puppeteer builds his or her doll with strings of adequate length and tension. Like a marionette, the human body also requires adequate strength and endurance to move body parts properly during single movements, as well as over the course of repetitive movements. And just like a marionette, humans need to have proper coordination and fluidity of movement for proper biomechanical functioning.

In the absence of acute trauma, such as fracture or dislocation, musculoskeletal pain is most often caused by or associated with alterations in proper biomechanics. Clinicians treating musculoskeletal pain should endeavor to improve their patients' biomechanics.

Whereas a puppet has no will and any repairs to faulty mechanics must be initiated by the puppet maker, a patient, if convinced the outcomes are worth the effort, can usually improve his or her own biomechanics through an appropriate home exercise program. Often, the assistance of a physical therapist is required to institute and facilitate the home exercise program. Patients also differ from puppets in that they need adequate nutrition for tissue healing.

By emphasizing biomechanical principles, the contents of this chapter represent a fundamental change from the customary emphasis on the use of physical therapy and physical modalities in treating musculoskeletal pain. Patients are often treated for musculoskeletal disorders with passive modalities such as hot packs, cold packs, massage, electrical stimulation, and deep heat. Unfortunately, these passive therapies are overused. While they certainly can play an important role in providing symptomatic relief of musculoskeletal pain, passive modalities should be used only as methods to facilitate *active* rehabilitation. The patient most needs to become actively involved in a therapeutic exercise program specifically designed to improve musculoskeletal functioning.

Musculoskeletal rehabilitation is a process whereby poor posture, muscle imbalances, and other biomechanical deficits are corrected using specific exercises to gain better static and dynamic control of the musculoskeletal system. The physical restoration process *may* involve passive therapeutic modalities to facilitate the exercise program. Clinicians treating musculoskeletal pain and dysfunction must identify and work to correct deficits in the patient's biomechanics.

This chapter introduces general concepts in clinical biomechanics that are crucial to the understanding of musculoskeletal rehabilitation. The first section, Basic Considerations, presents an overview of these biomechanical concepts. In the second section, Clinical Considerations, specific techniques used to treat musculoskeletal pain are reviewed. In keeping with the philosophy that *lasting* improvements in biomechanical functioning are due to exercise programs prescribed specifically for each patient's pain symptoms and biomechanical deficits, therapeutic exercise is emphasized; passive therapeutic modalities are given less attention. The concepts presented here can be applied to soft tissue injuries throughout the body. The diagnosis and treatment of specific injuries are covered in Part IV of this book.

BASIC CONSIDERATIONS

This section introduces basic concepts in musculoskeletal rehabilitation. Using specific examples, the importance of optimizing range of motion, strength, endurance, and neuromuscular control is reviewed. The role of muscle agonist/antagonist interactions and adverse neural tension (ANT) is included. There is a certain degree of overlap between the various biomechanical concepts that are presented. For example, although strength and endurance are related, they are presented separately because clinical pain syndromes related to deficits in strength differ from those related to deficits in endurance.

Range of Motion

Lack of adequate range of motion is probably the most common biomechanical deficit seen and one of the easiest to address. Deficits in range of motion can cause pain directly or may lead to pain elsewhere. An example of a range of motion deficit that causes pain directly occurs when electricians experience shoulder pain while doing overhead work because of limitations in glenohumeral forward flexion. An example of a range of motion deficit that leads to pain in a distant body segment occurs when electricians with limited glenohumeral forward flexion experience low back pain while performing overhead activities because they must increase their lumbar lordosis to compensate for the lack of shoulder elevation (Fig. 96-1). The compensatory increase in lumbar lordosis is an example of a maladaptive substitution pattern due to a biomechanical deficit (e.g., decreased latissimus dorsi length).

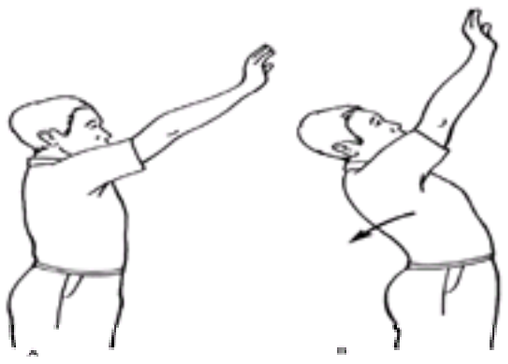

Figure 96-1. The individual with limited glenohumeral forward flexion **(A)** compensates with exaggerated lumbar lordosis during overhead activities **(B)**. This maladaptive substitution pattern can lead to low back pain.

The musculoskeletal clinician must have adequate examination skills to identify all range of motion limitations, decide which of these contribute most significantly to patients' symptoms, and implement appropriate therapies to correct the deficits. Range of motion restrictions can be due to shortening of muscle-tendon units, restrictions in joint capsule distensibility, ANT, or bone-on-bone contact at joint interfaces. The first three conditions are almost always amenable to specific stretching techniques. These are discussed under Clinical Considerations, later in this chapter. Range of motion deficits due to bone-on-bone contact are not improved with therapeutic exercise or physical modalities.

Strength

Deficits in strength do not always indicate that the patient has experienced a neurologic insult, a torn muscle or tendon, or prolonged bed rest. To those who perform manual muscle testing daily, it becomes readily apparent that few people in the general population have full strength in all muscle groups. Certainly, strength deficits occur with nerve injury, muscle or tendon tears, and prolonged inactivity. Strength deficits also occur in the absence of these conditions.

Two primary factors contribute to relative strength deficits in ambulatory patients without major nerve or muscle injury. The first might be considered a *relative disuse* weakness. In relative disuse, the body part is not immobilized but is infrequently used in a manner that develops strength. Triceps weakness in sedentary office workers is a good example of this. Although these individuals may be “pushing papers” all day long, they may go for decades without ever performing elbow extensions against enough resistance to prevent gradual weakness from developing. On manual muscle testing, they will likely earn an elbow extension grade of 4/5 to 5–/5. This relative weakness may never be symptomatic, unless the workload required in that individual's triceps muscle suddenly increases. This would occur, for example, if the person decided to build a deck onto the back of the house and began hammering for long periods.

Similarly, many of us do not maintain full strength in our hip extensors (especially for extension past the neutral position) or the muscles that help elevate the upper limbs, especially those that upwardly rotate the scapula. These simply are not movements that we do against resistance very often during routine activities of daily living. Mild strength deficits due to relative inactivity are frequently asymptomatic. They become symptomatic if the individual has a rapid increase in activity or if age-related changes such as loss of motor units or decreasing activity level further weaken muscle groups that already have mild strength deficits. Mild or relative weakness of the hip extensors and abductors has particular relevance in the setting of low back pain due to the functioning of the hip extensors and abductors as lumbopelvic stabilizers. Mild weakness of the scapular rotators has particular relevance in the setting of shoulder pain, due to the role of these muscles in overhead activities.

The second primary factor that contributes to relative strength deficits in ambulatory patients without major nerve or muscle injury is a process sometimes referred to as *muscle deeducation* (1). This is a process in which the individual fails to activate, or abnormally activates, a given muscle because of pain, fatigue, maladaptive biomechanics, or psychological reasons. Over time, the normal neuromuscular engram for the intended movement becomes harder to retrieve, and the neuromuscular control system has essentially “forgotten” the normal pattern of use for that muscle. Most often, muscle deeducation involves the patient losing the ability to fire a muscle with the correct timing, or strongly enough, for the movement intended. The patient adopts a maladaptive neuromuscular firing pattern and substitutes other muscles to perform the task. Sometimes the muscle deeducation process consists of the patient firing a muscle too strongly or losing the ability to relax the muscle appropriately.

An example of a patient substituting one muscle for another is the individual who preferentially fires hamstrings to perform hip extension, rather than using the strongest hip extensor, the gluteus maximus. If this maladaptive firing pattern continues over time, the gluteus maximus becomes deeducated and weak. This can result in poor pelvic control and secondary low back pain. The concept of muscle deeducation emphasizes the close interaction between neural control mechanisms and musculoskeletal function in the development of musculoskeletal pain.

A classic example of a patient losing the ability to appropriately relax a muscle is the individual who presents with unilateral upper back and posterior neck pain. This is often due to the patient holding the scapula in an elevated position. The levator scapulae and upper trapezius are short and tight, and there are pain and tenderness in these muscles. This hiked-shoulder posture is assumed when people work hunched over a desk or when they are tense. Some individuals do not bring the scapula back down to its normal position, and over time they “forget” how to relax the scapular elevators, and forget where their scapula should be normally positioned.

The clinician treating musculoskeletal pain must identify all strength deficits, decide which ones are clinically relevant to the patient's symptoms, and implement an appropriate rehabilitation plan to correct those deficits and reeducate muscles that have lost their normal patterns of firing.

Endurance

Deficits in endurance can exist in bone, muscle, tendon, ligament, and the nervous system. The concept of endurance is fairly self-explanatory. Biomechanically speaking, endurance is the ability of a tissue or body part to generate force, or withstand a force imparted to it, over an extended period or over repeated bouts of exercise (2). It is important to remember that endurance is different from strength. Deficits in endurance present differently than deficits in strength. Endurance is tested differently than strength, as shown in the following example.

A runner with L-5 nerve root irritation may complain of anterior leg pain after running a few miles. During a 2-month period, the pain has occurred at progressively shorter running distances. On manual muscle testing, he has 5/5 strength. When running, gait evaluation is performed on the treadmill; however, the patient begins to display high steppage gait, foot slap, and hip external rotation after 20 minutes. Strength is full, but there are severe endurance deficits in the ankle dorsiflexors due to the nerve irritation and subsequent impairments in normal neuromuscular recruitment. This example of neural fatigue emphasizes the importance of the interaction between the neurologic and musculoskeletal systems in many musculoskeletal pain syndromes.

Another example is that of a cafeteria worker who repetitively places large metal trays on an overhead shelf throughout an 8- hour shift. She may initially develop shoulder or back pain at the very end of the shift, which progresses to onset of pain at progressively earlier times during the day. Manual muscle testing in the shoulder girdle performed in the physician's office can be 5/5, but strength may drop to 4/5 after repetitively stressing the system. This indicates a deficit in muscular endurance contributing to a musculoskeletal pain syndrome.

The clinician treating musculoskeletal disorders sometimes needs to take the time to repetitively stress a muscle group to uncover endurance deficits. If endurance deficits are present and are felt to be clinically relevant to the patient's symptoms, the rehabilitation program must include endurance training.

Neuromuscular Control

Motor control is often overlooked in musculoskeletal rehabilitation. A muscle or muscle group may be quite strong, but if it does not fire at the appropriate time, it may as well not fire at all. Neuromuscular control is a combination of sensory feedback from the body part, pre–motor planning and motor execution (3,4). Impairments in

any of these pathways can lead to musculoskeletal dysfunction and pain. Normal neuromuscular control can be lost through injury or disuse and can be regained through appropriate retraining (5). For some movements, proper neuromuscular control is an easy task. For other movements, motor control requires practice.

For example, if you ask patients to fire their biceps muscles, they will be able to flex their elbows without any difficulty. But if you ask patients to fire their multifidus or lower trapezius muscles, they may not be able to do so even if you show them pictures of those muscles in an anatomy text and explain their actions (6,7). Multifidus and lower trapezius are under voluntary control just like biceps, but our ability to consciously use them to gain fine control over segmental spine motion and scapular rotation, respectively, is far less than our ability to consciously activate biceps to precisely flex the elbow. Specialized exercises can improve one's ability to execute fine control of the neuromusculoskeletal system.

When trying to gain fine motor control, one needs to maximize control of individual muscles and smoothly integrate the actions of different muscle groups in succession during dynamic activities (8,9 and 10). For example, when lifting an object, a person must first fire the foot and ankle muscles to stabilize the feet on the ground. Then one must fire the thigh muscles to stabilize the knee. Next, the hip girdle muscles must stabilize the pelvis before the spine extensors can elevate the torso. If the gluteus maximus fails to kick in before the erector spinae fires, the pelvis will remain anteriorly tilted and abnormal motion will occur in the lumbar spine.

Normal motor sequencing is a highly synchronized process that can easily break down. Several causes of deficits exist in neuromuscular control. One is a lesion in the motor pathways, either centrally or peripherally. This can be dramatic in obvious cases such as cerebellar lesions or cerebral palsy. Subtle nerve injury, however, can cause subtle loss of neuromuscular control. For example, mild irritation of the C-5 nerve root can cause abnormal firing patterns of the shoulder girdle muscles and result in upper back and shoulder pain (11). Mild irritation of the L-5 nerve root can cause abnormal firing patterns of ankle and lumbopelvic stabilizers and lead to ankle or lumbopelvic instability and pain. For optimal success, a comprehensive rehabilitation program addresses biomechanical deficits in both the musculoskeletal and neuromuscular systems.

Another cause of impairment in neuromuscular control is loss of sensory feedback from a body part. This can be dramatic in obvious cases such as occur with a lesion of the sensory portion of the internal capsule or severe vitamin B_{12} deficiency. More subtle loss of sensory feedback can also alter normal neuromuscular firing patterns, however. A common example of this is the inversion ankle sprain. One can strengthen the foot and ankle indefinitely, but if proprioception retraining is not added to the rehabilitation plan, the patient may have persistent ankle pain due to poor fine motor control of the ankle stabilizers (12,13). Proprioception and fine motor control training is crucial for many injuries involving the spine, knee, and shoulder, as well as the ankle (14,15,16,17,18,19 and 20).

The clinician must recognize deficits in neuromuscular control that may be contributing to the patient's musculoskeletal pain and implement a rehabilitation plan that includes correction of those deficits.

Muscle Balance and Agonist/Antagonist Interactions

Musculoskeletal pain and dysfunction are sometimes related to muscle imbalance and agonist/antagonist interactions. In its simplest form, muscle balance theory states that a strong, tight muscle group will reflexively inhibit the antagonist group (1,21). The clinical implications of such agonist/antagonist interactions are important. If a patient is having trouble strengthening a muscle group during a physical therapy program, simultaneous stretching of the antagonist muscle group may be necessary to facilitate strengthening of the target muscle group. Similarly, if the patient is not progressing with correcting range of motion deficits in a particular muscle group, the rehabilitation plan may need to include strengthening of the antagonist muscle group (22). This concept is best illustrated by the following common examples of muscle imbalance that are clinically associated with painful musculoskeletal dysfunction.

The first example is that of the patient with subacute or chronic posterior neck pain. This patient often presents with cervical hyperlordosis due to tightness of the long cervical extensors and weakness of the cervical flexors (23). Both of these biomechanical deficits need to be addressed to restore proper cervicothoracic posture and movement. Similarly, one contributor to abnormal motion at the patellofemoral joint, with subsequent patellofemoral arthralgia, is muscle imbalance in the structures that control the patella. Typical biomechanical deficits in this case are tightness of the laterally situated iliotibial band (ITB) and weakness of the medial thigh muscles, including hip adductors and vastus medialis obliques (24). In treatment, it is necessary to stretch the lateral patellar stabilizers and strengthen the medial patellar stabilizers to improve patellofemoral tracking.

Another common area of muscle imbalance is the shoulder girdle, where one frequently finds tightness of the strong anterior shoulder muscles, including pectoralis minor, pectoralis major, and latissimus dorsi, with associated inhibition and weakness of the posterior shoulder muscles, including middle and lower trapezius and rhomboids (25). This forward-rounded shoulder posture (Fig. 96-2) can be a cause of interscapular pain, rotator cuff pain secondary to abnormal scapular movement, and upper limb pain due to ANT in the brachial plexus.

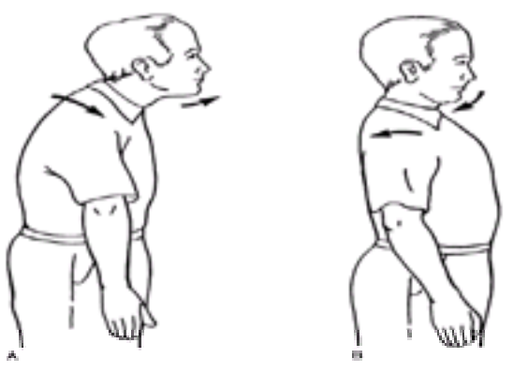

Figure 96-2. The forward-rounded shoulders posture offers a prime example of muscle imbalance that can lead to musculoskeletal dysfunction. The anterior shoulder muscles are tight and the neck and posterior shoulder muscles are put at mechanical disadvantage. **A:** Excessive cervicothoracic kyphosis necessitates a compensatory cervico-occipital extension to keep the eyes level. **B:** Posture rehabilitation includes stretching the anterior shoulder girdle, strengthening the scapular retractors, and chin tucks to improve cervicothoracic alignment.

Similar symptoms can be seen with imbalance between tight scapular elevators, principally levator scapulae and upper trapezius, and inhibited, weak scapular depressors, including lower trapezius and serratus anterior. This pattern of muscle imbalance causes the patient to have a shoulder-elevated posture and is also often seen in patients presenting with posterior neck and shoulder pain. The rehabilitation plan should include stretching of the tight muscle groups with simultaneous strengthening of their antagonists to restore normal muscle balance.

A fourth common site of muscle imbalance is the hip girdle, where tight hip flexors are often seen clinically with inhibited, weak hip extensors (1). Perhaps the most important clinical sequela of this type of muscle imbalance is not hip dysfunction *per se*. Instead, poor pelvic control by gluteus maximus results in an increase in anterior pelvic tilt, which leads to lumbar hyperlordosis and low back pain (26). The rehabilitation of low back pain almost always includes restoration of neutral lumbar posture. In this case, that would necessitate restoring full range of motion of the hip flexors as well as full strength of the hip extensors (27).

A few instances of agonist/antagonist interactions pose particularly troublesome problems for the neuromuscular control system. Consider again the relationship between the upper and lower trapezius. Working together, they couple forces to stabilize the scapula in a retracted and upwardly rotated position, a function crucial for all overhead activities. Yet, they also have antagonistic roles in that the upper trapezius is a scapular elevator while the lower trapezius is a scapular depressor. Such a complex relationship between two different parts of the same muscle, innervated by a single nerve, cannot always be accommodated by the neuromuscular control system and can result in scapulothoracic dyskinesis. In this case, the lower trapezius tends to become inhibited and weak.

An equally complex relationship exists between the tensor fascia lata and gluteus maximus, the two muscles that insert into and control the ITB. Working as agonists, the two muscles serve as hip abductors. Yet they are also antagonists in that the tensor fascia lata is a hip flexor and internal rotator, whereas the gluteus maximus is a hip extensor and external rotator. As in the above example, this can tax the resources of the neuromuscular control mechanisms that dictate appropriate firing patterns. In this example, the tensor fascia lata usually dominates, with the gluteus maximus becoming inhibited. If fine control of the ITB is lost, hip pain (trochanteric

bursopathy) or knee pain (ITB insertionopathy) can result.

Other examples exist where muscles serve paradoxic functions. The tibialis anterior and tibialis posterior (TP) work together to invert the foot and support the arch. Yet they are also antagonists in that the former is an ankle plantar flexor, whereas the latter is a dorsiflexor. At times, during normal walking gait, running gait, and going up or down stairs, both muscles must be active for dynamic arch support, but we need one or the other to stop firing because we need the action of its antagonist. Abnormal firing patterns of TP can lead to TP tendinopathy. Inhibition of either the tibialis anterior or TP can lead to arch collapse and foot pain.

Similarly, the extensor carpi radialis brevis (ECRB) and longus cooperate with the extensor carpi ulnaris to extend the wrist. But the ECRB is left in a quandary during wrist extension movements that require radial deviation, such as hitting a backhand in tennis, or repeatedly loading luggage onto a conveyer belt. At these moments, ECRB must fire to produce wrist extension and radial deviation. But the extensor carpi ulnaris, an ulnar deviator of the wrist, abandons its partner in wrist extension to allow radial deviation of the wrist to occur. This neuromuscular predicament impedes the ability of the wrist extensors to adequately concentrically generate or eccentrically absorb forces, and leads to ECRB overload (called *lateral epicondylopathy* or *tennis elbow*).

In each of the above examples of contradictory agonist/antagonist interactions, there exists a common, associated overuse injury such as rotator cuff tendinopathy due to scapulothoracic dyskinesis, ITB friction syndrome, posterior tibial tendinopathy, or forearm extensor tendinopathy.

The clinician must recognize muscle imbalances that contribute to the patient's musculoskeletal pain and implement a rehabilitation plan that restores proper balance by treating both the agonist and antagonist muscle groups involved. Neuromuscular control must be optimized through specific muscle education and training.

Neural Tension

Neural structures in the central nervous system (CNS) and peripheral nervous system (PNS) move when body parts move. Like muscles, tendons, and joint capsules, the connective tissue associated with the nervous system can lose its normal elasticity and range of motion. If symptomatic, this condition is called *adverse neural tension* (ANT). Alternative names include *adverse neurodynamic tension* or, sometimes, *dural tension*. ANT can be defined as abnormal physiologic or mechanical responses of the nervous system as its tissues are taken through a range of motion (28).

ANT is most commonly recognized as the condition that produces a positive straight-leg raise test. It is also commonly recognized as the entity that produces a positive Kernig's sign in a patient with meningitis. Less commonly recognized, however, is that ANT can exist in areas other than the lumbosacral roots that contribute to the sciatic nerve. Even in the absence of meningitis, it can exist in the spinal cord and the surrounding connective tissue, the cervical roots, brachial plexus, and peripheral nerves. ANT can cause range of motion restrictions, pain with movement, paresthesias in the distribution of the nerves affected, and diminished neuromuscular control.

Normal and abnormal movement of neural structures during movement of the musculoskeletal system has been partly characterized. The posterior part of the human spinal canal increases between 5 and 9 cm in length as the spine goes from full extension to full flexion (29,30 and 31). Thus, trunk and neck movement is associated with gliding movements of the spinal cord within the canal. The dura is connected to the bony and ligamentous structures of the spinal canal via the ligaments of Hoffman (32). Abnormal adhesions between the dura and surrounding structures may form, however, and have been implicated in enhancing pain consequent to disk herniations (33). Upper and lower limb movements also have mechanical consequences for the spinal cord and its roots (34). The median nerve elongates 20% as the upper limb moves from elbow and wrist flexion to full elbow and wrist extension (35). Further stretching of the nerve fibers in the brachial plexus is obtained by adding ipsilateral shoulder depression and contralateral cervical flexion (36).

The nervous system is linked to the musculoskeletal system in several ways. First, neural movement is mechanically coupled with musculoskeletal movement. Second, the nervous system is physiologically connected to the musculoskeletal system at the neuromuscular junction. Third, the nervous system itself can be considered to be in part a connective tissue. Myelin possesses elastic features that allow the myelin sheath to change conformation as nerves stretch, with opening of the clefts of Schmidt-Lantermann (37,38,39 and 40). The endoneurium, perineurium, and epineurium surrounding peripheral nerves all contain collagen (41), the common substrate of all connective tissue.

The connective tissues within peripheral nerves allow for the necessary gliding of adjacent fascicles against each other during limb movements, especially when the limb goes through its full range of motion. Also built into the neurodynamic system is an allowance for a considerable amount of motion between the peripheral nerve and the surrounding tissues in which it lies (35,42). Tunturi demonstrated the presence of elastin in the dura mater of dogs, suggesting that dura possesses the capability of distensibility (43).

Certain regions of the body exist in which the connective tissue of the nervous system is more abundant. For example, the fibular nerve (also called the *peroneal nerve*) has 17% more connective tissue associated with it as it passes around the fibular head than as it courses through the popliteal fossa (44). The amount of connective tissue in peripheral nerves ranges from 21% to 81%, with greater amounts present when the nerve passes a joint (45). The connective tissue elements associated with the CNS and PNS protect neural tissue from injury during gliding movements and compressive events.

The spinal nerve roots lie at the junction of the CNS and PNS and are at particular risk for mechanical stress and ANT for three reasons. The first is that the connective tissue covering the roots is at a transition between the CNS and PNS and is not as well developed as its more proximal or distal counterparts (46). Second, the spinal nerve roots are more tightly adherent to the walls of the intervertebral foramen than in other places (47,48). Third, stenosis of the intervertebral foramen, which can cause abnormal neural gliding, is a common occurrence.

Often, a close association exists between ANT and muscle tightness. A prime example of this is patients with lumbosacral nerve root tension who also have marked hamstring tightness. Both the nerve root and the muscle must be mobilized if normal biomechanics in the region are to be restored (49,50). ANT and muscle tightness often coexist and can easily be mistaken for one another. Careful physical examination is required to distinguish between the two.

Several special physical examination maneuvers that test for ANT in the spine and limbs are described later in the chapter. The clinician treating pain syndromes must be able to identify when ANT is contributing to the patient's symptoms and then implement an appropriate neural mobilization program.

Kinetic Chain Theory

Kinetic chain theory states that biomechanical deficits in one region can be responsible for symptoms in a distant body part. A corollary to kinetic chain theory is the concept of force distribution. A biomechanical system functions optimally when all its parts are able to absorb and generate forces appropriately. Loss of optimal function in one region of the kinetic chain may predispose to overload in another region. The following two examples illustrate this idea. First, if a volleyball player is generating inadequate hip extension or ankle plantar flexion moments during jumping, the athlete's quadriceps can become overloaded and patellar tendinopathy may result as the quadriceps is forced to compensate for the deficiencies of its kinetic chain partners. Second, if a golfer lacks adequate hip rotation, there will be a compensatory increase in lumbar axial rotation during the driving swing that may result in low back pain. Thus, the clinician must assess function in parts along the kinetic chain both proximal and distal to the painful area.

Kibler and colleagues (51,52 and 53) have eloquently synthesized a grand unifying theory of kinetic chain functioning. They describe how for any injury, there are five separate elements that make up the musculoskeletal injury complex that may be identified as contributing to the production or continuation of symptoms (Fig. 96-3). These elements include (a) the tissue injury complex—the actual area of anatomic disruption; (b) the clinical symptom complex—the group of symptoms the patient experiences, such as pain, stiffness, and impaired performance; (c) the functional biomechanical deficit—the set of muscle inflexibilities, weakness, and imbalance that cause inefficient mechanics; (d) the functional adaptation complex—the set of functional substitutions that the patient uses in an attempt to reduce pain and maintain performance; and (e) the tissue overload complex—the group of muscles and other soft tissue structures that are subject to overload injury secondary to the initial injury or maladaptive biomechanics, thus causing or prolonging symptoms. These five elements are often interactive and additive, setting up a vicious cycle of continuing musculoskeletal problems.

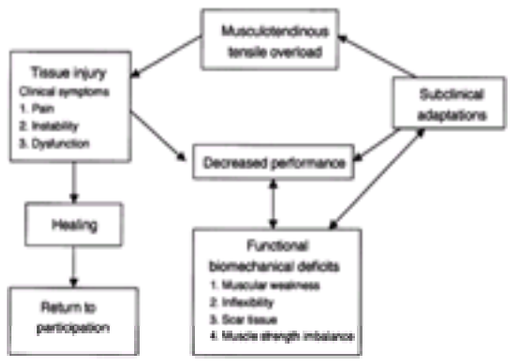

Figure 96-3. The vicious cycle: Tissue injury can lead to maladaptive biomechanical alterations, which in turn can lead to further tissue injury.

Prehabilitation and Posthabilitation

Prehabilitation refers to the process of identifying and correcting biomechanical deficits that might predispose individuals to musculoskeletal injury before they add stress to their musculoskeletal system by taking up a new sport, starting a new job, or otherwise increasing their activity level. The goal of prehabilitation is injury prevention. *Posthabilitation* refers to the process of ensuring that all relevant biomechanical deficits and maladaptive motor patterns are corrected, and remain corrected, after the patient becomes pain-free. It is important to remember that the absence of symptoms does not imply absence of pathology in the musculoskeletal system. The pain accompanying overuse injuries presents well after there are pathologic changes in the tissues and disappears before those tissues have fully healed. Therefore, the rehabilitation process must be comprehensive and continue after pain resolution. The goal of posthabilitation is prevention of injury recurrence.

Identifying Predisposing Factors

The astute musculoskeletal clinician searches for the reasons the patient developed an injury. In the case of acute trauma, the cause is obvious. In the case of soft tissue overload injuries, however, the clinician will need to look further. If the underlying precipitants of tissue overload are not addressed, the patient is at risk for recurrence.

Patient-Therapist Relationship

The relationship that the patient and therapist develop from their first session together and throughout treatment is crucial to the outcome of the rehabilitation process. The therapist must gain the trust of the patient and develop an exercise program that fits his or her musculoskeletal, cognitive, and psychological needs. Some patients require more information or more reassurance. Other self-motivated patients may simply need to be shown how to do their home exercise program correctly and require less attention from the therapist.

Regardless of the specific needs of the patient, the therapist and physician must empower the patient to become an active participant in the rehabilitation process. This is done by educating the patient about his or her particular musculoskeletal pathomechanics and ensuring that the patient is involved in a home exercise program designed to make lasting biomechanical improvements. It is the additional responsibility of the therapist to help motivate the patient to be conscientious about performing the exercises (see Chapter 94). Should the patient-therapist relationship hinder the rehabilitation process at any time, consideration should be given to having the therapist adopt different strategies for that particular patient or to changing therapists.

CLINICAL CONSIDERATIONS

Therapeutic Exercise

The musculoskeletal rehabilitation clinician uses therapeutic exercise like the cardiologist prescribes antihypertensive medication or the surgeon uses a scalpel. The goal of therapeutic exercise is to correct biomechanical deficits that are contributing to the patient's injury and restore and maintain normal structure-function relationships in the musculoskeletal system. Although it is appropriate for the exercise program to be overseen by a physician and therapist, patients should do the majority of exercises independently, either at home or in a gym setting. The importance of promoting patient independence in a home exercise program, with regular reevaluation and advancement of the rehabilitation program, is critical in our changing health care environment. The principal components of therapeutic exercise are flexibility, strength, and neuromuscular control training.

Flexibility Training

An individual's flexibility results from a combination of genetic factors (primarily collagen type) as well as musculoskeletal usage patterns. Injury and lack of use predispose to contracture of soft tissues. Potential benefits of flexibility training include increased range of motion, decreased risk of musculotendinous injuries, decreased soreness, and improved musculoskeletal performance (54,55). Several methods exist to improve flexibility. They include static stretching, ballistic stretching, contract-relax stretching, neural stretching, and manual mobilization. Each of these techniques is reviewed. Which technique to choose depends on the tissue to be stretched and the preferences of the physician, therapist, and patient.

Passive, Assisted Active, and Active Range of Motion. The terms *passive range of motion* (PROM), *active assisted range of motion* (AAROM), and *active range of motion* (AROM) refer to different levels of therapist and patient involvement in flexibility exercises (Table 96-1). PROM entails the therapist moving a joint through its range of motion with the patient maximally relaxed. The patient does not actively participate. PROM is often used in the early stages of rehabilitation and should be complemented with subsequent active participation by the patient. PROM is also used when the patient is unable to actively participate, for example, when trying to improve range of motion in a plegic limb. In AAROM, the patient actively moves the joint through its available range of motion as much as he or she is able, and then the therapist assists with overpressure at the end range of motion to make further gains in flexibility. AAROM is used when the patient is able to move the body part being targeted but not well enough at the end range of motion to improve flexibility. The goal of a progressive flexibility program is to enable the patient to perform the exercises independently. When possible, therefore, the patient should be advanced to AROM exercises without hands-on assistance from the therapist.

PROM	Passive range of motion
AAROM	Active assisted range of motion
AROM	Active range of motion

TABLE 96-1. Physical therapy categories

Static Stretching. In static stretching, the length of the muscle-tendon unit is slowly increased until the patient feels a mild to moderate pulling sensation in the belly of

the muscle being targeted. Sometimes the pulling sensation is felt at the musculotendinous junction or at the tendon-bone junction if there is overuse soreness or other pathology in these areas. If the patient feels pain or a severe pulling sensation, then the muscle-tendon unit is being overstretched and is at risk for injury. Severe discomfort during stretching is a signal that either the muscle should be relaxed by a few centimeters or a different stretch should be tried. During the course of a sustained static muscle stretch, the inverse myotatic stretch reflex is initiated, resulting in relaxation of the muscle (55,56). It is important to take advantage of this phenomenon by extending the stretch by a few degrees or centimeters every 10 seconds. Thus, “static” stretching is not truly static when appropriately performed. This slow, controlled method of stretching is generally considered the safest way to improve flexibility of muscle-tendon units.

Some debate exists over the optimum amount of time that a muscle should be placed on stretch to effect lasting elongation of the tissue. Most clinicians advocate that a stretch should be held for a minimum of 30 seconds (57); others prefer 120 seconds (58). Also, no clear guidelines exist on the frequency with which a muscle should be stretched to effect lasting elongation of the tissue. Generally, two or more stretches per day, each held for at least 30 seconds, are required to improve range of motion. Some prescriptions might call for stretching a muscle every 2 to 3 hours.

Ballistic Stretching. Ballistic stretching is a higher-level technique used to increase the length of the muscle-tendon unit. In ballistic stretching, the muscle is positioned near the end of its range of motion and then repetitively brought just past the point where it provides natural resistance. These repetitive “bouncing” motions can be low or high amplitude and low or high velocity. Repetitive low-velocity movements up to and just past the muscle's end range of motion are called *on-off stretching*. The primary advantage of ballistic stretching is that, when performed correctly, rapid and significant gains in flexibility can be achieved (59). The primary disadvantage is that it often requires the assistance of a qualified therapist or trainer. Another disadvantage is that the risk of over-stretching is greater than with static stretching. A session of ballistic stretching should be followed by static stretching of the target muscles.

Contract-Relax Technique. Contract-relax stretching is also considered a higher level stretching technique. Like ballistic stretching, the contract-relax technique has the potential to provide rapid gains in flexibility and it also often requires the intervention of a qualified therapist or trainer. This technique takes advantage of a period of muscle relaxation that follows muscle contraction. The patient firmly contracts the target muscle isometrically against resistance for approximately 5 seconds. Immediately following the contraction, the muscle is stretched. This contract-relax cycle can be repeated several times. Contract-relax stretching is sometimes referred to by the less descriptive term *proprioceptive neuromuscular facilitation* and is a form of the so-called muscle-energy stretching techniques.

Neural Tension Assessment and Mobilization. Restricted motion of neural elements can coexist and be interrelated with other soft tissue biomechanical deficits. Several reasons exist for this interrelationship. First, motion restrictions in the musculoskeletal system can cause secondary motion restrictions in the anatomically related neural elements. One example of this are tight, hypertrophied scalene muscles that restrict normal gliding of the brachial plexus as they pass out of the neck. Second, soft tissue edema or hematoma from acute trauma or chronic overuse can cause irritation of a nerve passing through the injured area. For example, sciatic ANT has been associated with repetitive hamstring strain (49,60). Third, primary nerve irritation, for example, from a discogenic inflammatory process, can cause abnormal neuromuscular control that leads to secondary biomechanical deficits in the muscles served by that nerve root. Thus, ANT is rarely seen in isolation and should not be treated in isolation from other biomechanical deficits.

Before adding neural mobilization to the rehabilitation program, the clinician must determine whether ANT is present and, if so, whether it is relevant to the patient's symptom complex. Several physical examination maneuvers can be performed that assess for ANT in the lower and upper limbs.

The best technique for assessing ANT in the lower limbs is the slump test (Fig. 96-4). The starting position for this test has the patient seated with hands placed behind the buttocks, palms up on the examination table. The patient then places the chin on his or her chest and slumps the torso forward. This motion draws the spinal cord cephalad (61). The examiner then sequentially extends the knee and dorsiflexes the ankle. These steps pull the lumbosacral nerve roots caudad (62,63). At each stage, the examiner asks the patient what he or she feels. If the maneuver reproduces the patient's usual leg pain, and having the patient extend the neck relieves symptoms, the test is considered positive for ANT. It is crucial that the geometric relationship between the thighs, pelvis, and thoracolumbar spine remains constant so as to avoid tensing and relaxing myofascial structures and thus better isolate movement in the neuraxis. A crossed slump test occurs when extending the asymptomatic leg reproduces pain in the patient's symptomatic leg. This is analogous to a crossed straight-leg test.

Figure 96-4. The slump test for adverse neural tension. Full spine flexion causes cephalad gliding of the spinal cord. Sequential knee extension and ankle dorsiflexion cause caudad gliding of the lumbosacral nerve roots. The examiner checks for reproduction of symptoms, side-to-side differences, and alleviation of symptoms with cervical extension.

The slump test is preferred over the better known straight-leg raise test for several reasons. First, the slump test is more sensitive because it adds cephalad gliding of the spinal cord, while the straight-leg raise maneuver only offers caudad gliding of the nerve roots. Second, the slump test adds specificity because neck flexion and extension help distinguish motion restrictions in neural tissue from other soft tissue inflexibilities. Using the standard straight-leg raise test, it is often difficult to distinguish between ANT and hamstring or gastrocnemius tightness. Both the straight-leg raise and the slump test can be modified to preferentially test tension in the peroneal/L-5 nerve fibers versus the tibial/S-1 fibers by inversion and plantar flexion of the foot (62).

The brachial plexus tension test is the upper limb homologue to the slump test. First, the cervical roots are pulled distally by sequential shoulder depression; shoulder abduction; and external rotation, forearm supination, and elbow, wrist, and finger extension. The examiner asks the patient what he or she feels at each stage. Reproduction of pain or paresthesias in the limb is considered a positive test. If the neck is side bent to the contralateral side, thus drawing the cervical cord away from the limb being tested, symptoms should be exacerbated. If the neck is side bent toward the ipsilateral side, symptoms should be alleviated (Fig. 96-5). Side-to-side comparisons should be done. The brachial plexus tension test was first described by Elvey (64) and has been subject to cadaveric and clinical verification (65).

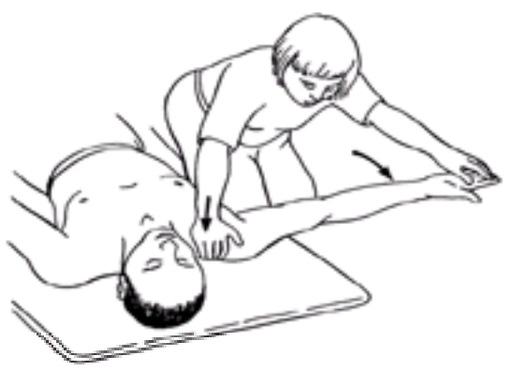

Figure 96-5. The brachial plexus tension test: The examiner sequentially performs shoulder depression and abduction, forearm supination, wrist and finger extension, and elbow extension. After each movement, the patient is asked about symptom production. Contralateral cervical lateral flexion should increase limb symptoms, and

ipsilateral cervical lateral flexion should alleviate limb symptoms.

Brachial plexus tension testing maneuvers with median, ulnar, and radial nerve bias have been described (28). Because it can be difficult to differentiate between tightness in neural elements versus inflexibilities of myofascial structures along the kinetic chain, some clinicians refer to these physical examination maneuvers by the more generic term *upper limb tension tests* rather than brachial plexus tension tests. If the maneuvers reproduce neurologic symptoms, then the clinician can feel more confident that ANT is present.

The results of the neural tension maneuvers guide the initial neural mobilization maneuvers. The therapist instructs the patient to place the limb in the position where neural tension is first noted. Then the patient is instructed to slowly relax the limb a few degrees to a more comfortable position and then stretch a few degrees back toward the position of symptom reproduction. By gently repeating this maneuver with ever larger amplitudes, the connective tissues associated with the nerve gradually regain normal gliding motion.

Manual Joint Mobilization. Joint mobilization is a technique applied by a therapist to a spinal or peripheral joint in which an oscillatory movement is performed to restore full range of motion in the joint. Manual joint mobilizations differ fundamentally from the previous types of range of motion techniques discussed. Mobilizations are aimed at improving accessory movements rather than voluntary movements. Voluntary movements are movements that individuals can perform themselves, such as glenohumeral joint flexion, interphalangeal joint flexion, and lumbar flexion. In contrast, accessory movements are joint movements that individuals have no ability to perform and only occur passively. Examples of accessory joint movements include anterior-posterior gliding of the glenohumeral joint, interphalangeal joints, and individual vertebral segments. Accessory movements can be gliding, rolling, spinning, or compression/distraction motions of the joint. Joint mobilization maneuvers target range of motion restrictions in the joint and joint capsule itself, rather than the muscles that span the joint. Joint mobilizations can be diagnostic as well as therapeutic: They can help distinguish capsular versus muscular patterns of tightness.

Joint mobilizations are classified into four categories of increasing aggressiveness. Grade I mobilizations are small-amplitude movements performed in the middle of a joint's normal range of movement. Grade II mobilizations are large-amplitude movements performed within the free range of the joint but not moving into any resistance or stiffness. Grade I and II mobilizations can prevent further loss of joint range of motion but do not increase range of motion. They almost always precede grade III and IV maneuvers during a therapy session. Grade III joint mobilizations are large-amplitude movements performed up to the limit of the available joint range of motion. Grade IV mobilizations are small-amplitude movements performed at and just beyond the limit of the joint's range of motion. Manual joint mobilizations should only be performed by a therapist or clinician with advanced training in these techniques. Experienced manual therapists can mobilize virtually any joint in the body.

Common Stretching Errors. Probably the most common cause of ineffective stretching is not holding the stretch long enough or not performing it frequently enough. Improper technique is another common cause of ineffective stretching. Often individuals will fail to make gains in flexibility because the stretches target the single joint muscles in a muscle group, rather than the more important biarthrodial muscles. A prime example of this is the classic standing quadriceps stretch, which might address the vastus lateralis, vastus intermedius, and vastus medialis but neglects the rectus femoris, which crosses the hip joint as well as the knee joint (Fig. 96-6). Sometimes a stretching position inadvertently stretches tissues other than the target tissue. Finally, the flexibility program must address all the relevant structures contributing to the inflexibility. Joint capsule mobilization maneuvers alone will not be successful if the muscles crossing that joint are also tight. Similarly, muscle stretching alone will not be successful if an underlying motion restriction exists in neural structures. Carefully documenting an exercise history will help determine whether the exercises are being performed correctly.

Figure 96-6. A common error in quadriceps stretching is failure of the patient to stabilize the pelvis. The position shown here provides pelvic stabilization and greater stretch to all four of the quadriceps muscles.

Strength Training

Strength deficits often contribute to musculoskeletal pain. Strength deficits can cause pain in one of two main ways. First, a muscle can be a primary pain generator if it lacks adequate strength or endurance to perform a given task and therefore fatigues. Second, a muscle group lacking sufficient strength to properly control a joint may cause abnormal, painful motion in that joint. Many ways exist to improve muscle strength.

Exercise Prescription. A strength training prescription should include the patient's diagnosis, the muscles to be worked, the modality of strength training, the frequency, the number of repetitions per set and number of sets per workout, the intensity of the exercise, and precautions. Exercise prescriptions should be flexible. The clinician must reevaluate the patient at appropriate intervals and modify the program as necessary.

Specificity of Training Effects. Training effects tend to be very specific to the type of exercise performed. For example, strengthening the biceps in isolation does not increase triceps strength. Training for quick, explosive power does not improve endurance, and vice versa. Training muscle groups to generate force does not necessarily increase their ability to absorb force. Strength training for the lower limb does not improve balance unless it is done in a manner that challenges balance. Therefore, the goals of the rehabilitation program must be clear, and the prescription must be written to fulfill those goals.

Neural versus Muscular Mechanisms of Strength Gains. Physiologically, strength gains come about through neural and muscular mechanisms. It is well established that neural mechanisms play a significant role in strength gains during training. As early as 1967, researchers showed that rats on a training program improved muscle strength without a concomitant increase in muscle bulk (66). The ability of muscle to undergo strength gains without hypertrophy has been confirmed in humans (67,68). The mechanism of strength gains without muscle hypertrophy has been shown to be improved synchronization of motor unit firing. Neural mechanisms are more important than muscular mechanisms in the early stages of training, before muscle hypertrophy has had a chance to occur (67,68,69 and 70). Later in the course of a training program, muscular mechanisms predominate. The quantitative electrodiagnostic techniques used to investigate changes in neural synchronization during strength training have been shown to be reliable and sensitive (71,72 and 73) and continue to be used to investigate training effects on the neuromuscular system (74,75 and 76).

Static versus Dynamic Strength Training

Static Strength Training. Strength training can be broadly classified into static or dynamic exercises. Static strength training is more commonly referred to as *isometric exercise*. In isometric exercise, a muscle or group of muscles works against a resistance without any change in muscle length or joint angle. Isometric exercise is the strength training method of choice in the earliest stages of rehabilitating injured muscle, tendon, ligament, or joints. Isometric exercise offers the primary advantage of avoiding movement in painful or frail structures, while allowing strength gains to occur. Isometric exercise is used in patients with osteoarthritis, if putting joints through a range of motion may be painful or impossible. Isometric exercise is also used in the initial stages of the rehabilitation of strains and sprains and advanced

tendinosis, when movement of the injured structure puts it at risk for further injury.

Isometric exercise of any given muscle or muscle group should be varied in several ways. First, the joint angle should be varied. For example, in the earliest stages of rehabilitation for forearm extensor tendinopathy, the patient should be given a light hand weight to hold for a set amount of time with the wrist in a neutral position. Then the patient should statically hold the weight with the wrist in varying degrees of flexion and extension. The exercise should be gradually advanced by adding weight and by increasing the length of time of each repetition. The position should be held until mild to moderate fatigue develops in the target muscles.

Isometric exercises can be performed to either isolate a single muscle or work several segments of the kinetic chain simultaneously. In the rehabilitation of forearm extensor tendinopathy, for example, the wrist extensor strengthening can be done with the entire upper limb supported, except for the hand. Alternatively, the upper limb can be unsupported to simultaneously work the shoulder girdle. The latter method offers the advantage of working proximal parts of the kinetic chain, where relative weakness may have predisposed to distal overload. At appropriate times during the rehabilitation course, the patient's program should be advanced to short arc and then longer arc dynamic strengthening exercises.

Dynamic Strength Training. Dynamic exercises have various classifications. One can speak of concentric versus eccentric exercise, isokinetic versus isotonic exercise, closed kinetic chain versus open kinetic chain exercise, and plyometric exercise.

CONCENTRIC AND ECCENTRIC EXERCISE. *Concentric muscular contraction* refers to an action in which the muscle shortens to move a body segment. An example of concentric movement is shortening of the quadriceps muscle as one extends the knee while ascending stairs. An eccentric muscle contraction is one in which the muscle lengthens while resisting a force. An example of an eccentric movement is controlled lengthening of the quadriceps muscle as the knee flexes while descending stairs. The muscle has to lengthen to accommodate the normal mechanics of descent and also has to fire to prevent the knee from buckling. Eccentric exercise works muscles harder and is more likely to cause muscle overload than concentric exercise (77,78,79,80 and 81).

Frequently, strength training regimens include both concentric and eccentric exercise. When rehabilitating a particular injury, however, one should emphasize the movement that overloaded the structure in the first place. For example, if a furniture mover suddenly overloaded his elbow flexors by trying to stop a falling couch with his forearm, the initial strength retraining program should progress from gentle isometric exercises to slow, gentle eccentric elbow flexor exercises. In normal human movements, one often finds an eccentric contraction preceding a concentric contraction in the same muscle. This sequence of eccentric and concentric contractions forms a natural pattern called the *stretch-shortening cycle* (82).

ISOKINETIC AND ISOTONIC EXERCISE. In isokinetic exercise, the target muscle moves a joint through a range of motion at fixed angular velocity, but the torque generated by the movement may vary. This is accomplished with the use of specialized equipment that can be programmed to provide resistance to joint movement at any predetermined fixed rate, usually measured in degrees per second. Although isokinetic exercise is useful for quantifying strength for research purposes, or quantifying a patient's progress during the course of rehabilitation, it is a type of movement that is rarely performed during real-life activities (83). The applicability of isokinetic movements performed in the laboratory is further limited because of the dissociation between joint angular velocities and muscle shortening (84,85). Therefore, rehabilitation protocols should emphasize more functionally relevant exercises.

Isotonic muscle contraction refers to a muscle contracting through a range of motion while maintaining either a constant tension within the muscle or a constant torque applied against a resistance. Like isokinetic movements, isotonic movement is rarely reproduced during daily activities and is therefore more of an academic concept than a practical one.

CLOSED AND OPEN KINETIC CHAIN EXERCISE. *Closed kinetic chain exercise* refers to work done with the distal end of the limb fixed in space. *Open kinetic chain exercise* refers to work done with the distal end of the limb free in space. When a person does push- ups, for example, the hands are fixed on the floor, and the upper limbs function in a closed kinetic chain situation. When someone throws a baseball, however, the hand moves through space and the upper limb functions in an open chain fashion.

Advantages and disadvantages exist to both open and closed kinetic chain exercise. In general, if the movement to be trained is an open chain movement, such as lifting boxes, then the clinician should prescribe open kinetic chain exercises. Closed kinetic chain work is preferred when the patient needs to strengthen muscles that are primarily used in closed kinetic chain situations, for example, when strengthening knee and hip extensors in a postpolio patient who is having difficulty arising from a chair. Closed kinetic chain work offers several additional advantages over open kinetic chain exercise. Closed kinetic chain exercise promotes co-contraction of multiple muscles that cross a joint, thus providing greater joint stability. It also tends to work more segments of the kinetic chain, thus providing a more complete workout while also promoting improved sequencing of movements. Finally, closed kinetic chain work generally demands greater proprioceptive feedback than open kinetic chain exercise, thus improving this important sensory modality.

COMBINATION STRENGTHENING EXERCISES. A current trend exists to simultaneously work multiple muscle groups throughout the kinetic chain, rather than strengthen individual muscles in isolation. Two primary advantages exist to exercising multiple body parts at once. First, it is more time efficient. Second, most normal activities involve activating multiple muscle groups simultaneously or in sequence. Therefore, combination exercises are considered more functional than exercises that isolate individual muscles. An advanced form of combination exercise is plyometric exercise.

Plyometric exercise is a higher level dynamic form of exercise that can combine strength, endurance, power, balance, and agility training. Plyometric maneuvers simultaneously bring multiple muscle groups through a rapid stretch-shorten cycle. A simple example of lower body plyometric training is step jumping (Fig. 96-7). In this exercise, the hip extensors, knee extensors, and ankle plantar flexors rapidly fire concentrically. On landing, they fire eccentrically while lengthening. An example of upper body plyometric exercise could be throwing a basketball at a target while balancing on one leg. To avoid injury, an individual must attain an adequate baseline level of strength and flexibility before starting a plyometric training program.

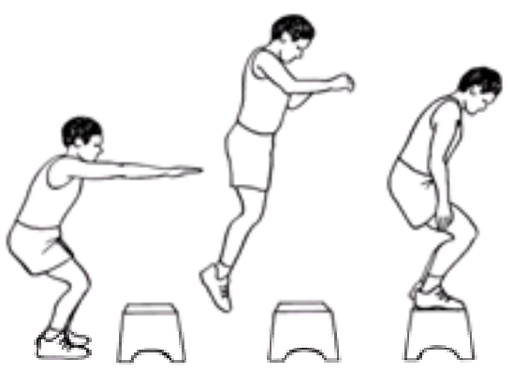

Figure 96-7. Lower body plyometric exercise: Step jumping builds strength, endurance, balance, and agility.

Manipulation

Manual manipulation of the musculoskeletal system dates back at least to the times of Hippocrates and Galen (86,87). After a long period of obscurity, manipulation reemerged at the end of the last century with the founding of osteopathy in 1874 (88) and chiropractic medicine in 1895 (87). Manipulation enjoys widespread popularity today, with an estimated 12 million Americans undergoing 90 to 120 million manipulations per year (89,90 and 91). Joint manipulation differs from joint mobilization in that manipulation employs low- amplitude high-velocity thrusts, while mobilization employs higher amplitude, low-velocity movements. Theoretically, if a manual therapist or chiropractor can improve a patient's joint alignment through manipulation, then biomechanics will also be improved (92,93 and 94).

Despite its popularity, the exact mechanism of action whereby manipulation alleviates pain remains unclear. Manipulation of the musculoskeletal system is postulated to have several beneficial effects. First, it is believed to help restore joint symmetry, particularly in reference to the spine (95,96 and 97). Second, it may aid in mechanical restoration of muscular and fascial range and ease of motion (98,99). Third, manipulative techniques have been theorized to induce sensory afference,

which may diminish pain through a gate theory effect (99,100 and 101). Fourth, some authors have postulated that manipulation increases endorphin release (92,97,99). These theories have not been subjected to rigorous scientific testing, however. Many believe that manipulation benefits patients primarily through a placebo effect (102).

In the past, many practitioners of manipulation have extended the benefits of this modality to areas beyond the musculoskeletal system, such as the endocrine, immune, and digestive systems (87). Such leaps in logic have led those in conventional medicine to question the practice of manipulation. Fortunately, a greater percentage of practitioners of manipulation now rely on this technique to restore structure-function relationships only in the musculoskeletal system.

Clearly, no current consensus exists on the mechanism whereby manipulation improves musculoskeletal function. Furthermore, there is no consensus on whether manipulation is beneficial at all, due to a lack of well-designed randomized controlled studies. One metaanalysis (103), two reviews (104,105), and two controlled clinical trials (106,107) indicate that manipulation decreases spine pain in selected populations, at least for short periods (e.g., less than 1 month). A review of randomized controlled trials found limited evidence that manipulation is better than placebo but not superior to other conservative measures for acute low back pain (108). The same review found strong evidence that manipulation is better than placebo and moderate evidence that it is better than analgesics, rest, and massage for chronic low back pain (108). Further study is needed to determine whether and how manipulation is effective.

Contraindications to high-velocity thrust manipulation include progressive neurologic impairment, unstable vertebral segments, severe osteoporosis, rheumatoid arthritis, bone or spinal cord tumors, spondyloarthropathy, bleeding diathesis, and poor manipulative skills. Risks are greater with cervical spine manipulations and include injury to nerve root, spinal cord, vertebral artery, and other soft tissue and osseous structures (109,110).

Spinal Traction

Like manipulation, spinal traction techniques date back to ancient times (111) and are widely used today, but are not universally accepted in conventional medicine circles. Also like manipulation, the literature on spinal traction is fraught with inconsistencies and methodologic flaws (108). Reviews of randomized clinical trials have failed to find proof of efficacy for spinal traction (108,112,113,114 and 115). However, numerous reports of positive results of traction exist (116,117,118,119,120,121 and 122), primarily in uncontrolled and/or nonrandomized clinical trials.

Proponents argue that if correctly performed, spinal traction can aid by widening the intervertebral foramina, decreasing intradisk pressure, allowing migration of herniated disk material back into place, decreasing facet joint friction, stretching paraspinal musculature, and straightening spinal curves, both in the lumbar (123,124 and 125) and cervical (126,127 and 128) regions. Three studies, two using epidurography (119,129) and one using computed tomography (122) to visualize disk herniations, have demonstrated reduction in disk prolapse following traction. Long-term maintenance of the reduction has not been demonstrated, however. In fact, disk material has been observed to return to its prolapsed state following traction therapy (129). It has been speculated, but not proven, that traction improves nutrition of the disk by decreasing intradisk pressure and facilitating imbibition (130). Traction has been advocated in the treatment of facet arthralgia and muscle spasm (131). Some argue that the primary benefit of traction is from immobilization rather than the traction itself (132).

Many ways exist to apply traction to the axial skeleton. Devices can be accommodated for use in a regular bed or hospital bed. There are also specially constructed, mechanical, single piece and split traction tables (133). Motorized and hydraulic traction tables are also available (132). A therapist can manually apply traction (88,134,135), although duration and force are more difficult to control when compared to mechanical or motorized traction. Some degree of traction can be obtained simply with positioning— for example, right side-lying on several pillows to provide left axial distraction. Autotraction is a technique that relies on patients' pulling their torsos cephalad with their arms, while the pelvis is fixed. Autotraction can be inexpensive and provides built-in protection against over-distraction because the patient controls the force applied. The patient's upper limb strength may be inadequate to generate the force necessary for distraction, however, and the time frame is limited by the patient's endurance (136,137). Furthermore, autotraction puts the patient at risk for shoulder injury. Some prefer gravity traction, in which the patient is suspended from a crossbar either in a fully inverted position or in an upright position. Both orientations provide distraction forces of approximately 50% body weight through the axial skeleton (138).

Traction devices can apply longitudinal, rotational, and side-bending forces. In addition to specifying the type of traction device used, traction prescriptions differ in terms of frequency of application, time per session, and force applied. No standardization of these parameters exists and prescriptions vary widely among practitioners.

Contraindications to traction are similar to those for high-velocity manipulation and include fracture, spine instability, osteoporosis, tumor, infection, pregnancy, hiatal hernia, and claustrophobia (139).

Physical Modalities

Physical modalities such as heat, cold, and electrical stimulation can be useful adjuncts to the physical restoration program. The primary goals of physical modalities are to decrease pain and inflammation to facilitate the exercise program. They should rarely, if ever, be used in isolation without an appropriate exercise program.

Heat

General Physiologic Effects of Heating Modalities. Many different heating modalities are available to raise the temperature in superficial and deep tissues. The physiologic effects of tissue heating can be broadly classified into hemodynamic, neuromuscular, joint and connective tissue, and analgesic effects.

The hemodynamic effects of tissue heating are related to increased blood flow. Forearm blood flow increases two- to threefold following application of heat (140). Vasodilation is postulated to speed healing of nonacute soft tissue injuries by increasing local metabolism and ingress of nutrients, leukocytes, and antibodies and increasing egress of breakdown products (141,142). Heat also increases nerve conduction velocities in most peripheral nerves (140,143). The clinical significance of this effect in musculoskeletal rehabilitation is unclear. A more relevant neuromuscular effect of tissue heating is the inhibition of group II muscle spindle fibers (144). Inhibition of spindle fibers can relax muscle and facilitate stretching.

Tissue heating facilitates stretching of muscle-tendon units by direct effects on connective tissue as well as by indirect effects via the muscle spindles. Lehmann and colleagues (145) showed that tendon distensibility increases with increasing temperature. They further showed that heat combined with stretching produced greater gains in tendon distensibility than heat or stretching alone. Heating superficial joints such as metacarpophalangeal joints can decrease stiffness in these structures and facilitate a stretching program (146).

Although heat is often used for its analgesic effect, the mechanism whereby heat reduces pain has not been clarified. Possible mechanisms include general relaxation effect, endorphin release, vasodilation causing washout of pain mediators, and vasodilation leading to a decrease in ischemic pain (147,148 and 149).

General Precautions for the Use of Heat. Heat use should be avoided in patients who are unable to provide feedback about their tissue temperature. This includes insensate patients and those whose cognitive condition impairs their ability to accurately warn the therapist of adverse effects—principally burns. Heat should also be avoided in patients with arterial insufficiency. The vasodilation produced can cause metabolic activity to exceed the ability of the arterial system to deliver oxygen to the area, resulting in tissue ischemia (141,150). Vasodilation can also result in increased bleeding in patients with a bleeding diathesis. Heat is contraindicated in acute musculoskeletal injury because it can increase acute hemorrhage and edema. Theoretical objections have been raised against the use of heat near tumors due to the fear of increased rate of tumor growth or hematogenous spread (149).

Superficial Heat. Heat may be transferred to body tissues by means of conduction, convection, or conversion. The first two are forms of superficial heat, while the last is used to heat deeper tissues. Superficial heat modalities are most useful for facilitating range of motion exercises in the hands and feet, where the target tendons and joints are superficial and not well protected by an insulating subcutaneous fat layer.

Hydrocollator packs, which transfer heat by conduction, are a commonly used modality to heat superficial tissues. They are made of silicon dioxide enclosed in canvas. These packs are heated to 65°C to 90°C and are applied to the skin over insulating towels for 20 to 30 minutes (151). Hydrocollator packs have been shown to raise tissue temperatures up to 3°C at a depth of 1 cm below the skin (152). The ability of Hydrocollator packs to significantly elevate the temperature of tissue deeper than 1 cm is questionable (152,153). Hot water packs, electrical heating pads, and chemical packs heat by convection. Hydrocollator packs have the advantage of offering greater temperature control than most of the convection modalities. Whirlpool and Hubbard tanks, however, provide superficial heat by

convection and offer very good temperature control. Heated water tanks should not exceed 40°C.

Perhaps the most common misapplication of superficial heating modalities occurs when it is used in an attempt to heat deep structures. Studies have shown that the modalities listed in this section do not raise the temperature in tissues deeper than the subcutaneous fat, which serves as an excellent insulator against heat (152,153).

Deep Heat

Ultrasound. Ultrasound is the safest and most commonly used of the deep heating modalities. Ultrasound employs sound waves above the frequency threshold of human hearing to heat deep tissues. The ultrasound frequencies used range from 0.8 to 1.0 MHz. Although ultrasound produces some nonthermal effects on biological tissues, such as streaming, microstreaming, cavitation, and standing waves, the effects of the nonthermal effects are not thought to be clinically significant (154,155,156 and 157). It is the thermal effects that are important.

The literature on the clinical benefits of ultrasound remains mixed. One group found no difference between exercise plus ultrasound and exercise plus sham ultrasound in a randomized, double-blind study in patients with lateral epicondylalgia, although both groups showed improvement over time (158). Similarly, ultrasound plus exercise showed no benefit over exercise alone in a randomized, double-blind, placebo-controlled study on patients with painful knee osteoarthritis (159). A review of the ultrasound literature concluded that most positive studies lacked adequate controls and that additional research was required to determine efficacy (148).

Shortwave and Microwave Diathermy. Ultrasound has largely replaced shortwave and microwave diathermy as the deep heating modality of choice. They are included here largely for historical reasons only.

Shortwave diathermy employs radio waves to heat deep tissues. The Federal Communications Commission has restricted medical use to specific frequencies and most shortwave diathermy machines in the United States operate at 27.12 MHz (160). Temperature elevations of 4°C to 6°C can be attained in muscle (161). Thermal effects tend to be greatest in water-poor tissues, however, and subcutaneous fat may be heated up to 15°C (162). Shortwave diathermy has been used to heat connective tissue in nearly every part of the body, including pelvic floor structures via transvaginal and transrectal application (163). Pulsed shortwave diathermy has produced statistically significant pain relief in patients with rotator cuff tendinopathy (164), neck pain (165), and other soft tissue injuries (166).

In addition to the general precautions of heat mentioned above, shortwave diathermy is also contraindicated in the setting of implants such as pacemakers, stimulators, surgical implants, contact lenses, and metallic intrauterine devices. Such devices can cause excessive heating to occur in the tissues immediately surrounding the implant. Additionally, shortwave diathermy can cause excessive bleeding if applied to the menstruating uterus. The safety of shortwave diathermy has not been established in those with immature skeletons and therefore is not recommended in the pediatric population.

Microwave diathermy differs from shortwave diathermy in that it employs electromagnetic radiation of much greater frequency. The Federal Communications Commission has approved microwave frequencies between 915 and 2,456 MHz for medical use. Lower frequencies penetrate to deep tissues better than higher frequencies (167,168). At 915 MHz, subcutaneous fat temperature may be increased 10°C to 15°C, with deep muscle temperature elevations of 3°C to 4°C at 2 to 4 cm below the skin (169).

The contraindications for other forms of deep heat application hold for microwave diathermy as well (see Fig. 96-1). Microwaves can produce cataracts, so both patients and therapists should wear protective goggles (170). Although human fetuses have been exposed to microwave diathermy without deleterious effects, the overall safety in fetuses and children has not been established and its use is therefore discouraged in pregnant women and young children. Because tissues with a high water content are selectively heated, application of microwave over fluid-filled cavities, cysts, or blisters can produce unacceptable local heating (171). The use of microwave diathermy has, however, been used to speed resolution of hematomas (172). Most clinicians feel that the presence of an acute inflammatory condition such as inflammatory arthritis is a contraindication to microwave diathermy (160). There are some reports, however, of improved patient comfort after application of microwave to rheumatoid joints (173,174).

Cryotherapy

Biological Effects. Cryotherapy has several benefits in the treatment of musculoskeletal pain. Its ability to slow nerve conduction (140,175,176 and 177) and produce local analgesia (178) is well known. It has also been shown to improve tendon distensibility (179) and modify muscle stretch reflexes (180,181,182,183 and 184). In combination, these effects can greatly facilitate a stretching program aimed at restoring full range of motion. Chilling a body part initially stimulates local reflexes to enhance sympathetic tone and produce vasoconstriction (185,186). Vasoconstriction reduces blood flow, slows local metabolism, and lessens swelling (187).

Technique. Ice packs, iced compression wraps, iced whirlpools, frozen steaks, and frozen bags of peas all work equally well in cooling body parts. The preferences of the therapist and patient usually determine the specific method of cryotherapy. Iced compression wraps offer a few advantages. Compression wraps help reduce swelling and can also add proprioceptive feedback for the individual who is exercising while icing (*cryokinetics*) or stretching while icing (*cryostretching*). Commercial products are available that are specifically designed for different body parts and that allow the individual to apply ice and compression simultaneously. These usually allow people to participate in other activities such as working or doing household chores because they do not have to fumble with a clumsy plastic bag of ice cubes. The recommended duration of cryotherapy is 20 to 30 minutes. This can be repeated up to once per hour. Longer periods of application increase the risk of local tissue damage and reactive hyperemia (188).

Precautions

The most common adverse reaction of cryotherapy is local tissue damage from overzealous icing. Skin burns, frostbite, and nerve injury can occur (189). Delayed tissue healing may occur if cryotherapy is used for extended periods, because of reduction in blood flow and slowing of local metabolism (190). Cryotherapy should be used judiciously or not at all in the extremities of patients with Raynaud's disease, cold urticaria, cryoglobulinemia, and atherosclerotic disease, because of the risk of inducing limb ischemia. As is true with heat therapy, cryotherapy is contraindicated in insensate patients who are unable to provide feedback on the status of the treated area. Properly applied ice treatments of less than 30 minutes in healthy individuals will not cause injury (178,184).

Functional Electrical Stimulation and Surface Electromyography

Transcutaneous electrical stimulation for the treatment of pain is discussed in Chapter 97. In the rehabilitation of muscle dysfunction, functional neuromuscular electrical stimulation (NMES) and surface electromyography (SEMG) are sometimes used to aid the muscle reeducation process. Muscles can become deeducated or lose their normal firing patterns for several reasons, including partial denervation, disuse from prolonged immobilization or bed rest, and maladaptive substitution patterns. Specialized muscle reeducation techniques are often useful after tendon transfers as well, when the muscle is being asked to fire in a new pattern (191). Electrical stimulation of muscle can help maintain muscle bulk during a period of disuse. It can also assist in the early stages of a muscle reeducation process, by giving the muscle a “jump start” (192,193 and 194). Once the patient feels the muscle firing with electrical stimulation, it is easier to start voluntarily firing the muscle. Feedback from the muscle can be transmitted to the patient using SEMG recordings. The patient can see the EMG signal recorded from the muscle undergoing reeducation and try to improve the firing pattern to make those tracings match a set of normal tracings. The use of SEMG as a biofeedback technique to help patients relax muscles that are overfiring is covered in Chapter 90.

The use of functional NMES/SEMG to help patients self-regulate the activity of motor units started in the 1960s (195,196 and 197). It has been used fairly extensively in the functional rehabilitation of stroke patients (198,199,200 and 201). In the nonstroke population, it has been used to reeducate muscles around the shoulder (202,203), forearm and hand (204,205 and 206), lumbar spine (207,208), and knee (209,210,211,212,213 and 214). As the benefits of functional NMES/SEMG become more widely appreciated, there will be greater elucidation of normal and abnormal firing patterns of muscle groups during dynamic activities.

Functional NMES is contraindicated in patients with pacemakers, local infection or malignancy, recent fracture or serious muscle/tendon disruption, local skin lesions, seizure disorder, and pregnancy (191).

Miscellaneous Physical Modalities

Numerous other physical modalities have been used through the millennia in the treatment of musculoskeletal pain ranging from aromatherapy to snake venom to healing touch. The majority of these alternative modalities are not discussed here due to a lack of scientific literature about their efficacy. Two less mainstream modalities that are becoming popular, vibration and low-energy laser therapy, warrant brief mention, however.

Vibration. A wide variety of vibration therapy products are commercially available. Physical therapists prefer models that operate with frequencies around 150 Hz and amplitudes around 1.5 mm (215,216 and 217). In uncontrolled studies, vibration therapy has been reported to be 70% successful in the treatment of sinusitis and musculoskeletal pain (218,219 and 220). These effects were not reversed by naloxone, suggesting that the mechanism of action did not involve stimulation of the natural opiate system (221).

French investigators have also reported success with vibratory stimulation in the treatment of chronic pain (222,223). In a prospective controlled study, Guieu and colleagues (223) found vibration to be more effective than sham treatment for short-term relief of chronic pain. Another arm of the same study found the combination of transcutaneous electrical nerve stimulation plus vibration to have additive effects for short-term relief of chronic pain (223). In a series of experiments, the same group of investigators has explored possible roles of vibratory stimulation in modulating the Met-enkephalin and substance P pathways via activation of large afferent nerve fibers (224,225,226,227 and 228). The definitive mechanism of action whereby vibration therapy reduces pain remains under investigation.

Low-Energy Laser. While low-energy laser treatments are available outside the United States for treating pain from osteoarthritis, back pain, headache, and neuritis, they are not yet approved for clinical use in this country. Energy levels used are usually in the range of 1 to 100 mW (229,230). Pain relief has been reported to be as high as 60% to 80% of subjects, although other investigators have found no benefit (229).

One double-blind controlled trial of low-energy laser versus sham treatment found it to be associated with decreased pain and improved grip strength in patients with lateral epicondylitis 4 weeks after treatment (231). Other randomized, placebo-controlled studies failed to find benefit from low-energy laser treatments in this condition (232,233) and in ankle sprains (234). A randomized, double-blind study evaluated the effect of low energy laser versus sham treatment on chronic low back pain. Both treatment groups were also placed on an exercise program. Both groups had a decrease in pain, but there was no difference between those who received laser treatments and those who received sham treatments (235).

The mechanism of action of low-energy laser remains unproven. Proponents of this modality report that it accelerates wound healing by stimulating DNA synthesis and collagen production and improves the function of damaged neurologic tissue (230). Further research is needed to definitively assess its efficacy and indications.

CONCLUSIONS

The goal of physical rehabilitation is to maximize the functioning of the patients' neuromusculoskeletal systems. Therapies are directed at correcting pertinent biomechanical deficits by restoring full, pain-free range of motion, adequate strength and endurance for the patients' desired activity levels, and proper neuromuscular control. The mainstay of treatment is therapeutic exercise. Most exercises can be done by the patient in a home exercise program after careful instruction by a therapist. Manual techniques by a specially trained therapist can be very helpful, especially in the early stages of the rehabilitation program. Patients' progress should be reevaluated at appropriate intervals, and their therapeutic exercise programs should be upgraded as needed. Therapeutic modalities such as ice and ultrasound can be helpful to facilitate the exercise program. The majority of the work in most successful programs is done by the patient, not the therapist.

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CHAPTER 97

Acupuncture

Stephen H. Butler and C. Richard Chapman

Acupuncture is a therapeutic procedure in which small, solid needles are inserted into the skin at varying depths, typically penetrating the underlying musculature. This method, derived from practices in ancient Asian medicine, was essentially unknown to most physicians in the United States when the first edition of this book was written. Bonica (1) mentioned acupuncture as a form of local therapy and cited its use by Osler for treating various painful conditions during the latter part of the nineteenth century. Because of the publicity given to Chinese demonstrations of acupuncture pain control for surgery in the 1970s, acupuncture has since become familiar both to the medical community and to the lay public. Its practice remains controversial, but in more than 34 states in the United States and many other countries, nonphysician acupuncturists have won the right to practice their trade either independently or under the auspices of a licensed physician. In the United States, there are more than 10,000 licensed nonphysician acupuncturists, plus 3,000 physician acupuncturists, as well as at least that many additional physicians using various acupuncture- related techniques. More than 1 million patients per year are treated by these practitioners (2). In 1993, the U.S. Food and Drug Administration reported that more than $500 million was spent on acupuncture therapies.

Acupuncture is of interest to physicians concerned with pain management in day-to-day practice for two reasons: (a) It offers a comparatively safe alternative or complementary treatment to the prescription of medication for pain problems, and (b) patients often ask their physicians for advice on whether they should engage the services of an acupuncturist or for referral to an acupuncturist. It is therefore worthwhile to have a working knowledge of acupuncture techniques, the potential of this approach for pain management, the issues surrounding its putative mechanisms, and its limitations.

This chapter provides an overview of current clinical and scientific knowledge about acupuncture for pain therapy. We discuss the use of acupuncture for the control of acute and chronic pain rather than its possible use for the prevention of pain during surgery. Acupuncture pain control in the surgical setting, although now recognized as a valid phenomenon, is of little clinical importance in Western medical practice, and its adoption in the West is no longer at issue for surgical anesthesia. There are, however, interesting reports of intraoperative “electroacupuncture” having opioid-sparing effects in the postoperative period (3). Bonica (4) wrote a definitive report on the use of acupuncture for surgery. Surgical use is of interest only to the extent that it sheds light on the mechanism(s) of acupuncture therapy for pain prevention or relief. Acupuncture in the treatment of disease states is not discussed, as that subject is beyond the scope of this book.

In addressing acupuncture pain therapy, which is practiced widely in the United States, this chapter draws heavily on the research produced in this area since 1980, but, where appropriate, earlier studies are also considered. The National Institutes of Health (NIH) Office of Alternative Medicine has provided more than $2 million for research since its creation in 1993 (2). In November 1997, the NIH issued a consensus report after a panel reviewed the current literature. They acknowledged that evidence was strong for the use of acupuncture for nausea and vomiting associated with surgery and for post–dental surgery pain but that more research was necessary to support the claims for other areas of pain relief. The political and economic issues surrounding acupuncture may have significantly influenced both the panel's recommendations and the popular interpretation of the usefulness of acupuncture.

The ancient Chinese acupuncture medicine is noted only briefly, because this information is of little relevance and is available in copious detail elsewhere (5,6,7,8,9 and 10). For those interested in a recent translation of the Yellow Emperor's 2,300-year-old treatise on Asian medicine, a portion on low back pain is available in English (11). The purpose of this chapter is to provide interested physicians with a working knowledge of the field so that they can judge the potential utility of acupuncture techniques for specific pain management problems.

The Basic Considerations section includes the three basic types of acupuncture therapies for pain and the indications for these therapies, a brief description of how acupuncture is performed, and a broad review and evaluation of the scientific basis for the use of acupuncture for managing pain. The Summary reviews the current state of knowledge in this field. The use of acupuncture needles in the treatment of musculoskeletal pain syndromes is discussed in Chapter 28. This is the only current use of the technology at the University of Washington Pain Center; we do not make use of traditional Chinese acupuncture in the treatment of chronic pain.

Since the prior edition of this text in 1990, the literature has expanded. A Medline search revealed 788 abstracts from 1988 to 1998 covering all aspects of acupuncture for pain in both the clinical and basic domains. There continue to be major difficulties with the literature. Fifty percent of the citations are in Chinese or other non-English languages, the latter mostly from Eastern Europe. Often they are without abstracts, which makes evaluation impossible. The studies continue to lump traditional acupuncture, electroacupuncture, intramuscular stimulation, and a new designation, *pharmacologic acupuncture*, together as if they were interchangeable therapies. Much of the basic research is in anesthetized animals, usually receiving electrical stimulation through acupuncture points that supposedly correspond to those in humans. The results are then interpreted in a human patient context—a tremendous leap of faith that is rarely addressed in these studies or in reviews of the subject.

BASIC CONSIDERATIONS

Types of Acupuncture Therapies

Review of the current medical literature reveals that the term *acupuncture* can refer to at least four different interventions: classic acupuncture based on Chinese medicine, acupuncture as a form of trigger point therapy, acupuncture as a procedure for electrical stimulation, and pharmacologic acupuncture, in which substances as varied as water, opioids, herbal mixtures, and steroid extracts are injected at acupuncture points. The use of lasers instead of needles is also becoming popular, but there is little information on the scientific basis for this and it is, strictly speaking, not a puncture. These are distinctly different therapies, and each should be considered separately. Unfortunately, the basic and clinical research studies often gloss over some fundamental differences in these techniques. However, many studies point out that electrical stimulation of acupuncture needles, in any position, and transcutaneous electrical nerve stimulation (TENS) are indistinguishable from electroacupuncture at classic acupuncture points (9).

Classic Acupuncture

The first and best-known form of acupuncture is the practice of traditional methods according to the principles of ancient Chinese medicine (10,11 and 12). Taoist doctrine saw human health as existing within the tensions created by opposing forces in nature, the yin (dark, female) and the yang (light, male). Medical intervention carried out within this tradition was undertaken to balance opposing energy forces considered out of harmony. A concept of energy flow that combined circulation and neurologic function was fundamental to the practice of classic acupuncture. Vital life energy was thought to flow through a set of interconnected channels, called *meridians*, that followed a circadian rhythm (Fig. 97-1).

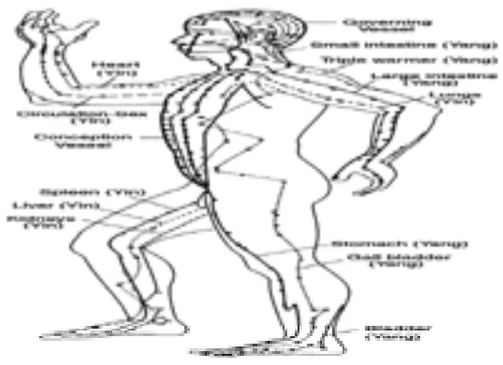

Figure 97-1. The practice of acupuncture derives from the principles of oriental medicine. The points that an acupuncturist stimulates by needle puncture follow a series of life force lines, or channels, called *meridians*. A vital life force, called *chi* (or sometimes *Qi*) flows through the channels. Chi flowing through meridians moves longitudinally, encircling the body. Essentially, the meridians are a closed system for the circulation of energy throughout the body. There are 12 main pairs of meridians (each is represented on both sides of the body) and two midline meridians on the ventral and dorsal midlines of the body. The meridians on the ventral surface are yin meridians; those on the dorsal surface are yang. The names of the meridians correspond to the various organs or functions for which they have a controlling influence. Excess, blockage, or deficiency of the flow of chi causes disease in the affected meridian distribution.

One of the internal organs was thought to be associated with each meridian, and the meridians are named according to organs. For example, the meridian for the gallbladder runs from the external canthus of the eye, back and forth along the skull, and down to the shoulders, from which it descends along the side of the body and ends at the fourth toe. It is a yang meridian—its function is balanced against that of its yin counterpart, the liver meridian. The latter runs from the great toe to the groin and into the chest, where it is said to disappear from the map of meridians because it courses deep into the body and has no surface representation. Diseases and discomforts such as pain were classified according to the meridians felt to be involved and according to whether they had a yin (cold, hypofunctional) or yang (hot, hyperfunctional) nature.

The meridians were said to be interconnected with the vital life energy, *chi*, flowing through them. Excesses or deficiencies in the flow of energy were said to cause pain, discomfort, hypo- or hyperfunction, and, with time, trophic changes. By inserting the needles strategically along individual meridians or at their junctures, the acupuncturist attempted to balance the flow of energy throughout the body.

Numerous variations on classic acupuncture exist. Among them is a system of ear acupuncture based on the belief that the pinna contains a map of acupuncture points representing the entire human body. Research on this type of diagnosis and therapy is expanding, but there are few controlled trials and those that have been undertaken have failed to yield supporting evidence (13). The many other embellishments of classic acupuncture are outside the scope of this chapter.

Today in Asia, many practitioners still use classic Asian medicine principles in the treatment of pain and disease states, and they are also popular in many parts of Europe, where they are used by physicians, nurses, and physical therapists as well as nonmedical practitioners. When Western physicians or other health care professionals practice traditional acupuncture it is often based on a cookbook approach in which a routine set of meridian points is used to treat each type of pain problem (5,6). This is neither bona fide Western nor Asian medicine, because classic practice in its pure form emphasizes the unique individual diagnosis of each patient.

Although these and other concepts of ancient medicine were exceptionally enlightened for their time (e.g., they conceived of circulation and certain basic principles of neurology), they are now primarily of historical interest to Western medicine. It is hardly surprising that much of the ancient folk medicine cannot be validated by modern science. For example, one organ postulated by the ancient Chinese to affect energy flow, the “triple heater,” is nonexistent. Similarly, meridians exist neither as anatomic structures nor as patterns of neurologic response. Whereas contemporary studies have shown that acupuncture points are often characterized by low electrical skin resistance and tenderness to palpation, these are also the characteristics of trigger points (see Chapter 28 and Chapter 29). The existence of correspondence between meridian pathways and patterns of referred pain or sensation produced by finger pressure at tender points/trigger points overlying muscle is not surprising and is well known to Western medicine (14,15 and 16). Such correspondences help to confirm that ancient Oriental therapists identified and treated conditions that are still observed and often undertreated today. They do not validate the notion that acupuncture has some special or mysterious origin that gives it an advantage over contemporary, scientifically based practices.

Variations of traditional medicine exist in a revised form in contemporary medicine in the Far East. For example, Japanese Ryodoraku treatment maintains most of the basic tenets of classic acupuncture, but the mechanism underlying treatment is considered to be the autonomic nervous system (17,18). Therapists attempt to balance sympathetic and parasympathetic functions of the autonomic nervous system and rely heavily on readings of electrical skin resistance at traditional meridian points for diagnosis. Meridians are considered to be patterns of autonomic activation. This and other hybrid therapies offer bridges between classic Asian medicine and modern science. Unfortunately, such possibilities remain in the realm of conjecture for want of scientific data to support the basic hypotheses.

It is difficult to justify the perpetuation of ancient folk medicine concepts, at least in their pure form, in contemporary medical practice, but the romance of ancient knowledge has gained a strong following among lay practitioners of folk medicine and among some physicians. It is strongly rooted in the culture of several major nations. In some industrialized countries, including Japan, Chinese medicine is taught in degree-granting institutions. Approximately one-sixth of the world's population relies occasionally on Chinese medicine.

Trigger Point Therapy

The second application of acupuncture is essentially neurologic and muscular. Degenerative changes in neural function related to stress, prior injury, and aging can upset the normal properties of skeletal muscle, as well as those of other tissues and organs, in subtle ways that might not be evident on conventional neurologic examination. Abnormal areas of skeletal musculature can be felt as tender, ropy strands or points associated with signs of excessive sympathetic activity (e.g., coldness, mild edema), pain on palpation, and general fatigue. Such points have been identified by Bonica (1,14), Travell and Simons (15), Sola (16), and others as *tender points* or *trigger points* that can be effectively treated by stimulation to achieve relief of persistent pain. Chapter 28 and Chapter 29 describe trigger points, their associated myofascial pain syndromes, and treatment of these syndromes.

When acupuncture needles are used to treat the tender points in muscle associated with chronic pain, acupuncture is nearly indistinguishable from trigger point therapy. The close relationship of trigger points as defined by Western medicine and acupuncture points as identified by ancient texts of Asian medicine has been addressed by Melzack (19) and Gunn (20). Although many trigger point therapists choose to inject local anesthetic or normal saline solution into tender areas, some use stimulation with an acupuncture needle at the same site. Many, like Sola, believe that trigger points are associated with sympathetic hyperactivity and that local chemical blockade of the trigger point eliminates the basic pathophysiology.

The possible mechanisms underlying trigger point therapy have been reviewed in depth by Travell and Simons (15) and Sola (16,21). We also postulate that such treatment may reverse the effects of chronic nerve damage, such as radiculopathy, on skeletal muscle (see Chapter 28). Pain of this type is almost invariably accompanied by prolonged muscle contractures, and pain relief is predicated on the release of painful contractures. These concepts and principles of treatment are not encompassed by traditional Chinese acupuncture theory or practice.

Electrical Stimulation Therapy

Electrical stimulation for pain relief might be as old as acupuncture itself. Records from the ancient Greeks and Romans indicated that fish such as the electric eel that could produce an electrical discharge were used to treat patients with pain. During prolonged surgeries in the early 1970s, Chinese acupuncturists found extended manual twirling with needles inefficient (and perhaps monotonous and tiring as well) and replaced this practice with electrical stimulation. In parallel, Western practitioners, inspired by the gate-control theory of Melzack and Wall (22), began to develop electrical stimulation therapies for pain control. This has led to the widespread use of TENS and the development of an industry in the United States (and other parts of the world) that manufactures TENS units. (TENS therapy for pain

is presented in Chapter 98.)

In an animal study, TENS and electroacupuncture were shown to have the same effects (23), and research in one area contributes information to the other. The two approaches have in common three sets of parameters for electrical therapy: (a) high-frequency, low- intensity stimulation (generally delivered at the area of painful focus); (b) low-frequency, high-intensity stimulation (typically delivered distal to the area of pain, perhaps at a classic acupuncture point); and (c) burst mode stimulation, in which brief bursts of high-frequency stimulation are given. These methods appear to have different effects in different situations. More detailed information on the parameters of choice for electrical therapy and the differential application of the three sets of parameters for selective pain problems is presented in Chapter 98.

Acupuncturists differ from TENS therapists in the use of needles rather than broad electrodes and in a tendency to use electrical therapy for systemic rather than local effects, although prominent exceptions to this rule are found. Because needles penetrate the skin and often underlying muscle, some therapists combine electrical and trigger point therapy.

Procedure

Classic Methods

The insertion of acupuncture needles is not technically demanding, but a surprising variety of techniques exists. Many claims have been made—but with no actual evidence—that different procedures of needle insertion produce different therapeutic results, and acupuncturists do not agree among themselves about optimal needle technique. Many classic therapists think it important to slant the needle either in the direction of assumed energy flow in the treated meridian or against the energy flow, and some use gold and silver needles for special purposes. In some cases, mugwort is pressed into a ball and attached to the top of the needle. The acupuncturist lights the herb after needle insertion, and the smoldering material gently heats the inserted needle. These practices and other exotic refinements related to classic theory are of no practical importance for Western medical application.

Modern Methods

Figure 97-2 demonstrates a typical procedure used by classic therapists for needle insertion. Individual therapists vary considerably in the way they manipulate the needle during insertion. Some use a lifting and twisting motion, others quickly insert it without rotation, and still others slowly penetrate the skin and underlying tissue. A few therapists penetrate only the skin and contend that no benefit is obtained by stimulating deeper tissues. Others argue that superficial and deep penetration are appropriate for different types of disorders. No right way exists, however, and patient comfort (or discomfort) is perhaps the most important criterion. Even this would be argued by the few acupuncturists who believe that stimulation of deep muscle and periosteum is of therapeutic benefit.

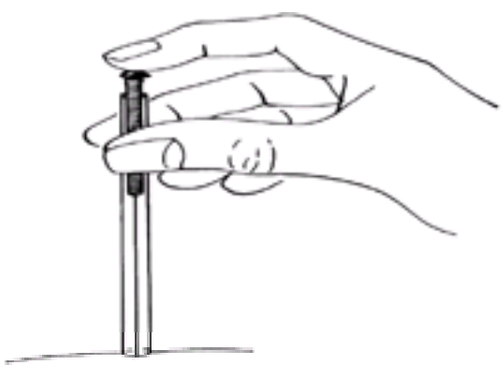

Figure 97-2. Classic acupuncture needle insertion techniques: the tapping method.

Students of acupuncture in China typically learn by inserting needles into themselves. This type of practice helps to ensure a technique that is minimally distressing to patients. Some physicians prefer to use needle guide tubes or devices that mount the needle in a guide cylinder equipped with a piston that taps the needle into place at the touch of a finger. Such methods help to minimize the distress of treatment and to maintain sterility. Figure 97-3 illustrates a Japanese needle system. Such equipment lends itself well to Western trigger point therapy, and we advocate the use of this type of instrument for dry needling as discussed in Chapter 28.

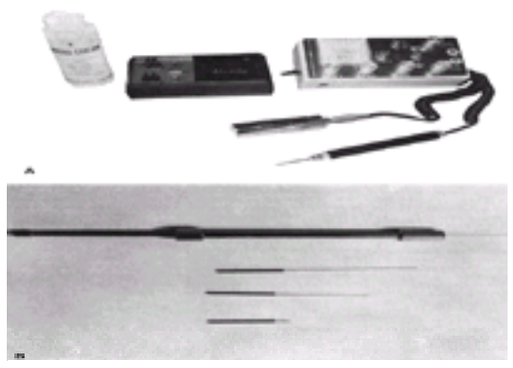

Figure 97-3. A needle system developed in Japan for acupuncture that is uniquely suited for trigger point therapy. **A:** Equipment to search for acupuncture points. From left to right: plastic container containing conducting cream, a battery pack, and a resistance meter with one lead (heavy upper) held by the patient and the other lead ending as a pencil point probe to detect acupuncture points. **B:** Three disposable acupuncture needles and a needle holder/plunger to assist in needle placement.

Chinese therapists emphasize the importance of *te chi* at the site of insertion: the underlying muscle appears to grab the needle and hold it firmly. The patient reports a concomitant feeling of heaviness or pressure or a deep ache where the needle is inserted. Trigger point therapists such as Sola (16) and Gunn et al. (24) have noted that the insertion of needles in muscle tissue that is not associated with a trigger point does not produce this response. In most classic practice the therapist does not remove the needle until the *te chi* has dissipated and the needle can be lifted from the tissue without effort.

The technique used by trigger point therapists for needle insertion has been borrowed from traditional acupuncture. Stainless steel acupuncture needles of varying lengths are commonly used. The length of the needle is dictated by the location of the point to be treated; deeper and thicker muscles require longer needles. A fine-gauge needle (30 gauge or less) with a pencil-point tip is believed to be less traumatic than the bevelled cutting edge of a hollow needle. The fine, flexible needle transmits the resistance and consistency of tissues penetrated, which adds a diagnostic component to the procedure.

The direction of needle insertion is generally perpendicular to the skin so as to penetrate the muscle zone of innervation. Tubular guides are used to facilitate skin penetration and to avoid touching the needle. We have used multiple needles for the several motor bands within a myotome belonging to both anterior and posterior primary rami that require treatment, but we now prefer the convenient use of only one needle in the plunger-type needle holder, which allows the same needle to be used at multiple loci.

Side Effects and Complications

Potential Complications

Acupuncture is a potential source of infection if sterile precautions are not taken. If an old, worn needle is used it can be broken during insertion and require surgical removal. In addition, improper needle insertion in the thorax or base of the neck can cause pneumothorax. The literature reveals a few cases in which patients have harmed themselves by inserting needles improperly (spinal cord injury in one instance), but few complications of acupuncture have been noted when performed by a trained physician. In the last 10 years, the literature has only ten citations related to complications, which list toxic shock with necrotizing fasciitis, bacterial meningitis, spinal cord injury, and pneumothorax. The safety of the technique compares favorably with the use of prescription medications, trigger point injections, and TENS.

The practice of acupuncture by nonphysicians is of growing concern to physicians as the use of acupuncture spreads. Most nonphysician practitioners are skilled and safe, but the possibility that serious problems might remain undiagnosed in patients under the care of nonphysicians is disquieting. Acupuncture can alleviate or mask symptoms that are of medical importance. This has been emphasized by the NIH consensus group as well as the need to standardize training and licensure. Therefore, the physician who has a patient who is also being seen by an acupuncturist should be certain that the patient has a thorough medical evaluation and should be alert to the fact that concomitant acupuncture treatment can affect or even suppress the symptoms with which the patient would normally present.

Precautions

It is essential to sterilize acupuncture needles and plungers by autoclave or gas because they could transmit hepatitis, human immunodeficiency virus, or other viral diseases. Alternatively, disposable needles for one-time use are preferable. Since repeated use weakens needles, the use of disposable needles minimizes greatly the possibility of breakage and retained needles. The skin should be cleansed with alcohol or another antiseptic at the site of treatment. The infectious complications of acupuncture therapy are minimal when sterile precautions and disposable needles are used. It is important to guard against pneumothorax when placing needles in the chest and shoulder areas, particularly when treating the parascapular and intercostal muscles. Treatment of the trapezius muscle requires particular caution because the patient might flinch with needle insertion, leading to inadvertent puncture of the apical pleura. When treating the paravertebral muscles, care should be taken to avoid excessively deep penetration that could injure the spinal cord. Vasovagal syncope responses are sometimes seen, typically when needles are inserted in the region of the brachial plexus, and it is good practice to have the patient lie down or sit in a supported position. The guidelines offered by Sola and Bonica in Chapter 29 and by Travell and Simons (15) for trigger point therapy are equally suitable for acupuncture.

Scientific Basis: Problems in Scientific Development

Traditional acupuncture is without a scientific basis (19). Modern research on acupuncture is a formidable undertaking, and work to date has been problematic at both the basic science and the clinical levels because scientific inquiry has not followed a logical progression. Just when the scientific community took interest in acupuncture in the mid-1970s, the raphe-spinal structures were identified as the mechanism subserving opioid analgesia and the enkephalins and endorphins were discovered. Many investigators rushed to hypothesize that endogenous opioids must be the mechanism of acupuncture pain control, and acupuncture research became caught up in the enthusiasm of endorphin researchers for linking all sorts of hitherto unexplainable phenomena to endogenous opioids (25,26,27 and 28). Over the last 20-plus years, the endorphin/opioid hypothesis has continued to intrigue acupuncture researchers. Of 46 articles reviewed that address this issue, 39 support the hypothesis for partial involvement and seven do not. Those in support all show only an incomplete effect and admit that this is not the whole story. All of this research interest in acupuncture in turn has led the scientific and clinical communities to engage for a time in backward reasoning: Acupuncture must be effective because so much work is being done to elucidate its mechanism(s). Proponents of acupuncture therapy have pointed proudly to animal studies that show links between acupuncture and endorphins, enkephalins, or dynorphins. The same animal models have been used to implicate all known structures in the ascending pain transmission systems from the spinal cord to the cerebral cortex as well as the descending inhibitory systems. Again, these effects are only partial and cannot be discriminated from the effects of noxious stimulation in studies that compare the two. Whether acupuncture analgesia in humans can be related meaningfully to effects seen in animals, many of whom are under the effects of general anesthesia for the studies, has not been considered. This unfortunate unsystematic progression has produced a knowledge base of limited value. To be fair, however, the problem of bias in research is not limited to the acupuncture field—it is well known in the philosophy of science. The tendency to be biased in interpreting scientific data that bear on clinical issues has been described (29), and “confirmation bias” of the sort demonstrated by some acupuncture researchers has been discussed by Greenwald and colleagues (30), Patel and colleagues (31), and Lewith and Vincent (32).

Unfortunately, the fundamental clinical research questions of whether acupuncture treatment can prevent or relieve acute and chronic pain are still inconclusively answered in spite of hundreds of studies over the past two decades. Indeed, many of the most basic questions remain unasked. As this review demonstrates, the literature is far from proving that acupuncture is effective in pain control. The American Medical Association reviewed this issue at its 1981 meeting and decided that insufficient evidence existed to conclude that acupuncture has any more effect on pain than a placebo or sham acupuncture (33). Sweet (34) was less kind, attacking acupuncture as essentially worthless. The issue has reemerged due to government pressure to scientifically assess alternative medicine. To address this issue, the NIH has founded a new department, and research funding has begun to flow. Clinical efficacy studies have, for the most part, been weak in design, measurement technology, and long-term follow-up. Consequently, it is still not known which acute and chronic pain problems, if any, can or cannot be helped by acupuncture.

Animal, human laboratory, and clinical research studies are reviewed broadly in the remainder of this section. The purpose of these overviews is to summarize the scientific knowledge base.

Animal Studies

A comprehensive review of the large literature on animals cannot be undertaken here, and its relevance for the clinician concerned with pain patients is moot. It is important, however, that the clinician not be misled by claims of acupuncture zealots based on data from animal researchers. Although valuable, animal studies often shed little light on the effects of acupuncture on patient care for the reasons to be described.

Many animal investigations of acupuncture analgesia have been done, mainly with small animals, but a few have used dogs or horses (35,36,37 and 38). Stimulation is primarily electrical with very few animal studies using classic manual stimulation. Measurement of pain has been restricted mostly to reflex responses or to simple behavioral indicators, such as escape from a stimulus. Only a few studies have tried to define the nature of acupuncture analgesia in a controlled fashion; most have attempted to identify a mechanism. In general, investigators have inappropriately made strong and direct generalizations to humans from animal data without regard to species differences and to the limited relationship of animal laboratory algesimetry models to human chronic pain as seen in the clinical setting. The question of points and meridians in animals is also a problem. In some studies, electrical stimulation is done in muscles corresponding to muscles underlying human acupuncture points. Is this acupuncture? In others, researchers use charts of points created for specific animals. In many cases, those doing the needling (or stimulating) have no previous knowledge of traditional acupuncture or any experience in needling.

The results of animal studies are inconclusive as evidence for acupuncture mechanisms in humans, partly because parallel findings have emerged in the animal literature concerned with acupuncture analgesia and with stress-induced analgesia (39,40 and 41). These findings indicate species-specific responses to acupuncture. When animals are subjected to intensive stress, such as cold water immersion, fright, or painful stimulation, a major hypothalamic-pituitary axis response is produced that includes liberation of cortisols, adrenocorticotropin, and b-endorphin, among other substances. Consequently, stress as a physiologic response is characterized by reduced sensitivity to injury or other pain challenge. Such analgesia is typically reversed by the opioid antagonist naloxone (39). In small mammals, such as rabbits, response to a stressor can take extreme forms, which include total immobility. It is not surprising that studies to look at both ascending and descending neural systems involved in pain show widespread changes in animal models without any differences in the effects produced by other noxious stimulation (40).

Frightening a small animal can induce a state popularly called *animal hypnosis* (having nothing to do with human hypnosis), in which the animal is quickly rendered unconscious and insensible (42,43 and 44). The more severe the stress, the longer the immobility of the animal, and fear potentiates this immobility response. In nature, such animals are often carried off by a predator and left near its den for a later meal. The putative hypnotic state gives them a chance to feign death, effect a recovery, and escape at a later time. This can be demonstrated in the laboratory by simply throwing a rabbit onto its back; one can then carry out an apparently painless laparotomy (43).

Under certain stressful and threatening circumstances, animals in a laboratory setting can go in and out of a putative hypnotic state (44). Because acupuncture is not understood by animal subjects to be benign, the process of handling and painful stimulation with needles can induce a stress response unique to certain species. Support for this possibility was provided by Galeano and associates (45), who performed acupuncture in rabbits while taking care not to induce stress. Under these conditions, acupuncture analgesia could not be induced. Some studies separate animals in a study population as to responders or nonresponders. Thus, animals

might not be suitable models for human acupuncture analgesia.

Failure to acknowledge the parallels in animal hypnosis and acupuncture analgesia in animals has led to the emergence of a literature that is difficult to interpret. Thirty-nine of 46 abstracted articles on acupuncture analgesia mechanisms identified through computer search for the period 1979 to 1998 supported the hypothesis that acupuncture analgesia in animals is partially mediated by endorphins. In contrast, none of the human research studies addressing the endorphin hypothesis during this period provided positive outcomes.

Human Laboratory Studies

The effects of acupuncture (usually electric) on pain sensibility in normal human subjects have been studied in various laboratory settings. In general, human studies differ substantially from animal work for three reasons: (a) Volunteers are not stressed during testing, and every effort is made to ensure their comfort and satisfaction with the experiment; (b) the subjects understand the purpose of the experiment and appreciate the safety precautions taken on their behalf; and (c) more complex measures of pain are used. Pain threshold, pain tolerance, psychophysical stimulus-matching techniques, visual analogue judgments, performance in a sensory decision theory stimulus–judgment task, and brain-evoked potentials have all been used to evaluate the efficacy of acupuncture as an analgesic intervention. Pain has been induced in the laboratory by stimulating teeth or skin electrically, heating skin, immersing limbs in ice water, and applying a tourniquet. How these artificial pain states resemble chronic pain is, of course, unclear. They may be better models for acute states, such as postoperative or posttraumatic pain.

The literature on human studies is less extensive than that on animals but is of sufficient size and complexity to present a full review here. The areas in which the studies have yielded consensus merit comment, however, as does the experience of our laboratory in a long-term research program on acupuncture analgesia. Chapman and colleagues (46,47,48,49,50 and 51) stimulated the teeth of study subjects in repeated studies to create safe but noteworthy experimental pain and measured the effects of acupuncture on pain perception using both sensory decision theory techniques and brain-evoked potentials. Consistent observations by Chapman and others include the following findings. First, outcomes were generally positive although some investigators could not demonstrate alteration of pain perception with acupuncture stimulation (52). Although most studies controlled appropriately for expectancy and placebo effects, it was found that belief in the efficacy of acupuncture can play a role in the subjects' ratings of acupuncture pain control in the laboratory (53,54). In our laboratory we could observe reliable positive outcomes in a series of four sensory decision theory studies and four evoked-potential studies carried out over several years (46,47,48,49,50 and 51). The effect was not seen in every subject but was typically clear in approximately 75% of the volunteers in any given experiment.

Second, the effect obtained, although statistically significant, was usually small or even minor from a clinical perspective. In one study we observed that acupuncture analgesia was approximately equal to the effects of inhaling 33% nitrous oxide in oxygen (46). In another study we found that the effects of acupuncture were no stronger than those of TENS delivered at the same sites in the same way (47). Only in rare cases did we see a subject who appeared to become totally insensitive to laboratory pain during electrical acupuncture. Other investigators have reported similar findings (53,54 and 55). These results are strikingly inconsistent with the demonstrations of apparently total pain control in the surgical setting in China. Confounding variables in acupuncture used for surgery in China are the use of intravenous meperidine and local infiltration of local anesthetics to supplement the acupuncture as well as having quick, gentle surgeons. The human studies are similarly problematic for the hypothesis that endorphins mediate acupuncture analgesia, because the effect is small. If such stimulation produces an endorphin-mediated response of sufficient strength to permit surgery without pain, it should appear more formidable in the laboratory.

Third, in accordance with observations of Chinese surgeries, laboratory investigators found that the analgesia can be elicited either by stimulating the subject within the same dermatome used for the delivery of the painful stimulus or by stimulating a meridian point (48,56,57). The importance of piercing the acupuncture point with precision remains a moot issue. We found that successful demonstration of acupuncture analgesia for dental pain requires exacting care in placement of the needle at the *hoku* point in the hands (located between the thumb and the first finger and corresponding to the position of the first dorsal interosseous muscle), but others disagree that this is critical (20).

Finally, electrical acupuncture requires low-frequency intense electrical stimulation (58) and appears to be an all-or-none phenomenon. Andersson and colleagues (59) observed that the dental pain threshold could be altered only when the intensity of low-frequency electric stimulation was strong enough to elicit a pounding or throbbing sensation. We found that the evoked potential elicited by painful dental stimulation is reduced only when the acupuncture stimulation is at a level just below the subject's tolerance (49). It was not possible to demonstrate a dose-response effect by varying the intensity of acupuncture stimulation.

Two studies that have contributed uniquely to the laboratory literature merit comment. Chapman and colleagues (50) addressed the question of whether culture affects the response to acupuncture stimulation. Three groups of subjects were studied: non-Asian Americans, second-generation Japanese-Americans, and Japanese living in Japan. Subjects were required to discriminate several levels of painful dental stimulation in a sensory decision theory task. Detection, discrimination ability, and response bias were measured both in control conditions and during electric acupuncture. Acupuncture yielded small but significant analgesia in all three groups, and neither race nor culture significantly affected the amount of pain control observed. Other studies looked at this from a different viewpoint. A study by Kreitler et al. (60) showed that belief is highly correlated to pain relief with acupuncture and therefore there may be a strong bias in volunteer populations for laboratory research.

Price and associates (56) examined the effects of acupuncture on patients with chronic low back pain using a laboratory paradigm. They attempted to bridge laboratory experimentation and clinical pain control by testing patients with an experimental pain stimulus. A hand-held contact thermode was applied to the back and volar forearm of the subjects to deliver noxious heat stimuli. Patients rated both clinical pain and experimental pain under baseline conditions and again after acupuncture. Regardless of whether acupuncture was performed in the dermatomes involved in the back pain or at distant meridian points, both the clinical and experimental pains were reduced 1 to 2 hours after treatment for many patients. When patients were tested again several days after treatment, the therapeutic effect of the treatment on back pain remained but the effect on experimental pain was gone. This study needs to be replicated and extended before firm conclusions can be drawn about the use of experimental laboratory methods with patients, but it suggests that laboratory findings can provide valid evidence for the clinical application of acupuncture.

Berman et al. (61) reviewed the existing literature on acupuncture for low back pain and found that most studies were not well done. Of those that had a rigorous experimental design, only one-half had a statistically positive benefit for acupuncture that, again, highlights the point that the effects are not strong. A parallel study by Cherkin (62) looking at the comparison of the effects of acupuncture with conventional treatments (medication/exercise) emphasized the poor quality of the studies and that positive results were exaggerated beyond the clinical relevance on a statistical basis. The Price et al. study needs to be considered with these clinical observations in mind.

Whether human acupuncture analgesia is mediated by endorphins has been hotly contested (26,51). Some investigators have attempted to resolve the issue by measuring plasma endorphins in association with acupuncture therapy, but plasma-borne endorphins cannot cross the blood–brain barrier and therefore are not “functional” in opiate receptor pharmacology. The existence of significant parallels between peripheral and central endorphin changes is still uncertain (28). It is difficult to reach firm conclusions from the evidence on either side of this issue at present. It can be confidently stated, however, that the mechanisms of acupuncture appear to be neither singular nor simple. The complexity increases when these questions are raised at the clinical level. For example, we cannot be confident that the neuropharmacology of the chronic pain patient is the same as that of the normal person or of the elective surgery patient who might respond well when given acupuncture for surgical pain control. Endorphin levels in plasma or cerebrospinal fluid might simply be one part of a larger constellation of neuropharmacologic responses to disease, to chronic pain, or to their treatment(s); they do not necessarily offer the ultimate explanation for pain control during acupuncture.

Clinical Studies

Clinical investigation in the field of acupuncture has been undertaken primarily in the area of chronic pain, with few exceptions (e.g., the study of its effects on postoperative dental pain) (63,64). There is some enticing acute pain clinical research looking at blinded patients having electroacupuncture during a general anesthetic for surgery. Their postoperative opioid requirements were one-half those of the control although no other parameters were altered (3).

Clinical chronic pain research has been extremely difficult to carry out effectively for several reasons:

- Chronic pain is a complex problem that often has psychological dimensions as well as organic pathology.
- Chronic pain syndromes are sometimes complicated by previous surgeries, other failed therapies, or prescription drug abuse or dependency.
- Selection of reliable and valid outcome criteria is difficult, and outcomes are meaningful only when long-term follow-up is undertaken.
- Placebo controls are difficult and rarely used. They need to be coupled with nontreatment controls as well to look at the natural history of the problem being

treated.
- No standards are available for correct acupuncture therapy for a given problem, such as back pain.

The last point is particularly problematic. If a cookbook set of acupuncture treatment points is chosen arbitrarily for the target pain syndrome to conduct the study in a systematic fashion, the principles of Asian medicine are immediately violated. On the other hand, allowing acupuncturists to diagnose and treat each case individually produces a data set that is not amenable to rigorous analysis.

When these major obstacles have been overcome, the investigator must decide whether to use intrasegmental or extrasegmental (meridian) treatment strategies; whether to use electrical stimulation and, if so, what parameters; whether to use controls, such as treating patients at the “wrong” points; and how many treatments should be given. A more detailed discussion of these and other design issues in acupuncture research has been provided by Vincent and Richardson (10). These same criticisms are addressed by Thomas and Lundberg's (58) look specifically at low back pain. The two clinical studies mentioned above review these same complaints (61,62).

Two types of errors threaten the integrity of any treatment outcome study. The first produces a positive outcome when no real treatment effect exists in nature. Failure to control for placebo effects and unreliable measures and failure to undertake long-term follow-up can produce such outcomes. The second type is the failure to detect a treatment effect when one has occurred. Too few treatments, too small a sample size to achieve reasonable statistical power, inappropriate or insensitive measurement techniques, and failure to use a homogeneous group of patients can produce misleading negative data. These issues are discussed further in Chapter 82. An overview of the large and growing literature in this area reveals that all these errors have been made repeatedly (65). Lewith and Machin (66) have formally addressed the problem of insufficient sample size in the literature. Firm conclusions are therefore difficult to attain. It is clear, however, that acupuncture is not a panacea of sufficient strength to overcome all these problems and to demonstrate consistent and powerful effects on chronic pain.

In addition to small sample size, poor pain measurement has plagued studies of acupuncture therapy. The complexity of clinical pain measurement problems was discussed in detail by Syrjala and Chapman (67) and is presented in Chapter 15 of this volume. When pain is chronic, it is necessary to use both subjective and behavioral outcome indexes tailored to the clinical problem in question, and long-term follow-up must be carried out to determine whether lasting benefits have been obtained. The chances of spontaneous recovery from chronic pain are small by definition, but chronic pain patients can leave any given physician with the polite impression that they have been helped significantly and then go on to another in the never-ending search for a cure. When follow-up procedures such as postal or telephone inquiries about satisfaction with outcome are used, few data of value can be obtained. A rigorous review would dismiss most of the published reports on the basis of these criteria alone.

The earliest clinical studies were largely uncontrolled investigations of mixed groups of chronic pain patients (68). Some early studies used no pain measurement at all. The data consisted of scaled judgments by the therapists themselves. With time, study designs improved and more suitable but still insufficient pain measurement methods were introduced. The most thoroughly studied clinical problems have been headache and back pain.

A brief review of the field prior to 1976 was provided by Mendelson (68), and more recent reviews have been offered by Lewith and Machin (66), Lewith (65), Richardson and Vincent (69), Berman et al. (61), and Cherkin (62). The last three have provided the most comprehensive reviews to date, with particular emphasis on back pain, headache, and other musculoskeletal problems. They evaluated each of the studies critically on the basis of controls, measurement technology, and follow-up. All of the above investigators deserve credit for their attempts to extract information in a critical fashion from a weak and problematic body of literature. In addition, a few negative reports have been helpful in delimiting the range of effects of acupuncture. For example, Lewith and colleagues (70) concluded that acupuncture is ineffective for postherpetic neuralgia.

What conclusions, if any, can be drawn from the literature? In their review of the overall efficacy of acupuncture therapy, Lewith and Machin (66) concluded that a positive response is given by approximately 70% of chronic pain patients with the use of real acupuncture, whereas the positive rate for sham acupuncture controls is approximately 50% and for placebo approximately 30%. Lewith (65) reviewed the following in detail: six studies that compared acupuncture with conventional medical therapy, ten studies that compared acupuncture with random placement of needles, and two studies that compared acupuncture with placebo treatment. He concluded that acupuncture works to some degree in approximately 60% of patients with chronic pain, that the effects of acupuncture are greater than those of random needling or placebo treatment, and that acupuncture is as effective for musculoskeletal pain as other treatments such as physiotherapy or drugs. The more recent reports simply support these observations. Lewith (65) noted that acupuncture causes fewer adverse reactions than the use of opioid analgesics and antiinflammatory medications. Richardson and Vincent (69) found good evidence from controlled studies that acupuncture can provide effective short-term pain relief; the figures for effective relief range from 50% to 80% for both acute and chronic conditions. Long-range follow-up data are lacking, however, so little evidence has been found for the long-range benefits of acupuncture. Despite their positive broad conclusions, Richardson and Vincent (69) cautioned that the “placebogenic” qualities of acupuncture treatment might be greater than those of placebo treatments matched to drugs: Acupuncture in some cases might simply function as a more effective placebo than its so-called placebo control. Patel et al. (31) reviewed the literature by metaanalysis and concluded that most studies were biased, that there were other methodologic problems, and that no studies had statistical confirmation of a positive effect for acupuncture although the pooled results did. A more recent attempt to refocus clinical research and suggest methodology improvements in design was presented again by Lewith and Vincent (32). Hopefully, critical reviews will lead to an improvement in the quality of future research so a clearer picture will emerge with the recent resurgence of interest in acupuncture.

Overall, given the above reviews, acupuncture appears to have positive therapeutic benefit, but it falls far short of the claims of its zealous advocates who believe it to be uniquely powerful. How important is the lack of a rigorous scientific database? Most therapies in modern medicine, including many common surgical procedures, would appear weak if evaluated rigorously on the basis of the supporting literature—most medical practice is not derived from a systematic program of scientific research. Much has been demanded of acupuncture because it is basically a folk medicine from a health/disease concept very foreign to allopathic medicine and because strong claims have been made by its advocates.

SUMMARY AND CONCLUSIONS

More than two decades after its introduction on a large scale in the West, acupuncture remains a mystery and a point of controversy. It seems clear from the results of animal, human laboratory, and clinical studies that acupuncture stimulation (particularly electrical stimulation) can alter pain perception and relieve pains in clinical practice. The human laboratory and clinical studies are consistent, however, in showing that acupuncture stimulation offers no panacea. The effects seen are inevitably modest when large groups of subjects or patients are examined, and the collective outcomes clearly fail to support the exaggerated claims of many of the advocates of acupuncture made in the early 1970s. When the overlap of acupuncture therapy with trigger point treatment and electrical stimulation therapy is considered, it becomes questionable whether classic acupuncture merits its own identity as a therapeutic procedure in Western medical practice and research. This situation suggests a pragmatic solution to the question of how acupuncture should be regarded by the physician concerned with pain management. The following three principles are offered as guidelines.

First, acupuncture should be addressed, considered, and scientifically investigated as a method for hyperstimulation therapy, as advocated by Melzack and Wall (57) or, more specifically, as a treatment for conditions of neural degeneration/muscular pain as proposed in Chapter 28. It is not of value as a form of Chinese medicine. The practice of classical Chinese medicine is without a scientific foundation in Western medical practice, but acupuncture techniques can be beneficially used for the practice of electrical stimulation therapy, trigger point therapy, or both. Viewed in this framework, such techniques draw on a scientific rationale and on clinical databases in two or more areas. Acupuncture techniques, stripped of their mystique, offer a safe and inexpensive therapeutic alternative to writing prescriptions. They need to be regarded as an alternative form of medicine only when practiced by nonphysicians.

Practitioners interested in acupuncture therapy should broaden their focus to include TENS and trigger point therapy. TENS is relatively cheap after the initial investment in equipment and has the advantage of giving the patient control over the therapy. Trigger point therapy differs little from acupuncture when a dry needle technique or saline injection is used. Both can be relatively expensive, especially if unscrupulous practitioners arrange frequent visits over an indefinite period. Because the tips of acupuncture needles are not bevelled like those of injection needles, acupuncture is less traumatic to tissue, causes less minor bleeding, and may be somewhat less painful.

Second, the possibility that acupuncture stimulation might be related to an alteration of endorphin levels should be deemphasized in discussing such methods with patients and in considering whether a therapeutic trial with acupuncture is indicated for a given patient. The animal literature clearly shows an association of acupuncture stimulation to endorphins, but advocates of acupuncture appear to be confusing stress-induced analgesia in animals with the (presumed) stress-reducing therapy performed in a physician's office. The link of endorphin levels to chronic pain states is as yet uncertain and controversial, and it is not known whether any long-term benefit of treatment would accrue to a patient with chronic pain even if acupuncture treatment resulted in endorphin release for a short period. Future

findings could have a great impact on this conclusion. This statement is unchanged in the decade since the chapter in the second edition of this text was written, indicating that 788 citations have done little to alter our view.

Third, despite the problems and limitations of the clinical literature, it is clear that acupuncture offers little hope for a miracle cure for chronic pain problems. It is appropriate to advise patients that controlled outcome studies, although favorable, show limited and modest positive benefits of treatment overall and that insufficient information has been obtained to determine whether positive gains are lasting when pain is chronic. The literature does support claims that acupuncture is a low-risk treatment when properly performed; the cost of such treatment can be of greater concern to patients than safety since most insurance plans do not yet cover this treatment. Physicians should be alert to the possible suppression of important symptoms of disease when patients undergo acupuncture therapy for pain.

It is most unfortunate that, after more than two decades of research in this area, the literature does not permit firm conclusions to be reached about therapeutic efficacy that could be summarized in a book such as this for clinical referral guidelines. It seems clear that classically performed acupuncture remains an experimental therapy. The clinical problems for which it is and is not appropriate have only begun to be defined. It is unsettling that no consensus has emerged in regard to how acupuncture should be practiced, who are fitting patients, and how many treatments are needed. The old truism remains, however: The absence of evidence is not equivalent to the evidence of absence. Broadly speaking, acupuncture appears to help patients suffering with chronic pain, primarily musculoskeletal, and to do so at a rate greater than that of control treatments. Care must be taken when patients engage the services of nonphysician acupuncturists because symptoms of clinically significant disease might not be brought to proper medical attention. When properly practiced, acupuncture is quite safe, and it offers an alternative to the conventional, often ineffectual, treatments including invasive surgery, repeated nerve blocks, and prescription of analgesic and other medication for patients with persisting pain.

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CHAPTER 98

Transcutaneous Electrical Nerve Stimulation

Charles Chabal

BASIC INFORMATION

History

For thousands of years and across all cultures, humans have used sensory and physical modalities to relieve pain. These modalities range from relatively pleasant counterstimulation, such as massage and heat treatment, to more severe counterirritation measures, such as cauterization, bloodletting (wet cupping), deep acupressure, and some forms of acupuncture. A review of the historical development of many of these ingenious folk medicine–based treatments is provided by Kane and Taub (1). Unfortunately, this history is marred by a number of treatments based on fraud and deception, while others have outcome measures that are difficult to separate from nonspecific treatment or placebo effects. Nevertheless, the unmistakable ability of counterstimulation and counterirritation to relieve pain for at least the duration of treatment is obvious to anyone who has taken a hot soak or shower to relieve aching muscles or placed his or her thumb under cold tap water after striking it with a hammer. The modern era of electrical stimulation of the skin for the relief of pain has an ancient heritage. In classical Greece, the electrogenic torpedo fish was imported from the Nile River and used to treat headaches and joint pains (1). In the Renaissance, electrostatic generators and Leyden jar condensers were used by physicians and charlatans alike to treat a wide array of ailments, including pain. When the electric battery was invented in the nineteenth century and the automobile spark coil at the turn of the century, a plethora of pain treatment devices were manufactured. Some of these were still used after World War II, but the dawn of the Sputnik era and solid-state miniaturized electronic circuits saw an explosion in the application of electrical stimulation for pain relief. This development was, of course, also facilitated by Melzack and Wall's gate theory, published in 1965. It should not, therefore, be surprising that science has at least provided a partial basis and explanation of the mechanisms and pathways involved in these pain-relieving treatments. This chapter focuses on the physiologic basis and mechanisms of transcutaneous electrical nerve stimulation (TENS) and applications in both acute and chronic pain conditions.

Theoretical Bases for Effect

All afferent nerve fibers seem to have the capacity to influence the activity of other afferent nerve fibers, mainly through mutual presynaptic inhibition (2). Based on results from animal experimentation as well as on clinical observations, Melzack and Wall (3) described, with later anatomic-histologic evidence from Kerr (4), a "gate" to sensory input. Located in the dorsal horn of the spinal cord, it is opened by activity in small-diameter nociceptive afferent nerve fibers that facilitate nociceptive transmission and closed by activity in large-diameter nonnociceptive mechanoreceptive nerve fibers, thereby reducing the transmission of nociceptive impulses. Although some aspects of the gate theory have been criticized (5), experimental and clinical evidence has supported the ability of both nonnoxious and noxious stimuli to temporarily inhibit transmission from small-diameter afferent nerve fibers to second-order neurons in the spinal cord.

If graded electrical stimuli are applied to a mixed nerve, whether buried in tissue or not, the first fibers to become activated are the large-diameter ones (6). It is thus possible to induce a substantial but nonpainful barrage of impulses selectively in large afferent fibers with a small, relatively uncomplicated current generator. The first clinical report using electrical stimulation to relieve chronic pain soon followed the publication of the gate theory (7). In fact, early research demonstrated, consistent with the gate theory, that other forms of peripheral stimulation such as vibration were very effective in reducing the perception of pain (8,9,10 and 11). The subsequent focus of research and commercial development on peripheral electrical stimuli in the form of TENS was largely related to the technological limitations and poor efficiencies of other applied peripheral forms of mechanical counterstimulation. Transcutaneous electrical stimulators are simple to build, highly portable, and relatively energy efficient. Mechanical vibratory stimulators are not.

The functional arrangement of large-diameter afferent fibers, mainly A-b fibers, is largely segmental and therefore requires that nonpainful counterstimulation, often in the form of paresthesias, be directed into the painful region of the body. In contrast, painful counterirritant therapies produce effects that are extrasegmental in nature and need not be applied directly to the painful region of the body. As a result of this neural organization, several different patterns of TENS stimulation have emerged. High TENS, also called *conventional TENS*, uses a nearly continuous high-frequency stimulation (60 to 100 Hz) and a relatively low-intensity current (10 to 30 mA). In conventional TENS, the electrodes are placed in the painful region of the body and the current is adjusted upwards until paresthesias are obtained. Some practitioners prefer increasing the intensity until mild muscle stimulation occurs. It is likely that the mechanism of action for conventional TENS involves gating of nociceptive fibers by stimulation of the large A-b afferents, as the effect appears to be resistant to the mu receptor antagonist, naloxone (12,13), and clinical success is correlated with the proper placement of the stimulating electrodes within the painful area of the body (14). In conventional TENS, increasing the intensity of stimulation by increasing stimulator pulse width, frequency of stimulation, or both will recruit more inhibitory pain fibers and theoretically increase the effect of TENS (15,16).

In contrast, low-frequency TENS, also called *acupuncturelike TENS*, uses burst patterns of 100 Hz in 1- to 2-Hz pulses at a high-intensity level (20 to 50 mA) or until a painful muscle twitch is elicited (7). Location of the stimulus is not necessarily limited to the painful region of the body, and the effects of low TENS are reversed by naloxone, suggesting that the effects are mediated through endogenous opioid receptor activity (12). Some studies have reported successful pain treatment with acupuncturelike TENS in patients who have not obtained pain relief with conventional TENS (17,18).

Experimental Evidence

There is solid evidence that the theoretical model of neuronal modulation within the spinal cord, demonstrated in the physiology laboratory, also occurs in humans. Using a human experimental pain model, TENS significantly increased the subjects' pain tolerance, with the effects most evident at higher stimulation frequencies (60 Hz) (19). Studies done under controlled conditions indicate that TENS, when applied over trigger points, reduces the report of pain associated with the trigger points. This effect is not due to local changes in trigger point sensitivity but is more likely related to central nervous system modulation (20). Better effects were obtained using conventional TENS (100 Hz); increasing efficacy was noted as the stimulation pulse width increased from 50 to 100 milliseconds at an intensity just at muscle stimulation threshold. Little effect was seen with acupuncturelike TENS (20). Indeed, patients often report that properly applied TENS produces an area of reduced skin sensitivity or numbness, consistent with the experimental findings.

The effectiveness of TENS in humans is further supported by a well-designed, well-controlled study in patients with low back pain of a variety of etiologies (21). Treatment sessions consisted of 30-minute experimental treatments twice a week for 10 consecutive weeks. In this study, conventional TENS (100 Hz and intensity set to produce a paresthesia) produced a significant reduction in pain over the short term when compared to placebo-TENS and a control group. The effect of TENS appeared cumulative and was present for up to 1 week after treatment was concluded. Similar results were not seen in the placebo-TENS or the control group. Consistent with experience from other analgesic trials, placebo-TENS also produced a significant reduction in some aspects of reported pain when compared to baseline measures, but the effects were statistically less than those produced by actual TENS treatment. There is also evidence that TENS may have effects apart

from simply gating nociceptive afferent impulses. In a number of studies, TENS has been shown to produce an increase in blood flow to the region of stimulation, indicating that the effect of TENS may not be limited to pain modulation (22,23 and 24). In conclusion, there is ample basic research that indicates neuronal modulation of nociceptive impulses occurs. There are also well-designed studies that indicate that TENS produces significant analgesia when compared to placebo treatments under short-term controlled conditions.

CLINICAL INFORMATION

Treatment of Acute Pain

TENS has been used very successfully for the treatment of acute pain. A significant literature evaluates the effect of TENS in a number of acute pain conditions. Many of the studies have been done using well-designed methodology. TENS has been successfully used to treat postoperative pain after a variety of surgical procedures (25,26), after trauma such as a fractured rib (27), a variety of oral-facial pains (28,29), and the pain associated with parturition (30,31). Many studies have measured not only the effect of TENS on pain but have included other outcomes such as pain medication use, measures of respiratory function, and incidence of postoperative complications such as ileus and atelectasis. Ali et al. (32) examined pulmonary function in 40 patients after cholecystectomy. Patients treated with TENS had significantly improved vital capacities and functional residual volumes when compared to patients who had not received TENS or had received a placebo-TENS unit. Similar improvements in peak expiratory flow rates and arterial oxygen concentration have been associated with TENS use in patients with multiple rib fractures after trauma (27). Conventional TENS has also been shown to reduce pain and opioid analgesic use in patients after major intraabdominal procedures (33,34 and 35) and orthopedic procedures (36) and to enhance postoperative rehabilitation in orthopedic patients (37). Other studies, while confirming the reduction of postoperative opioid use, failed to demonstrate an improvement in pulmonary function (38).

TENS has also been used to treat pain associated with labor (31,39). In these controlled studies, TENS produced moderate to good relief of back and abdominal pain in the first stage of labor. Pain relief associated with later stages of labor seems to be less amenable to treatment with TENS. An additional concern in the later stages of labor is related to the potential for TENS to interfere with some aspects of fetal monitoring.

TENS use after trauma, in the early stages of labor, or in the postoperative period is effective at reducing pain and may improve some objective measures of function. While, in most cases, TENS alone is not adequate as the sole analgesic treatment, it should not be overlooked as an adjunctive treatment for acute pain. TENS, unlike drugs such as nonsteroidal antiinflammatory drugs (NSAIDs), is virtually free of complications yet may significantly reduce pain of the postoperative period.

Long-Term Treatment of Chronic Pain

The effectiveness of TENS for the treatment of chronic pain is an area of controversy. The results have not been as consistent as laboratory-based or postoperative studies. The reasons for this controversy are multifactorial, related to a number of problems inherent in the design and execution of any complex clinical trial, and well discussed by Marchand et al. (21) and Deyo (40). In brief, outcome measures such as pain relief must be sensitive enough to detect small but clinically significant changes. For example, studies indicate that even powerful opioids produce only small changes in reported pain when used chronically in clinical pain trials, thus requiring very precise pain assessment techniques. In addition, any intervention has significant nonspecific effects including placebo; thus careful controls are an essential part of any study (see Chapter 81 and Chapter 82). The ability to design an active placebo control is particularly difficult in a treatment such as TENS that relies on the requirement of the patient to generate, with the TENS device, a distinct and sometimes strong paresthesia into the painful region of the body. Most trials use an inactive placebo-TENS device and suggest to the subject that he or she will feel a paresthesia from the placebo device. The suggestibility of subjects who endorse physiologically absent symptoms may produce a bias towards placebo-responding subjects and skew treatment groups. Alternatively, a placebo treatment may produce a real clinical effect resulting in confusing data. Table 98-1 summarizes a variety of experimental design issues that have often been inadequately addressed in long-term TENS outcome studies.

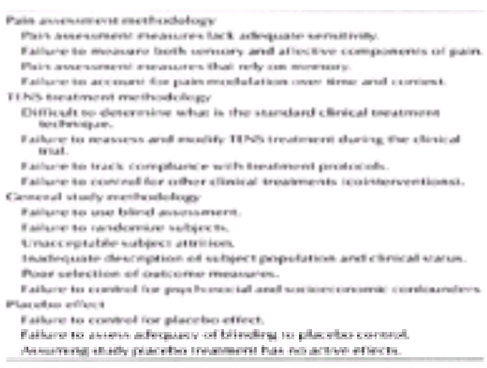
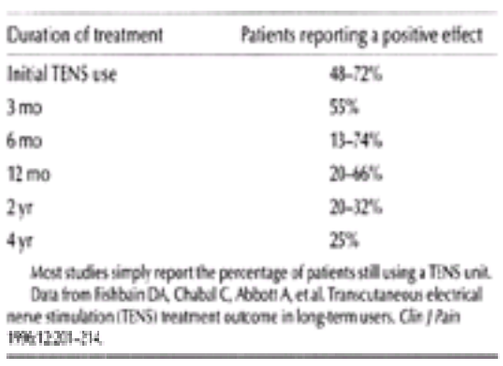

Pain assessment methodology
Pain assessment measures lack adequate sensitivity.
Failure to measure both sensory and affective components of pain.
Pain assessment measures that rely on memory.
Failure to account for pain modulation over time and context.
TENS treatment methodology
Difficult to determine what is the standard clinical treatment technique.
Failure to reassess and modify TENS treatment during the clinical trial.
Failure to track compliance with treatment protocols.
Failure to control for other clinical treatments (cointerventions).
General study methodology
Failure to use blind assessment.
Failure to randomize subjects.
Unacceptable subject attrition.
Inadequate description of subject population and clinical status.
Poor selection of outcome measures.
Failure to control for psychosocial and socioeconomic confounders.
Placebo effect
Failure to control for placebo effect.
Failure to assess adequacy of blinding to placebo control.
Assuming study placebo treatment has no active effects.

TABLE 98-1. Study design and methodologic considerations relevant to long-term transcutaneous electrical nerve stimulation (TENS) outcome trials

Over 600 articles on TENS have been published since 1970 (41). TENS has been reported as a successful treatment for a variety of neuralgias and neuropathic pain syndromes, peripheral vascular disease, chronic angina, and musculoskeletal pain. Long and Hagfors (42), Long (43), and Fishbain et al. (41) have provided comprehensive reviews of the long-term outcomes of TENS treatment. In 1991, Long (43) concluded that the literature indicated that TENS was an effective treatment for a pain from diverse etiologies, that TENS has a short-term benefit in about 50% of patients who suffer from chronic pain, that about 25% of patients will use TENS for many years, and that the effect of TENS cannot be explained simply as a placebo effect. The results from the review by Fishbain et al. are presented in Table 98-2. The compiled data indicate that a significant subset of TENS patients prescribed TENS continue to use their TENS unit for many months. From this set of studies it is difficult to conclude any impact on physical function, adjunctive medication use, or quality of life.



Duration of treatment	Patients reporting a positive effect
Initial TENS use	48–72%
3 mo	55%
6 mo	13–74%
12 mo	20–66%
2 yr	20–32%
4 yr	25%

Most studies simply report the percentage of patients still using a TENS unit.
Data from Fishbain DA, Chabal C, Abbott A, et al. Transcutaneous electrical nerve stimulation (TENS) treatment outcome in long-term users. Clin J Pain 1996;12:201–214.

TABLE 98-2. Synopsis of studies reporting the long-term use of transcutaneous electrical nerve stimulation (TENS) for chronic pain

A few long-term TENS studies have examined outcome variables other than pain relief. One study associated TENS use with increased socialization (19) and one with better sleep (44). Another study compared activity levels between a TENS treatment group and a non-TENS control group (45). The TENS treatment group showed a significant increase in activity as compared to the control group. There was no difference in analgesic medication use between the two groups at 1-year follow-up. A number of studies report that long-term TENS use helps reduce the consumption of pain medications (18,44,46,47 and 48). Most recently, in a survey of over 500 long-term TENS users, Fishbain et al. (41) reported that long-term TENS use was associated with a reduction in opioid analgesics, NSAIDs, sedative hypnotics, and steroid medications. These same patients also reported a significant reduction in pain's interference with work, home, and social activities; an increase in physical activity; and a reduction in use of physical occupational therapy resources. A cost outcome simulation done with these data at 6 months of TENS use

reported a significant reduction in the cost of pain-related medications and therapies associated with TENS use (49).

Perhaps one of the best designed studies on TENS use in chronic low back pain patients was reported by Deyo et al. (50). One hundred forty-five patients with chronic back pain (mean duration, 4.1 years) were divided into one of four experimental treatment groups: (a) daily TENS, (b) sham TENS, (c) TENS plus exercise, and (d) sham TENS plus exercise. Subjects were treated for 1 month. Both TENS and sham TENS treatment groups showed an improvement in pain outcomes. Exercise seemed to produce the greatest benefit, but by 2 months after the active study, most patients had discontinued their exercise program. The authors concluded that TENS had no greater benefit than placebo and that TENS added no benefit to exercise alone. The study has had a significant impact on the way many providers view TENS as a useful clinical treatment. However, the widespread extrapolation of these results to the realm of clinical care has been cautioned (51). An editorial in *The Lancet* offered a number of representative comments (52). The study maximized the effect of the placebo treatment; the relatively short study duration was not adequate to show an effect of active treatment; the treatment approach with active TENS was somewhat unconventional and not commonly used in clinical practice; and all treatment groups used hot packs and heating pads, which may have confounded the results of the study. Others have offered that pain assessment was done over short intervals and may not reliably measure true effects of treatment (21). In conclusion, a large body of literature evaluates long-term TENS use for the treatment of chronic pain, but valid conclusions are limited by a number of complex methodologic considerations (see Table 98-1). While TENS, like any other medical intervention, is associated with nonspecific effects, the numerous clinical reports of patients using TENS for many months indicate that for at least some patients, TENS is a useful treatment with effects that surpass those of placebo.

TECHNIQUES

Predictors of Use and Maximizing Effectiveness

Numerous studies attempt to predict success or failure of TENS therapy based on either patient characteristics or parameters of the TENS intervention, such as waveform and pulse duration. No patient physical predictors appear to be of substantial value. Nor do most of the technical considerations of the electrical impulses appear to have predictive value. Experience indicates that TENS has been used successfully in many different conditions. Depression, overwhelming psychosocial distress, and overt psychiatric problems increase the likelihood that TENS will be ineffective (53,54). In any of these instances, the underlying psychosocial problems need to be addressed and the patient must be making improvement prior to instituting TENS treatment.

Most experts endorse a TENS trial to evaluate the effectiveness of treatment prior to having the patient purchase a device (55). The optimal nature and duration of the trial are vague, usually depending on individual provider preference, and can range from 1 hour to several weeks and has changed over the years. In the past, some providers actually admitted patients to the hospital for such trials. In general, an evaluation is done in which a provider, often a physical therapist, uses a temporary spotting electrode to evaluate TENS electrode placement. This maneuver, based on the evidence that large-diameter afferent inhibition occurs at a segmental level, attempts to produce stimulation, most often paresthesias, in the region of the body that has pain. Experience from spinal cord stimulation supports the concept that for effective treatment to occur, one must be able to produce paresthesias in the anatomic region of pain. If this cannot be done, it is unlikely that conventional TENS will be of much benefit, and a trial of acupuncturelike TENS may be warranted. If after a period of successful treatment, a patient notes that his or her TENS no longer helps, it is usually worth reevaluation of the electrode placement to again maximize the effectiveness of the TENS treatment.

Patients should be educated and their expectations addressed prior to TENS treatment. They should be taught the theoretical basis of TENS treatment, that TENS effects are similar to those of a mild analgesic, and that pain will not usually be totally abolished with TENS use. They should be told to use the device at least several times per day, and alternative use strategies should be offered. Alternative use strategies include using the TENS only during particularly painful times such as riding in an automobile, only as a sleep aid, or to include TENS holidays, which may reduce tolerance to TENS effects. It is inappropriate to offer derogatory comments about TENS treatment or to use TENS treatment as an alternative to a more comprehensive approach in a patient with overwhelming psychosocial distress.

Technical Issues

Stimulator Selection

TENS stimulators are miniaturized current generators that produce a constant current and are usually powered by rechargeable batteries (Fig. 98-1). The constant current amplifier prevents surges in supplied current from changes in skin impedance. TENS devices now are approximately 10 × 5 × 3 cm. Further miniaturization would probably make the units, especially the controls, difficult for patients to handle. Stimulators have one or two separate output channels, the latter type being more versatile but also more expensive. The stimulation intensity and frequency are set by external dials, separate for each channel, and preferably linear with respect to output. A new version of a TENS unit has been approved for use (Fig. 98-2). This unit requires patients to turn the unit on and off by indicating their pain level on an electronic visual analogue scale. The device records patient use and treatment effects, which are later accessible to the health care provider (Empi Inc., Minneapolis, Minnesota).

Figure 98-1. Transcutaneous electrical nerve stimulation (TENS) unit with adjustments for impulse stimulation width, mode of stimulation, and rate of stimulation. Patients are taught how to adjust their own units to produce optimal pain relief. On the far left is a typical TENS electrode. On the near left is a temporary spotting electrode. The spotting electrode is used to locate the optimal placement of the conventional TENS electrode.

Figure 98-2. Transcutaneous electrical nerve stimulation (TENS) unit showing two stimulation channels with adjustment dials. The dials control the intensity of stimulation of the TENS unit. Patients are instructed to increase the intensity of stimulation until they feel paresthesias (conventional TENS) or until direct muscle contraction occurs (high-intensity TENS). The optimal stimulating parameters for any given patient are often determined by a series of trials and assessments.

Available stimulation modes should include single pulses between 30 and 100 Hz (variable) for conventional TENS and short trains of pulses that can be delivered at

a 1- to 2-Hz repetition rate for acupuncturelike TENS. In two-channel units, it is an advantage if the mode can be independently varied for each channel. Most patients prefer units with rechargeable batteries. For safety reasons, patients should not be able to treat themselves while a unit is being charged.

Stimulation Frequency

Most patients seem to prefer a stimulation frequency of 80 to 100 Hz with conventional TENS and 1 to 2 Hz with acupuncturelike TENS. To avoid unpleasant sensations from too high a stimulus intensity, stimulators with a burst mode should be used for acupuncturelike TENS to elicit muscle contractions. This burst may be a short impulse train of seven to ten pulses at a 100-Hz internal frequency applied to a 1- to 2-Hz repetition rate (17) (Fig. 98-3).

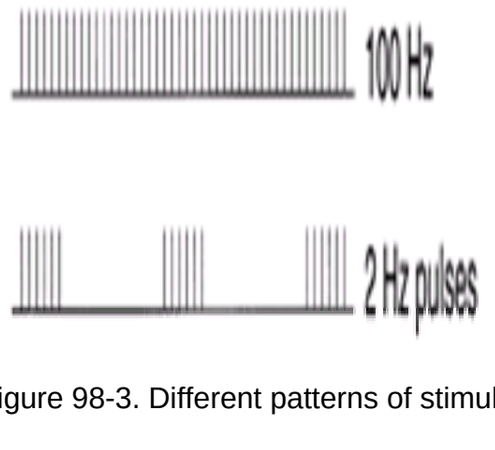


Figure 98-3. Different patterns of stimulation. **A:** Conventional transcutaneous electrical nerve stimulation (TENS). **B:** Acupuncturelike TENS.

Pulse Characteristics

For any type of nerve fiber, a strength versus duration curve can be plotted indicating which current intensity is needed to activate the fiber at a given stimulus duration. To elicit electrical paresthesia for the relief of pain, most patients prefer a pulse duration of 0.05 to 0.15 milliseconds, which is in the same range as that considered optimal for activation of large myelinated fibers in experimental situations (56). These and other experimental data strongly suggest that a monophasic square wave of 0.05 to 0.20 milliseconds is sufficient (and optimal) for both conventional and acupuncturelike TENS.

Biphasic pulses are not necessary to avoid polarizing phenomena due to the capacitive components of the skin. The current generator should be calibrated and be of the constant-current type, which compensates for the large variations occurring in the electrode-skin-electrode impedance. A current output of 50 mA per channel into a 2,000-W external load is necessary to activate deeply situated nerve bundles (e.g., the sciatic nerve), whereas superficially situated nerves in the facial region or distally in the extremities require less energy. Constant-voltage generators are less suitable, because the stimulation may be rendered ineffective if the impedance is unexpectedly high for a given output setting (57).

Electrodes

The electrodes are usually made of conductive rubber containing carbon and have a life span of 4 to 6 months in normal use. This material has a suitable internal resistance that produces an even current distribution over the electrode surface. The size of the electrodes—representing a compromise between the demand for current density and the risk of skin irritation—is usually 10 to 15 cm^2. Larger electrodes may be advantageous when distinct nerve bundles cannot be stimulated (e.g., with pain in the back or abdomen).

A thin layer of conductive gel is put between the electrode and the skin to facilitate contact. The electrodes are attached to the skin with hypoallergenic tape. A more expensive and short-lived alternative is self-adhesive electrodes made from conductive karaya rubber or synthetic substitutes, which eliminate the need for conductive gel and tape.

Selection of Treatment Parameters

Conventional TENS is the mode of choice in neuralgia, causalgia, and dull continuous pain referred to the skeleton (spine, joints, ribs) whether from arthrosis, cancer, or muscular origin. It should also be tried in central pain states. This mode of stimulation should always evoke electrical paresthesia in the painful area. Activation of most of the large afferent fibers requires an intensity two to three times that at the threshold for sensation, usually 10 to 30 mA with standard-size electrodes. Stimulus frequency should also be kept constant initially at 80 to 100 Hz. Later it can be varied according to the need and preference of the patient.

In some patients, the pathologic condition or previous treatment has destroyed the peripheral or central afferent pathways to the extent that a marked hypesthesia is present and electrical paresthesia cannot be elicited by conventional TENS. Acupuncturelike TENS should be tried whenever conventional TENS does not give satisfactory pain relief. In addition, it is the primary choice in projected pain such as radiculopathy (sciatica) and in deep pain such as in myalgia. A positive effect with this mode requires elicitation of forceful muscle contractions in the myotomes segmentally related to the painful area. Often, a stimulus strength three to five times that at the sensory threshold, commonly 15 to 30 mA, is required to produce muscle contractions. Stimulation must produce *visible* muscle contractions to be effective. The stimulation should be started with a set repetition rate (e.g., 1.5 Hz), and the patient is allowed only to modify it later after increased experience. If the stimulation causes discomfort before muscle contractions, the electrode positions should be adjusted slightly. The patient may feel muscle stiffness after the first few treatments, but this vanishes within a few days.

CONTRAINDICATIONS AND SIDE EFFECTS

TENS units should not be used in patients with cardiac pacemakers, as it is feared that the electrical impulses generated by the TENS unit will inhibit the function of the pacemaker. TENS electrodes should not be placed over the carotid arteries because of the risk of stimulating the carotid sinus reflex and causing bradycardia and hypotension. The most common and nearly only side effect of TENS is skin irritation under the sites of the stimulating electrodes. This is best resolved by changing the type of electrode, periodically moving the stimulation site, or using a different type of electrode gel.

CONCLUSIONS

Clinical TENS treatment is based on sound physiologic and experimental principles with strong support from a number of clinical studies. The positive effects of TENS are well defined in the acute pain setting but less clear-cut in the treatment of chronic pain conditions. Some of the confusion surrounding the role of TENS in treating chronic pain is due to the fact that TENS is not a powerful intervention. It is best described as a moderately effective, adjunctive analgesic on the order of an NSAID or very-low-dose opioid. Given these limitations, TENS is best viewed as a palliative component in a more comprehensive approach to chronic pain. However, TENS, unlike many analgesic medications, is totally free of side effects such as gastrointestinal distress, coagulopathies, and hepatic and renal toxicity. It is a useful component of comprehensive pain management.

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CHAPTER 99

Peripheral Nerve Stimulation

Jan M. Gybels and Bart J. Nuttin

BASIC INFORMATION

History

Two periods can be distinguished in the history of chronic stimulation of peripheral nerves (PNs) for pain relief using implanted devices. A first period started in 1967, when Wall and Sweet (1), to test in humans the prediction of the gate-control theory, showed that PN stimulation (PNS) could produce hypalgesia and could cause temporary abolition of clinical chronic pain outlasting briefly the duration of the stimulation. There was some initial enthusiasm, but variable results and the lack of commercially available adequate electrodes reduced interest in PNS. Subsequent attention was directed mainly to the development of spinal cord stimulation (SCS). The 1980s saw a second period of development of PNS with the advent of improved equipment, particularly the introduction of flat electrodes with several contacts (Resume by Medtronic, Inc., Minneapolis, MN), better surgical techniques, and, in at least one series, improved outcome studies.

Mechanisms of Pain Relief by Peripheral Nerve Stimulation

The mechanisms of effective pain relief are uncertain and many theories have been proposed. We discuss the more accepted hypotheses only.

At the peripheral level, it has been demonstrated that electrical stimulation can induce a peripheral blockade of nociceptive afferents (2). In pathologic situations such as nerve injury, such a blockade might become particularly significant: Among the physiologic properties of experimentally produced neuromas, spontaneous ongoing activity in both A and C fiber afferents is a common feature. It has been shown that a short period of repetitive electrical stimulation of the nerve in which a neuroma has been produced at a strength above threshold for the single fiber under study may completely stop the ongoing discharge for several minutes (3).

The pain-suppressive effects of PNS have also been explained by central mechanisms. Most attention has been paid to inhibitory mechanisms in the dorsal horn. It is on the basis of this aspect of the gate-control theory that the modern era of PNS for pain relief was initiated (see Chapter 4). There is experimental evidence in the intact animal that prolonged inhibition of spinothalamic tract neurons can be obtained by PNS (4). This inhibition was also observed in spinalized animals, indicating that it must depend in part on spinal cord neural circuitry. The A-d fiber group was most important for producing this inhibition, although significant additional effects were also produced by activation of the A-ab and C fiber group (4). Both from an experimental and clinical point of view, there is clear evidence that PN lesions induce profound changes centrally that may themselves be instrumental in producing pain, but there are no data available on how those central changes are modulated by PNS. We know, however, from recent work that tactile allodynia in a rat model of mononeuropathy involves a gamma-aminobutyric acid (GABA)–ergic mechanism and that SCS may operate by upgrading the spinal GABA-ergic system. The potential of SCS for producing pain relief is dependent on the availability of responsive GABA-containing inhibitory interneurons (5). It has become increasingly clear that different pathophysiologic mechanisms are involved in painful sequelae of nerve injury, and therefore one cannot expect that PNS will influence these painful sequelae in a uniform way.

It is somewhat amazing that in recent years much has been learned about the pathophysiology of damaged PN (6) but that the influence of electrical stimulation of the nerve on these pathophysiologic mechanisms has not yet been examined.

Advantages versus Disadvantages

PNS is a method of pain relief that does not require damage to the nervous system. It is therefore more acceptable to most patients and their referring physicians than an ablative procedure. PNS permits stimulation of the involved nerve without spread of paresthesias to the opposite side of adjacent body regions. A major advantage of PNS over SCS is that with an epidural percutaneously placed electrode, delayed electrode migration is a possibility and paresthesias may change both in intensity and topography with movement of the spine. Especially with an electrode placement in the cervical spine, it may be difficult to overlap the painful area with paresthesias, particularly when the painful area is only a specific part of the hand or the foot. Direct application of an electrode to a PN obviates this problem.

Disadvantages of PNS versus SCS are the following:

- When the electrode is placed over a mixed nerve, paresthesias can be accompanied with movement, but with a correct placement and appropriate parameters of stimulation this is rare.
- Scarring can occur around the nerve, even leading to neuropraxia, but with current techniques this has become exceptional.
- PNS requires a formal surgical procedure to place the electrode on the nerve; this is somewhat more invasive than percutaneously placed SCS but not more so than using an electrode that requires a laminotomy.

CLINICAL INFORMATION

Patient Selection Criteria

Figure 99-1 represents a treatment algorithm for peripheral neuropathic pain as proposed by Levy at a consensus meeting in 1996 (7). In this algorithm, PNS is recommended for peripheral neuropathic pain when noninvasive treatment modalities have failed in a patient with neuropathic pain in the territory of a single proximal or mixed nerve, provided there is no psychologic contraindication and there is a favorable response to an appropriate screening test. Almost all authors agree that when a neuromodulation procedure is indicated, pain in the distribution of a single traumatized PN is the optimal indication for PNS (Table 99-1 and Table 99-2).

Figure 99-1. Treatment algorithm: peripheral neuropathic pain. (DBS, deep brain stimulation; DREZ, dorsal root entry zone lesions; IT MS, intrathecal morphine sulfate; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation.) (Reproduced from Levy RM. Algorithms for treatment of neuropathic pain syndromes. In: North RB, Levy RM, eds. *Neurosurgical management of pain*. New York: Springer-Verlag, 1997:337–339, with permission.)

When transcutaneous stimulation of the nerve is not a feasible option (nerve too deep, patient too fat, or reaction of the skin to the applied material), temporary stimulation with an implanted electrode connected via percutaneous leads to an external stimulator is a useful method of providing the patient with a stimulation trial. This avoids the cost of an implanted receiver or pulse generator while the patient determines if good pain relief can be achieved. At a later date, the percutaneous leads can be removed and the electrode connected to either a radiofrequency (RF) coupled passive device or an implanted pulse generator. Externalized leads do increase the risk of infection.

The predictive value of a local anesthetic nerve block as a selection criterion has been advanced by some (1) but found ineffective by others (8). It is probably fair to state that although pain relief with nerve blockade does not ensure a good pain-relieving effect with PNS, continued pain despite a technically adequate nerve block makes it very unlikely that stimulation of the same nerve will be successful(9).

Implantation Technique

Different materials for chronic PNS in humans have been described, which can be either a fully implantable device or an RF-coupled system (Fig. 99-2). A permanent stimulator should be implanted only after a successful trial screening with an implanted electrode. Implantation of the electrode can be performed either under general, local, or wake-up anesthesia. Using one of the two latter types of anesthesia, in combination with intraoperative stimulation via the electrode, the position of the electrode in relation to the nerve may be optimized. No tourniquet is used. The electrode is implanted in close contact with the nerve (median, ulnar, radial, tibial, or common peroneal nerve or brachial plexus) proximal to the lesion (10).

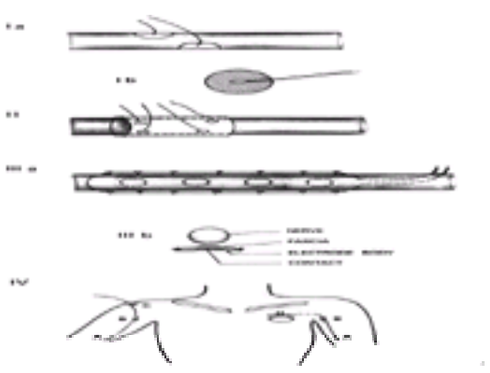

Figure 99-2. Different techniques for electrical stimulation of peripheral nerves in humans. **Ia:** Multicontact electrode directly sutured to the peripheral nerve (12). **Ib:** Platinum-iridium button electrode. **II:** Multiple-button cuff electrode (Avery Laboratories) (13). **IIIa:** On-point electrode Model 3987 (Medtronic, Inc.) sutured to the surrounding tissues underneath the nerve. A fascial flap is placed between the nerve and the electrode. **IIIb:** Transverse section through the nerve and the electrode at the level of an electrical contact. **IVA:** Electrode implant on median nerve. **IVB:** Connection between the electrode and the temporary percutaneous wires or the permanent extension cable. **IVC:** Percutaneous wires fixed to the skin with a suture. **IVD:** Implanted stimulation device.

If a plate electrode (On-point, see Fig. 99-2) is used, a fascial flap of 1 cm by 5 cm can be harvested (11). The fascial flap is sewn over the plate with multiple interrupted sutures, avoiding wrinkles. The flap prevents direct contact between the electrode and the nerve and can be compared with dura mater between electrode and spinal cord in SCS. In spite of the manufacturer's recommendation, it is not certain that this fascial flap is really necessary. The nerve is dissected free over a distance corresponding to the length of the electrode, with interruption of major vascular supply carefully avoided. The electrode itself is sutured to the surrounding tissues underneath the nerve.

A cuff electrode is usually not covered with fascia and the cuff diameter is adjusted to the nerve diameter. The authors have no experience in suturing the electrodes directly onto the nerve (12). Rubbing of the nerve against the electrode body as it progresses toward the extension cable should be prevented. Watching the nerve-electrode-complex during movement of the nearby joints before closure of the wound can point to traction on the electrode, which could potentially dislocate the contacts and/or injure the nerve.

A second incision is made proximal to the first incision above the nerve to allow space for the connector between the electrode and the percutaneous wires. In between both incisions the lead wire is placed in a subcutaneous tunnel. The percutaneous wires are also laid in a subcutaneous tunnel and leave the body at a distance from this second incision and also as far as possible away from the future subcutaneous tunnel for the permanent extension cable (see Fig. 99-2). The wires are connected to an external stimulator.

Implantation of a permanent pulse generator is usually done under general anesthesia but can also be performed under local. The percutaneous wires are removed and a permanent extension cable is connected to the electrode and is tunneled subcutaneously to a subcutaneous pocket, usually located in the infraclavicular region for the upper extremity or lower abdominal wall or lateral thigh for the lower extremity. There it is connected to the permanent power source, which can be either a fully implantable device or a radiofrequency coupled system. In the case of tibial nerve stimulation, the power source can be implanted subcutaneously in the lateral part of the thigh. If stimulation of the common peroneal nerve is considered, the stimulating device may be implanted just caudal to the iliac crest. It is important not to place the pulse generator or RF receiver over an osseous structure to avoid mechanical pain.

Results

Table 99-1 (8,9 and 10,13,14,15,16,17,18,19,20,21,22,23 and 24) summarizes the published results of PNS obtained with a permanent implant for the treatment of persistent pain. Most of the patients have suffered from chronic pain after a PN or root injury. The outcome (50% or more) pain relief is only approximately correct, as the different authors do not always report their results in this fashion, but obviously the criteria for “success,” “good” results, and “50% or more” pain relief are often inadequately specified (25). Most of the reports cited in this table present retrospective, uncontrolled, and incomplete data from a group of selected (and nonrandomized) patients. However, most of the data come from respected authors with a well-established reputation in the field of neurosurgical treatment of persistent pain. The absence of randomized clinical trials is not unique.

TABLE 99-1. Results of peripheral nerve stimulation

Of particular interest is the study of Hassenbusch et al. (24) because it is a prospective study of a consecutive series of 32 patients who were tested and of whom 30 (90%) were treated with an implanted PN stimulator.

Using clinical criteria, all patients were classified as having stage III reflex sympathetic dystrophy and according to the authors might be considered as having complex regional pain syndrome type II (see Chapter 20). Outcome criteria were quantified and included pain relief (spontaneous and evoked), physical changes (vasomotor tone, motor strength, trophic changes), and activity levels (employment, walking stairs, sleeping, eating). The most recent evaluation was conducted by a disinterested third party. Overall, 19 (63%) of 30 patients experienced good or fair relief on a consistent basis. Six (20%) of the 30 patients undergoing PNS placement returned to part-time or full- time work after being unemployed before stimulator implantation. Follow-up in these patients was 2.2 ± 0.6 years postimplantation.

In 1990, we published our results of treatment of pain due to nerve injury by electrical stimulation of the injured nerve (26). These results were obtained in 11 consecutive patients in whom a device was implanted between 1980 and 1987 and who were invited for follow-up examination in 1987.

The relevant clinical data at the time of operation are summarized in Table 99-2. The mean follow-up was 52 months (range 13 to 92). PNS was usually considered after a long period of unremitting and intractable pain.

TABLE 99-2. Long-term results of peripheral nerve stimulationpersonal series

After a successful trial with transcutaneous electrical nerve stimulation (TENS) applied to the involved nerve in cases one through ten, the procedure for stimulator implantation was carried out, usually under local anesthesia. A Silastic cuff with four electrode contact points (Avery) was wrapped carefully but not tightly round the nerve. In the 10 upper limb cases, the electrode was implanted at the level of the nerve trunk in the upper arm whereas, in the femoral nerve case, the electrode was implanted in the lesser pelvis— that is, always proximal to the site of the injury. The receiver (Avery) was placed in the subcutaneous tissue over the pectoral muscle or in the abdominal wall. The patients were able to control intensity and rate of stimulating current themselves. No specific instructions were given about the duration and frequency of use.

At the follow-up examination in 1987, the patients were asked to fill out a questionnaire. A visual analogue scale was used to quantify the intensity and degree of unpleasantness of the remaining pain, compared with the situation before the operation. The patients were asked about actual use of analgesics or other pain therapy, professional and daily activities, and modalities of use of the PNS device (intensity and rate of the current, frequency, and duration of use) and if the elicited paresthesias were still felt in the painful area. Clinical examination included sensory testing (cotton wool, pinprick, two-point discrimination, 128-Hz vibration, and joint position) without and during stimulation. In some patients quantitative testing for allodynia was performed during and without stimulation, as is shown in the following example. Patient 2 from Table 99-2 developed pain and allodynia in the stump and ulnar side of the left ring finger after an amputation of the distal phalanx of the left little finger. The patient's most important complaint was allodynia to thermal and mechanical stimulation. We ultimately treated her with an implanted PN stimulator, which she now has used for more than 12 years. She stimulates four to five times a day for 20 to 30 minutes and that completely relieves the pain and allodynia. The effects of nerve stimulation on the thermal and mechanical allodynia are shown in Figure 99-3.

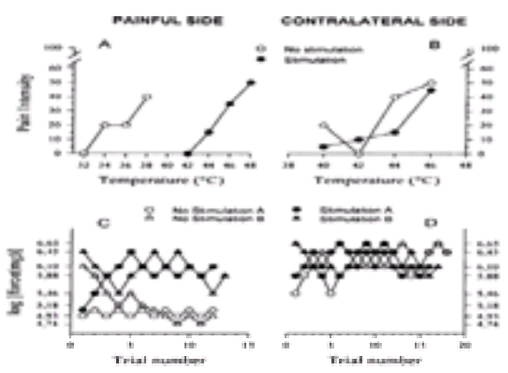

Figure 99-3. Effect of peripheral nerve stimulation (PNS) on allodynia to thermal and mechanical stimulation in a patient with neuropathic pain. The patient was tested twice, with an interval of 2 weeks, once with and once without PNS. In the no-stimulation session, the stimulator was turned off 24 hours before the start of the trial. Thermal and mechanical stimuli were applied in the ulnar region of the painful and contralateral hand. *Upper panel*: Response to thermal stimulation. The patient had to rate the painfulness of a series of ascending heat stimuli on a scale from 0 (no pain) to 100 (most intense pain imaginable). Each stimulus was presented three times. As shown, the patient had significantly lowered pain thresholds to thermal stimulation on the painful **(A)** compared with the contralateral **(B)** side. PNS completely abolished the allodynia on the painful side without affecting the thresholds at the contralateral side. *Lower panel*: Response to mechanical stimulation. A set of graded von Frey hairs was used. Filaments were applied in the painful and contralateral zone, and the patient had to indicate whether this evoked a painful sensation or not. In case the patient reported a pain sensation, a von Frey hair of a lower force was next applied; when the patient reported no pain, a von Frey hair one strength higher was taken. A double random staircase method was used (the suffixes A and B in the figures refer to the two staircases). In the figure, pain thresholds can be recognized by the sequence “ascending-descending.” As shown, the patient showed significantly lowered pain thresholds to mechanical stimulation in the painful **(C)** compared with the contralateral **(D)** hand. After PNS, the pain threshold at the painful side rose to the control values at the contralateral side. PNS had no effect on the threshold of the contralateral side **(D)**. (Reproduced from Kupers RC, Gybels JM. Evaluation of results of pain surgery. In: Gildenberg PL, Tasker

RR, eds. *Textbook of stereotactic and functional neurosurgery*. New York: McGraw-Hill, 1996:1311–1319, with permission.)

In nine of the 11 patients (see Table 99-2), the result was excellent: total pain relief in eight, almost total relief (70%) in one. None of these patients was receiving analgesics or other therapy, and all had returned to their normal professional situation, with the exception of one man. This patient was receiving lifelong workers' compensation with full pay after losing his right index finger in an accident during working hours, so he did not need to return to work, although he told us he could do so.

One patient (patient 8) is considered a moderate result. She reported pain relief of only 20% after PNS for ulnar nerve entrapment; before PNS she had three operations, during which neurolysis of the ulnar nerve was performed. However, with PNS she was able to return to work and abuse of tilidine (Valoron) was discontinued. Finally, one patient (patient 11) with femoral nerve injury after surgery for hip prosthesis reported no pain relief at all, and he suffered from motor activity in the quadriceps muscle during stimulation. However, in the first year after implantation, the result had been good. Reoperation and replacement of the electrode were performed without success. No other side effects or complications occurred.

For this chapter we have reevaluated the same patients 10 years later in 1997 (see Table 99-2). Using the same criteria, in 1997 the results were excellent in eight patients. The result remained a failure in one patient (patient 11). Two patients were lost to follow-up [patients 8 and 10, who in 1987 had a moderate (patient 8) and excellent (patient 10) result]. If we consider the two patients lost to follow- up to be failures, then 10 years after first evaluation we still have an excellent result in eight patients out of 11, which is 73%.

A most remarkable finding in our series of 11 patients, evaluated in 1987, was that all patients except one had to use the electrical stimulation progressively less frequently. In Figure 99-4, the duration of stimulation at latest follow-up in 1987, compared with the initial duration, is plotted logarithmically against time. The rate and intensity of the electrical current necessary to elicit paresthesias remained constant. At first, most of the patients used PNS continuously, some even during sleep. They gradually noted an “after effect”—that is, a pain-free interval after stopping the stimulation that increased with time. The return of the pain was gradual and stimulation was undertaken at that moment. Some patients reported that they had tried to delay stimulation when their pain started returning, but this resulted in a severe increase in the intensity of the pain. We stress that all this was found out by the patients themselves, without any suggestion from us. At the time of the last examination, some patients used the PNS less than half an hour every week.

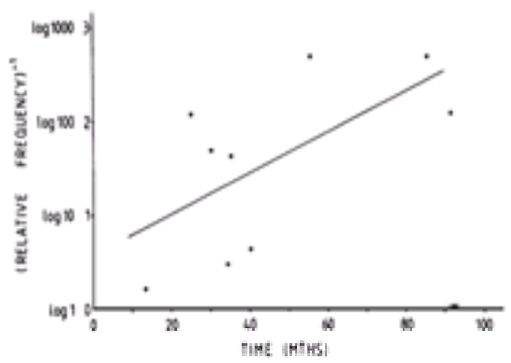

Figure 99-4. Inverse of relative frequency of use of peripheral nerve stimulation plotted against time. In the *x* axis, the follow-up period for the ten patients with good or moderate results is shown. In the *y* axis, a logarithmic scale is used for the inverse of the relative frequency of use at latest follow-up, compared with the initial use. With the least-squares method, a linear regression was performed with the nine patients who reported diminishing frequency of use. The equation of this straight line is $y = 0.022x + 0.55$. The correlation coefficient is 0.63. (Reproduced from Gybels JM, Van Calenbergh F. The treatment of pain due to peripheral nerve injury by electrical stimulation of the injured nerve. In: Lipton S, Tunks E, Zoppi M, eds. *Advances in pain research and therapy*. Vol 13. New York: Raven Press, 1990:217–222, with permission.)

At follow-up in 1997, most patients had to stimulate infrequently and some did not need to stimulate at all to remain pain free. It seems unlikely that with time the need to stimulate less can be attributed to a placebo effect or the “natural history.” None of the previous treatments had affected the pain syndrome, which had in all cases been unremitting before PNS. The time course of the effect was very similar in all patients and not related to the duration of the complaints before PNS. Some patients tried to delay stimulating when the pain reappeared, but this resulted in a further increased pain. In contrast to some studies, we found long-term and lasting good results in cases of neurogenic pain after nerve injury. Our success rate at more than 10 years' follow-up of at least 73% may be related to very careful patient selection: Only cases of neurogenic pain, preferably with injury to smaller, cutaneous branches in a well-defined nerve distribution, were operated on, and most of them only after a successful trial with transcutaneous electrical nerve stimulation was applied to the injured nerve.

Complications

In Table 99-1 is listed the complication rate as indicated by the different authors, ranging from 5% to 43%, with a mean of 18%. Complications include infection, idiosyncratic reaction to the implanted material, injury to the nerve as a consequence of implantation, scarring around the nerve, ischemia of the nerve (mostly reported with wrap-around electrodes that may have been too tightly fixed around the nerve), tenderness at the electrode or receiver site, repeat surgery for reposition of electrodes, and technical malfunctions of the stimulating equipment (mostly broken wires).

CONCLUSIONS

There is good clinical evidence that PNS may relieve certain forms of neurogenic pain. The indication for PNS is peripheral neuropathic pain in the territory of a single sensory or mixed nerve. Consequently, complex regional pain syndrome type II may be a good indication. A favorable response to appropriate screening tests is mandatory.

The following recommendations are made for the screening tests: (a) A preoperative percutaneous stimulation of the involved nerve must be done whenever possible, (b) a preoperative trial stimulation is useful for determining the distribution of the paresthesias and for the evaluation of eventual motor responses, and (c) when a preoperative trial stimulation cannot be performed, a post–electrode implant trial should be done before deciding to implant the stimulating device.

The predictive value of a preoperative evaluation of a local anesthetic nerve block has not been proven.

It is hoped that the companies making implanted electrical stimulators will develop appropriate electrodes for stimulation of PNs. The clinical experience thus far, although limited in numbers, is supportive of this strategy for the relief of pain secondary to nerve injury.

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CHAPTER 100

Spinal Cord Stimulation

Björn A. Meyerson and Bengt Linderoth

BASIC CONSIDERATIONS

From a historical perspective, electrical spinal cord stimulation (SCS) is presumably the first example that chronic pain can be effectively managed by a method that evolved from the laboratory, and it was directly transferred to extensive clinical application. The first experiment in humans, based on the concept of the gate-control theory (1), was performed by Wall and Sweet (2), who inserted needle electrodes in themselves close to the infraorbital nerve and observed that low-intensity stimulation produced hypalgesia in the territory supplied by the nerve. The idea that antidromic activation of the large fibers of the dorsal columns (DCs) could activate the proposed gating mechanisms in the first relay of primary afferents mediating pain signals in the dorsal horn (DH) was first used by Shealy et al. (3), who launched what was then referred to as *DC stimulation*. Also at that time, transcutaneous electrical nerve stimulation (TENS) was introduced, but it was meant to be used merely to select patients for subsequent SCS treatment, as it was believed to have a predictive value for the outcome. Even today, it is general experience that a positive response to TENS augments the likelihood of a favorable response also to SCS, but no systematic studies demonstrating such relationship have been performed (see also reference 4). It should be noted that TENS did not become a treatment by its own until several years after its introduction. In a way, it is a paradox that SCS has become indispensable in the management of neuropathic pain, considering that it emerged as a clinical application of the gate-control theory. According to this theory, it is postulated that signals evoked by acute and noxious peripheral stimuli mediated by thin A-d and C fibers can be inhibited by the activation of large fiber afferents giving off collaterals to the neuronal pool in the DH that serves as a relay for the nociceptive impulses. Thus, on the basis of this hypothesis, SCS, as well as TENS, would be efficient in suppressing both acute and chronic pain of a nociceptive nature. To some extent, that might be true for TENS, although its efficacy in relieving pain in general has been challenged in recent studies (5,6). However, the paradox is still valid with regard to SCS, which is preferentially, or perhaps exclusively, effective for neuropathic forms of pain (e.g., see reference 7) and there is much evidence, although often of an anecdotal nature, that nociceptive forms of pain, both acute and chronic, are not directly influenced by SCS.

In the first decade after its introduction, SCS was extensively practiced and applied to a wide spectrum of pain diagnoses: It probably was used indiscriminately. The results at follow-up were poor and the method soon fell in disrepute. Therefore, in the late 1970s and the 1980s SCS was, at least in the United States, still used only in a few specialized pain centers. In Europe, SCS was not introduced until the early 1970s and then practiced to a very limited extent. The first European meeting devoted to SCS was organized in Freiburg (Germany) in 1974, and at that time there were only a few European publications in the field. No clear distinction was made between neuropathic and nociceptive forms of pain; there was, in fact, no general awareness of the distinctive features of the two types of pain. However, it was evident already in those days that the great majority of patients who were reported to have a favorable outcome suffered from what we now refer to as *neuropathic pain*.

In the last decade, there has been a growing awareness of the fact that SCS is a reasonably effective therapy for many patients suffering from neuropathic pain for which there is no alternative therapy. In fact, SCS is now in many pain centers regarded as a routine treatment. There are several reasons for this development, the principal one being that the indications have been more clearly identified. Improvement of equipment technology has also largely contributed to the better long-term results. The most important technical advancement was the introduction of percutaneous electrode implantation, thereby enabling trial stimulation, which is to date commonly recognized as an indispensable step in the selection of patients. The improved design of electrodes, leads, and receivers/stimulators has substantially decreased the incidence of reoperations for device failure. A further reason for the renewed interest in SCS is its application for other indications than neuropathic pain. By the late 1970s it was reported that the stimulation may produce peripheral vasodilatation (8,9), but it took almost a decade before its usefulness in treating pain associated with peripheral vascular disease (PVD) was recognized. This indication has now been widely accepted, although in practice adopted mostly in Europe. In later years, much interest has focused on the use of SCS for the management of therapy-resistant angina pectoris, first reported from Australia (10) and from Sweden (11). There are now numerous studies documenting that the success rate for this indication is exceptionally high and superior to what can be achieved when the treatment is applied for neuropathic pain.

It is estimated that each year approximately 14,000 SCS implantations are presently performed worldwide: virtually all in North America, the western part of Europe, and Australia. In Europe, the highest rates of SCS implantations per capita are recorded in Belgium, Holland, Sweden, Switzerland, Italy, and Spain. In many countries, problems with reimbursement constitute a major obstacle for the dissemination of SCS, but there is also a lack of knowledge and a great deal of skepticism toward its usefulness even among pain clinicians. A major concern is the cost of the device, and it was not until recently that cost-effectiveness analyses have demonstrated that SCS treatment, when applied for proper indications, may pay for itself within a relatively short period of time (see Cost-Effectiveness of Spinal Cord Stimulation).

Like most surgical interventions, SCS treatment hardly complies with the strict criteria for evidence-based medicine. The inherent nature of SCS precludes double-blind studies in the strict sense since the perception of paresthesias covering the painful area is a prerequisite for pain relief, and this is the case also in treating pain associated with PVD and angina pectoris. Moreover, it was not until recently that preliminary results of a strictly randomized study comparing the outcome of SCS with repeat operations in patients suffering from what is referred to as *failed back surgery syndrome* (FBSS) have been reported (12). It should also be admitted that there is a lack of conformity in the methods of assessing outcome and in the definition of pain diagnoses. Therefore, the results often do not permit pooling in order to make a general evaluation of the efficacy of SCS in a certain pain condition. Moreover, many of the pain diagnoses for which SCS has been tried are relatively uncommon and represented only by small groups of patients. To convince not only the medical community but also payors of the usefulness of SCS, there is a great need for conformity in the selection of patients both for trial stimulation and for permanent implantation as well as for protocols for outcome evaluation that take into account not only the degree of pain reduction but also the consequences for quality of life, functioning in daily living, working capacity, and so forth. Therefore, the efficacy and clinical usefulness have to be documented by well-designed prospective and randomized studies. Indications for SCS and guidelines for its implementation have been specified in two consensus documents (13,14) (for reviews, see references 15,16 and 17).

MODE OF ACTION

In spite of the widespread use of SCS for more than 25 years, the mechanisms involved in its pain-relieving effect are still poorly understood. It is surprising that most users of a treatment modality such as SCS, which is both time-consuming and expensive, do not seem to ask how and why a pain-relieving effect may be produced. The technical advancement of the stimulation device and of the implantation technique is in sharp contrast to the lack of stringent indications and of validated prognostic factors. No doubt, the improved technology has increased safety and reliability, but a better understanding of the physiologic and biochemical background would provide a more solid base for the selection of patients. It would also enable the development of methods for potentiating the efficacy of the treatment with

adjuvant pharmacotherapy [extensive reviews on the mode of action of SCS have been published (18,19,20 and 21)].

Neuropathic Pain

Neurophysiologic and Behavioral Studies

Over the years, a large number of theories have been advanced to explain how pain relief can be produced by SCS. Although the notion of segmental gate control cannot in its details explain the clinical effect of SCS, the general conceptualization of a delicate interplay between different types of afferent input to the DH of the spinal cord has had a tremendous impact on the understanding of pain processing and its modulation (see Chapter 3, Chapter 4 and Chapter 5).

It was reported already in the early literature that SCS does not seem to be effective in suppressing acute nociceptive pain (e.g., postoperative pain, chronic nociceptive pain, and experimentally induced nociceptive pain) (e.g., references 22,23). Nevertheless, in the 1970s and 1980s a number of animal experiments were performed with the aim of elucidating the mechanisms of SCS using acute, noxious stimuli (heat, pinch, pressure, electric stimuli, algogenic substances) (e.g., references 24,25 and 26). In these experiments it was possible to demonstrate that neuronal activation in the DH by peripheral noxious stimuli could be inhibited by concomitant stimulation of the DCs (e.g., references 27,28). It has generally been assumed that stimulation of the DCs gives rise to antidromic activation involving collaterals that in the DH, indirectly via interneurons or directly via pre- or postsynaptic activation, may inhibit second-order nociceptive neurons. However, it has also been argued that the effect may be exerted via antidromic activation of DC pathways originating from cells in DH lamina 3 to 4 (29). Of particular interest in this context is a study by Chandler et al. (30), who demonstrated that noxious activation of spinothalamic tract neurons, identified from the ventroposterior lateral thalamus during pinching, could be inhibited by DC stimulation. It was concluded that SCS preferentially inhibits high-threshold nociceptive-specific spinothalamic tract cells, rather than wide-dynamic-range neurons. It should be noted that at variance with the time course of therapeutic SCS-produced pain relief, DC stimulation as well as noxious peripheral stimuli were applied for short periods of time and the effects were present only concomitantly with the stimulation. There are but a few animal studies in which longer periods of post–SCS inhibition of nociceptive discharge has been recorded (up to 30 to 40 minutes) (31).

Although it is universally accepted that the presence of paresthesias, indicating the activation of the DC, is a prerequisite for pain relief, it has also been argued that the tingling and vibratory sensations are merely epiphenomena. The therapeutic effects should instead be exerted via the activation of other pathways than the DC. One possibility would be a conduction block of the spinothalamic fibers partly as a result of “collision” between impulses mediating pain and the activation produced by the SCS (32,33 and 34). However, this explanation seems less likely in view of the fact that therapeutic SCS is never perceived as painful, suggesting an activation of spinothalamic pathways, and the majority of the these fibers are thin and have a high activation threshold. Moreover, nociceptive transmission in the spinal cord is not blocked or substantially attenuated by SCS because the perception of acute or experimentally induced nociceptive pain is spared (23,35; see also reference 36). A strong support for the crucial role of the DC in SCS is the fact that the treatment always fails in patients suffering from pain associated with extensive deafferentation due to degeneration after an extensive peripheral nerve lesion or direct injury of the DC fibers.

Adjacent to the DC is the dorsolateral funiculus, which contains serotonergic and noradrenergic pathways known to mediate descending pain control (37). It is possible that SCS exerts at least part of its pain-suppressive effect by the activation of these pathways, although most of the fibers are relatively thin. In ongoing studies on rats with experimental mononeuropathy (see below), we have found that stimulation applied to the DC may have a moderate inhibitory effect on DH neurons in spite of an extensive lesion of the ipsilateral DC produced between the sites of stimulation and recording (38). This finding could be explained either by inadvertent activation of the adjacent dorsolateral funiculus or by the activation of a supraspinal negative feedback loop. Contradictory observations have been reported by, for example, Dubuisson (27), who recorded abolition of the inhibitory effect of SCS on nociceptive-specific DH neurons after section of the DC between the sites of stimulation and recording.

There are some studies suggesting that the SCS effect is at least partially dependent on supraspinal mechanisms. In a series of experiments, Saadé and his group (39) have shown that the inhibitory effect of SCS persisted after transection of the DC caudally to the stimulating electrode, whereas it was abolished by a DC lesion rostrally to the stimulation site. It has also been demonstrated that an activation of the DC can excite cells in the anterior pretectal nucleus, from which a profound analgesia by inhibition of nociceptive DH neurons may be produced (18). Furthermore, relatively short-lasting SCS produced a long-lasting inhibition of DH neurons and this effect was shown to be mediated via the dorsolateral funiculus.

A few experimental studies on SCS mechanisms have used the flexor reflex as a marker of a nociceptive event. The outcome of these studies has, however, been contradictory: The main C fiber–mediated components of the reflex were reported to be partially but consistently inhibited in some studies (39), whereas in others it was instead moderately facilitated (40).

Most of the studies referred to above have a limited clinical relevance due to the fact that they have been performed on intact animals and with the use of acute nociceptive peripheral stimulation. To mimic a type of neuropathic pain that often responds well to SCS, we have performed a series of studies on rats with mononeuropathy produced by partial injury of the sciatic nerve according to Bennett and Xie (41) or Seltzer et al. (42). These rats display an increased hypersensitivity to tactile stimulation (allodynia) of the nerve-lesioned hind paw. When studied in light anesthesia, the threshold of the electrically evoked flexor reflex is significantly lower in the nerve lesioned than in the intact, contralateral leg. SCS, applied with current parameters similar to those used in patients, significantly increased the abnormally low threshold selectively of the first component of the flexor reflex. This component appears with a latency of 12 milliseconds and represents the activation of A-b fibers. The late C fiber–mediated component of the reflex was not influenced by the SCS (43). This effect on the early flexor reflex component could be retained also after spinal cord transection rostrally to the site of the SCS, indicating that the selective effect on low-threshold afferent fiber functions may be present without the involvement of supraspinal mechanisms (44).

When rats with experimental mononeuropathy are subjected to SCS via an implanted electrode, the hypersensitivity to innocuous tactile stimulation of the nerve-lesioned hind paw may be suppressed (43). This effect outlasts a stimulation period of 20 to 30 minutes for up to 1 hour. It was reported in 1975 (23) that SCS may effectively suppress allodynia and hyperesthesia both to tactile and thermal stimuli in patients with peripheral nerve injury (Fig. 100-1). Thus, the experimental findings in our rat model of SCS are strikingly similar to what can be observed in patients. It is now well established that tactile allodynia is primarily mediated via A-b fibers (45,46), and on the basis of our experiments we have concluded that SCS seems to have a selective effect on the abnormal functioning of the spinal projection of these nerve fibers. In electrophysiologic experiments, it has also been found that SCS may effectively suppress the hyperexcitability of wide-dynamic-range neurons, manifested both by the presence of abnormal spontaneous discharge and enhanced responsiveness to peripheral, innocuous stimuli (47) (Fig. 100-2).

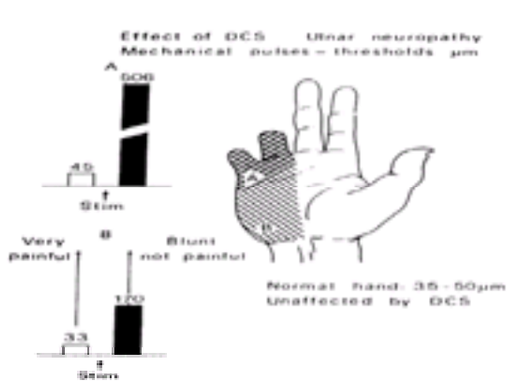

Figure 100-1. Records of thresholds to tactile stimuli (mechanical calibrated pulses) applied to a painful region of the hand after ulnar nerve injury. Before spinal cord stimulation (SCS) [dorsal column stimulation (DCS)] the thresholds were abnormally low and the stimuli perceived as very painful. After 20 minutes of SCS (“Stim”), which relieved the spontaneous pain, the thresholds were significantly elevated and the stimuli were perceived as blunt. Note that in the distal part of the hand and amputated fingers the thresholds became higher than in the intact hand disclosing a neuropathy in the form of hypesthesia. (From Linderoth B, Meyerson BA. Dorsal column stimulation: modulation of somatosensory and autonomic function. *Semin Neurosci* 1995;7:263–277.)

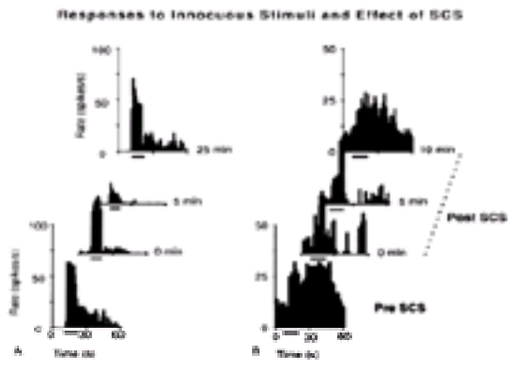

Figure 100-2. Peristimulus time histograms of press evoked responses in two dorsal horn neurons **(A,B)** in a rat with tactile allodynia after partial sciatic nerve injury before and after spinal cord stimulation (SCS). Responses before SCS are depicted in the bottom histograms. Time after cessation of SCS is shown to the right of each histogram. Bars under the histograms indicate the duration of innocuous pressure applied to the hind paw. Bin width = 1 second. (From Yakhnitsa V, Linderoth B, Meyerson BA. Effects of spinal cord stimulation on dorsal horn neuronal activity in a rat model of mononeuropathy. *Pain* 1999;79: 223–233, with permission.)

Neurochemical Mechanisms

Data from humans on biochemical correlates to SCS are sparse and partly contradictory. Several studies have been performed with cerebrospinal fluid analyses of neurotransmitters with a putative role in the effect of SCS (review, see reference 48). There are no solid data supporting the idea that the SCS effect involves endorphinergic mechanisms, and furthermore, no conclusion can be drawn about the possible role of monoamines. There is some evidence that substance P may play a role, as shown by an increased concentration in lumbar cerebrospinal fluid after SCS (49). Later experimental studies also showed a release of substance P, as well as of serotonin, in the DH by SCS (50).

In a 1985 study, Duggan and Foong reported that the SCS-induced inhibition of spinothalamic tract neurons could be counteracted by the gamma-aminobutyric acid ($GABA_A$) antagonist bicuculline (51). Later work has confirmed that SCS may produce a significant increase of GABA release, assessed by microdialysis in the DH of rats (52). In subsequent studies it was demonstrated that the DH release of GABA was significantly lower in rats displaying tactile allodynia after sciatic nerve injury than in intact animals. Moreover, SCS resulted in an increase of GABA release in animals that in preceding behavioral experiments had responded to SCS by a normalization of the withdrawal thresholds in the nerve-injured hind paw (53). In another microdialysis study, we have demonstrated that rats with nerve injury and tactile allodynia have an increased DH release of the excitatory amino acids glutamate and aspartate, and as a result of SCS this release is reduced concomitantly with an increased release of GABA (54). In behavioral studies, we have further observed that intrathecal administration of GABA or its agonists in nerve-injured rats markedly enhances the effect of SCS on tactile allodynia (55). A similar effect has been observed with intrathecal administration of adenosine in doses that by themselves were too small to influence the tactile allodynia in the hind paw (56,57). Figure 100-3 illustrates a simplified model of putative biochemical mechanisms involved in the pain-relieving effect of SCS. Our experimental studies further suggest that it would perhaps be possible to enhance the efficacy of SCS in patients by adjuvant pharmacological treatment. In fact, preliminary trials in patients have confirmed that intrathecal administration of baclofen may in some cases increase and prolong the suppression of pain after SCS (58). It should be emphasized, however, that a GABA-ergic mechanism is presumably only one of several biochemical correlates to the SCS effects.

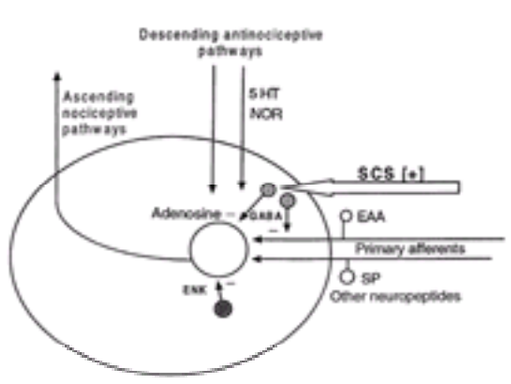

Figure 100-3. Schematic illustration of increased release of gamma-aminobutyric acid (GABA), resulting in a decrease of excitatory amino acid (glutamate and aspartate) (EAA) release in the dorsal horn after spinal cord stimulation (SCS) in nerve-lesioned rats with tactile allodynia. There is evidence that adenosine may play a role similar to that of GABA. (5-HT, serotonin; NOR, norepinephrine; SP, substance P). [Revised from Stiller CO. *Neurotransmission in CNS regions involved in pain modulation*. Stockholm: Karolinska Institute, 1997 (Thesis), with permission.]

Pain in Peripheral Vascular Disease

The physiologic background to the vasodilatory effect of SCS, which conceivably is the main cause for the pain-relieving effect in PVD, is only partially understood and still a matter of controversy. Since the turn of the century, it has been known that peripheral vasodilatation can be induced by high-intensity stimulation, activating C fibers, of dorsal roots and peripheral nerves (59). This antidromically produced alteration of peripheral circulation has been demonstrated in many subsequent studies (60,61), and it is supposed to be caused by a release of vasoactive substances—for example, prostaglandins, substance P, and so forth—from perivascular nerve endings. However, there are several indications that the clinically used SCS stimulus parameters do not enable recruitment of thin, high-threshold C fibers.

As an alternative to the antidromic activation of thin afferent fibers it has been argued that such activation also of large afferents may result in the release of vasoactive substances. Interest has been focused on the possible role of stimulation-induced peripheral release of calcitonin gene–related peptide (62,63). Recent experiments have supplied further support for this idea (64).

Numerous studies have demonstrated a SCS-induced increase of peripheral blood flow, both in the macrocirculation (65,66 and 67) and the microcirculation (68,69).

It has been argued that the peripheral vasodilatation after SCS is secondary to a direct suppression of pain that in turn would result in a decreased sympathetic tone associated with a vasodilatory effect (discussion, see reference 70). This hypothesis has been partly based on experimental findings that SCS may induce direct inhibition of transmission of nociceptive impulses via the spinothalamic tract (71). However, these experiments used peripheral noxious stimulation and studied the effect of very short periods of SCS. Therefore, the experimental situation differs in relevant aspects from the clinical use of SCS. On the other hand, the deep aching ischemic pain is a nociceptive form of pain and it is difficult to explain how such pain can be influenced by SCS, considering the well-established fact that SCS otherwise is not effective for such pain. However, this contradiction may be resolved by the assumption that the suppression of ischemic pain is secondary to a primary effect on the peripheral ischemia. This idea is further supported by the fact that pain from ischemic ulcers, which are common in these patients, does not respond to SCS, whereas the deep resting and activity-related pain may be effectively alleviated (for further discussion, see references 21 and 70).

In recent years, there has been a growing support of the idea that the SCS effect in PVD is primarily due to a modulation of the autonomic system. The well-known beneficial, but often partial, effect of sympathectomy on peripheral circulation provides circumstantial support for this idea. In a study of peripheral blood flow, various autonomous reflexes, and cardiac activity in patients subjected to SCS, it was demonstrated that during stimulation there were a moderate decrease in heart rate and a partial suppression of sympathetic reflexes concomitant with an increase of the peripheral blood flow (72). To experimentally examine the hypothesis that attenuation of sympathetic activity is responsible for the SCS effect, we have performed a series of experimental studies in rats. These studies included cutting of the ventral roots, sectioning the sciatic nerve, and bilateral lumbar sympathectomy, and each of these procedures abolished the vasodilatory effect of SCS (73,74). The same result was obtained using the ganglion blocker hexamethonium or pretreatment with guanethidine. These studies, together with clinical observations, give

further support to the idea that the beneficial effect of SCS on peripheral microcirculation is primarily due to a decrease of vasoconstrictor sympathetic tone. It has also been shown that the vasoconstrictor activity modulated by SCS is exerted mainly via nicotine receptors in the ganglia and a $_1$-adrenoreceptors at the neuroeffector junction (75). It should be emphasized, however, that experimental data presently available have been derived from normal, intact animals and therefore the clinical relevance of the findings may be questioned.

Angina Pectoris

TENS was the first stimulation technique to be applied in intractable angina pectoris and was introduced by Mannheimer in the early 1980s (76,77). The outcome was remarkably promising. At that time, SCS was tried for ischemic pain in the lower extremities and it was quite natural to place the spinal electrode at the T-1 to T-2 level to induce paresthesias in the area where angina is experienced.

There are many reasons to believe that the beneficial effect of SCS on angina is due to an improved balance between coronary oxygen demand and supply. It has been difficult to prove that there is an increase of coronary blood flow during SCS, but a Dutch group has presented data indicating a redistribution of flow using positron emission tomography (78,79). There is a continuing debate whether the main antianginal effect in cases with radiologic normal coronary arteries is due to direct inhibition of nociceptive transmission (30) or mediated by a local redistribution of blood flow (80,81) or by a decrease in the coronary oxygen demand (82). The latter mechanisms could be the result of a depression of cardiac sympathetic activity (discussion, see reference 83), but one study lends no support to this idea (84). There is some evidence that stimulation-induced changes of cardiac blood is neurally mediated because TENS has been demonstrated to increase coronary flow in normal humans whereas it failed to do so in patients with transplanted— and denervated—hearts (85). Furthermore, it has been reported that endogenous opioids are released to the cardiac circulation during SCS and actually this could contribute to a local sympathetic suppression—if any (86,87).

Recent observations on SCS applied at the T-1 to T-2 level in the dog (88) have shown that stimulation with “clinical parameters” and at intensities 60% and 90% of the motor threshold results in depression of the activity in intrinsic cardiac neuronal systems. Especially after provocation of activity in these circuits by local occlusion of coronary blood flow, SCS significantly suppressed the increased activity in the intrinsic neurons. These observations suggest that SCS may, at least partially, limit ischemia by inhibiting the local neuronal circuits that otherwise could induce arrhythmias, leading to more generalized ischemic threats.

CLINICAL CONSIDERATIONS

Which Patients Can Be Considered for Spinal Cord Stimulation

Preoperative Evaluation

SCS, as other forms of electrical stimulation in pain treatment, requires an active participation of the patient as compared with pharmacotherapy. Because the stimulation equipment is to be handled by the patient himself or herself, at least a general understanding of the conditions for pain relief is desirable—for example, that true pain relief should be differentiated from a possibly masking effect of the stimulation-induced paresthesias; that high-intensity stimulation does not provide better pain relief (rather the contrary); and that stimulation, when used intermittently, generally does not have a prophylactic analgesic effect, at least not in neuropathic forms of pain. The patient should also be aware of the fact that a reduction of pain cannot be expected to be complete but instead partial; SCS almost never produces an all-or-none effect as compared with a nerve block. It is therefore important that the patient's expectations are realistic and that he or she accepts partial pain abolishment as a successful outcome.

To be able to use the SCS device properly and to understand the instructions, the patient must also have the ability to communicate and describe the characteristics of the pain both from a quantitative and a qualitative aspect. In some cases it may be important to differentiate between steady and evoked pain components because the former is generally more likely to respond to the treatment. For these reasons, language and cultural barriers may render successful SCS treatment almost impossible. In particular, a reliable evaluation of the outcome of trial stimulation can be very difficult. These special features of SCS, particularly when applied for neuropathic pain but maybe less so for PVD and angina pectoris, also imply heavy demands on the treating physician. Everyone who takes on the responsibility of subjecting patients to SCS treatment must be prepared to supply an almost lifelong continuing support because patients suitable for SCS typically suffer from a chronic multifactorial disease with pain as the major but not the only reason for their incapacity. Furthermore, in spite of the much-improved quality and reliability of the SCS equipment, device-related problems as well as side effects requiring local surgical interventions are not uncommon.

The implementation of SCS treatment requires a great deal of experience in the management of chronic pain patients in general. Therefore, the best results are achieved by centers with access to multidisciplinary pain expertise, where these treatments are performed on a regular basis. In a nationwide Belgian study, it was found that results reported from centers with limited experience—that is, a few patients (two to five) treated annually—were far less satisfactory than those obtained in major pain centers treating each year more than ten patients (89).

Like other forms of symptomatic pain treatment, it is mandatory to ascertain that all possible etiologic treatments have been exhausted before SCS is considered. This implies that the responsible physician must also critically evaluate the examinations on which the underlying disease diagnosis is based.

A further prerequisite for SCS treatment is a thorough pain analysis. Clinical experience, as documented in a large number of publications, indicates that SCS is predominantly, or exclusively, effective for neuropathic forms of chronic pain. (The beneficial effects on angina pectoris and pain associated with PVD are exceptions that are dealt with separately.) For this reason, the diagnosis of a neuropathic pain condition must be well established. Besides commonly used pain measures and descriptors (including, for example, pain drawing), a pain analysis may include also pharmacologic tests (e.g., see reference 90). It is of particular importance to establish the existence and relative importance of a neuropathic pain in so-called mixed pain conditions—that is, coexisting neuropathic and nociceptive pain components. A thorough neurologic examination, including a detailed analysis of cutaneous sensibility, is mandatory. Often quantitative sensory testing may be of much help in quantifying abnormalities of the cutaneous sensibility, which are common in cases of neuropathic pain (review, see reference 89). The following aspects of the pain analysis are particularly important, as they may relate to the SCS outcome:

- Distribution of pain (large or limited extension).
- Radiating versus trunk and midline components. The latter pain sites are more difficult to influence.
- Maximal pain intensity. Very severe, excruciating pain corresponding to 80 to 90 of a 100-mm visual analog scale (VAS) is less likely to respond.
- Variability of pain intensity. Pain corresponding to the lower portion of the pain intensity span is more likely to respond.
- Spontaneous, steady versus evoked pain components. Evoked pain components are less likely to respond.
- Character. Paroxysmal and shooting pains are less likely to respond than steady pain.
- External factors influencing the pain. Pain related to posture and load is less likely to benefit than pain worsened by changes of external temperature, in particular cold.
- Disturbance of cutaneous sensibility. Location and extension of hypo- and hyperphenomena should correspond to the distribution of stimulation-induced paresthesias. Preservation of large-fiber DC functions is a prerequisite for inducing paresthesias, and the presence of prominent hypesthesia may indicate a loss of such fibers.
- Effect of medication. Positive response to membrane stabilizers (intravenous lidocaine, mexiletine), antiepileptics (carbamazepine), clonazepam, tricyclics, and so forth suggests that the pain is neuropathic. Conversely, a marked pain reduction by analgesics, including opioids, increases the likelihood that the pain is nociceptive.
- A positive effect of TENS increases the likelihood of a positive SCS response, although a lack of response does not in any way preclude a beneficial SCS effect.
- Effect of sympathetic blocks has no predictive value.

It is strongly recommended that the pretreatment evaluation should include a psychological examination performed by a psychologist or a pain-oriented psychiatrist. It is well documented that psychological factors highly correlate to the outcome of SCS (89,92,93 and 94; discussion, see reference 15). The psychological examination may include also personality tests and aims at an analysis of the impact of the pain on functioning in daily activities, in the workplace, and in the family and with regard to quality of life in general. These measures must be well defined and documented so that they can be repeated at follow-up.

Furthermore, the psychological examination is performed also to exclude patients with major personality disorders, poor capacity to collaborate and to communicate their pain problems, drug-seeking behavior or abuse, and poor pain coping (“chronic pain behavior”). The fact that patients are on regular opioid medication does not in any way constitute an exclusion criterion, provided that this medication has provided a true analgesic effect and that there is no history of rapid escalation of doses,

suggesting tolerance, drug seeking, or both. Patients involved in litigation related to their pain condition should not be excluded for that reason only.

Indications and Results

Surgical treatments such as SCS are difficult to include in controlled, randomized double-blind studies. Thus far, SCS cannot be regarded as validated by evidence-based medicine. Moreover, the validity of many SCS studies can be challenged because only one or two facets of the many possible outcomes have been addressed. Thus, the treatment result is usually classified only with regard to the degree of pain relief assessed by the use of VAS. As a rule, an arbitrary degree of pain relief of more than 50% is regarded as good and 90% as an excellent result (discussion, see reference 95). Unfortunately, it is generally not reported whether the evaluation of pain relief is averaged over time, refers to the effect of stimulation at its best, or refers to the pain intensity generally present just after a stimulation session. The important issues of quality of life and functioning, the patient's global satisfaction, and employment status are rarely addressed. Some studies have simply grouped the patients as users or nonusers of the stimulation device, and in a long-term perspective this seemingly rather simple dichotomy may reflect the patient's global satisfaction and the clinical usefulness (96). The magnitude of a placebo response is completely unknown (see Chapter 81).

In some studies, the outcome measures include the patients' global evaluation of the usefulness of the treatment, changes in analgesic medication, and changes in functional ability (97). The patient's satisfaction may also be evaluated by asking whether he or she would again undergo the procedure of electrode implantation having experienced all that this implies (98). An example of a multifactorial outcome analysis, used by North et al. (98), is shown in Figure 100-4. Such composite outcome measures offer the opportunity to analyze in more detail the efficacy of the treatment. Variability in the different outcome measures renders a conclusive evaluation of the clinical usefulness difficult. A further problem with the evaluation of many SCS studies is that the outcome assessment may be based only on patients who have been permanently implanted; the total number of patients originally subjected to trial stimulation often is not reported. The exclusion of the primary nonresponders makes a global evaluation of the usefulness and efficacy of the treatment for a certain diagnosis virtually impossible. A minimal requirement for a reliable evaluation of the treatment outcome should be that the follow-up assessments are performed by a disinterested third party without the participation of the treating physician. This condition has rarely been fulfilled in SCS studies.

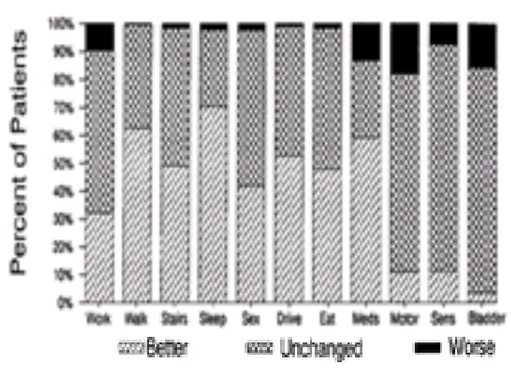

Figure 100-4. Changes of patients' ratings of their abilities to perform various activities in daily living related to impairment because of pain, ongoing medication, and neurologic deficits. The percentage of patients reporting gains, losses, or no change is represented in a stacked bar format. Data from a cohort of 171 permanently implanted patients with a mean follow-up of 7.1 years. (From North RB, Kidd DH, Zahurak M, et al. Spinal cord stimulation for chronic, intractable pain: experience over two decades. *Neurosurgery* 1993;32:384–395, with permission.)

An outcome measure of particular interest, not the least from an economic point of view, is a change in employment status. Contrary to expectations, there seems to be no obvious correlation between the degree of pain relief and work status, as reported in several studies (4,89,99,100). However, in one study reporting on patients with FBSS, 54% of the patients were able to work full-time after treatment, as compared with 41% before, and approximately 8% changed from part-time to full-time work (98). These results are in sharp contrast to what has otherwise been reported. Considering that the great majority of patients subjected to SCS are severely disabled and have long histories of chronic pain, it cannot be expected that many of them will be able to resume professional activities, particularly when unemployment is high.

In the evaluation and ranking of indications for SCS used for neuropathic pain, the shortcomings of the published studies discussed above must be taken into account. On the other hand, it should be noted that the relative efficacy of SCS, as shown in a large number of publications, for some common neuropathic pain diagnoses is surprisingly concordant (see also reference 101). Only those pain conditions for which the efficacy of SCS is well documented in larger series of patients are discussed. Numerous papers on SCS have been published since the early 1970s; we focus on studies performed in the last decade. In general, the principal indications have been for pain due to injury or disease in peripheral nerve or spinal roots. Occasionally, SCS may also be effective for pain of spinal origin, although the evidence for its efficacy on this indication is less well documented. The main indications are listed in Table 100-1.

TABLE 100-1. Indications

Neuropathic Pain

Pain Due to Peripheral Nerve Injury

Pain due to peripheral nerve injury is regarded by many to be the prime indication for SCS with the best chances of obtaining satisfactory and long-lasting pain relief (15,16,97,102,103). However, this view is not shared by others who have reported relatively modest results in such cases as compared with spinal root pain (98). Nerve injury associated with pain, both spontaneous and evoked, may follow trauma, surgery, entrapment, inflammation, and metabolic disorders. Often there is a combination of trauma and surgery, and it may sometimes be virtually impossible to identify the principal cause. This form of pain may occur as a result of both injury to one major nerve (e.g., ulnar nerve entrapment) and partial injury to distal nerve branches (e.g., incisional pain). Some nerve territories appear to be particularly vulnerable to surgical trauma, as evidenced by the fact that there is an overrepresentation of neuropathic pain conditions associated with some very commonly performed surgical interventions. A typical example is gynecologic surgery performed via a suprapubic incision (Pfannenstiel), which carries a considerable risk of resulting in a partial injury to the nerves supplying the groin (Table 100-2).

Pain location	Injured nerve(s)	Operation
Groin	Ilioinguinal	Herniectomy
	Iliohypogastric	Gynecologic surgery (Pfannenstiel)
	Genitofemoral	Appendectomy
Knee	Infrapatellar	Knee surgery (endoscopy)
	Saphenus	Varicose veins (stripping)
Ankle, foot dorsum	Superficial peroneal	Ankle joint surgery
Thoracic and abdominal wall	Intercostal	Thoracotomy
	Cutaneous abdominal	Mastectomy Renal surgery
Upper thorax, upper arm-axilla	Thoracobrachial	Mastectomy

TABLE 100-2. Examples of common postsurgical neuralgias likely to respond to spinal cord stimulation

A common but not unique feature of peripheral injury pain is the presence of disturbance of cutaneous sensibility. Often there is dysesthesia, allodynia, and hyperalgesia. These disturbances may have a tendency to spread outside the territory of the originally injured nerve(s). Occasionally, this progressive extension of cutaneous sensory disturbance may involve the entire upper or lower quadrant of the body; such conditions are for obvious reasons extremely incapacitating. This type of pain may fit the International Association for the Study of Pain criteria of complex regional pain syndrome (CRPS) type II (104). When the nerve injury pain is located in an extremity, or at least originates from a nerve injury in the hand or foot, it may be associated with signs of sympathetic dysfunction, and it may or may not be temporarily alleviated by sympathetic blocks, including regional block with guanethidine (105), and/or systemic administration of an a-adrenergic receptor antagonist (phentolamine) (106,107). CRPS type I affects the hand/arm or the foot/leg and is characterized by marked sensibility changes in the form of dysesthesia and allodynia, but there is no proven nerve injury.

Traumatic lesions of the brachial plexus may or may not be associated with injury of the cervical roots and may sometimes include root avulsion. It is important to establish whether the lesion is confined to peripheral preganglionic nerve structures or combined with root avulsion. In the latter case there is little chance that the pain may respond to SCS. It should be remembered that painful brachial plexopathy may occur also as a late sequela of radiation therapy; this form of pain may be effectively relieved by SCS.

In case of extensive peripheral nerve injury, the territory of the nerve may be markedly anesthetic. This may correspond to complete neuronal degeneration, comprising also the postganglionic portion of the sensory nerve root. In that situation there is often a lack of neuronal substrate in the DC, and it is not possible to induce paresthesias in the painful anesthetic region.

Pain after amputation, in the form of a phantom, is a most obvious example of pain due to complete deafferentation resulting from axotomy. In such conditions, it is sometimes not possible to produce paresthesias that cover the entire phantom and this is due to extensive degeneration of the corresponding DC fibers. This is one reason why patients with phantom pain sometimes do not respond favorably to SCS. However, for such pain, as well as stump pain, SCS should be considered as the first option of invasive treatment.

Postherpetic neuralgia is a form of nerve injury pain that is complex; it involves pathology of the ganglion cells as well as part of the spinal DH (see Chapter 22). Moreover, postherpetic neuralgia may present with a wide variety of sensibility disturbances. In general, the chance of a positive response to SCS is dependent on the integrity of large fiber functions; patients with signs of extensive deafferentation are less likely to respond.

The most extensive study, both with regard to number of cases and length of follow-up, on SCS in pain due to peripheral nerve injury is reported by Lazorthes et al. (97) (Table 100-3). This was a cooperative study from Toulouse and Zürich including 152 patients suffering from this type of pain. One hundred thirty-two patients were reported from Zürich with a positive long-term (2 to 20 years) result in 90% of the patients. The outcome was assessed not only with regard to the degree of pain relief but also to daily life functioning as well as to consumption of analgesics. Another relatively large study is that reported by Sanchez-Ledesma et al. (108). Out of 49 patients characterized as having “peripheral deafferentation pain,” 36 responded favorably to trial stimulation. They were followed for 5.5 years and reported substantial pain relief, 75%, in 57% of the patients. In a metaanalysis of 11 studies from the 1980s, pain due to peripheral nerve injury, often characterized as reflex sympathetic dystrophy or causalgia, was recorded to have favorable outcome from SCS in 70% of the patients originally subjected to trial stimulation (4; see also reference 109). Unfortunately, several of the studies had follow-ups shorter than 2 years. North et al. (98) reported that “peripheral pain syndromes” had a positive outcome of trial stimulation in 68% of the patients (n = 41), whereas Kumar et al. (100), in a series of 30 patients with pain associated with peripheral neuropathy, recorded no more than 14 who enjoyed long-term pain relief. In our own clinical practice, nerve injury pain remains the best indication for SCS, and a retrospective study revealed that 27 out of 38 patients with this form of pain were still dependent on regular use of their stimulators for up to 16 years (mean, 7 years) after implantation (96).

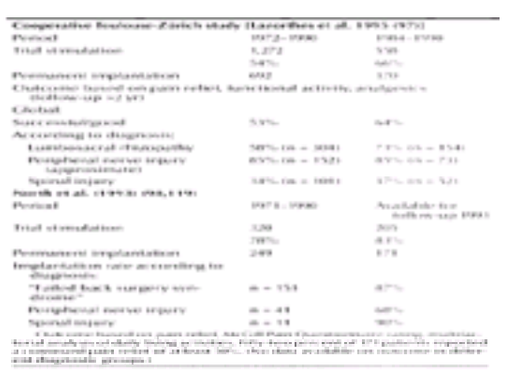

TABLE 100-3. Major spinal cord stimulation studies with long follow-ups (2-20 yr)

The most extensive series of patients with postamputation, stump/phantom pain is that of Krainick et al. (110), who reported on 64 patients with follow-ups of up to 5.5 years. At that time not more than 21% of the patients experienced pain relief of more than 50%. This is in contrast to the study by Lazorthes et al. (97), in which 13 patients out of 19 enjoyed good, long-term pain relief.

A beneficial effect of SCS in painful diabetic peripheral neuropathy has been demonstrated in a well-conducted study by Tesfaye et al. (110). Ten patients were in that series and six of them continued to note significant pain relief and used their stimulator as the sole pain treatment at 14 months' follow-up. It should be emphasized that in this study placebo stimulation was also used.

On the basis of available publications it is difficult to draw a general conclusion about the usefulness of SCS as treatment for postherpetic neuralgia because only small series of patients have been documented. It appears that the reported results are very contradictory; some studies have recorded relatively high rate of successes, whereas others have failed to obtain positive results in more than a few cases (4,108,112,113 and 114).

As concluded by Shetter in a review (17), it appears that the outcome of SCS for neuropathic pain of peripheral origin is equal and possibly superior to that for FBSS. However, it is difficult to draw any definite conclusions because the number of patients in each diagnostic category is small, and the lack of stringent diagnostic criteria makes a definite evaluation virtually impossible. Moreover, the new International Association for the Study of Pain terminology, CRPS type I and type II, will unfortunately make future retrospective metaanalyses of SCS treatment for pain after peripheral nerve injury even more difficult. The results of the two major up-to-date SCS studies are shown in Table 100-3.

Spinal Root Injury

In the majority of published series of patients subjected to SCS, lumbosacral rhizopathy is the most common indication and by many authors also regarded to be the best. This condition is often referred to in the literature as FBSS or *postlaminectomy syndrome*, which is a misnomer because it is neither a disease nor a pain diagnosis. Sometimes, the term *lumbosacral fibrosis* is used. In fact, these patients often present with a mixture of both nociceptive and neuropathic pain components. Although many of them have a history of surgery for disk herniation, the same form of mixed pain may occur spontaneously and often without any major pathology demonstrable by neuroradiologic and electrophysiologic examinations. Most authors contend that SCS predominantly influences the "radiating pain components," or "pain in the leg," conceivably corresponding to the neuropathic pain associated with lumbosacral rhizopathy. The differential effect of SCS in these conditions was first reported by Winkelmüller (115). It is widespread general experience that, at least with the usage of a single quadripolar lead electrode or a plate electrode, it is virtually impossible to produce paresthesias that cover midline and paravertebral parts of the lower back; the same applies to the neck, the thoracic back, the genitals, the perianal region, and the perineum (114,116). Thus, the selective effect of SCS on the rhizopathy-related pain also applies to the cervical region, and pain located in the neck with referred pain components into the back of the head, the shoulders, and the upper thoracic back can for the same reasons be expected not to respond (see also reference 16).

However, it has been argued that using a more complex configuration of electrodes such as dual 8-polar leads implanted in parallel may enable the production of paresthesias that also involve the midline regions of the back (117). It has further been claimed that such stimulation may also alleviate the pain in the low back region in spite of the fact that that pain presumably is of a predominantly nociceptive nature. It should be emphasized that there are no systematic studies addressing this issue, and thus, there are no robust data substantiating that SCS may effectively relieve pain confined to the lower part of the back.

In Table 100-4 are shown some SCS studies comprising a major portion of patients with lumbosacral rhizopathy ("low back pain"), and it appears that the long-term outcome is surprisingly concordant. Turner et al. (99) have performed a metaanalysis of publications (1967 to 1994) on SCS for chronic low back pain. The systematic literature synthesis resulted in 39 studies selected on detailed inclusion criteria. All these studies were case series, and no randomized trials could be retrieved. The majority of the studies presented data on the proportion of patients being permanently implanted after trial stimulation, and on average, 74% of the patients screened received stimulators. At follow-up (mean, 16 months), an average of 59% of patients had more than 50% pain relief. A few studies comprised follow-ups of up to 5 years with approximately the same outcome. It was concluded that the lack of randomized trials precluded conclusions concerning the effectiveness of SCS relative to other treatments, placebo, or no treatment. In an other prospective, multicenter study comprising 219 patients with "chronic back and extremity pain" subjected to trial stimulation 83% were permanently implanted. After 1 year's follow-up, 55% of the patients successfully "managed their pain" (118). In this context it should be noted that there is one prospective, randomized study, although still in progress, comparing the outcome of reoperation in patients suffering from FBSS (12). Preliminary results for the first 27 patients followed for more than 6 months showed a statistically significant advantage for SCS over reoperation.

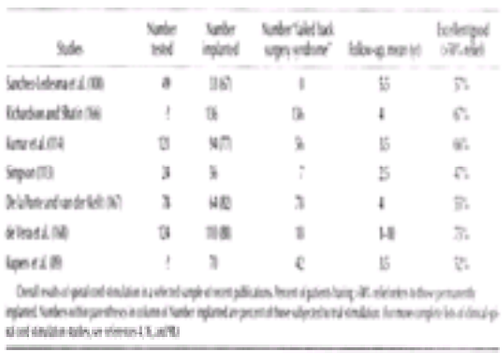

TABLE 100-4. Long-term results of spinal cord stimulation

One of the most detailed and well-performed studies is that of North et al. (98; see also reference 119), with a mean follow-up of 7 years (see Table 100-3). There were 153 patients with "postlaminectomy syndrome," and 87% of them received permanent electrode implants. It should be noticed that follow-up assessments were performed in this study by a "disinterested third party." In agreement with the commonly accepted standard for outcome assessment at least 50% pain relief was considered as a satisfactory result; also considered were the patient's global evaluation, functional gains in daily living, and medication and work status. It was concluded that approximately 50% of the patients could be classified as having a successful outcome. It should be emphasized that the patients with "FBSS" in that study were carefully selected because only those with a predominant radiating pain in the leg(s) were included.

Another extensive study with long-term follow-up and assessment of not only degree of pain relief but also daily life activities and medication is that of Lazorthes et al., referred to previously (97) (see Table 100-3). Data were collected for the period from 1972 to 1990; the total number of patients with "lumbosacral fibrosis" was 304, with a long-term (2 to 20 years) success rate of 58%. However, the results had improved over the years and in the late period 1984 to 1990 no less than approximately 70% enjoyed a favorable outcome.

There can be little doubt that lumbosacral rhizopathy (or FBSS) is a good indication for SCS treatment. In spite of the large number of publications, it is still difficult to precisely define the selection criteria. A major reason is that the patient materials are generally insufficiently presented and the relative severity of pain in the lower back and pain associated with rhizopathy are poorly described. There is in SCS outcome studies a great need for more detailed pain-related diagnoses based not only on pain history but also on thorough neurologic examination.

Spinal Cord Injury

In pain associated with disease or trauma affecting the spinal cord the results of SCS are generally disappointing (16,120). Examples are myelopathy of any etiology (e.g., tumor-related, stenosis, postmyelitis) and syringomyelia. However, partial spinal cord lesions, regardless of etiology, with some preservation of large fiber function may benefit from SCS. One example is pain in multiple sclerosis, as documented by Kumar et al. (114), who reported that seven of nine tested patients enjoyed useful relief, with a mean follow-up of 3 years. In one study, a cohort of 25 patients with spinal cord injury after trauma or surgery was subjected to SCS (121). Only those with incomplete lesions had a chance of obtaining some pain relief, but even in these the success rate was only 24%. In the largest series published, of a total of 101 patients followed for up to 20 years, 34% were considered to be successful (97) (see Table 100-3). A major problem is pain in complete spinal cord injury with extensive and total loss of motor and sensory functions below the injury level. That form of pain, which is a form of deafferentation pain and which is often felt in the lower extremities or trunk, does not respond to SCS. It is in these cases not possible to produce paresthesias in the painful part of the body conceivably because the DC fibers originating from below the injury have degenerated. In some patients, spinal cord injury pain may be present segmentally corresponding to the injury level, often in the transitional zone between partial sensory loss and normal sensibility. If the injury is located at the conus level, the pain may thus be felt in the legs corresponding to the root levels of the injury. Such pain is generally regarded to be a good indication (98). It should be noted that in many of the publications on SCS in spinal cord injury, information is rarely provided concerning either the completeness of the injury or the location of the pain (segmental or diffuse below the injury level). However, in view of what is now known to be at least a relative indication for SCS in these patients, it is reasonable to assume that patients reported to be successful refer to those with segmental pain or with significant preservation of DC fiber function.

Peripheral Vascular Disease

The application of SCS for treatment of pain associated with PVD was introduced by Cook and Weinstein in 1973 (8; see also reference 9), and they reported that together with the pain-relieving effect there was a tendency to a healing effect on ischemic ulcers. Their first reports, however, remained unnoticed for several years, and it was not until the mid-1980s that this new indication for SCS became recognized. In the following years, many studies confirmed the clinical usefulness of SCS in patients with ischemic pain due to disturbance of peripheral circulation, mostly in the lower limbs. Most of these studies were performed in a few European centers; SCS applied for PVD is still not commonly practiced in North America. One possible reason why the number of patients subjected to SCS on this indication is relatively small as compared with those treated for neuropathic pain is the skepticism among the vascular surgeons who are reluctant to refer their patients for this treatment. On the other hand, it has always been clearly stated that only patients for whom reconstructive surgery or pharmacologic treatments have been exhausted

should be considered as candidates for SCS treatment.

From the mid-1990s there has been a decreased interest in SCS treatment for PVD, and a major reason for this development might be that some recent controlled studies have failed to show convincingly positive results (122). On the other hand, these studies have included comparatively small groups of patients, and it is apparent that the patient materials have been heterogeneous. Moreover, it has to be remembered that insufficiency of the peripheral circulation is generally associated with a progressive underlying disease, and therefore, a possible beneficial effect of SCS can only exceptionally be expected on a long-term basis. On the other hand, the justification and usefulness of a treatment that is “palliative” and capable of providing efficient pain relief for several years cannot be disputed. At present, more stringent selection criteria are being defined and, it is hoped, will result in improved outcomes for SCS treatment in PVD in the future.

Indications and Clinical Results

It should be emphasized that SCS is indicated in conditions of PVD primarily because of pain. In the selection of patients, reference is generally made to the classification of Fontaine, and it is a universally accepted policy that the treatment should preferentially be applied only to patients in stage III. As evident from Table 100-5, the principal symptom in patients in this group is pain at rest, particularly in night, without signs of tissue involvement in the form of ulcers and gangrene. Patients in stage IV may be included, and there are several reports substantiating that ulcers smaller than 3 cm in diameter may heal. The main diagnoses have been arteriosclerosis and vasospastic disorders (e.g., Raynaud's disease, frostbite, and vasculopathy in scleroderma). Patients with Burger's disease also may respond (123,124). Arterial hypertension and diabetes have been claimed to correlate with a less favorable outcome (122,125), but other studies have in fact demonstrated better results in hypertensive patients (126,127). An important factor to be considered is the stability of the ischemic condition. Thus, patients with signs of a rapidly progressive disease and with a short history and manifest or impending gangrene should not be considered for treatment. Several of the patients who may be candidates for SCS due to PVD have previously been subjected to sympathectomy. It is generally agreed that this treatment does not preclude a beneficial effect of SCS.

Grade I	Arteriosclerosis with no symptoms
Grade II	Intermittent claudication with no symptoms at rest
	IIa Intermittent moderate claudication
	IIb Intermittent severe claudication
Grade III	Claudication + rest and night pain without tissue involvement
Grade IV	Grade III + tissue loss (ischemic ulceration, gangrene)
	IVa with local inflammation
	IVb with widespread inflammation

TABLE 100-5. The Fontaine classification of symptom severity in peripheral vascular disease

A number of methods for assessing the peripheral hemodynamics have been proposed both for the primary selection of patients and assessing the effect in the trial stimulation period. It appears that there is a good correlation between the clinical outcome and data on peripheral microcirculation obtained by measures of capillary density and flow velocity using intravital microscopy (128) as well as by measures of transcutaneous oxygen tension ($TcpO_2$) (124,126). Especially $TcpO_2$ seems to be an important predictor, and patients demonstrating a value between 10 and 30 mm Hg as measured on the foot dorsum preoperatively are more likely to have a satisfactory outcome with SCS than with conservative therapy (129,130). Augmentation of $TcpO_2$ values during the trial stimulation period is a positive prognostic sign. Thermography and laser Doppler flowmetry may also provide valuable information.

A review of the literature covering 20 publications from 1980 to 1989 on the long-term results of SCS in PVD showed that the proportion of patients with a successful outcome was 67% of those having been subjected to trial stimulation or for other reasons directly implanted (4). In the extensive review published by Simpson (15), “ischemic limb pain” is judged to be a condition with an exceptionally high success rate. In a cooperative study from 1986, 29 out of 36 permanently implanted patients still enjoyed effective pain relief after 25 months (67), and similar favorable outcomes have been reported in many other studies (112,125,128,131). Small ischemic ulcers have a tendency to heal as a result of the treatment. The SCS-induced peripheral vasodilation, which apparently may have a beneficial effect on ulcers, has raised the hope that the treatment may also result in limb salvage. Although such an outcome of SCS is still controversial, there are several reports in the literature that suggest that there is a decreased rate of amputation (122,124,125,128). A well-designed study using a matched control group has given further support to the hypothesis that amputation may be at least delayed (65; see also review, reference 132). Apart from the pain-relieving effect of SCS in PVD, there is a marked amelioration of claudication and walking distance increased, as reported in approximately 70% of the patients (see review, reference 16).

In 1977, Dooley claimed that vasospastic disorders would be a good indication for SCS (133). In a few studies, each reporting on relatively small numbers of patients, the favorable outcome of SCS applied for such conditions, including Raynaud's disease, has been confirmed (134,135 and 136). A positive effect has also been reported in frostbite, with relief of pain and healing of ulcers (137).

Angina Pectoris

Many patients suffering from disabling angina [New York Heart Academy (NYHA) classes III to IV] are elderly or suffer from concurrent disease, or both, making them unsuitable for major invasive procedures. Sometimes the coronary occlusions are too widespread or situated too distally to permit a successful surgical intervention. Furthermore, many patients suffer persistent, incapacitating angina even after successful bypass surgery or other interventions. In some patients with typical symptoms of angina, no obstruction of the cardiac circulation is demonstrable in the coronary angiogram. This is the so-called syndrome X, and it is debated whether the physiologic basis for the symptoms is “small vessel disease,” vasospasm, or some other disturbance difficult to demonstrate with available techniques. For these patients, classic medicine had little to offer beyond optimizing the pharmacotherapy (reviews, see references 79 and 138).

At first, SCS treatment for angina was met with skepticism, and it was feared that the stimulation would interfere with warning signals of a coronary infarction. However, numerous studies have subsequently demonstrated the effectiveness and safety of the method. Angina pectoris has in fact developed into the best indication for SCS, with a success rate above 80% (review, see reference 139). It is estimated that at present more than 1,000 SCS systems have been implanted for angina worldwide, of these approximately 500 in Sweden.

Patient Selection

Patients accepted for SCS should present with the following: (a) severe angina pectoris (NYHA classes III to IV); (b) significant coronary artery disease refractory to conventional treatment; (c) examinations that should demonstrate reversible myocardial ischemia; (d) or a diagnosis of syndrome X (small vessel disease). Pain alleviation with TENS may indicate a future positive response to SCS.

Exclusion Criteria

Exclusion criteria include (a) acute myocardial infarction; (b) other ongoing heart disease (e.g., peri/myocarditis); (c) low ability of cooperation or mental problems; (d) on-demand pacemaker (relative contraindication); and (e) magnetic resonance imaging investigation planned in the near future (relative contraindication).

The implanter should be aware that the SCS candidates often have been submitted to a thoracotomy, with subsequent pain problems of different etiology (e.g., postthoracotomy syndrome, intercostal neuralgia, psychogenic components).

Clinical Results

In general, 80% to 90% of the patients report significant pain relief, with reduced frequency of anginal attacks, diminished need for short-acting nitrates (but other medications often unchanged), fewer visits to the emergency room, and an enhanced quality of life (reviews, see references 78 and 135,136,137 and 138). There are many reports of stimulation-induced changes in various indices of coronary ischemia during workload, such as reduction of the ST segment depression in the electrocardiogram and alteration of cardiac lactate production to extraction paralleled by an increase in working capacity (78,82,142,143).

In the studies referred to previously, the multipolar electrode was often positioned with its center around T-1 to T-2. However, there is also a report of positive effects of SCS with the electrode tip at C-2 (144). That study comprised 23 angina patients followed for at least 3 months, and there was a decrease of anginal attacks from on average 124 per month to eight per month after surgery. The majority of the patients changed from NYHA angina class III to IV to class I after SCS.

Eliasson et al. (145) summarized results from 114 centers with a total of 517 patients with a mean follow-up of 23 months. The cardiovascular mortality was approximately 5% per year, and according to these authors there were no indications that SCS influences long-term mortality.

In one study, 104 patients with angina were randomized to SCS or to coronary artery bypass grafting (CABG) (146). Both groups experienced adequate symptom relief after the procedures and there were no significant differences. In the CABG group, the exercise capacity increased significantly and various indices of cardiac ischemia also changed positively. However, on an intention-to-treat basis, both the cardiovascular morbidity and the mortality rates were significantly lower in the SCS group. The conclusion was that SCS and CABG seem equivalent as to degree of symptom relief. However, it should be emphasized that considering the complications associated with bypass surgery, SCS is a favorable alternative, particularly for patients with increased risk of surgery.

Safety Aspects

In general, very few complications are reported with SCS therapy in angina (147,148). The most common is dislocation of the electrode, calling for reprogramming or open correction of position. There has been much concern about the hazardous issue of whether SCS may conceal critical coronary ischemia. Andersen et al. (149) reviewed 10 patients with SCS who sustained acute coronary infarction. In nine out of 10 patients (for the tenth, data are incomplete), this event was detected in spite of the stimulation therapy. Another question pertains to whether SCS may induce or aggravate arrhythmias. This has been investigated by Eliasson (83), who failed to demonstrate an arrhythmogenic effect of the SCS treatment.

METHODOLOGIC CONSIDERATIONS

Paresthesia Distribution

It is now universally recognized that it is a necessary, but not sufficient, precondition for effective pain relief that the stimulation-induced paresthesias cover the entire painful area. It is also generally believed that these paresthesias result from the activation of large, low-threshold fibers contained in the DC. This implies that in certain pain conditions associated with or due to degeneration of these fibers, there is a lack of neuronal substrate for the stimulation. The importance of the integrity of DC fibers has been emphasized by, among others, Sindou and coworkers, who rely on the presence of evoked potentials in response to peripheral stimulation of the painful area as a tool in screening candidates for SCS (150).

The notion that the effect of SCS is solely due to the activation of the DC has in recent years been challenged. Using a computerized model of the spinal canal and its content, it has in a series of publications been elegantly demonstrated that a stimulating electrode located in the epidural space may activate not only the DC fibers but also dorsal spinal roots and the root entry zone (e.g., 151,152) (Fig. 100-5A). Activation of the roots or the DC, or both, is dependent on the orientation of the fibers relative to the current field, the width of the dorsal subarachnoid compartment, and the electrode configuration.

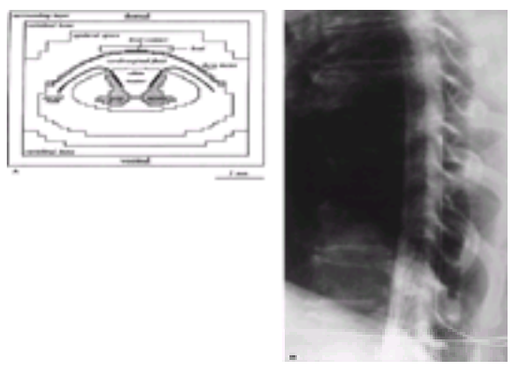

Figure 100-5. **A:** Computerized model of the spinal canal with its contents at the midcervical level. Note the proximity between the stimulating electrode ("lead contact") and the dorsal roots/root entry zone as well as the dorsal columns. (From Holsheimer J. Effectiveness of spinal cord stimulation in the management of chronic pain: analysis of technical drawbacks and solutions. *Neurosurgery* 1997;40:990–996, with permission.) **B:** Myelography of the thoracic region illustrating the wide subarachnoidal space and the wide space between the stimulating electrode and the dorsal aspect of the spinal cord.

The radiograph in Figure 100-5B illustrates the spatial relationship between the epidural electrode and the spinal cord at a thoracic level where the subarachnoid space is particularly wide. For obvious reasons, the activation of spinal roots will be associated with a segmental paresthesia distribution, whereas DC activation is likely to produce paresthesias in wider regions below the site of stimulation. However, it should be emphasized that the paresthesia distribution segmentally or in the trunk can often be influenced by varying the pulse duration. Thus, short pulses (50 to 150 microseconds) tend to evoke segmental sensations, whereas longer pulses (200 to 400 microseconds) are more likely to produce paresthesias with a wider spread in the trunk. In practice, it can be difficult to find the appropriate stimulation site from which paresthesias can be produced in the painful area. In thorough studies based on data derived from a large patient base, Barolat et al. (153) have provided guidelines for the optimal electrode placements for the induction of paresthesias in different parts of the body (see also reference 154).

Electrode Configuration

In 1972 to 1974, the first electrodes designed for percutaneous implantations were introduced (155,156 and 157) and these electrodes were monopolar and coupled as cathode with a separate anode plate or the case of the passive receiver as anode. Sometimes two such electrodes were used with the possibility of coupling either of them as cathode. Later, multipolar electrodes became available. There is now a great variability of electrodes available on the market (Fig. 100-6). The most commonly used electrode for percutaneous implantation is quadripolar, but octapolar ones are also available. The percutaneous electrodes have a tendency to dislocate and in order to maintain paresthesia distribution a quadripolar electrode in the form of a strip and implanted via a small laminotomy may be advantageous (Fig. 100-7). There is much evidence that quadripolar electrodes are far superior to monopolar or bipolar ones in controlling the paresthesia distribution. A new transverse tripolar electrode configuration has been introduced that may enable a better control in steering of the paresthesias by varying the coupling of the poles (158). This design has been partly developed on the basis of the computerized SCS model referred to previously.

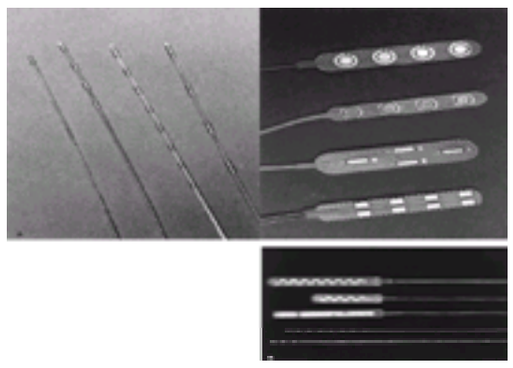

Figure 100-6. Different electrodes available on the market. **A:** From Medtronic Inc. **B:** From Advanced Neuromodulation Systems, Inc.

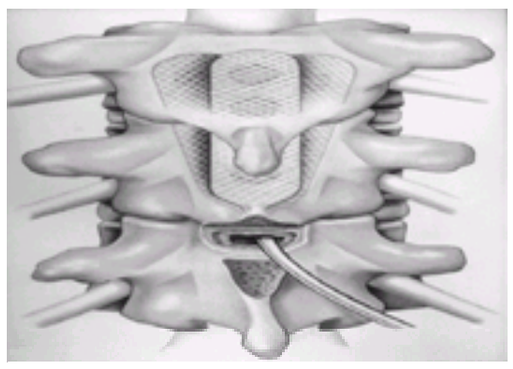

Figure 100-7. Schematic illustration of the technique for the introduction of a strip (plate) electrode. Note that angling of the strip to either side may enable activation of any specific part of the dorsal columns.

Surgical Technique

In the great majority of centers having experience with SCS treatment, a period of trial stimulation is considered mandatory before permanent receiver/stimulator implantation is decided (14). Trial stimulation is generally performed via a percutaneously implanted electrode. Disposable bipolar/multipolar electrodes for this purpose are available and with that type of electrode its proximal part is taped to the skin close to the percutaneous entry. It is also possible to use an electrode designed to be permanently implanted, with temporary connecting leads tunneled subcutaneously a short distance away from its spinal entry. Percutaneous electrode implantation should always be performed under local anesthesia and under fluoroscopic control to enable the placement at a site from where proper paresthesias can be induced. In principle, the same technique is used for implantation of electrodes both for trial and permanent stimulation.

In most centers, percutaneous electrode implantation is performed with the patient in a prone position. Although this position may appear comfortable for both the patient and the surgeon, it has the disadvantage that paresthesias, which in the perioperative test situation are adequately distributed, may change and no longer cover the painful area when the patient later tries the stimulation in a sitting or standing position. This problem can be avoided by performing the electrode implantation with the patient in a sitting position, which we have adopted as a routine procedure in neuropathic pain conditions. However, the sitting position is not advisable for implantation in patients with angina and cardiovascular disease.

The connection of the electrode to the receiver/fully implantable stimulator is preferentially performed under short-lasting general anesthesia or heavy sedation It is advisable to use prophylactic antibiotics in conjunction both with electrode and receiver/stimulator implantation.

Implantation of plate electrodes via a small laminotomy is generally performed under general anesthesia. Another option is to use propofol for anesthesia and awaken the patient for stimulation testing after the electrode has been positioned. However, some surgeons perform this procedure under local anesthesia only, which, however, is experienced as most uncomfortable by the patients, although it has the advantage of enabling perioperative trial stimulation. For implantation of such electrodes at mid- or lower thoracic levels, spinal anesthesia can be used, and in spite of complete anesthesia and paralysis of the lower part of the body, it is possible to induce paresthesias with stimulation at moderate intensity, thus avoiding the otherwise “blinded” electrode placement (159). It should be emphasized also that the final positioning of plate electrodes preferably is performed with fluoroscopic control.

There is a lack of conformity regarding the length of the trial period. In some centers, stimulation is applied for only a few days, whereas in others a period of several weeks is recommended. Regardless of the length of the trial period, it is advantageous that the patient is given the chance to evaluate the pain-relieving effect outside the hospital. The idea of trial stimulation is not only to assess the possible efficacy of the treatment, but also to minimize the influence of a placebo effect from being hospitalized and attended to. In some patients, the stimulation-induced paresthesias seem to have a purely masking or distracting effect, and the pain reappears immediately after turning off the stimulator. Although a continuous mode of stimulation is preferred by some patients, many use the stimulator intermittently. It is well known that a limited stimulation session, at least in patients with neuropathic pain, is generally followed by a poststimulatory pain relief lasting 1 to 2 hours (see also reference 119). In our experience, the presence of such a poststimulatory effect is a good indication that the stimulation has produced a “real” pain suppression, conceivably as a result of a protracted alteration of DH release of transmitter substances. Therefore, it is advisable to instruct the patient to apply stimulation intermittently for 30-minute periods and to assess the duration of a possible poststimulatory pain reduction using the VAS. This stimulation regimen should be applied at least for some days in the trial period and stimulator use ad libitum can be permitted during the rest of the period. A form that we have found to be very useful for assessing the SCS effect in the trial period is reproduced in Figure 100-8.

Form for Visual Analogue Scaling (VAS) of pain during trial stimulation

MARK THE LINE WITH A CROSS TO INDICATE PAIN INTENSITY JUST BEFORE STIMULATION

NO PAIN _____ WORST IMAGINABLE PAIN

SLIGHT MODERATE SEVERE

Stimulation started at: hrs Pain was felt to decrease at: hrs

Stimulation stopped at: hrs That is, after minutes of stimulation

MARK THE LINE WITH A CROSS TO INDICATE PAIN INTENSITY JUST AFTER STIMULATION

NO PAIN _____ WORST IMAGINABLE PAIN

SLIGHT MODERATE SEVERE

Pain started to reappear, or pain relief started to subside, at: hrs

I have taken analgesics/sedatives before next session of stimulation Yes / No

COMMENTS:

Figure 100-8. Form for visual analog scale evaluation of pain relief to be used primarily in the trial stimulation phase.

Trial stimulation in patients with pain due to PVD should be performed for at least 1 week. A beneficial effect of the stimulation in these cases is often not apparent until after many days. It is also recommended that these patients initially should use the stimulator almost continuously during the waking hours. The possible reason why there may be a delayed effect of the stimulation is that the pain relief presumably is the result of a reversal of peripheral ischemia with secondary metabolic changes in the tissue. It appears that these secondary effects of SCS may require some time to become apparent. In analyzing the outcome of the stimulation it is

important to differentiate the possible effects on resting and effort-related pain (claudication) and pain related to ulcers and gangrene because the latter pain cannot be expected to respond, at least not in the first weeks of the treatment. Although it is desirable that SCS-induced paresthesias cover the major part of the painful area, it seems that an effect on the peripheral vasculature can be achieved also in areas adjacent to the field of paresthesia distribution. Thus, it has been shown that an effect on the peripheral circulation, assessed by thermography and laser Doppler flowmetry, can be achieved also with stimulation just subthreshold to the production of paresthesias (*unpublished observation*; see also reference 70).

In patients subjected to SCS treatment for angina pectoris, the entire system, including the receiver/stimulator, is often implanted without a preceding period of trial stimulation. The reason why trial stimulation in these cases is not considered mandatory is that most of the patients have previously been subjected to TENS, which in these cases serves as a form of trial stimulation. Moreover, in well-selected patients with this diagnosis, the chances of a favorable outcome are exceptionally good. If uncertainty prevails whether pain confined to the thoracic wall or back is of cardiac ischemia origin, percutaneous trial stimulation is recommended.

After implantation of the receiver/stimulator patients may be free to use the stimulator at their own choice; there is no evidence indicating that continuous stimulation produces “fatigue” or “tolerance.” For angina, stimulation several hours daily at low intensity is recommended, with an increase to strong stimulation for a few minutes during anginal attacks or prophylactically during exercise. For patients who have implantable stimulators and who prefer continuous stimulation or stimulation for long and frequent periods, it is advisable to program the stimulator in a cycling fashion (e.g., 2 minutes on and 2 minutes off) to prolong battery life. The same applies in a situation in which high stimulus intensity is required to produce the paresthesias. For the same reason, the pulse duration and frequency should always be set at the lowest effective values. If excessive current is needed to obtain adequate paresthesias, a radiofrequency-coupled system should be chosen; otherwise, the life of the implanted pulse generator will be too short.

Complications and Side Effects

Serious complications with SCS treatment are rare. As with all surgery involving implantation of nonbiological material, there is a risk of infection. The most severe location of infection is, of course, in the spinal canal, where it may cause injury to the spinal cord. However, such events are very rare, whereas local infections at the site of the receiver/stimulator or in the back at the site of the connector between the connecting lead and the electrode are more common (5% to 10%) (e.g., 114,119). Local infections at these sites also may occur years after implantation presumably because of hematogenic bacterial spread. Needless to say, removing any SCS components from the region of infection is usually required, even when potent parenteral antibiotics are administered.

A word of caution is warranted concerning strip electrode implantation via a laminotomy in the cervical spine because in cases of severe spinal stenosis the introduction of the relatively stiff electrode plate in the epidural space carries the risk of producing spinal cord injury. The intraspinal introduction of the electrode with an obtuse angle should therefore be avoided.

Inadvertent dural puncture during percutaneous electrode implantation may result in long-lasting postpuncture headache. In case the electrode under these circumstances is introduced into the subarachnoid space, the stimulation threshold for inducing paresthesia is exceptionally low, and in such instances a subdural electrode location should always be suspected.

Many patients complain of local pain in the back at the site of the electrode connector. Therefore, care should be taken to place the connector deep in the paravertebral tissue and preferentially under the muscle fascia. It is also relatively common that the receiver/stimulator gives rise to local tenderness, particularly in lean patients with little subcutaneous fat. If the device is placed onto the lower chest, a lateral location may interfere with the patient's lying on that side in bed.

True reactions of rejection due to intolerance to the material of the implanted device are extremely rare. On the other hand, some patients tend to develop a fibrous reaction to the connecting cable that becomes palpable as a hard string, which may be mistaken as a sign that the cable is too short and stretched. Some patients subjected to SCS treatment present with marked signs of peripheral neuropathy extending into relatively large areas of the body. It seems that these patients have a general tendency of developing such abnormalities of cutaneous sensibility also following minor injury to the skin such as surgical incisions. Care should be taken to implant the receiver/stimulator as far away as possible from the painful neuropathic region. Nevertheless, local signs of neuropathy may occur in such patients as a result of the implantation of the SCS device (Fig. 100-9).

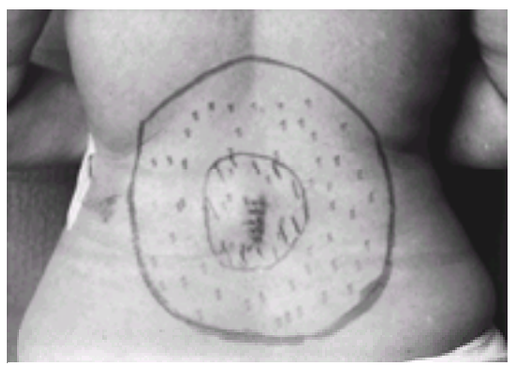

Figure 100-9. Signs of local neuropathy that developed, and persisted, as a result of the skin incision for permanent implantation of a spinal cord stimulation electrode. This patient was treated for a chronic pain condition originating from minor surgery in the knee with partial injury of the infrapatellar nerve. The inner circle denotes an area of marked tactile allodynia and the outer one the boundary of hyperalgesia (primary and secondary hyperalgesia, respectively).

By far, the most common complication requiring repeat surgery is a change of paresthesia distribution. In case of percutaneously implanted lead electrodes it is sometimes possible to visualize with x-ray a dislodgment of the electrode, but often it appears that the changed paresthesia distribution is caused by other factors—for example, a fibrous reaction around the electrode leading to an alteration of tissue impedance with a changed configuration of the current field. This is probably the reason why a similar phenomenon may occur also with strip electrodes. The incidence of replacement of electrodes is reported to be 25% to 30% in many studies (99), whereas in the long-term study by Lazorthes et al. (97), only 50 out of 692 patients were reoperated for that reason over a 20-year period.

The technology of the stimulation equipment has much improved in later years and considerably increased the reliability and safety. A major reason why repositioning of electrodes has become less common is the use of multipolar electrodes, with which it is possible by reprogramming to manipulate the distribution of paresthesias. Moreover, the access to handheld patient programmers has decreased the need to see patients for adjustment of the stimulation parameters. The marked decline of device-related failures with the use of multichannel electrodes has been elegantly demonstrated by North et al. (98) using Kaplan-Meier survival analysis.

COST-EFFECTIVENESS OF SPINAL CORD STIMULATION

SCS treatment implies relatively high health care cost; the device is expensive and the implantation procedure with trial stimulation, evaluation, programming, and so forth is time consuming. It should be recognized that in recent years, there is growing awareness that it is no longer possible to justify a treatment modality merely on the basis of personal experience and with regard to its efficacy from a strictly medical point of view. In fact, with tight regulations for reimbursement both in public health service and in relation to private insurance, it is demanded that the cost-effectiveness of any form of medical treatment must also be proven. The incidence and prevalence of disabling chronic pain are extremely high and represent a considerable portion of society's cost for health care. It is not until recent years that cost-effectiveness analyses of various treatment modalities have been performed, and with regard to SCS only a few studies are available. They are all focused on the treatment of low back/lumbosacral rhizopathy, or FBSS, comparing the estimated cost of long-term SCS treatment versus a mixture of other therapies including surgery. The very first study on that topic (160) demonstrated that the relatively high initial costs for equipment and hospital stay were more than compensated for by the considerable decrease of cost of medication and the ability to return to work, which in that study occurred in an exceptionally high proportion of the patients. In a study performed by the Health Technology Assessment Information Service (161), the 5-year cost ratio was analyzed for 100 FBSS patients treated with SCS versus another 100 subjected to alternative therapies. It was found that in comparison with repeat surgery with an efficacy of less than 80%, SCS was cost-effective. The costs for an SCS device is approximately the same as the cost for a spinal fusion procedure; however, the latter procedure is associated with much more extensive

rehabilitation and the cost for medication is considerably higher.

In one study, a thorough cost-effectiveness analysis was performed of SCS in the treatment of FBSS in the United States (162; see also reference 12). Reference was made to the tremendous costs that this condition represents to society, which in the United States are estimated to be at approximately $25 billion. It was also concluded that on the basis of available data it can be stated that a great majority of repeat surgery and other interventions for this condition are excessive and inappropriate (163). The analyses provided robust evidence that SCS treatment with a 56% efficacy will pay for itself within 2 to 3 years. If the analysis is based only on those presenting with a favorable outcome, the SCS treatment is paid for within 2.1 years by reducing the demand for other forms of medical care. It should be added that in this study, as well as in the Health Technology Assessment Information Service study referred to previously, the gains in pain relief and improvement of quality of life have not been economically evaluated. Another study reports that the application of SCS costs on average $3,660 per patient per year, and it is concluded that in spite of this relatively high cost, the cost-effectiveness compared favorably to other therapies with a high incidence of failure (164).

There are no data on the cost-effectiveness of SCS treatment in PVD; SCS applied for angina pectoris has been subjected to such a study by a Danish team (165). It was found that the SCS on this indication resulted in a considerable reduction of costs both for hospital and home care, amounting to a total savings of approximately $8,500 per year, per patient (1989 prices).

A problem with the cost-effectiveness analysis of a treatment such as SCS is that most data are based on costs in the United States, where doctors' fees and cost of hospitalization are considerably higher than in most other countries. Because the cost of the device is approximately the same in most countries, SCS treatment in many countries outside the United States presumably compares somewhat less favorably to alternative therapies.

CONCLUSIONS

SCS is not evidence based in the strict sense because of the paucity of prospective controlled studies. Moreover, due to the presence of paresthesias as a precondition for pain relief, double-blind study designs are not possible. Nevertheless, for more than two decades there have been numerous studies documenting its efficacy in the treatment of certain pain conditions that are otherwise notoriously difficult to manage. The facts that there is for most of these patients no alternative therapy that has not already been tried and that a referral for SCS treatment is often a last resort imply that controlled studies are in practice virtually impossible to perform. However, an analysis of the many studies available in the literature reveals that the results with regard to pain relief are surprisingly concordant. There has also been a tendency for the results to improve over the years; this development is largely due to advancement of device technology, the adoption of trial stimulation, and a more adequate selection of the patients based on differentiated pain analysis. The recognition of psychological factors as being of paramount importance for the long-term outcome is a further reason why the results are now more predictable.

Among experienced pain clinicians, there is a general agreement that SCS is an indispensable treatment modality for many patients with chronic neuropathic pain, particularly pain after lesions of peripheral nerves or spinal roots. There is no evidence that SCS may influence nociceptive forms of pain, and its effect on pain in PVD is conceivably secondary to the stimulation-induced peripheral vasodilatation.

The application of SCS in PVD is to date practiced to a relatively limited extent in spite of the favorable results reported in a large number of earlier studies. Pain in PVD is a condition that is particularly suitable for controlled studies because alternative treatments are available. To convince referring physicians of the usefulness of SCS in this condition, there is a great need for such studies with stringent inclusion criteria to ensure the homogeneity of the patient material.

SCS in intractable angina pectoris has not yet become an established treatment modality and is still practiced in only a few centers. However, much evidence has already accumulated that for well-selected cases SCS may result in a substantial reduction of both frequency and severity of anginal attacks in an exceptionally high proportion of patients.

SCS is a minimally invasive procedure that is well tolerated by patients and associated with very low risk of serious complications. The side effects are often trivial and can generally be overcome by minor surgical interventions or adjustment of stimulation parameters or electrode couplings.

SCS is presently underused and to promote its further dissemination, it should, to a larger extent, be practiced also outside the neurosurgical profession—that is, adopted by other pain specialists. On the other hand, it should be used only within a multidisciplinary pain team context in centers with extensive experience in managing difficult pain cases. SCS treatment is resource demanding, as it is time consuming and requires long-term, continuing doctor-patient contact and expensive equipment. However, studies indicate that SCS treatment is cost-effective.

The lack of a thorough understanding of the physiologic and biochemical mechanisms involved in the pain-relieving effect of SCS has hampered both its further dissemination and development. No doubt, there is a great need for continuing investigation of its mode of action, which would promote a more general acceptance and also make possible the development of strategies leading to enhancement of its efficacy.

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CHAPTER 101

Brain Stimulation: Intracerebral and Motor Cortex Stimulation

Björn A. Meyerson and Bengt Linderoth

In the late 1970s a number of clinical studies provided evidence that intracerebral stimulation (ICS) (often referred to as *deep brain stimulation*) is a reliable method for the management of pain otherwise resistant to any therapeutic modality (1,2 and 3). However, many of the ensuing long-term follow-up studies failed to confirm the first optimistic reports, particularly with regard to the efficacy of the treatment for neuropathic forms of pain (4,5). On the other hand, some studies have established that long-lasting positive effects can be maintained with stimulation applied in the medial thalamus as treatment of nociceptive pain—for example, in conditions such as low back pain (6,7). Although ICS has been in use for more than two decades, there are still discordant opinions as to the indications, the preferred stimulation targets, incidence of tolerance and possible countermeasures, biochemical mechanisms involved, and so forth. Some years ago we undertook a limited inquiry to a number of established neurosurgeons with long experience in pain treatment. It became obvious that most of them had ceased to practice ICS because they only rarely found a good indication and considered the outcome unpredictable or had themselves often failed to obtain satisfactory results.

Considering the very few studies published in recent years, it is obvious that ICS presently is practiced only in a few centers. This gives the impression that the development of the method has come to a standstill and that no major progress leading to an improvement of the efficacy and reliability has been made. One reason why new data are sparse is that a novel and improved intracerebral electrode has not yet been approved by the U.S. Food and Drug Administration, implying that ICS in the United States has reverted to experimental status. The previous research protocol was discontinued in 1995. However, the new electrode, which is extensively used for ICS in movement disorders, is now freely available both in Europe and in Canada.

Although it appears that the majority of neurosurgeons involved in pain treatment have a skeptical attitude toward the usefulness of ICS for pain, a thorough analysis of several of the major studies with long follow-ups published in the last decade provides convincing evidence that this is a treatment modality that without good reason has fallen into disrepute. ICS can offer long-lasting and efficient pain relief for a relatively large proportion of patients for whom there is nothing else to offer. Even though it is an invasive procedure, it carries a relatively small risk of complications and side effects.

ICS has evolved along two lines, corresponding to the two major target regions for stimulation: the sensory thalamic nuclei (thalamic sensory nucleus, ventral posterior lateral thalamic nucleus) and the periaqueductal-periventricular gray region (PAG/PVG). Conceivably, stimulation in these two regions may influence pain by the activation of different mechanisms and/or systems. There is robust evidence that stimulation in the sensory thalamus is selectively effective for neuropathic, often referred to as *deafferentation*, pain, whereas PAG/PVG stimulation (in the following referred to as PVG when used in a clinical context) appears to affect preferentially nociceptive forms of pain. The distinction between these two principal types of pain is crucial for defining indications for ICS and for the choice of stimulation target. This makes the preoperative pain analysis of fundamental importance and, in fact, a prime precondition for optimizing the chances of a successful outcome.

In later years a novel mode of central nervous system stimulation has attracted much interest—that is, stimulation of the precentral motor area (Brodman 4) applied via a four-pole stimulating electrode placed epidurally. This treatment, which was introduced and pioneered by Tsubokawa et al. (8), has proven to be efficient particularly for central poststroke pain. This is a form of neuropathic pain that is notoriously difficult to manage, and it is not responsive to ICS in the sensory thalamus or the internal capsule. Moreover, motor cortex stimulation (MCS) appears to be a promising treatment for painful trigeminal neuropathy, including facial anesthesia dolorosa, and perhaps also for other forms of pain due to peripheral nerve injury (9,10).

INTRACEREBRAL STIMULATION

Basic Considerations

Sensory Thalamic Stimulation

The first trials with stimulation in the sensory thalamic nucleus, performed by Mazars et al. in the early 1960s (11,12), were based on the classic theory introduced 1911 by Head and Holmes (13). They had postulated that pain can occur as a result of insufficient activity in the epicritic (nonnociceptive) sensory system, and the idea with sensory thalamic stimulation was to restore the balance between the epicritic and protopathic (nociceptive) systems by artificial activation of the former. Basically, this idea appears to be very similar to the concept of the gate control. With the introduction of spinal cord stimulation, which was a direct clinical application of the gate-control theory, it was logical to consider the possibility of applying stimulation at a higher level in the lemniscal system—that is, at its second relay in the thalamus. It is unlikely that those who pioneered this new approach, Hosobuchi et al. (14) and Adams et al. (15), at that time were aware of the earlier experiences in Paris. It should be added, however, that some early attempts to relieve pain by stimulation in other intracerebral targets had been made [e.g., stimulation of the caudate nucleus by Ervin et al. (16) and the septal region by Heath and Mickle (17) and by Gol (18)].

Only a few experimental studies have sought to elucidate the mechanisms by which pain can be relieved by sensory thalamic stimulation. In view of the similarities between this form of stimulation and spinal cord stimulation (e.g., presence of paresthesias covering the painful area, time course of the pain-relieving effect, preferential effect on neuropathic forms of pain), it was natural to postulate the presence of supraspinal gating mechanisms. In fact, it was experimentally demonstrated that nociceptively evoked activity in the medial thalamus could be inhibited by stimulation of the dorsal columns (19). In experiments in monkeys, it has also been shown that stimulation in the ventrobasal complex of the thalamus can inhibit wide-dynamic-range spinothalamic neurones in the dorsal horn activated both by innocuous and noxious peripheral stimuli (20,21). It was further proposed that this inhibition may be due to antidromic activation of axons projecting to the sensory thalamus from pain-inhibiting relays in the brainstem. Activation of a thalamo-cortico-thalamic loop may also play a role. Furthermore, it has been demonstrated that stimulation of the sensory thalamus may modulate neuronal activity in the medial thalamus (center median and parafascicularis nuclei) evoked by peripheral noxious stimulation (22). On the other hand, sensory thalamic stimulation in the rat failed to attenuate the tail flick response as well as other measures of acute pain (23; discussion, see reference 24). There are hardly any data from experimental studies in patients subjected to sensory thalamic stimulation. Gybels et al. (25) reported that the paresthesias evoked by such stimulation had a masking effect on induced pain sensation in the threshold range, but that more intense induced pain was not attenuated. Similar observations were reported by Boëthius et al. (26).

There is much evidence that neuropathic pain, in particular central pain, leads to profound functional changes of the sensory thalamus. A series of crucial studies using microstimulation and recording in patients during stereotactic interventions has demonstrated that in patients with such pain the thalamic somatotopy is reorganized and there are marked signs of neural hyperexcitability and changes of response properties (27,28 and 29; review, see reference 2). Although stimulation in the somatosensory, as well as in the intralaminar nuclei, in patients undergoing surgery for movement disorders (Parkinson's disease) evokes only sensations of paresthesias, warmth, and cold, the same stimulation applied in patients with central pain often gives rise to a burning type of pain, usually referred to the painful region of the body. A pain-provoking effect of the stimulation appears to be more likely in patients presenting with peripheral signs of neuropathy in the form of allodynia and dysesthesia (30).

The clinical relevance of the animal experimental studies referred to previously may be questioned for the same reasons that apply to similar investigations performed to explore the physiologic mechanisms involved in spinal cord stimulation. Thus, these studies have used phasic noxious peripheral stimuli applied in intact animals,

under general anesthesia, and the effects observed were transient and short lasting. However, there is an electrophysiologic study performed using cats that apparently has been designed to mimic the condition of neuropathic pain (31). The animals were subjected to trigeminal deafferentation, resulting in increased spontaneous neuronal discharge in the spinal trigeminal nucleus. Stimulation, both of the sensory thalamus and the internal capsule, inhibited this deafferentation hyperactivity in approximately 40% of the neurons, and there was a long-lasting poststimulatory effect. Of particular interest is also a behavioral study by Kupers and Gybels (32) performed on a rat model of mononeuropathy. After a partial sciatic nerve-injury these animals display signs of neuropathy in the form of tactile hypersensitivity in the hind paw of the nerve-ligated leg. Stimulation applied to the sensory thalamus resulted in a marked suppression of this hypersensitivity that outlasted a 30-minute stimulation period by approximately 30 minutes. This study is of particular clinical relevance in view of the fact that in some patients undergoing sensory thalamic stimulation for neuropathic pain of peripheral origin, allodynia and dysesthesia can be markedly attenuated as well.

Stimulation of the posterior sensory limb of the internal capsule was introduced primarily for the treatment of central pain originating from lesions in the thalamus (15). Stimulation in this target gives rise to paresthesias indistinguishable from those evoked by sensory thalamic stimulation, suggesting that the same physiologic mechanisms are involved. On the other hand, it is apparent that the posterior limb of the internal capsule, comprising the sensory part, also contains fibers with motor function, because when stimulation is applied in this region, the stimulus parameters have to be carefully adjusted to avoid inducing muscular activation (33). For this reason, it cannot be excluded that the mechanisms involved in pain relief with capsular stimulation may also, at least partially, be similar to those underlying the pain-relieving effect of MCS (see later in this chapter).

Periaqueductal-Periventricular Stimulation

Stimulation of the PAG/PVG region has evolved from animal experiments and from observations during the course of stereotactic thalamic operations. In 1969, Reynolds (34) reported that stimulation of the periaqueductal gray matter in rats could produce a powerful analgesia and this observation was later confirmed in a large number of studies (23,35). These investigations marked a major breakthrough in modern pain research because they demonstrated for the first time the existence of an endogenous pain-controlling system. Later it was found that stimulation applied in the posterior part of the wall of the third ventricle, the periventricular gray region, also could produce analgesia (36,37). It has also been demonstrated that stimulation of the parafascicularis nucleus can excite a large population of PAG neurons similar to the excitation that may be induced by peripheral noxious stimulation. Moreover, these excited PAG neurons were found to project to the nucleus raphe magnus, a well-known relay for descending pain-inhibiting pathways (38). These findings are of particular clinical relevance because in patients the PVG area is often preferred to the PAG, where stimulation may induce unpleasant sensations of fear and anxiety. In humans, the site of stimulation in the PVG partly corresponds to nucleus endymalis and the medial part of parafascicularis (39) (Fig. 101-1).

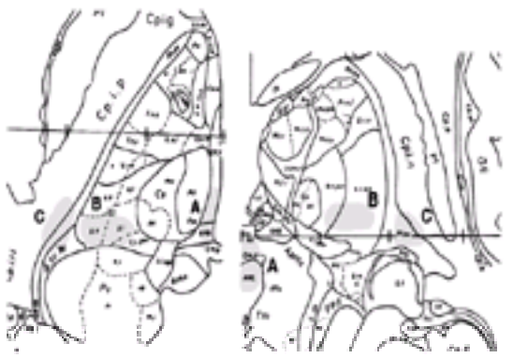

Figure 101-1. Approximate location and extent of stimulation susceptible regions in (A) the periventricular gray matter (PVG), (B) the sensory thalamic nuclei VPM/VPL, and (C) the internal capsule. Note that the PVG comprises the nucleus endymalis and at least part of the parafascicularis nucleus. The internal capsular target region is located in the most posterior and medial portion and comprises part of area triangularis and nucleus reticularis pulvinares (31). Left: Horizontal section 2 mm above the intercommissural plane. Right: Transversal section corresponding to the posterior commissure. Distances between marks on the horizontal lines in each figure represent 10 mm. (Adapted from Schaltenbrand G, Bailey P, eds. *Introduction to stereotaxis with an atlas of the human brain*. Stuttgart, Germany: Georg Thieme Verlag, 1959, with permission.)

Most of the experimental data on pain suppression by PAG/PVG stimulation may not be relevant for clinical applications. These experiments have been designed for the study of acute nociceptive events, and well-defined and reproducible pain-evoked reflexes such as tail flick and paw withdrawal on hot plate have been used. The relevance of nociceptive reflexes is debatable because the mechanisms underlying chronic pain are presumably different from those involved in acute nociception. There are several reports concerning the effect of PVG stimulation in patients with experimental pain induced by, for example, intense electrical stimulation, hot plate, or pinprick, but no attenuating effect could be demonstrated (40,41). However, there is one preliminary report that PVG stimulation may significantly increase the mechanical pain threshold as well as that for thermal nociception, both with regard to heat and cold pain (26). Furthermore, attenuation of pain perception using an ischemia test has been documented (42), although this is at variance with other reports (43).

There is but one experimental study that appears to be of particular clinical relevance because it has been performed on an animal model of chronic nociceptive pain (37,44). Rats that were rendered arthritic were subjected to stimulation in the periventricular area, which was found to suppress scratching and biting behaviors that were interpreted as signs of ongoing pain.

The demonstration that the analgesic effect of PAG/PVG stimulation in experimental animals is associated with the activation of the endogenous opioid system (45,46) suggested that a similar mechanism is involved in the clinical application of such stimulation. It has further been demonstrated that the central “opioid system” comprises not only the PAG/PVG area but also extends all the way from the arcuate to the raphe nuclei. It has been argued that stimulation anywhere along this system would have an analgesic effect, and in fact, several of these alternative stimulation targets have been explored (47). The involvement of opioid mechanisms was further supported by the observation that the stimulation-induced analgesia could be reversed with naloxone (48) and it was subsequently found that in patients stimulation produced an increased release of b-endorphin in the cerebrospinal fluid (49). In later studies, a direct relationship between the release of met-enkephalin and pain alleviation with PVG stimulation was demonstrated, whereas stimulation of the sensory thalamus failed to influence this release (50). The pain-relieving effect of PVG stimulation has also been found to be naloxone reversible (40). However, this is not a reproducible phenomenon in all patients (51,52), an observation that may relate to the finding that the dorsal part of the PAG area appears not to be associated with opioid-dependent mechanisms (53,54).

The development of tolerance to stimulation and the phenomenon of cross-tolerance between stimulation and the analgesic effect of exogenous opioids have been described (55). However, it appears that the incidence of tolerance development is maximal during the first 2 years and less common thereafter (56). There is evidence that the phenomenon of tolerance is perhaps not primarily related to the opioid system *per se,* but rather due to exhaustion of monoaminergic systems. The possible involvement also of serotonergic and noradrenergic mechanisms (57) has led to trials to counteract the development of tolerance by the administration of the precursor l-tryptophan (58), but the potency of this substance in restoring the pain-relieving effect of stimulation has not been confirmed. Moreover, serious side effects have been reported (7) (for further discussion on the physiologic background of PVG stimulation, see references 3 and 59.)

Clinical Considerations

Indications and Choice of Stimulation Target

In spite of having been in clinical use for more than two decades, ICS still cannot be regarded as an established treatment modality to be routinely applied. Therefore, it should be practiced only in centers with extensive experience in dealing with difficult pain problems and with a thorough knowledge of stereotactic procedures. It is a treatment approach that should be considered only when other less invasive therapies have failed. On the other hand, it might be that in some pain conditions ICS may compare favorably with intrathecal morphine infusion in a long-term perspective and particularly with regard to side effects.

There is much evidence indicating that stimulation applied to the sensory thalamus is effective only for pain identified as neuropathic. Therefore, the indications for this target are, in principle, the same as for spinal cord stimulation. Stimulation of the sensory thalamus is also indicated for similar pain conditions with supraspinal etiology, in particular pain originating from the trigeminal system. Some forms of neuropathic pain are associated with extensive degeneration of the primary afferent

fibers projecting in the dorsal columns, and these conditions are generally not amenable to spinal cord stimulation. Obvious examples are pain after spinal cord injury and pain after dorsal root avulsion or section. Patients with extensive peripheral nerve injury may present with profound deafferentation and the same may apply to postherpetic neuralgia. Other examples of deafferentation are phantom limb pain, trigeminal neuropathic pain, and facial anesthesia dolorosa. All these conditions may respond to sensory thalamic stimulation. There are reports also of patients with sensory thalamic stimulation applied for lumbosacral rhizopathy as part of the mixed condition of “low back pain” or “failed back surgery syndrome” (60).

In principle, the indications for sensory thalamic stimulation apply also to stimulation of the sensory limb of the internal capsule, albeit this target has been primarily used for the treatment of central poststroke pain (61,62). Such pain has, in a limited number of cases, also been reported to respond to stimulation in the sensory thalamus, but this is for obvious reasons not possible in the case of pain that originates from a thalamic lesion.

There is to date general agreement that PVG stimulation is mainly efficacious for pain characterized as nociceptive (in some studies referred as *somatogenic*). In practice, this often refers to what in the literature is described as “low back pain”—that is, pain confined to the lower part of the back and primarily originating from pathology in nonnervous tissues, such as muscles, joints, and ligaments. The syndrome of low back pain often represents a mixed form of pain comprising both nociceptive and neurogenic components. To identify and evaluate the relative importance of these components, a thorough pain analysis is mandatory for the proper selection of stimulation targets. Hosobuchi (60) has advocated the use of an intravenous morphine test that had proven to be helpful in predicting the possible responsiveness of the pain, or a pain component, to PVG stimulation. Although the reliability of such testing has been challenged on the grounds that some rare cases of neuropathic pain may respond to opioids, the test has in clinical practice been widely used and found to be helpful in differentiating nociceptive and neuropathic pain or pain components (63,64 and 65).

Notwithstanding, there are some patients with a definite diagnosis of neuropathic pain who have been reported to benefit from PVG stimulation (42).

Furthermore, there are a few reports of PVG stimulation applied in patients with chronic pancreatitis, ostitis, osteoporosis, and so forth, but the number of cases in each diagnostic group is too small to evaluate the usefulness of these indications. Previously, PVG stimulation was also applied to patients with cancer-related pain for which opioids provided insufficient relief or produced intolerable side effects (66). However, because of the advances in cancer pain treatment, ICS is no longer indicated for such pain.

Results of Clinical Studies

The outcome of major recent studies is summarized in Table 101-1 and Table 101-2. From these data, it appears that the efficacy of stimulation in either of the targets is quite variable, ranging from 30% to 80%. In a number of publications, the world literature on ICS has been summarized (6,7,24,67), and it appears that there is a tendency that somewhat better results are reported in studies from United States than from Europe. It should be noted, however, that there are hardly any publications originating from European centers in the last 10 years. Bendok and Levy (68) have performed a thorough metaanalysis of all studies including more than 15 patients. In 13 studies comprising 1,114 patients, the long-term good results varied between 19% and 79%. There was a clear tendency that the incidence of favorable overall results decreased during the first year, and for example, Richardson (3) reported a gradual reduction of good results with PVG stimulation, from 85% to 65%. The corresponding figures for the outcome of stimulation for neuropathic pain have been reported to be 61% and 30%, respectively (5).

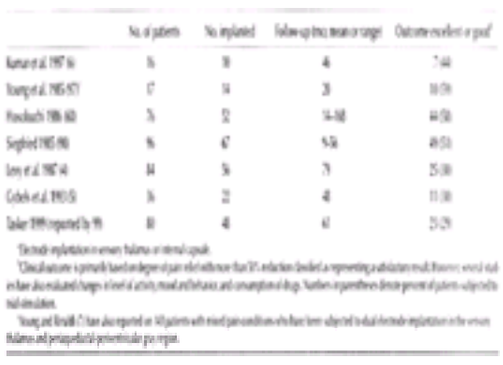

TABLE 101-1. Results of recent studies on intracerebral stimulation applied for neuropathic pain

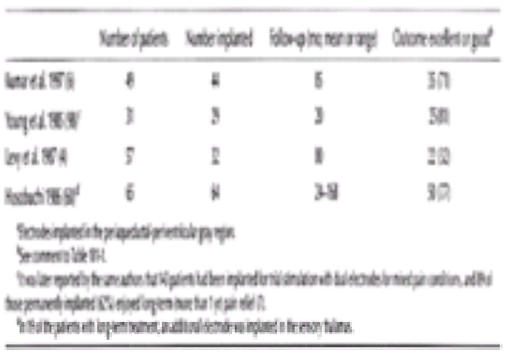

TABLE 101-2. Results of studies on intracerebral stimulation applied for nociceptive pain

The results of several of the major ICS studies with long-term follow-ups clearly show that the outcome is more favorable in patients with nociceptive than neuropathic forms of pain. Young and Rinaldi (7) reported 70% and 50% success rates for the two types of pain, respectively, and the corresponding figures in the above-mentioned metaanalysis were 61% and 42%. However, the difference with regard to neuropathic and nociceptive pain is at variance with the extensive study by Levy et al. (4), reporting that in patients with nociceptive pain subjected to PVG stimulation, a long-term favorable outcome was recorded only in 32% of those originally subjected to trial stimulation. In the most recent study it was concluded that low back pain is the best indication for ISC (6). With PVG stimulation, and in a few cases with dual electrodes (electrodes both in PVG and in sensory thalamus), 71% (35 out of 49 patients) reported excellent or good pain relief (more than 50%), considerable reduction of analgesic intake, and improvement in work tolerance. Apart from low back pain with or without radiating leg pain as a sign of lumbosacral rhizopathy necessitating dual-electrode implantation, the number of patients in each diagnostic group of neuropathic pain is too small to permit any definite conclusions concerning the efficacy of ICS. According to the metaanalysis referred to previously, it is apparent that PVG stimulation may be effective also for neuropathic pain, and in fact, no less than 23% of those having long-term success had been treated with stimulation in that target. The possibility that PVG may be efficacious also for neuropathic pain is further substantiated by the observation that pain relief may be accompanied by an objectively demonstrable suppression of peripheral signs of neuropathy in the form of allodynia and dysesthesia (69). On the other hand, sensory thalamic stimulation seems to be completely ineffective for nociceptive forms of pain. Some of the major studies provide data for the different types of neuropathic pain treated with sensory thalamic stimulation. However, it appears that the results are extremely variable and inconsistent, and, for example, anesthesia dolorosa is reported to respond favorably in many studies, whereas in others it is concluded that this diagnosis is a bad indication (2). In a group of 36 patients suffering from various forms of neuropathic pain (e.g., thalamic, cervical root avulsion, phantom, postherpetic) reported by Gybels et al. (5), 22 had a favorable short-term outcome, but only in 11 (30%) was the effect retained after 4 years' follow-up. The results in central pain, generally referred to as *thalamic pain*, as well as pain in spinal cord injury, indicate that these conditions have low probabilities of a favorable response. Conversely, the results in lumbosacral rhizopathy are reported to be successful in approximately 70% of the cases, although this diagnosis is reported separately from a low back syndrome only in a few studies.

Surgical Technique

Stereotactic electrode implantation should be performed under local anesthesia in order to enable communication about effects of intraoperative stimulation to ascertain correct positioning of the electrode. Target localization can be performed with the aid of ventriculography, computed tomography, or magnetic resonance imaging. Three types of electrodes suitable for ICS are available: a monopolar and two quadripolar electrodes with different spacing between the stimulating poles (Fig. 101-2). The quadripolar type of electrode is advantageous because it makes the placing of the electrodes with regard to depth less critical (for details concerning the technique for implanting and fixing the electrode, see the manufacturers' manuals). The connector to the percutaneous leads for trial stimulation as well as for the lead to the receiver/pulse-generator is preferably placed on the skull. To minimize protrusion from the connector it should preferentially be placed in a groove made with high-speed burr in the outer table of the skull. All patients require preoperative assessment of coagulation. Platelet-altering drugs such as nonsteroidal antiinflammatory drugs and aspirin must be discontinued.

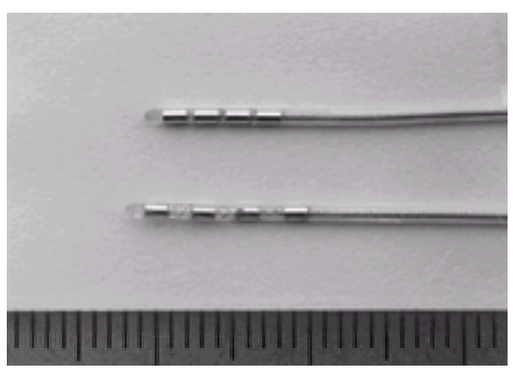

Figure 101-2. The two types of intracerebral stimulation electrodes presently available (Medtronic, Inc., Minneapolis, MN).

A prerequisite for obtaining pain relief with stimulation of the sensory thalamic nuclei is the elicitation of paresthesias in the painful area. To find the appropriate part of the sensory nucleus, the detailed atlas by Emmers and Tasker (70) is helpful. There is some evidence that stimulation in the basal part of the nucleus corresponding to the transitional zone of the medial lemniscus, where the threshold for evoking paresthesias is low, can be a more effective stimulation target than the nucleus itself (60).

The sensory thalamic nucleus is a comparatively large structure, whereas the PVG region in the medial diencephalic-mesencephalic junction zone, from where stimulation-produced pain relief is obtainable, is small. In particular, the mediolateral extension of the susceptible region, which does not exceed 2 to 3 mm, makes the electrode placement critical (39,60) (Fig. 101-3). The extreme precision that is required for implantation of electrodes in the PVG region, as well as the adjacent parts of this region being linked to both opioid and nonopioid mechanisms, accounts for some of the variability in the clinical results reported with this stimulation target.

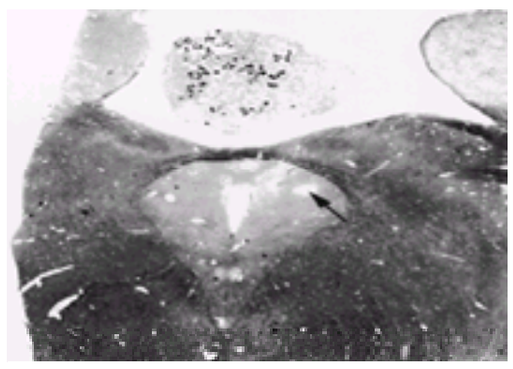

Figure 101-3. Autopsy specimen showing the uppermost part of the periaqueductal gray from a patient successfully treated with periaqueductal- periventricular gray region stimulation for visceral cancer-related pain. (*Arrow*, electrode tract.)

In contrast to stimulation of the sensory thalamic nucleus, PVG stimulation generally is performed with an intensity subthreshold to subjective sensations. At the onset of stimulation, however, patients generally report a pleasant feeling of warmth invading the trunk or the face, but this sensation does not necessarily imply that pain relief can be achieved. Even though stimulation is performed unilaterally, the evoked sensations have a symmetric, truncal distribution. Increased stimulation intensity may produce ocular oscillation and unpleasant sensations of fear, oppression, or anxiety. The approximate location and extent of the stimulation susceptible parts in the internal capsule, the sensory thalamus, and the periventricular region are depicted in Figure 101-1.

For details concerning stereotactic target localization and intraoperative stimulation and recording, the reader is referred to the paper by Tasker (71).

Stimulation Regimen

There are several reasons why trial stimulation should be performed for a period of at least 1 to 2 weeks. First, one has to ascertain that the electrode is correctly placed, as evidenced by the presence and distribution of paresthesias in case of sensory thalamic stimulation and of sensations of warmth and ocular movement (often diplopia) at higher intensity of stimulation in the PVG target. Second, a few patients perceive the stimulation-induced paresthesias as unpleasant or even painful (72). Third, the evaluation of the pain-relieving effect is, of course, necessary for the determination of whether to proceed to permanent implantation. It is a general experience that pain relief of less than 50% does not justify a permanent implantation. Of course, a few weeks' period of trial stimulation is not sufficient to eliminate the risk of a placebo effect (see Chapter 81). However, it is our experience that the presence of a poststimulatory pain-relieving effect lasting for at least 1 hour is suggestive of a true suppression of the pain rather than the result of placebo. It is therefore important to record in detail the time course of the stimulation effect. Fourth, different couplings of the stimulating poles should be tried to find the optimal combination. It should be noted that stimulation of the sensory thalamus should be applied with an intensity just suprathreshold for evoking paresthesias in the painful area. In the PVG target, pain relief may be obtained also with stimulus intensity subthreshold to any subjective sensations. This gives the opportunity, in this target, to use sham stimulation during the trial period, using, for example, an exhausted battery.

As a rule, stimulation of the sensory thalamus must be continued for 15 to 30 minutes to obtain pain relief. In general, the poststimulatory effect lasts for several hours and in exceptional cases it may persist for a considerably longer period of time. The patient should be allowed to choose the frequency that is perceived as the most comfortable (generally 40 to 70 Hz). It should be noted that the pulse duration may be critical for the paresthesia distribution and extension. Although it is a well-known phenomenon that the pain-relieving effect of sensory thalamic stimulation often tends to fade during the course of the first year, there is no evidence that there is a development of tolerance or fatigue that could be counteracted by restricting the use of the stimulator.

In the PVG region, the usual stimulation frequency is 30 Hz and the pulse duration 200 µsec. In this target there is at least some rationale for suspecting development of tolerance, and for that reason the patients are instructed not to stimulate themselves for longer than 20 to 25 minutes at one time and, if possible, not more than three or four times per 24 hours.

The great majority of patients reported in studies until the last 5 years have been implanted with a passive receiver, activated by an external radiofrequency-emitting generator. The fully implantable and programmable pulse generators presently available offer many advantages. However, it is important that the generators are programmed with a low maximal intensity and preferably also for limited periods of stimulation. Erroneous handling of the stimulator can lead to an inadvertently high stimulation intensity, which may produce unpleasant sensations with strong and almost painful paresthesias from the sensory thalamus and nausea, diplopia, and

anxiety from the PAG/PVG.

Complications and Side Effects

Serious surgical complications rarely occur with intracerebral implantation of electrodes. A survey of major studies reveals that hemorrhages have occurred in approximately 3% of the patients. A new design of ICS electrodes, now available, will presumably reduce the risk of producing intracerebral bleedings. Introduction of an electrode into the sensory thalamus may result in mild, local dysesthesia confined to the area corresponding to the part of the nucleus implanted, but this is generally a transitory side effect. Electrode implantation in the PAG/PVG may cause a slight but also transitory diplopia.

Infection at the receiver side or along the subcutaneous leads has been reported in some cases (approximately 3%), but the risk is minimized by the use of prophylactic antibiotics. Even though the trial stimulation period via percutaneous extension leads is often prolonged for several weeks or even months, only a few cases of intracranial infections have been reported. Otherwise, side effects related to the implanted material and equipment failures are similar to those with spinal cord stimulation (see Chapter 100).

Concluding Remarks

Similar to other invasive procedures, scientific criticism can be leveled against most studies on ICS as pain treatment. The lack of controlled studies, heavy influence from physician bias due to the lack of third-party evaluation, and no use of placebo stimulation (which would be possible at least with PVG stimulation) are all factors that preclude classification of ICS as evidence-based medicine. Moreover, the reported results are highly variable, ranging from 30% to 70% success, and the outcome measures are often relatively simplistic. Nevertheless, a thorough examination of the few recent publications with long-term results unequivocally reveals that a comparatively large proportion of patients with chronic pain who have failed to respond to any other treatment modality have enjoyed a useful and sustained alleviation of their pain. Although there are reasons to argue that the clinical data available to date “prohibit an objective appraisal of the clinical efficacy of deep brain stimulation,” as stated in a paper by Duncan et al. (24), we strongly believe that ICS should remain in the treatment armamentarium of a large pain center. It is most regrettable that medicolegal regulations in the United States in practice have deprived many patients of this therapy. It is true that the application of ICS requires considerable experience and expertise, but it should be emphasized that it is an invasive procedure that carries a relatively low risk of complications and side effects. The availability of a new type of electrodes designed to minimize the trauma to cerebral tissue can be expected to further reduce the incidence of serious complications because of intracerebral hemorrhages. Many patients who have benefited from ICS on a long-term basis suffer from pain in the lower part of the back, with or without signs of rhizopathy, and many of them may be candidates for long-term intraspinal morphine administration in case spinal cord stimulation has failed. Intraspinal morphine has gained in popularity in recent years, and there are a large number of reports substantiating its efficacy. However, many patients subjected to this therapy suffer serious side effects as well as the development of tolerance. We believe that for these patients ICS should be considered as an alternative therapeutic approach.

MOTOR CORTEX STIMULATION

Basic Considerations

As compared to stimulation of the sensory thalamus, and to some extent the sensory limb of the internal capsule, there seems to be little rationale for selecting the motor cortex strip (area 4) as a stimulation target for pain. MCS has been in use for approximately 8 years; however, the underlying mechanisms of its pain-relieving effect are poorly understood, and there are few experimental data pertaining to its mode of action.

At the International Association for the Study of Pain World Congress on Pain in 1990 in Adelaide, when Tsubokawa and collaborators (8) first reported on their clinical experience of MCS applied for central pain, there was also another report from the same group describing experiments in cats subjected to MCS (73). In these animals, thalamic neurons had been rendered hyperactive by spinothalamic tractotomy and it was demonstrated that stimulation of the motor, but not the sensory, cortex could suppress the increased neuronal spontaneous discharge. It should be noted, however, that Namba and Nishimoto (31) earlier had performed trigeminal denervation in cats, resulting in deafferentation hyperactivity in the spinal trigeminal nucleus. In their experiments, hyperactive wide-dynamic-range neurons could be inhibited by stimulation of *both* the sensory and of the motor cerebral cortex. It was further found that the activated corticofugal pathways were passing by the sensory limb of the internal capsule and the sensory thalamus. Because the latter two stimulation targets have since long been used for the management of certain forms of neuropathic pain, it is in this context relevant that MCS appears to be exclusively effective for such types of pain.

It has long been known that electrical stimulation of the sensory-motor cortex in rats, cats, and monkeys, not subjected to previous deafferentation, may produce presynaptic inhibition of spinal primary afferents and also of spinothalamic tract neurons (74,75,76 and 77).

In a neuroanatomic study using neuron labeling, the connections of the motor cortex were further examined with the purpose of exploring possible mechanisms involved in MCS (78). It was demonstrated that the motor cortex is reciprocally connected not only with the sensory cortex but also with a part of the sensory and posterior nuclei of the thalamus (for details concerning motor corticothalamic connections, see reference 79). Such connections have, in fact, been the basis for a theory advanced by Tsubokawa to explain the pain-relieving effect of MCS (80,81). It is hypothesized that pain after a cerebral lesion is the result of a deficient inhibitory pain control. Ortho- or antidromic activation of large-fiber reciprocal connections between the motor and sensory cortices by MCS would in turn activate nonnoxious fourth-order sensory neurons, giving rise to a restoration of the inhibitory pain control. Circumstantial evidence, compatible with Tsubokawa's hypothesis for neuronal activation, or synaptic events, in the cortex is provided by the finding that in a case of parietal cortex hypoperfusion, demonstrated with single photon emission computed tomography, MCS produced normalization of the regional cortical circulation (82). On the other hand, there are in the literature accounts of three patients, one reported by Peyron et al. (83) and two by Nguyen et al. (10), who benefited from MCS in spite of the fact that they presented with extensive parietal lobe infarctions involving also the sensory cortex. Moreover, in a positron emission tomography study, no cortical activation could be demonstrated in conjunction with MCS (83), and the same observation has been made by Hsieh et al. (84). Instead, a significant cerebral blood flow increase, reflecting augmented neuronal activity, was present in the ipsilateral thalamus, the cingulate gyrus, the orbitofrontal cortex, and the brainstem. It was concluded that the integrity of the somatosensory cortex and the lemniscal system does not seem to be a necessary condition for obtaining pain relief by MCS. These findings are thus at variance with Tsubokawa's theory. Instead, there is reason to believe that the thalamus, and presumably also the brainstem, is the main relay for pain control with MCS, and the fact that in one of the patients studied, somatosensory evoked potentials were clearly abnormal suggests that also the sensory thalamus is not necessarily involved. On the other hand, it is not yet clear how the thalamus and the brainstem as well as the cingulum may be activated by MCS without any signs of cerebral blood flow changes reflecting neuronal activity in the motor cortex. Moreover, there are several patients with extensive thalamic lesions who are reported to have benefited from MCS, although details on the extent and configuration of the lesions have not been published.

Clinical Considerations

Selection of Patients

There is substantial evidence indicating that MCS is efficacious only for certain forms of neuropathic pain, and no data suggest that it may influence nociceptive pain. The principal indications are central supraspinal pain and pain in trigeminal neuropathy. It should be remembered that MCS is still to be regarded as an advanced form of pain treatment that is not yet established as a routine, and it should be practiced only in major centers with extensive experience of the management of difficult pain conditions. Therefore, it is mandatory that all other less demanding and less invasive therapies should first have been tried. As with all forms of central nervous system stimulation for pain, MCS may be a lifelong therapy, and the continuity in the physician-patient relationship must be guaranteed. A mandatory requirement is that the patient has realistic expectations about the possible outcome and also is able to communicate and evaluate the possible effects. Otherwise, inclusion and exclusion criteria are very much the same as for spinal cord stimulation (see Chapter 100).

Particularly when applied for a central pain, the outcome of MCS is variable and there exist to date no reliable predictors. In a thorough study of patients with such pain, Yamamoto et al. (85) have used pharmacologic tests with the aim to relate the analgesic potency of barbiturate (thiamylal), morphine, and ketamine to the outcome of MCS. Thirty-nine poststroke pain patients with demonstrable thalamic or suprathalamic lesions were subjected to tests with these drugs administered intravenously. Definite pain reduction occurred in 21% of the patients with morphine, in 56% with thiamylal, and in 48% with ketamine. The responsiveness to the different drugs did not correlate to the site of the lesion. Conversely, there was a clear relationship between a positive outcome of the subsequent MCS treatment and thiamylal and ketamine sensitivity as well as morphine resistance. However, only 59% of the patients were responsive to thiamylal or ketamine, indicating that the predictive power of these pharmacologic tests is incomplete, although they may be of some help in selecting the patients.

It might be that the use of other drugs for testing may be useful in the selection of patients for MCS (86). For example, it has been reported that propofol at a low dose may alleviate poststroke pain (87), and the same seems to apply for intrathecal administration of baclofen (88).

There is an interesting report describing a patient with central pain in whom repetitive magnetic coil stimulation of the motor cortex for 30 minutes produced 30% pain relief. In that patient, subsequent long-term MCS proved to be effective, whereas another case failed to respond to both types of stimulation (89).

It has been described that focal transcranial magnetic stimulation integrated with frameless stereotactic technique enables a highly selective activation of individual muscles or groups of muscles (90). The preoperative application of this novel method of magnetic stimulation could be helpful.

The significance of the integrity of the corticospinal motor system in predicting the responsiveness to MCS has been emphasized in a study by Katayama et al. (91). Thus, it was found that in patients with central pain the long-term outcome was much more favorable in those with no or mild motor weakness than in those with more pronounced deficits. There was a similar relationship with regard to whether or not it was possible to induce muscle activation by high-intensity, low-frequency cortical stimulation.

Results

The most common indications for MCS are supraspinal pain after hemorrhage, infarction, or neurosurgery and painful trigeminal neuropathy, including facial anesthesia dolorosa. Occasional cases of pain after cervical root avulsion, pain in paraplegia or tetraplegia, as well as pain after peripheral nerve injury have been reported, but the number of patients with each of these diagnoses is too small to permit an evaluation. Both central pain and trigeminal neuropathy are otherwise notoriously difficult to manage (Fig. 101-4), and sensory thalamic or internal capsular stimulation rarely provide long-term beneficial results. Tsubokawa (80) in particular has emphasized that for central pain both these stimulation targets are effective in less than one-third of the patients, whereas MCS has a considerably better chance of success (2). The largest series of patients with central pain are those reported by Yamamoto et al. (85; see also references 80 and 92), Nguyen et al. (10), and Katayama et al. (91). As shown in Table 101-3, the overall positive results vary between approximately 45% and 75% of permanently implanted patients. An analysis of the patient materials reveals that there is no clear relationship between outcome and site of lesion. This implies that pain associated with a thalamic or suprathalamic lesion has an equally good chance of benefiting from the treatment. Also extensive lesions of the parietal cortex, comprising the sensory cortex, do not seem to preclude the possibility of a favorable outcome.

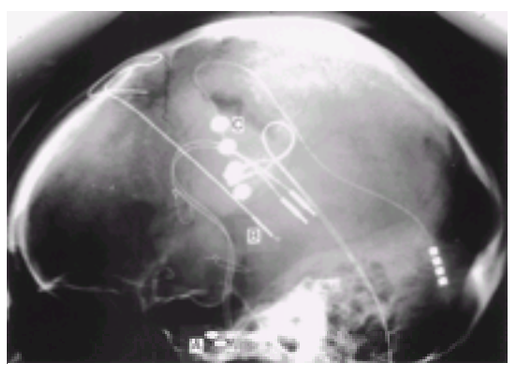

Figure 101-4. Radiograph of a patient suffering from trigeminal neuropathy with incapacitating chronic pain. This case illustrates that such pain may be extremely difficult to manage and that various invasive procedures may fail. This patient had been subjected first to stimulation of the gasserian ganglion (A) and then to sensory thalamic stimulation (B) as well as to stimulation of the spinal trigeminal tract (not illustrated). She has now for 7 years had a good, but not complete, pain relief with motor cortex stimulation (C).

	Number of patients trial/implanted	Follow-up (mo)	Number of patients with excellent or good outcome[a]	Average degree of pain relief
Tsubokawa et al. 1991 (80)[b]	110	24	51/80	>50%
Yamamoto et al. 1997 (85)	28	>12	13/46	>50%
Katayama et al. 1998 (91)	31/25	>24	15/48	>50%
Nguyen et al. 1999 (10)	13	27	10/26	>50%
Meyerson et al. 1993 (9)	10		8	
Katayama et al. 1994 (100)[c]	1	3-5	2	<50%
Peyron et al. 1995 (83)	2	12	1	20%

[a] Number and/or percentage of patients subjected to trial stimulation.
[b] Five patients in this study are later reported also by Yamamoto et al. (85) and Katayama et al. (91).
[c] Wallenberg syndrome.

TABLE 101-3. Motor cortex stimulation for central poststroke pain

As apparent in Table 101-4, MCS applied for trigeminal neuropathy tends to provide somewhat better results than in cases of central pain. The alternative treatments in this condition are stimulation of the trigeminal ganglion/rootlets or sensory thalamic stimulation. It is a general experience that the former treatment, which is easier to perform from a technical point of view, does not provide a satisfactory outcome in more than approximately 40% of the patients, and besides, it is not applicable in cases of extensive deafferentation due to a retroganglionic lesion of the trigeminal nerve. Sensory thalamic stimulation often fails, at least in a long-term perspective. For these reasons it is probable that MCS will become the treatment of choice for trigeminal neuropathy.

	Number of patients trial/implanted	Follow-up (mo)	Number of patients with excellent or good outcome	Average degree of pain relief
Meyerson et al. 1993 (9)	5/6	6-30	3/5	>60%
Tasker et al. 1994 (96)	7/8	1-24	3/5	>50%
Nguyen et al. 1999 (10)[a]	12	27	8/11	>60%
Herregodts et al. 1999 (101)	17/15	18-24	8/11	>50%

[a] Two patients still enjoy excellent pain relief after 5–7 yr; in three patients the effect progressively diminished and eventually disappeared.
[b] Excellent/good outcome has also been reported in some case of three of patients with pain in paraplegia and in three out of four with pain of peripheral origin.

TABLE 101-4. Motor cortex stimulation for trigeminal neuropathy

Some patients with central pain report the presence of paroxysmal, shooting pain components besides the deep, aching, and sometimes burning type of spontaneous, continuous pain. It has been reported that also the former intermittent type of pain may be effectively alleviated by MCS (10).

A majority of patients with central pain as well as trigeminal neuropathy present also with various forms of evoked pain because of the presence of allodynia and

dysesthesia; in some cases there are also signs of hyperalgesia, often being more prominent in subcutaneous tissue than in the skin. In several studies, it has been reported that the evoked pain components may be markedly relieved by MCS. An example of this effect is shown in Figure 101-5, which illustrates the reduction of dysesthesiae and allodynia in parallel with the relief of spontaneous pain in a patient with severe trigeminal neuropathy. There was no relief with placebo stimulation (not illustrated), possibly because stimulation did not produce any subjective sensations and the patient was thus unaware of whether it was on or off.

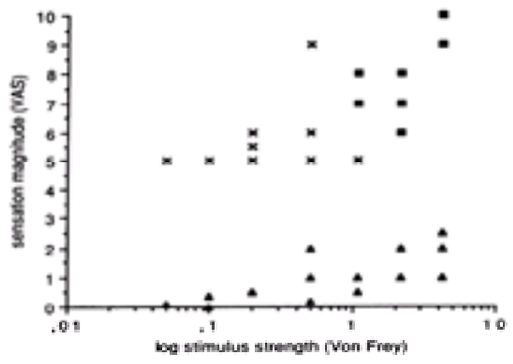

Figure 101-5. Effects of motor cortex stimulation on facial dysesthesia and allodynia assessed by von Frey filaments (stiffness expressed in grams of bending pressure on the abscissa) before and after a period of 30 minutes of stimulation. Note that the stimulation per se did not evoke any sensations. (Evoked pain: n, dysesthesia; x, allodynia before stimulation; s, sensation after stimulation.) Spontaneous pain: visual analog scale (VAS) 80/100 before and 20/100 after stimulation. [Reprinted from Meyerson BA, Lindblom U, Linderoth B, et al. Motor cortex stimulation as treatment of trigeminal neuropathic pain. *Acta Neurchir Suppl (Wien)* 1993;58:150–153, with permission.]

Surgical Technique

The crucial part of the implantation procedure is to localize not only the precentral motor gyrus but also to identify the appropriate portion of the gyrus according to its somatotopic organization. To ensure an optimal electrode position, one cannot rely on bony landmarks only. More sophisticated anatomic and functional means of localization must be used. For the purpose of identifying the central sulcus, Tsubokawa and collaborators, in their first report (8), described the use of preoperative examination with somatosensory-evoked potentials. The site where the N20 deflection of the response was phase-inverted into a positivity was marked on the skin of the skull and used as a point of reference for placing the burr hole and inserting the epidural electrode. An elegant method for anatomical identification and location of the motor cortex was introduced by Herregodts et al. (93,94). They produced preoperative three-dimensional magnetic resonance images of the cortical surface, and the location of the selected part of the precentral gyrus was identified in relation to the intersections of tubes, which were filled with magnetic resonance contrast–enhancing liquid, glued together as a net, and taped to the patient's head. In relation to this net the relative location of the chosen section of the motor gyrus was marked on the skin. This approach has been further developed by Nguyen et al. (10), who used a neuronavigator system enabling perioperative visualization and localization of the cortical gyri. It is recommended that craniotomy rather than only a burr hole be used for optimal positioning of the electrode, because it is then possible to further localize the central sulcus and motor cortex by both somatosensory-evoked potential recording and high-intensity, low-frequency stimulation, which produces peripheral muscle contraction. With this technique it has been possible to map the somatotopy of the motor cortex in detail, partly confirming the classic description by Penfield and Rasmussen (95) of the motor homunculus. It is also claimed that electrode placement via a craniotomy rather than a burr hole reduces the risk for epidural bleeding. Figure 101-6A is an example of the functional topography of the lower part of the motor gyrus and its spatial relationship to adjacent premotor gyri. The corresponding portion of the cerebral surface visualized with three-dimensional magnetic resonance imaging is depicted in Figure 101-6B.

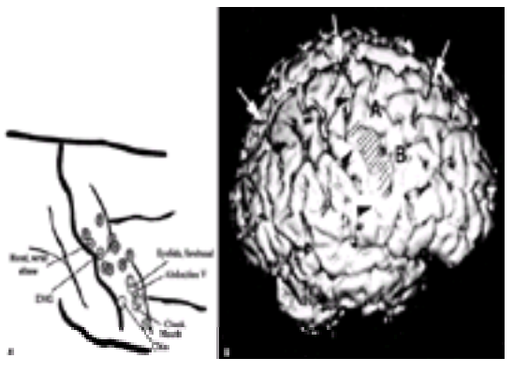

Figure 101-6. **A:** Somatotopic organization of the ventral part of the motor cortex according to Nguyen et al. (10). [Reprinted from Nguyen JP, Lefaucheur JP, Decq P, et al. Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. *Pain* 1999;82:245–250, with permission.] Circles denote sites where stimulation induced muscular activation in the hand (*dark gray*) and the face (*light gray*). (Abduction V, abduction ot the fifth finger; C, cheek; F, fingers; H, hand; M, mouth). **B:** A three-dimensional magnetic resonance image of the cortical surface where the approximate extent of the corresponding part of the motor gyrus, illustrated in the left figure, is striped. White arrows denote the interhemispheric fissure and the black arrowheads the central sulcus. *A* and *B* correspond to the superior and inferior frontal sulci, respectively. Note the location of these sulci in relation to the portion of the motor cortex representing muscular activation in the face and hand.

Many patients present with central pain that involves the entire side of the body but pain is perceived as most severe in the distal parts (face, hand, foot). Because MCS has to be applied strictly according to the somatotopic organization of the primary motor cortex it is not possible to cover the entire hemibody with one electrode strip. To enable suppression of pain in both foot and hand, a second electrode, connected to a separate pulse generator, must be used. To get access to the interhemispheric part of the motor cortex representing the lower extremity, the electrode must be positioned subdurally (83). However, the cortical representation of leg and foot is quite variable. In many patients it has been found to extend onto the medial part of the hemispheric convexity, implying that it may be possible to activate the leg-foot area by applying stimulation epidurally close to the midline [for a thorough discussion about motor cortex somatotopy, see Nguyen et al. (10) and Tsubokawa (81)].

There is no general agreement concerning the optimal orientation of the electrode strip. If oriented longitudinally onto the precentral gyrus (80), it is possible to activate a relatively large portion of the cortex. Others (10) apparently prefer placing the electrode perpendicularly to the central sulcus, with the stimulating pole onto the motor gyrus and one pole coupled as cathode and one pole as anode over the postcentral gyrus. This latter electrode orientation obviously makes the anterior-posterior placement less critical, although a much smaller section of the cortex can be activated and the location in the dorsoventral dimension must exactly fit to the somatotopy.

Complications and Side Effects

No serious complications associated with the implantation procedure or long-term application of MCS have been reported. As with all forms of implanted material there is a certain risk of local infection necessitating the removal of the system. Too few patients have presently been reported to permit an estimation of the infection incidence, but it is likely to be in the same order of magnitude as with spinal cord stimulation and ICS. Epidural hematoma, but without sequelae, has been reported to occur in a few patients. Several cases with stimulation-induced local pain at the site of the electrode have been described (10). This pain originates from the dura and it may be so troublesome that it necessitates a craniotomy and denervation of the dura by cutting and resuturing the part underlying the electrode.

In the trial stimulation phase (see later), when different stimulation parameters are explored, stimulation-induced seizures are relatively common. Of course, there is a fear that long-term stimulation could have a kindling-like effect, resulting in a state of epilepsy. No such case has been documented in the literature, but we have had

experience of one patient who, after 2 years of MCS treatment, developed an intractable epilepsy of the jacksonian type that persists after 4 years. However, it is not proven beyond doubt that the epilepsy was the result of MCS, *per se*, because it started shortly after an intervention for denervation of the dura because of unbearable local pain. The fits necessitated a reexploration that revealed a thin subdural clot measuring approximately 4 × 4 cm. At inspection no cortical lesion could be detected and the cortical surface had a normal appearance. The electrode was of course removed. Subsequent magnetic resonance imaging and positron emission tomography examinations have failed to reveal any local pathology that could account for the persisting daily motor fits. Because there is thus no definite proof that the stimulation was the principal cause for the development of epilepsy, we have not previously reported this case.

Stimulation Regimen

As with spinal cord stimulation and ICS, trial stimulation via percutaneous extension wires should always be performed during a period of at least 2 weeks. In most cases, trials with different stimulation parameters and electrode couplings are quite time consuming. It should be noted that the coupling of the stimulating poles can be very critical for obtaining relief of both spontaneous and evoked (allodynia, dysesthesia) pain in the entire painful region. This is especially the case if the electrode is positioned longitudinally over the precentral gyrus. The coupling appears to be particularly important in cases of facial pain, conceivably due to the extensive facial cortical representation and its strict somatotopic organization. This is illustrated in Figure 101-7, which shows a drawing made by a patient who suffered from severe and widespread trigeminal neuropathy.

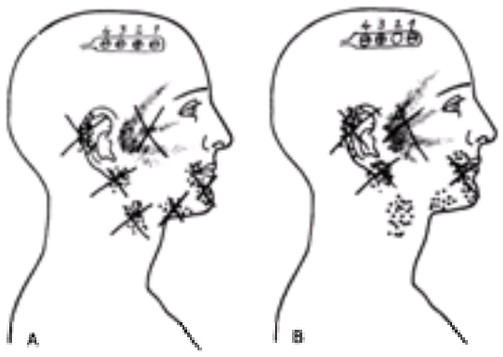

Figure 101-7. Drawings, made by a patient, showing the different areas of the face and neck where motor cortex stimulation, with different couplings of the stimulating poles of the electrode (shown in top of the figures), abolished spontaneous as well as evoked [allodynia (*dotted area*)] pain (*marked with crosses*). Note that stimulation with the electrode couplings indicated in **B**, as compared to those shown in **A**, failed to suppress ongoing pain and allodynia in two areas in the cheek region.

There is in the literature discordant information concerning the presence of stimulation-induced subjective sensations. Thus, Tsubokawa et al. (80) maintain that most patients experience faint tingling sensations. Conversely, most other studies report that stimulation is generally not accompanied by any sensations (9,10).

A pain-relieving effect is generally reported after 5 to 10 minutes of stimulation, and a further pain suppression is achieved during the subsequent 10 to 15 minutes. Complete abolition of the pain is exceptional. There is generally a poststimulation effect that may last for several hours. Most patients to date are treated with fully implantable pulse generators (ITREL 2 or 3; Medtronic) that are programmed for continuous stimulation or in a cycle mode with short intervals, 3 minutes on and 3 minutes off (10), or longer periods of stimulation, 30 minutes on and 3 hours off (96). In most studies, the stimulus intensity is generally set at a value corresponding to approximately 80% of that required to induce peripheral muscle contraction, assessed by stimulation applied at low frequency, and this implies that the voltage may be highly variable (2 to 7 V). It appears that the other parameters are not critical and stimulation both with high and relatively low frequency (40 to 130 Hz) and different pulse durations (60 to 350 µsec) have been reported to be effective.

Concluding Remarks

MCS must be regarded as a treatment modality under development; it cannot yet be recommended for a routine use. There is evidence that it has an approximately 50% chance of providing partial pain alleviation (more than 50%) of central supraspinal (poststroke) pain. Its efficacy seems to be somewhat better in painful trigeminal neuropathy (presumably including also anesthesia dolorosa), with an approximately 70% to 80% success rate. The positioning of the electrode is critical and should be performed with the aid of computed tomography or magnetic resonance visualization of the precentral gyrus and intraoperative electrophysiologic control. Optimal stimulation parameters remain to be assessed. Although no serious side effects have been reported, the possible risk of producing permanent focal epilepsy cannot be neglected. Because stimulation of the motor cortex as a rule is not accompanied by subjective sensations, it is for the first time possible to assess the effect of neurostimulation for pain using a double-blind procedure. In view of the promising results obtained in the treatment of pain conditions for which there is otherwise little to offer, a systematic exploration of the possible efficacy of the MCS for other likewise difficult pain conditions, such as pain of spinal origin and cervical root avulsion, is warranted.

CONCLUSIONS

Direct electric stimulation of the brain (ICS and MCS), although not generally providing complete pain relief, still offers therapeutic possibilities in painful conditions for which standard treatment modalities have been exhausted. These procedures deserve to be parts of the armamentarium of major pain treatment centers. MCS seems to be promising, particularly in view of the possibility of offering an efficient treatment for patients suffering from central or trigeminal neuropathic pain.

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CHAPTER 102

Regional Anesthesia with Local Anesthetics

F. Peter Buckley

This chapter discusses techniques that use local anesthetics (LAs) to interrupt neural conduction, most importantly afferent, but in some circumstances efferent, in the treatment of pain of a variety of sources. *Regional anesthesia* (RA) is chosen as a convenient descriptive phrase for these techniques, rather than more precise but cumbersome phrases such as *regional neural blockade*. It must also be acknowledged that these techniques may also be classified as anesthetic techniques, as they are not selective for neural transmission of nociceptive traffic. They interrupt both afferent and efferent neural conduction.

The techniques described in this chapter are illustrated in figures with technical descriptions detailed in the legends. This chapter is not intended as a definitive technical manual for those practicing RA and anesthesia. Rather the objective is to present the physician who is treating patients in pain but is not familiar with RA with some sense of what the techniques entail and their indications, contraindications, benefits, and risks. This approach is consistent with Dr. Bonica's long-held, oft-repeated belief that physicians treating patients with pain should have a broad-based knowledge of all therapeutic procedures used to treat pain, the better to treat and serve the suffering patient (1,2,3,4,5,6 and 7).

BASIC CONSIDERATIONS

Rationale for Use

RA is effective in managing patients with pain because it interrupts nociceptive input at its source or transmission of nociceptive information in afferent nerves. RA may also interrupt the afferent limb of abnormal reflex mechanisms, which contribute to the pathogenesis of some pain syndromes. RA can also interrupt the conduction of efferent sympathetic neural traffic that contributes to postoperative or posttraumatic pain and some chronic pain syndromes that possess a sympathetic component [e.g., complex regional pain syndromes (CRPS)]. Interruption of efferent sympathetic traffic also increases peripheral blood flow in circumstances of decreased flow, such as limb ischemia.

LAs are somewhat selective in interrupting neural traffic. Neural traffic in small nerve fibers and unmyelinated nerve fibers, such as A-d and C fibers, respectively, may be interrupted with low concentrations of LA, with only modest effects on larger myelinated fibers, which are predominantly efferent. Thus a nerve block may produce an analgesic, but not particularly paretic, body part. However, the use of higher concentrations of LA will result in interruption of all afferent and efferent neural traffic producing an analgesic and paretic body part, a situation that may be of therapeutic benefit in some circumstances (e.g., when neurally mediated muscle spasm is part of a pain syndrome).

The duration of the analgesic affect of an RA technique varies depending on the drug used (e.g., of brief duration with procaine, of much longer duration with bupivacaine). The duration of effect of the drug is determined by the drug's physicochemical characteristics and by the presence of vasoconstrictors that impede absorption of the drug into the vascular system and away from the site of action. In some pain states the duration of analgesia may outlast, by hours or days, the transient pharmacologic effect of the LA. In these pain states, afferent input may be activating or maintaining central neural processes that produce “central pain.” Interruption of the afferent input may quiet these processes (8,9,10 and 11).

Indications

RA can be used as a diagnostic, prognostic, or therapeutic tool, or as a combination of these.

Diagnostic Blocks

Diagnostic blocks can help with the following:

- Determine the anatomic source of pain: Pain from trigger points, neuromata, or painful joints may be eliminated by local infiltration. Peripheral nerve blocks may distinguish between a peripheral and central source of nociception.
- Determine nociceptive pathways: Via selective blocks, the anatomic pathways of a nociceptive process can be explored.
- Differentiate local from referred pain: Pain in proximal structures can produce pain referred to distal structures (e.g., hip disease may present as knee pain); RA of the knee will help determine the nociceptive source.
- Differentiate somatic from visceral pain: For example, pain of the trunk may be of somatic or visceral origin. Blockade of the intercostal nerves will interrupt the trunk wall somatic afferents without affecting the visceral afferents.
- Determine the sympathetic nervous system contribution to some pains: The sympathetic nervous system may contribute to, or be responsible for, a variety of pain syndromes (see Chapter 3, Chapter 4, Chapter 20) (12,13). Careful, precise sympathetic blockade may help to refine the diagnosis, be therapeutic, or both.
- Determine whether a painful deformity (e.g., in a limb) is caused by neurally mediated muscle spasm or by fixed deformities: Deafferentation and deefferentation (producing a paretic limb) will permit these distinctions to be drawn.
- Differentiate peripheral from central pain: Some pain syndromes may result from either a peripheral process or a central (spinal cord or brain process). Blockade of peripheral nerves may aid in the distinction of these two processes.
- Determine the role of nociceptive processes in complex pain syndromes: The pathophysiology of complex pain syndromes, particularly those of long duration,

may involve processes other than nociception alone. Regional block may aid in determining the role and extent of nociception in these syndromes.

Prognostic Blocks

These may be done to afford the patient and the physician the opportunity to observe the pain relief, sensory deficits, and other possible effects of a nerve block, as a prelude to a procedure that could produce a longer benefit than that afforded by an LA nerve block. Examples are a celiac plexus block in a patient with upper abdominal pain from a pancreatic tumor before a neurodestructive block or peripheral nerve blocks before consideration for dorsal rhizotomies or ganglionectomies. In these latter circumstances, it is unwise to proceed to a neurodestructive procedure on the basis of the result of a single block as there may be powerful placebo effects in operation. Several prognostic blocks, with LAs of differing duration of action, perhaps performed with the patient blind to the possible duration of effect, or the use of a continuous LA technique, may aid in the accuracy of prognostic blocks.

Prophylactic Blocks

Various nerve blocks may be used to ablate or diminish pain from trauma or surgery and these may exert an influence that transcends the duration of the blocks. There is evidence that epidural blocks maintained through the perioperative period may influence the incidence of postamputation phantom limb pain (14). In some postoperative pain studies, there is evidence that the single application of an LA block, before the patient experiences trauma or undergoes surgery, results not only in a diminution in pain during the period of efficacy of the block but also in an improvement in pain relief for prolonged periods beyond the efficacy of the block. This has been termed *preemptive analgesia*. Metaanalysis of the results of multiple studies of preemptive analgesia in postoperative pain are not strongly supportive of its clinical significance (15).

Therapeutic Blocks

Nerve blocks appropriate to the site of injury can diminish or ablate much of the pain following some operations or trauma. Single-shot nerve blocks such as brachial plexus blocks provide such relief for the duration of the LA's action. The duration of pain relief may be extended by days or weeks by using techniques that apply LA continuously to neural structures. The continuous techniques may be achieved by placing catheters alongside peripheral nerves (brachial plexus) or the epidural space or other spaces (e.g., interpleural space) and continuously infusing LA. The efficacy of continuous epidural LA techniques is greatly enhanced by the inclusion of low doses of opioid in the infused mixture (see Chapter 84).

In some chronic pain syndromes, nerve blocks may be efficacious in disorders involving the sympathetic nervous system (e.g., limb ischemia). In some circumstances (e.g., CRPS), regional blocks may be directly clinically efficacious and also provide analgesia to permit the application of mobilization techniques, which are an important component of therapy.

Principles of Application

RA has a useful and definitive role to play in the management of pain. However, for their optimal use, these techniques must be applied in the appropriate circumstances, in the appropriate manner, by an appropriately skilled practitioner, as propounded by Dr. Bonica (16,17,18 and 19).

The Physician

There are several requirements of the physician:

- While technical knowledge and expertise are crucial, it is also important that the physician have a thorough understanding of pain syndromes, their evaluation, possible treatments, and the side effects and complications of the possible treatments.
- Detailed knowledge of the anatomic basis of the procedure.
- Detailed knowledge of the side effects and complications of the procedure and the preparedness and skill to deal with them should they arise.
- Technical excellence and gentleness in performing the procedure. Patients with pain problems are poor subjects on whom to learn nerve blocks.
- A clear understanding of what to expect from the procedure.

Patient Assessment

The physician must be willing to fully evaluate the patient and the pain problem in order to be able to decide if a procedure is warranted, and if so, which procedure (see Chapter 12, Chapter 16). Before evaluating the patient, it is often appropriate to have patients keep pain diaries, which are patient-kept records of pain levels, activity levels, sleep, and other relevant symptoms. In the office, elements of the evaluation include the following:

- History from the patient and records with particular emphasis on the pain, its type, distribution, exacerbating and relieving factors, including drugs. Records may include pain diaries.
- Physical examination, with the emphasis on neurologic examination, particularly of the affected area.
- Review of available investigations and obtaining other investigations if necessary.
- Scrutinizing pain measurement tools such as a visual analog scale and pain evaluation questionnaires such as the McGill and the Minnesota Multiphasic Personality Inventory.
- Psychological or psychiatric evaluation.

The information derived from the evaluation enables the physician to decide whether any regional analgesic technique may be helpful in the evaluation, management, or both, of the patient's pain problem.

Communication with the Patient

When a regional analgesic technique is being contemplated, it is imperative that the physician tell the patient what is being advised, for what purpose (diagnostic, therapeutic, prognostic etc.), what to expect from the block (short-term and long-term), and how many blocks are advised. The physician should also discuss the risks and side effects of the procedure, what will be done to minimize the risks, and what will be done to maximize patient comfort. The patient should sign an informed consent form, which details the procedure and its risks.

Performing the Blocks

The procedures should be performed with the knowledge of the anatomy of the relevant region in mind and with an accent on avoiding complications. The use of needle placement aids, such as peripheral nerve stimulators, fluoroscopy with or without contrast medium, or ultrasound, is advised. For prognostic and diagnostic blocks, it is advisable to accurately place very small amounts (2 to 3 mL) of LA on the target nerve to produce the desired block without overspill of LA onto other structures. Repeating the block on two to three occasions with LA of varying durations of action or using a continuous technique may also provide useful information and patient experience. For therapeutic blocks, accurate placement is essential but there is more latitude about the choice of volume of LA. LAs of longer duration of action are most appropriate.

Efforts should be made to minimize patient discomfort during the procedure. This may be accomplished by the systemic use of modest doses of short-acting opioids (fentanyl, alfentanil, remifentanil) and sedatives (thiopentone, midazolam, propofol), although these have the potential to cause sedation and analgesia that may complicate the accurate assessment of analgesic efficacy with diagnostic or prognostic blocks. Good procedural technique and the use of small needles and liberal use of locally injected LA will contribute to patient comfort.

Assessment of Results of a Block

At intervals subsequent to the block, its physiologic effects and its pain-relieving effects should be ascertained. For obvious reasons, the block should be shown to be technically satisfactory. For somatic nerve blocks, sensory deficits to stimuli (light touch, scratch, pinprick, pinch) and motor deficits (weakness, reflex impairment)

should be sought and should be consistent with the anticipated effect of the block. For sympathetic blocks of the limbs, tests include increases in skin temperature, impairment of sweating, and skin conductance. For diagnostic or prognostic sympathetic blocks, it is important to test somatic sensory modalities, as LA may spill over onto somatic nerves and hence influence outcome and interpretation.

Provided that a block is technically satisfactory, its effect on pain and other pathophysiology should be observed and recorded. This observation and recording initially should be done in the clinic and then should be continued after the patient is discharged. The patient or relatives should record pain levels on a pain scoring sheet that categorizes pain levels and type of pain and block effects (numbness, weakness) for the next few hours and days. Duration of physiologic effect of the block and its correlation with duration of pain relief are important. With technically satisfactory blocks of the correct target, one expects duration of pain relief to be consistent with the duration of action of the LA used. A duration of pain relief shorter than that expected implies technical imperfection, that the wrong peripheral target was chosen, or that the neural source of pain is proximal to the site of the block. A duration of pain relief longer than expected implies a potential placebo effect or that the block interrupts self-sustaining neurophysiologic processes that can cause pain. Because of the uncertainties of interpretation of effects of the diagnostic or prognostic blocks, *it is advisable to perform the blocks with LAs of differing durations on several*(*usually about three*)*occasions before reaching conclusions about the effect of the blocks on the neural targets and the pain complaint*.

Limitations of Neural Blockade

Nerve blocks produced either by a single dose of LA or maintained by an infusion of LA through a percutaneous catheter are effective in relieving postoperative or posttraumatic pain. Because the damaged tissue may encompass many dermatomes, it is often necessary to also provide supplementary analgesia with opioid or nonopioid analgesics.

When used as diagnostic and prognostic entities, the limitations of nerve blocks should be borne in mind. In certain patients, provided technical and observational excellence is used, they are a useful addition to the available diagnostic and prognostic tools.

In patients with complex, chronic, and disabling pain problems, nerve blocks have a limited role. Blocks can be helpful as a way of jump-starting a pain management/reduction program but should be used in the context of a more comprehensive treatment program (see Chapter 11). Neurophysiologic and nociceptive abnormalities are only part of the etiology of these patients' pain and pain complaints, which also often have environmental, psychological, cultural, and disuse components. These latter components must be addressed if therapy is to be successful. Even in pain problems where the predominant initial etiology is probably neurophysiologic (e.g., CRPS), by the time a few weeks or months have passed other pathologies may be part of the pain syndrome (e.g., muscle contractures and weakness). These pathologies require specific therapy, which cannot be supplied by nerve blocks alone.

Pharmacology of Local Anesthetics

Safe and effective use of regional anesthetic blocks with LA requires a thorough knowledge of the pharmacology and properties of LA drugs. Table 102-1 lists important characteristics of commonly used LAs.

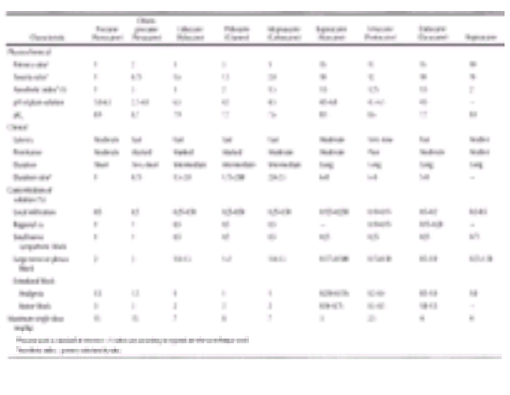

TABLE 102-1. Pharmacologic and clinical characteristics of local anesthetics

LAs produce temporary impairment of conduction of neural impulses by reversibly blocking nerve sodium conductance channels and maintaining the nerve in a polarized state. To achieve this effect, sufficient drug must be applied to the nerve membrane to produce a drug concentration that produces block; when the nerve concentration of drug falls, nerve function resumes. For *in vitro* studies of single nerve fibers in a nerve bath, sufficient drug to produce a block equates to drug concentration. When the drug is removed from the bath, the drug level in the nerve falls and nerve conduction resumes.

In the *in vivo* use of LAs, ingress to, and egress of, LA from the nerve, and the resulting onset and fading of neural block, are more complex. A number of pharmacologic and physiologic factors are at play (see Table 102-1) (20):

- Nerve size: To produce a block of a given nerve, the drug must penetrate the epineurium and perineurium to achieve a blocking concentration in the nerve and its fibers. Small nerve fibers (C, A-d, preganglionic sympathetic B) are blocked with low concentrations of drug; larger fibers (A-b and A-a) require higher concentrations. Small nerves (e.g., digital nerves: 1 to 2 mm in diameter) may be blocked with small volumes of low concentrations of LA (e.g., 1 to 2 mL of 0.5% lidocaine). Large nerves (e.g., sciatic nerves: 10 to 15 mm in diameter) require larger volumes of more concentrated LA (e.g., 12 to 20 mL of 1.0% to 1.5% lidocaine).
- Potency: Potency is an *in vitro* derived measure, confirmed by clinical studies, of the concentration of drug necessary to produce a block. Note that as potency increases there is a tendency for toxicity to increase, also expressed as anesthetic index of potency/toxicity.
- Drug pH and pK_a: To maintain product stability, most manufacturers of LAs formulate drugs at a low pH (4.5 to 6.0). However, the pK_a of most commercial LAs is between 7.0 and 8.0, and at that pH, the majority of drug is present as the ionized water-soluble form, as opposed to the unionized fat-soluble form.
- Penetrance: Drug penetrance (the perceived ability of the drug to cross barriers—a desirable property) is a function of the unionized form. Commercial drug must be alkalinized in the body for maximal effect (commercial drug may be alkalinized by the judicious addition of bicarbonate— *vide infra*). Penetrance roughly parallels the fat solubility of the drug.
- Latency: Latency is the relative speed with which the drug penetrates biological membranes *en route* to its target. Penetrance roughly parallels fat solubility and is influenced by pH.
- Duration: Duration is the time during which the drug produces its effect on the nerve. Duration roughly correlates with fat solubility and is also influenced by the mass of drug placed on the nerve (a bigger mass of drug takes longer to be removed from the site of action by the circulation).
- Blood flow at the site of injection: When LA is injected, it immediately begins to be absorbed by the circulation, distributed systemically, metabolized, and excreted. The quicker the LA is absorbed, the less stays at the site of injection to block nerve conduction. A block will, therefore, be of shorter duration. Different sites of drug deposition have differing blood flows: LA injected into areas with high blood flow such as the epidural space, will be absorbed more quickly and have shorter durations of effect than LA injected into areas with lesser blood flows such as the sciatic nerve.
- Inclusion of a vasoconstrictor in the injected solution: Most LAs produce vasodilation, enhancing circulatory absorption. Blood flow to a site of LA injection may be temporarily reduced, for about an hour, by the inclusion of a vasoconstrictor (commonly epinephrine 1:200,000, 5 µg per mL; lesser concentrations in children and the elderly) in the LA solution. The inclusion of epinephrine will tend to speed onset of LA block, reduce peak systemic blood levels of LA, and prolong the duration of effect of short- and medium-duration LAs (e.g., lidocaine, mepivacaine). Epinephrine has only a minimal effect on duration of block with longer-acting LAs (e.g., bupivacaine, ropivacaine) but does reduce peak systemic blood levels of drug.
- Alkalinizing LA: Most commercial LAs have a pH much below the pK_a of the drug and the majority of the drug exists in the ionized moiety. Raising the solution pH increases the concentration of the unionized moiety, which is believed to penetrate nerves more completely, leading to a faster onset and longer duration of effect. Raising the pH of lidocaine by carbonation has produced mixed results (21,22), but alkalinization of bupivacaine with bicarbonate may produce a faster onset and longer duration of effect (23,24).
- Attempted prolongation of LA effect: A number of agents have been mixed with LAs in the hope of prolonging duration of effect. Low-molecular-weight dextran has produced conflicting results (25,26,27,28,29 and 30), but high-molecular-weight dextran may produce a prolongation of effect (31,32) by alkalinization of the

solution. Substances that act as depot release agents for LA are under development and investigation. When bupivacaine is associated with liposomes, duration of epidural analgesia may be prolonged twofold, with less motor block when compared to plain bupivacaine (33). Similar effects may be produced in peripheral nerve blocks by the association of bupivacaine with biodegradable polymer microspheres (34).

Preliminary Considerations

Before any regional anesthetic procedure, other than minor procedures in which a minimal amount of LA is used, steps should be taken to ensure that the procedure can be carried out safely and effectively and that logistic issues concerned with safe discharge of the patient home are assured.

Nil per Os, Evaluation, and Consent

The patient should have an empty stomach to minimize the risks of nausea, vomiting, or regurgitation of stomach contents, and their potential pulmonary aspiration, either during the procedure or if complications occur. In practice this means no solid food for at least 8 hours and no clear liquids for at least 4 hours before the procedure.

Arrangements should be in place for the patient to be transported home by a responsible caregiver and for the patient to have access to a caregiver for 12 to 24 hours after the procedure.

The site and side of pain should be confirmed, the painful area should be reexamined, and the current presence of pain should be ascertained. It is pointless to perform diagnostic or prognostic blocks in the absence of pain.

The reason for the procedure, the steps of the procedure, and what the patient should expect to experience should be discussed. The expected outcome of the procedure, the duration of effect, and the incidence of common complications should be discussed. Based on these discussions, a written informed consent, witnessed by another adult, should be obtained.

Procedure Room and Equipment

The procedure should be performed in a room of sufficient size to accommodate the patient, stretcher, monitoring equipment, fluoroscope, and any other necessary equipment.

Regional anesthetic blocks have predictable effects on, and an incidence of complications affecting, the cardiovascular, respiratory, and central nervous systems. Hence, monitors capable of detecting these effects and complications, and equipment to deal with them, should be readily available. A means of ventilating a patient with 100% oxygen with a bag and mask, or via an endotracheal tube, and suction should be available. Airway management equipment and appropriate drugs to deal with procedure complications and resuscitation should be readily at hand (Fig. 102-1). There should be easy access to a “code cart” with drugs and equipment (e.g., defibrillator) required to manage a cardiac arrest.

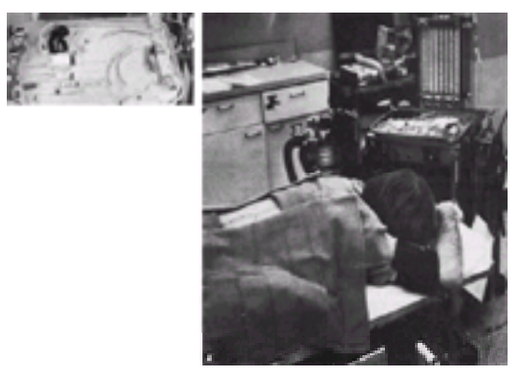

Figure 102-1. **A:** Position of patient for bilateral celiac plexus block. An anesthesia machine, resuscitation equipment, and drugs are next to the patient, ready for immediate use. **B:** Close-up of the tray on top of the machine. The tray contains ampules and syringes for administering epinephrine, ephedrine, diazepam (Valium), thiopental (Pentothal), and succinylcholine; behind these are different sizes of oropharyngeal and nasopharyngeal airways (left). The tray also contains a Macintosh laryngoscope, two endotracheal tubes, a Magill forceps for guiding tubes into the trachea, and a syringe for inflating the cuff of the endotracheal tube (right). The anesthesia machine is not necessary as long as equipment is available for immediate administration of oxygen and for carrying out assisted or artificial ventilation. Note: The patient has an intravenous catheter in a vein of the right hand and a continuous infusion of fluid for the prompt injection of resuscitative drugs if reaction occurs.

The person performing the procedure should be assisted by a staff member who is familiar with the procedures, the equipment and its use, and emergency management. This individual should also assist in patient positioning, comfort, and any emergencies that arise.

Patient Safety, Comfort, and Monitoring

Other than for minor procedures using minimal LA, all patients should have an intravenous line placed and kept patent by a slow fluid infusion (see Fig. 102-1). This assures access for the rapid administration of fluids and drugs (sedative, analgesic, resuscitation) should these be necessary.

Before any premedicant drugs are administered, the patient's vital signs should be obtained. The patient's vital signs should be monitored either continuously (electrocardiography and pulse oximetry) or at frequent intervals [blood pressure (BP) every 3 to 5 minutes], throughout the procedure.

Many patients are apprehensive, anxious, scared, or even frankly terrified of procedures such as nerve blocks. Hence, premedication with modest doses of short-acting opioid analgesics or sedatives should be routinely considered. Typical drug and doses are analgesic (fentanyl, 0.5 to 1.0 µg per kg i.v.) and sedative (midazolam, 10 to 20 µg per kg i.v.; thiopental, 1.0 to 1.5 mg per kg i.v.; propofol, 0.25 to 0.50 mg per kg). Lesser doses are appropriate in the older, smaller, and sicker patients. Premedication may be relatively contraindicated in circumstances where the drugs' central effects might impair the patient's subjective interpretation of the effects of the procedure (e.g., diagnostic or prognostic blocks). However, the short duration of effect of these drugs makes this of lesser concern than with longer-acting drugs. All sedative and analgesic drugs cause respiratory depression to some degree; patients receiving these drugs should be given supplemental oxygen.

Block Equipment and Drugs

Preservative-free LA drugs should be used for regional blocks, as this formulation has a higher pH and because the presence of a preservative may increase the risk for neural damage. Any epinephrine used should be added to the drug at the time of the block—commercial LA solutions with epinephrine have very low pH and contain preservative. The commonly used concentration of epinephrine used in regional blocks is 1:200,000 (5 µg per mL), although the concentration should be reduced to 1:400,000 (2.5 µg per mL) in the elderly and the young and when large volumes of dilute solution are used.

Needles should be of appropriate diameter and length—2.5 cm, 25 to 30 gauge for skin infiltration, 22 gauge for peripheral nerve blocks, 25 to 27 gauge for lumbar puncture for subarachnoid blocks (SABs), and various specialized epidural needles for epidural blocks. Short-bevel needles are advised for peripheral nerve blocks as these are believed to put the nerve at a lower risk of damage (35).

Accurate Location of Nerve Block Targets

RA requires that the LA is placed directly and correctly onto the intended neural target by placing the injecting needle close to or on the neural target. The classical approach to identifying correct needle placement is to gently probe the nerve with the tip of the needle. This maneuver produces a paresthesia in the area of the somatic distribution of the nerve. Once a paresthesia is produced, the needle is held steady and LA is injected. This technique has limitations. Probing some nerves (e.g., autonomic nerves) will not produce a paresthesia. There is evidence that producing paresthesia may increase the incidence of post–nerve block symptoms of neural damage (36). To avoid producing paresthesia and to help ensure accurate needle and drug placement, a number of different aides may be used. The use of aides to confirm correct needle placement and drug deposition is no substitute for detailed understanding of the anatomic and technical aspects of the block.

When blocking a mixed motor/sensory nerve, locating the nerve can be made easier by using an insulated needle connected to a peripheral nerve stimulator. By passing a current down the needle, the motor fibers in the nerve are stimulated, producing a twitch in the muscles supplied by that mixed nerve. This stimulation is usually not painful, as motor fibers are fired at lower current intensity than sensory fibers. Some patients may be alarmed at the uncontrolled twitching, and it is sensible policy to describe this in the preprocedure discussion. Characteristically, a stimulus frequency of 1 to 2 Hz (one to two stimuli per second), at a current strength of 1 mA, is used to advance the needle close to the nerve. Once a satisfactory muscle twitch is produced, the current intensity is reduced to 0.4 to 0.5 mA and the needle manipulated closer to the nerve, as evidenced by a maximal muscle twitch at the lower current intensity. A well-defined muscle twitch at this low current intensity implies that the needle is within a few millimeters of the nerve and LA is injected.

Radiography, fluoroscopy, and ultrasound are useful aids when accurate placement of the block is important (e.g., in diagnostic or prognostic blocks). These aids are particularly helpful when blocking pure sensory nerves, where the only other aid for accuracy is to probe the nerve with the needle and produce a paresthesia, or sympathetic nerve blocks where neither motor stimulation nor paresthesia is available as an aid. Preliminary injection of contrast media with radiographic visualization before the injection of LA can help confirm accuracy of needle placement and the potential spread of the LA. In addition, a permanent radiograph is an objective record of some of the details of the performance of the block.

Contraindications

Absolute contraindications to nerve blocks are as follows:

- A patient who is unwilling to accept the block or who does not sign an informed consent form.
- A patient who has a true allergy to the drugs used. True allergy to the ester LAs (procaine, tetracaine, chloroprocaine) is not uncommon, particularly as they share common allergenic features with sulfonamide antibiotics. However, these drugs are relatively rarely used. True allergy to the amide LAs (lidocaine, bupivacaine, ropivacaine) occurs but is exceedingly rare. Nonetheless, many patients report being told that they have an allergy to LAs, as manifest by side effects associated with the use of LAs, most frequently in dentistry. These effects are often not true allergy; rather they are often tachycardia or arrhythmias associated with the rapid absorption of epinephrine (1:100,000 epinephrine, 10 µg per mL, is commonly used in dentistry) or a vasovagal or psychogenic effect associated with an injection.
- Infection at the site of injection.
- Questionable blood clotting status.

Relative contraindications to nerve blocks are as follows:

- A clinical situation where a block may conceal the development of an untoward complication (e.g., a dense prolonged peripheral nerve block in a limb with a recent fracture which is at risk of a compartment syndrome).
- Debilitated, ill, and hypovolemic patients in whom the effects to the block, either of the injected agent or from a sympathectomy from the block, may produce an unacceptable degree of cardiovascular compromise.

Side Effects and Complications

RA is not a risk- and complication-free enterprise. To detect complications, patients should receive vigilant and continuous physiologic monitoring (electrocardiography, BP, pulse oximetry, staying in verbal contact with the patient to detect changes on sensorium, level of consciousness, and any unusual psychic phenomena) during and subsequent to the block. In addition, delayed complications (e.g., pneumothorax) should be sought. It is essential that the patient has an intravenous line *in situ* and that the drugs and equipment that might be needed to deal with complications are kept close at hand.

The complications that can arise can be categorized as follows:

- Systemic effects of the LA and its injection
- Physiologic effects of the procedure
- Inadvertent damage to nonneural structures
- Inadvertent damage to neural structures
- Systemic effects of the LA and its injection
- Psychogenic reactions

These commonly occur when little or no LA has been injected and may range from common scenarios such as a vasovagal episode to a panic episode. Treatment is symptomatic.

Epinephrine Effect

Rapid absorption of epinephrine in the LA solution, or the inadvertent intravascular injection of a small amount of the solution, can produce predictable epinephrine effects: tachycardia, hypertension, palpitations, pallor, shakiness. These must be distinguished from a potential toxic effect of the LA (*vide infra*). If the effects are minor, reassurance of the patient may suffice. If the effects are severe, or if they produce adverse cardiovascular system (CVS) effects in patients with CVS disease, hypertension should be treated with vasodilators (labetalol, 5 to 10 mg) and tachycardia with beta blockade (esmolol, 5 mg; metoprolol 2.5 to 5.0 mg).

Allergic Reactions

Allergy to the ester LAs (procaine, tetracaine, chloroprocaine) is known and probably occurs with cross sensitivity with sulfonamides. Allergy to amide LAs is rare. The physiologic consequences and treatment are as with any allergic reaction.

Effects of High, Toxic Blood Levels of Local Anesthetic

LAs have direct toxic effects on a number of body systems, most importantly the central nervous system (CNS) and the CVS. These CNS and CVS effects become increasingly pronounced as blood levels of LA rise. The effects and the clinical symptoms associated with rising blood levels of LA are depicted in Table 102-2.

Plasma concentration (µg/mL)	Effect
1–5	Analgesia
5–10	Lightheadedness
	Tinnitus
	Numbness of tongue
10–15	Seizures
	Unconsciousness
15–25	Coma
	Respiratory arrest
>25	Cardiovascular depression

TABLE 102-2. Systemic effects of lidocaine

High, or quickly rising, blood levels of LA can occur for a number of reasons: inadvertent intravascular injection of LA, unusually rapid absorption of LA, the use of an excessive amount of LA with normal absorption. The clinical circumstances influence how quickly blood levels of LA will rise; following an inadvertent intravascular injection, blood levels of LA will rise more rapidly than following injection of an excessive amount of drug. Irrespective of the circumstance, the end result is the same, rising or high blood levels of LA, which produce toxic effects.

To guard against the development of toxic CNS and CVS effects, the doses of LA should be kept within advised limits (see Table 102-1). To detect, and hence guard against, an inadvertent intravascular injection of LA, a number of practical maneuvers can be used. The needle should be aspirated frequently, after each 5 mL of injectate, to ensure no bloody return. A “test dose” of 3 to 4 mL of a mixture of LA plus 1:200,000 epinephrine (i.e., 15 µg epinephrine) may be injected as the first dose. If injected intravascularly, this mixture will, with a high degree of probability, cause a brief and transient (2 to 3 minutes) rise in the heart rate of 20 to 25 beats per minute and a rise in systolic BP of 20 to 30 points detected by continuous monitoring, due to the beta and alpha effects of the included epinephrine (37). This effect is significantly blunted if the patient is taking drugs that block the b-adrenergic effects of epinephrine. This technique was originally developed to detect inadvertent intravascular injections in epidural analgesia, but it may be used in other regional techniques.

A rising, or high, blood level of LA can be detected by monitoring the patient for the CNS symptoms described in Figure 102-2 and Table 102-2. This monitoring can only effectively occur in a patient who is fairly awake and lucid; hence, the use of sedation should be judicious. The classical sequence of events for LA toxicity with lidocaine, for example, is for severe CNS effects (convulsions) to occur at lower blood levels of LA (50% to 75%) than cause serious CVS effects. The hypoxia that may accompany a convulsion may exacerbate any direct CVS toxic effect. However, the sequence of CNS toxicity preceding CVS toxicity may not occur with bupivacaine, which can cause significant myocardial depression and cardiac arrhythmias at blood levels of LA that cause only modest CNS toxic effects (38).

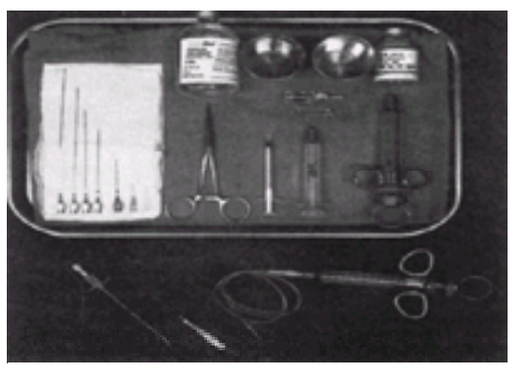

Figure 102-2. Equipment for regional analgesia and anesthesia. On the sponge are five 22-gauge security needles of different lengths, from left to right: 15 cm, 12 cm, 10 cm, 8 cm, and 5 cm. On the far right is a 25-gauge, 1.5-cm disposable needle. Hemostatic forceps for grasping sponges when applying antiseptic solution to the skin, a 1-mL tuberculin syringe for measuring epinephrine solution, a 2-mL Luer-Lok syringe for injection of small volumes of local anesthetics and for aspiration tests, and a 10-mL Luer-Lok control syringe used for most regional anesthetic blocks (because it facilitates aspiration and other maneuvers performed with one hand) are all shown to the right of the sponge. Above the syringes are a safety pin for skin testing and a 1-mL ampule containing 1 mg of epinephrine (1:1,000 concentration). A bottle of saline solution, a container for mixing the saline with local anesthetic solution to any desired concentration, a container for the antiseptic solution, and a bottle of local anesthetic are seen at the back of the tray. Below the tray, a Tuohy needle with a catheter threaded through it and a syringe for local anesthetic are shown. The injecting needle is attached to the syringe by a flexible extension tube, which prevents the transference of aberrant movements of the syringe to the needle, thereby reducing the chance of the needle moving away from the target. The tubing set is used for relatively superficial blocks in which the depth of the needle insertion is so shallow that it does not afford any stability (e.g., interscalene and axillary blocks) and for femoral sheath block.

If, during the course of injection of LA, the patient begins to manifest symptoms or signs of LA toxicity, steps must be taken to minimize the toxic effects of the LA immediately:

- Assistance should be immediately enlisted or summoned.
- The injection should be stopped.
- Oxygen (100%) via a bag and mask should be commenced immediately. This will ensure a store of oxygen in the patient's lungs should the toxicity proceed to convulsions. If the patient's oxygen saturation, judged from pulse oximetry, falls below 90%, positive pressure ventilation should be commenced. There is some evidence that hyperventilation, by producing hypocarbia, increases the threshold for convulsions.
- A small, anticonvulsant, dose of thiopental (50 to 100 mg) should be administered.
- Cardiovascular parameters should be closely monitored and adverse effects treated: hypotension with fluids and pressors (ephedrine, 5 to 10 mg), hypertension with vasodilators (labetalol, 5 to 10 mg), and tachycardia with beta blockers (esmolol, 5 mg; metoprolol, 2.5 to 5.0 mg).

These measures will often abort progressive LA toxicity. However, if the toxicity appears to be proceeding toward convulsions (agitation, limb jerking, loss of consciousness), further measures are necessary:

- Positive pressure ventilation with oxygen to ensure an oxygen saturation of greater than 90%.
- If ventilation is difficult, or if the patient convulses, muscle paralysis with 50 to 100 mg of succinylcholine should be used to ensure adequate ventilation.
- Cardiovascular monitoring and treatment of adverse CVS effects should continue.

Physiologic Effects of the Procedure

Expected Effects. Regional blocks with LA produce blocks of both somatic and sympathetic nerves and will produce the expected physiologic effects of neural paralysis. Somatic nerve blocks of nerves that maintain vital functions may produce physiologic impairments (e.g., phrenic nerve block causing respiratory impairment). Sympathetic nerve blocks, or intraspinal sympathectomies, such as may occur with epidural or SABs, can produce significant hypotension.

Unanticipated Effects. Many nerve blocks are performed in areas closely adjacent to other neural structures. Appropriately applied LA for a particular block may spill over to affect adjacent neural structures, producing unanticipated effects (e.g., interscalene brachial plexus blocks result in a high incidence of both cervical sympathectomy and phrenic nerve block). LAs may also be inadvertently deposited at unintended sites, producing unanticipated effects (e.g., inadvertent epidural or subarachnoid placement of LA, producing epidural or SABs, with thoracic paravertebral or intercostal blocks). Complications of this nature are described in the text for individual nerve blocks. Patients receiving regional blocks should be monitored closely for these adverse effects, which should be treated early and vigorously.

Damage to Adjacent Nonneural Structures

The needles used for regional blocks have the potential to pierce and damage structures adjacent to the site of the block. This complication can be minimized by careful technique and the use of aids such as fluoroscopy. Particular nerve blocks are associated with an incidence of such complications, even in expert hands (e.g., pneumothorax following intercostal nerve block or supraclavicular brachial plexus block). The complications associated with particular nerve blocks are discussed in the text.

The potential exists in all nerve blocks for the block needle to pierce a blood vessel and produce bleeding or a hematoma. In patients with normal clotting mechanisms, it is rare for such bleeding and hematomata to produce significant sequelae. Patients who have abnormal clotting mechanisms, either as a consequence

of disease or because they are receiving anticoagulant drugs, and receive nerve blocks are at significant risk of significant sequelae. The sequelae may be bleeding, to the extent that a patient becomes hypovolemic, or a hematoma that causes pressure effects on surrounding structures. This latter is of particular concern in epidural or SABs where hematomata of small size may lead to paraparesis and paraplegia (39). Hence, the presence of abnormal clotting mechanism is a strong relative contraindication to the use of RA.

In contemporary analgesic practice, continuous epidural analgesia with LAs and possibly opioids is commonly used for the control of postoperative pain following painful major operations (intraabdominal, intrathoracic, major orthopedic). The significant incidence of deep vein thrombosis (DVT) after such operations may be much reduced by the use of either low-dose heparin or its analogs [low-molecular- weight heparin (LMWH)]. The concurrent use of regional techniques in patients receiving such DVT prophylaxis is controversial. The concurrent use of epidural analgesia and heparin in complex management regimens (block placed before the institution of and terminated after the cessation of anticoagulation; postponement of the procedure if a bloody puncture occurs; monitoring the degree of anticoagulation) has been reported to have a low incidence of intraspinal hematomata (40). Nonetheless, intraspinal hematomata occur with a variety of regimens (41). LWMH appears to be a different matter, perhaps because there appears to be no reliable way to judge its degree of effect. There have been a number in the reports from the United States of epidural hematomata resulting in severe neurologic sequelae (42) and leading to the U.S. Food and Drug Administration's publishing warnings about the concurrent use of RA and LMWH. The concurrent use of LMWH and RA in Europe has not produced a similar incidence of complications, perhaps as a consequence of smaller doses of LMWH resulting in lesser degrees of clotting impairment (43). Ironically, the use of continuous epidural analgesic techniques using LA also produces a significant reduction in the incidence of postoperative DVT, possibly to the extent of the reduction produced by anticoagulant techniques (44). If an intraspinal hematoma producing neurologic sequelae is suspected, appropriate investigations (magnetic resonance imaging/computed tomography) and neurosurgical consultation should be rapidly obtained. If a hematoma causing neurologic sequelae has occurred, the faster it is decompressed, the greater the degree of eventual recovery.

Inadvertent Damage to Neural Structures

Placing needles close to nerves and injecting LA onto those nerves is associated with a definite but small incidence of neural complications ranging from minor paresthesia to severe nerve damage. The damage may be due to direct nerve trauma by needle or catheter, either accidental, or as a consequence of seeking paresthesia (36,45). It may be due to direct drug effects, inclusion of preservatives in the solution, or inclusion of epinephrine in the solution (46,47). It may be due to neuronal ischemia for a variety of causes. Precise data on the incidence of neural damage after nerve blocks alone are scarce. Much of the literature on nerve injuries is derived from the literature on anesthesia for operative surgery in which the majority of peripheral nerve injuries is not RA related (41). The quoted range of incidences of neural damage after epidural analgesia ranges from 1:11,000 (48) to 1:1,000 (49) with preexisting spinal column pathology being a risk factor.

LOCAL APPLICATIONS OF REGIONAL ANALGESIA

The infiltration of LAs into various body structures and their topical application onto mucous membranes are simple and frequently used techniques in the management of pain. For convenience, the use of these techniques is first considered for acute painful problems and then for chronic pain syndromes.

Local Infiltration

Acute Pain

Postoperative Pain. Local infiltration of a dilute solution of a long-acting LA (e.g., 0.125% to 0.250% bupivacaine) for orthopedic soft tissue procedures (50) and superficial operations such as excision of breast lumps (51) and inguinal hernia (52) produces effective postoperative pain relief for 8 to 12 hours, with a consequent significant decrease in the total amount of systemic analgesic required. Injection of LA through catheters with multiple openings, placed in the wound at operation, can provide even longer pain relief (53,54) (Fig. 102-3). Although such a procedure relieves abdominal or chest wall somatic pain, it usually needs to be supplemented by appropriate doses of nonsteroidal antiinflammatory drugs and opioids to relieve the visceral pain.

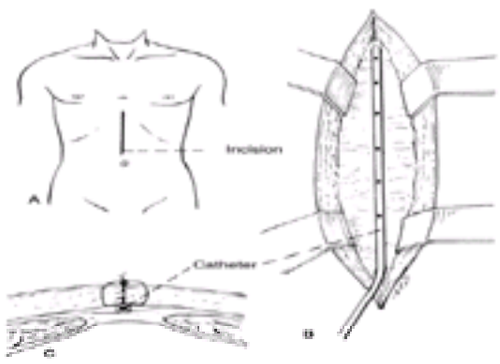

Figure 102-3. Postoperative analgesia after a midline incision **(A)** in the upper abdomen. **B:** Just before closing the wound, a catheter with multiple holes (*black*) is placed with its proximal end connected to the hub of a needle that fits into the catheter. The hub is kept sterile between injections of boluses of local anesthetic. **C:** Cross section of the abdominal wall showing the position of the catheter. Injection of a bolus of 10 to 15 mL of 0.25% bupivacaine with epinephrine results in diffusion of the drug to the surrounding structures, thus producing analgesia of the anterior abdominal wall adjacent to the incision.

Postoperative Joint Pain. Acute pain following intraarticular operations can be effectively relieved by the installation of 20 to 30 mL of LA, common bupivacaine, into the joint cavity before the joint closure. This technique is particularly effective for arthroscopic knee operations (55).

Acute Bursitis. Painful acute subacromial, subcapsular, prepatellar, and trochanteric bursitis can be promptly relieved with LA infiltration. The bursa should be infiltrated with 8 to 10 mL of dilute solution (e.g., 0.25%) of bupivacaine with epinephrine, with the addition of 40 mg of methylprednisolone (Depo-Medrol). Pain relief occurs in 10 to 15 minutes and can last 8 hours, and not infrequently 12 hours, after which pain returns and is often intense. The patient should therefore be given systemic nonopioid or opioid analgesics to manage the postblock pain. Several injections are frequently necessary. If the effusion of a joint is pronounced, frequent aspiration is indicated.

Tendinitis. The most frequent types of tendinitis include bicipital tendinitis, lateral epicondylitis (tennis elbow), medial epicondylitis (golfer's elbow), and supraspinatus (rotator cuff) tendinitis, often associated with subacromial bursitis (Chapter 58). Infiltration of these structures with 0.25% bupivacaine provides prompt relief of pain for 8 to 12 hours (Fig. 102-4). A long-acting steroid compound can be included in the solution for the first injection, but most orthopedic surgeons avoid repeated use because of the possible myotoxic effects and delayed sequelae (e.g., Cushing's syndrome) from the use of steroids. The inclusion of steroid in the LA for the first injection produces prolonged pain relief for 1 to 3 or 4 weeks. LA infiltration can be repeated several times until permanent relief is achieved.

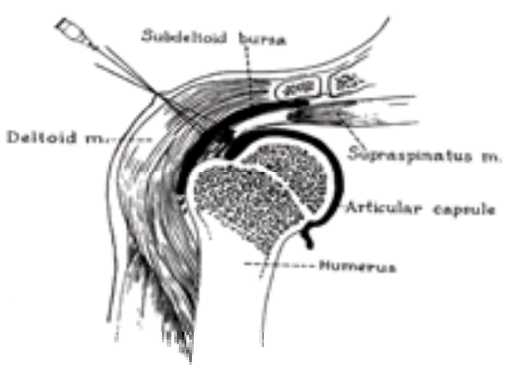

Figure 102-4. This frontal section of the shoulder region illustrates injection technique for treatment of supraspinatus tendinitis and subacromial bursitis. Note the calcium deposit in the supraspinatus tendon.

In some patients, the steroid causes a burning pain in the site of injection 24 to 48 hours after the procedure. As with other LA injections into bursa or tendon, patients may experience postblock pain, which should be managed with systemic analgesics.

Muscle Spasm. Muscle spasm with consequent severe pain can develop after injury in various locations, particularly in the low back. Muscle spasm can also be caused by poor posture or deformity of the spine (1). In all such cases, LA infiltration with a dilute solution (e.g., 0.125% bupivacaine) into the entire muscle causes prompt relief of the pain and muscle spasm that can last 8 to 12 hours. The injection should be followed by the application of heat, massage, and corrective exercises, as indicated.

Infiltration of an LA into a muscle can also be used as a diagnostic and therapeutic procedure in the rare cases of pyriformis or scalenus anticus syndrome.

Chronic Pain

Painful Scars. It is unusual for a whole scar to be painful but “trigger points” may be found in a scar. These can be associated with hyperesthesia and radiation of the pain along dermatomes from the scar. Infiltration of the scar with a dilute solution of bupivacaine (e.g., 0.25%) on about six occasions at 3- to 5-day intervals may produce persistent relief. If pain relief does not persist following a series of injections of LA, transcutaneous electrical nerve stimulation should be tried. If this fails, consideration should be given to injection of 1 mL of alcohol into the specific trigger points, which is said to produce a high incidence of success (56).

Neuromata. Neuromata can develop in nerves idiopathically, due to nerve entrapment, subsequent to traumatic nerve section or after surgery or amputation. Infiltration of the neuroma with an LA is a useful diagnostic procedure for determining whether the pain is arising from the neuroma. Moreover, injection of a solution containing an LA (without adrenalin) and a depot corticosteroid such as methylprednisolone (Depo-Medrol) into the neuroma can suppress the spontaneous ectopic discharges that are probably producing pain and paresthesia. Experimental studies have shown that the steroid stabilizes the nerve membrane for 2 weeks or longer (57). Therefore, patients with painful neuromata can be given a trial with this combination at 1- to 2-week intervals for the first month and at 2- to 3-month intervals thereafter. The management of patients with this type of pain is discussed in detail in Chapter 21.

Myofascial Syndromes with Trigger Points. One of the most effective clinical applications of infiltration of LA, with or without steroids, is in the management of myofascial pain syndromes with trigger points. Trigger points can develop in almost every muscle in the body, as well as in tendons and ligaments, producing local and referred pain, tenderness, reflex muscle spasm, and other signs and symptoms. In some patients, such trigger points can be in the vicinity of classic acupuncture points (58). Repeated injections of trigger points with an LA alone or combined with steroid or with saline solution usually produce permanent relief of pain and eliminate the other signs and symptoms (59) (see Chapter 29).

Arthritis. An intraarticular injection of a dilute solution of LA alone or in combination with steroids is also indicated as a diagnostic and therapeutic procedure in patients with pain of chronic arthritis involving major joints in the limbs or spine (Fig. 102-5 and Fig. 102-6). It has been suggested that injection of corticosteroids into tender spots along the nerves supplying an osteoarthritic joint produces much better relief of pain than intrasynovial injection of steroids (60,61). The inclusion of 0.125% bupivacaine with the steroid eliminates the postinjection burning pain.

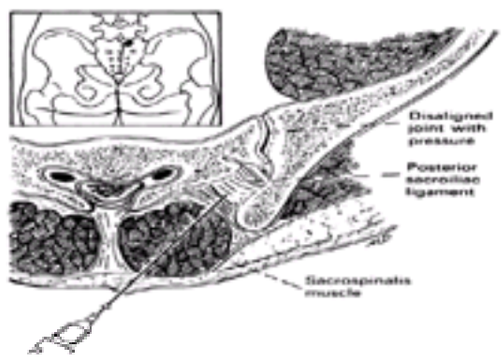

Figure 102-5. Injecting the ligaments of the right sacroiliac joint, which is shown subluxated. Inset: The skin wheal (*black dot*) used to anesthetize the skin for insertion of a larger needle is made in the midline at the level of the posterior superior spines of the ilium. The needle is inserted toward the affected side to make an angle of 45 degrees with the midsagittal section. Once the point is in the ligament, the LA is injected. Then an attempt is made to advance the needle into the subluxated joint, where 3 to 5 mL of solution is injected.

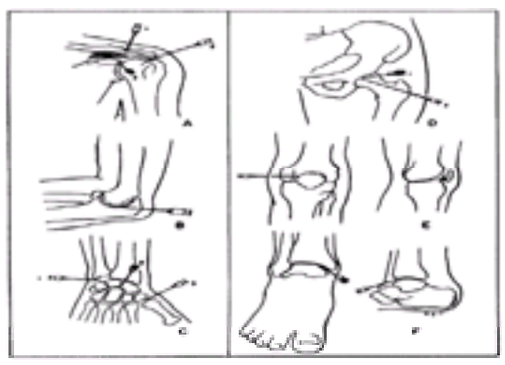

Figure 102-6. Intraarticular injection of various joints. **A:** Techniques for injecting part of the shoulder using a 22- or 25-gauge, 5-cm needle: the acromioclavicular joint (1), the supraspinatus tendon for treatment of tendinitis (2), and the scapulohumeral joint (3). **B:** Injecting the elbow (humeroulnar) joint. **C:** Intraarticular injection of the wrist: ulnar approach (1), dorsal approach (2), and injection into the carpometacarpal joint of the thumb (3). **D:** Injection of the left hip joint by the anterior (1) and lateral (2) approaches. Note the direction of the shaft of the needle to the bone. When inserted just anterior to the greater trochanter in a sagittal direction and pointed toward the middle of Poupart's ligament, the needle point slides anterior to the periosteum and enters the joint space anteriorly near the upper reflection of the synovial sac. **E:** Injecting the knee joint: anterior and lateral views. After a skin wheal is made on the anteromedial surface of the knee, 1 to 2 cm from the medial border of the patella, a needle is inserted in a lateral and slightly posterior direction, in a line, with the goal of sliding it between the posterior surface of the patella and the patellar groove of the femur. Synovial fluid can be aspirated as soon as the joint cavity is entered. **F:** Injecting the ankle joint: anterior and lateral views. (Reprinted from Bonica JJ. *Clinical applications of diagnostic and therapeutic nerve blocks.* Springfield, IL: Charles C Thomas Publisher, 1959, with permission.)

Facet Syndrome. Intraarticular injection of LAs into the facet joint in the lumbar, thoracic, and cervical regions (Fig. 102-7) has been used as an important diagnostic procedure. Although *facet syndrome* (a term first used in 1933 for diseases of the zygapophyseal joints) (62) as a cause of back pain remains controversial, it is believed that precise injection of the joint can be a valuable diagnostic tool in indicating whether pathophysiologic changes in the joint are a source of pain (63). The value of steroid injection into the facet joint as a therapeutic measure is also controversial; some clinicians have reported persistent relief of pain for at least 6 months in two- thirds of the patients, while others have reported relief in only 25% of patients. Moreover, a number of studies have suggested that this procedure or block of

the medial branch of the posterior primary divisions that provide articular branches to the zygapophyseal joints above and below the nerve can be used diagnostically. Figure 102-7 depicts both the intraarticular injection technique and block of the medial branch of the posterior primary division in the lumbar and cervical regions.

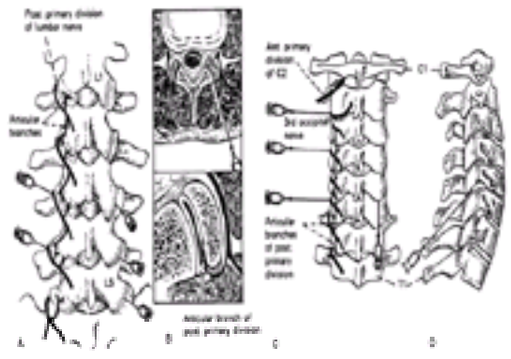

Figure 102-7. Local injection to relieve pain resulting from pathology of a facet joint in the lumbar region **(A,B)** and the cervical spine **(C,D)**. **A:** Posterior view of the lumbar spine depicting the approach for blocking the medial branch of the posterior primary division of the lumbar spinal nerves (left) and the intraarticular zygapophyseal joint (right). Each medial branch sends articular filaments to adjacent facet joints so that each joint is supplied by two (and sometimes three) adjacent nerves, which must be blocked to interrupt sensory fibers to the particular joint. **B:** Cross section of lumbar spine indicates the direction of the needle (top) and insertion of the bevel of the needle into the joint (bottom). **C:** Posterior view of the cervical spine depicting the approach for blocking the medial branches of the posterior primary divisions of the cervical nerves (left) and the direction of the needle for penetrating the zygapophyseal joint on the right. **D:** Lateral view of the cervical spine showing the course of a needle into the cavity of the right C-5–6 zygapophyseal joint. (Modified from Bogduk N. Back pain: zygapophyseal blocks and epidural steroids. In: Cousins MJ, Bridenbaugh PO, eds. *Neural blockade in clinical anesthesia and management of pain,* 2nd ed. Philadelphia: JB Lippincott Co, 1988.)

Topical Application

Topical application of an LA, either in solution or in paste form, is used to provide temporary relief of severe excruciating pain of the mucous membranes in the mouth, throat, and often the bladder. The most frequently used agents are 2% to 4% lidocaine, 4% to 6% cocaine, and 30% benzocaine solution to produce topical mucosal analgesia. For skin, analgesia jellies or creams such as eutectic mixture of local anesthetic (EMLA), a mixture of 2% lidocaine and 2% prilocaine; 2.5% to 5.0% lidocaine; and 4% tetracaine produce effective skin analgesia and may be useful in the management of some chronic pain problems such as postherpetic neuralgia (PHN) (see Chapter 22 and Chapter 87). Because topical anesthetic solutions are absorbed rapidly from the vascular mucous membranes, the amount applied must be carefully measured and limited to a total dose of one-third to one-half of the total dose shown in Table 102-1. Ointments are used to relieve the pain of mucositis in cancer patients receiving chemotherapy, rectal suppositories are used for anal or rectal pain, and jellies or creams are used for pain in the urethra or urinary bladder.

BLOCK OF SPINAL NERVES

Outside the spinal canal, the spinal nerves can be blocked in the paravertebral region or at points along their course (Fig. 102-8). Such procedures are usually done to interrupt nociceptive pathways in the management of severe acute or chronic pain, to block somatomotor nerves to relieve pain of muscle spasm, or to block sympathetic nerve fibers.

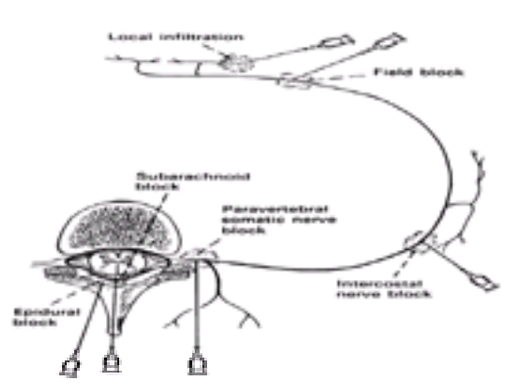

Figure 102-8. Various sites at which a typical (thoracic) spinal nerve can be blocked.

Cervical Spinal Nerves

The origin, course, and distribution of the cervical spinal nerves are described in Chapter 46 and depicted in Figure 102-9. These nerves may be involved in transmitting nociceptive information from the neck and upper limb and consequently are candidates for diagnostic/prognostic and therapeutic nerve blocks. The nerves can be blocked as they exit from the intervertebral foramina or distal to the vertebral column.

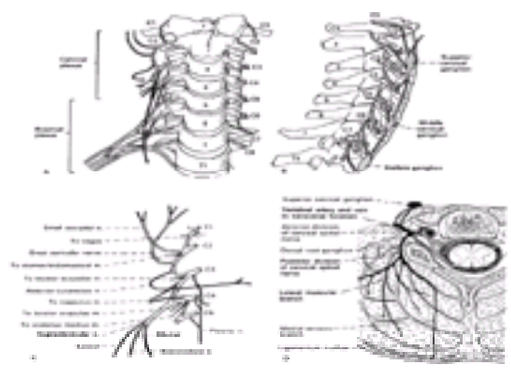

Figure 102-9. Anatomy of the cervical nerves. **A:** Anterior view. **B:** Side view. **C:** Plan of the cervical plexus showing its origin from the anterior primary division of the upper four cervical spinal nerves and its main branches. **D:** Schematic representation of a transverse section in the neck showing the relationship of the formed nerve to various structures. Each nerve passes distally within the sulcus of each transverse process. The posterior tubercle of the transverse process is larger and more superficial, and therefore is more easily palpable, than the anterior tubercle. The vertebral artery is just anterior to the formed nerve.

Paravertebral Block

Indications. Paravertebral block of the cervical nerves may be used diagnostically to identify the specific nerve segment(s) in patients with segmental neuralgia caused by herniated intervertebral disk, osteophytes, root sleeve fibrosis, or paravertebral lesions, such as tumor or aneurysm. The blocks may be used

prognostically in patients with cancer pain who are scheduled to have neurolytic or neuroablative interruption of nociceptive pathways. The technique is useful for the temporary relief of pain resulting from musculoskeletal pathology or for the manipulation of a painful or frozen shoulder joint.

Technique. The cervical nerves exit the spinal canal passing laterally within the sulcus of the transverse processes. Each transverse process has a small anterior tubercle and a larger and more superficial posterior tubercle, which is easily palpable in the average individual (see Fig. 102-9). The nerves can be blocked as they lie within the sulcus in the transverse process, most commonly using a lateral approach (Fig. 102-10) or a posterior approach. The lateral approach can be used to block all the cervical nerves except the C-8 nerve. To block the C-8 nerve, an intracutaneous wheal of LA is made in the skin overlying the transverse process of the C-7 vertebra. The needle is directed caudad and slightly mesiad and advanced slowly until contact with the nerve is made, indicated by eliciting paresthesia in its distribution.

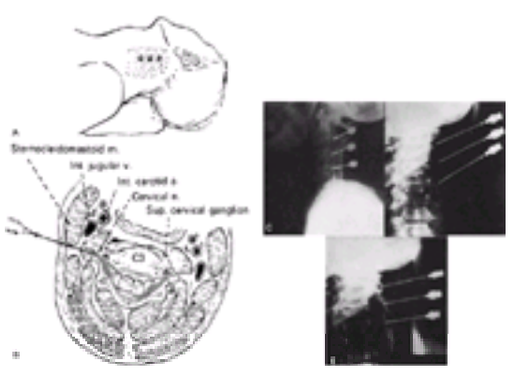

Figure 102-10. Lateral paravertebral block of the cervical nerves. **A:** Position of the patient. **B:** Cross section of the C-3 vertebra with the needle in place. The patient's head is turned to the opposite side, and a small pillow is placed under the upper portion of the thoracic spine and neck to make the transverse processes of the cervical vertebrae more prominent. The posterior tubercles of the transverse processes of the C-3–7 vertebrae usually can be easily palpated, but this can be difficult in an obese patient. A line is drawn between the tip of the mastoid process and Chassaignac's (C-6 posterior) tubercle, which is the most superficial and most easily felt. The second line is drawn 0.5 cm posterior to the first. Because the transverse process of the second is difficult to palpate, it is usually located 1.5 cm caudad to the tip of the mastoid process on the second line. The tip of the transverse process of each subsequent vertebra is generally 1.5 cm caudad to the tip of the preceding transverse process. In a very tall or long-necked (or both) patient, the distance between adjacent transverse processes can be 1.7 cm, and even as much as 2 cm.
After identifying the tip of the transverse process of the nerve or nerves that are to be blocked, the skin is prepared with an antiseptic solution. After 1 minute, the excess is removed and an intracutaneous wheal is produced over the transverse process containing the nerve to be injected. With the fingers of the left hand immobilizing the skin, a 5-cm, 22-gauge needle is inserted medially and slightly caudad and advanced until the nerve or the transverse process is contacted, usually at a depth of 2.5 to 3.0 cm (but possibly as deep as 4 or 5 cm in an obese patient). For diagnostic purposes, the nerve can be identified by eliciting gentle paresthesia or by using a nerve stimulator. If doubt exists, the nerve can be identified by lateral **(C)** and anteroposterior **(D)** radiographs. If the point of the needle is on the nerve (not *inside*), 2 mL of local anesthetic is sufficient to produce block without involving adjacent segments. If the procedure is done for therapeutic purposes, which require block of several nerves, a needle can be inserted for each segment to be blocked and 2 to 3 mL of solution injected. Alternatively, one needle can be inserted into the middle of the various segments to be blocked and 5 to 8 mL of solution injected. **E:** Anteroposterior radiograph taken 5 seconds after injecting 5 mL of 35% Diodrast solution through the middle needle. Note the wide diffusion of fluid.

The more technically difficult posterior approach is used in patients in whom the lateral approach is contraindicated (Fig. 102-11). Because some patients already have a neuropathy, care must be exercised to avoid further damage to the nerve. Moreover, because nerve blocks are primarily used for diagnostic purposes, and because of the close proximity to other nerves, the use of small volumes of LA is advised. To identify a specific nerve, either paresthesia can be elicited *gently* or a peripheral nerve stimulator can be used.

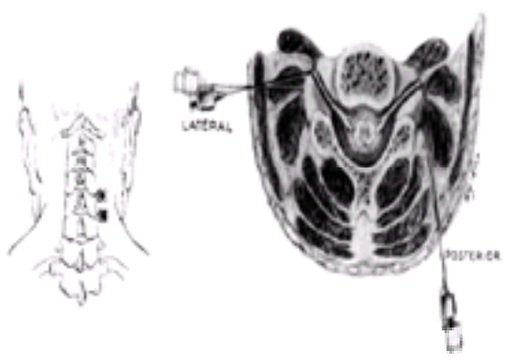

Figure 102-11. Paravertebral block of one or more cervical nerves by the posterior approach. After identification of the transverse process or of the processes that contain the nerves to be blocked, a line is drawn posterior to the midline with an indelible pen or marker. The patient is placed prone with a pillow under the chest, and the neck is flexed. After preparing the field, an intracutaneous wheal is made 3 cm from the midline on the marked line that is at the same cross-sectional level as the transverse process of the vertebra. An 8-cm, 22-gauge needle is inserted perpendicular to the skin and advanced anteriorly and slightly medially until the articular pillar is contacted, whereupon the needle marker previously threaded on the needle is placed flush with the skin. The needle is withdrawn until its point is in the subcutaneous tissue and redirected slightly more laterally so that its point is 1 cm lateral to the point of the first contact, as indicated by the needle marker. The marker is placed 1 cm from the skin, and the needle is slowly advanced until contact with the nerve is made, as indicated by paresthesia. For diagnostic purposes it is essential to elicit paresthesia; it might be necessary to make several insertions, directing the needle slightly more cephalad or caudad. It is also advisable to take radiographs. Paresthesia is not necessary for therapeutic purposes, but the point of the needle must be in the paravertebral space, which communicates freely in the cervical region and permits the anesthetic solution to diffuse easily to adjacent levels. The volume of local anesthetic is 2 to 3 mL for each segment or 8 to 10 mL for three or four segments.

Complications. Paravertebral block in the cervical, thoracic, lumbar, and sacral regions is associated with the risk of inadvertent subarachnoid, subdural, or epidural injection. In the cervical region, these complications may result in respiratory compromise because of phrenic nerve block or, in the case of a subarachnoid injection, because of rapid diffusion of the drug to the respiratory center. Inadvertent injection of LA into the vertebral artery, which runs in close proximity to the intervertebral foramina, is a definite complication of these blocks. Because the drug is delivered directly to the hindbrain, an intravertebral artery injection of very small amounts of LA (0.5 to 1.0 mL) will produce CNS toxicity (loss of consciousness, apnea, convulsions). Respiratory compromise and CNS toxicity should be treated *promptly* with artificial ventilation and support of circulation until the LA drug is redistributed and biotransformed. Other complications include cervical sympathetic block, with development of Horner's syndrome, involvement of the superior or recurrent laryngeal nerve, and even the trunk of the vagus. Because of the risk of respiratory compromise from either recurrent laryngeal and/or phrenic nerve block, it is advisable to perform cervical paravertebral blocks unilaterally at any one session.

Occipital Nerve Block

Indications. Block of the greater and third occipital nerve can be used as a diagnostic, prognostic, or therapeutic measure in managing patients with occipital headache, neuralgia, and other painful conditions in the posterior portion of the head.

Technique. The greater occipital nerve is usually blocked just above the superior nuchal line, 2.5 to 3.0 cm lateral to the external occipital protuberance (Fig. 102-12).

If it is difficult to contact the nerve and elicit paresthesia, 5 mL of LA can be injected on the medial side of the artery, 2 mm superficial to the skull.

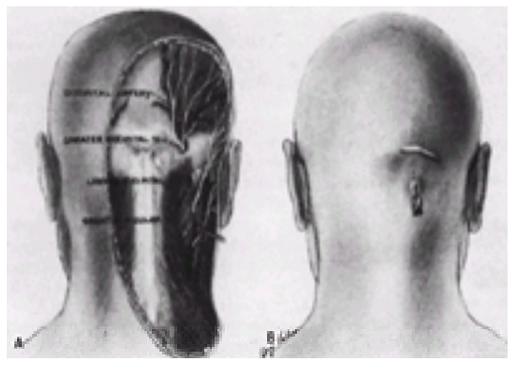

Figure 102-12. Occipital nerve block. **A:** Anatomy of the greater and lesser occipital nerves: The greater occipital nerve is 2.5 to 3.0 cm lateral to the external occipital protuberance and just medial to the occipital artery, which serves as the most reliable landmark for blocking of this nerve. The third occipital nerve, which is not shown, is usually located medial to the greater occipital nerve, while the lesser occipital nerve is located about 2.5 cm lateral to the artery. **B:** Occipital nerve block: The greater and third occipital nerves are usually blocked just above the superior nuchal line at a point medial to the occipital artery, which is easily palpated. After a thorough cleansing of the hair and scalp with an antiseptic solution, a 5-cm, 25-gauge needle attached to a 5-mL syringe filled with local anesthetic is introduced about 1 cm below the level of the target and directed anteriorly and slightly superiorly, directing its point just medial to the artery. Contact with the nerve elicits paresthesia along its course, whereupon 1 mL of local anesthetic is injected if the procedure is being done for diagnostic purposes or 2 to 3 mL of solution is injected for therapeutic purposes. Anesthesia of the scalp in the distribution of the greater and third occipital nerves develops within 5 to 10 minutes. If the procedure is repeated for therapeutic purposes, and it is difficult to elicit paresthesia, 5 mL of local anesthetic is injected on the medial side of the artery 2 mm superficial to the skull. The lesser occipital nerve can be blocked about 2.5 cm lateral to the site of the greater occipital nerve block. If all three nerves need to be blocked with a single injection for therapeutic purposes, a simple technique involves subcutaneous injection of local anesthetic along the elevation of skin across the scalp above the needle shown in **B**.

Complications. Complications are rare. Inadvertent intraarterial injection is usually inconsequential because of the small volume of LA injected.

Phrenic Nerve Block

Indications. Phrenic nerve block may be used diagnostically in patients with shoulder pain believed to be caused by irritation of the diaphragm. It can also be useful in the diagnosis or treatment of patients with intractable hiccups, in whom unilateral block is done to determine whether the condition involves one or both halves of the diaphragm.

Technique. The primary root of the phrenic nerve is the C-4 nerve, but it also receives fibers from the C-3 and C-5 cervical nerves. These join at the lateral border of the anterior scalenus muscles; the nerve then courses caudad on the anterior surface of the muscle and enters the chest (see Chapter 60). Block of the phrenic nerve is best achieved by depositing 5 to 10 mL of solution onto the anterior surface of the scalenus anticus muscle, approximately 3 cm above the clavicle (Fig. 102-13). Localization of the nerve may be assisted by the use of a peripheral nerve stimulator, which will produce an easily discernible diaphragmatic twitch. Because of the risk of respiratory compromise from diaphragmatic paresis, it is advisable to perform only unilateral phrenic nerve block at one session.

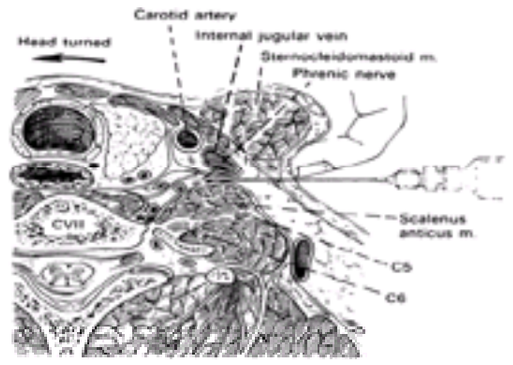

Figure 102-13. Blocking the phrenic nerve. The cross section at the level of the C-7 vertebra shows the position of the phrenic nerve anterior to the fascia of the scalenus anticus muscle, with the point of the needle just touching the nerve. This procedure is best accomplished by having the patient in the supine position with the head turned to the opposite side. The posterior border of the sternocleidomastoid is identified 3 cm above the clavicle by having the patient lift the head while it is turned to the opposite side and by hooking the physician's index finger around the posterior border of the muscle. A wheal is made at this point; a short-beveled 5-cm, 22-gauge needle is introduced through the wheal in a medial direction and guided with the finger of the left hand so that it passes posterior to the border of the sternocleidomastoid muscle. If the short-beveled needle is advanced slowly and carefully, one can better appreciate piercing of the superficial fascia. Injection of 3 to 5 mL of solution is usually sufficient for complete block.

Complications. Respiratory compromise, especially in patients who have preexisting respiratory disease, may result from hemidiaphragmatic paresis. Inadvertent injections of even small amounts of LA into the carotid or vertebral arteries will result in CNS toxicity (see above). Inadvertent intravenous injection into internal jugular or other veins may result in systemic toxicity.

Brachial Plexus Block

Indications

Diagnostic Block. Brachial plexus block can be used as a diagnostic procedure in causalgia, CRPS, phantom limb pain, and other types of postamputation pain. It can also be used to differentiate pain of peripheral neuralgia from pain of more central origin (e.g., brachial plexus avulsion). Because all sympathetic fibers to the hand and forearm are carried within the brachial plexus, block of the plexus can help confirm completeness of an upper extremity LA or surgical sympathectomy.

Brachial plexus block can be used diagnostically in patients with arm pain and joint deformities due to either guarding and muscle spasm caused by pain or to fixed lesions of joints or muscles. In the former case the block will permit passive range of movement, whereas in the latter the deformity will remain fixed. In patients with a fixed deformity of the arm, repeated plexus brachial blocks may assist in mobilization.

Prophylactic Block. Brachial plexus block for upper limb surgery delays the onset of postoperative pain and the time for the first postoperative request for analgesics and significantly reduces the amount of postoperative pain incidence (64). Studies that will be cited in Section F in connection with epidural analgesia provide reason to believe that continuous brachial plexus block instituted and maintained for 3 days before amputation may reduce the incidence of postamputation phantom limb pain.

Therapeutic Block. Brachial plexus block may provide temporary pain relief in patients with acute pain following trauma or surgery and in patients with vascular compromise due to arteriolar spasm or an embolus. Continuous brachial plexus block, providing both pain relief and a sympathectomy, is useful in patients who have

undergone reimplantation of a severed portion of an upper limb and in patients in whom the blood supply to the extremities is compromised.

Technique. The anatomy of the brachial plexus is summarized in Chapter 54 and depicted in Figure 102-14 and Figure 102-15. A number of brachial plexus block techniques have been described; the most commonly used are the supraclavicular (65) (Fig. 102-16), interscalene (66) (Fig. 102-17), and axillary approaches (67) (Fig. 102-18). In early RA practice, the supraclavicular technique was favored because it placed the LA in the plexus at a point where the plexus was closely compressed as it passed over the first rib and produced central and distal distribution of the drug and a reliable block. However, because the point of LA injection is close to the dome of the pleura, this technique carries a significant incidence of pneumothorax. Interscalene block, in which the LA is deposited on the plexus at a more central point, at about the level of C-6, has a much lower incidence of pneumothorax and is more commonly used for pain in the upper dermatomes of the brachial plexus. Interscalene block does not usually produce analgesia in the two lower roots of the plexus (C-8, T-1). The axillary block poses the least risk of serious neurologic or pulmonary complications but, unless large volumes are used, the branches of the plexus given off above the first rib tend not to be blocked.

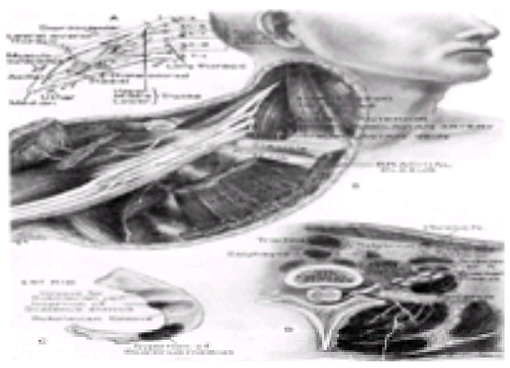

Figure 102-14. **A:** Schematic depiction of the makeup of the brachial plexus. **B:** Anatomy of the brachial plexus: The brachial plexus extends from the interval between the anterior and medial scalenus muscles to the lateral border of the pectoralis muscle. The three trunks emerge from the interscalene space at the lower border of these muscles and continue anterolaterally and inferiorly to converge toward the upper surface of the first rib, where they are closely grouped and thus accessible to injection of local anesthetic. In the posterior triangle of the neck, the plexus is located superficially and is covered by the superficial fascia, platysma, and deep fascia. At the lateral edge of the rib, each trunk divides into anterior and posterior divisions, which pass beneath the midportion of the clavicle to enter the axilla through its apex. Over the first rib, the subclavian artery, lying immediately anteromedial to the plexus, is also superficial, thus affording a palpable landmark to the plexus. Throughout their course, the brachial plexus and the subclavian artery are enclosed in a fascial sheath that extends from the anterior and middle scaleni muscles as far as the lower part of the axilla and the upper part of the arm (see Fig. 102-15). This sheath forms a relatively avascular enclosed space into which a local anesthetic solution can be injected, thus resulting in prolonged neural blockade (see Fig. 102-15). **C:** Superior view of first rib showing the subclavian groove, on which the brachial plexus and subclavian artery rest. **D:** Semidiagrammatic cross section to show relationships of the plexus, muscles, blood vessels, and apex of lung.

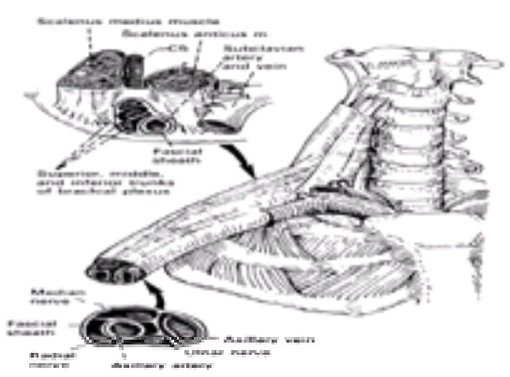

Figure 102-15. The brachial and axillary neurovascular sheath. The sheath is a lateral prolongation of the prevertebral fascial layer that encloses the roots of the brachial plexus and the scalenus anticus and medius to form a vertical tube, continuing laterally to enclose the brachial plexus and subclavian artery. In its position above the first rib, the subclavian vein is not enclosed in this sheath (upper inset) but, more distally, it is covered by a thin fascial sheath that tends to fuse with the larger neurovascular sheath. Lower inset: Cross section in lower part of the axilla showing the relationships of the three major nerves derived from the brachial plexus to the axillary artery and axillary vein. Small fascial septa subdivide the main sheath to enclose each of these structures, which might constitute a fascial barrier to the diffusion of local anesthetic. (Modified from Thompson GE, Rorie DK. Functional anatomy of the brachial plexus sheaths. *Anesthesiology* 1983;59:117–122.)

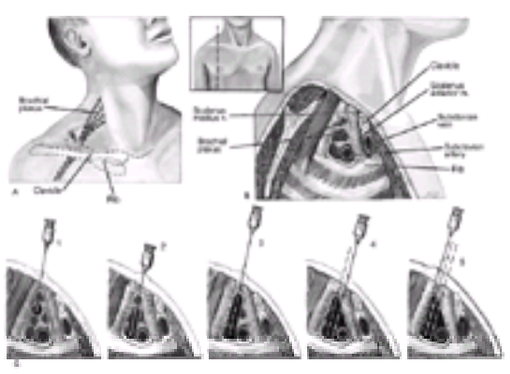

Figure 102-16. Brachial plexus block by the supraclavicular approach using the Bonica three-needle insertion technique. **A:** Anterior schematic showing the position of the plexus and direction of the needle. **B:** Parasagittal section (inset: *dashed line*) showing the subclavian artery and brachial plexus surrounded by a sheath derived from the fascia of the scalenus anticus and scalenus medius muscles. **C:** Injection of local anesthetic solution (*black*) for each of three insertions. After informing the patient about the pr ocedure and requesting that the patient promptly signal any feeling of paresthesia, the two ends of the clavicle are identified and the subclavian artery is palpated. The field is prepared, and a skin wheal is formed about 1 cm above the midpoint of the clavicle, just posterior to the palpable subclavian artery. A 5- or 8-cm (depending on the size of the patient), 22-gauge needle attached to a 10-mL Luer-Lok control syringe filled with local anesthetic solution is inserted in a caudad and slightly dorsad and mesiad direction **(A)** until paresthesia is elicited, whereupon the needle is arrested and aspiration is carried out in two planes; if negative, 3 to 4 mL of local anesthetic solution is injected. The needle is then carefully advanced until the upper surface of the first rib is contacted (*1*). After injecting 2 to 3 mL on the rib, the remainder of the 10 mL of solution is injected as the needle is withdrawn between the first rib and the superficial fascia (*2*). To avoid accidental intravenous injection, the needle should be withdrawn in a stepwise fashion and aspiration done before the injection of 1 to 2 mL of solution (*3*). When the point of the needle is in the subcutaneous tissue, the skin is moved 1 cm anteriorly and then advanced so that the shaft of the needle is parallel to the first insertion, and the same procedure is repeated (*4*). Following the second step, with the needle point again subcutaneous, the skin is moved 2 cm posteriorly (i.e., 1 cm posterior to the first insertion), the needle is advanced with its shaft parallel to that in the first two steps, and the procedure is repeated (*5*). By injecting 10 mL of solution through each of these three insertions, a wall of anesthesia is created within the entire fascial sheath (*black*) containing the neuromuscular bundle through which the plexus passes.

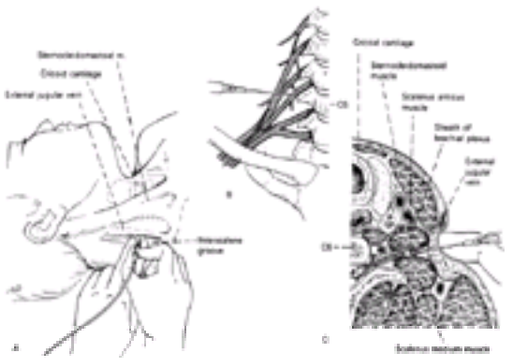

Figure 102-17. Interscalene block of the brachial plexus. **A:** The patient lies supine with the head on a pillow and rotated to the opposite side. The interscalene groove is identified by asking the patient to lift the head, which places the scaleni muscles in tension. The insertion point is determined by drawing a line that extends laterally from the cricoid cartilage to intersect the interscalene groove at the level of the transverse process of C-6. After formation of a skin wheal, and with the second and third fingers of the left hand palpating the interscalene groove, a 3- or 5-cm, 23- or 25-gauge, short- beveled needle is inserted in a medial and slightly caudad direction toward the sulcus of the C-6 transverse process. **B:** The needle is advanced slowly for 1.5 to 2.0 cm until paresthesia is elicited; this indicates contact with a nerve, which is usually the C-7 root of the plexus. **C:** Cross section at level of C-6 vertebra showing the bevel of the needle approaching the nerve, which is located between the anterior and middle scalenus muscles. The 30 to 40 mL of local anesthetic solution injected diffuses cephalad, caudad, and laterally to block the roots, trunks, and divisions of the brachial plexus and often the roots of the cervical plexus. Although this volume of solution can be injected by adapting a 10-mL Luer-Lok syringe directly to the hub of the needle, it is best to attach a length of tubing to the needle hub with its proximal end adapted to a 50-mL syringe containing the local anesthetic (as shown in **A**). To avoid unintentional intravenous or subarachnoid injection, attempts at aspiration are made before and after injection of 1 to 2 mL of solution and repeated frequently as the entire volume of the solution is injected. For a continuous technique, an 18- or 20-gauge intravenous catheter is similarly introduced, the stylet removed, and the catheter taped into place with its hub connected to a 10- to 15-cm length of tubing attached to the syringe containing the local anesthetic. Repeated injections of 20 to 30 mL of 0.250% to 0.375% bupivacaine every 6 hours, or an infusion of 0.25% bupivacaine at a rate of 6 to 12 mL per hour, produce continuous blockade.

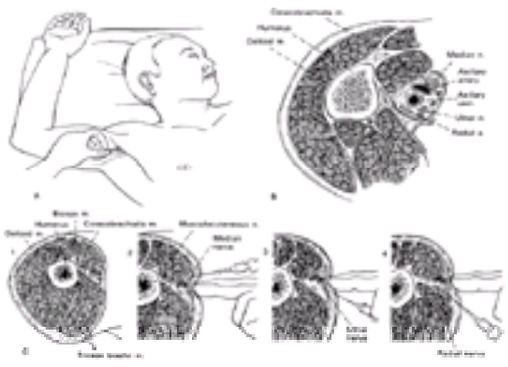

Figure 102-18. Axillary block of the brachial plexus. **A:** The patient is supine with the arm abducted to 90 degrees and rotated externally. **B:** Cross section of the upper part of the axilla showing the relation of the nerves to the axillary vessels. The axillary artery is palpated and traced as far as possible proximally within the axilla, ideally to the pectoralis major muscle. After appropriate preparation of the skin, a skin wheal is formed over the artery and a 3- or 5-cm, 23- or 25-gauge, short-beveled needle (attached to tubing connected to an anesthetic-filled syringe; not shown) is inserted through the wheal. The shaft of the needle should be at a 45-degree angle with the medial aspect of the arm **(A)**, directing its point cephalad toward the apex of the axilla and advancing it slowly. A short-beveled needle can be felt to penetrate the sheath, within which lie the lower portion of the axillary artery and the four major nerves of the plexus. Penetration of the fascial sheath is felt as a “click,” after which the needle is advanced 1 to 2 mm to ensure that the bevel is within the fascial sheath. Elicitation of paresthesia obviously indicates contact with one of the major nerves. Injection of 30 to 40 mL of solution while pressure is placed firmly on the neurovascular bundle and its surrounding sheath below the needle enhances diffusion of the solution proximally so as to involve all the branches of the brachial plexus, except those that leave it above the first rib. **C:** Some physicians prefer to elicit paresthesia and inject each of the three major nerves at the uppermost part of the arm at the beginning of the brachial artery (*1*). After identifying the artery, an intracutaneous wheal is formed just medial to the artery. A 5-cm, 25-gauge, short-beveled needle attached to a 10-mL Luer-Lok control syringe containing the local anesthetic solution is inserted through the wheal, and the skin is moved anteriorly about 0.5 cm. While palpating the artery with the second and third fingers of one hand, with the other hand the needle is advanced laterally through the fascial sheath, which can be felt. The needle is advanced another 2 or 3 mm until contact with the median nerve produces paresthesia in its distribution (*2*). Injection of 2 to 3 mL of solution is sufficient to anesthetize the nerve. For block of the ulnar nerve, the maneuver is repeated except, after inserting the needle through the wheal, the skin is moved posteriorly 0.5 cm and advanced until contact with the ulnar nerve elicits paresthesia in its distribution (*3*). To reach the radial nerve, which is posterolateral to the artery, the needle must be inserted 0.5 cm posterior to the point of injection of the ulnar nerve, with the needle passing posterior to the ulnar nerve in a lateral and slightly anterior direction (*4*). At this level, the musculocutaneous nerve has passed laterally and is in the substance of the coracobrachialis muscle. To block this nerve, it is necessary to insert the needle 0.5 cm anteriorly to where the median nerve is located and to advance the needle laterally into the substance of the muscle, in which 5 mL of solution is usually sufficient to diffuse and block the nerve. For a continuous technique, a 5-cm, 18-gauge intravenous catheter is introduced through an opening in the anesthetized skin that has been made with a larger sharp needle. The catheter is directed at an angle of 30 degrees with the skin in a central direction toward the apex of the axilla. Once the tip of the catheter pierces the sheath containing the neurovascular bundle, it is advanced about 2 cm along the side of the artery, the stylet is removed, the solution is injected, and the catheter is fixed firmly in place. Subsequent injections are repeated as necessary.

Regardless of which one of the three techniques is used, a common feature is that the LA is deposited within the fascial sheath surrounding the brachial plexus (see Fig. 102-15). Provided that an adequate volume of drug (30 to 40 mL in an adult) is injected into the sheath, it tends to spread longitudinally within the sheath to affect all components of the brachial plexus. Circumferential spread might not be as reliable, particularly with a small volume of solution (68).

For diagnostic purposes, 1% lidocaine produces a 2- to 4-hour block. For therapeutic purposes, 0.250% to 0.375% bupivacaine with epinephrine produces analgesia and sympathetic block for 8 to 12 hours. In a significant proportion of patients, the use of a higher concentration (e.g., 0.5%) of bupivacaine produces a prolonged block of up to 16 to 24 hours' duration.

Techniques to produce a continuous brachial plexus block have been described for the supraclavicular (69), interscalene (70), and auxiliary routes (71,72). The plexus is located by paresthesia or loss of resistance or with the assistance of a nerve stimulator. A catheter is passed either directly into the fascial sheath or after initial dilatation of the sheath with a few milliliters of LA, or a guidewire can be passed into the sheath and a catheter passed over the guidewire (73). The catheter is fixed in place either with sutures or transparent adherent dressings. Analgesia can be maintained with periodic injections of 20 to 30 mL of 0.25% bupivacaine every 6 hours or by a continuous infusion with an infusion pump delivering 0.25% bupivacaine at a rate of 6 to 12 mL per hour. With the use of these techniques, the resulting blood levels of drug have been reported to be near toxic limits (74,75). Such catheters have been left in for considerable periods of time, up to a week, with few or no complications (73).

Complications. Complications of the use of interscalene block include epidural, subdural, or subarachnoid block; inadvertent intravertebral artery or intravenous injection; block of the sympathetic and recurrent laryngeal nerves; and a 70% to 90% incidence of phrenic nerve block. Complications of the use of the supraclavicular route include phrenic nerve block, cervical sympathetic block, and, perhaps the most serious, pneumothorax with an incidence of between 0.5% and 6.0% (65). Complications of the use of the axillary route include intravascular injection, with a seizure incidence of 1.5% reported in some series (36,45), and axillary artery damage. Minor neurologic damage has been reported to occur in up to 3% of patients (36,45), but average incidence is likely lower (76).

Suprascapular Nerve Block

Indications. The suprascapular nerve, a branch of the brachial plexus, is the major sensory nerve supply to the shoulder joint. Suprascapular nerve block is useful for

the management of severe pain caused by bursitis, periarthritis, or arthritis if these conditions are not amenable to intraarticular and periarticular injection of LA and steroids.

Technique. The anatomy of the suprascapular nerve is described in Chapter 54. It springs from the C-4, C-5, and C-6 contributions to the upper trunk of the brachial plexus from which the formed suprascapular nerve emerges. It then proceeds laterally, posteriorly, and inferiorly beneath the omohyoideus and trapezius muscles, but superficial to the plexus, to reach the superior border of the scapula, where it passes through the suprascapular notch beneath the superior transverse scapular ligament to enter the supraspinatus fossa (Fig. 102-19A).

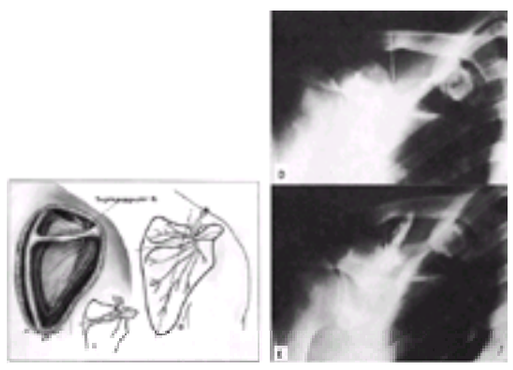

Figure 102-19. Suprascapular nerve block. **A:** Anatomy of the suprascapular nerve. **B:** Needle placement: After identifying the spine of the scapula, a line is drawn on the skin overlying it, with another line bisecting the inferior angle of the scapula (*dashed lines*). The outer triangle formed by the two intersecting lines is bisected and a wheal is formed on this line, about 1.5 cm from the angle. An 8-cm, 22-gauge needle is introduced through this wheal so that its shaft is directed anteriorly and slightly caudad and mesiad to make contact with the supraspinatus fossa just lateral to the suprascapular notch. The needle is withdrawn until its point is in the subcutaneous tissue and reintroduced so that its point is directed 5 mm medial to the point of first contact. Advancing the needle in this direction usually causes its point to enter the notch, make contact with the nerve, and elicit paresthesia. **C:** If the second insertion fails to produce paresthesia, a third or fourth insertion is made in search of the notch. Usually 3 to 5 mL of a local anesthetic solution produces block of the nerve. The radiographs show the point of the needle in the suprascapular notch before **(D)** and after **(E)** injection of 3 mL of 30% Diodrast. Note the diffusion of the dye.

The technique for suprascapular nerve block is described in Figure 102-19B, Figure 102-19C, Figure 102-19D and Figure 102-19E. This is usually a relatively simple block, but it is sometimes difficult to contact the nerve. Fluoroscopy or a peripheral nerve stimulator can be used to aid in placement of the needle.

Complications. Side effects include paralysis of the supraspinatus and infraspinatus muscles, producing transient disability. The most serious complication is pneumothorax occurring from the needle passing the upper border of the scapula into the chest wall, pleura, and lung.

Block of Median, Ulnar, and Radial Nerves

Indications. Block of the median, ulnar, or radial nerves at the elbow is useful as a diagnostic or prognostic tool in patients with pain in the distribution of each specific nerve. This procedure can also be used to produce a sympathetic block in the region supplied by each nerve. Block of the median or ulnar nerve, or both, at the level of the wrist can also be used for the same purpose.

Technique. The technique for blocking these nerves is described in Figure 102-20. Because the procedure entails approaching the nerve with the shaft of the needle at an angle that is perpendicular to the nerve, it is possible to impale the nerve with the needle against the underlying bone. It is essential to avoid nerve damage by using a fine (25-gauge), short-beveled needle and to elicit paresthesia gently or use a nerve stimulator. Usually 5 mL of 1% lidocaine or 0.25% bupivacaine is sufficient to block each nerve.

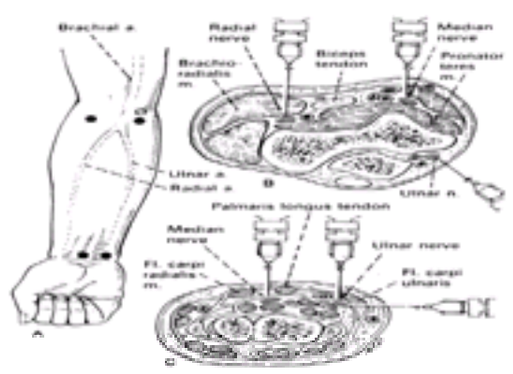

Figure 102-20. **A:** Sites of blocking of the major nerves at the elbow and wrist. (*Open circle*, brachial artery; *solid circle*, points.) **B:** Cross section of the arm at the elbow. The median nerve is medial to the brachial artery and is at a point midway between the medial epicondyle and the medial edge of the biceps tendon. To block the radial nerve, the needle is introduced 1 cm lateral to the lateral edge of the biceps tendon and advanced posteriorly. The ulnar nerve can usually be palpated just medial to the ulnar artery. Care must be exercised to use a fine needle with a short bevel to avoid damage to the nerve or eliciting paresthesia. **C:** Cross section of the arm at the wrist with needles in place to block the median and ulnar nerves. For median nerve block, a skin wheal is made between the tendons of the palmaris longus and the flexor carpi radialis. A 3-cm, 25-gauge needle is introduced perpendicular to the skin and advanced posteriorly until the nerve is contacted and paresthesia is elicited. For ulnar nerve block, the wheal is made just lateral (radial) to the tendon of the flexor carpi ulnaris and medial to the palpable ulnar artery. A 3-cm, 25-gauge needle is introduced perpendicular to the skin and directed posteriorly until the nerve is contacted. The ulnar nerve can also be blocked by a median approach, but care must be taken so that the needle is inserted just posterior to the posterior edge of the flexor carpi ulnaris tendon and advanced laterally until paresthesia is elicited.

Complications. In addition to possible nerve damage, other complications include inadvertent intravenous injection but, because the total amount of drug administered with each injection is small, this should not cause any systemic toxicity.

Thoracic Spinal Nerves

The thoracic spinal nerves transmit nociceptive information from the chest and abdomen and therefore are good sites for diagnostic, prognostic, prophylactic, or therapeutic procedures for various painful disorders involving these structures. Paravertebral blocks are performed as the nerve exits the intervertebral foramen and blocks the anterior and posterior primary divisions and the rami communicantes, which contain autonomic fibers from and to the thoracic and abdominal viscera. The anterior primary division of the thoracic nerve, the intercostal nerve, can be blocked at various sites along its course.

Paravertebral Block

Indications. Paravertebral block of the thoracic spinal nerves is helpful in painful disorders of the thoracic spine, thoracic cage, and abdominal wall. Because this block includes the recurrent nerve that supplies the vertebrae and meninges, it is helpful to determine the nociceptive pathways in patients with segmental neuralgia caused by vertebral pathology. Unless a prolonged block (3 to 5 days) can be achieved, its value in predicting the effects of neurolytic block of thoracic nerves or surgical

rhizotomy is questionable.

Paravertebral block can be used therapeutically to treat acute herpes zoster (77,78), rib fractures, and postoperative thoracotomy pain (79). This procedure has also been used to manage patients with chronic postthoracotomy and posttraumatic pain.

Repeated injections can be used for surgical or traumatic injuries to the chest wall or upper abdomen, or a catheter can be placed in the paravertebral space (80). The injection of an appropriate volume of LA through the catheter produces a block of two or three segments.

Technique. The anatomy of the thoracic spinal nerve is described in detail in Chapter 60 and is shown in Figure 102-21 and Figure 102-22. In the classic technique, the needle is inserted 4 to 5 cm lateral to the spinous process and advanced anteriorly and medially at a 45-degree angle to the midsagittal plane. When the needle strikes the appropriate transverse process, it is withdrawn until subcutaneous and then readvanced so that it passes inferior to the transverse process until its tip reaches the nerve. Using this approach, the needle traverses a concavity that contains the posterior border of the lung, thus risking pneumothorax. Moreover, if the needle is passed further, the intervertebral foramen might be entered, with consequent puncture of the dura and even of the spinal cord.

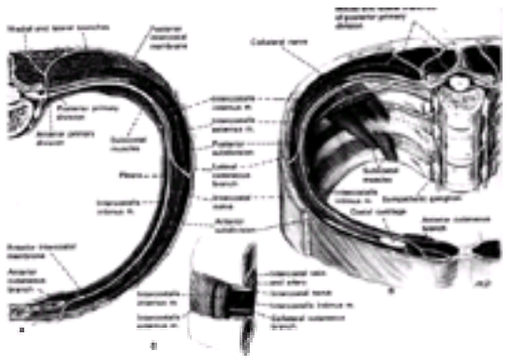

Figure 102-21. Anatomy of the thoracic spinal nerve. **A:** Superior view of the intercostal space. **B:** Anterior view of the chest. **C:** Cut section of two adjacent ribs. Note that the nerve exits through the intervertebral foramen to reach the paravertebral region, where it promptly divides into the posterior and anterior primary divisions. The anterior primary division, which becomes an intercostal nerve, proceeds between the posterior intercostal membrane and the endothoracic fascia and adjacent pleura. At the angle of the rib, it is located between the subcostal muscles and the internal intercostal muscle, and just distal to that it is situated between the intercostalis intimus and the internal intercostal muscles. The lateral cutaneous branch leaves the parent nerve near the angle of the rib. Note in **B** the relation of the intercostal nerves and their branches and these structures and the thoracic sympathetic chain; **C** shows the direction of fibers of the intercostal muscles and the position of the intercostal vessels and nerves. (Modified from Netter FH. *The CIBA collection of medical illustrations.* Vol 7, Respiratory system. West Caldwell, NJ: Ciba Pharmaceutica, 1979:11.)

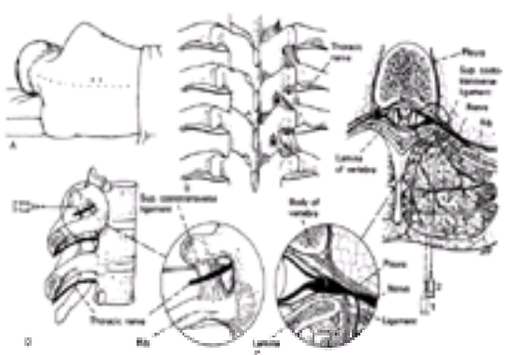

Figure 102-22. Thoracic paravertebral somatic nerve block. **A:** Position of the patient for block on the right side. Because placement of the needle depends on the relationship between the tips of the spinous processes and the laminae, it is essential to identify each spinous process and to mark it with an indelible pen or marker. After sterilizing the skin, a skin wheal is formed 1.5 cm lateral to the tip of the spinous process of the vertebra above. For block of the somatic nerve, it is best to make contact with the upper portion of the lateral aspect of the lamina. **B:** A 5- or 8-cm, 22-gauge, short-beveled needle is inserted through the skin wheal perpendicular to the skin. **C:** The needle is advanced until the lateral edge of the lamina is contacted (1). The needle is then withdrawn until its point is in the subcutaneous tissue, the skin is moved laterally about 0.5 cm, and the needle is readvanced until its point slips just lateral to the upper part of the lateral edge of the lamina and its point engages the uppermost part of the superior costotransverse ligament just below the proximal portion of the transverse process (2). Once the point of the needle is in the ligament, a 2-mL glass syringe filled with saline solution is attached to the needle and an attempt is made to inject the saline. It is important to test the syringe before its adaption to the needle to ensure that its plunger slides easily. As long as the tip of the needle is within the ligament, some resistance to the injection can be felt. By exerting constant pressure on the plunger of the syringe with the right hand and advancing the needle *slowly* with the left hand, a lack of resistance is felt as soon as the bevel of the needle passes through the upper part of the superior costotransverse ligament and is in the paravertebral region in the immediate vicinity of the nerve. If paresthesia is not elicited, a nerve stimulator is used to ascertain that the bevel of the needle is on the nerve **(C)**. The needle is directed in a true sagittal plane rather than at an angle, as is the case with the classical approach (see text). **D:** Lateral view showing the penetration of the superior part of the superior costotransverse ligament and the advancement of the needle until it comes in contact with the nerve.

To circumvent these problems, Bonica (2) developed the paralaminar technique described in Figure 102-22. For diagnostic purposes, 3 mL of 1% lidocaine or 0.25% bupivacaine is used. For treatment of severe acute pain, 5 mL of 0.375% to 0.500% bupivacaine with epinephrine is appropriate. With larger volumes of injectate (10 to 20 mL) the drug will pass up and down the paravertebral areas and result in a multilevel block. A continuous block technique can be achieved by placing a catheter in the paravertebral space (80).

Complications. Possible complications include accidental subarachnoid or epidural injection, intravascular injection, and pneumothorax, and, with large volumes of injectate, hypotension due to a sympathectomy.

Intercostal Nerve Block

Indications. Intercostal nerve block is a useful diagnostic procedure for defining nociceptive pathways of segmental chest and abdominal wall pain, but it must be used and interpreted with caution when differentiating somatic from visceral pain. Visceral afferent nerve fibers leave the nerve root at the intervertebral foramen, proximal to where intercostal nerve blocks are usually performed. However, the LA from intercostal nerve blocks may spread proximally from the site of injection to the intervertebral foramen and thus block both somatic and visceral fibers. The more distal the block is performed and the smaller the volume of injectate, the lesser the likelihood of spread of the LA to the paravertebral area. If there is doubt about the pain etiology (i.e., somatic versus visceral), it is best to perform a cervicothoracic sympathetic block for thoracic visceral pain or a splanchnic or celiac plexus block for abdominal visceral pain.

For therapeutic purposes, intercostal nerve block is a useful procedure for the relief of severe acute posttraumatic, postoperative, or postinfection pain in the thoracic or abdominal wall (1,81,82,83,84,85,86,87,88 and 89). Unilateral intercostal block is effective for chest pain after thoracotomy (81,84), subcostal (Kocher's) incisions (88,89), and after renal surgery through flank incisions (90,91). Bilateral intercostal blocks are necessary for sternotomy and midline upper abdominal incisions. To obtain satisfactory pain relief, it is necessary to block the nerves supplying the segments through which the incision passes, plus the segments above and below, and in the case of thoracic surgery, the segments through which chest drains pass.

The analgesia produced by intercostal nerve block may be superior to that produced by conventional narcotic analgesia. Postthoracotomy patients managed with

intercostal nerve blocks (Table 102-3) show less impairment of effort-dependent measures of respiratory function (forced vital capacity and peak expiratory flow) (26,88,91,92,93,94,95 and 96) and of arterial oxygenation (26,88) than patients receiving narcotic analgesia. Following abdominal operations, patients receiving intercostal blocks may have a better and earlier global recovery, an earlier discharge from hospital (81), better results on tests of respiratory function (e.g., forced vital capacity, peak expiratory flow), less impairment of arterial oxygenation, and a reduced incidence of respiratory complications (82) (Table 102-4). Detailed studies (82,89) imply that single unilateral posterior intercostal blocks in patients with subcostal incisions produce appreciable respiratory benefits, whereas bilateral blocks in patients with midline incisions may produce less benefit.

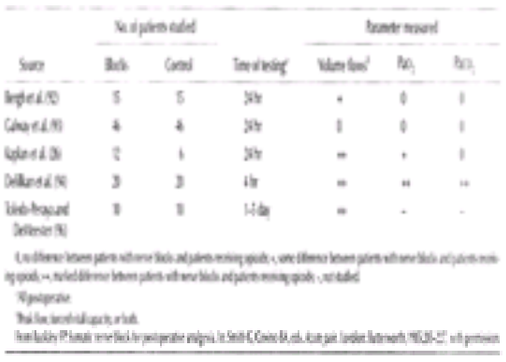

TABLE 102-3. Respiratory outcome in postthoracotomy patients given singledose intercostal blocks with bupivacaine

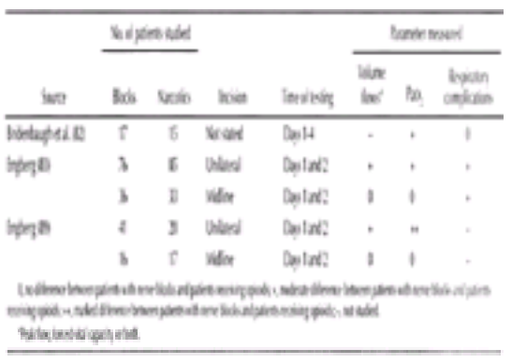

TABLE 102-4. Respiratory outcome in post–abdominal surgery patients: narcotics versus intercostal blocks

Studies of the influence of intercostal blocks on postoperative respiratory morbidity have been performed, predominantly in fit patients who have a relatively low incidence of postoperative respiratory morbidity. There is little information on the efficacy of these blocks in patients who would be expected to have a higher incidence of respiratory morbidity (i.e., those with preexisting respiratory disease), who might be expected to achieve greater benefits from intercostal nerve blocks. Anecdotal reports (97,98) suggest that bilateral posterior intercostal blocks in patients with respiratory compromise could precipitate respiratory failure, possibly as a consequence of changes in abdominal and chest wall mechanics and in functional residual capacity (99) produced by the blocks (99,100 and 101). In patients with respiratory compromise, it is probably advisable to perform intercostal blocks as far distally as possible along the course of the intercostal nerve to achieve maximal sparing of chest wall and abdominal muscle power. Patients receiving intercostal blocks that produce analgesia limited to the thoracic or abdominal wall usually require supplemental analgesia with modest doses of narcotics to relieve pain arising from the viscera and from drains or nasogastric tubes.

The use of intercostal blocks for postoperative or posttraumatic chest and abdominal pain has largely been supplanted by the use of continuous segmental epidural analgesic techniques with LA with or without opioids (see Chapter 103). Intercostal nerve blocks may have a limited niche role when epidural techniques are impossible or contraindicated. Intercostal nerve blocks with bupivacaine produce analgesia for 8 to 12 hours (102), permitting analgesia to be obtained with blocks two to three times a day. Disadvantages of the use of intercostal block compared with epidural block include the need to make multiple injections and the risk of pneumothorax.

Technique. The anatomy, course, and distribution of the intercostal nerves are discussed in Chapter 60 and shown in Figure 102-23 and Figure 102-24. Although the intercostal nerves can be blocked at any point along their course, they are usually blocked at the four sites depicted in Figure 102-23.

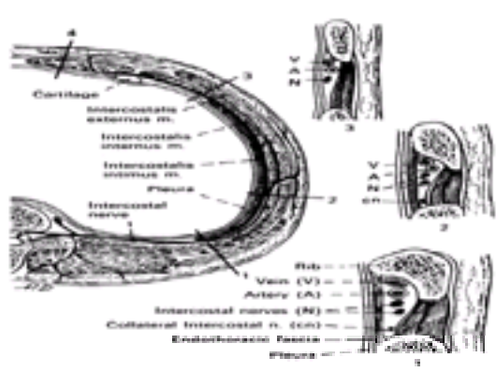

Figure 102-23. Typical intercostal nerve and the optimal sites for intercostal block. The cross section on the left shows the course of the nerve. Cross sections on the right show the relationship of the intercostal nerves to the vessels and the muscles. Angle of rib where the intercostal space is a triangular structure that contains the vein, artery, principal nerve and its lateral cutaneous branch, and collateral branch (*1*). The space is bound medially by the pleura and the endothoracic fascia and the beginning of the intercostalis intimus muscle and laterally by the intercostal groove and the internal and external intercostal muscles. Cross section along the posterior axillary line (*2*). Note the difference in shape of the space and of the cross section of the rib. Cross section at the anterior axillary line (*3*). Cross section at costochondral junction (*4*).

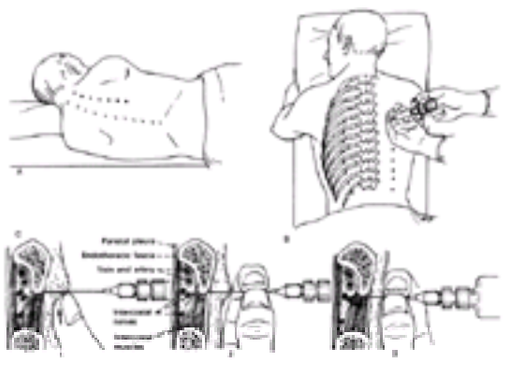

Figure 102-24. Posterior intercostal block. The injections are done at the angles of the ribs. **A:** The patient lies on the side comfortable for a unilateral block. **B:** The patient is in a prone position to facilitate bilateral block. The dots indicate the sites of injection. **C:** Details of injection. After identifying the space and sterilizing the skin over it, an intracutaneous wheal is made just below the lower edge of the rib **(B)**. A 3-cm, 25-gauge, short-beveled needle is inserted through the wheal, after which the second finger of the left hand is placed over the intercostal space and the skin is pushed slightly cephalad so that the lower edge of the rib above can be palpated at the same time the skin over lower edge of the rib is immobilized (1). This finger also protects the intercostal space, thus decreasing the risk of passing the needle too far into the lung. The needle is advanced until the lowermost part of the lateral aspect of the rib is contacted. After the rib is impinged on, the needle is grasped between the thumb and index finger of the left hand, 3 to 5 mm from the skin (2). The skin is moved caudad with the left index finger to allow the needle to slip just below the lower border of the rib. The needle is advanced until the fingertips grasping the needle are flush with the skin (3). This simple maneuver minimizes the possibility of advancing the needle too deeply and entering the lung. With the needle held steady between the second and third fingers of the left hand, aspiration is attempted; if negative, 3 to 4 mL of solution is injected.

Posterior Intercostal Block

Posterior intercostal block is most easily performed at the angle of the rib where the rib is most easily palpable, the rib is thickest, and the intercostal groove is broadest and deepest. At this point, the intercostal space is triangular, has an area of approximately 0.75 cm ^{2}, and is filled with fat within which the intercostal nerve, its lateral cutaneous branch, and the collateral branch are grouped relatively close together (1,89,103). As noted in Figure 102-21 and Figure 102-23, the space is bound externally by the intercostal groove, posterior intercostal membrane, and internal and external intercostal muscles and internally by the thin intercostalis intimus muscle and the pleura. The internal and external intercostal muscles are substantial structures bound on their internal aspects by the posterior intercostal membrane and on their external aspects by the fascia and cutaneous structures.

Posterior intercostal nerve block technique is described in Figure 102-24. Injection of 3 to 4 mL of LA at the angle of the rib results in LA spreading several centimeters distally and also proximally to the paravertebral area. Spread of LA to the paravertebral area may result in block of sympathetic afferents (100), thus helping to relieve visceral as well as somatic pain. Injection of larger amounts of LA results in both paravertebral and epidural spread of the drug (104) and, if many segments are involved, arterial hypotension can develop. Injection of LA at one intercostal site may spread subpleurally to adjacent intercostal nerves (88), although this is not a consistent finding (103). Single injections of 20 mL of LA may produce analgesia that involves multiple intercostal nerves (105,106 and 107).

Lateral Intercostal Block

Lateral intercostal block is best achieved at the posterior axillary line, 3 to 4 cm posterior to the midaxillary line (Fig. 102-25), prior to where the lateral cutaneous nerve pierces the intercostal muscles and divides into the anterior and posterior branches (see Fig. 102-21). The anterior branch supplies the skin and subcutaneous tissues of the anterolateral chest and abdominal wall as far as 7 cm from the midline, while the posterior branch supplies these tissues as far as 7 to 10 cm from the spine.

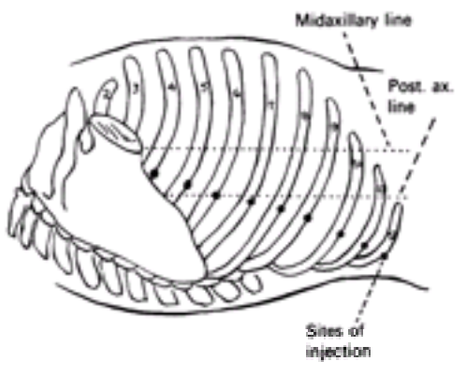

Figure 102-25. Lateral intercostal block along the posterior axillary line. The black dots indicate the sites of injection posterior to the exit of the lateral cutaneous branches. The technique for introducing the needle is similar to that shown in Figure 102-24.

When compared with posterior intercostal block, a lateral intercostal block with 3 to 4 mL of LA is less likely to spread to the paravertebral region and may be a better choice of technique when attempting to distinguish between somatic and visceral pain. For therapeutic use, however, lateral intercostal nerve block may not affect visceral pain, which may require supplemental systemic analgesics.

Continuous Intercostal Block

The practice of attempting to produce continuous intercostal nerve blocks by the insertion of catheters into intercostal spaces dates from the 1960s (108,109). More recently the placement of epidural catheters along the intercostal nerves at the end of an intrathoracic or renal operation, with the distal ends protruding through the closed incision (110), has been described.

Following the realization that the injection of a large volume of LA through a single intercostal injection produces multiple intercostal nerve blocks, techniques using this finding have been developed. An epidural catheter inserted into a single space and injected with 20 mL of 0.5% bupivacaine at intervals of 6 to 12 hours or a continuous infusion can sustain the analgesia after an initial injection has proven to be effective.

Intrapleural Block

The technique for intrapleural block (Fig. 102-26) (111) entails the insertion of an epidural Tuohy needle into the pleural space 8 to 10 cm from the posterior midline and the passage of an epidural catheter into the pleural space. The catheter is fixed in place and, after a negative aspiration, 0.5% bupivacaine with epinephrine is injected in amounts varying from 1 to 3 mg per kg body weight (i.e., 7 to 21 mL of 0.5% bupivacaine) (112). The technique produces unilateral analgesia, presumably because the LA diffuses through the pleural space in amounts sufficient to block the intercostal or paravertebral nerves. The block is maintained with repeat doses every 9 hours on average (range, 5 to 26 hours). In patients undergoing thoracotomy, the epidural catheter is introduced through a Tuohy needle one or two intercostal spaces above the incision, and the internal end of the catheter is loosely sutured next to the vertebra. In patients with thoracotomy, there is concern that intrapleural analgesia might be ineffective because LA may be removed through chest drains. This may be combated by clamping the chest drains for 10 to 15 minutes after injection of the LA (112). The technique may be used for various operations on the chest, upper abdomen, and breast and for herniorrhaphies. The technique may also be used for some more chronic pain problems, such as herpes zoster, chronic pancreatitis, and PHN, and to produce an upper extremity sympathectomy (113).

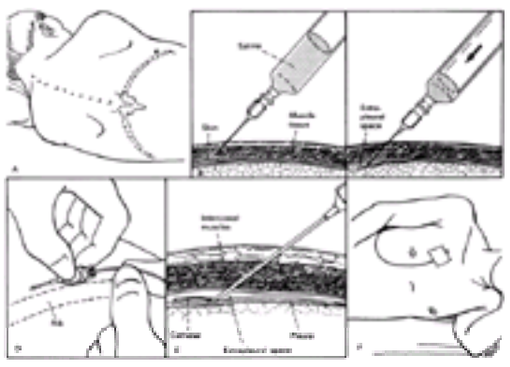

Figure 102-26. Intrapleural block. **A:** The patient lies on the unaffected side, resting comfortably on a pillow. The dot over the rib outline (*dashed lines*) shows the site of injection of a local anesthetic with a 25-gauge needle before insertion of the large Tuohy needle. **B:** A 17-gauge Tuohy needle attached to a syringe containing saline solution is introduced through the wheal with the bevel facing superficially as shown in E. The needle is directed so that its shaft makes a 60-degree angle with the skin. The needle is advanced slowly and carefully through the intercostal muscles and endothoracic fascia into the pleural space. **C:** The entrance of the bevel into the pleural space is indicated by the fact that the saline is sucked into the space by negative intrapleural pressure. **D:** Once the needle is in place, a catheter is introduced. **E:** The catheter is advanced 4 or 5 cm, the needle is removed, and the catheter is taped in place. **F:** The patient remains with the painful side uppermost, and 20 mL of 0.5% bupivacaine with epinephrine (average adult dose) is injected.

When repetitive injections of LA or infusions are used, caution must be exercised, as the resulting blood levels of LA may rise to within the toxic range (114).

Anterolateral and Anterior Intercostal Block

Anterolateral intercostal block (Fig. 102-27) is performed at the anterior axillary line proximal to the takeoff of the anterior cutaneous branches of the intercostal nerves. It is useful for poststernotomy and sternal fracture pain or pain in the abdominal distribution of the thoracoabdominal intercostal nerves (T-7 to T-10). In the latter case, the block is performed just proximal to the costochondral articulation. Figure 102-27 also depicts parasternal injection, done bilaterally to relieve sternal pain. Like lateral intercostal block, this block does not interrupt visceral nociceptive pathways. Patients with elements of visceral pain may require systemic analgesics or a combination of both.

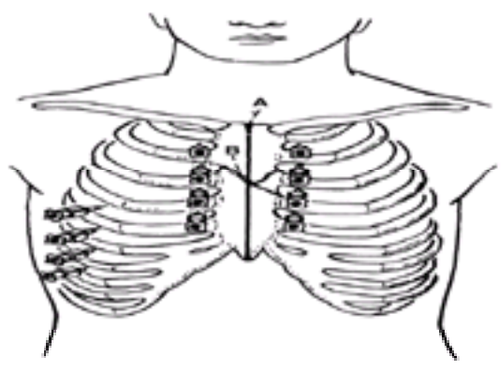

Figure 102-27. Anterolateral intercostal nerve block at the anterior axillary line (*right*). At this point the intercostal nerve and vessels lie between the internal intercostal muscle and the endothoracic fascia and pleura (see Fig. 102-24C). To relieve the pain of sternotomy (A) or fracture of the sternum (B), an anterior intercostal block is done 2 cm lateral to the lateral edge of the sternum; the block is supplemented with subcutaneous infiltration above the sternum and medial part of the clavicle to block the branches of the cervical plexus. The technique for introducing the needle is similar to that shown in Figure 102-25.

The most serious complication of percutaneous intercostal block is pneumothorax, with a quoted incidence ranging from 0.13% to 4.00% (102). Among a variety of nerve blocks, performed with a given mass of LA, intercostal nerve blocks produce among the highest peak blood levels of LA, because absorption of LA occurs at a faster rate and to a greater extent than after injection elsewhere (115,116). Hence, there is a clear potential for systemic toxic reaction, especially after injection of large therapeutic doses or repetitive blocks. Peak blood levels of LA can be reduced by adding epinephrine to the LA and by the use of an optimal concentration and reasonable volume of the drug (see Table 102-1). Inadvertent intravascular injection of drug is rare.

Although LA can spread to the paravertebral area following a percutaneous block, cardiovascular homeostasis is usually undisturbed. Following intrathoracic block (i.e., block done by the surgeon while within the thoracic cavity), hypotension or cardiovascular collapse has been reported to have been caused by SAB (117,118) or by widespread paravertebral block (119,120).

Rectus Block

Bilateral rectus block (Fig. 102-28) can be used to relieve midline abdominal incisional pain. As noted in Figure 102-21 and Figure 102-28, the anterior branch of the intercostal nerve enters the abdominal wall by passing behind the costal cartilages and entering the space between the transversus abdominis and internal oblique muscles. These anterior cutaneous nerves then pass medially within this space as far as the semilunar line, where they perforate the posterior sheath of the rectus abdominis muscle near its lateral margin. Within the sheath, they course between the posterior aspect of the muscle and the posterior sheath as far as the middle of the muscle, where they turn anteriorly and pass through the substance of the muscle and perforate its anterior sheath to become the anterior cutaneous nerves of the abdominal wall. While within the rectus sheath, they give off branches to the rectus abdominis muscles. Below the arcuate line, the rectus abdominis muscle lacks the posterior sheath and is separated from the peritoneum only by the transversalis fascia and extraperitoneal fat.

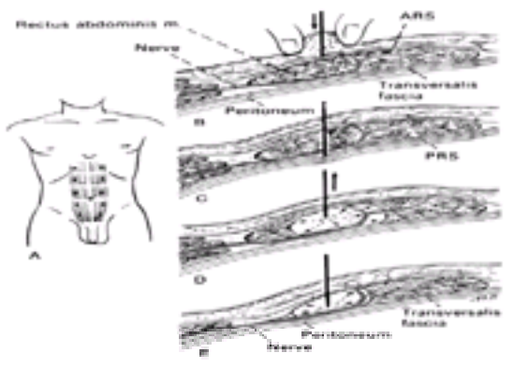

Figure 102-28. Rectus block (left side). **A:** Sites of insertion of the needle in the middle and slightly lateral part of each segment of the rectus muscle body, which can be palpated between the tendinous insertions. For an upper abdominal midline incision, the upper three sites are injected bilaterally, whereas the lower two or three sites are injected bilaterally for a lower midline incision. Skin wheals and injections of the superficial subcutaneous tissue are produced at the appropriate sites for the introduction of a 5-cm, 22- or 23-gauge, short-beveled needle attached to a Luer- Lok control syringe filled with a local anesthetic. The needle is then passed through the skin and subcutaneous tissue. **B:** Facilitating penetration of the skin by the short-beveled needle. The skin around the wheal is grasped between the thumb and second finger as the needle is passed through the skin and subcutaneous tissue and advanced until it meets the firm resistance of the anterior rectus sheath (*ARS*). The needle is advanced with steady pressure to penetrate the sheath. This is felt as a definite “snap.” **C:** The needle is advanced slowly through the softer belly of the

muscle until it meets a second site of resistance as it contacts the posterior rectus sheath (*PRS*). (The distance between the ARS and PRS should be noted to estimate the thickness of the muscle accurately.) **D:** As the needle rests on the PRS against which the nerve lies, 3 to 4 mL of local anesthetic solution is injected and the needle is withdrawn slowly. At the same time another 2 to 3 mL of solution is discharged within the belly of the muscle. **E:** Below the semicircular line of Douglas, the PRS is lacking and the nerve is against the transversalis fascia, which provides no resistance to the needle. Therefore, after penetration of the ARS, the needle is cautiously advanced for the same distance as noted for the upper levels of the muscle before injection of the anesthetic solution.

Rectus sheath block may be helpful in relieving abdominal pain following surgery, including laparoscopy (121).

Lumbar and Sacral Spinal Nerves

The lumbar and sacral nerves are considered here together because they both supply the pelvis and lower extremities and are often both involved in conditions that need analgesic block. Because these nerves, like those of the upper extremities, contain somatosensory, somatomotor, and sympathetic fibers, blockade can be used to manage the same disorders as those discussed in connection with block of the brachial plexus (see above).

Paravertebral Lumbar Somatic Nerve Block

Indications. Paravertebral block of the lumbar nerves is a useful diagnostic procedure for determining the specific nociceptive pathway(s) associated with vertebral, disk, or peripheral nerve pathology and for predicting the effects of blocking the nerves involved in spasm of leg muscles in patients with neurologic disease. For such blocks, the vertebral level of the needle placement and its closeness to the nerve must be verified radiographically and/or using a peripheral nerve stimulator. Lumbar paravertebral block may be used therapeutically for postnephrectomy pain or pain following lumbar vertebral fractures.

Technique. The anatomy of the lumbar and sacral nerves and the nerves derived from the lumbar and lumbosacral plexuses is described in Chapter 75 and illustrated in Figure 102-29. As they exit the intervertebral foramina, the lumbar nerves and plexuses are located in the psoas compartment formed by the posterior fascia of the psoas muscle anteriorly, the anterior fascia of the quadratus lumborum and the transverse processes and intertransverse ligaments posteriorly, and the bodies of the vertebrae medially. This has an important clinical application.

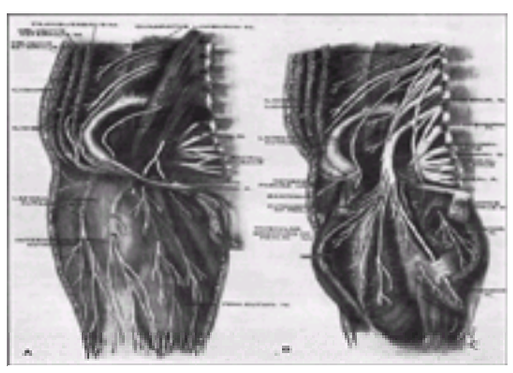

Figure 102-29. Anatomy of the lumbar and sacral nerves, lumbar and sacral plexus, and the nerves derived from these. **A:** Course of the iliohypogastric, ilioinguinal, lateral femoral cutaneous, and genitofemoral nerves. **B:** The iliopsoas, inguinal ligament, and deep fascia of the thigh have been removed to show the formation of the lumbar and sacral plexuses and the nerves derived from the lumbar plexus. The ilioinguinal and iliohypogastric nerves are derived from the anterior primary division of the L-1 nerve, while the lateral femoral cutaneous nerve is derived from the L-2 and L-3 nerves. The femoral nerve, which is derived from the L-2, L-3, and L-4 nerves, begins to divide into its muscular and cutaneous branches just behind (posterior to) the inguinal ligament and lateral to the femoral artery. The obturator nerve is formed within the substance of the psoas muscle by the union of the ventral branches of the anterior primary divisions of the L-2, L-3, and L-4 lumbar nerves. It emerges from the muscle and descends, accompanied by the obturator vessels, passes through the obturator foramen, and enters the upper thigh, where it breaks up into branches.

The technique for paravertebral block of the lumbar nerves is similar to that of blocking the thoracic paravertebral block (Fig. 102-30). For diagnostic or prognostic purposes, small volumes (e.g., 2 mL) of LA should be injected after radiographic verification of correct needle placement. For therapeutic purposes, 5 mL of LA should be used to achieve longer analgesia, but this is likely to spread, via the paravertebral area, to adjacent segments. Indeed, because the lumbar nerves and plexus are located in the psoas compartment (see Fig. 102-29), injection of 25 to 30 mL of LA solution through one needle placed at L-3 or L-4 and advanced 1 cm anterior to the transverse process to place it in the compartment will cause the solution to diffuse cephalad and caudad sufficiently to block all the sympathetic nerves, the lumbar plexus, and even the lumbosacral trunk. A special technique for “psoas compartment block” has been described (122), but it is more complicated and is associated with a higher incidence of failure to block the lumbar plexus completely than the technique described here.

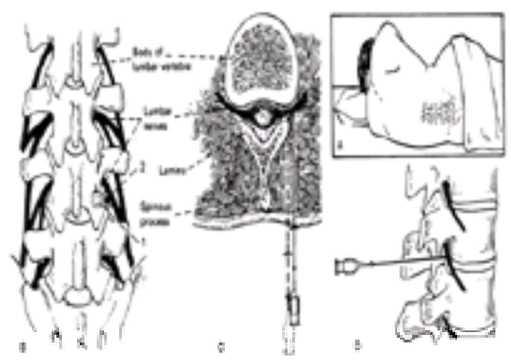

Figure 102-30. Lumbar paravertebral somatic block. **A:** Position of the patient (sterile drapes omitted for clarity). After identifying the spinous process of the appropriate vertebra (or vertebrae) and marking it with an indelible pen or marker, the skin is prepared with an antiseptic solution and a skin wheal is raised 1.5 cm lateral to the upper portion of the quadrilaterally shaped spinous process. Using a 5-cm, 25-gauge needle, the subcutaneous and deeper structures are infiltrated with 5 to 7 mL of a dilute solution of local anesthetic (e.g., 0.5% lidocaine or 0.125% bupivacaine) until contact with the lamina of the vertebra is made. This infiltration should produce a region of analgesia about 2 cm in diameter for the painless introduction and advancement of an 8-cm, 22-gauge, short-beveled needle. **B,C:** The 22-gauge needle is inserted perpendicular to the skin in a parasagittal plane and advanced until it makes contact with the upper lateral part of the ipsilateral lamina of the vertebra (*dashed line* of hub of needle; step 1). Care should be taken so that the point of the needle contacts the uppermost part of the lateral edge of the lamina, because this is at the same cross-section level as the nerve as it exits from the intervertebral foramen. Once the lamina is contacted, a rubber marker is placed on the needle shaft 1.5 cm from the skin, the needle is withdrawn until its point is subcutaneous, and the needle is then moved laterally about 0.5 cm. The needle is advanced until either the lateral edge of the lamina is contacted or the needle passes so that the marker is flush with the skin and its point makes contact with the nerve, eliciting paresthesia (step 2). It might be necessary to carry out a second or third insertion before the needle passes just lateral to the edge of the lamina. Because of the large size of the lumbar nerves, contact usually is easily made and paresthesia elicited. If difficulty is encountered, a nerve stimulator is helpful. **D:** Lateral view to show position of needle.

Complications. Complications of lumbar paravertebral block are similar, with the exception of pneumothorax, to those of thoracic paravertebral block.

Transsacral Block

Indications. Block of one or more of the sacral nerves by the transsacral technique is used for diagnostic or prognostic purposes. Block of the S-1 nerve is useful for determining specific nociceptive pathways in patients with herniated intervertebral disk of this nerve root. Block of the S-2, S-3, and S-4 nerves is also useful as a diagnostic or prognostic procedure in patients with perineal pain and can help to define specific nociceptive pathways in patients with pain in pelvic structures, such as the bladder or prostate. Because pudendal nerve block does not involve the nerves to the leg, it is preferable to transsacral block for acute pain in the perineum.

Technique. The technique for transsacral nerve blocks is illustrated in Figure 102-31. For diagnostic or prognostic purposes, a small volume of LA (e.g., 2 mL) should be used. For therapeutic purposes, a larger volume (e.g., 3 to 5 mL) can be used.

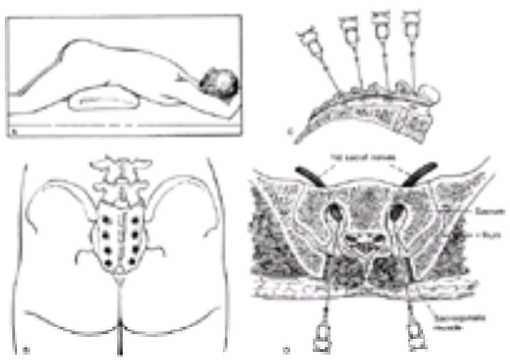

Figure 102-31. Transsacral nerve block. **A:** Position of the patient. **B:** Posterior view of the sacrum showing location of points of insertion. **C:** Sagittal view showing directions of needles. **D:** Cross section showing needles in position for block of the first sacral nerves. After identifying the posterior superior iliac spine and the sacral cornu on the ipsilateral side, a line is drawn between a point 1.5 cm medial to the spine and a point 1.5 cm lateral and cephalad to the ipsilateral cornu. For block of the S-1 nerve, a wheal is made on the drawn line, 1.5 cm cephalad to the level of the iliac spine. For block of the S-2 nerve, the wheal is made 1.5 cm below the level of the iliac spine. Because some variation exists in the location of the foramina, it is necessary to make a systematic search until the needle is felt to go through the posterior foramen to the transsacral canal. Contact with the nerve produces paresthesia.

Complications. Accidental intravenous injection is possible but, as the volume of LA is small, toxic effects are unlikely. Neuronal damage, either direct or by compression, is possible as the nerves are blocked within a bony canal of finite volume.

Femoral Nerve Block

Indications. Block of the femoral nerve just below the inguinal ligament can be used as a diagnostic procedure in patients with severe anterior thigh pain or it can be used, along with a sciatic nerve block, to produce sympathetic interruption of the lower limb. The most common use is for posttraumatic or postoperative pain in the region of the distribution of the femoral nerve, femoral fractures, and femoral and knee operations (123,124).

Technique. The anatomy of the femoral nerve is described in Chapter 75. Figure 102-32 describes the technique for femoral nerve block. The nerve usually does not branch until it emerges from beneath the inguinal ligament and, hence, the nerve trunk can easily be located by paresthesia or with a stimulator. In some individuals, however, the nerve divides into several branches above the inguinal ligament, and it is more difficult to contact these small nerves. Usually 8 to 10 mL of 1% lidocaine with epinephrine produces analgesia for 3 to 4 hours, and 8 to 10 mL of 0.25% bupivacaine with epinephrine produces analgesia for 6 to 8 hours. If longer analgesia is required, the concentration of the bupivacaine can be increased to 0.5% with epinephrine or a continuous block can be used by placing a catheter as described in Figure 102-33.

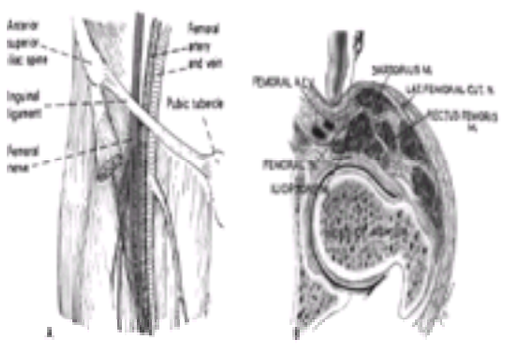

Figure 102-32. Blocking the femoral nerve. **A:** Anterior view of the region showing the relation of the femoral nerve to the artery and vein. **B:** Cross section of the femoral nerve just below the inguinal ligament. With the patient lying supine, a line is drawn joining the anterior superior iliac spine and the pubic tubercle. The midpoint of this line usually overlies the femoral artery, which is easily palpated. After preparation of the skin, a skin wheal is raised 1 cm lateral to the junction of the femoral artery and inguinal ligament. With the second finger of the left hand palpating the artery, a 5-cm, 22- or 25-gauge, short-beveled needle is introduced through the wheal perpendicular to the skin and advanced until paresthesia is elicited in the distribution of the femoral nerve. If paresthesia is not elicited, a nerve stimulator can be used. If a continuous block of this nerve is needed, a 5-cm, 20-gauge intravenous catheter can be introduced so that its shaft makes an angle of 60 degrees with the skin distal to the point of insertion, which aids in threading the catheter into the femoral sheath (see Fig. 104-35 for details of insertion).

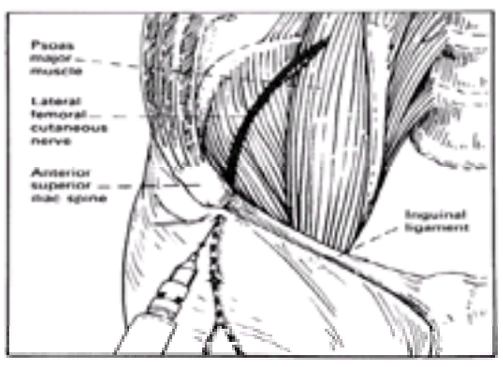

Figure 102-35. Lateral femoral cutaneous nerve block. After preparation of the skin, a wheal is produced 1.5 cm caudad to the anterior superior iliac spine just below the inguinal ligament. A 5-cm, 22- or 25-gauge, short-beveled needle is introduced through the skin wheal with its shaft at an angle of about 60 degrees with the skin. The needle is advanced until paresthesia is elicited or the bone is contacted. In the latter case, the needle should be withdrawn until its point is subcutaneous and the skin wheal moved 0.5 cm lateral and superior; the needle is then reinserted and advanced until paresthesia is elicited. The nerve is usually located by making several insertions through the same wheal in a line parallel to the inguinal ligament. A volume of 5 to 8 mL of local anesthetic is injected.

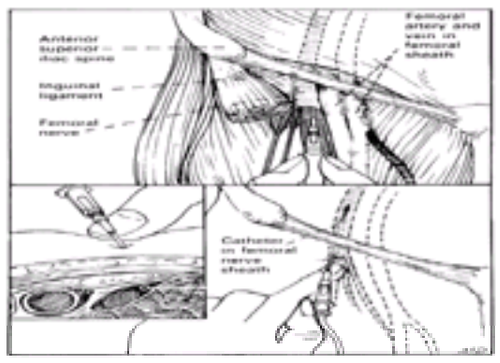

Figure 102-33. Continuous inguinal perivascular block. **A:** Following preparation of the skin with an antiseptic, an intracutaneous wheal is formed 1 cm lateral to the palpable femoral artery and 1 cm below the inguinal ligament. A 5-cm, 18-gauge, Teflon-coated intravenous catheter threaded over a 9-cm, 22-gauge spinal needle is used. It might be necessary to make a small skirt incision to facilitate introduction of the intravenous catheter through the skin. The needle is introduced through the skin wheal and advanced cephalad parallel to the artery, with its shaft making a 30-degree angle with the skin distal to it. This angle permits the catheter to be advanced within the sheath cephalad and minimizes damage to the nerve. **B:** Entrance into the tough sheath that surrounds the femoral nerve can be felt as a click or snap. The catheter is advanced about 3 cm within the sheath, the needle is removed, and the catheter is fixed in place. Once the catheter is in place, aspiration is carried out; if negative, 30 mL of solution is injected while the second finger of the left hand presses forcefully on the artery just distal to the entrance of the catheter (inset), thus forcing the fluid to flow proximally. With this volume of solution, block of the femoral, lateral femoral cutaneous, and obturator nerves is achieved.

Complications. The only possible complication of femoral nerve block involves accidental intraarterial or intravenous injection if the needle is placed medially.

Obturator Nerve Block

Obturator nerve block can be used as a diagnostic or prognostic procedure in patients with adductor muscle spasm and pain caused by neurologic injury.

Technique. The technique for obturator nerve block is described in Figure 102-34. Because the nerve is not close to bony landmarks but is located in the center of the obturator canal, it is desirable to use a peripheral nerve stimulator to ensure accurate needle placement. Usually injection of 10 to 15 mL of 1% lidocaine with epinephrine produces analgesia for 3 to 4 hours. With injection of 0.25% bupivacaine with epinephrine, the duration of analgesia is increased to 6 to 8 hours, and with 0.5% bupivacaine it can be as long as 8 to 12 hours.

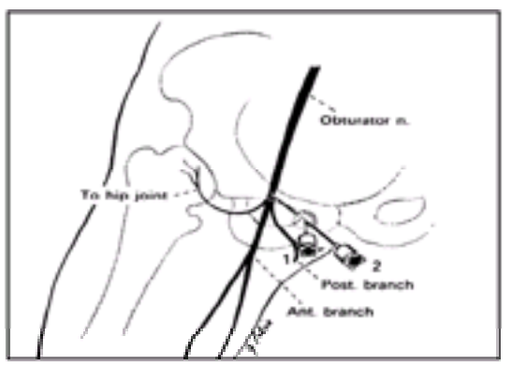

Figure 102-34. Obturator nerve block. The pubic tubercle is located and marked with the patient lying supine. After preparation of the skin, a wheal is raised 1.5 cm lateral and inferior to the tubercle. An 8-cm, 22-gauge needle is introduced through the wheal perpendicular to the skin and advanced posteriorly until contact is made with the inferior ramus of the pubis (*1*). A needle marker is placed 2.5 cm from the skin, and the needle is withdrawn until its point is in the subcutaneous tissue. The point of the needle is redirected in a lateral and slightly superior direction so that the shaft of the needle is parallel to the superior ramus of the pubis. The needle is slowly advanced while its point is kept in contact with the inferomedial surface of the superior ramus of the pubis, until the marker is flush with the skin or contact with the bone is lost (*2*). Because paresthesia is often difficult to elicit, a nerve stimulator is used to position the point of the needle on the nerve. A volume of 10 to 15 mL of local anesthetic is injected.

Complications. Accidental injection into the obturator vein is likely to produce a mild systemic reaction.

Lateral Femoral Cutaneous Nerve Block

Indications. Lateral femoral cutaneous nerve block is done primarily as a diagnostic procedure in patients with pain in the anterolateral thigh, especially those who have a presumptive diagnosis of meralgia paresthetica.

Technique. The technique for lateral femoral cutaneous nerve block is described in Figure 102-35. Injection of 5 to 8 mL of lidocaine with epinephrine produces analgesia for 3 to 4 hours. With 5 to 8 mL of 0.25% bupivacaine with epinephrine, analgesia lasts for 6 to 8 hours, and with 0.5% bupivacaine with epinephrine, it lasts for 8 to 12 hours.

Complications. Complications are rare and consist of transient neuropathy in cases of accidental damage to the nerve.

Inguinal Perivascular (Three-in-One) Block

The lumbar plexus nerves, like those of the brachial plexus, are invested in a fascial sheath that originates from the transverse processes of the vertebrae and continues distally to enclose the plexus. This sheath forms a cone whose apex is at the femoral canal. By introducing a large volume (30 mL) of LA into the femoral nerve sheath at the femoral canal and obstructing the sheath distal to the point of injection, LA flows proximally within the sheath. The LA may spread as far as the paravertebral region, bathing the lumbar nerve roots, thus producing block of the femoral, lateral femoral cutaneous, and obturator nerves in a high proportion of cases (125).

Indications. Block of these three nerves can be used for postoperative or posttraumatic pain in the area supplied by these nerves. This technique, combined with block of the sciatic nerve, produces analgesia of the entire lower limb and sympathetic block of the foot, leg, and lower two-thirds of the thigh. It can therefore be used to confirm the effects of lumbar sympathetic block when the results of the latter technique are in doubt. The technique can produce complete paralysis of the muscles of the lower limb when attempting to differentiate limitation of motion and deformity caused by reflex muscle spasm from that produced by irreversible changes in muscles and tendons, as discussed in connection with brachial plexus block (see above).

Technique. The technique for the inguinal perivascular or (three-in-one block) is similar to that described for femoral nerve block, with slight modifications (see Fig. 102-33). Injection of 30 mL of 0.25% or 0.50% bupivacaine with epinephrine produces analgesia of the three nerves for 8 to 16 hours. To produce prolonged analgesia, a catheter is inserted into the femoral sheath and LA is infused at a rate of 10 mL of 0.25% bupivacaine per hour (126).

Complications. Complications can include accidental intravenous or intraarterial injection or damage to the femoral nerve.

Sciatic Nerve Block

Indications. The sciatic nerve contains most of the sensory and sympathetic fibers of the leg. Thus sciatic nerve block can be used to control posttraumatic or postoperative pain in its distribution or to produce a sympathectomy of the leg. By combining sciatic nerve block with a three-in-one block, analgesia and sympathetic interruption of the entire lower limb can be achieved. The indications for these procedures are similar to those described for brachial plexus block for the upper limb (see above).

Technique. The anatomy of the sciatic nerve; the peripheral nerve supply to the skin, muscles, and bones of the lower limb; and the sympathetic nerve supply to the vessels of the lower limb are described in Chapter 75. The anatomy of the sciatic nerve and its major branches is shown in Figure 102-36.

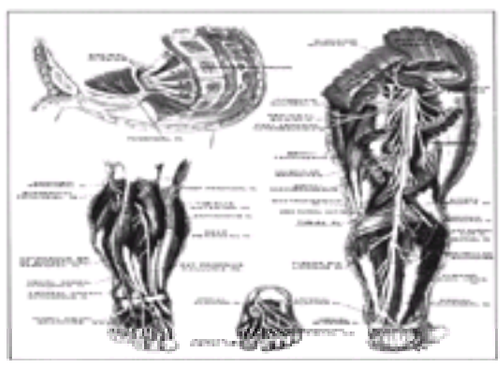

Figure 102-36. Anatomy of the sacral plexus **(A)** and of the sciatic, tibial, and peroneal nerves and their branches **(B,C). D:** Plantar surface of the foot. Block of the sciatic nerve is usually performed just below the piriformis muscle. See Chapter 70 and Chapter 75 for a detailed description of these nerves.

To block the sciatic nerve, the classic approach of Labat (127) (Fig. 102-37) or the lateral approach (Fig. 102-38) (128) is used. The lateral approach is technically challenging but useful in patients who cannot move to the lateral position required for Labat's technique.

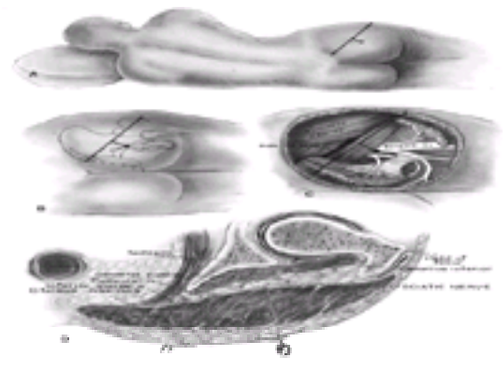

Figure 102-37. Labat's sciatic nerve block technique. **A:** The patient lies in a modified Sims position. A line is drawn between the posterior superior iliac spine and the superior border of the greater trochanter of the femur. The line is bisected at its midpoint and a perpendicular line 3 cm long passes caudad to it, with a solid dot indicating the site of the skin wheal and site of subsequent insertion of the block needle. **B:** Relation of the line to the bone and nerve. **C:** Relation of the nerve to muscles, with the lines superimposed. Following the creation of a skin wheal and infiltration of subcutaneous tissue, a 10-cm, 22-gauge security needle is introduced in a direction perpendicular to the skin and advanced until paresthesia is obtained or bone is contacted. In the latter case, the needle is withdrawn until its point is subcutaneous and is directed a little more obliquely, either cephalad or caudad. Several such explorations should be sufficient to locate the nerve. If difficulty is encountered, a nerve stimulator can be used to locate the nerve. **D:** Bevel of the needle on the nerve to elicit paresthesia, which radiates to the leg and foot. Bone depth varies from 5 cm in thin individuals to 8 cm in obese or muscular patients. If the landmark has not been determined accurately or if the needle has been improperly inserted, its point can miss the nerve and bone completely; if advanced too far, the needle can enter the pelvis.

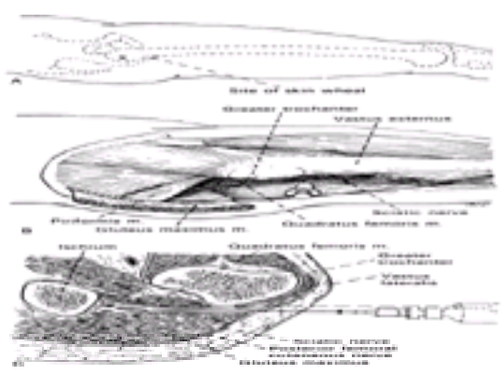

Figure 102-38. Sciatic nerve block by the lateral approach. **A:** With the patient supine the outline of the femur (*dashed lines*) is drawn. An *X* indicates the most prominent part of the greater trochanter. The skin wheal indicates the point of penetration of the skin. **B:** View of the right thigh with the skin and subcutaneous tissue removed to show the relationship of the sciatic nerve to muscles. The sciatic nerve is anterior to the gluteus maximus and posterior to the quadratus femoris, which has been cut. The syringe is positioned so that the point is on the nerve. **C:** Cross-sectional view illustrating the technique. Following preparation of the skin and creation of a skin wheal, a dilute solution of local anesthetic (e.g., 0.125% bupivacaine) is introduced through the skin wheal using a 5-cm, 25-gauge needle attached to a 10-mL Luer-Lok syringe containing the anesthetic solution. The needle is advanced slowly through the skin, subcutaneous tissue, and vastus lateralis until it contacts the posterior surface of the greater trochanter. While the needle is steadily advanced, the local anesthetic solution is injected into the subcutaneous tissue and the fascia of the muscle, with 1 or 2 mL injected into the periosteum. The depth of contact should be noted. The needle is then withdrawn until its point is in the subcutaneous tissue, the skin is moved 1 cm posteriorly and advanced in a trajectory parallel to the first injection, and dilute solutions of the local anesthetic are injected. These leave a track of anesthesia for the subsequent painless introduction of the larger needle. A 12- or 15-cm, 22-gauge needle is adapted to a 10-mL Luer-Lok control syringe containing a solution of greater strength of the local anesthetic (e.g., 0.5% bupivacaine with epinephrine) and these two steps are repeated. When the point of the larger needle contacts the periosteum or the posterior surface of the greater trochanter, the depth is noted and the needle is withdrawn until its point is in the subcutaneous tissue, and the skin is moved 1 cm posteriorly in the same fashion as earlier. The shaft of the needle should be parallel to the floor of the room. The needle is then slowly advanced. Normally, when the needle has advanced twice the distance of that in the first step, it should come in contact with the sciatic nerve and elicit paresthesia. If paresthesia is not elicited and the needle encounters bone (representing the ischial tuberosity), it is withdrawn and reinserted 2 or 3 mm anterior to its position in the second step and advanced. It might be necessary to make several penetrations before the nerve is contacted. If further difficulty is encountered in eliciting paresthesia, a nerve stimulator should be used. Special caution should be exercised in advancing the needle slowly and stopping as soon as the patient experiences paresthesia, because if the needle penetrates the nerve some axons could be damaged. It is important to inject the solution around rather than inside the nerve, because rapid expansion could also cause axonal damage. With experience and care it becomes easier to determine when the injection is extraneural because of lack of resistance. If the point of the needle is in the nerve, however, resistance can be felt and the patient experiences paresthesia during the

injection.

Efforts to achieve continuous sciatic nerve block, by introducing a catheter through a large needle and having its tip on the sciatic nerve, have historically been unsuccessful because movement of the leg can displace the tip of the catheter from the nerve. A technique for continuous sciatic nerve block has been described (129).

For single-dose techniques, injection of 10 to 15 mL of 0.25% to 0.50% bupivacaine provides analgesia for 8 to 12 hours. For the continuous technique, hourly infusions of 5 to 8 mL of 0.25% bupivacaine are used (129).

Complications. Complications include inadvertent intravascular injection and neural damage.

Nerve Block at the Knee, Ankle, and Foot

The nerves to the leg and foot can be blocked at the level of the knee to produce analgesia, sympathetic blockade, or both (Fig. 102-39). The tibial and common peroneal (lateral popliteal) nerves can be blocked in the popliteal fossa. The common peroneal nerve can also be blocked as it winds around the neck of the tibia, while the saphenous nerve can be blocked as it lies on the medial condyle of the tibia, at the cross-sectional level of the apex of the patella (Fig. 102-40).

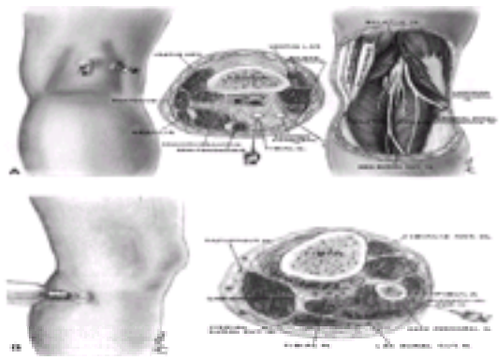

Figure 102-39. Block of the three major nerves at the level of the knee. **A:** Block of the tibial and peroneal nerves in the popliteal fossa: With the patient in the prone position, the bend of the knee is determined by having the patient flex the leg 90 degrees on the thigh and the junction of the two cutaneous surfaces is traced on the skin. After skin preparation, the popliteal artery is palpated 2 cm above the bend of the knee and a skin wheal is raised 1 cm lateral to this point. A 5-cm, 22- or 25-gauge needle is introduced through the wheal in a direction perpendicular to the skin and advanced slowly until paresthesia radiating to the back of the leg and sole of the foot is elicited, whereupon 5 mL of local anesthetic solution is injected without moving the knee. If paresthesia is not obtained, the nerve can be found by systematic exploratory fanwise insertions made in the mediolateral plane. To block the peroneal nerve, the posteromedial margin of the biceps femoris is palpated at about the same level as that for tibial block. A skin wheal is raised just medial to the edge of the biceps femoris muscle, and a 5-cm, 22- or 25-gauge needle is introduced through it. The needle is made to pass just medial to the inner margin of the biceps and is slowly advanced until paresthesia radiating to the anterolateral aspect of the leg and dorsolateral aspect of the foot is elicited, whereupon 5 mL of solution is injected. Analgesia occurs within 5 to 8 minutes. An alternate method of blocking both nerves with one needle involves injection of 10 to 15 mL of solution when the tibial nerve is blocked. Because the two nerves are located in loose areolar tissue, the drug easily diffuses to block both nerves. **B:** Block of the peroneal nerve at the neck of the fibula: With the patient in the supine or lateral position, the head of the fibula and the depression just below it, which is the neck of the fibula, are palpated. By moving the finger up and down, the cordlike common peroneal nerve can be palpated. It is not necessary to make a skin wheal if a 25-gauge, 2.5-cm needle is used. With the nerve held stationary by the index finger of the left hand, the needle, attached to a 10-mL Luer-Lok syringe, is introduced through the skin in a direction perpendicular to it and slowly advanced until the nerve is gently contacted, as indicated by paresthesia. A volume of 3 to 4 mL of solution is sufficient to block the nerve.

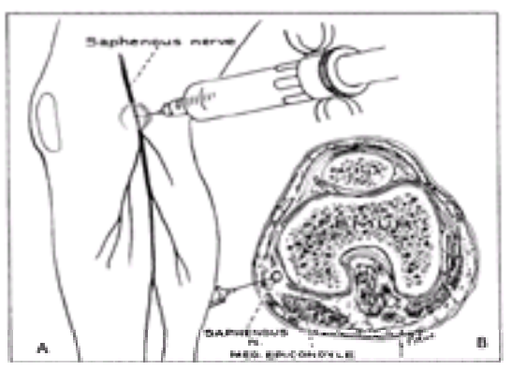

Figure 102-40. Blocking the saphenous nerve at the knee: After preparation of the skin with the patient in the supine or lateral position, a wheal is raised on the skin **(A)** over the medial surface of the medial condyle of the femur at the cross-sectional level of the apex of the patella **(B)**. A 5-cm, 25-gauge needle is inserted through the wheal in a direction perpendicular to the skin and advanced slowly until paresthesia along the saphenous nerve is elicited or until the bone is contacted. Several exploratory fanwise insertions are usually sufficient to locate the nerve, which is usually blocked with 3 to 5 mL of local anesthetic solution.

Analgesia and sympathetic blockade of the foot can be achieved by blocking the deep peroneal and tibial nerves about 2 cm above the level of the malleoli (Fig. 102-41). Block of these two nerves, plus a subcutaneous infiltration around the ankle, produces analgesia of the entire foot.

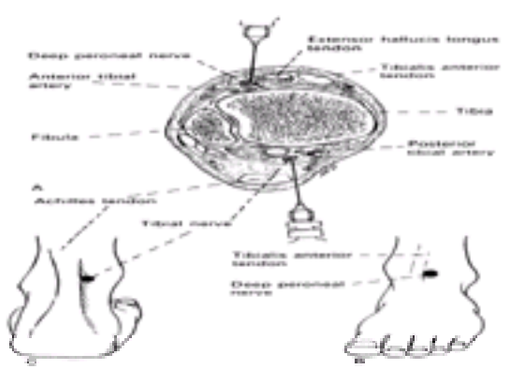

Figure 102-41. Blocking the tibial and deep peroneal nerves at the ankle. **A:** Cross section of the ankle just above the level of the malleoli. **B,C:** Anterior and posterior views showing sites of injection. The deep peroneal nerve is blocked by palpating and identifying the tendon of the extensor hallucis proprius and the anterior tibial artery. The nerve is situated between these two structures. With the patient in the supine position and the tendon and artery identified, a 5-cm, 25-gauge needle is introduced through the skin **(B)**, without making a preliminary skin wheal, and slowly advanced until paresthesia is elicited. If the nerve is not contacted before the needle point impinges on the anterior surface of the tibia, the needle is withdrawn until its level is subcutaneous and then reinserted so that its point is directed a little more laterally. The nerve is usually located with several fanwise insertions made along a transverse line across the ankle. Injection of 3 to 5 mL of local anesthetic

solution is sufficient to produce a complete block. **A,C:** The posterior tibial nerve is blocked at the level of the malleoli. **C:** A skin wheal is raised at this level just medial to the medial border of the Achilles tendon and just lateral to the palpable posterior tibial artery **(A)**. A 5-cm, 25-gauge needle is introduced in an anterior direction and advanced until paresthesia is elicited or until the posterior aspect of the tibia is contacted without paresthesia. In the latter case, the needle is withdrawn and reinserted so that its point is directed a little more medially. With several fanwise insertions in the cross-sectional plane, the nerve can usually be located. Injection of 3 to 5 mL of local anesthetic solution is sufficient to effect a complete block. Block of these two nerves, together with a subcutaneous infiltration around the ankle to block the subcutaneous sural, saphenous, and superficial peroneal nerves, produces complete anesthesia of the foot.

Block of the digital nerves is indicated for severe pain involving one or more fingers or toes, the distal portion of the metatarsal bones, or the bones of one or more toes (Fig. 102-42). LA with epinephrine should not be used for digital blocks as solution is injected close to the digital arteries. Because they are end arteries, diminution in blood flow in the digital arteries could lead to digital ischemia.

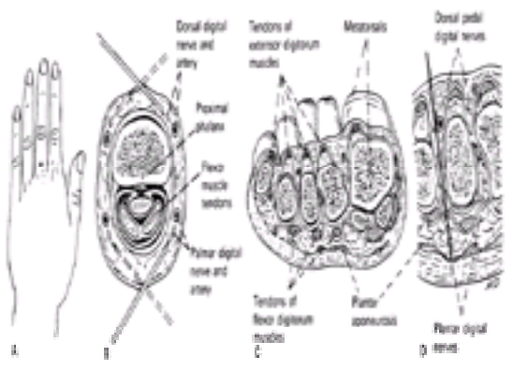

Figure 102-42. Blocking digital nerves. **A,B:** Block of the digital nerves in the fingers. **A:** An intracutaneous wheal is created on the dorsal and volar surfaces of the finger, and a 2-cm, 25-gauge needle is introduced. **B:** The needle is directed first to one side and then the other; 1.5 to 2.0 mL of 0.25% bupivacaine *without* epinephrine is injected at each site. Because the four digital nerves are in the same fascial space, the solution diffuses to produce complete anesthesia of the finger distal to the site of injection. **C:** Cross-sectional view of the foot at the metatarsal level. **D:** Relationship of the dorsal and plantar digital nerves. Skin wheals are raised on the dorsal pedal surface of the foot over each metatarsal space that bounds the toe (or toes) to be anesthetized. A 5-cm, 25-gauge needle is inserted and advanced toward the plantar surface until its point meets the resistance of the plantar aponeurosis. The needle is withdrawn 5 mm, and 2 to 3 mL of local anesthetic solution is injected to block the plantar digital nerves. The needle is then withdrawn, slowly injecting 1 or 2 mL of solution between the plantar and dorsal surfaces. When the point of the needle is at the dorsal subcutaneous space 2 to 3 mL is injected, for a total of 5 mL of anesthetic solution for each metatarsal interspace.

Pudendal Nerve Block

Indications. Block of one or both pudendal nerves is a useful diagnostic procedure in perineal pain and can be used for postoperative or posttraumatic pain in the perineum. If the pain is on one side of the perineum, a unilateral block is sufficient, but often it is necessary to carry out a bilateral pudendal nerve block.

Technique. The optimal site for injecting the pudendal nerve is just posterior to the attachment of the sacrospinous ligament to the ischial spine. In the female this can be done transvaginally, and in the male a transperineal approach can be used (Fig. 102-43). Usually 5 to 7 mL of 0.25% bupivacaine is sufficient to produce block of the nerve on one side.

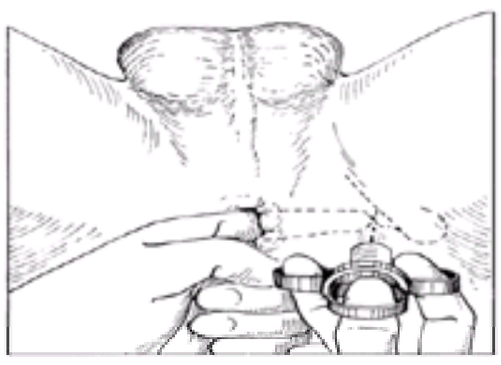

Figure 102-43. Pudendal nerve block by the transperineal approach. With the patient in the lithotomy position, the perineum is prepared and a skin wheal is made about 2.5 cm posteromedial to the tuberosity of the ischium and the subcutaneous tissue is infiltrated with a dilute solution of LA (e.g., 0.25% lidocaine). The small needle is then exchanged for a 12-cm, 22-gauge needle with a security bead, which is inserted perpendicular to the skin. The index finger of the left hand (*dashed lines*) is inserted into the rectum, first to palpate the spine of the ischium and the sacrospinous ligament and then to guide the needle just posterior to the junction of these two structures, which is the optimal site for injection of the nerve. The needle is slowly advanced through the ischiorectal fossa toward the ischial spine by having it pass behind to the urogenital diaphragm and levator ani muscle. As the needle approaches the ischial spine, it is pushed posterior to it by the guiding finger. After attempting to aspirate in two planes to ensure that the point of the needle is not in a blood vessel, 5 to 7 mL of local anesthetic solution (e.g., 0.25% bupivacaine) is injected just posterior to the tip of the spine.

Complications. Inadvertent block of the sciatic nerve and inadvertent intravascular injection are complications of pudendal nerve blocks.

Penile Nerve Block

Indications. Penile nerve block can be used as a diagnostic procedure, but its most important application is providing postoperative analgesia subsequent to penile operations, particularly circumcision in infants and children.

Technique. The anatomy of the dorsal nerve to the penis is described in Chapter 70 and depicted in Figure 70-17. The technique for blocking the dorsal nerve of the penis is described in Figure 102-44. The recommended dose of 0.25% plain bupivacaine (epinephrine strictly contraindicated) is 1 mL for infants up to 1 year of age, 3 mL for children 1 to 5 years of age, 4 to 5 mL for those 6 to 12 years of age, and 5 to 7 mL for those 13 years of age or older (130,131 and 132).

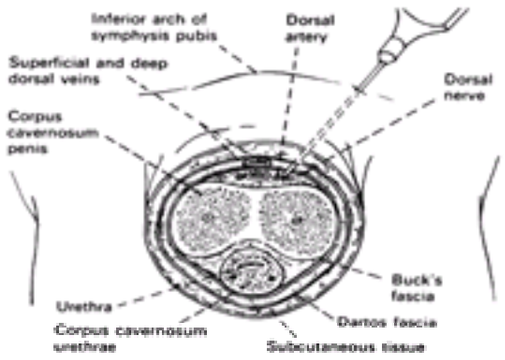

Figure 102-44. Penile nerve block: The dorsal nerves of the penis can be blocked as they pass from the pelvis to the penis. With the patient in the supine position, the skin over the symphysis pubis and the base of the penis is cleansed with antiseptic solution. The inferior border of the symphysis pubis is identified, and a mark is made at a level 1 cm from the midline. In an adult, a 3-cm, 25-gauge needle is used, but in infants a 1-cm, 30- gauge needle adapted to a Luer-Lok control syringe containing the local anesthetic solution is introduced through the mark and directed toward the midline at an angle of 30 degrees to the skin. As the needle advances, it pierces the skin, subcutaneous tissue, dartos fascia, and Buck's fascia, which can be felt as a click. Once the needle has pierced the fascia, which is 4 to 6 mm deep, an attempt at aspiration of blood is made and, if negative, 0.25% plain bupivacaine solution is injected. (The volumes to be injected, according to the age of the patient, are listed in the text.)

Complications. Complications include puncture of the corpus cavernosum or the dorsal vessels of the penis, but if a thin (27- or 30-gauge) needle is used and intravascular injection is avoided, no serious complications develop.

BLOCK OF THE SYMPATHETIC NERVOUS SYSTEM

The functional relationship between the sympathetic nervous system and many disease syndromes has long been recognized. Moreover, much experimental and clinical evidence has been accumulated to indicate that interruption, by LA or neurolytic blocks, of certain portions of the sympathetic nervous system has beneficial effects in many of these disorders (1,2 and 3). Figure 102-45 depicts the entire sympathetic chain.

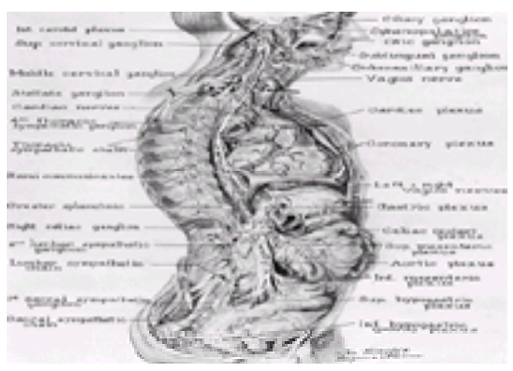

Figure 102-45. Anatomy of the autonomic nervous system depicting the position of the right sympathetic trunk, its branches, and the prevertebral ganglia.

Peripheral sympathetic pathways can be interrupted at a variety of sites: (a) the subarachnoid space; (b) the epidural space; (c) the paravertebral and prevertebral regions; (d) the peripheral nerves; and (e) the endings of postganglionic axons (Fig. 102-46). Because subarachnoid, epidural, and peripheral nerve blocks are discussed elsewhere in this chapter, this section is limited to paravertebral and prevertebral sympathetic blockade. Individual segmental paravertebral injections are preferable for diagnostic and prognostic blocks because specific sympathetic pathways can be blocked by a small volume of LA. This is also true when alcohol or phenol is to be used for therapeutic block where the volume is limited to 2 to 3 mL of solution. If the use of a large a large volume of LA is acceptable, blocking individual segments is unnecessary as the anatomic configuration of the sympathetics is such that they can be interrupted at certain “key” regions: cervicothoracic, celiac, and lumbar regions (Fig. 102-47).

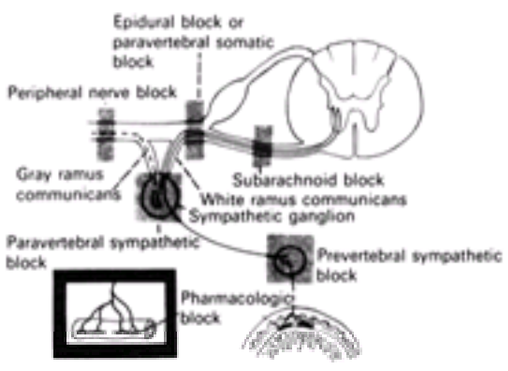

Figure 102-46. The course of preganglionic and postganglionic sympathetic fibers and techniques that can be used to interrupt them. (Modified from Bonica JJ. *Clinical applications of diagnostic and therapeutic nerve blocks.* Springfield, IL: Charles C Thomas Publisher, 1959.)

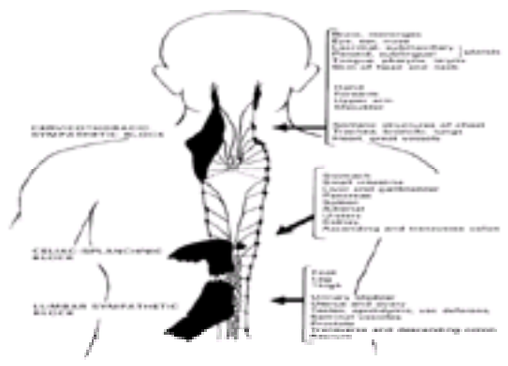

Figure 102-47. Three critical sites that can be used to interrupt the peripheral sympathetic nervous system. Left: Pattern of diffusion (*black*) of local anesthetic solutions injected in the vicinity of the cervicothoracic (stellate) ganglion, celiac plexus, and lumbar sympathetic ganglia. Injection of 15 to 20 mL of local anesthetic solution into the proper fascial plane near the stellate ganglion spreads sufficiently to involve the sympathetic chain from the lower portion of the superior cervical ganglion to the T-5 ganglion, so that all the sympathetic fibers to the head and neck, upper extremities, and the heart, and most of the fibers to the esophagus and lungs, are interrupted. Injection of 15 to 25 mL of solution bilaterally near the celiac plexus spreads sufficiently to interrupt all the sympathetic (and vagal) efferent fibers to and afferent fibers from the viscera in the upper abdomen. Injection of 15 to 20 mL of solution through a needle with its tip at the anterolateral surface of the

L-2 or L-3 vertebra interrupts all the sympathetic fibers to the ipsilateral lower extremity and pelvis. These sympathetic nerve structures are apparently contained within fascial planes that can be considered as relatively closed spaces (or even pouches) that facilitate the spread of the local anesthetic solution, so that an extensive sympathetic block is produced. Right: Names of the structures that are denervated with each block. (Modified from Bonica JJ. *Clinical applications of diagnostic and therapeutic nerve blocks.* Springfield, IL: Charles C Thomas Publisher, 1959.)

With paravertebral or prevertebral techniques, the LA (or neurolytic) solution interrupts all efferent and afferent fibers. In contrast, the more recently developed technique for blocking sympathetic function to a limb by intravenous injection of guanethidine or other adrenolytic agents by the Bier technique (see below) blocks only efferent impulses.

Indications

Complex Regional Pain Syndromes, Types I and II

Block of the sympathetic pathways to the limbs is an important mode of therapy for patients who have what was formerly termed *reflex sympathetic dystrophy* and *causalgia*, now termed *CRPS* (133) types I and II, respectively (Chapter 20). An unknown proportion of patients suffering from either disorder have a component of sympathetically influenced pain (134).

Causalgia. CRPS type II (causalgia) is a condition associated with damage to a peripheral nerve, such as a median or sciatic nerve, and is characterized by burning pain, hyperalgesia, hyperpathia, allodynia and, not infrequently, by vasomotor and sudomotor disturbances.

Studies (135,136) have shown that patients with nerve injuries can be of two types: those with sympathetically maintained pain (SMP) and those whose pain is independent of sympathetic hyperactivity, sympathetically independent pain (SIP). In these studies, SMP pain and hyperalgesia were reduced by sympathetic block, whereas in patients with SIP sympathetic blockade was ineffective and block of the somatic nerve relieved pain. Patients with mechanical hyperalgesia and SMP had increased pain with mild cooling (1.5° to 2.0°C) of the skin with acetone, or ice water, or alcohol. In contrast, only approximately one-third of SIP patients tested reported pain response to cold, implying that the response to cold stimulus can be used, in addition to sympathetic block, to differentiate patients with SMP from those with SIP.

In patients with CRPS type II with or without SMP, selective block of the regional sympathetics with an LA is a useful diagnostic procedure in demonstrating a sympathetic component. Subarachnoid, epidural, or Bier blocks with LA or guanethidine (see below) are not sympathetically selective; they all have the potential to affect somatic nerves. Specific selective sympathetic blocks require accurate placement of small quantities of LA on the sympathetic chain (fluoroscopy is advisable), demonstrating that a false-positive response is not observed (no somatic block by physical examination) and that a false-negative does not occur (a complete sympathectomy demonstrated by tests of sympathetic function; see below).

Sympathetic blocks can produce prolonged and often curative effects in CRPS type II (Chapter 20), but it is essential that a complete sympathectomy be produced. Following LA sympathectomy, patients often derive relief of many of the symptoms associated with CRPS type II. If only temporary relief is obtained from LA sympathectomy, repeated LA blocks or a neurolytic procedure should be considered. Some patients may respond to a series of six to 12 blocks; however, the role of the block is to facilitate physical therapy while pain is reduced.

For those who have not had sufficient experience with regional sympathetic blocks, intravenous injection of guanethidine by the Bier block technique is the procedure of choice. Guanethidine block lasts 24 to 72 hours (see below). In Chapter 20 it is noted that phenoxybenzamine, an a-adrenoreceptor blocker, has also proven to be effective in patients with causalgia.

Complex Regional Pain Syndrome Type I. CRPS type I is a term applied to a diverse group of seemingly unrelated disorders formerly called *reflex sympathetic dystrophy*, *minor causalgia*, *posttraumatic spreading neuralgia*, *Sudeck's atrophy*, and *shoulder-hand syndrome* (Chapter 20). This group of disorders is characterized by prolonged pain, vasomotor and sudomotor disturbances, delayed functional recovery, and the development of trophic changes, often with minimal signs of injury. CRPS type I occurs more frequently than CRPS type II and is often misdiagnosed, with a consequent delay in instituting therapy. Early treatment with repeated or continuous sympathetic block for 7 to 10 days is indicated.

Postamputation Pain Syndromes

The various pain patterns that follow amputation are described in Chapter 21. Following extremity amputation, most patients experience a phantom limb (or part); a smaller percentage develop phantom limb pain or stump pain. Pain in a limb, or phantom, usually falls in one of three categories: (a) a burning, throbbing, aching pain not unlike that of CRPS types I and II; (b) pain due to an abnormal position of the phantom limb, which is felt to be in a twisted, cramped, rigid, or flexed posture that cannot be released by the patient; or (c) a combination of these two patterns of pain. Pain in the stump is of three predominant types: (a) a constant, diffuse, burning, throbbing pain similar to that of CRPS types I and II; (b) shooting pain in a segmental or peripheral nerve distribution; or (c) a combination of these. Stump pain is usually associated with vasomotor and sudomotor disturbances.

In patients with phantom or stump pain and evidence of sympathetic disorder (vasomotor and sudomotor changes) LA sympathectomy is often helpful. If the LA block provides relief, repeated blocks should be considered with neurolytic or surgical sympathectomy considered if relief is not long-lasting.

There is some evidence that the choice of analgesic and anesthetic technique in the perioperative period may preemptively influence the incidence of postamputation phantom pain (19). Epidural analgesia with LA with or without an opioid initiated several days before an amputation, and continued for some days after amputation, may reduce the incidence of short-term and long-term phantom pain, when compared to control groups receiving systemic analgesics.

Other Neuropathic Painful Disorders

Regional sympathetic blockade and guanethidine or bretylium intravenous blocks have also been found to be effective in relieving burning pain associated with hyperesthesia, hyperpathia, allodynia, and sensitivity to cold. Patients with painful neuromata and a number of patients with pain after brain or spinal cord injury may be helped by sympathetic blockade by LA sympathectomies or RA with intravenous guanethidine (137,138 and 139) or RA with intravenous bretylium (140).

Issues with Sympathetic Blocks

In Chapter 20, several important points were made about the use of sympathetic block for sympathetic associated pain. First, the earlier the treatment, the better the prognosis for prolonged relief of the pain. Second, if patients experience even partial relief, the LA sympathectomy should be repeated on two to three occasions because occasionally subsequent blocks relieve the pain. Third, when sympathectomy is indicated, this can be done either chemically or surgically. However, it is essential to ascertain that sympathetic interruption is complete, especially in patients who derived complete relief of the burning pain with an LA sympathetic block, but who experienced only partial or no relief after sympathectomy. In such cases it is likely that, although the LA diffused widely enough to involve the sympathetic chain and anomalous sympathetic pathways (which are often present in the lower cervical and upper thoracic chain and in the lower thoracic and upper lumbar region), the operation was not extensive enough, did not include the anomalous pathways, or both. In such cases, two or three sympathetic blocks should be repeated.

Peripheral Vascular Disease

Historically sympathectomy (by LA, chemical, or surgical means) played an important role in managing the pain, ischemia, and trophic changes consequent to peripheral vascular disease. The advent of effective therapy using vascular stents, bypass grafts, and anticoagulant therapy has decreased the importance of sympathetic block in treating this group of disorders. Nevertheless, temporary or prolonged sympathetic interruption can still be a useful adjunct (Chapter 33).

Acute Vascular Disease

Some acute vascular disorders may benefit from LA sympathectomy, including posttraumatic vasospasm; vasoconstriction caused by intraarterial injection of irritating substances; acute arterial occlusion caused by thrombosis, embolism, or direct injury; acute venous thrombosis; and peripheral vascular damage from cold injuries (Chapter 33). In these conditions, it is believed that ischemia is due to direct vascular lesions; in addition, the lesion initiates reflex spasm of collateral vessels. Sympathetic block, initiated before endothelial changes that favor thrombosis in vasospastic collateral vessels have developed, may improve collateral vessel blood flow and hence reduce further ischemic damage.

Sympathetic block in these cases may help determine whether ischemia results from organic obstruction, division of the blood vessel, or vasospasm. The use of LA sympathectomy in these cases is often complicated by the fact that patients may be receiving anticoagulants or have other blood-clotting disorders. In patients with blood-clotting disorders (iatrogenic or otherwise), the use of neuraxial blocks is strongly contraindicated because of risks of bleeding producing intraspinal hematomata and neural damage. In these patients, sympathectomy outside the neuraxis carries a significant risk of bleeding, though the consequences may not be as severe as within the neuraxis. If anticoagulants are being used, sympathetic interruption may be achieved with intravenous regional sympathetic block (IRSB) with guanethidine.

Chronic Vasospastic Disorders

Chronic vasospastic disorders that may be helped by LA sympathectomy include Raynaud's disease, Raynaud's phenomenon, cold injuries, acrocyanosis, and livedo reticularis. The blocks can be used as a diagnostic and prognostic procedure in patients in whom sympathectomy is being considered, or blocks or IRSB with guanethidine (141) may be used to tide patients over difficult times (e.g., winter months). (Chapter 33 presents a detailed discussion of all aspects of these and other peripheral vascular diseases.)

Chronic Occlusive Arterial Disease

Chronic occlusive arterial disease produces decreases in tissue blood flow resulting in, progressively, claudication, rest pain, and tissue damage ranging from ulceration to gangrene. The first lines of therapy are aimed at improving blood flow by surgical means (vessel dilation, stents, bypass grafts, etc.). For patients in whom these measures do not suffice or are contraindicated, chemical sympathectomy is effective in relieving rest pain, enhancing the healing of ischemic lesions, and postponing amputation (142,143). If and when amputation becomes necessary, it can be performed at a more distal level of the limb (142) (Chapter 33). The value of chemical sympathectomy in these conditions is discussed in Chapter 104.

Visceral Pain

Block of the sympathetic nerves to thoracic or abdominal viscera relieves pain in those areas and is useful for blocking afferent and efferent arms of visceral reflexes, which may contribute to the pathophysiology. The pathophysiology may be a consequence of local sympathetic activity and/or systemic sympathetic activity (e.g., raised cardiac output, BP, heart rate). In patients with such pain, opioids in appropriate doses and by the appropriate route produce adequate pain relief but do not eliminate the abnormal reflex responses. In contrast, block of the sympathetic nociceptive pathways blocks the afferent and efferent limbs of these reflexes and thus prevents or at least minimizes the reflex responses. These comments are especially relevant to certain acute thoracic and abdominal visceral painful conditions.

Thoracic Visceral Pain

Acute Myocardial Infarction. Acute myocardial infarction produces pain and associated reflex responses that can aggravate myocardial pathophysiology. Relieving pain, anxiety, and mental stress in patients with acute myocardial infarction effectively decreases these reflex responses (Chapter 61).

Effective pain relief can be achieved with appropriate doses of intravenous opioids; however, opioids may not produce complete pain relief, may not change reflexes, and may be associated with side effects. The value of sympathectomy is suggested by a number of animal and human studies (144,145,146,147 and 148). In patients with pain that persists, despite opioids, cervicothoracic (stellate) sympathetic block may provide effective analgesia for 8 to 10 hours or more. In patients with unilateral pain, a unilateral block usually suffices. If the pain is bilateral, the block is done on the side with the most severe pain first and, after an interval of 30 minutes, is repeated on the opposite side, provided that the side effects of the stellate block (recurrent laryngeal nerve block, phrenic nerve block) are not present as contraindications.

Angina Pectoris. Modern management of angina by medical or surgical means is highly effective. However, in patients in whom angina has not been relieved, despite maximal therapy, prognostic cervicothoracic sympathetic blocks with 0.25% bupivacaine may be helpful and may predict results of subsequent chemical or surgical sympathectomy (1). The technique for neurolytic block of the upper thoracic sympathectomy is discussed in Chapter 104.

Abdominal Visceral Pain. Patients with abdominal pain from intraabdominal pathology can have their pain relieved by LA sympathectomy in the case of reversible disorders or chemical sympathectomy in the case of intractable disorders.

Acute Pancreatitis. Acute pancreatitis (Chapter 67) is often associated with severe abdominal pain and systemic disturbances. It may be managed by block of the nociceptive afferents by splanchnic nerve block, celiac plexus block (149), or continuous segmental (T- 5 to 10) epidural block (150,151). The use of regional block may decrease the severity and duration of the disease (151).

Biliary and Ureteral Colic. The pain of biliary and ureteral colic may be relieved by intravenous opioids, though these drugs may increase the smooth muscle tone in the biliary or ureteric tracts. LA sympathectomy by paravertebral block of the splanchnic nerves and of the L-1 and L-2 ganglia or a continuous segmental (T-10 to L-2) epidural block provide pain control and avoid the unwanted effects of opioids.

Adynamic Ileus. Adynamic ileus following intraabdominal surgery or following thoracic vertebra fracture has a component of sympathetic activity that can be lessened by segmental epidural block. The efficacy of this procedure in the treatment of adynamic ileus is discussed in detail in Chapter 66.

Acute Herpes Zoster and Postherpetic Neuralgia

For over 60 years LA sympathetic block has been used with variable success in the treatment of herpes zoster (152,153,154,155,156,157,158 and 159). The results of studies are summarized in Table 102-5. Sympathetic block, plus or minus somatic block, used early in the course of acute zoster eruption and pain, produces a high incidence of pain relief and probably decreases the severity of pain and eruption and may accelerate healing. The longer the interval between the start of eruption and pain, the less the quality and quantity of relief. A regimen of daily blocks for 5 to 7 days and then two to three blocks a week is advised until relief is obtained or a total of approximately ten blocks have been performed. The efficacy of such a regimen in acute zoster is supported by double-blind studies (158) but probably has little or no effect on the incidence of PHN (159).

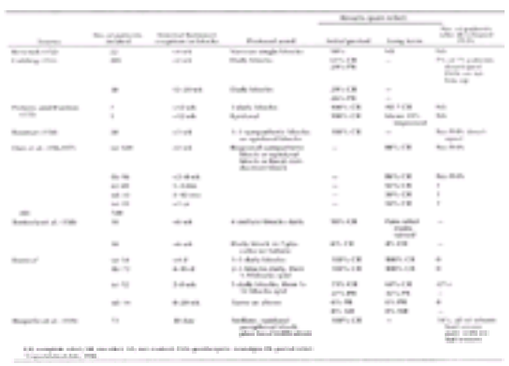

TABLE 102-5. Effects of sympathetic, somatic, or epidural blocks for acute herpes zoster

The early administration of antiviral drugs (vidarabine, acyclovir) in the acute phase of zoster reduces the spread of the zoster eruption, accelerates healing, and prevents both cutaneous dissemination and visceral complication (160). These drugs should be combined with nerve blocks to provide patients with prompt relief of pain that is not obtained with the use of antiviral agents alone.

Once PHN, usually defined as persisting pain 3 months after eruption, is established, sympathetic or other neural blockade with LA produces a low (20% to 40%) incidence of initial pain relief, which falls to 10% on long-term follow-up (153,157,161,162) (Table 102-6). It has been implied, however, that such blocks performed within 1 year of eruption produce an appreciably greater incidence of pain relief than if patients are managed only with the usual medical therapy (161,163). If RA is used for PHN, a series of blocks done every other day, for a total of seven to ten blocks, is recommended.

Source	No. of patients	Eruption to blocks	Protocol	Results: Initial success	Results: Long-term success
Colding (1953)	34	3 mo to 10 yr	3–4 blocks	48%	10%
Forrest (1963)	74	4 mo to 8 yr	3 epidural LA + steroid	Mean pain score decreased from 8/10 to	
Zhao et al. (1986)	69	1–3 mo	Various blocks	52% good	
	31	3–12 mo		39% good	
	22	>12 mo		13% good	
Milligan and Nash (1962)	34	<1 yr	Single ganglion block	38% good, 26% improved	
	1	>1 yr		25% good, 25% improved	

LA, local anesthetic; VAS, visual analog scale.

TABLE 102-6. Results of nerve blocks for pain relief in postherpetic neuralgia

Cancer Pain

Sympathetic blocks can be effective in relieving the burning, aching discomfort that is experienced by some patients with cancer of the face and head. Moreover, sympathetic blocks of the upper or lower limb are indicated in patients in whom cancer infiltration or compression of the brachial or lumbosacral plexus produces the symptoms and signs characteristic of CRPS type I (Chapter 20).

Musculoskeletal Disorders

Sympathetic blocks, used in combination with local infiltration of trigger areas or other therapeutic measures, are frequently helpful in relieving the pain, decreasing the pathophysiology, and shortening the disability in patients with myofascial pain syndromes (13).

Technical Considerations

Monitoring the Effects

When performed correctly, sympathetic nerve blocks produce virtually no measurable effects demonstrable by routine examination. Evaluating the effect of a sympathetic block, or its completeness, requires that specific tests of sympathetic function be used. Methods include (a) the skin conductance response, formerly known as the *sympathogalvanic reflex* (Fig. 102-48); (b) sweat tests, including the Ninhydrin, cobalt blue, and intravenous starch tests; and (c) skin plethysmography and the “ice response test.” Blood flow in the skin can be measured by change in skin temperature, a laser Doppler, healing of ulcers, or tissue Pa O_2. Blood flow in muscle can be monitored by plethysmography, radioisotope clearance tests, and electromagnetic measurements. Thermography has proven to be effective for measuring the effects of vasoconstriction and the changes in blood flow following sympathetic interruption.

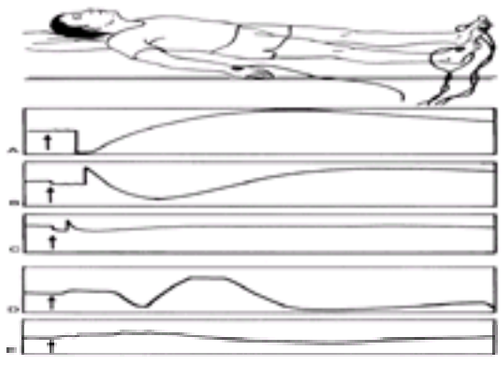

Figure 102-48. Monitoring sympathetic function by the skin conductance response: Electrodes are placed on the front and back of the hands or feet and a ground electrode is placed elsewhere on the body. **A,B:** Any unpleasant stimulus, such as a pinch or taking a deep breath, produces a typical curve. The *arrow* indicates the point where the pinch was applied. **C:** Flattening of the curve indicates absence of the reflex on the left leg after a left lumbar sympathetic block. **D:** Normal curve in the hand before the T-2 and T-3 sympathetic ganglia were blocked with 6% phenol. **E:** Tracing taken of the same hand as in **D** 2 months after the block.

Cervicothoracic Sympathetic Block

Although the cervicothoracic sympathetic block is usually colloquially referred to as *stellate ganglion block*, LA or neurolytic injected at the usual site often spreads beyond the immediate area of the stellate ganglion. Radiologic studies following the injection of contrast medium show that when the needle is correctly placed, and the agent injected into the correct fascial plane, 5 mL of injectate spreads as far as the T-2 thoracic and intermediate cervical ganglia, 10 mL of injectate spreads from the upper part of the C-5 to the T-3 or T-4 and 20 mL of injectate spreads from C-3 to the T-5. The latter will therefore likely interrupt sympathetic and visceral afferent and efferent pathways to the head and neck, upper limb, and thoracic viscera.

Anatomic Basis

The neuroanatomic basis for cervicothoracic sympathetic blocks is shown in Figure 102-49 and Figure 102-50. The sympathetic nerve supply to the head and neck is discussed in Chapter 46, that to the upper limb is described in Chapter 54, and that to the thoracic viscera is described in Chapter 60. Figure 102-49 depicts the four cervical and upper three thoracic ganglia and their relationship to the brachial plexus and thoracic spinal nerves. Precise knowledge of the anatomy of the stellate ganglion and its relationship to the upper thoracic and lower cervical ganglia is helpful when performing this block (see Fig. 102-50).

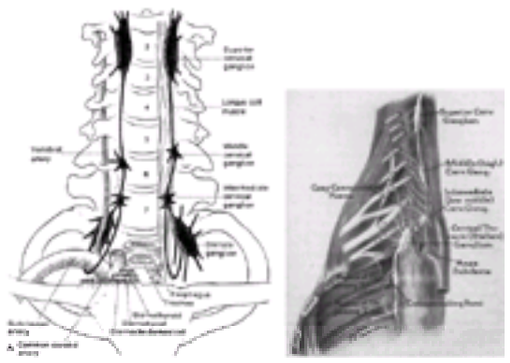

Figure 102-49. Anatomy of the cervical sympathetic chain. **A:** Anterior view of the deep region of the lower portion of the neck showing the relationship of the sympathetic ganglia to the cervical and upper thoracic vertebrae, the longus colli muscle, and the vertebral artery. (From Bonica JJ. *Blocks of the sympathetic nervous system.* Vol 2. Chicago: Frank J Corbett, 1981:64, with permission.) **B:** Relationship of the cervical and upper thoracic sympathetic chains and the gray rami communicantes, which connect the chain to the brachial plexus and other spinal nerves. Note the inconstant intrathoracic ramus from the T-2 nerve to the T-1 nerve and from the T-3 nerve to the T-2 nerve. Also note the beginning of the lower branches of the stellate ganglion, which include the ansa subclavia, the inferior cardiac nerve, and the nerve to the internal mammary artery. From the upper pole of the ganglion arises the vertebral nerve, which passes to the vertebral artery where it breaks up into the vertebral plexus (not shown). (From Moore DC. *Stellate ganglion block.* Springfield, IL: Charles C Thomas Publisher, 1954, with permission.)

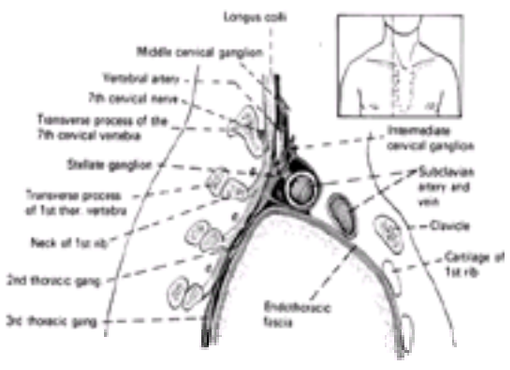

Figure 102-50. Sagittal section of the lower portion of the neck and upper part of the thorax (*inset*) showing the relationship of the stellate ganglion and other parts of the sympathetic chain to bones, blood vessels, and apex of the lung. The longus colli muscle separates the ganglia from the bones and the stellate ganglion is immediately posterior to the beginning of the vertebral artery. Injection of a local anesthetic solution within the fascial plane containing the sympathetic chain causes the solution to diffuse cephalad and caudad to block various parts of the chain (see Fig. 102-52).

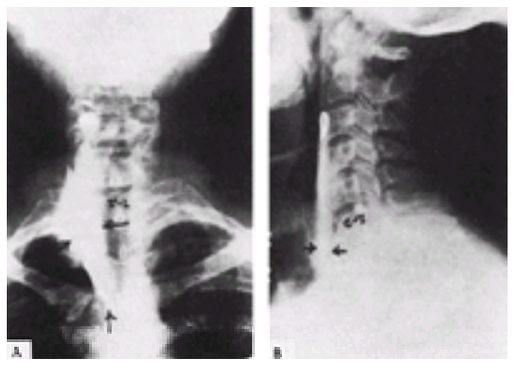

Figure 102-52. Roentgenograms showing the characteristic pattern of diffusion (*arrows*) of 10 mL of contrast medium (Diodrast) injected in the same fascial plane as the cervicothoracic sympathetic chain. **A:** Anteroposterior view showing the spread from the top of the C-5 vertebra (which includes the middle cervical ganglion) to the T-4 vertebra at the level of the T-4 or T-5 sympathetic ganglion. **B:** Lateral view. (From Moore DC. *Stellate ganglion block.* Springfield, IL: Charles C Thomas Publisher, 1954, with permission.)

The stellate ganglion is an oval mass, 2.5 cm long, 1 cm wide, and 0.5 cm thick, located just behind the subclavian artery at the point of origin of the vertebral artery and in front of the neck of the first rib near the costovertebral articulation. The ganglion lies within a concavity limited inferiorly by the posterior aspect of the pleura, medially by the portion of the vertebral column covered by the longus colli muscle, laterally by the scalenus muscle mass, anteriorly by the subclavian and vertebral arteries, and posteriorly by the neck of the first rib, the transverse process of the C-7 vertebra, and the interspace between these two structures. In most instances, the ganglion extends above the first rib so that its upper half is in front of the interspace (see Fig. 102-50). The ganglion is 5 mm anterolateral to the bony structures, separated from them by loose areolar and adipose tissue and the longus colli muscle. The loose areolar and adipose tissue facilitate diffusion of anesthetic solutions deposited near the ganglion. The branches of the stellate ganglion include the communicating, anastomotic, vascular, and muscular branches; the inferior cervical cardiac and vertebral nerves; and the ansa subclavia. The gray rami communicantes that are given to the C-7 and C-8, T-1, and sometimes the C-5 and C-6 spinal nerves constitute the major part of the sympathetic nerve supply to the upper limb (see Fig. 102-49).

The other cervical sympathetic ganglia consist of the intermediate, the middle, and the superior cervical ganglia (see Fig. 102-49). The superior ganglion is the largest, the middle is the smallest, and the intermediate ganglion is intermediate in size. These ganglia lie on the longus colli muscles and are thus in the same fascial plane as the stellate ganglion. The lower part of the stellate ganglion connects with the T-2 sympathetic ganglion, which contains the largest number of synaptic connections between the preganglionic and postganglionic sympathetic fibers that supply the upper limb.

Usually all the sympathetic nerves that supply the head and neck, and most of those that supply the upper limb, traverse the stellate ganglion. Thus, blocking this structure effects a temporary sympathetic denervation of these areas. In a significant number of individuals, however, an intrathoracic somatic branch arising from the T-2 spinal nerve joins the T-1 spinal nerve, which of course, takes part in the formation of the brachial plexus (see Fig. 102-49, and Fig. 102-50). This intrathoracic branch is almost always joined by gray rami communicantes carrying postganglionic fibers that arise from cell bodies in the T-2 sympathetic ganglion and possibly in lower ganglia. In a smaller percentage of individuals, an intrathoracic somatic branch is also present, which arises from the T-3 spinal nerve and passes to the T-2 spinal nerve. This second intrathoracic nerve, which also contains postganglionic sympathetic fibers that arise from the T-3 ganglion, joins the T-2 spinal nerve near the branch that the latter sends to the T-1 nerve. These anomalous pathways, known as *Kuntz's nerves*, bypass the stellate ganglion so that blocks limited to the stellate ganglion or a pure stellectomy do not necessarily produce complete sympathetic denervation of the upper limb. In such cases, it is also essential to block the T-2 and T-3 ganglia to denervate the limb completely. Moreover, because all the fibers to the upper limb pass through the T-2 and occasionally the T-3 ganglia, they are key relay stations that can be blocked with a small volume of neurolytic agent.

Technique

A variety of techniques have been described: anterior paratracheal, lateral, anterolateral, superior, and posterior approaches. Here only the paratracheal approach is described (Fig. 102-51). The posterior approaches to the thoracic sympathetic chain, including those that supply the upper limb, are described in Chapter 102.

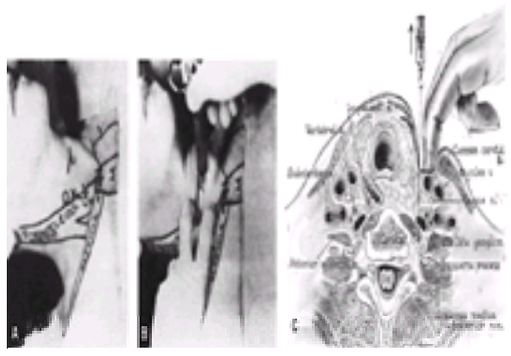

Figure 102-51. Stellate block by the anterior paratracheal approach. **A:** Outline of the clavicle and sternocleidomastoid. The level of the cricoid cartilage (c) is at the same cross-sectional level as the transverse process of the C-6 vertebra (o). *X* lies anterior to the transverse process of the C-7 vertebra and is the point on the skin where an intracutaneous wheal is formed. **B:** With the second and third fingers of the nondominant hand hooked around the medial edge of the sternocleidomastoid and the underlying carotid sheath, with its vessels and nerves retracted laterally, the needle is inserted through a wheal, directed posteriorly in the parasagittal plane, and advanced to the base of the transverse process of the C-7 vertebra. **C:** Cross section of the neck at the level of the C-7 vertebra depicting the placement of the needle for anterior paratracheal stellate ganglion block. The second and third fingers of the hand are retracting the medial aspect of the sternocleidomastoid muscle and the underlying vessels, and the needle is advanced to the base of the transverse process of the C-7 vertebra. After bone is contacted, the needle is withdrawn about 0.5 cm to place its bevel anterior to the fascia of the longus colli muscle. Injection of a local anesthetic solution anterior to the fascia permits it to diffuse cephalad, caudad, and slightly laterally to block the chain. (**A** and **B** from Moore DC. *Stellate ganglion block.* Springfield, IL: Charles C Thomas Publisher, 1954, with permission.)

When performing the paratracheal technique the tip of the needle is close to the vertebral artery and dural cuff of the C-8 nerve. Hence when LA is injected, it is important to ensure that the needle is not intravascular or subarachnoid by aspiration of the needle in two planes and the use of a test dose (1 mL of injectate) and waiting a few minutes to ensure no adverse CVS or CNS effects.

Stellate ganglion blocks for head and neck disorders can be accomplished with 3 to 5 mL of LA. If the block is intended to interrupt all sympathetic fibers to the ipsilateral upper extremity, 12 to 15 mL of solution is injected. This is sufficient to spread to and block all the sympathetic nerves that supply the upper limb, even in a patient with the anomalous Kuntz's nerves. If the block is intended to interrupt the afferents and efferents to the heart, 20 mL of solution is injected, with the patient in a semirecumbent or sitting position (Fig. 102-52).

Successful block of sympathetic fibers to the head is indicated by the appearance of Horner's syndrome (ptosis, miosis, enophthalmos, anhidrosis of the neck and face). Successful block of sympathetic fibers to the upper limb is indicated by engorgement of the veins in the back of the hand, a rise in skin temperature, absence of a skin conductance response, plethysmography, thermography, a sweat test, or a combination of these. Maximal evidence of an arm sympathectomy may take 15 to 20 minutes.

Complications

Complications of the anterior paratracheal technique include inadvertent intraarterial or intravenous injection of LA, pneumothorax; unintentional brachial plexus block, recurrent laryngeal nerve block, or accidental subarachnoid injection. These complications, their prophylaxis, and treatment have been discussed (see Basic Considerations, earlier in this chapter).

Block of the Thoracic Sympathetic Chain

Block of one, or more, of the thoracic sympathetic ganglia and the intervening interganglionic chain is indicated as a diagnostic procedure for identifying pathways or as a therapeutic measure for treating herpes zoster or other chest wall pain. Because segmental thoracic sympathetic blocks are technically difficult, many clinicians use segmental epidural block and paravertebral block for patients with chronic pain (Chapter 102).

Block of the Celiac Plexus

Block of the celiac plexus is useful for relieving pain caused by acute visceral disease and hepatic embolization. Celiac plexus block interrupts both afferent and efferent sympathetic pathways to the viscera and modifies the effects of sympathetic outflow on visceral functions. Because the celiac plexus contains vagal afferent and efferent fibers, block of this structure interrupts sensory fibers that transmit nonnociceptive information and the parasympathetic outflow to the abdominal viscera.

Celiac plexus block can be used in treating adynamic ileus. Celiac plexus block with LA should be done to predict the effects of neurolytic celiac block, which is used in patients with upper abdominal cancers. The various techniques and their use are discussed in Chapter 102 (164,165).

Splanchnic Nerve Block

The indications for splanchnic nerve block are very similar to the indications for celiac plexus block, except that this procedure does *not* produce a block of the lumbar sympathetic chain. Splanchnic nerve block requires smaller volumes of agents and probably has a lesser incidence of complications. Because splanchnic nerves are usually blocked with neurolytic agents to control chronic pain, the technique is discussed in Chapter 104.

Lumbar Sympathetic Block

Indications. Lumbar sympathetic block is a useful diagnostic, prognostic, or therapeutic procedure for pain syndromes involving the pelvis or lower limbs and for peripheral vascular disorders (see Cervicothoracic Sympathetic Block, earlier in this chapter). It has a role in predicting the effects of neurolytic blockade in patients with peripheral vascular disorders of the lower limbs.

Neuroanatomic Basis. The anatomy of the lumbar sympathetic chain is discussed in detail in Chapter 70 and Chapter 75. The lumbar sympathetic trunks consist of two ganglionated cords that extend from the L-1 to the L-5 vertebrae and are continuous above with the thoracic portion and below with the pelvic portion of the sympathetic trunk (Fig. 102-53). Each chain lies on the anterolateral surface of the vertebral column, being more medial and anterior than the thoracic chain. Both lumbar chains are situated anteriorly and slightly medially to the aponeurotic arcades giving rise to the psoas muscle and the psoas fascia, which is also attached medially by a series of arched processes to the intervertebral disks and by the prominent upper and lower margins of adjacent vertebrae. The intervals between the arched processes of the psoas muscle and fascia and the constricted part of the vertebrae transmit the lumbar arteries and veins and sympathetic nerves that connect the lumbar sympathetic chain with the somatic lumbar nerves. The relation of the sympathetic trunks to the great vessels differs on each side. On the right side, the trunk lies posterior to the lateral edge of the vena cava, which in most cases completely covers the trunk. On the left side, the chain is rarely covered by the aorta, being 4 to 10 mm lateral to the lateral edge of the vessel; on this side it is usually covered by the lumbar lymph glands and peritoneum. Inferiorly the cords pass posterior to the iliac vessels to become continuous with the sacral sympathetic trunks.

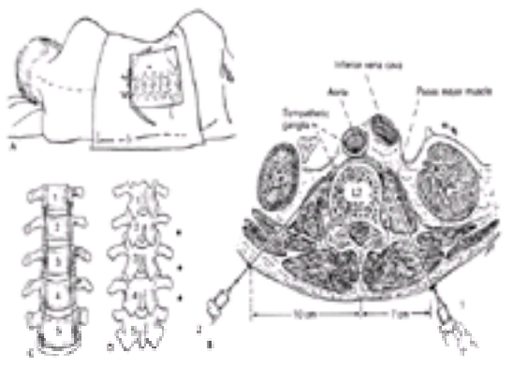

Figure 102-53. Lumbar sympathetic block. **A:** The patient lies on the side with the affected side uppermost. **B:** Cross section at L-2 to show the two techniques that can be used, a so-called classic technique (using three or four needles) or a lateral technique. For the classic technique (needle 1), a skin wheal is raised 6 to 7 cm lateral to the midline at the midpoint of the quadrilaterally spaced spinous process of the lumbar vertebrae. In many patients, 22-gauge, 8-cm security needles with rubber depth markers are used. For patients who are obese or muscular it is best to use 10- or 12-cm, 22-gauge needles. For diagnostic purposes it is best to inject through two or three needles at the levels of the L-2 and L-4 or L-2, L-3, and L-4 vertebrae. Each needle is inserted through the skin wheal and advanced anteriorly and medially. The shaft of the needle should make an angle of 75 to 80 degrees with the skin lateral to it. The needle is advanced until the lateral aspect of the lumbar vertebra is contacted, usually at a depth of 6 to 8 cm from the skin in thin or normal individuals but possibly as deep as 10 cm from the skin in obese individuals. The skin marker is placed 2 cm from the skin, and the needle is withdrawn until its point is subcutaneous and then redirected more laterally so it passes through the psoas major muscle. It might be useful to adapt a Luer-Lok control needle to a 2- or 5-mL syringe filled with air or saline solution. As the needle traverses the psoas muscle, some resistance to injection is encountered. The needle is further advanced slowly while gentle pressure is applied to the plunger of the syringe. As the point of the needle passes through the thick medial junction of the psoas fascia, significant resistance is encountered. As soon as the bevel pierces the fascia, however, a sudden lack of resistance can be felt and the air or saline can be injected easily, indicating that the needle point is in the retroperitoneal space and is near the sympathetic chain. The local anesthetic solution is injected after a negative aspiration test in four quadrants. If a diagnostic procedure is being done with three needles, 3 mL of solution injected through each of the needles is sufficient. If two needles are used, 5 mL of solution is injected at L-2 and L-4. One needle at L-2 or L-3 can be used for therapeutic purposes, and 15 to 20 mL of local anesthetic solution injected. If the needle is in the proper fascial plane (anterior to the vertebral insertion of the psoas fascia) the solution spreads cephalad and caudad to involve the entire lumbar sympathetic chain. The lateral technique (needle 2) entails the insertion of the needle through wheals made 10 cm lateral to the midline. With this technique, no attempt is made to contact the lateral aspect of the vertebra, but the needle is advanced through the psoas muscle mass for 6 or 7 cm, after which the same test volume of air or saline solution is used as for the classic technique. As soon as the needle passes through this psoas fascia, a sudden lack of resistance indicates the proper position. The rest of the technique is similar to that already described. **C:** Anterior view of lumbar vertebrae showing position of sympathetic chain. **D:** Posterior view showing sites of wheals for the lateral technique.

The anatomy of the lumbar sympathetic chains is more variable in its general form and in the number of ganglia than the rest of the sympathetic chain. The chain anatomy varies between individuals and between two sides of an individual (1). It is almost exceptional to find five ganglia—it is more usual to find only four, with a fusion of the L-1 and T-12 ganglia. The location of the ganglia is also inconstant: In some individuals they are segmentally located, while in others they are closely grouped and lie over a particular segment. The most common location is between the L-2 and the inferior border of the L-4 vertebrae. The ganglia can be situated on the body of the vertebra or anterior to the psoas aponeurotic arcades. In most people, they lie anterolaterally to an intervertebral disk with one portion of the ganglion in front of the lower part of the vertebra above and the other portion of the ganglion in front of the upper part of the vertebra below. The same degree of variability exists in regard to the size of the ganglia and the interganglionic cord and the number of branches extending from them. Ganglia range in size from 3 to 5 mm wide and 10 to 15 mm long.

The lumbar sympathetic chain contains both the preganglionic and postganglionic neurons that supply the pelvic viscera and vessels of the lower limbs and afferent (sensory) fibers, some of which transmit nociceptive information. The cell bodies of the sympathetic preganglionic neurons that supply the lower limbs are located in the T-11 and T-12, L-1, L-2, and sometimes the T-10 and L-3 spinal cord segments. Their axons pass through anterior roots of the corresponding spinal nerves and through the lower four, five, or six white rami communicantes to the sympathetic trunk (see Fig. 8-15 and Fig. 75-22). They descend to end in the lower three lumbar and upper three sacral ganglia, wherein they synapse with cell bodies of postganglionic neurons.

Some axons of postganglionic neurons pass directly to the iliac and femoral arteries, around which they form a plexus that passes as far as the junction of the upper and middle thirds of the thigh. Most of the postganglionic axons pass as the gray rami communicantes, however, which join the spinal nerves that form the lumbar plexus and the lumbosacral plexus. These sympathetic fibers pass distally as components of the femoral, sciatic, and obturator nerves and their branches and are given off segmentally to the vessels of the lower limb (see Fig. 75-23). Thus, by blocking the L-2 and L-3 ganglia, through which most of the fibers going to the lower limb pass, almost complete sympathetic denervation of the limb can be effected. In some subjects, however, some of the sympathetic pathways to the lower limb and pelvis bypass the sympathetic chain and make their synaptic connections in somatic spinal nerves. In these individuals, surgical sympathectomy limited to excision of the sympathetic chain fails to denervate the sympathetic supply to the limb completely.

Other branches given off by the lumbar sympathetic chain include the osseous branches, which supply the vertebrae; muscular branches, which supply the psoas muscles; and vascular branches, some of which accompany the lumbar arteries. They also give off four lumbar splanchnic nerves that pass anterior to the lower part of the celiac plexus to the aortic plexus and to the superior hypogastric plexuses and the plexuses that accompany the iliac vessels (Chapter 65).

Technique. Two techniques for lumbar sympathetic block are shown in Figure 102-53. The classic technique entails insertion of four needles at the L-1, L-2, L-3, and L-4 vertebral levels. This has been simplified to a two-needle technique at L-2 and L-4. A single-needle technique with needle tips placed at L-2 or L-3 has been reported to be satisfactory, even for injection of neurolytic agents (166). A two- or three-needle approach should be used for neurolytic blocks (Chapter 104). Because the sympathetic trunk crosses the lumbar arteries at the midpoint of the vertebral body, it is best to avoid placing the tip of the needle at this level. Instead, the point of the needle should be placed anterior to the attachment of the aponeurotic arcades of the psoas muscle and its fascia. This not only permits the fascia to be used for the lack of resistance test (see Fig. 102-53) but also decreases the risk of damaging the vessels and of LA solution flowing posteriorly to involve somatic nerves. To achieve the placement of the needle so that its point is in front of the aponeurotic arcades, the needle should be inserted at the level of the upper part of the spinous process of the vertebra. The insertion is made a variable distance from the midline so that the needle passes either just above the tip of the transverse process or more laterally (see Fig. 102-53B).

If block is achieved with a fairly large volume of solution (8 to 10 mL for each needle) for therapeutic purposes, radiologic visualization is not necessary. Fluoroscopic assistance is advised when using small volumes of injectate for diagnostic purposes or for neurolysis.

Complications. The complications of lumbar sympathetic block include accidental injection of the drug into the inferior vena cava (on the right) or into the aorta (on the left), damage to the lumbar vessels, unintentional contact and consequent paresthesia of somatic nerves, or diffusion of the drug to block the somatic nerves.

INTRAVENOUS REGIONAL BLOCKADE

In this section we consider the use of the Bier block technique (167), which involves the isolation of the limb from the systemic circulation by a tourniquet inflated to a pressure above systolic BP. Drugs, LA, or adrenergic blocking agents are injected into the vascularly isolated limb and left in place for a brief period after which the tourniquet is released.

Intravenous Regional Sympathetic Blockade

Systemic sympatholytic drugs, that interrupt sympathetic (efferent) function either at the pre- and postganglionic synapses or at the endings of postganglionic fibers, may be used to treat various pain disorders. The use of systemic administration of sympatholytic is simple but produces systemic sympathectomy that may be incomplete and will produce significant side effects. In 1974, Hannington-Kiff (168) proposed a technique to produce prolonged sympathetic interruption in a limb, which largely circumvents the disadvantages of systemic drugs or regional sympathetic blocks. This procedure entails the injection of the antiadrenergic agent guanethidine into the venous system of the limb after the circulation has been temporarily occluded with a tourniquet. The technique, which has become known as

intravenous regional sympathetic blockade (IRSB), has become widely used for the relief of various painful conditions in which sympathetic dysfunction is thought to be present.

Basic Considerations

Guanethidine produces a prolonged unselective sympathetic blockade. It initially displaces norepinephrine from presynaptic storage vesicles and subsequently prevents a reuptake of norepinephrine (141). Consequently, norepinephrine is rapidly depleted, resulting in the impairment and eventual loss of sympathetic adrenergic nerve function, which has the effect of sympathetic blockade. The blockade lasts for many hours, often days, and sometimes weeks because of the strong binding properties and its slow elimination.

Controlled studies have now documented the efficacy of IRSB with guanethidine in increasing blood flow (169,170,171 and 172) and skin temperature (169,171) while decreasing the vasoconstrictor ice response (170) and relieving pain in vascular disease (169,170 and 171) and CRPS type I (169,172). Sweating is not reduced because this function is mediated by cholinergic postganglionic sympathetic fibers, which are unaffected by guanethidine. The duration of effect and efficacy of guanethidine IRSB and stellate ganglion block in patients with CRPS type I is quite similar on both short- and long-term follow-up (169).

Clinical Evaluations

Advantages. The IRSB technique using guanethidine has certain advantages when compared to regional sympathetic blocks. IRSB is less invasive and more comfortable for patients, it is technically simple and may be used by physicians who do not posses RA skills, it may be used in patients with blood clotting abnormalities, and the potential complications of regional techniques are avoided.

Disadvantages. The IRSB technique has some disadvantages when compared to regional anesthetic techniques: The drug initially causes a transient release of noradrenaline with a consequent burning pain, especially in patients who have painful limbs, and some of the active drug is released into the systemic circulation at tourniquet release, resulting in some degree of systemic sympathetic blockade. The procedure can only be used in a limb. It cannot be used in patients with burning pain in the head and neck or trunk and is of no value in relieving visceral pain. IRSB with guanethidine is not as specific as regional sympathetic blockade in differentiating SMP from SIP in patients with neurologic disorders (134), possibly because guanethidine does not block cholinergic fibers. IRSB with bretylium is an effective alternative to IRSB guanethidine (140).

Technical Considerations

IRSB should be carried out observing all the precautions used for a regional anesthetic: patent intravenous line, monitoring, available resuscitation drugs and equipment (see Basic Considerations, earlier in this chapter). Modest premedication with midazolam, 0.5 to 2.0 mg, plus or minus a modest dose of opioid (fentanyl, 20 to 50 µg), helps diminish anxiety and tourniquet pain. Tourniquet pain may also minimized by using a double-cuff tourniquet and mixing a small dose of lidocaine (25 to 50 mg) in the injectate.

For IRSB of the arm, the injectate should be 10 to 20 mg (1 to 2 mL) of guanethidine in 25 mL of saline; for the leg, the injectate should be 15 to 20 mg guanethidine in 50 mL of saline, although the total dose may be raised to 30 mg of guanethidine (141). The dose of bretylium for IRSB is 3 to 4 mg per kg in 40 mL of saline (140).

Technique

After the patient has an intravenous line established in both affected and unaffected limbs and monitoring has begun, the limb should be wrapped in a thin layer of padding and the tourniquet secured. The limb should be exsanguinated by elevating the limb above heart level for at least a minute—preferably longer. Limb exsanguination can be more completely achieved by tightly wrapping a rubber bandage around the limb from fingers proximally. However, this is often impossible because of the patient's pain. With the arm elevated, the tourniquet should be rapidly inflated to 100 mm Hg above systolic BP. The limb is returned to the horizontal, and the solution is injected over a 2- to 3-minute period. Faster injections may raise the isolated arm's intravascular pressure to rise above tourniquet pressure and risk leakage of the drug under the tourniquet to the systemic circulation. The tourniquet should be maintained for about 20 minutes to allow the drug time to fix to tissues. Tourniquet times may be reduced in patients with limb ischemia; but, the shorter the tourniquet time, the more drug is released systemically at tourniquet release and the greater the incidence of systemic side effects. Side effects include hypotension, faintness, nasal congestion, and sedation. Following the procedure, patients should remain supine with appropriate CVS monitoring. Patients should be closely supervised when they get up to ensure that there is no systemic hypotension or syncope. Blocks might need to be repeated at 3- day intervals in severe cases; otherwise, weekly blocks are advised. The most common requirement is for two or three blocks (141).

Intravenous Regional Analgesia

Historical Background

The German surgeon, August Bier, reported the first use of intravenous RA with LA to alleviate pain (167). In the 1930s, Leriche and Fontaine (173) reported the use of intraarterial injection of procaine to afford relief in cases of painful arteritis obliterans. Later they advocated both IV and intraarterial injection of procaine for other painful conditions, including Raynaud's disease, causalgia, traumatic arthritis, painful phantom limb, and leg ulcers.

Indications

Although intravenous RA is a popular method of producing surgical anesthesia, it has only been used to a limited degree in the management of acute and chronic pain. It is a convenient method for determining whether the pain arises from a peripheral source in a limb and can be used as a temporary measure to relieve pain. Boas and Cousins (174) suggested that pain relief can be assessed only while the cuff is inflated because the LA may produce systemic analgesic effects as soon as the LA is released into the circulation.

Technique

The technique is similar to that described for IRSB with guanethidine, but LA, 30 to 40 mL of 0.5% plain lidocaine or prilocaine, is injected over 2 to 3 minutes. As the drug is injected, the skin usually becomes mottled and analgesia develops rapidly. Usually sufficient analgesia and muscle relaxation develop within 5 to 10 minutes. The tourniquet should be kept inflated for at least 20 minutes to prevent toxic doses of LA being released into the systemic circulation.

Continuous Infusion of Intravenous Local Anesthetics

Indications

Historically single doses and infusions of LA have been reported to be helpful for a variety of painful conditions (1,174). Intravenous LA infusions have more lately been shown to be effective in the treatment of a number of central pain states (13,175,176), as have orally administered LA congeners of LA such as tocainide and mexiletine (177). Tocainide and LA have been shown to selectively depress C-afferent fiber–evoked activity in the spinal cord (178).

Technique

Because intravenous LA is associated with a risk of LA toxicity, LA infusions must be performed in an environment in which such toxicity can be rapidly detected and dealt with (see Basic Considerations, earlier in this chapter). A variety of regimens have been described. A standard technique is lidocaine, 4 mg per kg over 1 hour, which achieves blood levels of lidocaine of 1.2 to 2.0 µg per mL. The period between treatments is usually 1 to 2 weeks, and four to six treatments may be required (174,179). Close scrutiny of efficacy immediately after treatments and at repeat visits is necessary with repeat treatments being performed according to need.

NEURAXIAL BLOCKADE

Subarachnoid Block

SAB, also known as *spinal anesthesia*, is achieved by introducing a small amount of LA (e.g., 50 to 100 mg procaine, 25 to 50 mg lidocaine, or 5 to 10 mg bupivacaine) into the subarachnoid space where the LA mixes with cerebrospinal fluid (CSF). Unlike other forms of RA, the LA comes into direct contact with nerve axons and does not have to traverse epineurium and perineurium. It thus produces a rapid onset of effect with a small amount of drug. SAB is one of the technically simplest RA techniques and, in experienced hands, permits a somewhat better control of the degree, extent, and duration of block than can be obtained with other regional techniques. The LA solution may be made hyperbaric (specific gravity greater than CSF) by the addition of dextrose or hypobaric (specific gravity less than CSF) with water, both of which enable the spread of block to be controlled to some degree by patient positioning.

Notwithstanding these advantages, SAB with LA has a limited place in managing patients with acute or chronic pain, except as a diagnostic "differential" block or a prognostic block before subarachnoid injection of a neurolytic agent. The prognostic technique, which entails injection of very small amounts of LA at a vertebral level at which the subarachnoid space contains the rootlets of the midportion of all the spinal segments to be blocked, is described in detail in Chapter 104. Here we limit our comments to "differential" or graduated SAB.

Indications

Differential SAB was introduced as a method for differentiating pain caused primarily by sympathetic hyperactivity from that caused by nociceptive input along somatic nerves and for differentiating peripheral nociception from central pain. This procedure was based on the long-held assumption that nerve fibers of different sizes are blocked by different concentrations of LA. It was believed that the small sympathetic preganglionic axons, being the smallest diameter fibers, were susceptible to a concentration of LA that did not block somatic nociceptive impulses, and that the A-d and fibers in somatic nerves could be blocked by concentrations of LA that would not block the large A-b and A-a fibers that carry tactile and motor functions. Differential or graduated SAB (180,181) has been used to permit differentiation of the source of pain. The technique was considered suitable for investigating patients with lower extremity, pelvic, lower abdominal, and lumbar spine pain. It was considered less suitable for investigating patients with pain from the upper abdomen, thorax, or cervical spine, because these blocks often entail an extensive autonomic block, accompanied by cardiovascular sequelae.

This classic concept of differential SAB is of dubious validity. It is not possible to obtain "pure" block of sympathetic, sensory, or motor fibers, and properties of LA, such as frequency-dependent conduction block and spinal cord long tract block (174), call the interpretation of the results of the technique into question. Moreover, preganglionic fibers in the subarachnoid space, though smaller than A-d fibers, may be more resistant to low concentrations of LA than nociceptive fibers (182). These findings make the concept of the differential neural blockade increasingly tenuous and cast considerable doubt on the interpretation of such block. A graduated SAB *can* be used to determine the segmental level from which pain is derived or transmitted by producing an ascending SAB with dose increments that produce rising segmental anesthesia (174).

Technique

Before a differential or graduated SAB the patient should be properly prepared and the sympathetic, sensory, and motor functions assessed and vital signs continuously monitored. A spinal needle is inserted at the chosen spinal interspace with different solutions at 10-minute intervals in the following sequence (Fig. 102-54):

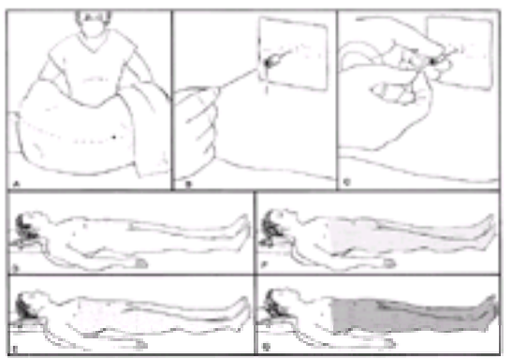

Figure 102-54. Graduated subarachnoid (spinal) block. **A:** Lumbar puncture and insertion of the catheter: lateral position for the puncture. **B:** After formation of the skin wheal, a special 25-gauge needle is advanced toward the subarachnoid space. The point of the needle is in the subarachnoid space, as shown by the emergence of cerebrospinal fluid. **C:** Introduction of the thin catheter through the needle into the subarachnoid space. **D:** The patient is supine. After injection of 8 mL of saline solution, no change is noted in sensation. **E:** Injection of 8 mL of 0.25% procaine produces a sympathetic nerve block (*light stippling*). **F:** Injection of 8 mL of 0.5% procaine produces analgesia to pinprick, pin scratch, and pinch (*heavy stippling*). **G:** Injection of 8 mL of 1% procaine produces motor block and dense anesthesia (*very heavy stippling*), as indicated by the inability of the patient to move the limbs; also, the abdominal wall is relaxed.

1. Eight to 10 mL of saline solution is injected. Because there is controversy about whether normal saline solution produces a change in sensation (183,184), the aspiration and reinjection of 8 mL of CSF may be preferable.
2. Eight to 10 mL of 0.25% procaine is injected, which should produce a sympathetic nerve block as indicated by measuring sympathetic function.
3. Eight to 10 mL of 0.5% procaine is injected, which should produce a sensory block as assessed by pinprick, pin scratch, and pinch.
4. Eight to 10 mL of 1% procaine is injected, which should produce a motor block.

After each stage of the procedure, the amount of pain the patient has, the sensory level of block, the neurophysiologic and behavioral changes in response to the block, and the analgesia produced should be assessed and noted. Interpreted simplistically, pain that responds to "placebo" is presumed to have a nonnociceptive origin and has been classified as psychogenic. Pain reliably removed by a sympathetic blockade and accompanied by objective evidence of sympathetic interruption, has been interpreted to imply a sympathetic component to the pain. Some evidence casts doubt on these assumptions (see Chapter 81) (174,185). Elimination of the pain by 0.5% or 1.0% procaine solution indicates a somatic origin of the pain. Failure of any solution or block to relieve pain implies a central pain.

The distinctions between the various causes and responses are by no means as concrete as those implied by these simplistic interpretations. It is almost impossible to produce a pure sympathetic block or a pure block of A-d fibers. Moreover, the method by which the patient is questioned and how the technique is presented can contribute to difficulties in interpretation. It is important that the technique be used according to a strict protocol that minimizes bias in both the patient's report and the observer's interpretation. The results of such a diagnostic block must be interpreted within the context of the other clinical, investigative, and behavioral information that has been obtained about the patient and the pain problem (185). Finally, the graduated procedure can be used to determine the uppermost segment of nociceptive input into the neuraxis.

Epidural Neural Blockade

Epidural neural blockade for the management of pain involves the injection of an LA into the epidural (extradural, peridural) space. The site of injection can be into the sacral canal (the so-called caudal block) or in the lumbar, thoracic, or cervical epidural space. The block can be achieved with a single injection of LA through a needle placed at the appropriate level or, more preferably, by the introduction of a catheter through a thin-walled, 18- or 17-gauge needle, advancing the tip of the catheter to the vertebral level that is considered to be the optimal site for injection.

Basic Considerations

General Indications. Continuous epidural block is one of the most versatile techniques for managing patients with acute and chronic pain. Placing the catheter at different levels of the extradural space can lead to analgesia of one or more spinal segments in almost any part of the body below the head. Continuous segmental

epidural analgesia is a most effective and practical procedure for relieving the pain of acute pancreatitis, biliary colic, renal or ureteral colic, rib fractures, and other severe posttraumatic pain and postoperative pain in the thorax, abdomen, pelvis, and lower limbs. It is also useful for providing temporary relief of severe local and segmental pain caused by herniated intervertebral disk or by fractures of the vertebrae. Continuous segmental epidural block provided through a variety of specially designed catheter systems may be extended for weeks or months for relief of pain due to cancer or nonmalignant conditions (e.g., CRPS).

Anatomic Basis. The epidural space is the interval between the periosteum that lines the vertebral canal and the various ligaments that connect the vertebrae and the pachymeninges (dura arachnoid) surrounding the spinal cord and roots in all of their extension from the foramen magnum to the conus terminalis, which in the adult extends to the S-2 vertebra (186,187 and 188). The epidural space continues inferiorly as the sacral canal, and laterally it communicates with the paravertebral tissues and spaces by the 48 intervertebral foramina through which the spinal nerves make their exit (Fig. 102-55).

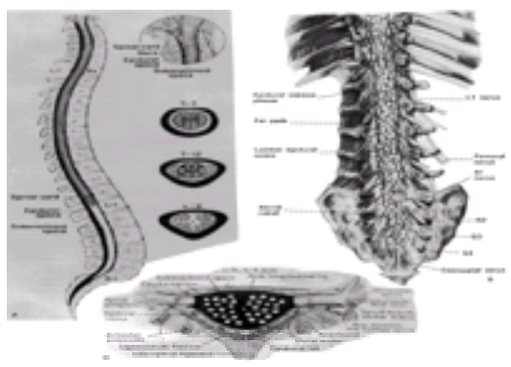

Figure 102-55. Anatomy of the epidural space. **A:** Sagittal section of the spinal column. Inset: Enlarged view of the upper cervical region indicates that the epidural space does not extend beyond the foramen magnum, where the dura attaches to the entire circumference of the foramen. Below the inset are three cross-sectional views of various levels of the vertebral column. The epidural space has a different shape in the midthoracic and midlumbar regions. (From Bonica JJ. *Principles and practice of obstetric analgesia and anesthesia.* Vol 1. Philadelphia: FA Davis, 1967:622, with permission.) **B:** Posteroanterior view of the epidural space after the spinous processes and laminae have been removed, showing that its contents consist of an internal vertebral venous plexus accompanied by loose areolar tissue and fat. **C:** Schematic cross section of the spinal canal at the level of the intervertebral disk between the L-3 and L-4 vertebrae showing the shape and size of the epidural space and its contents and the position of the rootlets that make up the cauda equina. (**B**,**C** from Bonica JJ, McDonald JS. *Principles and practice of obstetric analgesia and anesthesia,* 2nd ed. Baltimore: Williams & Wilkins, 1995:412–413, with permission.)

The width of the epidural space varies greatly, with the anterior portion being narrow and almost theoretical because of the close contact of the dura with the posterior longitudinal ligament (see Fig. 60-7). The posterolateral portion of the epidural space is found between the dura and the ligamenta flava and laminae. Because of the shape of the spinal canal, the epidural space in the posterolateral region is somewhat triangular, being widest in the midline between the dura and the junction of the two laminae. This triangular space varies in its anteroposterior diameter as follows: 1.5 to 2.0 mm at C-7, 3.0 to 4.0 mm at T-2, 3.0 to 5.0 mm in the midthoracic region, 5.0 to 6.0 mm at L-2, and only 2 mm at the lumbosacral junction (185,186).

The contents of the epidural space include solid and liquid fat and loose areolar tissue, through which run the internal vertebral venous plexus, lymphatics, and the dural projections that surround the spinal nerve roots (see Fig. 102-55). Fat is abundant in the posterolateral space, where it forms pads that intervene between the dura and the laminae and ligamenta flava. Although this tissue is loosely adherent to the vertebral canal and dura, it is easily stripped from the dura by fluids that disperse from the point of injection.

Because the spinal cord ends at the level of the lower part of the L-1 or the middle part of the L-2 vertebra in 90% of adults, the dura arachnoid below the L-2 vertebra contains only the cauda equina. This obviates the risk of injuring the conus medullaris with the epidural needle or catheter if the puncture is done below L-2. Experienced anesthesiologists, however, can safely perform epidural punctures and introduce catheters at any level, including the lower cervical, thoracic, or lumbar region, as well as the sacral canal to produce caudal analgesia.

Technical Considerations

Spinal Epidural Block. The single-injection technique for block of the epidural space in the lumbar, thoracic, or cervical region is best carried out with a 20-gauge, short-beveled spinal needle. For the continuous technique, a special 18-gauge, thin-walled needle (e.g., Tuohy) that allows passage of a catheter is used. The most important part of the procedure is to advance the point of the needle through the thick ligamentum flavum *slowly*, using the lack of resistance test, and *promptly* arresting the advance of the needle once its bevel has passed into the epidural space. Unless this step is done slowly and cautiously, with full control of the advance of the needle, the needle could be accidentally advanced too far and enter the subarachnoid space. For a single injection, the midline approach can be used (Fig. 102-56 and Fig. 102-57). To introduce a catheter, the paramedian approach, first described by Bonica (188), may be preferable (Fig. 102-58 and Fig. 102-59). Figure 102-60 illustrates the paramedian approach, which facilitates the advance of the catheter in the epidural space.

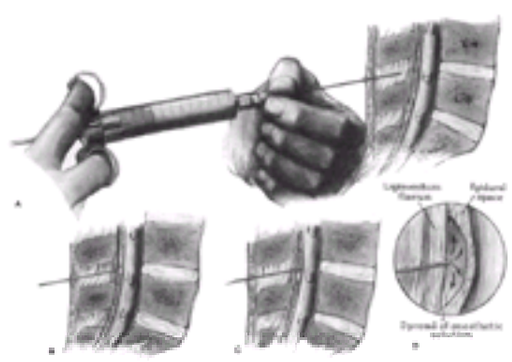

Figure 102-56. Epidural puncture into the lumbar region using the midline approach. **A:** After producing an intracutaneous wheal in the midline between the tips of adjacent spinous processes, a 20-gauge, short-beveled needle attached to a syringe filled with saline solution is introduced into the interspinous ligament. The back of the left hand is held against the patient's back, with the thumb and index finger grasping the hub of the needle; these act as a fine control of the advance of the needle while it is being pushed anteriorly with the right hand. An attempt to inject the saline solution while the point of the needle is in the interspinous ligament meets with some resistance. **B:** The point of the needle is in the ligamentum flavum, which offers marked resistance and makes it impossible to inject the solution. **C:** Entrance of the point of the needle into the epidural space is discerned by the sudden lack of resistance to the injection of the saline solution. **D:** The force of injection of 8 to 10 mL of saline solution pushes the dura-arachnoid away from the point of the needle. (From Bonica JJ, McDonald JS. *Principles and practice of obstetric analgesia and anesthesia*, 2nd ed. Baltimore: Williams & Wilkins, 1995:431, with permission.)

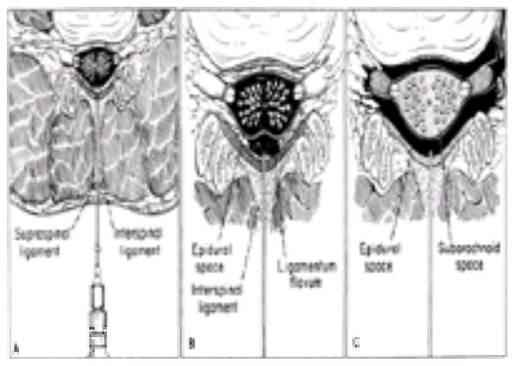

Figure 102-57. Cross section at the midlumbar region to show the technique for epidural puncture using the midline. **A:** The point of the needle is in the ligamentum flavum, which offers marked resistance to the injection of saline solution. **B:** Injection of saline pushes the dura slightly anteriorly, thus decreasing the risk of puncture of the dura by the bevel of the needle. **C:** Injection of the local anesthetic solution causes diffusion throughout the epidural space and penetrates the dura-arachnoid to involve the rootlets. (From Bonica JJ, McDonald JS. *Principles and practice of obstetric analgesia and anesthesia,* 2nd ed. Baltimore: Williams & Wilkins, 1995:432, with permission.)

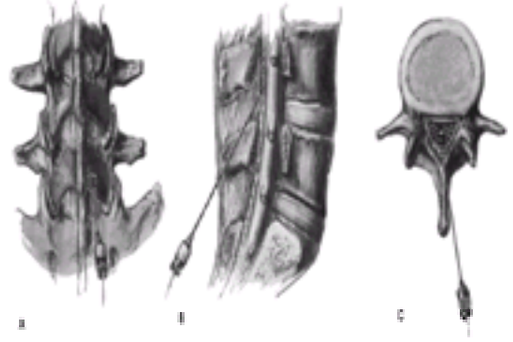

Figure 102-58. Continuous epidural block in the lumbar region using the paramedian approach. **A:** Posterior view showing the relationship of site of puncture, direction of needle, and spinous process. The anesthetic wheal is made 1.5 cm, from the midline at the same cross-sectional level as the lower tip of the spinous process. Following formation of the wheal, a 22-gauge needle is used to infiltrate the subcutaneous tissue, muscle, and upper medial part of the lamina with about 10 mL of a dilute local anesthetic solution (0.5% lidocaine). A special 18-gauge, thin-walled Tuohy needle is introduced so that its axis makes an angle of approximately 15 degrees with the midsagittal plane. **B:** Side view showing the same relationship and position of tubing in the epidural space as in A. The laminae and pedicles of the vertebrae have been removed. The needle makes a 35- degree angle with the skin inferior to the point of insertion. **C:** Superior view showing the relationship of the needle to the midsagittal plane and the position of the needle point in the epidural space, with the bevel of the needle facing cephalad. (From Bonica JJ, McDonald JS. *Principles and practice of obstetric analgesia and anesthesia,* 2nd ed. Baltimore: Williams & Wilkins, 1995:433, with permission.)

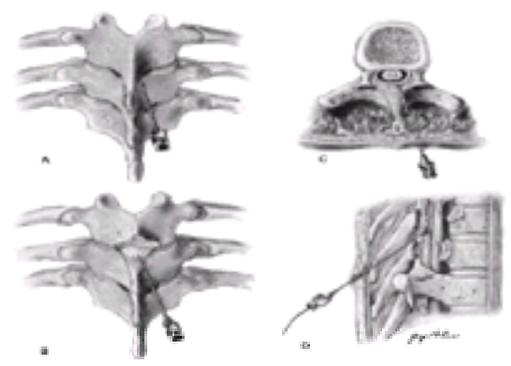

Figure 102-59. Continuous epidural block in the midthoracic region using the paramedian approach. **A:** The obliquity of the spinous processes is extreme, and bony spurs are usually on the surface of the adjacent spinous processes, making introduction of the needle through the supraspinous and intraspinous ligaments difficult, so the paramedian approach facilitates the puncture and the introduction of a catheter. The skin wheal is made 1.5 cm lateral to the tip of the spinous process of the vertebra above the interspace to be penetrated. The first step is to contact the medial upper part of the lamina. (The syringe, which is usually attached to the needle throughout its advancement, is not shown for the sake of clarity.) **B:** The bevel of the needle is in the ligamentum flavum in the midline. At this point injection of saline solution creates resistance until the ligament is traversed, after which a sudden lack of resistance can be felt. **C:** Cross-sectional depiction of the relationship of the needle to the soft tissue, spinous process, lamina, and ligaments. The bevel of the needle is near the midline of the epidural space and is facing cephalad. **D:** Sagittal section with the lamina and pedicles removed showing the relationship of the needle to the surrounding structures and to the catheter in the epidural space. (From Bonica JJ. Continuous peridural block. *Anesthesiology* 1956;17:626–630, with permission.)

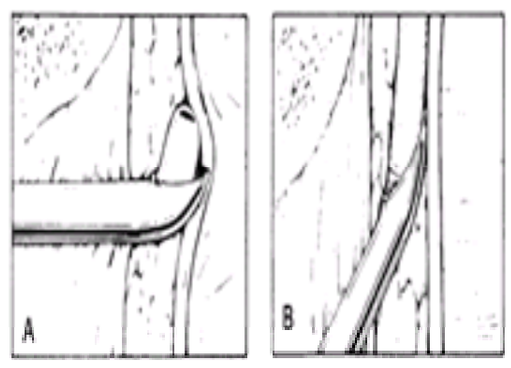

Figure 102-60. Schematic depiction of the advantage of introducing the Tuohy needle by a paramedian approach in the lumbar region at an angle that facilitates advancement of the catheter through the needle as compared to use of the midline approach. **A:** A Tuohy needle is introduced through the midline and advanced sufficiently so that its entire bevel is within the epidural space. If the space is narrow the dura might be partially punctured. Also, because of the direction of the bevel of the Tuohy needle, the tip of the catheter is directed anterosuperiorly against the dura in an attempt to make a 90-degree turn cephalad; not infrequently it is prevented from advancing by a fat pad or a vein lying on the dura. **B:** A paramedian approach with the Tuohy needle causes the catheter to be directed more cephalad, thus facilitating its advance within the epidural space. Moreover, because the point of the needle is directed cephalad, the possibility of puncturing the dura is small. (From Bonica JJ. *Obstetric analgesia and anesthesia.* Seattle: University of Washington Press, 1980:102, with permission.)

Once the bevel of the needle is actually within the epidural space, an injection can be made. Alternately, a catheter is passed through the needle and the needle is subsequently withdrawn. Using currently available catheters, only 4 to 5 cm should be inserted into the epidural space beyond the bevel of the needle. Attempts to introduce a greater length of catheter, or to thread the catheter to points remote from the site of puncture, lead to an unpredictable position of the catheter tip

(189,190). Epidural catheters can be threaded under fluoroscopic control, particularly if they have a wire stylette.

When segmental epidural analgesia is being used, the site of injection or catheter placement should be close to the center of the spinal segments that the physician wishes to block with the LA. This ensures that drug placement is accurate and that the dose of drug necessary to produce the desired effect is relatively small when compared to that of an injection at a remote site (191).

Indications and Techniques

Diagnostic Block. Segmental epidural blockade can be used as a diagnostic aid in determining the levels of nociceptive input in patients with visceral or somatic disorders. This procedure is not as useful as a selective sympathetic or somatic nerve block, because the technique invariably produces a block of both sympathetic and somatic nerves. The use of a differential epidural block may overcome some of the limitations of differential SAB; it allows better patient movement and associated testing for pain, while providing for repeated tests if some responses are equivocal. However, diagnostic differential epidural LA block carries the same limitation of interpretation as subarachnoid differential block (174). On the other hand, by using a volume of anesthetic at various intervals, the segmental level(s) of nociceptive input can be established.

A further variant of diagnostic epidural block is the “differential” epidural opioid blockade combined with epidural lidocaine as a diagnostic tool in patients with chronic pain. This procedure is based on the assumption that epidural opioids block nociceptive input at the level of the dorsal horn, leaving sensory, sympathetic, and motor functions unchanged without giving patients “cues” that blockade has occurred (192). At 20-minute intervals, patients receive epidural injections: two injections of normal saline (placebo), one injection of 1 µg per kg fentanyl, 0.4 mg intravenous naloxone, and, depending on the results obtained, 15 to 20 mL of 2% lidocaine injected through the epidural catheter. If the visual analog pain score decreased following epidural fentanyl and subsequently increased following naloxone, then a predominantly physical basis for the pain was considered to be likely. In contrast, little change in the visual analog score following the administration of fentanyl and naloxone suggested a predominantly emotional basis for the pain. The specificity of the technique has been called into question as the opioids reach both CSF and systemic circulation, providing CNS “clues,” and some types of pain are not well relieved by spinal opioids (174,193). Recommendations for a modification of the original technique are given in Table 102-7 (174).

Step	Amount and agent used	Injection type
1	10 mL of 0.9% saline without preservative	Epidural; placebo
2	10 mL of 0.9% saline without preservative	Epidural; placebo
3	10 mL solution of fentanyl, 100 µg	Epidural
4	Naloxone, 0.4 mg	I.V.
5	Lidocaine 2%, 20 mL	Epidural

Note: A visual analog scale is used to record pain relief. The pattern on response is suggested as being useful.

From Boas RA, Cousins MJ. Diagnostic neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural blockade*. 2nd ed. Philadelphia: JB Lippincott Co, 1988:899, with permission.

TABLE 102-7. Diagnostic epidural opioid blockade

Prognostic Block. Epidural blocks with LA can be used as prognostic procedures as an alternative to individual nerve blocks but suffer the same limitations as noted above in regard to diagnostic blocks. A more recent indication is the use of epidural blocks as prognostic indicators for the possible efficacy of epidural opioids in patients with cancer pain. Most physicians who use epidural opioids for pain therapy confirm catheter placement and the efficacy of the technique by injecting an LA into the epidural space and noting its analgesic spread (Chapter 103).

Prophylactic Block. The potential preemptive effect of perioperative epidural analgesia with LA and opioid on the incidence of phantom limb pain after amputation was mentioned earlier (14). This technique involves beginning the epidural preoperatively and continuing the block for several days postoperatively. A substantial reduction in the incidence of phantom limb in both short- and long-term follow-up has been reported. The possible mechanisms of this phenomenon are discussed in Chapter 9 and Chapter 41.

Therapeutic Blocks. Continuous segmental epidural or caudal analgesia with LA can be used for the relief of acute postoperative or posttraumatic pain that occurs below the clavicle (Fig. 102-61). The introduction of continuous epidural narcotics with or without added LAs for the relief of acute postoperative or posttraumatic pain has markedly decreased the indications for which LAs alone are used. This technique permits the use of smaller amounts of LA, with less risk of systemic effects, while at the same time providing the advantages of LAs as well as the relief of pain (194).

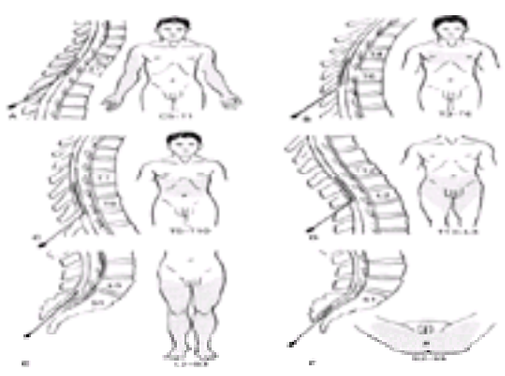

Figure 102-61. Patterns of segmental epidural analgesia, achieved with injection of a local anesthetic for the relief of pain in various regions of the body. On the left of each part of the figure is a sagittal section showing the site or level of the epidural puncture for placement of the Tuohy needle and subsequent insertion of the catheter (*black*), which is advanced 4 to 5 cm in the epidural space so that its tip is in the center of the band of analgesia desired. The right part depicts the region of the body in which pain is relieved (*stippled area*). **A:** Analgesia for pain in the upper limbs bilaterally. **B:** Analgesia to control pain in the upper part of the chest. **C:** Analgesia to control pain following upper abdominal surgery. **D:** Segmental analgesia following lower abdominal surgery to control pain and to produce continuous lumbar epidural block. **E:** Analgesia to relieve pain in the deep pelvis and the lower limbs. **F:** Continuous low caudal analgesia (S2-5) to relieve pain after hemorrhoidectomy or after other operations involving the perineum.

Epidural Blockade for Acute Pain

Chest Injuries. Patients with chest injuries present a spectrum of severity of trauma (Fig. 102-62). At the worst end of the spectrum are patients with chest wall instability and pulmonary contusion leading to pulmonary failure. At the other end of the spectrum are patients with chest wall injury with or without instability, little or no pulmonary contusion, and little or no evidence of respiratory failure. Patients with pulmonary failure require tracheal intubation and ventilation. Patients with chest wall instability and no pulmonary failure, once hemothoraces and pneumothoraces have been drained, can be managed with supplemental oxygen and respiratory therapy maneuvers (195,196), especially when effective epidural analgesia is provided (197,198 and 199). Patients with similar degrees of chest and lung injuries but suitable for conservative management regimens have had lower morbidity and mortality rates and a shorter duration of intensive care unit stay (196).

Figure 102-62. Management protocol for patients with chest injury. CPAP, continuous positive airway pressure. (Modified from Dittmann M, Steenblock U, Kränzlin M, Wolff G. A rationale for epidural analgesia in the treatment of rib fractures. *Intensive Care Med* 1982;8:89–92.)

Trials of conservative regimens show their benefit (Table 102-8). Patients with severe pulmonary contusions and respiratory failure should be treated with tracheal intubation and positive pressure ventilation (see Table 102-8, group 1). Patients with major pulmonary injury, or those who might need artificial ventilation for other reasons, should initially be treated with artificial ventilation. But, as the pulmonary lesion and pulmonary status improve, they can be weaned from such support, have the endotracheal tube removed, and be managed with spontaneous ventilation and epidural analgesia (see Table 102-8, group 2). Patients with chest wall instability but little or no discernible pulmonary injury and respiratory failure, once hemothorax and pneumothorax are drained, can be managed with epidural analgesia, oxygen, and respiratory therapy (see Table 102-8, group 3). If patients are managed by the conservative protocol, as in group 3, it is important to monitor the pulmonary status closely and to treat any incipient or declared respiratory failure by positive pressure ventilation. This was necessary in five of 112 patients (200) (see Table 102-8, group 3).

	Stacklund et al. 1986			Dittmann et al. 2010		
	Group			Group		
Parameter	1	2	3	1	2	3
No. of patients	13	7	16	155	27	112
Mean no. of rib fractures	5.7	4.7	5.5	6.6	–	6.8
No. of patients with hemo- or pneumothorax	9	3	8	92	–	48
No. of patients with pulmonary contusion	13	2	4	38	–	1
Mean duration of hospitalization in days	27	11	18	26	–	17
Deaths	2	0	1	18	0	5

Group 1: Endotracheal intubation and positive pressure ventilation.
Group 2: Endotracheal intubation and positive pressure ventilation followed by early extubation and pain management with epidural local anesthesia.
Group 3: Epidural local anesthesia plus supportive oxygen and respiratory therapy only. See text for more detailed definitions of groups.
[a]The group, which was part of group 1 primarily ventilated, could be weaned early under thoracic epidural analgesia without additional measure.

TABLE 102-8. Results of management of chest injuries

If epidural analgesia is to be used in patients with chest injuries, it is critical that the technique not be started until the patient has been adequately resuscitated with blood or crystalloid solutions, as needed. The adequacy of resuscitation should be ascertained by the measurement of central venous pressure and other parameters. The technique should also be used with caution in patients with CNS injuries or extensive injuries elsewhere.

When epidural analgesia is used for chest injuries, the catheter should be placed close to the middle of the segment(s) in which the analgesia is desired. If it is anticipated that the catheter might have to be in place and in use for a long period, consideration should be given to tunneling the catheter subcutaneously to minimize the risks of catheter displacement and infection. The doses of LA necessary for providing epidural analgesia are 5 to 8 mL of 0.5% bupivacaine with epinephrine or an infusion of 0.25% bupivacaine at a rate of 6 to 8 mL per hour (201) or mixtures of LA plus opioid (Chapter 103). Epidural opioids alone can be used as a baseline analgesic technique (202) or supplemented with epidural injection of LAs for painful maneuvers such as coughing (203) or with opioid/LA mixtures (44).

Postoperative Pain. Historically, segmental epidural analgesia with LA alone has been used to provide pain relief after thoracic, abdominal, pelvic, and leg operations. The drug was delivered either by intermittent injections, which could result in spotty pain control and a substantial incidence of side effects, or by constant infusions of LA. Epidural analgesia with LA alone but has been superseded by epidural analgesia with opioids alone (Chapter 103) or by the use of epidural analgesia using a combination of opioids and LA. This latter technique may provide superior analgesia and be associated with a lesser incidence of unwanted effects compared to the other two techniques. Epidural opioid and LA anesthesia is usually achieved with an infusion of a dilute solution of LA (bupivacaine 0.0625% to 0.1250%, ropivacaine 0.1% to 0.2%), at a rate to provide a “thin” block of the affected segments. The opioid is either a moderate duration of action opioid injected intermittently (morphine, 2 to 4 mg 4 hourly) or included in the infused LA solution (morphine, 10 to 40 µg per mL; fentanyl, 1 to 4 µg per mL).

Irrespective of whether the segmental epidural analgesia is produced with LA alone, opioid alone, or a mixture of the two, certain practical tenets apply with respect to catheter placement (see Fig. 102-61). The catheter tip should be placed in an interspace that corresponds with the center of the spinal segment affected by the surgical trauma. If the catheter is placed at a segment distant from the center of the affected areas, larger doses of drug will be needed to produce the desired effect, analgesia may not be as effective, and doses of drug will be larger. For thoracic operations where the incision usually passes through the fifth intercostal space, the catheter tip should be placed at T-6 to T-7. For midline sternotomy operations, the catheter tip should be placed at T-4 to T-5. For upper abdominal operations where the incision passes through T-5 to T-10, the catheter tip should be placed at T-8 to T-9. For lower abdominal operations with incisions through T-10 to L-1 to L-2, the catheter tip should be placed at T-12 to L-1. For hip, pelvic, or leg operations, the catheter tip should be placed at L-3 to L-4 or L-4 to L-5. The caudal route is a feasible route for catheter placement for the latter operations but is little used because of concern of infection in the gluteal cleft.

The manner in which LA, or LA plus opioid, is delivered follows from obstetric practice of slow infusions. The infusions are titrated to produce pain control and evidence of somatic block and to avoid side effects. Typical rates of infusion are as follows: thoracic, 4 to 8 mL per hour; upper abdominal, 8 to 10 mL per hour; lower abdominal, 8 to 19 mL per hour; and pelvic and leg, 10 to 14 mL per hour. More recently, patient-controlled epidural analgesia, using patient-controlled analgesia technology, has been shown to be effective and safe (204).

Postoperative pain relief provided by systemic opioids administered by intramuscular injection has been widely criticized as being of poor quality. The quality of pain relief has been clearly improved by the introduction of techniques (e.g., opioid patient-controlled analgesia) that permit the more pharmacokinetically and pharmacodynamically rational delivery of opioids (Chapter 84). However, other postoperative sequelae (respiratory, cardiovascular, endocrine) are little changed by these techniques. Epidural techniques with LA alone, opioid alone, or mixtures of LA and opioid provide superior analgesia, and their use is associated with other postoperative benefits.

Abdominal surgery, particularly upper abdominal surgery is followed by significant changes in indices of respiratory function and arterial oxygenation and by a high incidence of chest infection (Chapter 41). When compared to patients receiving conventional narcotic analgesia, patients receiving epidural analgesia with LA tend to maintain a more normal PaO_2 (204,205,206,207 and 208) and to have a lower incidence of chest infection (205,210). Patients have a better forced vital capacity and peak expiratory flow rate (205,206) and perhaps functional residual capacity (209,210 and 211). Patients in high-risk groups (e.g., morbidly obese patients) have a decreased incidence of respiratory complications (212,213). More recent studies in high-risk patients show significantly lower incidences of respiratory failure and respiratory infection in patients receiving epidural analgesia (214).

Surgery is associated with significant perioperative cardiovascular stressors that are manifest in a significant incidence of myocardial ischemia, arrhythmias, and myocardial infarction in patients at risk. Improved pain control, and perhaps other factors, associated with the use of epidural analgesia results in significant

improvements in incidence of arrhythmias, myocardial ischemia, and perioperative myocardial infarction (215,216).

Following surgery, there is a predictable hypercoagulable response that appears to be attenuated by LA epidural (217), and patients receiving epidural analgesia have a lesser incidence of DVT (44) and graft clotting (218).

Continuous epidural block from T-5 to the sacral segments during the perioperative period after lower abdominal operations markedly reduces the postoperative metabolic and neuroendocrine response to surgery. The marked increases in levels of the catabolically acting pituitary hormones (e.g., growth hormones, prolactin, adrenocorticotropin, antidiuretic hormone), adrenal hormones (e.g., cortisol, aldosterone, catecholamines), and serum glucose normally seen in patients given general anesthesia during surgery and managed with postoperative narcotics are minimized (219,220). Patients receiving epidural analgesia show fewer changes in hepatic enzymes (221). The significance of the reduction of these metabolic and neuroendocrine responses to trauma is not certain. Segmental epidural anesthesia for upper abdominal surgery and epidural analgesia during the postoperative period has fewer effects on these responses to tissue damage than are seen after lower abdominal and leg operations (220), probably because the vagus and the phrenic nerves are not blocked.

Acute Visceral Pain. Although celiac plexus block or splanchnic nerve block relieves the pain arising from the viscera, segmental continuous epidural block has the following advantages: (a) The block is technically easier; (b) it is more effective in relieving pain, not only that coming from the viscera but also that caused by irritation of the peritoneum (which is supplied by somatic nerves); and (c) it is much easier to produce sustained analgesia for a number of days than with other techniques.

For acute pancreatitis, the catheter is best placed with its tip at the T-7 or T-8 spinal cord segmental level. Dosage regimens should be as for upper abdominal surgery. The use of epidural analgesia to manage acute pancreatitis has been reported to reduce the incidence of early surgery and halve the mortality rate (151).

For the relief of biliary colic, a segmental analgesia of the same type is used, whereas for the relief of ureteral colic, the segments to be blocked are lower and depend on the site of the impacted stone. For pain caused by obstruction in the pelvis of the kidney or ureter, block of T-10 to L-2 provides pain relief.

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CHAPTER 103

Regional Analgesia with Intraspinal Opioids

L. Brian Ready

BASIC CONSIDERATIONS

History

Opiate receptors were first identified in the central nervous system in 1973 (1); subsequently large populations of these receptors were localized in the dorsal horn of the spinal cord (2). These observations, coupled with the discovery of endogenous opioids (3), led to animal studies that demonstrated the ability of intrathecal opioids to produce analgesia (4).

In 1979, Wang et al. reported pain relief using intrathecal morphine in cancer patients (5), and in the same year, Behar et al. achieved the same result injecting the drug into the epidural space (6). Subsequent studies have confirmed that selective, long- duration analgesia is possible using these techniques in a variety of clinical settings. As experience increased, it became clear that a number of side effects might be expected, ranging from annoying (sedation, pruritus, nausea, vomiting, or urinary retention) to life-threatening (respiratory depression). It is now apparent that with attention to patient selection, appropriate choice of drugs, dosage, route of administration, and adequate patient monitoring, the benefits of intraspinal opioid analgesia can be obtained with a high degree of safety (7).

This chapter contains a discussion of the basis and clinical application of intraspinal opioids for the management of pain. The term *intraspinal* is used to include both intrathecal (subarachnoid) and epidural routes when considering them together. This chapter is devoted primarily to the use of intraspinal opioids. However, the evolution of clinical practice has led to combinations of intraspinal opioids and local anesthetics; these are also included. Brief mention is also made of a number of other drugs that produce intraspinal analgesia. These include clonidine, ketamine, neostigmine, and amitriptyline.

Theoretical Bases

Anatomy

Nerve impulses resulting from noxious stimuli and transmitted predominantly by slowly conducting A-d and C fibers are modulated in the spinal cord before ascending to higher nerve centers in the brain. This modulation occurs through interactions at sensitive interneurons and associated receptors found in high concentration in the substantia gelatinosa of the dorsal horn (2). It is mediated by endorphins—naturally occurring peptides that selectively impair the transmission of nociceptive impulses and consequently the perception of pain without affecting somatic, autonomic, or motor functions.

Since the initial discovery of central nervous system opioid receptors, five types have been demonstrated: mu, kappa, delta, sigma, and epsilon (8). Opioids administered by the intrathecal or epidural route can, like endorphins, act on these receptors to produce profound selective analgesia. It is likely that the specificity, affinity, and intrinsic activity of each agent reaching the various receptors will determine its pharmacologic effects. The mu receptor is the dominant site in mediating analgesia, although delta and kappa receptors are also believed to play a role. The receptors most important in mediating somatic pain may differ from those mediating visceral pain (9). This could explain the clinical observation that although intraspinal opioids may completely relieve incisional pain after surgery, bowel distension accompanying ileus is often not affected.

Mechanisms of Action

Intrathecal. With the injection of an opioid into the cerebrospinal fluid (CSF), a reservoir of drug is created that passively diffuses into the dorsal horn of the spinal cord. There it binds to opioid receptors, where it is presumed to inhibit the release of substance P, a neurotransmitter believed responsible for relaying nociceptive information across synapses. This inhibition is reversible with opioid antagonists such as naloxone.

Epidural. An opioid injected into the epidural space produces analgesia by two mechanisms. First, a portion of the drug crosses the dura mater to enter the CSF. From there, it penetrates into the dorsal horn of the spinal cord as after direct intrathecal injection (10). Second, systemic absorption of the extradural bolus produces a plasma profile similar to that after intramuscular injection (11). The systemic levels of opioids make a contribution to analgesia, as the drug is distributed to both the brain and spinal cord. That contribution varies with the opioid's lipophilicity and may be substantial.

Comparison of Intrathecal and Extradural Injection

When an opioid is injected into the CSF directly, only small doses are required because there are no anatomic barriers to be crossed and removal by vascular absorption is slow. Administration by this route creates a reservoir of concentrated drug close to its site of action, where its effects are limited primarily to the spinal cord. If the epidural route is chosen, the opioid dose must be higher than with the intrathecal route to produce comparable analgesia. In the case of morphine, a tenfold increase is needed (11). The CSF uptake of morphine administered into the epidural space is only approximately 2%, but morphine concentrations achieved in CSF are more than 100 times higher than those found after intramuscular injection. The highly vascular epidural space clears opioids more rapidly than the relatively avascular subarachnoid space. Even so, at least in the case of a hydrophilic opioid (e.g., morphine), the epidural dose is only a fraction of that required to produce analgesia by intramuscular or intravenous administration. After initial human experience with both intrathecal and epidural opioids, the epidural route has achieved much greater popularity. This is due in part to the ease with which indwelling catheters can be placed in the epidural space for extended use.

Comparison with Regional Analgesia Using Local Anesthetics

It is useful for the clinician familiar with offering pain relief with local anesthetic neuraxis blocks (spinal, epidural) to compare and contrast these with intraspinal opioids. Table 103-1 provides this information in a manner used previously by Cousins and Mather in a comprehensive review (12). A major difference from local anesthetic techniques relates to the highly specific “block” of nociceptive pathways with intraspinal opioids and the implications that this selectivity has for patient mobility and activity.

Combinations of opioids and dilute local anesthetics are now widely used. The rationale is to reduce the dose of each component of the mixture while preserving effective analgesia, reducing side effects, and preserving function. Experience with these techniques is discussed later in this chapter.

	Opioid	Local anesthetic
Anesthetic action		
Site	Opioid receptor in dorsal horn of spinal cord	Nerve roots
Inhibition	Neuronal excitation	Axonal membrane impulse conduction
Pathways blocked	Pain	Pain, sympathetic, sensory, motor, proprioception
Side effects		
Cardiovascular	None	Hypotension
Respiratory	Early depression (systemic absorption) Delayed depression (rostral spread in cerebrospinal fluid)	None
Sedation	Variable; less than with systemic opioids	None
Nausea/vomiting	Yes	Occasional
Pruritus	Yes	None
Urinary retention	Yes	Yes (if sacral nerve roots blocked)
Convulsions	Associated with very high doses and meperidine	With high systemic drug levels

TABLE 103-1. Comparison of intraspinal opioid and local anesthetic block

Pharmacokinetics and Pharmacology

Uptake and Distribution of Intraspinal Opioids. The efficacy of intraspinal opioids is dependent on their passage from their site of injection to the spinal cord receptors in the dorsal horn. After intrathecal injection, the rate at which a drug penetrates the tissue of the spinal cord is closely related to its lipid solubility. More rapid uptake and more rapid onset of action are seen with highly lipid-soluble drugs such a fentanyl and meperidine than with a less lipid-soluble agent such as morphine. Table 103-2 contrasts a drug of low lipid solubility (morphine) with one of high lipid solubility (fentanyl) with regard to their clinically observable analgesic effects.

	Lipid solubility of opioid	
Effect	Low (e.g., morphine)	High (e.g., fentanyl)
Spinal cord receptor uptake (onset of analgesia)	Slow	Rapid
Clearance from CSF (duration of action)	Long	Short
CSF concentration	High	Low
Rostral spread of opioid	Extensive	Limited
Systemic blood levels	Low	High

CSF, cerebrospinal fluid.

TABLE 103-2. Effects on analgesia of opioid lipid solubility

After epidural injection, an opioid must also penetrate the dura mater—a relatively thick membrane—and the arachnoid membrane. Both significantly slow its rate of diffusion. Arachnoid protrusions in the spinal root sleeves represent a possible route for passage of epidural injectates into CSF (13). The possible role of uptake and delivery to the dorsal horn by the posterior radicular arteries has also been described (12). Studies have refuted these concepts; the arachnoid itself seems to be the effective barrier to the CSF (10).

The rate of dural penetration of epidural opioids is influenced by lipid solubility (14), molecular weight (15), and their dissociation constant (pK_a). Fentanyl, meperidine, and methadone all have a relatively high pK_a. Because this favors high concentrations of freely diffusible unionized molecules, these drugs exhibit a rapid onset and limited duration of spinal analgesia. Morphine, with a lower pK_a, has a lower concentration of unionized molecules after injection. This factor contributes to its slow onset and long duration of action.

After epidural injection, vascular absorption decreases the concentration gradient across the dura, thus reducing the rate of transfer. The addition of epinephrine to epidural morphine has been reported, by reduction of systemic absorption, to increase speed of onset, quality of analgesia, duration of analgesia, and intensity of side effects (16). In another study, only an increased frequency of side effects was found (17). A majority of clinicians do not use solutions that contain epinephrine for epidural administration.

Some portion of an opioid injected into the epidural space diffuses into fat and thus does not cross the dura. Uptake by blood vessels in the epidural space results in serum levels that contribute an element of supraspinal analgesia. The more lipophilic drugs show the fastest and greatest uptake by fat and thus the highest serum levels. These agents, exemplified by fentanyl and meperidine, also move rapidly from CSF into the lipid-rich tissues of the spinal cord. With such agents, onset of spinally mediated analgesia is rapid and the effect is relatively segmental near the injection site. Low lipid solubility, as in the case of morphine, leads to prolonged high CSF drug concentration, low tissue fixation, and the possibility of rostral spread in CSF. The sustained exposure of spinal cord opioid receptors results in a long duration of action.

Metabolism and Clearance of Intraspinal Opioids. It is not yet established what role metabolism plays in the termination of the spinal action of opioids after intrathecal or epidural injection, but considering the high concentrations of drug present, it is unlikely that it is a major factor. Loss of analgesia after intraspinal injection primarily results from drug clearance from the site of action. Strong receptor binding seen with polar agents such as morphine retards clearance compared with more lipophilic agents.

Intrathecal opioids are eliminated by two routes: diffusion along the neuraxis and vascular absorption. Rostral spread of CSF from the spinal subarachnoid space to the supraspinal cisternae has been demonstrated (18), making clearance through intracranial arachnoid granulations one likely mechanism. Vascular absorption of intraspinally administered opioids may occur as a result of movement into spinal cord blood vessels or, after epidural injection, into the venous plexus found in the epidural space. High lipid solubility favors passage of drug into blood vessels at either site.

Tolerance to Intraspinal Opioids. Tolerance, the decrease in effect over time of a given dose of drug, has been demonstrated in animals with both intrathecal and epidural opioids (19), as has cross-tolerance between intrathecal and systemically administered morphine (20). In humans, conflicting information is found. Rapid development of tolerance similar to that seen in animals has been reported in cancer patients who received 1 mg of intrathecal morphine per day (21). In contrast, cancer patients receiving epidural morphine in divided doses by intermittent injection showed little or no need for increased dose for as long as 280 days (22).

The mechanism leading to the development of tolerance is not known, although there is growing evidence in support of a role of the glutamate receptor of the *N*-methyl-d-aspartate type (23,24 and 25). A number of clinical observations may be of practical importance. First, consumption of parenteral opioids before commencing epidural treatment may increase the required dose (26). Second, the rate of onset of tolerance seems proportional to the concentration of the opioid at the receptor—that is, the degree of receptor activation. Therefore, it is speculated that the rate of development of tolerance might be minimized by (a) selection of the lowest effective opioid dose, (b) precise placement of opioid for optimal segmental effect, (c) small divided doses rather than large single daily doses, and (d) the use of low-dose continuous infusion systems when there is a need for extended periods of analgesia.

Toxicology of Intraspinal Opioids

The toxicology of intraspinal opioids has been examined in a number of animal and clinical situations. Repeated intrathecal and extradural injections of analgesic doses of opioids lead to no neurologic symptoms or observable adverse effects on spinal cord cells or fibers. No turbidity is seen when morphine, meperidine, or methadone is added to CSF, but it is present after the addition of heroin, suggesting precipitation of CSF protein.

A vast worldwide human experience with intraspinal opioids, sometimes administered in high doses for long periods, has not led to signs of neural injury. A number of opioids are supplied by their manufacturer in solutions containing no additives. Others contain preservatives, antioxidants, and buffering agents. It is not known whether any of these additives can be damaging after intraspinal or epidural injection. Sodium bisulfite, an antioxidant present in some local anesthetic solutions and some opioid solutions, does appear to be a dose-related neurotoxin (27). Preservative-free preparations of morphine (Duramorph, Astramorph) are marketed specifically for intraspinal use. These are considerably more expensive than preservative-containing morphine preparations—a significant consideration in cancer patients who may require large doses for extended periods of time.

Advantages and Disadvantages

Intraspinal opioids have dramatically improved the management of many painful conditions, and as a result, hundreds of thousands of patients worldwide have experienced pain relief. In general, opioids acting on spinal cord receptors provide distinct advantages over the same agents acting through supraspinal mechanisms. Under most circumstances, the quality of analgesia is greater, sedation is less, function is preserved, and a variety of outcomes are improved.

Side effects are common using intraspinal opioids but they are probably no more frequent or severe compared with the doses of systemic opioids required to produce equivalent analgesia. The administration of intrathecal opioids requires additional knowledge, skills, and institutional organization to achieve optimal efficacy and safety. Practice guidelines have been developed and should be considered by practitioners interested in using intraspinal opioids for their patients (28).

CLINICAL INFORMATION

Applications

Acute Pain

Postoperative Pain. Intraspinal opioids have been reported to control pain effectively after a wide variety of surgical procedures. Intrathecal opioids have the appeal of ease of administration, either at the time of spinal local anesthetic injection for surgical anesthesia or as a separate technique when general anesthesia is administered. Because most clinicians give a single injection, this technique is most appropriate when surgical pain is expected to be of relatively short duration. Many patients remain comfortable for 24 hours or more after a single injection of intrathecal morphine. Some of these will require no additional pain relief during their postoperative course or will find their remaining pain easily managed by oral analgesics.

The epidural route has been used much more extensively than the spinal route for postoperative pain control. Reasons include popularity of the technique alone or in combination with light general anesthesia during surgery, ability to leave an epidural catheter in place for extended periods to maintain analgesia, familiarity with postoperative analgesia using local anesthetics, and freedom from the risk of post–lumbar puncture headache. Epidural opioids have been effective in patients of all ages, including children (29,30,31,32,33 and 34).

A number of reports regarding the use of epidural opioids for postoperative pain are of special interest. Stenseth et al. reported a prospective study of the efficacy and side effects of epidural morphine in 1,085 patients after thoracic, abdominal, urologic, or orthopedic surgery (35). This large experience from a single institution provides a wealth of observations that are instructive to the clinician contemplating the use of epidural opioids.

Rawal et al. (36), in a randomized double-blinded study of 30 obese patients undergoing gastroplasty for weight reduction, compared the effects of intramuscular and epidural morphine with respect to analgesia, time to ambulation, gastrointestinal motility, early and late pulmonary function, duration of hospitalization, and occurrence of deep vein thrombosis in the postoperative period. The protocol allowed morphine to be given by the assigned route until pain was adequately controlled. The salient findings are detailed in Table 103-3.

	Intramuscular morphine	Epidural morphine
Mean morphine use over 36 hr (mg)	66	9
Patients with adequate pain relief (%)	93	100
Patients ambulating at 24 hr (%)	13	93
Mean time to passage of flatus (hr)	75	57
Patients with pulmonary complications (5)	40	13
Evidence of deep vein thrombosis (5)	20	0
Mean postoperative hospitalization (days)	9	7.1

Data from Rawal N, Sjostrand U, Christoffersson E, et al. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: influence on postoperative ambulation and pulmonary function. Anesth Analg 1984;63:583–592.

TABLE 103-3. Effects of epidural opioids on grossly obese surgical patients

Yeager et al. (37) compared outcome of high-risk surgical patients randomized to receive either general anesthesia and conventional postoperative analgesia or epidural anesthesia and epidural morphine analgesia. The epidural group had significantly lower mortality and lower incidence of major complications, shorter intensive care unit and hospital stays, and lower hospital and physician costs.

The use of intraspinal opioids for control of pain after cesarean section is widely practiced. This is offered when spinal or epidural anesthesia is provided for surgery (38), although most reports focus on the latter application. Pain after a large episiotomy repair or perineal repair may also be managed by intraspinal opioids.

It is now apparent that epidural analgesia after surgery, in addition to providing patient comfort, can facilitate accelerated recovery—an approach labeled *postoperative rehabilitation* by Kehlet (39). With this approach postsurgical patients receive not only effective pain relief but also immediate postoperative intake of oral nutrition, reduction in perioperative stress responses and organ dysfunction, early mobilization, avoidance of fatigue, and early hospital discharge.

Posttraumatic Pain. A small dose of epidural morphine (2 mg) was reported to be effective in controlling the pain that accompanies rib fractures (40). Its advantages over epidural bupivacaine for the same purpose were longer duration of action and absence of hypotension. Pain resulting from lower extremity fractures has also been relieved by epidural morphine (41).

Morphine by both the spinal and epidural route has been used to treat pain after multiple trauma in patients on mechanical ventilator support in an intensive care setting (42). Because communication was difficult or impossible in this group, adequacy of analgesia was documented by noting the marked reduction in doses of parenteral opioids and sedatives needed to eliminate objective signs of pain (restlessness, sweating, tachycardia, lacrimation, pupil dilatation, hypertension). Another group of intensive care patients who could communicate clearly after multiple trauma also experienced good analgesia with epidural opioids (43).

Other Acute Painful Conditions. The pain of acute myocardial infarction has been treated effectively with 0.5 mg of intrathecal morphine (44). The comfort it produced was more rapid in onset, more intense, and of longer duration during the first 24 hours than that obtained in a control group with total doses of parenteral morphine 40 times larger. In another report, 1.2 to 3.6 mg of epidural morphine was effective in relieving postmyocardial infarction pain in six patients after conventional intravenous analgesic agents had failed (45).

Patients with a variety of other acute painful conditions have experienced relief with intraspinal opioids. These conditions include acute lumbar disk prolapse, thrombophlebitis, acute herpes zoster, nephrolithiasis, and ischemic pain (41,42 and 43). Patients in an intensive care unit suffering severe pain as a result of pancreatitis were improved with either spinal or epidural opioids (42). Although the results of these reports are promising, the numbers of patients receiving treatment were small. Spinal opioids can reduce muscle spasm and associated pain in patients with spinal cord lesions. Implanted infusion devices have been used in some of

these patients, permitting treatment to continue for extended periods. More recently, intrathecal baclofen infusions have largely replaced morphine for this purpose.

Labor Pain. Intrathecal or epidural opioids and opioid–local anesthetic mixtures are widely used to provide pain relief for women in labor. A combination of the two techniques is also used (46). Because it is beyond the scope of this chapter to discuss obstetric analgesia in detail, the interested reader is referred to Chapter 71.

Cancer Pain

Many published reports have demonstrated effective pain relief in patients with cancer using either spinal or epidural opioids (see Chapter 36). The fact that effective doses and the need for supplemental analgesics differ among reports likely reflects differences in the magnitude of the pain problems in the populations studied. Patients with the most severe pain typically receive large systemic opioid doses before intraspinal opioids are used. Effective intraspinal doses in these groups are higher than those needed in opioid-naive patients. With advancing disease and increasing pain, intraspinal opioids combined with local anesthetics, other intraspinal drugs (e.g., clonidine), or supplemental agents by another route may be required for satisfactory analgesia.

Intraspinal Opioids. Both the spinal and epidural routes are effective. Intermittent injections through conventional catheters, catheters tunneled subcutaneously, implanted reservoirs, and infusion pumps all have their advocates. Compared with systemic opioids, the benefits of intraspinal opioids to control cancer pain relate in large part to the reduced dosage required. As a result, patients remain more alert. This in turn facilitates ambulation and social activities. Increased appetite and weight gain are also frequently noted. All these advantages facilitate patient care at home, leading to a higher quality of life and substantial economic savings compared with institutional care. Unlike local anesthetic or lytic blocks, sympathetic tone, motor power, and sphincter function are preserved. Compared with neurosurgical procedures, no irreversible changes are produced, but therapy must continue as long as the patient survives. Patients must also have access to health care providers trained in the techniques of refilling and programming pumps.

Reports of opioid tolerance with the need for escalating doses and frequency of injection vary among investigators. Tolerance appears to be an uncommon problem during the first several weeks or even months of therapy but it becomes progressively more likely the longer therapy is continued. Tolerance can be difficult to distinguish from rapid malignant tumor progression. A sudden increase in pain should prompt thorough reevaluation for new disease (e.g., tumor extension into the neuraxis). It is well known that nonorganic factors such as anxiety or depression may also lead to reporting of increased pain. Appropriate treatment of these conditions should not be overlooked.

Certain technical problems with spinal or epidural catheters are common in patients with cancer pain. These include obstruction, leaking, and dislodgment. Such problems result in failure of the injected opioid to reach its site of spinal action, with an accompanying increase in previously well-controlled pain. Periodic catheter replacement may be necessary in some patients. Infection can also occur and requires prompt diagnosis and treatment (47).

Radicular pain in some patients during epidural catheter injection has been noted. Caputi et al. (48) have stated that this symptom is due to the opioid fluid bolus causing distension of the dural sleeve of a spinal nerve root near the tip of the catheter. They found it could be resolved by the injection of triamcinolone through the catheter several times at intervals of 3 or 4 days. Others have found that catheter replacement solves the problem.

Serious respiratory depression is rare in cancer patients treated with intraspinal opioids, even when very high doses have been administered. It is believed that exposure to opioids by other routes before starting intraspinal injections confers tolerance to the respiratory depressant effects sometimes seen in other populations of patients. Myoclonus with high doses of intrathecal opioids in cancer patients is a well-recognized complication (49). It is discussed later in this chapter.

Intraventricular Opioids. An alternative approach to providing analgesia for patients with cancer is the injection of morphine into the lateral ventricle of the brain. Leavens et al. in 1982 described early clinical experience with a technique of ventricular catheter insertion and attachment to a subcutaneously implanted Ommaya reservoir (50). Lobato et al. also reported experience with the technique and have analyzed the results of seven other authors (51). The review showed that among 197 patients treated, 95% obtained excellent pain relief with initial morphine doses of 0.25 to 4.00 mg. With continued use, dose requirements increased to as high as 36 mg. Obbens et al. found that patients who had previously used large doses of oral and parenteral opioids required higher intraventricular doses (52). With the development of tolerance, as much as 15 mg of morphine every 6 hours was needed by some patients. Complications of intraventricular morphine administration include reservoir malfunction and contamination resulting in meningitis. The most common side effects were nausea and somnolence.

Nonmalignant Chronic Pain

There has been considerable experience with intraspinal opioids in patients with a number of chronic nonmalignant pain syndromes. Cohn (53) alleged that a single epidural administration of morphine with methylprednisolone acetate produced pain relief lasting from 6 to 12 months in 100% of patients with chronic postlaminectomy low back pain. Other investigators have been unable to duplicate this result. Magora et al. (41) found that over an observation period of a few days, approximately half of their patients with chronic low back pain reported good relief. Coombs et al. (54) found that compared with cancer patients with similar levels of reported pain, chronic low back pain patients showed no sustained improvement. Some subsequent reports found higher efficacy (55,56) and cost savings (57).

Magora et al. (41) used epidural opioids in small numbers of patients with a variety of other chronic pain syndromes. These included ischemic pain due to peripheral vascular disease, causalgia, cervical spine syndrome, and an old vertebral fracture. Results of epidural opioids in this group were comparable to other more standard methods of treatment (physical therapy, extradural block, and nerve block with local anesthetics and steroids). Bach et al. (58) reported dramatic reduction in postoperative lower extremity phantom limb pain by pretreating patients with epidural analgesia before amputation.

Early experience with intraspinal opioids for chronic nonmalignant pain involved single-dose injections or a series of injections through percutaneous epidural or subarachnoid catheters. More recently, implanted reservoir/pump systems have gained widespread popularity. Becker et al. (59) treated two patients with intractable reflex sympathetic dystrophy with intrathecal morphine. Hassenbusch et al. (60) treated 18 patients with a variety of intractable chronic pain syndromes. An overall 39% reduction in pain scores was reported. The complication rate was high. Winkelmüller and Winkelmüller (61) treated a group of chronic pain patients for an average of 3.4 years. Average pain was reduced by 58%, with an average decrease in visual analog scale scores from 9.4 to 3.9. However, 31 of 120 patients were deemed treatment failures for a variety of reasons, including inadequate pain relief, intolerable side effects, development of tolerance, or surgical/technical complications.

The published literature on intraspinal opioid infusion for the relief of chronic pain has been reviewed by Stangl and Loeser (62). These reviewers found a lack of properly conducted clinical trials. Problems included failure to mention pretreatment trials of spinal opioids; lack of data on pretreatment psychological or functional assessment; no standardized methods of assessing pain, pain relief, or functional performance; and lack of control groups or randomization. Because of these flaws, the only possible conclusions from the review were superficial generalizations. Approximately one-third of patients apparently get good long-term pain relief without complications or side effects. Many patients require the addition of local anesthetics, and some never get effective relief.

Contraindications

Under some circumstances, intraspinal opioid analgesia should probably be avoided. These include (a) inexperience in performing lumbar puncture or epidural block, particularly in the cervical or thoracic regions; (b) inadequate nursing education or monitoring capabilities; (c) patient rejection; (d) known opioid allergies; and (e) systemic or local infection at the site of needle insertion. It is not certain whether these techniques can be used safely in patients with coagulopathies or while receiving anticoagulant therapy. Decisions should be made case by case after consideration of the relative risks and benefits for individual patients as well as the risks and benefits of alternative therapy.

Techniques

Patient Selection

Patients suffering from painful medical conditions, cancer, or trauma or undergoing a variety of surgical procedures may benefit from the superior analgesia possible with intraspinal opioids. This is particularly true in situations in which uncontrolled pain may compromise pulmonary function, leading to atelectasis and pneumonia. Examples include patients with rib fractures or pain resulting from upper abdominal or thoracic incisions. In patients receiving regional anesthesia for surgery, it is easy to offer intraspinal opioids for postoperative pain. For example, a single dose of morphine may be added to the local anesthetic solution chosen for subarachnoid injection before transurethral prostatectomy. Alternatively, an opioid may be injected repeatedly or infused continuously into a catheter that was placed in the epidural

space to provide anesthesia for patients undergoing a wide variety of surgical procedures (e.g., gastrectomy, hip surgery, thoracotomy). If general anesthesia was used for surgery, an epidural catheter may be placed any time in the postoperative period should pain control by conventional methods prove inadequate. It appears to be easier to establish good pain control immediately after surgery with these methods than to treat severe pain once it is established (63).

Intraspinal opioids should be considered in patients with cancer pain when oral or parenteral analgesics (including opioids) are ineffective or when they cause distressing side effects that cannot be adequately controlled. With the introduction of intraspinal opioids, elimination or marked reduction in the dose of systemic opioids may be possible. Reductions should be made gradually to avoid symptoms of opioid withdrawal.

Needle and Catheter Placement

Subarachnoid. Lumbar puncture is usually performed at the second or third lumbar interspace using techniques described in Chapter 102, but it can be done at other levels by those experienced with the techniques. For a single injection of opioid, a small needle (25- or 26-gauge) will minimize the risk of post–lumbar puncture headache. When it is necessary to provide analgesia for extended periods, an epidural catheter may be threaded into the subarachnoid space through an epidural needle. The catheter is then secured to the skin at its exit site and is used for bolus injections or continuous infusion of opioid. Alternately, it may be tunneled subcutaneously to exit ventrally, where it is less likely to become dislodged and where it is more accessible to the patient. There it may be injected intermittently or attached subcutaneously to a reservoir or infusion device that can be refilled as necessary with transdermal injections.

Epidural. Opioids may be introduced into the epidural space through the sacral hiatus (caudal approach) or in the lumbar, thoracic, or cervical regions using techniques described in Chapter 102. When the site of injection is close to the desired site of action, it may be possible to produce satisfactory analgesia with lower doses of opioid. If a mixture containing a local anesthetic is used, the site of catheter placement is critically important. The local anesthetic must be delivered in proximity to the spinal nerves that conduct the nociceptive impulses. For example, to effectively block chest wall pain with an epidural local anesthetic after a thoracotomy, the catheter should be placed in the thoracic region with its tip near the center of the involved dermatomes.

As with intrathecal opioids, a single injection may be used through a needle placed in the epidural space. For use expected to last a few days (e.g., after surgery), an epidural catheter is advanced through the needle and secured to the skin at its point of exit. For extended use over several weeks or months, an epidural or special Silastic catheter may be tunneled subcutaneously to a convenient location on the anterior abdominal wall. There, as with spinal catheters, it may be injected intermittently or attached subcutaneously to a reservoir or infusion pump that is refilled through the skin using a syringe and small-gauge needle.

In the cervical, thoracic, or high lumbar regions, the spinal cord is near the tip of a correctly placed spinal or epidural needle. To minimize the risk of spinal cord injury, needle and catheter placement in these areas are most safely accomplished in patients who are awake and able to report paresthesias or severe pain indicative of impending spinal cord damage. Epidural needle or catheter placement in the thoracic or cervical regions should be performed only by experts in regional anesthetic techniques.

Micropore filters are used on intrathecal and epidural catheters by some practitioners. These filters may reduce the risk of contamination by pathogenic organisms and prevent injection of foreign material such as glass particles. Even when filters were not used in surgical patients, infections have not proved to be a frequent problem. Aspiration of epidural catheters to check for intravenous or subarachnoid migration is made more difficult with some models of filters in place. Needles with filters in their hubs can be used to remove particulate matter (e.g., glass) while drawing up opioid solutions for injection or infusion. Patients receiving intraspinal opioids in a hospital setting require intravenous access to facilitate immediate treatment of side effects or complications. The use of double filters may help to reduce infection rates.

Patient-Controlled Epidural Analgesia

There is currently considerable interest in combining the potent analgesic effects of drugs delivered into the epidural space with the advantages of patient participation associated with the patient-controlled analgesia (PCA) concept (64,65,66,67,68,69,70 and 71). These studies compared the effectiveness of several epidural opioids administered on demand. It was found that the self-administered dose of morphine required to provide analgesia was significantly less than amounts required by continuous epidural infusion or by intravenous PCA. Sjöström et al. (72) reported the use of morphine via patient-controlled epidural analgesia (PCEA) (bolus: 1 mg; lockout: 30 minutes) averaged 0.5 mg per hour. Walmsley et al. (73) reported effective and safe PCEA morphine in more than 4,000 postoperative patients using a 2- to 3-mg loading dose, bolus dose of 0.2 mg, lockout of 10 to 15 minutes, and continuous infusion of 0.4 mg per hour. The maximum hourly dose was limited to 1.2 mg. PCEA fentanyl has been widely used (69,71,74,75 and 76). PCEA sufentanil (74,77,78 and 79) and alfentanil (80) have also been reported. Hydromorphone is a popular PCEA opioid with some therapists (81,82 and 83). PCEA hydromorphone requirements after cesarean section were four- to fivefold less than in patients receiving intravenous PCA hydromorphone (81). Additional observations included more rapid return of bowel function and shorter hospital stay.

Although PCEA appears to have great future potential, there has been little systematic comparison of different drugs and dosing regimens. There appear to be almost as many formulae as there are publications on the subject, and many of the clinical reports to date relate to use of the technique in obstetric patients. Considerable further research will be needed to establish criteria for patient selection, optimal drugs or drug mixtures, and PCA pump settings. Table 103-4 includes a few of the many recommended protocols. Dose schedules are generally those recommended for use through lumbar epidural catheters. They should be reduced when a thoracic epidural catheter is used.

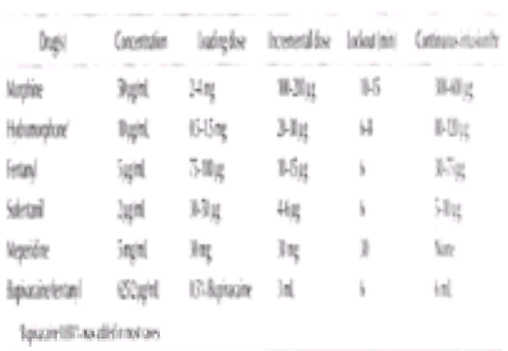

TABLE 103-4. Sample protocols for using patient-controlled epidural analgesia

Choice of Opioids

Table 103-5 lists a number of intraspinal opioids, suggested dose ranges, expected latency, and duration of analgesia. Doses necessary to produce analgesia and their duration of effect will vary considerably from one patient to another depending on age, medical condition, site of injection, type of pain, and other factors. The recommended doses are therefore only guidelines. Frequent assessment of adequacy of pain relief for each patient with changes in dose or frequency of injection as necessary is therefore the logical approach. The interested reader will find much more information is available on the subject of choosing epidural opioids (84).

Bioactic drug	Single dose (mg)[a]	Onset (min)	Duration of single dose (hr)[a]	Infusion rate (mg/hr)[a]
Epidural				
Morphine	1–6	30	6–24	0.1–1.0
Meperidine	20–50	5	4–8	5–10
Methadone	5–10	10	6–10	0.5–1.5
Hydromorphone	1–2	15	6–16	0.1–0.2
Diamorphine	2–6	5	12	–
Fentanyl	0.025–0.100	5	1–4	0.025–0.150
Sufentanil	0.01–0.05	5	1–4	0.006–0.01
Alfentanil	0.5–1	15	1–2	0.2
Subarachnoid				
Morphine	0.1–0.3	15	8–24+	–
Meperidine	10–20	–	15–24+	–
Diamorphine	1–2	–	20	–
Fentanyl	0.005–0.025	5	3–6	–

[a] Some doses may be effective in older patients or when injected in the thoracic or cervical regions.
[b] Duration of analgesia is often relatively longer than dose-to-recover duration.
[c] Use for the opioid alone or in combination with a local anesthetic.

TABLE 103-5. Suggested dose ranges, latency, and duration of analgesia with intraspinal opioids

Elderly patients in particular may require remarkably small intraspinal opioid doses. In reviewing experience treating women after abdominal hysterectomy, a significant negative correlation was found between age and effective 24-hour dose of epidural morphine (85). The relationship can be expressed by the following equation: Effective 24-hour epidural morphine dose (mg) = 18 – (age in years × 0.15). Based on this and similar additional observations, a list of suggested initial doses of epidural morphine for incisional pain in a variety of clinical situations is provided (Table 103-6).

Patient age (yr)	Nonthoracic surgery (lumbar or caudal catheter)	Thoracic surgery	
		Thoracic catheter	Lumbar catheter
15–44	4	4	5
45–65	3	3	4
66–75	2	2	3
76+	1	1	2

[a] These doses should be considered only as guidelines. Safe and effective doses for individual patients may vary considerably. Patients with opioid tolerance may require higher doses. These doses are based on the use of undiluted 0.1% preservative-free morphine.

TABLE 103-6. Initial dose (mg) of epidural morphine for acute pain [a]

Morphine is the most widely used opioid for both spinal and epidural injection. It is available in some countries specifically for intraspinal analgesia as a preservative-free isobaric solution in single-use ampoules. Standard commercial preparations have been used in a wide range of concentrations with no apparent difference in efficacy or safety. Although most early experience with morphine involved intermittent injection, it has also been used with success as a continuous infusion with a variety of external pumps or implanted devices.

A lipophilic agent such as fentanyl is useful when rapid onset of epidural analgesia is important. Its short duration, a drawback for most applications, can be offset by the use of a 50- to 100-µg epidural bolus followed by a continuous infusion (25 to 150 µg per hour) with an infusion pump. Although epidural fentanyl is widely used, questions remain regarding the primary mechanism by which analgesia is provided. There are now a number of convincing studies that show that equivalent analgesia is obtained with either epidural or intravenous fentanyl infusions (86,87,88,89 and 90). Furthermore, plasma fentanyl levels by either route are the same. Such findings are not surprising. Because fentanyl is lipid soluble, it passes rapidly and in large quantities from the epidural space into the epidural venous plexus. As with other opioids, opioid-related side effects, including respiratory depression, can occur with fentanyl.

Many other opioids have be used to produce intraspinal analgesia. These include meperidine (68,91,92 and 93), methadone (94), sufentanil (95,96,97 and 98), alfentanil (98,99 and 100), buprenorphine (101,102 and 103), and tramadol (104,105 and 106).

Regional Analgesia with Opioid/Local Anesthetic Mixtures

Although continuous infusions of local anesthetics in the usual commercial concentrations produce effective analgesia, they also produce undesirable, effects including hypotension, sensory and motor block, nausea, and urinary retention. To a lesser degree, these problems persist with combinations of dilute local anesthetics and opioids infused continuously (Table 103-7). Nociceptive pathways are interrupted at different sites with the two drugs—namely, at the level of the nerve axon with the local anesthetic and at the spinal opioid receptor with the opioid. Bupivacaine has been well suited to this application because it produces less motor block than other local anesthetics. Even so, motor function in many patients is impaired (Fig. 103-1). Early experience suggests that ropivacaine, a new local anesthetic, may spare motor nerves even more, thus preserving function better. It remains unclear whether the combination of epidural opioids and local anesthetics is superior to opioids alone.

Function blocked	Possible problem
Sympathetic	Hypotension (thoracic > lumbar)
Proprioception	Difficulty ambulating
Sensory	Pressure injury
	Mask a complication
Motor	Loss of function (cough, ambulation)

TABLE 103-7. Possible problems with epidural local anesthetic techniques

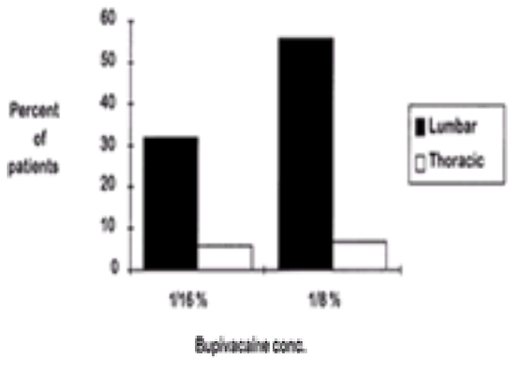

Figure 103-1. Motor block impairment of ambulation with epidural local anesthetic infusions. (conc., concentration.)

In addition to the monitoring used for patients receiving only epidural opioids, frequent measurement of blood pressure as well as sensory and motor examination is recommended. Dilute concentrations of local anesthetics produce considerable sensory and motor blockade in some patients. A 0.125% bupivacaine infusion through a lumbar catheter will render approximately 60% of patients unable to ambulate. The number drops to approximately 30% of patients if 0.0625% is used. This problem occurs in only 6% to 7% of patients if a thoracic catheter is used with either bupivacaine concentration (see Fig. 103-1).

Other Agents with Intraspinal Analgesic Properties

A number of other agents have been administered via the intrathecal or epidural route to produce pain relief. Clonidine is the only one of these currently approved for clinical use.

a_2-Adrenergic Agonists. Epidural clonidine, an a_2-adrenergic agonist, given alone or in combination with a local anesthetic, has pain-relieving properties (97,107,108 and 109). Its strongest indication to date has been in the treatment of neuropathic pain unresponsive to other measures, especially in patients with cancer (109). Side effects include sedation (110), hemodynamic instability (111), and rebound hypertension and acute withdrawal when therapy is abruptly interrupted (112). Future generations of a_2-adrenergic agonists with more selective actions may prove more useful than clonidine.

Ketamine. Epidural ketamine has been reported by a number of authors for treatment of postoperative pain (113,114,115,116 and 117). It has been used to provide labor analgesia (118) and has been found to benefit patients with reflex sympathetic dystrophy (119). Dysphoria associated with its use has been noted, and caution has been recommended until its safety (especially a lack of neurotoxic effects in humans) is established (117).

Neostigmine. In a report by Hood et al. (120), it was noted that intrathecal neostigmine produces dose-dependent analgesia, nausea, weakness, and diminished deep tendon reflexes in healthy volunteers, all of which resolve in 6 to 12 hours.

Intrathecal neostigmine provided analgesia after cesarean section (121,122) and was further evaluated after perineal surgery in women (123). In that study, 50 to 100 µg of intrathecal neostigmine produced analgesia for vaginoplasty surgery similar in duration to 50 to 100 µg of intrathecal morphine. It was noted that the combination of intrathecal morphine and neostigmine may allow reduction in the dose of each component. Lauretti et al. (124) found maximal analgesia after surgery may occur at doses of less than 25 µg intrathecally. After abdominal surgery an intrathecal dose of 100 µg caused severe nausea and vomiting (125). Antiemetics were not effective.

Amitriptyline. In sheep, a 5-mg intrathecal dose of amitriptyline produced antinociception. There was no behavioral evidence of neurotoxicity. Heart rate, blood pressure, cardiac output, spinal cord blood flow, and CSF catecholamines remained normal (126). Whether or not there is a clinical future for intrathecal amitriptyline remains to be determined.

Monitoring of Patients Receiving Intraspinal Opioids

Monitoring the Effects of Opioids. Until it is possible to identify and eliminate the factors that occasionally lead to severe respiratory depression in patients receiving intraspinal opioid analgesia, it must be assumed that all patients offered these techniques are at risk. Table 103-8 lists factors believed to be associated with increased risk of respiratory depression.

1. Age older than 50
2. American Society of Anesthesiology physical status III, IV, or V
3. Surgical site (thorax or upper abdomen)
4. Duration of surgery of more than 4 hr
5. Anesthetic (opioids or other long-acting central nervous system depressants used before or during surgery)
6. Epidural morphine dose (6 mg or more)
Subarachnoid morphine dose (0.5 mg or more)
[a]These are only suspected risk factors. Others may apply to individual patients.

TABLE 103-8. Predictors of patients at risk for intraspinal opioid- induced respiratory depression [a]

To prevent serious injury or death, there is no substitute for a high level of vigilance. This may be provided by nurses who check rate and depth of respiration, level of consciousness, and the general status of patients at regular intervals. Respiratory monitors that sound an alarm if ventilation is not detected may augment this process, but these devices are not necessary in most circumstances and should not be viewed as substitutes for alert, well-trained human observers.

Intensive care facilities are well suited to the monitoring needs of higher-risk patients (e.g., advanced age, serious underlying medical conditions, extensive surgery). However, the expense and limited availability of these facilities render them impractical for routine use. Some practitioners advocate “step-down units,” intermediate between intensive care and a regular ward with regard to the level of monitoring and nursing care available. It has been shown that with appropriate nursing education, appropriate patient selection, regular evaluation of ventilation, protocols for immediate treatment of complications, and immediate availability of medical personnel, intraspinal analgesia can safely be offered on conventional hospital wards (7). A set of preprinted “standard orders” used throughout an institution can facilitate maintaining a high standard of care. A sample of such a set of orders is found in Table 103-9. Such documents must be individualized to meet the unique needs of each institution. Delegation of all responsibility for pain control to one group of physicians within an institution can minimize errors of conflicting or duplicated orders or inadvertent administration of parenteral opioids to patients receiving intraspinal opioids.

TABLE 103-9. Sample of intraspinal opioid (and local anesthetic) preprinted orders

Monitoring the Effects of Local Anesthetics. Intraspinal local anesthetics, alone or in combination with opioids, may produce undesirable effects. When local anesthetics are administered, analgesia occurs as a result of their effects on the axonal membranes of nerves carrying nociceptive impulses. Further details on the actions of local anesthetics are provided in Chapter 102. No currently available local anesthetic at any single concentration is selective enough to block only nerves conducting nociceptive impulses. Other nerve fibers (sympathetic, sensory, proprioceptive, and motor) may also be affected. Table 103-7 summarizes the clinical consequences of blockade of these nerve fibers. Local anesthetic systemic toxicity is also possible.

Monitoring for the possible undesirable effects of local anesthetic is essential. This begins with appropriate education, especially including of bedside nurses. With a clear understanding of the actions and side effects of local anesthetics, appropriate nursing protocols and procedures can be developed. These include measures for anticipation, early recognition, and treatment of hypotension, sensory block, and motor block. In the case of patients receiving a mixture of a local anesthetic and opioid, monitoring protocols for both components of the mixture must be used.

Results

Throughout this chapter, repeated reference has been made to the results associated with using intraspinal analgesic techniques. In this section, selected additional information on the subject is provided. Studying outcomes is a complex task. This is true in part because results are a function not only of the therapy provided but also of the knowledge, expertise, and dedication of the therapists. Furthermore, when a group of reports on a subject is examined, it is not unusual to find that the study designs were inconsistent, and not surprisingly, findings were commonly contradictory. The body of literature on the subject of intraspinal analgesia outcomes is huge, and many excellent individual studies have been conducted. Some of these individually have changed our understanding. In general, the most meaningful outcome information is obtained through a systematic process of examination of the published literature (e.g., metaanalysis). As a part of the task of developing clinical practice guidelines, several such extensive works have been undertaken (28,127,128 and 129). In the case of perioperative pain, Kehlet has provided an outstanding review of current outcome data (39). Table 103-10 summarizes the most salient clinical results. It should be noted that the benefits seen may relate to intraspinal opioid, local anesthetic, or both in combination.

Parameter	Result of intraspinal analgesia
Mortality	Limited reduction after acute surgery for hip fracture
Blood loss	Reduced approximately 30% during operations in the lower part of the body
Thromboembolic complications	Favorable effects on pathogenic mechanisms and clinically important reduction in these complications
Pulmonary infective complications	Insufficient data to allow conclusions
Cardiac complications	Positive effects on hemodynamics; insufficient data to allow conclusions regarding cardiac outcome parameters
Cerebral complications	No favorable influences
Gastrointestinal function	Epidural opioids: little or no benefit Epidural local anesthetics: improve intestinal motility
Convalescence, fatigue, and hospital stay	Intraspinal analgesia alone does not alter these parameters Based on preliminary data, when combined with stress reduction, early oral nutrition, and early mobilization, improvements are likely to be seen

*Based on a review of controlled studies by Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. In: Cousins MJ, Bridenbaugh PO, eds. Neural Blockade. Philadelphia: Lippincott-Raven, 1998:1291–1304.

TABLE 103-10. Effects of intraspinal anesthesia/analgesia on the perioperative morbidity [a]

It is reasonable to expect that improved outcomes resulting from use of intraspinal analgesia should result in a reduction in health care consumption and less cost. In the case of perioperative pain, many studies conclude this is true (39,130,131,132,133,134,135,136,137 and 138). But unless improved relief of pain is combined with a more comprehensive approach to accelerated recovery (39), these gains are not likely to be impressive.

Complications

Respiratory Depression

The real incidence of respiratory depression is not known. It is dependent on a number of factors, including the population studied, monitoring practices, and the definition of respiratory depression used by investigators. In a large, multiinstitutional Swedish questionnaire survey, the incidence of “depression requiring naloxone” was 0.25% to 0.40% (139). In one prospective postoperative study of 1,085 postoperative patients in a single institution, the incidence of respiratory depression based on respiratory rate was 0.9% (35). In another prospective study of 1,100 postoperative patients from a single institution, the incidence was 0.2% based on the administration of naloxone (7).

Early respiratory depression occurring in the first 2 hours after opioid injection is a feature only of epidural opioid administration and is a result of vascular uptake and redistribution (i.e., the same mechanism that follows intramuscular injection). Delayed respiratory depression is likely the consequence of rostral spread of opioid in CSF. The target site is thought to be the respiratory center, located superficially in the floor of the fourth ventricle. The risk of severe delayed respiratory depression after intraspinal morphine appears to be greatest 6 to 12 hours after beginning therapy. Risk factors appear to include large intraspinal opioid doses, advanced age, concomitant use of systemic opioids or other central nervous system depressants, high-risk surgical patients, and extensive surgery (see Table 103-8). A history of obstructive sleep apnea also may be associated with increased risk (140).

It is not known whether the risk of severe respiratory depression is greater after intraspinal opioids than after opioid administration by more conventional routes. It has been reported that in 860 hospitalized patients receiving conservative doses of morphine orally or systemically, 0.9% developed “life-threatening respiratory depression” (141).

Respiratory rate alone is not an adequate indicator of ventilatory status in volunteers (142) or in postoperative patients (7,143) receiving epidural opioids. A more global assessment is necessary, particularly during the first 24 hours of treatment. This should include assessment of level of consciousness, because increasing sedation (presumably due to carbon dioxide narcosis) has commonly been noted with advanced respiratory depression (38,144). Healthy volunteers breathing carbon dioxide mixtures have been noted to lose consciousness at arterial carbon dioxide tension levels of approximately 80 mm Hg (145). Table 103-11 illustrates a bedside sedation scale that can be used by nurses to recognize deterioration in level of consciousness in patients receiving intraspinal opioids. Every patient receiving intraspinal opioids whose level of consciousness deteriorates unexpectedly should be assumed to have respiratory depression until disproved by arterial blood gas analysis.

Sedation level	Description
0 None	Patient alert
1 Mild	Occasionally drowsy; easily aroused
2 Moderate	Frequently drowsy; easily aroused
3 Severe	Somnolent: difficult to arouse
5 None	Normal sleep; easily aroused

TABLE 103-11. Bedside sedation scale for evaluation of respiratory depression

The immediate treatment of severe respiratory depression is support of ventilation. Equipment to deliver oxygen with positive pressure must be readily available and personnel in the area must be familiar with its use. Naloxone titrated in small doses (0.1 mg) intravenously will usually restore adequate spontaneous ventilation, but repeated doses are sometimes necessary. Stimulating the patient to breathe by verbal and mechanical means will help prevent apnea until the naloxone can be administered.

Pruritus

Pruritus is common and sometimes distressing to patients. The itching may be generalized or localized, with the face being the most common site. Pruritus is seen both with opioids containing preservatives and preservative-free preparations. Although probably not due to histamine release, antihistamines often provide symptomatic relief. Diphenhydramine, 12.5 to 25.0 mg, is a common prescription for this purpose. Nalbuphine in doses of 2.5 to 5.0 mg intravenously is also effective and does not cause the sedation commonly seen with an antihistamine. Naloxone is also often effective but it may need to be administered frequently or given as a continuous infusion, thus adding complexity and cost to therapy. The mechanism of action by which pruritus occurs is not known with certainty.

Urinary Retention

The incidence of urinary retention has been higher in volunteers than in patients and higher in males than females. Naloxone may help prevent or reverse urinary retention, but doses approaching those that antagonize analgesia may be needed. Some patients will require bladder catheterization. In many patients receiving intraspinal opioids, urinary retention is not an issue because bladder catheters are maintained postoperatively for unrelated reasons.

Nausea and Vomiting

These distressing symptoms are believed to be the result of rostral spread of opioid in CSF to the vomiting center and the chemoreceptor trigger zone, located superficially in the floor of the fourth ventricle. The symptoms usually subside with continuation of therapy, so they are rarely a problem in cancer patients receiving long-term therapy. Relief is frequently possible with antiemetics, but these agents may produce unwanted sedation and even contribute to the risk of respiratory depression (146). Transdermal scopolamine patches applied to the mastoid area and designed to deliver 0.5 mg per day are remarkably effective in reducing the incidence and severity of nausea and vomiting in patients receiving epidural morphine (147,148).

Sedation

When a patient receiving intraspinal opioids appears excessively sedated, hypercarbia should be suspected and, if present, treated. The possible contributing role of other drugs that depress the central nervous system, such as anxiolytics, sedatives, and antiemetics, should also be considered.

Sedation produced by intraspinal opioids may be the result of spread of the drug in CSF to receptors in the thalamus, limbic system, or cortex. Pharmacologic treatment is seldom indicated but physostigmine, 1 mg intravenously, may be effective (149). Delirium after surgery is common, especially among older patients (150). This condition can occur for many reasons, yet it is very commonly attributed to analgesic techniques, including intraspinal opioids. It is possible that postoperative pain itself is a contributing etiologic factor (151).

Myoclonus

Occasional patients receiving high doses of intraspinal opioids develop myoclonus. Such dose requirements are usually seen in patients with cancer pain who have developed tolerance. The interested reader is referred to a review of myoclonus (49).

Neurologic Changes

Temporary. As discussed earlier in this chapter, administration of intraspinal local anesthetic solutions can produce unwanted changes involving blockade of sympathetic, sensory, proprioceptive, or motor nerves. Table 103-7 summarizes the clinical implications of these events. An issue of special concern is the possibility of dense sensory blockade masking or delaying diagnosis and treatment of a serious postsurgical complication. An example of such a complication is postoperative compartment syndrome in the lower extremity. The task of the pain therapist is to use an analgesic technique that achieves goals for comfort and function while preserving the ability to identify this complication. The best available information suggests that this can be done (152,153). Other complications that are typically recognized as a result of the pain they produce include deep vein thrombosis, pulmonary embolus, bowel obstruction, peritonitis, and myocardial infarction.

Irreversible. Serious and irreversible neurologic complications are rare events, but when they occur, they can be devastating both to patients and to their therapists. Of greatest concern in this regard is the development of neuraxial hematomas (154,155), abscesses (156,157 and 158), or direct injury to the spinal cord or nerve roots from needle or catheter placement (13). A discussion of these topics is beyond the scope of this chapter.

Technical Problems

A variety of technical problems commonly occur when large numbers of patients are treated with intraspinal analgesics. Examples include nonfunctioning epidural catheters, premature catheter dislodgment, one-sided analgesia, catheter-connector separation, technical problems with infusion pumps, and migration of epidural catheters to intravenous or subarachnoid locations. Each institution should systematically examine the frequency of such problems. With a continuous quality improvement program, the incidence of these and many other problems can be reduced.

CONCLUSIONS

Intraspinal opioids represent a powerful tool for controlling pain. The selective manner in which nociception is blocked provides unique advantages over other methods of producing analgesia. Because the potential exists for serious complications, a high level of vigilance must accompany their use. Although it is not known whether the risks accompanying the use of intraspinal opioids exceed those associated with more traditional methods of controlling severe pain, concern about possible complications has been the major factor limiting widespread acceptance of intraspinal opioid analgesia into clinical practice. Well-organized institutional approaches to the use of these techniques can facilitate effective and safe therapy.

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CHAPTER 104

Neurolytic Blockade and Hypophysectomy

Stephen H. Butler and J. Edmond Charlton

This chapter consists of two sections that have been revised from the previous edition: an updated review of neurolytic blockade and a truncated review of hypophysectomy, which is waning in popularity as a first-line treatment for cancer pain. The same is also true of neurolytic blockade, which in the past was a primary treatment for many types of cancer pain. It was also used somewhat indiscriminately for many chronic pain problems of nonmalignant origin. More sophisticated use of continuous spinal drug infusions, better application of systemic drugs, and more effective anticancer therapies have altered the role of neurolysis in the approach to treating cancer pain. For chronic noncancer pain, more sophisticated approaches and the appreciation of the potential side effects as well as limited duration of relief of pain have relegated neurolysis to a very minor position in the treatment paradigm. At the University of Washington, it is little used in our patient population for chronic pain of noncancerous origin.

Neurolysis implies the destruction of neurons by placing a needle close to the nerve(s) and either injecting neurodestructive chemicals or producing neural damage with cold (cryotherapy) or heat (radiofrequency coagulation). The injected chemicals are usually ethyl alcohol, phenol, or glycerol, although in the past ammonium salts and chlorocresol were also common. New studies have looked at high concentrations of local anesthetics, primarily lidocaine (1) and butamben, as kinder and gentler therapies that may prove to have wider application for chronic, noncancer pain.

Since specific nerve block techniques are discussed in detail in Chapter 102, comment on technique is restricted to modifications necessary to produce optimum results with the specific agents.

BASIC INFORMATION

History

Neurolytic blockade was widely used during the first six decades of the twentieth century (2). The specificity theory of pain was popular, and it indicated that destruction of peripheral nerves or pain pathways would lead to lasting relief of intractable pain of any origin. Other than pharmacologic therapy, which was not very sophisticated, the only option besides neurolytic blockade, especially for cancer patients, was neuroablative surgery. Many patients were not considered fit enough to tolerate the combined stress of anesthesia and surgery. Opioid use was limited because of concerns for side effects, tolerance, and addiction, which were considered even a greater deterrent to appropriate use then than they are now.

There appears to be a renewed interest in neurolytic techniques, judging by the number of texts released lately (3,4), as the more recent technical approaches to pain relief are seen more realistically now than through the rose-colored glasses so common with any new therapy. Perhaps we are also somewhat more critical of our results as outcome studies show we have not always done as well with cancer pain as many believed. The newer neurolytic agents may also broaden the indications for neurolysis as the initial studies hint that side effects are more benign. Certainly, in regions where neurosurgical skills are not widespread, where the health care system cannot afford newer expensive technologies, or where medications are not available to utilize the World Health Organization ladder, neurolytic procedures have much greater importance and should be used, especially in patients with pain due to cancer. Neuroablation, by any means, should be thought of as only part of the pain therapy, not as a curative modality, since most studies show that it is rare for patients not to need pharmacologic or other support after a neurolytic procedure for pain.

Theoretical Bases

Alcohol

Ethyl alcohol is the classic neurolytic agent and has been used extensively in concentrations from 33% to 100% (2). It was first described by Schlosser (5) in the early 1900s, and he studied and wrote on its effects on peripheral nerves. Attempts have been made to limit the effects to the sensory system by using lesser concentrations of ethanol. There have been reports of a differential block with good pain relief using 33% ethanol that spares motor nerves.

The effects of ethanol on various parts of the nervous system have been described, but there are no pathologic studies on the differential effects on axons. The cellular and subcellular changes accounting for alcohol's nervous system effects are in general those secondary to high concentrations of ethanol.

Ethanol has a neurodestructive effect on somatic nerves, leading to wallerian degeneration, which usually spares the basal lamina around the Schwann cell tube. This permits regeneration that accounts for the return of function and pain some weeks to months after a block. The mechanism of degeneration is through the extraction of cholesterol, phospholipids, and cerebrosides and precipitation of lipoproteins and mucoproteins. Topical ethanol on peripheral nerves therefore damages both the axons and Schwann cells with disruption of the myelin sheath. There is destruction and absorption of all components of the nerve except the neurolemma. *In vivo* electrophysiologic studies in cats following alcohol deposit on peripheral nerves showed depression of compound action potentials at 8 weeks. This effect was slightly more marked using 100% alcohol than with 50% (6,7 and 8).

Clinical studies by Labat and Greene in the 1930s (9) looking at varying concentrations of ethanol concluded that 33% was the minimal concentration to produce pain relief and was accompanied by little motor effect. Long-term follow-up was not recorded, so we do not know whether duration of effect or side effects vary with concentration.

The effects on the sympathic nervous system are somewhat different. If the ganglia are affected, changes are permanent, since the cell bodies are destroyed and regeneration is not possible. However, ganglia cells are somewhat more resistant than nerve fibers and total destruction does not always occur, accounting for the gradual return of function (and pain) over time after neurolytic ganglion block. The rami communicantes suffer the same fate as somatic nerves, however, producing a temporary block. Regeneration is present at 90 days and is complete at 170 days. Retrograde changes in the cell bodies can occur as well, so with this block, recovery is variable. Blockade of preganglionic and postganglionic fibers does not affect the ganglia, and these fibers react to alcohol as do somatic nerves (10). With subarachnoid injection, effects are seen in the roots, rootlets, Lissauer's tract, and posterior columns. Wallerian degeneration can involve not only the roots and rootlets, but also the dorsal horn. There may also be local inflammatory change of the meninges (11). Alcohol is removed rapidly from the subarachnoid space, with only 10% present at 10 minutes (12).

Phenol

Phenol for neurolytic blockade has a shorter history than ethanol (13). Phenol's neurolytic properties were first described by Doppler in 1925; he and others subsequently used phenol for sympathetic neurolysis around vascular and visceral structures (14). It was not used specifically for pain until the 1950s, when it was proposed for subarachnoid use in pain and spasticity (1). The early 1960s saw its use expanded to peripheral nerve blocks, and it has been used extensively since. As with alcohol, attempts have been made to limit the neurolytic effects to C, A-d, and A-g fibers for optimum effects on pain and spasticity (15). Concentrations below 1% produce local anesthesia without toxicity; concentrations from 1% to 7% cause indiscriminate damage to afferent and efferent nerve fibers.

On peripheral nerves, phenol has an axonotmetic effect that is maximal with a concentration of 12% (16). Evaluation by light and electron microscopy shows variable degeneration in all nerve fibers from extraneural or intraneural application. There is protein coagulation and necrosis with axonal and wallerian degeneration. Electrophysiologic studies show a concentration-related depression of compound action potentials at 2 weeks. At 4 weeks, regeneration has begun but, unlike alcohol, phenol damages the neural tube and thus the regeneration is nonspecific since there is no predetermined path for the regenerating axon to follow (17).

Animal studies on the effects on the sympathetic nervous system again show differences from ethanol. There is complete necrosis of the sympathetic ganglia at 24 hours, with degeneration complete at 45 days and evidence of regeneration at 75 days, a much more rapid recovery than with alcohol. This is compatible with the clinical observations.

The most complete clinical information on phenol is on its action in the subarachnoid space, since this was the major clinical use initially (18). The data on neural effects *in vivo* and/or *in vitro* are limited. It was originally thought to have a differential effect on various nerve fibers, but animal work showed this not to be the case, other than a trend with low concentrations below 3%, not a clinically useful solution. The primary subarachnoid effect seems to be on the nerve rootlets and perivascular nerves. The effects are seen on both anterior and posterior roots with accompanying arachnoiditis, vascular thrombosis, and even spinal cord infarct (19).

Finally, there are a few pathophysiologic findings to bear in mind when weighing different agents for clinical use. Information has been available for some time showing the vascular effects of phenol. It can denature the protein in vascular structures as well as nervous structures, which may explain some of the catastrophic complications seen with spinal cord infarction in many applications. Phenol has little effect on Gore-Tex artificial vessels, but it does destroy Dacron grafts (20). Alcohol, more than phenol, causes vascular spasm, another potential cause of spinal cord infarction (21). As a final note, intravascular phenol can cause arrhythmias and cardiac arrest by an unknown mechanism (22). Seizures after intravascular injection have also been reported. These effects must be considered when deciding on the use of specific agents near the neuraxis or in large doses.

Glycerol

Håkanson's report (23) of the efficacy of glycerol injected into the trigeminal ganglion for the treatment of trigeminal neuralgia without producing significant sensory deficits led to its widespread use in the treatment of this condition (24,25) and to further histologic and electrophysiologic studies. Topical application of 50% glycerol solution on the nerve produces localized subperineurial damage but, following intraneural injection, glycerol is more damaging than topical application (26). Histologic changes include the presence of numerous inflammatory cells, extensive myelin swelling, and axonolysis (27).

Myelin disintegration occurs weeks after the injection, along with concomitant axonolysis during periods of myelin restitution, indicating an ongoing nerve fiber injury possibly caused by secondary events such as compression of transperineurial vessels and ischemia. Electron microscopic studies have revealed evidence of wallerian degeneration and, with intraneural injection, almost all nerve fibers are destroyed (27). Lipid droplets are seen in Schwann and phagocytic cells, and mast cell degranulation occurs. Burchiel and Russell (28) carried out studies on rat saphenous nerve and found differential effects of glycerol on the electrophysiologic function of the nerve. At this time, however, histologic data to support these observations are lacking.

Ammonium Compounds

In 1931, Judovich prepared an aqueous solution derived from a pitcher plant distillate (*Sarracenia purpurea*) and found that it relieved the pain of neuralgia without producing changes in skin sensation and deleterious effects on motor nerves (29). This selective action on the pain was of much longer duration than with procaine. Subsequent laboratory investigations revealed that the ammonium ion, in the form of ammonium chloride or ammonium hydroxide (depending on the pH of the distillate), was the active component. Using the unsophisticated technology available at that time, Judovich and Bates found that ammonium salts eliminated C fiber potential, with only a small effect on A fibers. In 1942, Bates and Judovich (30) reported 5,000 administrations of ammonium salts (in a 6% concentration) by paravertebral injection or local infiltration, with highly favorable results. Bonica (2) reported on extensive clinical trials that yielded disappointing results: The drug was found to lack uniformity of action, and it produced pain relief in a small percentage of cases and in an unpredictable manner. Similar results were reported by F. A. D. Alexander (*personal communication,* 1951), one of Bonica's peers and an authority on neural blockade. We have not used these compounds at the University of Washington Pain Center. A study of intrafascicular injection of ammonium sulfate in rats showed no pathologic effects (31), which may account for Bonica's impressions.

Cryotherapy

It has long been known that cooling causes a reversible conduction block in nerves. In 1945, Denny-Brown and colleagues (32) reported on the pathology of nerves subjected to cold and noted the sensitivity of A-d and C fibers to damage. Subsequent studies have revealed that a prolonged axonal potential results when nerve fibers are cooled to 5°C (27). Early cytopathologic studies revealed abnormalities of Schwann cells and endoneurial capillaries that were attributed to accelerated enzyme production, which affected Schwann cell metabolism (27). More recent studies have shown that freezing results in the formation of ice crystals and causes necrosis of all tissue elements, including nerves (33). Freezing produces a longer-lasting clinical deficit and has become a method of neurolysis of intercostal nerves following thoracotomy for relief of postthoracotomy pain.

The technique is based on the freezing of a small nerve segment with a 2-mm-diameter cryoprobe cooled to approximately –60°C by the rapid expansion of pressurized nitrous oxide from its tip. When the cryoprobe is left in contact with the nerve for 60 seconds, a 2- to 4-mm-diameter ice ball forms, freezes the nerve, and completely damages the nerve fibers (34). This initially produces severe vascular injury and edema, with diapedesis of polymorphonuclear cells through vessel walls (27). The endoneurial fluid pressure (EFP) is elevated within 90 minutes of the lesion and rises to a level of approximately 20 cm H_2O, or twice that observed in edematous neuropathies developing more slowly. In the ensuing 24 hours, the EFP is reduced, presumably due to changes in the elastic characteristics of the perineurium (27). The EFP then increases again to reach a plateau at 6 days that is associated with wallerian degeneration of the distal fibers, a prominent pathologic feature that affects the entire nerve. Although freezing causes complete damage to the nerve, the basal lamina is fortunately spared and provides a conduit for nerve fiber regeneration. Thus, freezing causes an acute and severe injury to all nerve fibers that persists for about 1 month, after which regeneration occurs; this is aided by the presence of Schwann cell basal lamina, which makes the complete and appropriate reinnervation of distal structures possible (27).

Laser and Radiofrequency Lesions

Heating of peripheral nerves with ultrasonic energy produces three levels of nerve conduction effects: enhancement, reversible depression, and irreversible depression, with the latter characterized by a functional deficit that lasts longer than 18 hours (35). With such lesions the axis cylinder is fragmented but the perineurium is unaffected. Lasers have been used to heat peripheral nerves more precisely: The energy produced by the laser heats the nerve directly without affecting the surrounding tissue, and the output of the laser can be controlled in regard to both magnitude and duration. Laser irradiation of peripheral nerves produces localized lesions characterized histologically by a concentric zone of coagulation necrosis surrounded by persistent nerve edema (36). The perineurium is not damaged, but the resulting edema increases the EFP. Sections of laser-injured nerves show discrete endoneurial lesions characterized by greatly swollen axons packed with organelles; these changes are characteristic of the axonal dystrophy that occurs during acute wallerian degeneration (27). Because laser injury produces wallerian degeneration and can be finely controlled and focused, it should prove to be useful as a neurolytic technique, provided direct visual access to the nerve is possible. Radiofrequency lesions also produce coagulation of the nerve (see Part V, Section G).

Conclusions

Neurolytic agents in the form of alcohol, phenol, and glycerol injected around or into a nerve produce pathophysiologic changes of varying degree, depending on the concentration of the agent that comes in direct contact with the nerve tissue. These agents, applied to the surface of the nerve or nerve rootlets (in the subarachnoid space), alter perineurial permeability with damage to axons or occasionally to nerve cells. Intraneural injection of these agents produces severe nerve damage,

consisting of significant axonal abnormality and wallerian degeneration. Techniques that physically damage the nerve with cold (via the cryoprobe) or with heat (via a laser or radiofrequency) produce similar results. It has been shown that a differential block of only A-d and C fibers, without affecting larger fibers and with good pain relief still being obtained, is usually not possible. Although variations in concentration produce different clinical findings, suggesting a dose-related response, the nerve needs to be damaged sufficiently to produce wallerian degeneration to achieve desirable long-lasting pain relief. The persistence of basal lamina around the Schwann cell tube allows the successful and appropriate regeneration of nerve fibers, thus eliminating the formation of painful neuroma. This is in contrast to surgical section of a nerve, which invariably results in neuroma formation. Complete and permanent transection of a nerve can only be accomplished with surgical resection; however, a painful neuroma may result.

CLINICAL INFORMATION

Block of Cranial Nerves

Indications

From 1900 to 1960, block of the gasserian ganglion or of branches of the trigeminal nerve with alcohol or other neurolytic agents was widely used for the treatment of trigeminal neuralgia, severe intractable cancer pain, and a few other chronic pain syndromes. Block of the facial nerve with a local anesthetic or alcohol has been used for the treatment of facial spasm. Block of the glossopharyngeal and vagus nerve with a local anesthetic has been used as a diagnostic or prognostic procedure in patients with neuralgia or cancer pain in the distribution of these nerves. Even block of the spinal accessory nerve has been used to treat spasm of the trapezius muscle.

The advent of the use of anticonvulsant drugs, of the highly successful microvascular decompression operation, and of controlled thermogangliolysis has superseded the use of neurolytic blocks for the relief of the pain of trigeminal neuralgia. The use of thermogangliolysis and other more sophisticated neurosurgical procedures has also reduced the use of neurolytic block in the treatment of cancer pain.

Nevertheless, neurolytic block of the gasserian ganglion or of one of the major branches of the trigeminal nerve is a potential treatment for severe intractable facial pain caused by cancer or neuralgia and other types of severe chronic pain when sophisticated neurosurgical techniques are unavailable.

Although block of branches of the trigeminal nerve or of the glossopharyngeal and vagus nerves with local anesthetic is not used widely, these procedures can be effective in patients who have severe acute postoperative or posttraumatic pain or pain caused by other self-limiting conditions. As mentioned below, block of the nerve as well as of the gasserian ganglion with local anesthetic should be done prior to the injection of a neurolytic agent or destruction of the nerve.

Optimal results with these procedures require adherence to the requirements and preliminary considerations discussed in Chapter 102. One of the most important is a thorough knowledge of the anatomy of the target nerve, of adjacent structures with which the solution might come in contact, and of structures traversed by the needle. The anatomy of the cranial nerves is discussed in detail in Chapter 46, Chapter 47, Chapter 48, Chapter 49, Chapter 50, Chapter 51, Chapter 52 and Chapter 53.

The physician must also follow the principles of the technique noted in Chapter 102 and should be aware of contraindications. When carrying out these procedures, it is essential to have fluoroscopic control of needle placement and to determine the pattern of diffusion of the contrast medium injected prior to or with injection of the neurolytic agent.

Based on his extensive experience in carrying out these procedures, Bonica believed it essential to carry out two or three diagnostic or prognostic blocks with a long-lasting local anesthetic to determine whether the neurolytic blockade can provide complete pain relief. Moreover, a local anesthetic block provides the patient with an opportunity to evaluate the degree of pain relief as well as to experience the sensory anesthesia that follows alcohol or phenol injection.

Because neurolytic agents diffuse to a much lesser extent than local anesthetics, prognostic blocks require that the volume of local anesthetic be the same as or less than the volume of neurolytic agent to be used. For example, neurolytic block of the gasserian ganglion with 1 mL of alcohol should be preceded by two prognostic blocks with 0.75 to 1.00 mL of bupivacaine, done at intervals of 1 day or longer between the blocks and before the neurolytic block.

The face and head have special meaning for most people. Because having a needle inserted into these structures invariably causes a great degree of anxiety, and because the procedures do produce moderate discomfort, it is best to administer an anxiolytic drug and/or a short-acting opioid just before the procedure.

Techniques

Gasserian Ganglion Block. The anatomy of the trigeminal nerve is depicted in Figure. 104-1, and that of the gasserian ganglion is shown in Figure. 104-2. Figure. 104-3 depicts the common sites of blocking the trigeminal nerve and its branches. Block of the gasserian ganglion is achieved by various intraoral, oral, or extraoral routes, but the best and most commonly used technique is that originally described by Härtel (37,38) (Fig. 104-4).

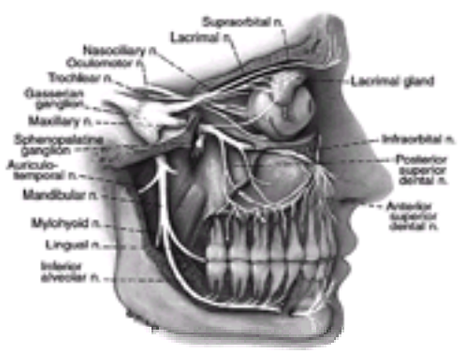

Figure 104-1. Anatomy of the trigeminal nerve. The root of the trigeminal is short, extending from the ventrolateral surface of the pons to the apex of the petrous portion of the temporal bone, where it expands into the gasserian ganglion. The crescent-shaped gasserian ganglion lies lateral to the internal carotid artery and cavernous sinus and occupies Meckel's cave, located just posteromedial to the foramen ovale. The ophthalmic nerve passes through the superior orbital fissure to reach the orbit. The maxillary nerve passes through the foramen rotundum and leaves the cranial cavity to reach the pterygopalatine fossa, where this nerve can be blocked. The mandibular nerve is formed by the union of a large sensory root and a smaller motor root that arises from the pons and passes beneath the gasserian ganglion to reach the foramen ovale, through which, together with the sensory root, it leaves the cranial cavity.

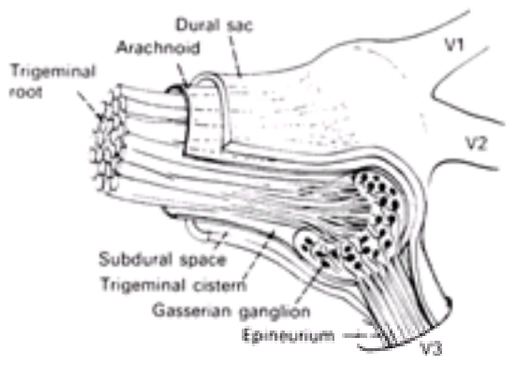

Figure 104-2. Gasserian ganglion, which contains cell bodies that have pseudounipolar axons. These break up into central branches that constitute the sensory root

of the trigeminal nerve and into peripheral branches that comprise the three major nerves. The ganglion is canoe shaped, with the three peripheral branches of the nerve attached to its anterior convex aspect. The roots emerge from the concave side of the ganglion to compose the triangular portion of the root. A variable number of anastomoses exist between the group bundle in this triangular portion, which is just behind the ganglion. The dural-arachnoidal envelope surrounding the ganglion is an evagination of the dura from the posterior cranial fossa to a position under the dura mater of the middle fossa. The dural-arachnoidal pouch behind the ganglion constitutes the trigeminal cistern, which normally contains cerebrospinal fluid that communicates with the infratentorial bases of the cisterns through the trigeminal porus. The anterior convex surface of the ganglion is adherent to the dural-arachnoidal covering and, as the latter passes distally, it becomes the epineurium of the mandibular, maxillary, and ophthalmic nerves. Also note the relationship of the subdural and arachnoid spaces. (Modified from Ferner H. The anatomy of the trigeminal root and the gasserian ganglion and their relations to the cerebral meninges. In: Hassler R, Walker AE, eds. *Trigeminal neuralgia.* Stuttgart, Germany: Georg Thieme Verlag, 1970.)

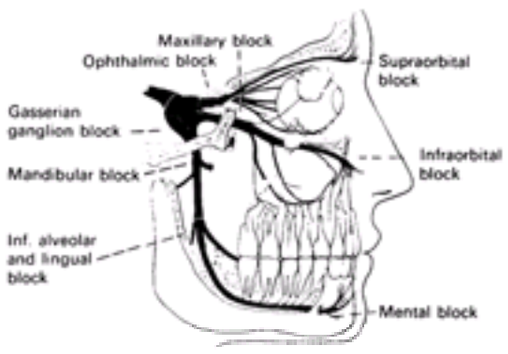

Figure 104-3. Various sites (*stippled areas*) at which the gasserian ganglion, the three major nerves, and their most important branches can be blocked.

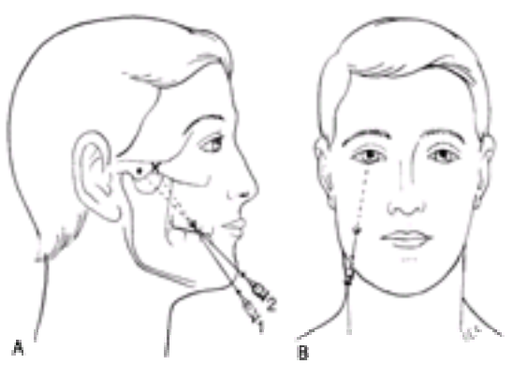

Figure 104-4. Technique of injection of the gasserian ganglion or of the mandibular nerve by the anterolateral (Härtel) approach. **A:** A skin wheal is made 3 cm lateral to the angle of the mouth at the level of the upper second molar. A 10-cm, 22-gauge needle (1) threaded with a depth marker is introduced through the wheal and advanced posteromedially and superiorly so that, when viewed from the side, its axis points to the midpoint of the zygomatic arch (*X*). **B:** When viewed from the front, the axis of the needle points to the pupil. A guiding finger of the other hand is placed in the oral cavity to ensure that the needle does not enter the mouth, which could introduce contaminating bacteria into deeper structures. As the needle advances, it passes through the buccinator muscle, beneath the mucous membrane between the mandibular ramus and tuberosity of the maxilla, and finally through the external pterygoid muscle before it contacts the infratemporal plate lateral to the base of the pterygoid process and just anterior to the foramen ovale, at a depth of 6.0 to 7.5 cm. The depth marker is placed 1.25 cm from the skin surface, and the needle is withdrawn until its point is subcutaneous. The needle is then reinserted (2) so that the axis of the needle, when viewed from the side, points to the articular tubercle (•) and, when viewed from the front, it still points to the pupil. When the needle has been advanced to a depth just 1 cm short of the rubber marker, its point usually contacts the mandibular nerve, causing paresthesia along its course. The needle is further advanced until the marker is flush with the skin.

The following anatomic points are useful in introducing the needle from the point of insertion in the skin to the foramen ovale:

- The foramen is an elliptic canal 5 mm long, with an axis that has an inferior and slightly anterolateral direction. Its greater diameter averages 8 mm, and its smaller diameter is 4 mm.
- It is situated immediately posterior to the smooth hard infratemporal surface of the greater wing of the sphenoid bone. The center of this plate, which serves as an important landmark, is approximately 4 cm medial to the midpoint of the zygomatic arch in the same frontal plane.
- The foramen is approximately 4 cm medial to the articular tubercle of the zygomatic arch in exactly the same frontal plane.

It is best to insert the needle with the patient in the supine position to avoid any orthostatic hypotension that might occur as a result of apprehension by the patient. For the injection of alcohol, the patient can remain in this position but, during the injection of phenol or glycerol, the patient should be in the sitting position to keep the agent in Meckel's cave. Usually a 10-cm, 22-gauge needle threaded with a depth marker is used for this procedure. Aspiration should be attempted with a 2-mL Luer-Lok syringe to ensure that the needle point is not in a blood vessel or the subarachnoid space. It is best to guide the placement of the needle by radiographic control (Fig. 104-5). Aliquots of 0.1 mL of alcohol, 5% phenol, or glycerol should be injected. After each injection, detailed sensory testing is done and the patient is questioned about the extent of analgesia and numbness to determine the effects of each aliquot. A total of 0.50 to 0.75 mL is injected, depending on the needs and responses of the patient.

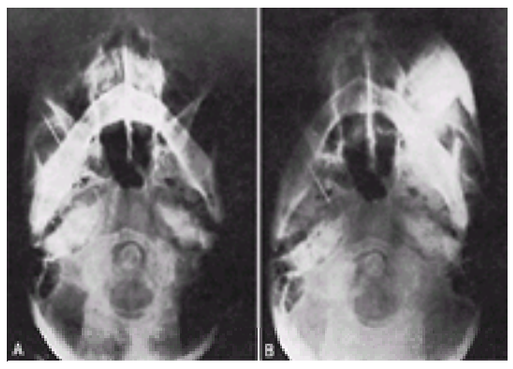

Figure 104-5. Radiographic visualization of gasserian ganglion block. **A:** The point of the needle is entering the foramen ovale. **B:** The needle has passed through the foramen and rests over the trigeminal depression of the petrous portion of the temporal bone. After B was taken, absolute alcohol, in 0.1-mL aliquots, for a total of 0.5 mL, produced analgesia of the second and third divisions.

Modifications. During the 1960s and 1970s, several refinements of blocking the gasserian ganglion or the sensory root were done to decrease the risk of serious complications. These included modifications of blocking with alcohol and the introduction of phenol in glycerin and of glycerol for gasserian ganglion block. The most

important of these are briefly described.

ALCOHOL. Ecker and Perl (39) developed a technique using radiographic control to position the needle. The patient is supine with the head extended so that the needle is inserted in a direction perpendicular to the floor. The needle is advanced through the center of the foramen ovale so that its tip lies on the target, exactly 4 mm beyond the posteromedial border of the foramen ovale and 2 mm above the base of the skull, at the petrosphenoid junction. The injected alcohol enters the ganglionic sinus where the juxtaganglionic rootlets are arrayed as in the peripheral division and where they are thinnest, most widely spread, and least intertwined. With the patient in this position, the mandibular fibers are the highest so that the alcohol, injected in tiny increments, rises to affect them and usually spares corneal sensation. Ecker and Perl (39) injected the alcohol in 0.05-mL aliquots and then tested sensation in the painful area. Additional aliquots were injected until the desired effects were obtained, usually with 0.2 to 0.3 mL of absolute alcohol. Delfino (40) modified Ecker's technique using an image intensifier to locate the exact center of the foramen ovale: 0.2 mL of 2% lidocaine solution as a prognostic block 30 minutes before injecting the ethyl alcohol in 0.05-mL aliquots, up to a total of no more than 0.2 mL.

PHENOL. Putnam and Hampton in 1936 (41) were the first to report on the use of the injection of phenol into the gasserian ganglion under roentgenographic control for the treatment of trigeminal neuralgia, but they published no follow-up of their preliminary report. In 1963, Jefferson (42) reported on the use of 5% phenol in glycerin for the treatment of trigeminal neuralgia and for postherpetic pain and cancer pain. The technique entailed inserting the needle into the foramen ovale under radiographic control, getting spinal fluid about half the time, and sitting the patient up with the head flexed forward on the chest so that the needle points vertically upward. Jefferson (42) then injected increments of 0.05 to 0.10 mL of phenol in glycerin until the desired results were achieved and then kept the patient upright for 20 to 30 minutes.

GLYCEROL. The technique for injecting glycerol into the trigeminal cistern, as advocated by Håkanson (43), is similar to that shown in Figure 104-4 and Figure 104-5. The notable difference is that the needle is inserted while the patient is in the sitting position and the dura-arachnoid is intentionally penetrated so that there is spontaneous flow of cerebrospinal fluid (CSF). Håkanson (42) has emphasized that, if spontaneous CSF drainage through the needle does not occur, the needle is not in the proper position and it is necessary to reposition it or to use the first needle as a guide and insert a second needle into its proper place. Once the needle is considered to be in the correct place and the CSF fluid has drained, 1 mL of contrast is injected slowly in 0.2-mL increments using a 1-mL tuberculin syringe and its diffusion is visualized by fluoroscopy. To fill the cistern completely, 2 mL of contrast is injected with the patient's chin against the chest. If the point of the needle is in the proper position, the contrast medium is seen to fill the cistern and to escape into the posterior fossa through the trigeminal porus.

Lateral and anteroposterior radiographs are then taken to show the pattern of diffusion of the contrast medium and to define the outline of the cistern. After the correct position of the needle tip has been verified, the contrast is evacuated from the trigeminal cistern by removing the syringe from the needle and placing the patient in a recumbent position for approximately 5 minutes. A total of 0.2 to 0.4 mL of pure sterile glycerol is then injected slowly. Because the size and shape of the trigeminal cistern are highly variable, it is necessary to vary the total volume of glycerol injected. To affect all three divisions, one must fill the cistern entirely, using 0.3 to 0.4 mL of glycerol with the patient's head in a ventrally flexed position (Fig. 104-6). For relief of neuralgia in the third division or in the second and third divisions, 0.20 to 0.35 mL of glycerol is injected. Because the specific gravity of glycerol is 1.242 (compared to that of CSF, which is 1.0065 to 1.007), with the patient's head in the flexed position, the glycerol remains in the inferolateral portion of the trigeminal cistern, which contains the rootlets of the mandibular and maxillary nerves (see Fig. 104-6A). Because the specific gravity of some contrast is even heavier than that of glycerol (1.329 versus 1.242), leaving a small amount of contrast in the bottom of the cistern protects the rootlets of the third branch in patients who have trigeminal neuralgia in the first and second divisions (see Fig. 104-6B).

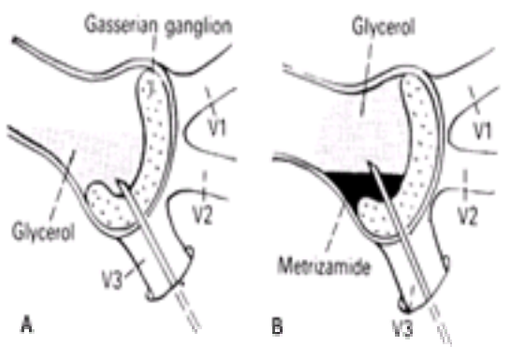

Figure 104-6. Håkanson's technique of injecting the sensory root of the trigeminal nerve with glycerol. **A:** After drainage of the cerebrospinal fluid and subsequent injection of metrizamide (see text), pure sterile glycerol is injected in 0.1-mL aliquots for a total of 0.4 mL if all three divisions are to be affected. By adjusting the volume of injected glycerol, it is possible to affect the different trigeminal divisions selectively. Because of the density of glycerol, it remains in the bottom of the cistern and a smaller volume (0.2 mL) therefore affects only the third division, while a larger volume also involves the second division. **B:** For the treatment of first- and second-division neuralgia, the rootlets of the third division can be spared by leaving a small amount of metrizamide, which is heavier than glycerol, in the bottom of the cistern. The amount of metrizamide left in the cistern is controlled before the glycerol is injected. (Modified from Häkanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. *Neurosurgery* 1981;9:638–646.)

Results: Neuralgia

Ethyl Alcohol. In one of the largest series on the use of ethyl alcohol for trigeminal neuralgia, Harris (44) treated a total of 1,433 patients. Of 457 patients followed for 3 years or longer, 360 (78%) had no recurrence of pain; unfortunately, the incidence of keratitis or of anesthesia dolorosa was not reported. The results obtained by others using ethyl alcohol, phenol, and glycerol are shown in Table 104-1 Most of these reports, however, lack specific data on the incidence of complications.

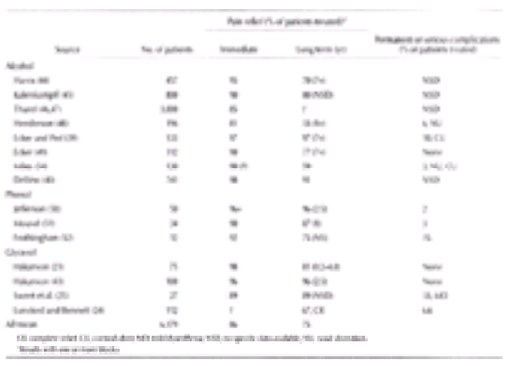

TABLE 104-1. Results of therapy with neurolytic gasserian ganglion block for the pain of trigeminal neuralgia

Bonica (2) has described the use of the Härtel technique of gasserian alcohol block with ethyl alcohol in 28 patients. He described a technique of blocking only the second and third divisions within the ganglion in four other patients who had had injections of the nerves outside the skull and had recurrence of pain. The 32 patients received 39 injections. Of those in this group, 28 patients (88%) had good relief following the injection, but the pain recurred in 17 patients (53%) during the follow-up period, which ranged from 14 months to 8 years or until the death of the patient. Of the 28 patients who had complete trigeminal analgesia, four (14%) developed keratitis (despite meticulous ophthalmologic care), one developed anesthesia dolorosa, and one sustained paresis of other cranial nerves from an accidental subarachnoid injection of the alcohol. This was the most serious complication he encountered during his extensive experience with neurolytic blocks. These complications and the advent of more refined and specific neurosurgical operations caused Bonica to discontinue the use of gasserian ganglion block with alcohol for

the treatment of trigeminal neuralgia in the 1950s.

Modern radiologic technology using the image intensifier, the advent of newer and safer contrast media, and the use of glycerol, together with skillful administration, make gasserian ganglion block easier and safer than it was two decades ago (Table 104-2; see Table 104-1). Notwithstanding the better results obtained with neurolytic blocks, patients with the pain of trigeminal neuralgia not relieved by drug therapy today should be managed with microvascular decompression or gangliolysis as discussed in Chapter 107.

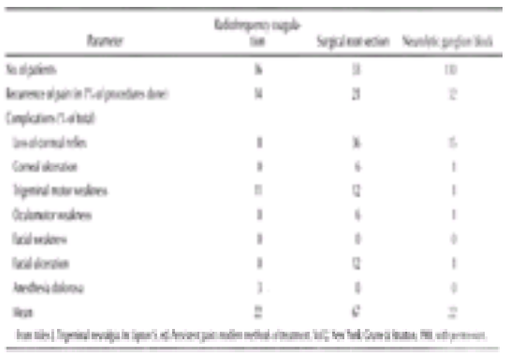

TABLE 104-2. Comparison of results of treatment of the pain of trigeminal neuralgia

Results: Cancer Pain

In contrast to its use in a trigeminal neuralgia patient with a long life expectancy, alcohol block remains a useful procedure for those with severe intractable pain in the anterior two-thirds of the face caused by advanced or terminal cancer. Radiofrequency gangliolysis is also useful for such patients. Prior to selection of the optimal method, it is essential to determine the type of cancer, the predicted rate and direction of spread, the condition of the patient, and the availability of a physician skilled in block techniques. If the neoplasm is slow growing and involves structures in the second or third division, or in both, block of the nerves is preferable to avoid keratitis. If the neoplasm could spread to affect the first division, or if it is difficult to block the second division because the tumor occupies the pterygopalatine fossa, it is better to carry out gasserian ganglion block at the outset. This should produce a widespread field of analgesia into which the cancer can spread without producing subsequent pain. Although this technique carries the risk of corneal anesthesia and possibly keratitis, the problem is different than when dealing with a patient with trigeminal neuralgia in whom life expectancy is long and in whom corneal ulcer would be a serious complication. In a patient with advanced or terminal cancer, effective relief of excruciating pain is considered to be worth the risk of these complications.

Obtaining radiographs prior to block is useful and necessary to ascertain that the foramen ovale has not been invaded, which could make proper positioning of the needle difficult. In patients with carcinoma of the nasopharynx and floor of the mouth, the tumor can destroy bone structures of the base of the skull and make it impossible to identify the foramen ovale. In such cases a different approach for the block must be adopted or a different procedure must be used. Because alcohol diffuses poorly in tissues, the point of the needle must be in the precise position. Another important step is to carry out block with a local anesthetic to predict the efficacy of the neurolytic agent before it is injected.

Between 1945 and 1977, Bonica used gasserian ganglion block with absolute alcohol in 107 patients (2). Of these, 79 patients (74%) obtained effective pain relief and, together with small or moderate doses of sedatives, codeine, or adjuvant drugs, they were made comfortable until their death, 2 weeks to 7 months later. Another 16 patients (15%) obtained only partial relief with the first injection and required either a second injection of the ganglion (nine patients) or a supplementary injection of one of the major nerves (nine patients), together with modest doses of drugs. The procedure produced little or no relief in the remaining 12 patients, and they were managed with opioids. Similar results were reported by Madrid at the First International Symposium on Cancer Pain in 1979 (53).

Complications. Most of the complications that occur with neurolytic block of the gasserian ganglion block have been mentioned. Some complications and unwanted side effects are avoidable, and some are not. Unavoidable side effects that are usually transient and not serious include Horner's syndrome from block of the paratrigeminal sympathetic fibers, and involvement of the motor root, with transient weakness of the muscles of mastication. If the entire ganglion is affected by the neurolytic agent, several problems can occur. Corneal anesthesia, with consequent loss of corneal reflex and possibly paralytic keratitis, loss of sensation on the ipsilateral side of the face and half of the tongue, paresthesia, herpetic eruptions, trophic ulcerations, and anesthesia dolorosa can and do develop. The incidence, degree, and duration of these complications from neurolytic blockade vary depending on the completeness of the destruction of nerve cells.

With injection of a larger amount (more than 1 mL) of neurolytic substance, these complications are likely to occur more frequently and to last longer. Miles (54) confirmed this when comparing the effects of neurolytic ganglion injection with those of surgical root section and radiofrequency coagulation in one center where each procedure was carried out by highly skilled personnel (see Table 104-2). The data suggest that the use of neurolytic ganglion block results in fewer complications than surgical root section, but they also show that the incidence of the recurrence of the neuralgia is greater with neurolytic ganglion block (32% versus 21%). Techniques of gasserian ganglion block that spare the cell bodies or rootlets of the first division, such as those used by Håkanson (43), Ecker and Perl (39), and Jefferson (42), are not followed by corneal ulceration or anesthesia dolorosa. Accidental subarachnoid injection of alcohol is likely to involve other cranial nerves and is probably the most serious complication of this technique. Its incidence can be minimized by repeated attempts at aspiration prior to injection of each aliquot.

Block of the Ophthalmic, Maxillary, and Mandibular Nerves Indications. Block of the maxillary or mandibular nerve, or both, remains useful for the relief of severe tic douloureux or of cancer-related pain affecting one or both of these nerves if neuroablative procedures cannot be carried out. For patients with trigeminal neuralgia, it is essential to use prognostic blocks with local anesthetics to determine which branch needs to be blocked, especially in those who have trigger areas in one branch and pain distribution in another branch. If touching the upper lip causes pain in the lower jaw, for example, it is likely that the second division needs to be blocked instead of the third division. Occasionally, however, both nerves need to be blocked.

NEURALGIA. In their classic textbook (55), White and Sweet listed six uses for injection of the major branches of the trigeminal nerve in patients with trigeminal neuralgia

- To provide prompt pain relief so that patients weakened by poor fluid intake might be strengthened preparatory to an operation for permanent relief.
- To enable those likely to die soon to live out their lives pain-free and without major surgery.
- To aid in the differential diagnosis of patients whose pain has characteristics transitional between those of trigeminal neuralgia and other forms of facial neuralgia.
- To relieve pain on the second side of the face when bilateral neuralgia has developed so as to avoid complete, lasting anesthesia on both sides of the face.
- To relieve pain by the use of alcohol block in the distribution of branches of the first division without involving the eye, to avoid the corneal anesthesia produced by rhizotomy of the ophthalmic nerve.
- To help patients adjust to the dysesthesia that might follow posterior rhizotomy.

The advent of anticonvulsant drugs has virtually eliminated the first two indications. Block with a local anesthetic remains useful to help in the diagnosis of patients with neuralgia with confusing symptoms and to obviate the need for bilateral rhizotomy in patients with bilateral neuralgia. White and Sweet (55) stated that neurolytic block should be used prior to trigeminal rhizotomy to give a clear and sustained (but reversible) indication of the sensory changes that accompany denervation to help patients decide whether they prefer temporizing drugs or surgery to produce lasting anesthesia and consequent permanent relief.

CANCER PAIN. Block of the maxillary or mandibular nerve, or both, with neurolytic agents remains useful in managing patients with severe and intractable cancer-related pain, especially if experienced neurosurgeons are not available and if life expectancy is shorter than 3 months. Cancer of the nasal cavity and paranasal structures is predominantly adenocarcinoma, which is highly malignant and all too often is inoperable when first seen. Eventually this cancer produces severe symptoms, including nasal obstruction, nasal discharge, epistaxis, and intractable pain, which is usually diffuse, dull, and aching and is frequently referred to the face. The pain can be relieved satisfactorily by blocking the maxillary nerve with alcohol. If the pterygopalatine fossa is invaded and block of the second division is

impossible, gasserian ganglion block must be carried out.

Cancer of the lower jaw, particularly Ewing's sarcoma and osteogenic sarcoma, often produces severe intractable pain. The ulcerating type of carcinoma of the lower gingiva and floor of the mouth that has resulted in extensive invasion of the mandible or overlying skin, or both, also produces intense pain. In many of these cases the pain becomes progressively more intense and is often accompanied by trismus and otalgia, all of which prevent patients from eating and sleeping, thus enhancing cachexia. Because many of these patients are in poor physical condition, alcohol block of the mandibular nerve alone or in combination with block of C-2 and C-3 is indicated. Alcohol block of the lingual nerve should be considered in those with severe pain caused by cancer of the tongue, especially if the pain involves both sides, thus obviating bilateral masticatory paralysis, which usually follows bilateral mandibular nerve block. Inferior alveolar nerve block should also be considered for patients with severe pain caused by cancer of the mandible.

In 1951, Bonica (56) analyzed the results of neurolytic blocks. These were included in the first edition of this book (2). A total of 76 patients were studied; they had undergone 102 neurolytic blocks of the maxillary or mandibular nerve or a combination of these of one of their branches. Of these, 53 patients (69%) had complete or almost complete relief of pain, 14 (19%) had partial relief of pain, and the remaining nine (12%) had no relief; there were no deaths in this group. Progressively fewer of these procedures have been done at the University of Washington Pain Center, for three major reasons: (a) Many of these patients are managed by former trainees of the Pain Fellowship Program and by other anesthesiologists practicing in other hospitals; (b) the Pain Center has become involved predominantly in the management of patients with complex, nonmalignant, chronic pain problems; and (c) more aggressive management by otolaryngology is being used. These techniques remain important tools, however, especially in those hospitals in which sophisticated neurosurgical techniques are not available and in medical centers in developing countries. Properly done, they provide much-needed relief to patients with cancer pain.

OTHER INDICATIONS. Block of the mandibular or maxillary nerve, or of both, with long-lasting local anesthetic (e.g., 0.5% bupivacaine) can be used in patients who experience excruciating pain postoperatively or postinjury. The block usually lasts 8 to 12 hours and can be repeated one, two, or even three times to tide patients over. Obviously, patients with posttraumatic pain can have distortion of the bones of the face, making the classic lateral extraoral route difficult or impossible. In such cases, the orbital (Matas) route is used.

Retrobulbar Block. Retrobulbar block, with varying concentrations of alcohol for the relief of severe persistent eye pain, has been used in the first half of the twentieth century. In 1918, Grüter (57) reported the injection of 3 mL of 80% to 90% ethyl alcohol as an alternative to the enucleation of blind painful eyes. In 1930, Weekers (58) first described the use of a dilute solution of alcohol in those with “seeing eyes” (i.e., patients who had vision) to relieve severe persistent eye pain consequent to corneal ulcers, keratitis, uveitis, and glaucoma. Since then many ophthalmologists have used alcohol block for the relief of pain in both types of patients, as well as for the control of photophobia and blepharospasm following corneal surgery and penetrating keratoplasty. The duration of pain relief varies but usually is 3 to 6 months and even longer, although pain can return sooner if the underlying pathologic process remains uncontrolled.

In 1949, Maumenee (59) published a report summarizing this technique, the results obtained by Grüter from the time he first described the technique to 1943, and those of others up to 1949. Maumenee also described the technique of injection of 95% alcohol in 41 eyes with less than 10/200 vision (“blind eyes”) and in 15 patients whose visual acuity ranged from 10/200 to 20/20 (“seeing eyes”). Of the patients with “blind eyes,” 68% had glaucoma and the remainder (32%) had corneal ulcers, keratitis, uveitis, and keratoplasty. Those with “seeing eyes” had various forms of infectious keratitis, including herpes zoster, uveitis, glaucoma secondary to uveitis, and epidemic keratoconjunctivitis. No patients in the latter group had reduction of visual acuity after the injection of alcohol and, in all of these patients, vision improved with therapy of the underlying condition. Histologic studies of the optic nerves of 15 eyes that had been removed after alcohol injection showed no evidence of damage to the nerve from the alcohol. It was concluded that the optic nerve is apparently protected from the effects of alcohol by the thick sheath that surrounds it (59). Newer ophthalmologic treatments have reduced the indications for this procedure.

Techniques. The anatomy of the ophthalmic, maxillary, and mandibular nerves is described in detail in Chapter 47, Chapter 48, Chapter 49, Chapter 50, Chapter 51, Chapter 52 and Chapter 53. Figure. 104-7 illustrates various techniques of blocking the branches of the ophthalmic nerve, and Figure. 104-8 shows the technique of retrobulbar alcohol block. Figure. 104-9 depicts procedures for blocking the maxillary nerve by the lateral and anterolateral extraoral routes. Figure. 104-10 shows the technique of maxillary nerve block by the orbital (Matas) route, which is used if the lateral technique cannot be carried out because of a tumor in the path of the needle. Figure. 104-11 shows mandibular nerve block by the lateral extraoral route, which is the most frequently used technique for injection of this nerve.

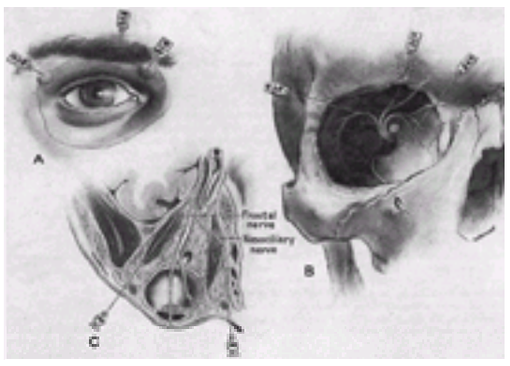

Figure 104-7. Block of the branches of the ophthalmic nerve. **A,B:** Anterior views showing, from left to right, lateral orbital block, supraorbital block, and medial orbital block. **C:** Schematic cross section of the orbit with the nerves left intact to show the techniques of lateral and medial orbital block. To block all the branches within the orbit, the lateral superior route is used. A 5-cm, 25-gauge needle is introduced through a wheal made just above the lateral canthus and advanced posterolaterally until contact is made with the bone of the lateral wall of the orbit. With its bevel flush with the bone, the needle is then advanced posteromedially toward the apex of the orbit, keeping constant contact with the bone. At a depth of 3.5 cm, the point of the needle usually loses contact with the bone, being situated at the lateral portion of the superior orbital fissure. It is then advanced another 3 to 5 mm, aspiration is attempted, and if no blood or cerebrospinal fluid is obtained, 2 to 3 mL of local anesthetic is slowly injected. To block the supraorbital nerve as it curves around the supraorbital ridge, a 1.5-cm, 30-gauge needle adapted to a 2-mL syringe, which contains a local anesthetic, or to a 1-mL tuberculin syringe, which contains alcohol, is held like a dart and thrust through the skin of the upper lid in a direction perpendicular to it. The supraorbital foramen, or notch through which the nerve passes, is easily palpable through the skin of the upper lid by retracting the eyebrow upward at a point 2.5 cm from the midline. The needle is advanced slowly until paresthesia is elicited or bone is contacted. For neurolytic block, it is essential to contact the nerve, and several reinsertions may be necessary to locate it so that the neurolytic agent can be deposited intraneurally. To block the nasociliary nerve or its branches, a 5-cm, 25-gauge needle is inserted through a wheal 1 cm above the inner canthus and directed posterolaterally, always keeping contact with bone. At a depth of 2 cm, the point of the needle should be at the anterior ethmoidal foramen, and 1.5 to 2.0 mL of local anesthetic solution is then injected. This blocks the anterior ethmoidal nerve, which eventually becomes the internal and external nasal branches. The needle is then advanced 1 cm further to reach the posterior ethmoidal foramen, where 1.5 to 2.0 mL of solution is injected to block the posterior ethmoidal nerve that supplies the ethmoidal cells and the sphenoid cavity. These two injections are also likely to block the infratrochlear nerve, which supplies the conjunctiva, lacrimal sac, inner canthus, and root of the nose.

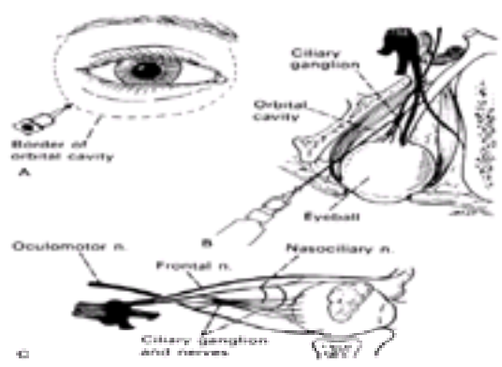

Figure 104-8. Technique of retrobulbar alcohol block. **A:** Following appropriate preparation of the field, the needle, adapted to a 5-mL syringe containing 1% or 2% lidocaine, is inserted into the lateral third of the lower eyelid just above the rim of the orbit. **B,C:** The needle is advanced and passed through Tenon's capsule (the thin membrane that envelops the eyeball), between the lateral rectus and inferior rectus muscles, into the muscle cone. The needle should be advanced until its tip is

just behind the globe. Aspiration is attempted to ensure that the bevel of the needle is not in a blood vessel; if negative, 2 mL of lidocaine is injected. The syringe is then removed, leaving the needle in place. After 15 to 20 minutes, a 2-mL Luer-Lok syringe containing either 50% alcohol (for patients with vision) or absolute alcohol (for patients with no vision) is adapted. An attempt at aspiration is again made to ensure that the needle has not entered a blood vessel, and the alcohol is injected slowly.

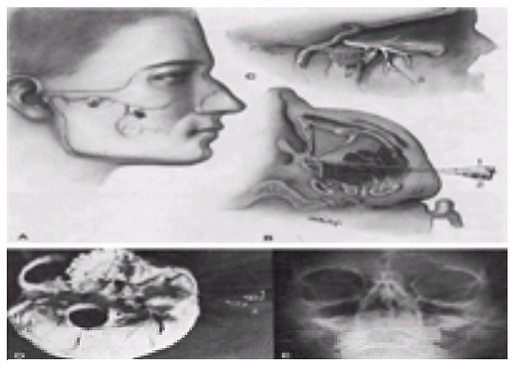

Figure 104-9. Technique of maxillary nerve block. **A:** Needles in place for the lateral and anterolateral routes. For the lateral route, a wheal is raised below the sigmoid notch of the zygomatic arch, and an 8-cm, 22-gauge needle threaded with a depth marker is introduced through it perpendicular to the skin and slowly advanced until the point strikes the lateral pterygoid plate at a depth of about 4 cm (**B:** 1). The marker is then set 1 cm from the skin, the needle is withdrawn until its point is subcutaneous, and it is readvanced in a slightly anterior and superior direction so that its point is 1 cm anterior and 1 cm superior to the point of bone contact made on the first insertion. The needle is carefully advanced in this direction until the marker is flush with the skin and the point of the needle is within the pterygopalatine fossa (**B,C:** 2). For local anesthesia, 2 mL of a local anesthetic may be injected slowly. If a neurolytic block is required, it is essential that the bevel of the needle be on or in the nerve. The nerve is located by eliciting paresthesia or by using a nerve stimulator. If the point of the needle is on the nerve, 1 mL of alcohol is injected, but, if the needle bevel is within the nerve, 0.4 mL is sufficient to destroy the nerve. **D:** Inferior view of the skull showing needle 1 with its bevel against the lateral pterygoid plate and needle 2 with its distal centimeter in the pterygopalatine fossa and its bevel in front of the foramen rotundum. **E:** Radiograph showing the needle in place and its bevel in front of the foramen rotundum. For the anterolateral route, a skin wheal is raised at the angle formed by the coronoid process of the mandible and the inferior border of the zygomatic arch, and an 8-cm, 22-gauge needle is introduced and advanced medially, superiorly, and slightly posteriorly **(A,C)**. At a depth of 4 cm, the upper part of the posterior surface of the maxilla is contacted and the needle is advanced further with its bevel facing the bone to a depth of 4 to 5 cm, where contact with the bone is lost and paresthesia in the upper jaw is elicited. If difficulties are encountered, a nerve stimulator and radiographic control can be used. Once contact is made, the same volumes of local anesthetic or neurolytic agent, as mentioned for the lateral route, are injected.

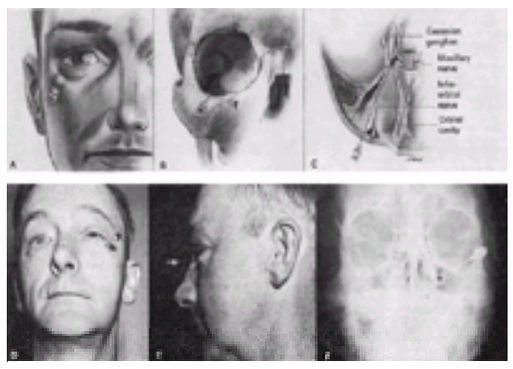

Figure 104-10. Maxillary nerve block by the orbital (Matas) route. **A:** An 8-cm, 22-gauge needle is introduced through a wheal made just above the inferior orbital margin, 1 cm medial to the inferior lateral angle of the orbital rim. Contact with the floor of the orbit is made, and the needle is advanced posteriorly and slightly medially, keeping constant contact with the bone. **B:** At a depth of about 3.5 cm, the point of the needle enters the inferior orbital fissure and loses its contact with bone. **C:** The needle is then slowly advanced so that its point passes through the pterygopalatine fossa, and it finally enters the foramen rotundum at a depth of about 5 cm. Paresthesia can be elicited while the needle is advancing through the pterygopalatine fossa and should always be elicited when the needle enters the foramen rotundum containing the nerve. **D,E:** Patient with the needle in place. **F:** Radiograph showing the bevel of the needle within the foramen rotundum. Injection of 0.5 mL of alcohol is sufficient to destroy the nerve.

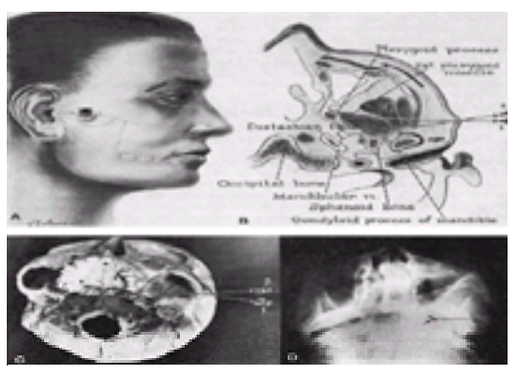

Figure 104-11. Mandibular nerve block by the lateral extraoral route. **A:** A skin wheal is raised just below the midpoint of the zygomatic arch, and an 8- cm, 22-gauge needle threaded with a rubber marker is inserted through it perpendicular to the skin. **B:** The needle is advanced until its point strikes the lateral pterygoid plate at a depth of about 4 cm from the skin (1). The marker is set 5 mm from the skin surface, and the needle is withdrawn until its point is subcutaneous and reinserted so that its point is 1 cm posterior to its previous position (2). The needle is gently advanced until the marker is flush with the skin, at which depth the bevel of the needle usually contacts the nerve just inferior to the foramen ovale and elicits paresthesia. For a diagnostic block, 2 to 3 mL of local anesthetic can be injected on the nerve but, for a neurolytic block, it is best to inject 1 mL of alcohol intraneurally. Because intraneural injection of alcohol is painful, it is essential to either give the patient a short-acting opioid, such as fentanyl, before injecting the alcohol or inject 0.5 mL of 2% lidocaine, wait about 30 minutes, and then inject the alcohol. **C:** Inferior part of the skull showing two needles in place. Needle *1* has its bevel against the lateral pterygoid plate, while needle *2* has its bevel in the center of the foramen ovale. **D:** Radiograph showing the needle (*arrow*) below the foramen ovale.

A neurolytic block should be preceded always by a block with a long-lasting local anesthetic, such as bupivacaine. As noted, the volume of local anesthetic should be the same or smaller than the volume of neurolytic agent to be used. Bonica preferred alcohol injected intraneurally to obtain a longer-lasting neural blockade. This is best done with the mandibular nerve because of its size and position below the foramen ovale. The maxillary nerve in the pterygopalatine fossa is smaller, and it is more difficult to place the point of the needle in the nerve. In any case, good results require that the point of the needle be in or very near the nerve as indicated by eliciting paresthesia. If difficulty is encountered, a nerve stimulator could be used.

With absolute alcohol, the average duration of blockade, as reported by many workers, has been 12 to 14 months for the maxillary nerve and 16 to 18 months for the mandibular nerve (55,60). In Bonica's series, maxillary nerve block afforded relief for an average of 14.6 months, with a range of 8 to 27 months, and mandibular

nerve block provided relief for an average of 18.4 months, with a range of 7 to 29 months (2).

The technique of injecting alcohol to relieve persistent eye pain (see Fig. 104-8) is somewhat different from that described for ophthalmic nerve block. Most ophthalmologists use a 3.5-cm, 22-gauge needle, but a 25-gauge needle produces less tissue damage. As part of the psychological preparation, patients should be reassured about the procedure and instructed to alert the physician promptly if a flash of bright light is experienced, which indicates that the needle has penetrated the optic nerve. In some patients, the injection is done during the course of surgery with general anesthesia.

Complications

RETROBULBAR BLOCK. Following retrobulbar alcohol injection, patients have routinely developed some degree of ptosis, proptosis, chemosis, and extraocular muscle palsy within hours of injection, but all these resolve in 2 days to several weeks (59). Temporary muscle paralysis is commonly seen if injection is done too far posteriorly in the muscle cone, instead of using the technique described above. Properly done, little or no risk of optic nerve damage is involved, because the nerve is protected by the thick sheath that surrounds it. Moreover, no permanent muscle palsy or other serious complications have been noted. Several cases of optic nerve damage have been reported following accidental injection of alcohol into the optic nerve.

MAXILLARY NERVE BLOCK. Because of the highly vascular nature of the contents of the pterygopalatine fossa, bleeding often occurs with maxillary nerve block but is usually not serious. Injection of neurolytic agents in excess of 1 mL increases the risk of having the drug pass through the inferior orbital fissure into the orbit and of damage to the oculomotor and abducens nerves, producing visual difficulties; for reasons noted above, this does not damage the optic nerve. Moore (61) reported a case of necrosis of the mucosa and cartilage of the palate, with a consequent large defect in half of the roof of the mouth on the ipsilateral side following alcohol injection of the maxillary nerve. In view of the numerous patients who have received maxillary nerve blocks with alcohol, these are rare complications that can be minimized and even eliminated by using a small volume of alcohol and precise technique.

MANDIBULAR NERVE BLOCK. Minor complications of mandibular nerve block are postinjection pain and hemorrhage into the cheek, which occur during and following mandibular block by the anterolateral extraorbital route. Both have transient effects. The most frequent, more serious complication is involvement of the motor root with consequent weakness or paralysis of the muscles of mastication of the affected side, which causes the mandible to deviate from the midline. If more than 1 mL of alcohol is injected into the mandibular nerve, it is likely that some of the solution can diffuse cephalad and affect the lower part of the gasserian ganglion.

Block of Branches of the Maxillary and Mandibular Nerves. Figure. 104-12 depicts the technique of blocking the infraorbital nerve, Figure. 104-13 shows the technique of blocking the lingual and inferior alveolar nerves, and Figure. 104-14 illustrates the technique of blocking the mental nerve by the intraoral and extraoral routes. Injection of these branches with a long-acting local anesthetic (e.g., bupivacaine) can be used to relieve severe acute postoperative or posttraumatic pain and to control the severe pain of herpes zoster in the distribution of each of these branches. Because of their simplicity, injections can be repeated twice daily until the pain subsides.

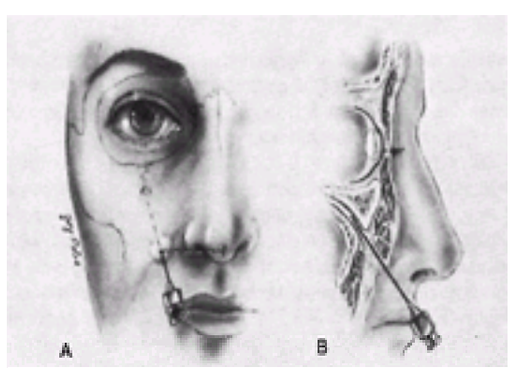

Figure 104-12. Technique of infraorbital nerve block. **A:** A 5-cm, 25-gauge needle attached to a 2-mL Luer-Lok syringe and containing a local anesthetic, or to a 1-mL tuberculin syringe containing alcohol, is introduced through a skin wheal made 1 cm lateral to the middle part of the ala nasi, or 2.5 cm from the midline, and advanced superiorly, posteriorly, and slightly laterally. The bone just inferior to the foramen is contacted at a depth of 1.0 to 1.5 cm, and paresthesia is elicited, usually radiating to the upper lip. To block the branch that supplies the lip, the injection is made at this point, but, to block the nerve supply to the front teeth, it is necessary to pass the needle into the canal 7 to 10 mm **(B)**. Paresthesia is usually elicited during the advance. After negative aspiration tests, 1 mL of local anesthetic or 0.3 to 0.5 mL of alcohol is sufficient to destroy the nerve.

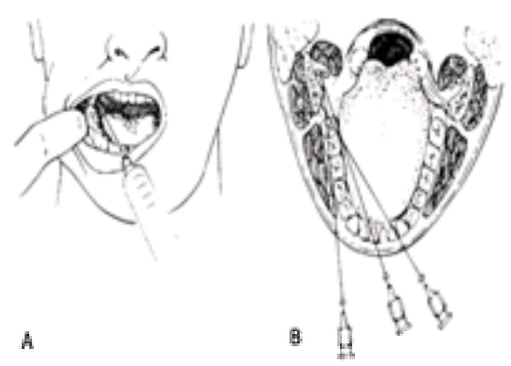

Figure 104-13. Technique of blocking the inferior alveolar and lingual nerves by the oral route. **A:** After the mucous membrane of the retromolar trigone is topically anesthetized and prepared with an antiseptic solution, a 10-cm, 22-gauge needle attached to a 5-mL syringe containing local anesthetic, or to a 1- mL tuberculin syringe containing alcohol, is introduced 1 cm above the triturating surface of the last molar tooth. **B:** The angle is such that the shaft of the needle rests 1 cm above the dental arch between the canine and first premolar tooth of the opposite side (1). After contact is made with the trigone at its medial side, the needle is swung horizontally so that its shaft rests parallel to the teeth of the same side and it is gently and slowly advanced so that its point slips to the medial border of the trigone (2). The needle is swung back so that its shaft finally rests above the first incisor of the same side, and it is advanced about 1.5 cm to bring the point midway between the anterior and posterior margins of the ascending ramus (3). At this juncture, the bevel of the needle is just medial to the mandibular foramen, where 2 to 3 mL of local anesthetic solution (or 1 mL of alcohol) is injected. For neurolytic block, it is essential to contact the inferior alveolar and lingual nerves separately and to elicit paresthesia before injecting alcohol.

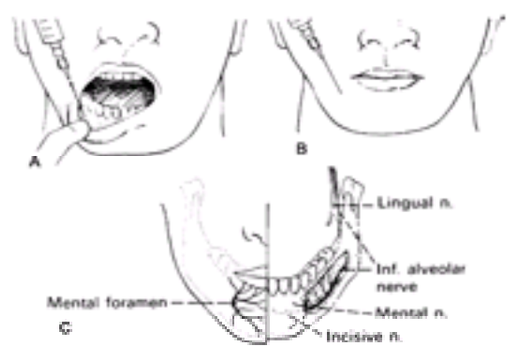

Figure 104-14. Technique of mental nerve block by the oral and extraoral routes. **A:** Oral route. A 5-cm, 25-gauge needle is introduced through the gingivobuccal reflection on a line drawn between the premolar teeth. After contacting the upper margin of the mandible, the needle is advanced inferiorly on the same line to a point

midway between the upper and lower margins, where the nerve is usually contacted and paresthesia is elicited. **B:** Extraoral route. A 5-cm, 25-gauge needle is introduced through a wheal raised on the skin of the lower lip inferior and anterior to the root of the second premolar tooth. On making contact with the bone, the needle is advanced anteriorly, inferiorly, and medially until it passes into the foramen, which faces posteriorly, superiorly, and laterally, and paresthesia is elicited. Usually, 2 mL of local anesthetic is used for prognostic block, but, for neurolytic block, 0.3 mL of absolute alcohol is injected intraneurally or into the mental canal. **C:** View of the mandible to show the emergence of the mental nerve through the mental foramen (left) and dissection of the inferior alveolar canal to show the distribution of the inferior alveolar nerve to the teeth.

Alcohol block of these nerves is used as a prognostic and therapeutic procedure in patients with tic douloureux, postherpetic neuralgia, and severe cancer pain limited to their distribution. For optimal results, it is best to inject the drug intraneurally to destroy these nerves, thus producing a prolonged effect. Some patients develop postinjection neuropathy with neuralgia, with degeneration of the nerve. Local ulceration and necrosis have been reported.

Block of the Glossopharyngeal and Vagus Nerves

Indications. Block of the glossopharyngeal or vagus nerve, or both, is indicated for patients with severe intractable pain caused by ticlike neuralgia or with cancer-related pain in the distribution of these nerves. Block of these nerves with a long-lasting local anesthetic is used to help in the differential diagnosis of ticlike pain in the angle of the jaw, which can be caused either by glossopharyngeal or mandibular neuralgia. Glossopharyngeal block is used in differentiating glossopharyngeal neuralgia from the geniculate ganglion neuralgia that causes pain deep in the ear and has some of the features of glossopharyngeal neuralgia. Because geniculate neuralgia involves the sensory root of the facial nerve (nervus intermedius), glossopharyngeal nerve block at the jugular foramen or below the styloid process does not relieve it. In such cases, the initial step involves provoking glossopharyngeal neuralgia by applying a cotton applicator to the tonsils, posterior pharynx, or back of the tongue and then applying a topical anesthetic such as 4% cocaine or 0.5% bupivacaine to produce analgesia of the trigger points within 10 to 15 minutes.

A small percentage of patients develop a variant of glossopharyngeal neuralgia, in which the vagus nerve is also involved. Robson and Bonica (62) reported a method of aiding the diagnosis of this type of neuralgia. In two patients who presented with typical clinical pictures of glossopharyngeal neuralgia, complete topical anesthetization of the entire pharynx, which completely relieves the pain of neuralgia limited to the glossopharyngeal nerve, failed to do so. Block of the glossopharyngeal and vagus nerves below the jugular foramen, however, afforded complete relief. In these patients, resection of the sensory root of the glossopharyngeal nerve, as well as of the anterior half of the sensory root of the vagus nerve, produced permanent and complete relief of the neuralgia.

Block of the vagus nerve with a local anesthetic is also useful as a diagnostic or prognostic procedure in those with cancer pain in the tracheobronchial tree. This type of pain is effectively treated with section of the vagus nerve below the recurrent laryngeal nerve. Because block of each of these two nerves is best done at the base of the skull, motor nerves are also interrupted, and therefore neurolytic blocks are contraindicated because they produce prolonged paralysis of the pharyngeal and laryngeal muscles and consequent loss of the ability to swallow and phonate.

In earlier years, Bonica advocated the cautious use of unilateral glossopharyngeal block with neurolytic agents for the relief of severe cancer pain in patients who could not tolerate intracranial rhizotomy. The development and clinical application of percutaneous thermocoagulation of the glossopharyngeal nerve, described by Broggi and Siegfried (63) and used by other workers for the treatment of glossopharyngeal neuralgia and cancer pain, have decreased the need for unilateral neurolytic blockade of this nerve. Using the thermocoagulation procedure (see Fig. 104-5), several workers have reported good pain relief in about half of patients with glossopharyngeal neuralgia and in about two-thirds of patients with cancer pain. The procedure produces transient vagal dysfunction and occasionally causes dysarthria and dysphagia. This procedure is done only in a few medical centers worldwide, however, and is not available to most patients with severe cancer pain in the throat. If patients can tolerate it, intracranial section of the sensory root of the glossopharyngeal nerve should be done, but if patients are in poor physical condition and the pain cannot be controlled with opioids, a unilateral neurolytic block should be considered.

Block of the internal laryngeal branch of the superior laryngeal nerve with local anesthetic and subsequently with alcohol or phenol can be used to control severe neuralgia, cancer pain, or other chronic painful conditions in the larynx. In patients who have cancer pain involving branches of the glossopharyngeal or mandibular nerves, block of the internal laryngeal nerve must be supplemented with block of these nerves.

Techniques. The anatomy of the glossopharyngeal and vagus nerves is described in detail in Chapter 46 and Chapter 47. The technique of blocking the glossopharyngeal nerve is depicted in Figure. 104-15, and block of the vagus nerve is shown in Figure 104-16 Because of the proximity of both nerves just below the jugular foramen, selective block of the glossopharyngeal nerve is difficult. Inserting the needle just posterior to the angle of the mandible, which is approximately 5 cm below the level of the jugular foramen, the glossopharyngeal nerve is 1.5 to 2.0 cm anterior to the vagus nerve (see Fig. 104-15C). Using a nerve stimulator and an insulated needle, the nerve is contacted 2 or 3 cm below and anterior to the tip of the styloid process. Once the nerve has been contacted, 1.0 to 1.5 mL of 0.5% bupivacaine with epinephrine is injected. If the block produces analgesia limited to the distribution of the glossopharyngeal nerve, one can consider following it up with the injection of 5% aqueous phenol to obtain a block of several months. Figure. 104-17 shows the technique of blocking the internal branch of the superior laryngeal nerve.

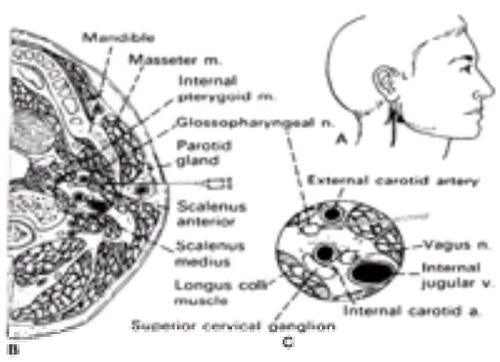

Figure 104-15. Technique of glossopharyngeal nerve block. **A:** A skin wheal is made just posterior to the angle of the mandible, and a 5-cm, 22-gauge Teflon-coated needle attached to a stimulator is passed through the wheal. At this level, the glossopharyngeal nerve is 1.5 to 2.0 cm anterior to the vagus nerve and can be blocked exclusively with small volumes of solutions without involving the vagus nerve. **B:** The needle is advanced medially and just posterior to the mandible until its bevel is 4 cm deep, and the stimulator is used to help locate the nerve. Once the nerve has been found, 2.0 to 2.5 mL of the local anesthetic or 1.5 to 2.0 mL of alcohol is injected. **C:** Enlargement of the circled area in **B** to show the point of the needle on the nerve. Because the section is below the tip of the styloid process, this is not seen as it is in Figure. 104-16C. If the nerve cannot be located with the stimulator at this level, the classic approach is used. This involves the passage of the needle through a wheal raised at the point of bisection of a line drawn between the mastoid process and the angle of the mandible. The needle is advanced perpendicular to the skin until the styloid process is contacted, the rubber marker is placed 5 mm from the skin, and the needle is withdrawn and reintroduced to pass anterior to the styloid process and advanced until the marker is flush with the skin, at which point paresthesia should be elicited.

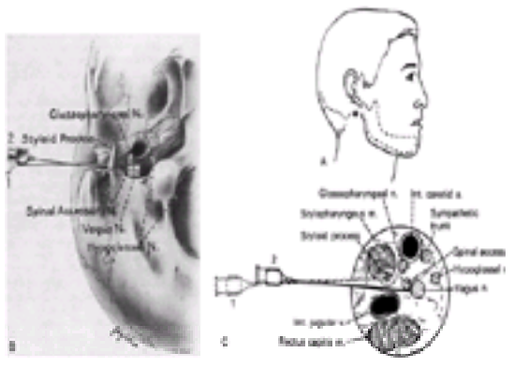

Figure 104-16. Technique of vagus nerve block. **A:** A skin wheal is raised just anterior to the mastoid process and immediately below the external auditory meatus. **B:** The relations of the styloid process and cranial nerves IX, X, XI, and XII. **C:** Cross-sectional enlargement of the area just below the jugular foramen. Note the close proximity of the various nerves, vessels, and the styloid process. A 5-cm, 25-gauge needle is introduced through the wheal and advanced until the styloid process is contacted (**B,C:** 1), whereupon the needle marker is placed 1 cm from the skin. The needle is withdrawn until its bevel is subcutaneous and reintroduced so that it passes posterior to the styloid process until it is flush with the skin (**C:** 2). A volume of 2 to 4 mL of local anesthetic solution is injected, which is likely to block not only the vagus but also the ninth, eleventh, and twelfth cranial nerves because of their close proximity. Neurolytic block of the vagus nerve is not done at this level.

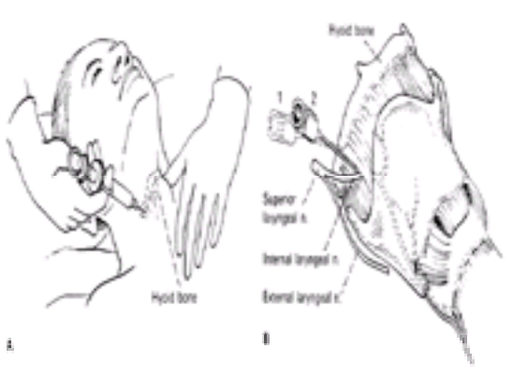

Figure 104-17. Technique of blocking the internal branch of the superior laryngeal nerve. **A:** After identifying the great cornu of the hyoid bone on the side to be blocked (facilitated by exerting pressure on the opposite side of the bone to render the great cornu more prominent), a wheal is raised in the skin overlying the tip of the cornu. A 5-cm, 25-gauge needle is inserted through the wheal and advanced perpendicularly (1) to the skin until the hyoid bone is contacted. **B:** The needle is withdrawn (2) and redirected inferiorly and slightly medially until its bevel lies midway between the inferior border of the hyoid bone and the superior border of the thyroid cartilage, about 1 cm anterior to the lateral thyrohyoid ligament, where the nerve is usually contacted. Injection of 2 mL of local anesthetic produces analgesia of the laryngeal inlet down to the level of the vocal cords. Injection of a neurolytic agent (e.g., 0.5 mL alcohol) should be done only when the nerve is contacted.

Complications. Glossopharyngeal block causes dysphagia from paralysis of the pharyngeal muscle, whereas block of the vagus causes paralysis of the ipsilateral vocal cord with impairment of phonation, and block of vagal fibers to the heart produces tachycardia. If the block is done below the jugular foramen, it is likely to involve the spinal accessory and hypoglossal nerves. In this case, the patient develops paralysis of the trapezius muscles and of half of the tongue on the same side as the block. Furthermore, use of excessive amounts of neurolytic solution can cause sloughing and fibrosis in surrounding tissues, particularly the carotid artery and internal jugular vein, but this is usually a result of improper technique.

Neuraxial Neurolytic Blocks

Injection of a neurolytic agent into the subarachnoid, extradural, or subdural space is one of the most effective methods of relieving severe intractable pain caused by advanced or terminal cancer. The use of these techniques for chronic nonmalignant pain is to be discouraged except in special circumstances that are considered in this section.

Agents that have been used for this purpose include ethyl alcohol, phenol in glycerin, chlorocresol in glycerin, aqueous phenol, hypertonic saline solution, and ammonium compounds. Most of this section discusses basic considerations, including indications, techniques, results, and complications of the use of subarachnoid alcohol and subarachnoid phenol in glycerin. Extradural neural blockade and subdural neural blockade are also considered briefly.

Subarachnoid Neurolytic Block

Basis for Application. The bases for the injection of a neurolytic agent into the subarachnoid space to relieve severe pain include the following

- Most nociceptive impulses from the skin, subcutaneous tissue, deep somatic structures, and viscera pass to the spinal cord through the posterior roots and their rootlets.
- By proper positioning of the patient, hypobaric ethanol or hyperbaric phenol in glycerin can be made to diffuse predominantly to the posterior rootlets involved in the transmission of nociceptive information.
- On contact with the rootlets, neurolytic agents destroy axons (wallerian degeneration) of the rootlets, extending from the dorsal root ganglion to their attachments to the spinal cord. With alcohol, the dorsal root ganglion and dorsal root entry zone may also be involved.
- By using appropriate technique, the solution can be made to block as many segments as are involved in the transmission of pain information. Thus, with this method, it is possible to produce a predominantly posterior chemical rhizotomy to relieve pain for weeks, months, and even for a year or more.
- Because cell bodies may not be affected, regeneration can occur over varying periods, depending on the degree of destruction caused by the neurolytic agent.

Indications and Advantages. In properly selected patients, subarachnoid rhizotomy is an effective method for controlling severe intractable pain located below the head. Dogliotti (64), when first describing the technique, advocated the use of subarachnoid alcohol not only for the relief of cancer pain but also for severe nonmalignant pain caused by other pathologic processes. The procedure has been used mostly for the management of cancer pain in the trunk. The technique has also been used for the relief of pain in the neck, upper limbs, pelvis, and lower limbs, but in such patients it is associated with varying degrees of complications (see below). Subarachnoid neurolysis has been used also for managing patients with spasticity.

Intrathecal neurolysis is relatively simple to carry out. It is not associated with much pain and causes few serious complications. It can be carried out in patients in poor physical condition and in the elderly. Because it involves only a brief stay in the hospital, it can be made available to a relatively large number of patients and requires no special, costly, or highly sophisticated equipment or facilities. Subarachnoid neurolytic injection can be repeated or extended if the pain spreads or persists. In those with terminal cancer, the duration of pain relief is usually sufficient to afford a relatively comfortable end.

In individuals who are in fairly good physical condition and who have an anticipated survival of longer than 4 to 6 months, an open or percutaneous cordotomy can provide a longer and more certain period of pain relief. In patients with a shorter life expectancy and in those who are unable, unfit, or unwilling to undergo surgery, however, intrathecal neurolytic injection offers a good prospect of worthwhile pain relief so that patients can remain ambulatory and on minimal oral analgesic medication. Subarachnoid neurolytic blockade is also valuable for patients with extensive bilateral cancer pain, in whom the risk of performing bilateral cordotomy is significant. The risk can be minimized by performing cordotomy on the side with the most intense and extensive pain, and the subarachnoid neurolytic block can be done on the other side.

Some authorities (65) have stated that, in those with bilateral pain, subarachnoid neurolysis should be used with great caution, if at all. Derrick (66) has advocated

treating bilateral pain by placing patients prone, but to obtain effective relief, it is necessary to use a large volume of neurolytic agent, which consequently increases the risk of complications. It is extremely important to avoid increasing disability through motor weakness, sphincter incompetence, and loss of positional sense, unless it can be justified by the degree of pain relief achieved. Usually ambulatory patients choose not to lose control of bladder function, even if pain relief with the use of an alternative method is inferior. However, in a patient whose bladder is already involved with a tumor and/or has a bladder catheter in place, bladder paresis is not a problem.

Disadvantages and Contraindications. The major disadvantages of intrathecal neurolysis (or of any other neurolytic procedure) are inadequate pain relief and complications. Inadequate pain relief results either from failure of the original injection to interrupt all the nociceptive pathways completely or from spread of the pain beyond the anesthetized region.

The block might initially interrupt the nerves to the painful region and afford complete relief of pain but, in days to months, the neoplasm can spread beyond the confines of the analgesia and cause additional pain. Fortunately, the block can be repeated several times with relatively little inconvenience to the patient, so not all these disadvantages are as significant as they might seem.

A more important disadvantage includes complications that can occur during or following the procedure. Muscle weakness in the limbs and involvement of the rectal and bladder sphincters are the most serious. Relative contraindications to the use of subarachnoid neurolysis include the following:

- Pain that is extensive and poorly localized.
- Intraspinal tumor infiltration, with involvement of the cord or the spinal column at the level of injection.
- Two diagnostic or prognostic procedures with a local anesthetic provide no relief of pain.

Principles of Application. Subarachnoid neurolytic block should be used as part of a comprehensive program, which should include opiates as well as sedatives, antidepressants, and anxiolytic drugs and, most importantly, psychological care for the patient's anxiety, depression, and other serious emotional reactions (Chapter 24, Chapter 25 and Chapter 26). Bonica (2) has stressed that optimal results require adherence to the following steps and principles

- If subarachnoid neurolytic blockade is considered as the method of choice for controlling severe pain, it should be carried out at the earliest possible time.
- Patients should be admitted to the hospital 1 or 2 days before the procedure to allow proper preinjection assessment and management, including one or more diagnostic or prognostic blocks at intervals of 8 to 10 hours between each injection.
- Even with a detailed history and a comprehensive physical and neurologic examination from the previous outpatient consultation, it is necessary to reassess the patient. This includes recording the site, quality, intensity, and other characteristics of the pain using the visual analog scale, descriptors, or other measures discussed in Chapter 12, Chapter 15, and Chapter 16. It is also important to repeat a neurologic examination even if one has been done because it is important to determine whether any changes have occurred during the interval between the preceding and the present examinations.
- The patient, family, and referring physician should be thoroughly informed about the incidence and degree of pain relief expected and about any complications associated with the procedure. It is important to inform patients that the procedure might not relieve all the pain and that it is frequently necessary to repeat the injection once or twice to achieve optimal pain relief. Patients must also be told that the procedure is intended to relieve the pain and not to cure the disease, so that they do not develop a false hope of cure when the pain is eliminated.
- Diagnostic blocks should be carried out at least 12 hours prior to the intrathecal neurolysis. If alcohol is to be used for the neurolysis, hypobaric local anesthetic is used, whereas if phenol in glycerin is to be used, hyperbaric drugs are used. The slow injection of 0.2 mL of local anesthetic using a tuberculin syringe for precise measurement usually blocks the rootlets of one or two segments.
- Generally, premedication should be avoided, because the full cooperation of patients is necessary to decide on immediate localization of the neurolytic solution after it is injected. If patients are unduly apprehensive, an anxiolytic, sedative, or combination should be given in moderate doses that do not impair mentation. Swerdlow (67) has suggested that no opioid analgesic be given for 4 hours before the block to assess the degree of pain and pain relief with the procedure properly. However, circumstances do exist in which the position required for the injection is so painful that modest doses of short-acting opioids should be given intravenously. This not only helps patients but also permits dural puncture during the peak effects of the analgesic and thus decreases any associated discomfort.

Although some difference has been noted between the use of hypobaric alcohol or hyperbaric phenol in glycerin in regard to the degree and extent of nerve damage, the incidence of pain relief and complications is similar with both techniques. Different results occur primarily because of the knowledge, skill, and experience of the anesthesiologist with a particular agent and the technique used. On the other hand, the comparison between the two agents given below does suggest differences in the hands of some who have had extensive experience with both techniques.

Techniques

Subarachnoid Alcohol. The technique of subarachnoid alcohol block is based on the fact that ethyl alcohol is a neurolytic agent that is hypobaric, with a specific gravity of 0.789. Therefore, when it is slowly injected into the CSF, which has a specific gravity of 1.0065 to 1.007, the alcohol diffuses upward and forms a layer on top of the spinal fluid (Fig. 104-18). To achieve the best results it is therefore necessary to have the patient placed on an operating table that can be moved to various positions (Fig. 104-19, Fig. 104-20, Fig. 104-21 and Fig. 104-22). Once the patient is in position and the area has been properly prepared, puncture is carried out with an 8- or 10-cm, 22- or 25-gauge, short-beveled needle using the technique depicted in Figure. 104-23.

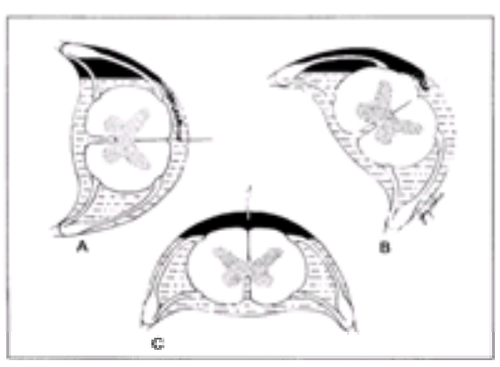

Figure 104-18. Diffusion of alcohol into the subarachnoid space. **A:** With the patient in the lateral position, both the anterior and posterior roots are affected. **B:** The patient is in the lateral-prone position, with the posterior rootlets uppermost. The bevel of the needle is just anterior to the dura- arachnoid. The alcohol, which is hypobaric, is injected in small aliquots so that it diffuses along the surface of the arachnoid membrane and comes in contact predominantly with the posterior rootlets. **C:** With the patient in the prone position, small amounts of alcohol are insufficient to affect the posterior rootlets. The use of larger volumes increases the risk of damaging the posterior columns of the spinal cord and of other complications.

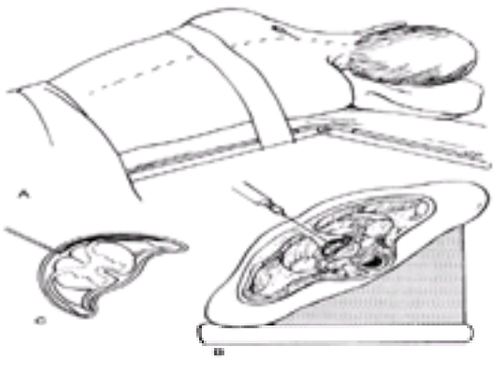

Figure 104-19. Subarachnoid alcohol block for pain in the lower cervical and upper thoracic regions. **A:** Position of the patient, showing the angle of the body with the surface of the table. **B:** Cross-sectional representation of the body showing the angle it makes with the table. **C:** Enlargement of the intrathecal structure showing diffusion of the alcohol to bathe the posterior rootlets and root.

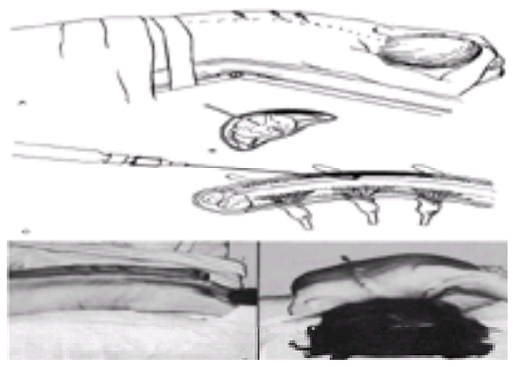

Figure 104-20. Position of a patient for subarachnoid alcohol block in the thoracic region. **A:** One or two pillows are placed under the region to be blocked, and the table is flexed to produce a scoliosis of the spine, with a maximum curve corresponding to that of the nerve rootlets conveying the nociceptive impulses. This places the posterior (sensory) nerve rootlets and roots uppermost, with the head and extremities lower than the point of injection. **B:** Cross section of the thoracic subarachnoid space, showing diffusion of the alcohol uppermost to involve the posterior rootlets. **C:** Schematic of the spinal cord (posterolateral view). The alcohol diffuses to affect the rootlets of two segments by injection of 0.1-mL aliquots over 90 seconds, repeated at 3-minute intervals until 0.4 to 0.5 mL of alcohol has been injected through each needle. **D,E:** Patient in position for block of the left side to relieve chest pain caused by metastasis to and multiple fractures of the ribs. These conditions produced pain during normal respiration and severe pain during deep respiration, causing the patient to hypoventilate markedly. Three needles were used to permit injection of small volumes of solution and thus minimize complications. The first injection on the left side produced good relief from pain, extending from T-4 to T- 10. The procedure was repeated 10 days later on the right side, and the patient derived sufficient pain relief to permit adequate ventilation for 4 weeks. A second series of blocks produced relief until death, 7 weeks after the second series of subarachnoid alcohol therapy, for a total of 11 weeks of pain relief.

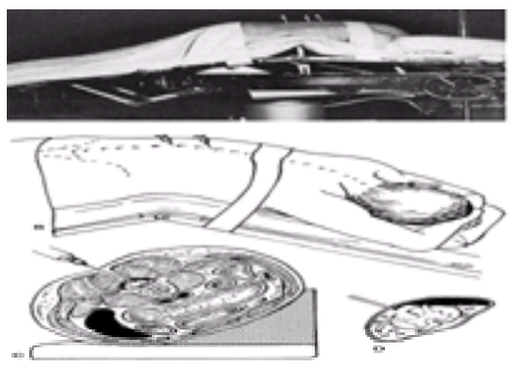

Figure 104-21. **A,B:** Position of the patient for subarachnoid alcohol block of the lower thoracic vertebral levels for the relief of cancer pain in the pelvis and thigh. The gallbladder lift and the pillow over it are used to obviate lumbar lordosis. The table was then moved so that the upper part of the body was lower than the lower trunk. Three needles are in place for the injection of 0.05-mL aliquots of alcohol. **C:** Cross-sectional representation of the body showing the angle it makes with the table. **D:** Diffusion of the alcohol to bathe the posterior rootlets and roots.

Figure 104-22. **A:** Patient in steep Kraske's position for injection of alcohol to destroy the rootlets of S-4, S-5, and the coccygeal nerve to relieve severe perineal pain. The needle puncture is made at the L-5 to S-1 interspace, with the bevel of the needle just anterior to the dura-arachnoid. **B:** Injection of hypobaric alcohol drop by drop causes the alcohol to rise to above the cerebrospinal fluid level and eventually to settle in the lowest part of the sac. **C:** Diffusion of the alcohol is limited to S-4, S-5, and the coccygeal nerves. Properly done, this produces analgesia in the perianal region and posterior part of the perineum. The procedure is especially indicated for patients with severe pain after abdominoperineal resection and subsequent metastasis to the region.

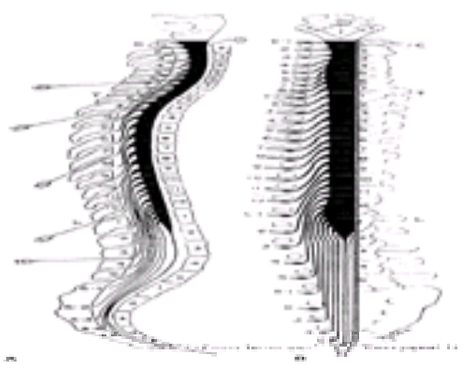

Figure 104-23. Schematic of relationships of the spinal column, spinal cord, spinal nerves, and sites of attachment of their rootlets. **A:** Lateral view showing the angles of the shafts of needles inserted for dural puncture at different vertebral levels. **B:** Posterior view showing relationships of the vertebrae to the spinal cord segments and to the rootlets of various spinal nerves.

The patient is placed in the lateral position on the side opposite the one to be blocked, with one or two pillows under the region to produce a scoliosis with a maximum curve corresponding to that of the nerve rootlets conveying the nociceptive impulses (see Fig. 104-19, Fig. 104-20). The convexity of the curve, which is upward, can

be accentuated by “breaking” the table or by using the kidney lifts (see Fig. 104-21, Fig. 104-22). This places the involved posterior nerve rootlets uppermost, with the head and lower part of the body below the puncture site. In addition, the patient is turned forward 45 degrees so that the posterior rootlets of the nerves of the upper side are horizontal (see Fig. 104-18) and they become bathed with the injected solution, while the anterior roots are (theoretically) less affected. The patient is made as comfortable as possible and is loosely strapped in place to prevent movement from the desired position.

The site of puncture also depends on the segments involved. It is best to deposit the alcohol at the level where the involved rootlets originate from the spinal cord and not at the point of exit of the roots through the intervertebral foramen, as suggested by some. Where the roots attach to the cord are eight to 12 fila radicularia, which provide a greater surface area and are thus much more susceptible to the action of the neurolytic agent than the root or the dorsal root ganglion. To place the bevel of the needle precisely at the desired segment(s), it is necessary to recall that below the third cervical spinal segment the spinal cord levels from which the rootlets of a spinal nerve originate are not at the same levels of the corresponding vertebrae (see Fig. 104-23). This is particularly true for the thoracic, lumbar, and sacral segments. Although a patient might not have the exact correlation between spinal cord segments and vertebrae as that shown, it is sufficiently accurate that it can be followed with a certain degree of assurance. Once the interspaces are decided on, the spinous processes of the vertebrae must be counted carefully, beginning with C-7 downward, and the findings confirmed by counting from the L-5 interspace upward. Confirmation by x-ray is helpful.

Puncture in the lumbar region is usually simple because the interspaces are wide and almost perpendicular to the skin and the subarachnoid space contains the cauda equina, but puncture is much more difficult above the T-11 or T-12 interspace. Between the T-2 and T-8 or T-9 vertebrae, the laminae and spinous processes of the vertebrae are imbricated, making the interspaces narrow. Also, elderly people can have bony spurs on the tips of the adjacent spinous processes and, in some cases, the supraspinous ligament is ossified, making a midline approach impossible. Also, the subarachnoid space in this region is much narrower. Thus, the greatest of care must be exercised in placing the short bevel of the needle in the posterior part of the subarachnoid space just anterior to the dura-arachnoid. Equally important, the injection must be made in the most posterior part of the subarachnoid space so that the alcohol rises along the curvature of the arachnoid to the top of the CSF as a layer and thus bathes only the desired posterior rootlets. Using the technique illustrated in Figure. 104-24, it is possible to puncture the dura-arachnoid safely and obtain CSF and to inject the neurolytic agent without difficulty.

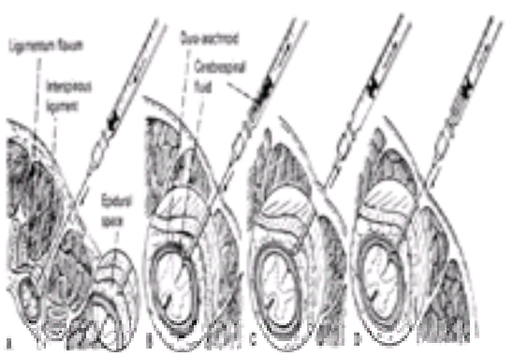

Figure 104-24. Technique of puncture of the dura-arachnoid for subarachnoid injection of neurolytic agents. It is essential to have the bevel of the needle just anterior to the anterior surface of the arachnoid membrane to limit diffusion of the neurolytic agent to the posteromedial part of the subarachnoid space. **A:** The needle is inserted in the usual manner except that, when the needle is felt to pass through the tough ligamentum flavum and into the epidural, the needle is attached to the 2-mL Luer-Lok syringe and advanced 3 to 4 mm within the lumbar epidural space or 2 to 3 mm in the thoracic epidural space and 1 to 2 mm in the cervical epidural space. To detect penetration of the dura-arachnoid promptly, the plunger of the syringe is withdrawn while aspirating to cause a negative pressure at the bevel of the needle. **B:** The needle is advanced slowly until its passage through the dura-arachnoid and its entrance into the arachnoid space are indicated by the usual snap and the almost simultaneous appearance of cerebrospinal fluid (CSF) in the syringe. **C:** The proper position of the bevel of the needle is further ascertained by first reinjecting the CSF into the subarachnoid space and then attempting to aspirate fluid with the empty syringe while the needle is slowly withdrawn, until the free flow of fluid stops. If the needle point has been properly placed, it need only be withdrawn 1 or 2 mm before its point leaves the subarachnoid space. **D:** The needle is advanced again until CSF can be aspirated once more. Because aspiration of fluid is frequently impeded by a veil of arachnoid and in the lumbar region by nerve rootlets, the injection of 0.3 to 0.5 mL of air or saline solution causes the obstructing structure to move away from the bevel. Once the bevel of the needle is just anterior to the anterior surface of the arachnoid, the neurolytic agent can be slowly injected. (Insets represent an enlargement of the region to show details of the structures.)

Once the bevel of the needle is in the subarachnoid space, the alcohol is slowly injected in 0.1-mL aliquots with 60 to 90 seconds between each injection. Before and during injection, the patient should be told to expect a feeling of warmth, burning pain, and tingling that lasts a few seconds and then fades. In addition, the skin of the segments involved manifests hyperemia. After injection of each aliquot, the effect of alcohol in producing hypalgesia should be assessed by the pin scratch technique.

Bonica believed that if more than two segments of the spinal cord are involved in transmitting nociceptive impulses, it is preferable to insert multiple needles and inject small amounts through each needle rather than to inject a large amount of alcohol through one needle to obtain a widespread effect. If, for example, the pain involves the T-5 to T-10 segments, a needle is placed in the T-3, T-5, and T-7 interspaces and 0.2 mL of alcohol is injected through each needle in 0.1-mL aliquots. This drop-by-drop injection technique prevents widespread diffusion of the alcohol and thus increases its concentration to the target rootlets and decreases the risk of complications. This is especially important in blocks to provide relief of pain in the upper limb, where it is essential to minimize the diffusion of the alcohol to the anterior roots.

During and following the injection, the vital signs are noted and recorded. The patient should remain in the same position for 25 to 30 minutes to ensure that the alcohol is completely “fixed” to the nerve tissue and that none is left in the CSF to diffuse to undesired rootlets. Precautions to prevent postdural puncture headache may be followed but the use of small-gauge needles usually is sufficient.

Subarachnoid Phenol. The technique of injecting phenol in glycerin is different from that for subarachnoid alcohol for several reasons. The first is that because the solution is hyperbaric, the patient needs to be placed on the table with the affected rootlets lowermost. The second is that because the solution is viscid, a 20-gauge, short-beveled needle is required, and the injection with the tuberculin syringe requires considerable force. Finally, the onset of definitive blockade can be evaluated with a day of the injection, whereas it requires a longer period with alcohol. The procedure is carried out with the affected side down and the back turned, so that its surface makes a 45-degree angle with the surface of the table (Fig. 104-25 and Fig. 104-26). Swerdlow (67) has used a total dose of phenol in glycerin ranging from 0.5 to 1.0 mL, depending chiefly on the number of segments being blocked, the length of the spine, and the part of the spine being injected. Thus, a smaller volume is injected in the sacral segments and a larger one in the thoracic region.

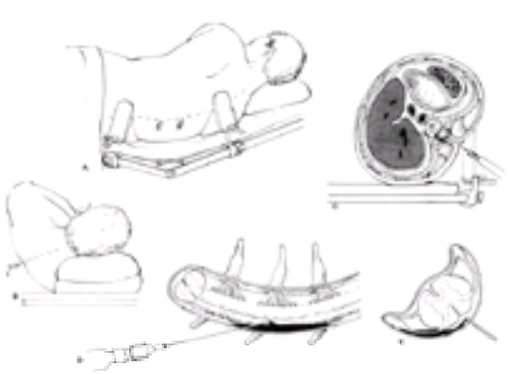

Figure 104-25. Technique of subarachnoid injection of hyperbaric phenol in glycerin. **A:** The dura-arachnoid puncture is made with the patient on the side, with the affected side underneath. **B:** Once cerebrospinal fluid emerges from the hub of the needle, the upper part of the body is displaced posteriorly so that the posterior surface of the back makes an angle of 45 degrees with the superior surface of the table. **C:** Cross-sectional representation of the body in the same position as **B**. This position is maintained with kidney rests or with wide adhesive tape across the patient's body attached to the lateral edges of the table. Schematic longitudinal section

(D) and cross section **(E)** show diffusion of hyperbaric phenol to the posterior (sensory) rootlets that transmit nociceptive information, which are lowermost.

Figure 104-26. Technique of injecting hyperbaric phenol in glycerin to block the rootlets of the lower sacral and coccygeal nerves. **A:** Position of the patient for puncture at the L-5 to S-1 interspace. **B:** Position of the patient for injection of phenol to achieve bilateral block. **C:** Position of the patient for unilateral block of the lower lumbar and sacral roots. **D:** Diffusion of phenol along the left side of the subarachnoid space to contact the rootlets of the S-4, S-5, and coccygeal nerves.

Evaluation of Results and Reinjection. When the block is effective and is localized to the involved segments, the relief of pain is remarkable. Such relief can occur within a few hours or a day after injection of phenol, or it might not be complete until several days after injection of alcohol. Following injection, zones of hypalgesia, analgesia, and hypesthesia occur, frequently with diminution or complete loss of pinprick and temperature sensation. The stretch afferents usually are blocked and certain reflexes are diminished or absent. Sometimes a zone of hyperesthesia extends beyond the zone of analgesia, possibly also with fibrillary muscle twitching and muscle jerking; all of these effects disappear within a few days. Because the maximum effect of alcohol block might not be obvious for several days, assessment must be postponed until 3 to 5 days after injection. If the patient is still having pain after this period, it is advisable to reinject the various segments that remain painful. It has been our experience that the initial injection provides adequate relief in approximately 60% of patients, so that approximately 40% require a second injection and 50% of these require a third injection.

If a patient has been on a strong opioid for over 2 weeks and derives good pain relief with one or more subarachnoid neurolytic injections, tapering of the opioid should be done rather than discontinuing it suddenly to prevent withdrawal symptoms from developing. Such symptoms might cause patients to complain and confuse the issue of whether the subarachnoid neurolytic blockade is completely effective. Often it is necessary to continue to give patients small or moderate doses of opioids to relieve “other pain” that might be present outside of the area of the neurolytic blockade. There has been some concern in the literature that sudden pain relief with neural blockade in those on high-dose opioids can produce respiratory depression and possibly arrest. This has not been the case in our experience with these procedures.

In individuals who have bilateral pain, it is preferable not to attempt to block both sides with one injection, because this would require a large volume of solution and consequently increase the risk of complications. Usually the side that has the most intense pain is blocked and the injection is repeated until good relief is achieved. After an interval of several days, blocks are carried out for the other side.

It has been claimed that subarachnoid alcohol or phenol does not produce the same beneficial effect in the upper thoracic and cervical segments (67,68). Several factors are involved. The dural sheath in which the neurolytic agent “settles” in the cervical segments is relatively short, and the cervical nerve roots and rootlets have a short intrathecal course and therefore have less exposure to the neurolytic agent. Also, the spinal canal is narrow, with a stronger current of CSF that tends to carry the neurolytic agent away from the target nerve rootlets. Bonica obtained good results, however, by inserting a needle through each of the interspinous spaces involved and injecting 0.2 mL of absolute alcohol in 0.05-mL aliquots through each of two or three needles (see Fig. 104-20). Others have used extradural or subdural injection of phenol for this purpose.

Results. Various reports on the results of therapy using subarachnoid neurolytic blockade are difficult to compare because of differences in the assessment of pain and of pain relief, the types and sites of tumor for which the procedure was done, and the sites and doses of alcohol injection. Moreover, many of the reports lack specific data on the incidence, severity, and duration of side effects and complications.

Table 104-3 summarizes some of the most important reports of results with subarachnoid alcohol, and Table 104-4 summarizes some reports of results obtained with phenol in glycerin. *Good* pain relief means the patient obtained complete or almost complete relief of pain for which the procedure(s) was done until the patient's death; *fair* relief means complete relief of pain for less than 1 month or pain relief of 50% or more until the patient's death; and *poor* relief means that the patient experienced partial relief for a few days or no relief at all. In many cases, more than one block was done to achieve the reported results. Based on personal experience, Bonica believed that in those reports in which the incidence of combined good and fair relief was lower than 60%, an improper technique was used. For example, the neurolytic agent was injected into the lumbar region and then change in posture was used in an attempt to direct the neurolytic agent to the affected segments in the mid- or high thoracic area. As Bonica (2) emphasized, this practice not only produces inadequate pain relief but also results in an unacceptably high complication rate.

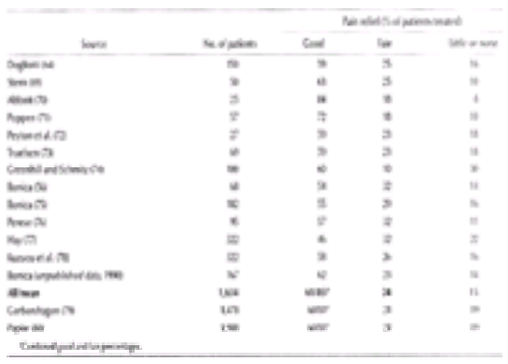

TABLE 104-3. Comparison of results with subarachnoid alcohol block for the relief of cancer pain

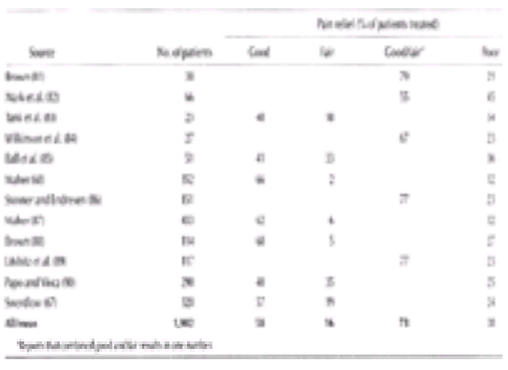

TABLE 104-4. Comparison of results with intrathecal phenol in glycerin or iophendylate for cancer pain

In 1951, Bonica (56) presented the first report analyzing the results obtained in 194 patients with cancer pain who were treated with various neurolytic techniques, including 68 patients who received 107 subarachnoid blocks with alcohol. As noted in Table 104-3, 37 patients (54%) obtained complete or almost complete relief of pain, which permitted the gradual reduction in dosage of strong opioids in those who had received them. Another 22 patients (32%) had partial relief and were made comfortable with moderate doses of opioids and adjuvants (usually less than half the amount they had been receiving at the time of the block). Despite one or even two reinjections, nine patients (14%) derived only transient relief of pain and required strong opioids.

Seven years later, in 1958, Bonica published a summary (75) of the results obtained in an additional 114 patients, which was added to the results of the first group and shown as a second series in Table 104-3. Although the results regarding pain relief were similar, those in the second group experienced a lower incidence of complications (Table 104-5), because the earlier experience (when one needle was used to inject 1.0 to 1.5 mL of alcohol to block several segments) prompted him to adopt the multiple-needle technique and to inject small volumes of alcohol as explained above. In the ensuing 19 years, Bonica carried out subarachnoid block with alcohol in an additional 167 patients, who received a total of 228 blocks (see Table 104-3) (*unpublished data*). As noted in Table 104-3 and Table 104-5, the analgesia improved slightly, with a further decrease in complications, reflecting a more conservative attitude and a more careful selection of patients.

Source	No. of patients	Complications (% of patients treated)*			
		Bladder paresis	Bowel paresis	Muscle weakness	Other
Alcohol					
Peyton et al. (72)	27	29–44		15–30	4–30
Bonica (56)	68	7–15	4–7.5	9–22	3–15
Bonica (75)	162	4–15	1–2.5	8–15	4–13.9
Hay (77)	202	0.7	1	1	14
Kucuru et al. (78)	322	0.6–8.9	0.6–0.1	1.1–0.9	1.5
Bonica (unpublished data, 1958)	167	3–15	4–7.5	7–15	
Phenol in chlorocresol					
Pagni and Tinca (90)	210	4.7–1.5		6.8–13.8	
Stoever and Lindeveer (86)	151	4–15	1.5–13.5	7–22	2
Lifshitz et al. (89)	133	22	2.2	23	
Swerdlow (67)	300	12	1.5	3.3	4

*Percentages in parentheses represent prolonged complications.

TABLE 104-5. Complications with the use of subarachnoid neurolytic block for cancer pain

It is generally acknowledged that, in the hands of those who have experience extensive enough with one or the other agent to be considered an “expert,” the results of therapy with subarachnoid alcohol are similar to those obtained with phenol in glycerin. Pain relief appears to be better and to last longer with alcohol, however, than with phenol. On the other hand, Maher (68) stated that phenol is easier to handle, spares “non–pain-conducting fibers,” and yields better results than alcohol. The latter two advantages are disputed by the histologic evidence previously cited in Basic Information, earlier in this chapter, and also by the clinical experience of those who have used both agents. Brown (91) stated that “alcohol has proved to be easier to control and to achieve better results than when phenol solutions are employed.”

Important causes of failure with the use of subarachnoid neurolytic agents include intraspinal tumor infiltration, which prevents the neurolytic agent from coming into contact with the rootlets. Therefore, prior to carrying out the procedure, it is essential to rule out this possibility by appropriate radiographic tests, such as computed tomography (CT) or magnetic resonance imaging, especially in patients who have tumors that are likely to spread or metastasize to the intraspinal canal. If such screening has not been done and the first injection effect, one should consider this possibility. Prior radiation therapy to the spinal canal can also interfere. It is also important to consider assessing patients for other sites or causes of pain, such as physical disabilities. A frequent cause of “failure” is the extension of the lesion, with consequent pain beyond the area in which block for the previous pain remains effective. In such a case it would be necessary either to carry out an additional subarachnoid block or another neurolytic technique. Consideration should also be given to cordotomy in such a patient (Chapter 106).

Complications. Complications can occur even when a flawless technique is used, but the incidence of serious complications can be minimized by proper selection, preparation, and positioning of patients and by the use of precise technique. Some complications are transient; others occur rarely and only with a break in aseptic technique, whereas still others can occur as a result of diffusion of the neurolytic agent to the anterior roots in the lower cervical and T-1 regions or to the lumbosacral region. Headache can occur following the block, but this is transitory and responds well to conservative therapy. Aseptic meningitis, caused by irritation by the neurolytic agent, occurs but is rare. Septic meningitis can also occur, but only a few cases have been reported (60).

Paresis or paralysis of muscles occurs if the anterior rootlets are sufficiently involved in the pathophysiologic process to interrupt motor function. Involvement of the anterior roots by the neurolytic agent in the three middle sacral segments interrupts the parasympathetic fibers to the bladder, the rectum, and lower colon, which could cause loss of sphincteric function, urinary retention, and bowel incontinence. Annoying and sometimes distressing side effects of block of the posterior rootlets include loss of proprioception and touch and dysesthesias. Complication rates reported by various authors are presented in Table 104-5. Fortunately, most of these complications are transient. A case of fatal meningitis was believed to have been caused by meningeal irritation by silver nitrate incorporated into the phenol solution (60). A few patients with postblock paraplegia were subsequently found to have vertebral metastasis (71).

Muscle weakness in the upper or lower limbs occurs as a result of involvement of the anterior roots, the risk being much higher in the lower limbs because of the proximity of the anterior and posterior roots in the lumbosacral enlargement of the cord (at the T-10 and L-1 vertebral levels). Below the L-1 level, injection is made into the cauda equina, where the anterior and posterior rootlets are not as well separated as above these levels. Except in patients who have severe respiratory , paresis of the intercostal muscles, of segments of the abdominal muscles on one side, or even of a few segments bilaterally, do not significantly affect ventilation.

Bladder dysfunction occurs most frequently with injection below the T-10 interspace. Although some have reported that injection to relieve perineal pain at the L-5 interspace is associated with an incidence of bladder paresis ranging from 25% to 60% (92), use of the technique shown in Figure. 104-22 is associated with an incidence lower than this.

Gerbershagen (79) reviewed reports that provided data on the duration of 303 complications (Table 104-6) and obtained the following results: 28% disappeared within 3 days, 23% disappeared within 1 week, 21% disappeared within 1 month, 9% disappeared within 4 months, and 18% lasted longer than 4 months. Table 104-7 presents an analysis by Swerdlow (67) of the incidence of complications in 300 patients managed with 5% or 7% phenol in glycerin, 2% or 2.5% chlorocresol in glycerin, or a combination of these.

Complication	No. of patients with complications (%)		
	Transient	Permanent	Total
Paresis or paralysis	92 (4.3)	18 (0.8)	110 (5.2)
Bladder dysfunction	137 (6.4)	16 (0.8)	153 (7.2)
Bowel disorder	8 (0.4)	3 (0.1)	11 (0.5)
Other	19 (0.9)	10 (0.5)	29 (1.4)
All/mean	**256 (12)**	**47 (2.2)**	**303 (14.3)**

From Gerbershagen HU. Neurolysis: subarachnoid neurolytic blockade. *Acta Anaesthesiol Belg* 1981;32:45–47, with permission.

TABLE 104-6. Complications of 2,125 alcohol subarachnoid blocks

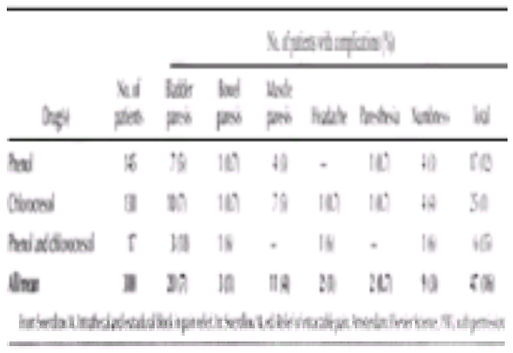

TABLE 104-7. Complications lasting longer than 7 days

Epidural Neurolytic Blockade

The theoretical advantages of the use of epidural injection over intrathecal neurolysis include less risk of meningeal irritation, less spread of the solution to cranial nerves, and supposedly less risk of bladder and rectal involvement. Swerdlow (67) used epidural neurolytics in noncancer intractable pain, and a fair degree of success was achieved with the injection of phenol in glycerin. Madrid (93) used 7.5% phenol in glycerin and noted good pain relief in a high percentage of patients. Others have used aqueous phenol injected through an epidural catheter. Raftery (94) reported using an epidural catheter and used intermittent doses of 0.5 to 1.0 mL of 6% aqueous phenol, which produced good pain relief in 65% of 27 patients. While staff members of the Clinical Pain Service at the University of Washington, Colpitts and associates (95) used epidural phenol on patients with cancer-related pain and obtained prolonged pain relief in slightly more than 80% of patients. Racz and coworkers (96) have used phenol in saline for the same purpose. More recently, Korevaar (97) reported favorable results using transcatheter thoracic epidural neurolysis achieved with ethyl alcohol.

Most authors use phenol in glycerin, but some use an aqueous solution of phenol. The technique of epidural puncture is described in detail in Chapter 102. A 22-gauge needle can be used for a single injection of aqueous phenol, but it is necessary to use a 20-gauge spinal needle for injection of phenol in glycerin. Once the bevel of the needle is in the epidural space, the patient is tilted backward into a 45-degree angle (as for subarachnoid phenol injection) and a test dose of 0.2 mL of phenol is injected. After ascertaining that the solution has not been deposited into the subarachnoid space, approximately 2 mL of 7% phenol in glycerin or of 8% to 10% aqueous phenol is injected for each nerve root to be blocked. Swerdlow (67) has recommended that in the cervical region the dose should be 1.5 mL per dermatome. After injection the patient remains in the tilted position for approximately 40 minutes. With successful blocks, pain disappears in 10 to 15 minutes.

Swerdlow (67) reported relief of pain for as long as 9 months, but Madrid (93), using 7.5% phenol in glycerin for pain in the neck, noted that pain relief lasted only a few days. Some clinicians have used an epidural catheter to allow repeated injections of phenol in glycerin into the cervical region. The epidural puncture is made at the C-7 to T-1 interspace and the catheter is advanced 4 to 5 cm.

Placement of the catheter can be checked by injection of a small amount of contrast medium, which should produce a rather diffuse outline immediately anterior to the posterior wall of the pierced canal. Catheter placement can also be checked by injection of small doses of a local anesthetic, such as 2 mL of 1% lidocaine at 15- to 20-minute intervals, and this should produce a narrow band of segmental sensory loss. If a local anesthetic is used for this purpose, it is essential to allow the anesthetic to dissipate and to wait 2 hours more after its disappearance before the neurolytic agent is injected.

In a series of 18 patients with cancer pain treated with this technique (98), six of 11 patients (54%) with metastatic cancer and six of seven patients (86%) with primary cancer derived good relief. In patients with primary cancer, pain relief lasted less than a month in one patient (17%), 1 to 3 months in three patients (50%), 3 to 6 months in one patient (17%), and longer than 6 months in one patient (17%). In those with metastatic cancer, the figures were 3 months (50%), 2 months (33%), 0 (0%), and 1 month (17%). Among those patients whose pain returned within 1 month, a second series of injections increased the duration of relief by 1 to 3 months.

In treating patients with cancer-related pain, Colpitts and associates (95) first stabilized them on a narcotic-containing “pain cocktail” (Chapter 84). Once patients were stabilized, the amount of opioid was gradually reduced until patients began to experience moderate pain. The epidural catheter was inserted and placed with its tip in the center of the band of pain and 3 to 4 mL of 1% to 2% lidocaine was injected to ascertain the proper position of the catheter and the volume of phenol required to relieve the pain. They then injected the same volume of phenol, and patients were observed for 24 hours. Patients were followed in a Veterans Administration hospital, where they were either inpatients or outpatients who returned for follow-up every 2 weeks. Pain relief lasted until all the patients who had initial relief died, which varied from 3 weeks to 4.5 months.

Korevaar (97) has recently reported on the use of a technique similar to that reported by Raftery (94) for phenol. He used “transcatheter” thoracic epidural neurolysis with alcohol in 36 consecutive inpatients with intractable somatic or visceral pain of malignant and nonmalignant origin that was referable to the cervical or thoracic nerve roots. These included 14 patients with cancer of the pancreas, 13 with metastatic cancer in the abdominal or thoracic region, four with chronic pancreatitis, two with postherpetic neuralgia (in the T-4 and T-5 regions), and three with diffuse abdominal pain of unknown origin.

The epidural catheter was introduced so that its tip was in the center of the dermatomal pain distribution (97). Five to 7 mL of 0.25% bupivacaine was injected in 2-mL increments to determine correct catheter placement. Patients were in a 30-degree, head-up supine position for bilateral visceral or somatic pain or were positioned with the affected side up in a lateral position for unilateral somatic pain. Once the efficacy of the local anesthetic block had been ascertained, Korevaar (97) injected increments of 0.2 mL of absolute alcohol until 3 to 5 mL of neurolytic agent had been injected over a 20- to 30-minute period.

After completion of the alcohol injections, the catheter was flushed with 0.25 mL of the 0.25% bupivacaine solution and capped (97). Patients were returned to their hospital rooms 30 minutes after completion of the injections and followed for pain relief. The second and third alcohol injections were done on a daily basis unless patients experienced 100% pain relief that persisted over a 24-hour period and decreased their opioid use by at least 25%. On the second and third days, 3 to 5 mL of ethyl alcohol was slowly injected 10 minutes after the catheter was tested using 2 mL of 0.5% bupivacaine.

Patients were monitored closely; 89% of patients reported 70% pain relief or greater, supported by a decrease in opioid dose of 25% or more; this was defined as successful treatment (97). All 27 patients who had pancreatic and metastatic cancer had immediate pain relief that continued for the first week, as compared to pain relief in 55% of patients with nonmalignant chronic pain. The overall duration of pain relief for patients who had been successfully treated ranged from 2 weeks to 7 months (mean, 3.3 months), reflecting the large number of patients who died of their underlying illness during the period of study. Twelve patients with cancer died within 4 months after treatment. Twenty patients who died during the study reported continued relief of pain until death, and 12 patients survived long enough to have recurrence of pain. The duration of pain relief in these patients extended from 3 weeks to 7.25 months (mean, 4.4 months). Although a few complications such as hypotension, vomiting, pain on injection, and pain at the site of the catheter during the first 3 days were noted, no long-term serious complications occurred. Korevaar's results (97) are impressive and suggest that the technique should be given a more extensive trial.

Subdural Neurolysis

In 1960, Maher (68) introduced the use of the subdural injection of phenol in glycerin for the cervical and upper thoracic regions as an alternative to subarachnoid neurolysis. Since then, the technique has been used by only a few others and the results have not been impressive.

Neurolytic Sympathetic Blockade

Chapter 102 reviews indications for sympathetic blocks with local anesthetics for various painful conditions in the upper limb, visceral pain, severe pain caused by disease of the thoracic or abdominal viscera, and other painful conditions in the lower limbs. This section describes the injection of neurolytic agents to cause destruction and consequent prolonged interruption of sympathetic pathways in various parts of the body, including indications, techniques, results, and complications of neurolytic block of the thoracic chain, celiac plexus, splanchnic nerves, and lumbar sympathetic chain.

To obtain optimal results with these procedures it is essential to adhere to the basic principles of application, including preliminary preparation and various other considerations (Chapter 102). Because the use of neurolytic agents can be associated with serious and unwanted side effects and complications, neurolytic blocks of this part of the nervous system must be preceded by two or more diagnostic or prognostic blocks using local anesthetics with different durations of action. These give information on the diagnosis and pathophysiologic mechanism(s) underlying the condition and help to ascertain whether prolonged interruption is going to be beneficial.

Block of Thoracic Sympathetic Chain

Indications

Block of Sympathetics to the Upper Limb. Block of the sympathetics to the upper limb achieved by the neurolytic blockade of T-2 and T-3 and the interganglionic part of the chain is indicated in the management of complex regional pain syndromes (CRPS) types I and II, postamputation pain syndromes, and other painful neuropathic conditions discussed in detail elsewhere in this book. Block of the same structures is indicated for certain chronic occlusive vascular diseases affecting the upper limb in individuals in whom preliminary blocks with local anesthetic have indicated that prolonged interruption would prove beneficial.

There are anatomic and physiologic bases for limiting neurolytic block to the T-2 and T-3 ganglia and the interganglionic chain to produce prolonged interruption of the sympathetics of the upper limb. The peripheral portion of the sympathetic supply to the upper limb is composed of preganglionic neurons whose cell bodies are in the intermediolateral horn of the spinal cord at the T-2 to T-8 or T-9 levels, while their axons pass along the anterior root of the spinal nerves, the white rami communicantes, and pass to the lateral sympathetic chain. Here they ascend cephalad and synapse with the postganglionic fibers, primarily in T-2 but also in T- 3 and in the stellate and middle cervical ganglia. By blocking T-2 and T-3, which are considered to be “key” synaptic stations, all the sympathetic nerves destined for the upper limb can be interrupted.

Sympathetic block of the upper limb is usually achieved by anterior paratracheal block of the cervicothoracic sympathetic chain (see Chapter 102 and Fig. 102-51). With this technique, however, injection of a neurolytic agent carries a high risk of producing a prolonged Horner's syndrome, prolonged block of the recurrent laryngeal nerve with impairment of phonation, unintentional block of the brachial plexus, or accidental injection of the neurolytic agent into the vertebral artery. Moreover, a small number of patients apparently have fascial barriers that prevent the caudad diffusion of the neurolytic agent to involve the T-3 and sometimes even the T-2 ganglia. In the latter case, this would result in an incomplete sympathetic denervation of the upper limb in those patients who have the anomalous sympathetic pathway known as *Kuntz's nerve*, which bypasses the stellate ganglion. The posterior approach to the T-2 and T-3 sympathetic ganglia and the interganglionic chain obviates this problem and is less likely to produce the other complications of paratracheal block.

Block of Sympathetics to the Chest. Neurolytic block of the sympathetic chain at the levels of the T-1 to T-5 ganglia is used for the relief of pain in the rare patient with severe intractable cardiac pain that is not relieved by medical therapy and is not amenable to aortocoronary bypass surgery or to percutaneous intramural angioplasty. Neurolytic block of the sympathetic chain from T-2 to T-8 using multiple needles can be used in those with severe intractable pain caused by carcinoma of the esophagus or by some other chronic pathologic process of the upper two-thirds of the esophagus. If the lesion is in the lower part of the esophagus, it is necessary to block the splanchnic nerves, which contribute an important sensory nerve supply to the lower third of the intrathoracic part and to the abdominal portion of the esophagus.

In all these cases, neurolytic block is intended to destroy the sensory fibers that convey nociceptive impulses from the thoracic viscera. Interruption of sympathetic efferent fibers can also help to relieve pain by eliminating any arterial vasospasm. Finally, neurolytic block of the sympathetic chain extending from T-2 to T-6 is indicated in patients who have chronic intractable pain caused by aortic aneurysm and who are not suitable for neuroablative surgery. White and Sweet (55) used this technique in a number of patients with large and intensely painful aneurysms of the aortic arch after a preliminary block with procaine produced complete pain relief.

Block of Sympathetics to the Abdominal Viscera. Neurolytic block of the lower two-thirds of the thoracic sympathetic chain is indicated in patients with severe intractable pain produced by cancer of one or more of the viscera. It may be considered cautiously in chronic pancreatitis or in some other chronic disease of one or more of the abdominal viscera that is not amenable to other therapy. Block of individual segments that supply each of the various viscera with a local anesthetic can be used as a diagnostic procedure. However, in most patients with severe intractable persistent pain, it is preferable to carry out a neurolytic block of the celiac plexus or of the three thoracic splanchnic nerves (see below).

Technical Considerations. The anatomy of the thoracic sympathetic trunk is discussed in detail in Chapter 102 and depicted in Figure 102-27 as well as in Figure 104-27 and Figure 104-28 in this chapter.

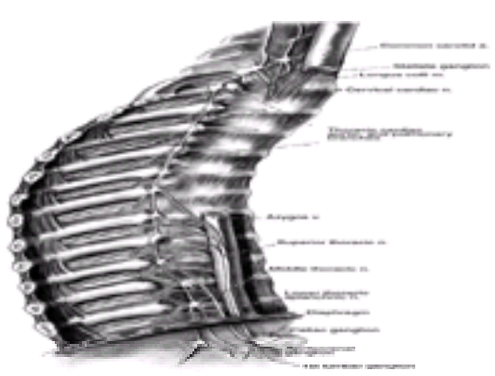

Figure 104-27. Anatomy of the right thoracic sympathetic chain showing the precise relation of the ganglia to the vertebrae and ribs at various levels, as well as the major branches given off by the chain. The T-2 sympathetic ganglion is located anterior to the medial portion of the neck of the rib, the T-3 to T-6 ganglia are located in front of the head of the corresponding ribs, the T-7 to T-10 ganglia are located anterior to the radiate ligaments of the costovertebral joints, and the T-11 to T-12 ganglia are more anteriorly placed than the rest and are on the lateral surface of the vertebral bodies. In the upper three or four segments, the lower half of each ganglion is located in front of the upper portion of the neck or head of the rib. In the lower thoracic segments, the ganglia are located in front of the head of the ribs, extending their total length. This is clinically significant because the point of the needle cannot be placed in contact with the lower ganglia. In the upper three segments, the intercostal vessels are immediately posterior to part of the ganglia, whereas in the lower segments, where the ganglia rest wholly on the periosteum of the neck or head of the ribs, these vessels are superior to the ganglia. The somatic spinal nerves pass posterior and cephalad to the interganglionic chain. Moreover, the pleura is immediately in front of and closely related to the ganglia, being separated from the ganglia by the thin endothoracic fascia.

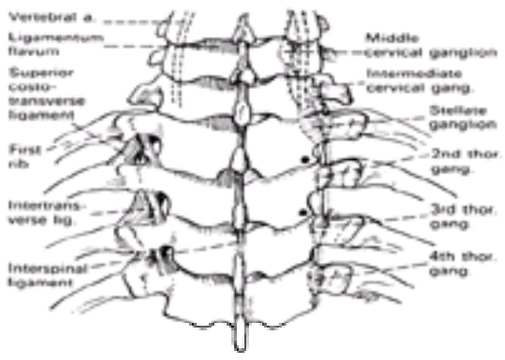

Figure 104-28. Posterior view of the lower cervical and upper thoracic vertebrae showing the relationships of the sympathetic chain to the vertebra and vertebral artery. The supraspinous ligament has been removed to more easily identify the posterior tips of the spinal processes. The sympathetic ganglia (on the right, depicted by *stippled areas* surrounded by *dashed lines*) are lying in front of the necks of the ribs. The black solid circles indicate the site of contacting the lower and lateral part of the lamina with the bevel of needles inserted by the paralaminar technique (see Fig. 104-29). Injection at the level of the T-2 and T-3 ganglia causes block of this portion of the chain and consequently completes interruption of the sympathetic supply to the upper limbs, while block of T-1 to T-5 denervates the heart. (Modified from Bonica JJ. *Sympathetic nerve blocks for pain diagnosis and therapy.* New York: Breon Laboratories, 1981.)

To obviate the problem of pneumothorax, commonly seen with the classical approach, Bonica developed the paralaminar technique (Fig. 104-29). For injection of the neurolytic solution, an 8- or 10-cm, 22-gauge, short-beveled needle is used with a 2-mL glass syringe that has been tested to ensure that its wet plunger fits properly so that it can be advanced and withdrawn without any resistance. This is crucial to the second step of determining passage of the bevel of the needle through the superior costotransverse ligament. For verification of the level of the injection, it is highly desirable to use an image intensifier and to know the relationship between the posterior lower end (tip) of the spinous process of one vertebra and the lamina to be contacted at the cross-sectional plane (Fig. 104-30).

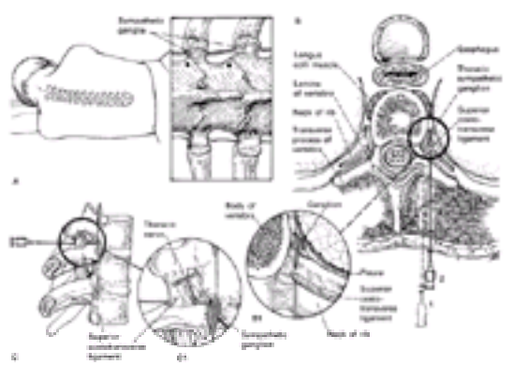

Figure 104-29. Paralaminar technique of blocking the thoracic sympathetic ganglia and interganglionic part of the chain. **A:** Position of the patient on the side, with the spine flexed. Inset: Close-up of the T-5 and T-6 vertebrae shows the relation of the sympathetic ganglia anterior to the necks of the ribs and the sites of contact of the bevel of the needles with the laminae of the vertebrae. At this level, the site of puncture is at the same cross-sectional plane as the posterior end of the spinous processes of one vertebra above (T-4 and T-5). Skin wheals are made 2 cm lateral to the midline of the back with a 5-cm, 25-gauge needle, which is then inserted and directed anteriorly. The dilute local anesthetic solution is liberally injected into the subcutaneous tissue and muscle and onto the periosteum of the ipsilateral laminae to produce a tract of analgesia. **B:** Cross-sectional view at the level of the T- 5 vertebra showing the two steps in placing the point of the needle. After a few minutes, an 8- or 10-cm, 22-gauge, short-beveled needle adapted to a 2- mL glass syringe with a Luer-Lok and containing saline is inserted and advanced until the lamina is again identified (needle 1). At this point, a depth marker is placed 1.5 cm from the skin, the needle is withdrawn until its point is in the subcutaneous tissue, and the skin is moved 0.5 cm laterally. The needle is then advanced in the same sagittal plane parallel to the first insertion (needle 2). When advanced to the same depth as the lamina, its point contacts either the lateral edge of the lamina or the superior costotransverse ligament, which is lateral to the lateral edge of the lamina and just above the transverse process of the vertebra below. Here the needle encounters a structure that is much less resistant than bone but more resistant than muscle—the superior costotransverse ligament—as shown in **C**, which is a schematic lateromedial view of the vertebrae, the proximal parts of the ribs, and the superior costotransverse ligament. Once the point of the needle has engaged the ligament, the needle is advanced slowly (2 mm at a time) while exerting continuous unremitting pressure on the plunger of the syringe. A sudden loss of resistance indicates that the bevel of the needle has traversed the ligament and is wholly anterior to the anterior surface of the ligament. The needle is then advanced another 7 to 10 mm so that its bevel is in the same coronal plane as the anterior surface of the neck or head of the rib, as shown in position 2 **(B)** and in inset **B1**, which is an enlargement of the circled area in B and shows the point of the needle in contact with the upper pole of the sympathetic ganglion. **C1:** Enlargement of the circled area in C showing the needle through the ligament. Its point is in contact with the upper pole of the ganglion. Once the needle is considered to be in a proper position, 1 mL of saline solution is injected to dislodge any tissue in the needle. Aspiration is then attempted in two planes to ensure that the point of the needle is not in a vessel or within a prolonged dura-arachnoid cuff. After a negative aspiration, a test dose of 1 mL of 0.5% bupivacaine anesthetic solution is injected. If no sign of subarachnoid block or other complications is evident, 2 to 3 mL of 0.25% bupivacaine or 2 to 3 mL of a neurolytic agent is injected. This volume is usually sufficient to block one segment (a ganglion and its upper interganglionic fibers). The procedure is repeated at subsequent lower levels.

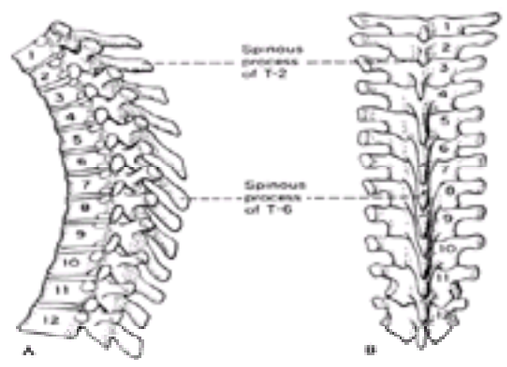

Figure 104-30. Posterior view **(A)** and lateral view **(B)** to show relationship at the cross-sectional level of the lower tip of the spinous processes and laminae. The lower tip of the spinous process of the T-1 vertebra is at the same cross-sectional level as the lamina of the T-2 vertebra. Because of the greater imbrication of the spinous processes in the middle thoracic region, the spinous process of the T-6 vertebra is at the same cross-sectional level as the upper portion of the lamina of T-8 (i.e., two segments below). In the lower portion of the thoracic vertebra, much less imbrication is present and, consequently, the spinous process of T-11 is at the same cross-sectional level as the lamina of T-12 and the spinous process of T-12 is at the same cross-sectional level as the middle of the lamina of L-1.

The needle is inserted only 2 cm lateral to the spinous process, and its contact is made in the lower portion of the lateral part of the lamina. The second insertion places the bevel of the needle just above the upper surface of the rib below and at some distance below and anterior to the thoracic somatic nerve (see Fig. 104-29C, Fig. 104-29C1). This placement decreases the risk of involving the somatic nerve with the neurolytic agent. Compare Figure. 104-30 with Figure 102-22, which shows the technique of blocking the thoracic somatic nerve. For somatic nerve block, the needle is inserted more cephalad to contact the upper portion of the lateral part of the lamina and then is made to pass through the upper portion of the superior costotransverse ligament below the transverse process of the vertebra above.

If the technique is carried out by someone who has a thorough knowledge of the anatomy, is skilled in regional analgesia, and proceeds slowly and cautiously, the

risk of contacting the somatic spinal nerve and puncturing the dura is lower than with the use of the classic posterior approach. Even the approach described here, however, requires patience and skill to avoid advancing the needle too far anteriorly, which could pierce the lung.

Complications. Possible complications of the paralaminar technique for blocking the thoracic sympathetic chain include puncture of the lung from placing the needle too far anteriorly, producing pneumothorax; puncture of the intercostal vein or artery; or contact with the thoracic somatic nerve if the bevel of the needle is placed higher than recommended. If aspiration is not carried out in two planes, the neurolytic agent might be injected into the vessel, with consequent necrosis, or into the subarachnoid space of a prolonged dural cuff, with consequent diffusion to the subarachnoid space, prolonged block of the somatic nerve, or both. All of these complications can be prevented with proper technique.

Neurolytic Block of the Celiac Plexus

Indications. Neurolytic block of the celiac plexus is useful in relieving severe intractable pain caused by cancer or chronic visceral disease. In addition to blocking all the nociceptive (pain) pathways that supply the viscera in the upper abdomen, the procedure relieves visceral vasospasm and other pathophysiologic processes caused by abnormal reflexes consequent to persistent noxious stimulation by the disease process. Because the celiac plexus contains vagal afferents and efferents, block of this structure interrupts the sensory fibers that transmit nonnociceptive information and the parasympathetic outflow to the abdominal viscera. Prior to neurolytic block of the celiac plexus, it is essential to carry out at least one and preferably two diagnostic or prognostic blocks with a local anesthetic. Doing so enables prediction of the effects of the neurolytic blockade. The neurolytic agent diffuses to a lesser extent than the local anesthetic, so it is essential to carry out the preliminary block with a volume of local anesthetic that is about two-thirds the volume of neurolytic agent to be injected.

Anatomic Basis The neuroanatomic basis for block of the celiac plexus is summarized and illustrated in Figure. 104-31. More than 60 years ago, Hovelacque (99) emphasized that, contrary to the classic textbook description, the celiac ganglia vary in number, size, and location; more recently, Ward and associates (100) "rediscovered" this fact. The number of ganglia varies from one to five, and the size of each ranges from 0.5 to nearly 5.0 cm in diameter. Moreover, they are located at a variable distance in the anteroposterior plane from the anterior surface of the L-1 vertebra, which is used as a landmark in blocking the plexus. In addition to understanding the anatomy of the celiac plexus itself, it is also essential to understand the anatomy of the surrounding structures, which might be subjected to trauma by needles, drugs, or both. On the right side, and anterior to the plexus, is the inferior vena cava, and on the left side is the aorta, with the kidneys posterolateral to these vessels. Anteriorly, the plexus is near the posterior surface of the pancreas.

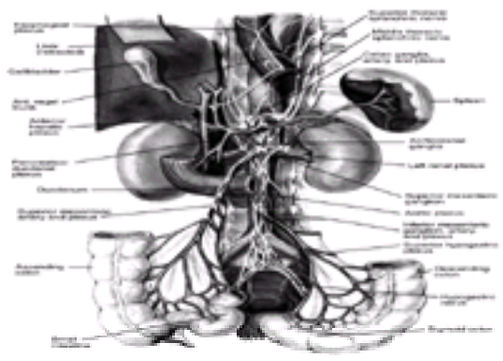

Figure 104-31. Anatomy of the celiac plexus and subsidiary plexuses. The celiac plexus occupies an area 3 cm long and 4 cm wide between the two adrenal glands. It is located in the epigastrium just anterior to the crura of the diaphragm around and below the celiac axis and on either side of the midline. It is often subdivided into right and left portions and consists of a number of prevertebral ganglia and a dense network of autonomic fibers that unite and enmesh these ganglia. The autonomic fibers include sympathetic preganglionic fibers contributed by the thoracic splanchnic nerves, sympathetic postganglionic fibers provided by the lumbar splanchnic nerves (contributed by the lumbar sympathetic chain), and parasympathetic preganglionic fibers contributed by both vagus nerves. Sensory fibers are contributed by the phrenic nerves, the vagus nerves, and the splanchnic nerves, which provide sympathetic afferents. Only the phrenic and sympathetic afferents transmit nociceptive information from the upper abdominal viscera. Although the celiac ganglia are usually depicted as two large masses, semilunar in shape and located on each side of the origin of the celiac axis, their shapes and sizes are actually variable. Note the location of the superior and inferior mesenteric ganglia and plexuses.

Technique The technique of neurolytic celiac plexus block (NCPB) is illustrated in Figure. 104-32. Preparation of patients should include discontinuing antihypertensive agents, which could enhance the hypotensive effect of the block, and anticoagulants, which could produce excessive bleeding. No sedatives or narcotics should be given for the prognostic block, which, if done correctly, should be rather painless. Because the injection of alcohol causes severe pain, sedatives and opioid analgesics can be given parenterally 15 minutes before the block and should not interfere with the results. All patients should have supplemental intravenous fluids in doses of 10 to 15 mL per kg as a bolus at the time of the alcohol block.

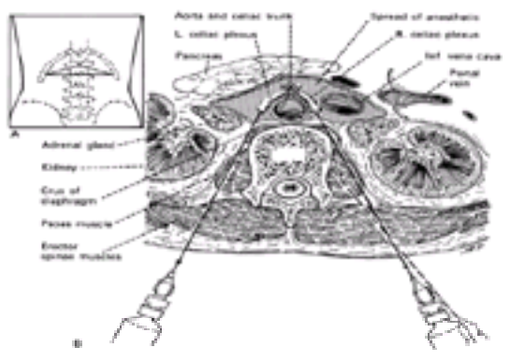

Figure 104-32. Technique of blocking the celiac plexus. The patient is placed prone with a pillow under the abdomen after an intravenous infusion has been started. **A:** The spinous processes of T-12 and L-1 are marked, as are the lower borders of both twelfth ribs, and these are connected to make a flattened isosceles triangle. Skin wheals are raised 6 to 7 cm lateral to the inferior part of the quadrilaterally shaped spinous processes of L-1. **B:** Using a 25- gauge disposable spinal needle, the subcutaneous fascia and muscles are infiltrated with a dilute solution of local anesthetic. Security needles of proper length are selected for injection of the local anesthetic or of a neurolytic agent. Each needle, with a depth marker attached, is inserted through the skin wheal with its bevel facing medially and directed so that its shaft makes an angle of 40 degrees with the midsagittal plane. The first needle should be inserted on the left so that contact with the lateral aspect of the aorta can be ascertained by feeling the transmitted pulsation up the shaft of the needle, which is held firmly. This provides an approximation of how far the right needle needs to be advanced. The needle is then advanced slowly until contact with the lateral surface of L-1 is made, usually at a depth of 8 to 9 cm. If bony contact is made more superficially, it is likely that the needle has contacted the transverse process; if this occurs, the needle must be withdrawn and redirected to advance below the transverse process. Once the needle impinges on the lateral side of the body of the L-1 vertebra, the rubber marker is placed 4 cm from the skin. The needle is withdrawn until its point is in the subcutaneous tissue, the angle is decreased by 30 degrees on the left side, and it is readvanced slowly until the marker is flush with the skin. At this point, the pulsation of the aorta should be felt, indicating that the needle is lateral to the vessel. If bone is encountered before the marker is flush with the skin, the needle is withdrawn and readvanced so that its shaft makes an angle of 25 degrees with the sagittal plane. This permits passage of the needle without further bony contact; it is then advanced until the marker is flush with the skin. The depth is noted, and the right needle is similarly inserted and advanced, except that, on the second insertion, the needle is directed so that its shaft makes an angle of 35 degrees. If bone is contacted, the needle is withdrawn and the angle is decreased to 30 degrees because the aorta is to the left of the midline. Once the needles have been positioned, aspiration is attempted in four quadrants to rule out accidental intravascular or subarachnoid injection. For diagnostic purposes with local anesthetics, 15 mL of 0.5% bupivacaine with epinephrine is injected through each needle. This is usually sufficient to spread and involve the celiac and subsidiary plexuses laterally as far as the adrenal glands. The injection of solution should offer no resistance because it is made into the loose areolar tissue of the retroperitoneal space. An effective block generally relieves abdominal pain within 15 minutes, and the patient manifests orthostatic hypotension. If difficulty is encountered, it is advisable to use an image intensifier or computed tomographic scanning to place the bevels of the needles correctly. A volume of 15 to 20 mL of 50% alcohol is injected through each needle for a neurolytic block.

It is important to use a needle that is of sufficient length—10 cm for thin individuals, 12 cm for average patients, and 15 cm for obese or muscular persons. There is some discussion in the literature: Thompson and Moore (101) preferred a 20-gauge needle, Brown et al. (102) had no preference, and Bonica preferred a 22-gauge needle to a 20 gauge since it was less traumatic.

The neurolytic solution consists of equal parts of absolute alcohol and saline solution or, preferably, 0.75% bupivacaine or 2% lidocaine to lessen the severe alcohol-induced pain. If radiographic control of the spread of the solution is to be done, a mixture containing 25 mL absolute alcohol, 18 mL local anesthetic, and 7 mL of contrast medium should be used.

The needle should pass through the crura of the diaphragm and have its bevel lateral to both sides of the aorta, just below the level of the celiac plexus (see Fig. 104-32). Although the plexus is presumably in loose areolar tissue behind the pancreas, which enhances the diffusion of local anesthetic drugs, Moore (103) verified needle placement and spread of injected solution by conventional radiography and by CT scan and showed that spread of the solution tends to be confined to the side of the injection. Therefore, it is essential to do a bilateral block to obtain maximum pain relief.

Several modifications of the classic technique have been described. Some authors insist that radiographic control is absolutely essential for proper placement of the needle and visualization of the neurolytic agent. In a critical analysis of results in 136 patients who underwent NCPB for the relief of pancreatic cancer pain, Brown and associates (102) found that radiographic verification of needle position does not influence the quality of the block. Nevertheless, radiographic control can be helpful, especially to those who have not had extensive experience with celiac plexus block. It should be used if the initial block fails to produce complete pain relief (Fig. 104-33).

Ischia and colleagues (104) have developed a technique that uses a combination of fluoroscopy and fingertip feel to penetrate the aorta with a 20-gauge needle intentionally. The needle is advanced until its bevel penetrates the anterior wall and no blood can be withdrawn. Theoretically, this places the bevel of the needle directly in the middle of the preaortic network of the celiac plexus and should guarantee correct placement, but it confers the risk of producing postblock hemorrhage: In this series, six patients developed retroperitoneal hematoma, as shown by CT scan.

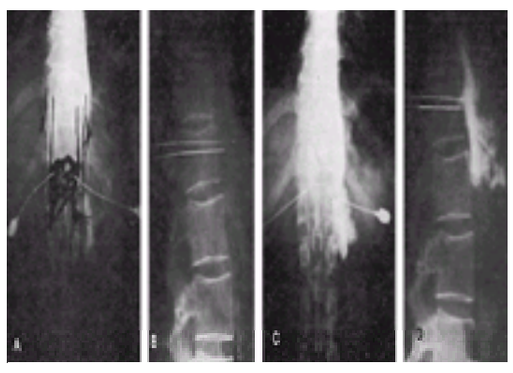

Figure 104-33. Radiographs showing needles in place for injection of the celiac plexus. **A:** Anteroposterior view with drawing of the plexus superimposed in front of the body of the L-1 vertebra in the upper part of the L-2 vertebra. **B:** Lateral view with both needles in place. The distal 3 cm of the needle are anterior to the anterolateral surface of the vertebral body. **C,D:** Diffusion of 10 mL of 35% Diodrast injected through the right needle, with most of the spread being anterior to the anterior surface of the L-1 and upper part of the L-2 vertebrae.

A series of modifications to celiac plexus block have been described. The anterior approach is being used by many radiologists (105,106), possibly because it is a more comfortable position for patients with pancreatic disease. The radiologists at the University of Washington, who do many procedures for pain relief of liver metastases, report that it is less successful in their hands, 75% versus 95% (Feeney, *personal communication*, 1990). The use of ultrasound to guide needle placement is also popular (106,107 and 108).

Results The results obtained by some who used the classic technique and by others using modifications of the technique are shown in Table 104-8. With the classic technique, between 70% and 85% of patients with severe upper abdominal cancer pain obtained pain relief lasting from 1 month up to 1 year. Best results were obtained in those with severe pain caused by cancer of the pancreas.

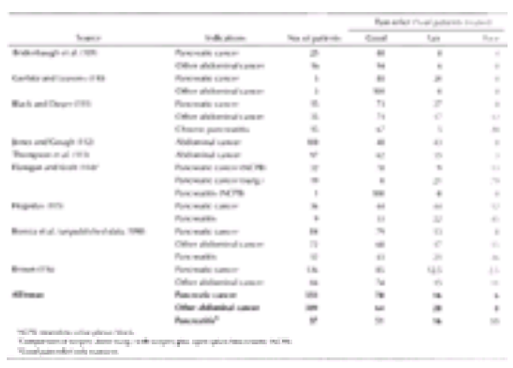

TABLE 104-8. Comparison of results with neurolytic celiac plexus block

Brown and colleagues (102) analyzed 166 patients with cancer of the pancreas and found that 141 patients (85%) obtained good pain relief, which lasted until death in 75% and for longer than 50% of the survival time in an additional 12.5%. Analysis of patient variables revealed that the quality of the block was not affected by age or sex; by whether they had metastasis; or by anticancer therapy such as surgery, chemotherapy, radiation therapy, or a combination of these. When block was repeated for recurrence of pain after a successful first block, 81% of patients again obtained beneficial pain relief. Moreover, repetition of the block did not increase the incidence of complications, which were limited to pneumothorax in two patients. In patients in whom an initial poor result was obtained, a second NCPB was performed with CT scanning to verify the spread of injected solution. In a subsequent report by Brown (116) on another 66 patients who had other types of abdominal cancer pain and who underwent 75 NCPBs, 48 patients (73%) had good pain relief until their deaths. Four reports from the Virginia Mason Medical Center in Seattle (102,109,113,114) indicated that those in the group led by Moore carried out a total of 370 NCPBs over a 25-year period, with an impressive success rate. Many of these were done without radiographic control. An important factor in their high success rate is Moore and associates' routine use of celiac plexus block combined with intercostal nerve block for most patients undergoing upper abdominal surgery.

The value of NCPB for the management of severe pain caused by unresectable cancer of the pancreas has been impressively demonstrated by Flanigan and Kraft (114). They compared pain relief from palliative surgery alone, including biliary and duodenal bypasses, to pain relief obtained from surgery plus injection of the celiac plexus and splanchnic nerves with 15 to 20 mL of 6% phenol at the time of operation. All patients had severe preoperative pain. Of the 19 patients who had conventional operations alone, only four patients (21%) experienced partial relief of pain postoperatively, whereas, of the 32 patients who had the operation and NCPB, 28 patients (88%) experienced excellent pain relief postoperatively for a mean duration of 4.3 months. The mean postoperative survival time was 5 months, and 84% of patients experienced no recurrence of their pain prior to death. In view of these and other results, it is surprising that most surgeons do not use neurolysis of the celiac plexus and splanchnic nerves during the course of surgery.

In the treatment of chronic pancreatitis and other nonmalignant chronic pain syndromes, the initial results were almost as good as those in patients with cancer pain, but the pain recurs with time, so that long-term results can be considered to be only fair. In most patients, the technique should be viewed as a temporary measure to aid in the management of these patients. The same comment could apply to other nonmalignant abdominal chronic pain syndromes. Intrathecal opioids may have value in the management of patients with pancreatic pain (Chapter 103).

Complications A frequent adverse side effect of celiac plexus block with a local anesthetic is extensive vasomotor block because the drug diffuses to involve not only the plexus but also the upper part of the lumbar sympathetic chain, and subsequently hypotension develops. The degree of hypotension in normovolemic patients in the supine position is mild, but elderly patients, or those who are hypovolemic, are likely to develop moderate to severe orthostatic hypotension, especially if they attempt to assume the upright position too quickly. The treatment of hypotension is discussed under Basic Information, earlier in this chapter.

Possible complications include accidental injection of the entire volume of local anesthetic into the inferior vena cava causing a systemic toxic reaction. Accidental injection of the drug into the aorta is less likely to cause a reaction because it is diluted as it passes with the blood to the lower part of the body before being returned to the heart. Accidental intravascular injection of alcohol or phenol can produce necrosis of the vessels. In patients with coagulation defects, puncture of the inferior vena cava with a large needle can result in retroperitoneal hematoma. Pneumothorax can develop if the pleura extends below its normal caudad border of the twelfth rib.

Other more serious complications of NCPB reported include postinjection neuropathy with neuralgia, paraplegia consequent to thrombosis of a major feeder artery to the spinal cord, accidental neurolytic injection into the kidney with consequent necrosis or hemorrhage, and failure of ejaculation (presumably because of involvement of the hypogastric plexus) (71). Paraplegia is arguably the most devastating complication, and its genesis is discussed by Brown and Rorie (117). Cardiac arrest has also been reported but is likely due to intravascular phenol (22).

Neurolytic Block of Splanchnic Nerves

Indications for neurolytic block of the splanchnic nerves are similar to those for celiac plexus block except that the procedure is less likely to involve the lumbar sympathetic chain. The technique is therefore more discrete, requires a smaller volume of neurolytic agent, and offers a lower risk of complications. Boas (118,119) has indicated a preference for block of thoracic splanchnic nerves rather than celiac plexus block because it has the advantage of being a true compartmental block, and thus is safer for the patient.

Technique The anatomy of the thoracic splanchnic nerves is discussed in detail in Chapter 65 and depicted in Figure 104-34 and Figure 104-35 where the technique is outlined. Other approaches using CT guidance have also been described (120,121).

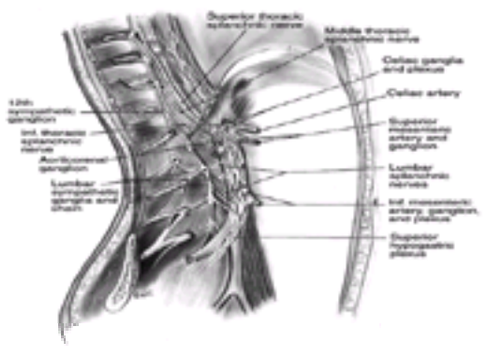

Figure 104-34. Relationship of the lower thoracic and lumbar sympathetic chains, splanchnic nerves, celiac ganglia and plexuses, and their branches (lateral view). These relationships serve as a basis for block of the splanchnic nerves and block of the lumbar sympathetic chain.

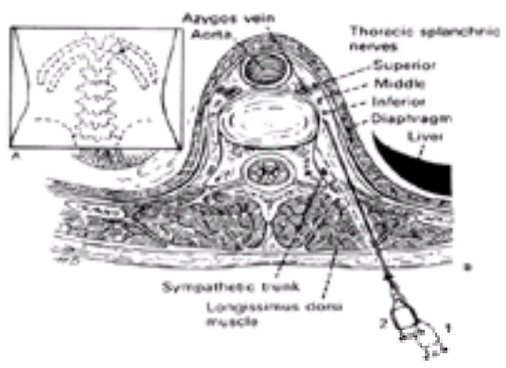

Figure 104-35. Technique of blocking the thoracic splanchnic nerves. **A:** Following identification and marking of the lower tip of the spinous process of the T-11 vertebra, the area is prepared and an intracutaneous wheal is produced 6 to 7 cm lateral to the lower tip of the spinous process of the T-11 vertebra (*black dot*). This is at the same cross-sectional level as the upper part of the body of the T-12 vertebra. A 10- or 12-cm, 22-gauge needle is adequate for the thin or average individual, whereas a 15-cm, 22-gauge needle is necessary for an obese or muscular person. **B:** The needle is introduced through the skin wheal and directed anteriorly and medially so that its shaft makes an angle of 45 degrees with the midsagittal plane. The needle is advanced until the posterolateral surface of the upper part of the body of the T-12 vertebra is contacted (1). A marker is then placed approximately 2 cm from the skin. The needle is withdrawn until its point is in the subcutaneous tissue and reinserted in a slightly more lateral direction, which places the bevel of the needle just lateral to the anterolateral surface of the body of the vertebra where the three thoracic splanchnic nerves are located near each other (2). To avoid damage to the pleura, it is essential that the bevel of the needle be maintained in contact with the vertebra during its anterior advance. Injection of 10 mL of 0.25% to 0.50% bupivacaine with epinephrine solution diffuses throughout the region to involve all three nerves on one side. A bilateral block is often essential for the relief of upper abdominal pain.

Complications Hypotension consequent to vasomotor block is seen less often with splanchnic block than with celiac plexus block because the lumbar sympathetics are usually not interrupted. Pneumothorax occurs if the needle is not kept in contact with the lateral surface of the vertebra. Accidental injection of the neurolytic agent into the azygos vein on the right side or into the hemiazygos vein on the left side can result in necrosis of these vessels. The thoracic duct might be damaged, leading to a chylothorax, or it might become obstructed, leading to lymphedema. All of these complications can and must be prevented by correct technique.

Neurolytic Lumbar Sympathetic Block

Chapter 102 presents the indications for lumbar sympathetic block with a local anesthetic. The neuroanatomy and technique are also described in Chapter 102. Here, the indications for neurolytic blockade of the lumbar sympathetic chain are discussed.

Indications Neurolytic block is indicated for the relief of various chronic painful conditions in the lower limbs in individuals who achieve good but transient results from local anesthetic block but are elderly and not suitable for surgical sympathectomy. These conditions include CRPS types I and II, phantom limb and other postamputation pain, other neuropathic conditions that are temporarily relieved with local anesthetics, various chronic peripheral vascular disorders, pain caused by cancer of the pelvic viscera, and severe persistent tenesmus. Duthie and Ingham (122) reported on patients with persistent lower abdominal pain that was not relieved by surgical excision of various organs but was completely relieved by several lumbar sympathetic blocks with local anesthetic. These results prompted them to carry out lumbar sympathectomy with 7.5% aqueous phenol. All nociceptive pathways from the uterus and cervix pass through the lumbar sympathetic chain (Chapter 70);

patients with persistent pain caused by cancer limited to the uterus or nonmalignant chronic painful conditions not amenable to other forms of treatment should be given several bilateral diagnostic or prognostic lumbar sympathetic blocks with local anesthetic. If good relief is obtained, bilateral sympathectomy can be considered. These procedures are ineffective once cancer begins to infiltrate the lumbosacral plexus.

The largest experience to date with neurolytic lumbar sympathetic block is in the treatment of occlusive vascular disease of the lower limbs. Based on Bonica's experience, as well as that of Löfstrom and Zetterquist (123), Reid and colleagues (124), Boas and associates (125), Löfstrom and Cousins (126), and Cousins and coworkers (127), it is clear that chemical sympathectomy is highly effective in relieving rest pain and in helping to heal ischemic lesion. It can even relieve the pain of intermittent claudication in a smaller percentage of patients. The procedure is indicated in patients for whom bypass graft surgery cannot be used because the obliterating disorder is too extensive.

Better surgical procedures and improved medical therapy have decreased the demand for neurolytic lumbar sympathetic block in peripheral vascular disease. In Europe, spinal cord stimulation has supplanted the procedure (Chapter 100).

Technique The neuroanatomic basis for block of the lumbar sympathetic chain is described in Chapter 102.

The lumbar sympathetic chain is the most variable portion of the sympathetic system, particularly in regard to the number of ganglia and the general form of the two chains. These differ greatly, not only among patients but also on either side of the same patient. In most individuals, they lie anterolateral to the intervertebral disk, with one portion of the ganglion in front of the lower part of the vertebra above and the other portion of the ganglia in front of the upper part of the vertebra below. In addition, the size of the ganglia and the interganglionic cord and the number of branches extending from them exhibit great variation. The lumbar sympathetic chain contains both preganglionic and postganglionic neurons that supply the pelvic viscera and vessels of the lower limbs and have afferent (sensory) fibers, some of which transmit nociceptive information.

Boas (118) has effectively used a single needle placed at L-2 or L-3 and has found it to be satisfactory for injection of the neurolytic agent. It is best, however, to use two needles at L-2 and L-4 or even three needles at L-2, L-3, and L-4, placed in the center of the vertebral body. Insertion of the needle is the same as that illustrated in Figure 102-53. For placement of the block needle, it is essential not only to anesthetize the skin but also the subcutaneous tissue and fascia of muscles, using the lack of resistance test to determine passage of the point of the needle through the psoas fascia.

Although some clinicians have the patient in the prone position during the procedure, the lateral position is preferable because it facilitates monitoring of diffusion of the solution in the lateral view, probably diminishes its retroperitoneal spread, and enhances its cephalad-caudad spread. Once the needles are in place, the positions of the bevels are checked with fluoroscopy. The lateral view should show the bevel of the needle near the anterior of the bodies of the vertebrae. The anterolateral view should show the bevels of the needles to be 1 cm medial to the lateral edges of the vertebral body, and the anteroposterior view should show the needles close to the lateral aspects of the vertebral bodies. When this placement has been accomplished, a 2-mL syringe containing a contrast solution is attached and aspiration is attempted in two planes to ensure that the bevel is not in a blood vessel or in a dural cuff. If the aspiration is negative, 0.5 mL of contrast solution is injected under image intensifier monitoring using the lateral view. If each needle is in the correct position, the contrast medium spreads in a thin linear fashion that conforms to the anterior edge of the vertebra (Fig. 104-36). The appearance of a “blob” or fuzzy patch of the contrast medium indicates that the injection was made into the psoas muscle or fascia, both of which offer resistance to injection. Occasionally, a small vessel is entered without backflow of blood during aspiration, but on injection of the contrast medium it is promptly whisked away along the path of the vessel. In either case, the needle should be readjusted and the preliminary injection of contrast medium should be repeated.

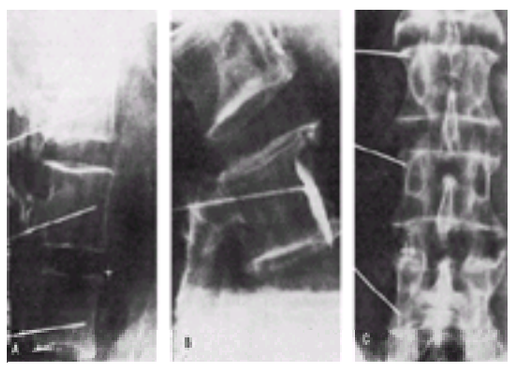

Figure 104-36. **A:** Radiographs showing lateral views of lumbar vertebrae with needles in place to carry out lumbar chemical sympathectomy. **B:** Injection of 1 mL of 10% phenol in Conray-420 at each level causes spread of the solution from L-2 to L-4. **C:** Posteroanterior view. (From Cousins MJ, Reeve TS, Glynn CJ, et al. Neurolytic lumbar sympathetic blockade: duration of denervation and relief of rest pain. *Anaesth Intensive Care* 1979;7:121–135, with permission.)

Once it has been confirmed that the bevels of all the needles are correctly positioned, 3 to 4 mL of 10% phenol in contrast medium is injected through the needles at L-2 and L-4. If three needles are used, 2 mL of solution is injected at L-2 and L-3 and 3 mL of the solution is injected at L-4. With one needle at L-2 or L-3, 10 mL of phenol–contrast medium is injected. The image intensifier is used to monitor the spread of the solution. Using these volumes, the phenol-containing solution spreads in the same linear fashion as above, extending from the upper level of L-2 or the lower level of L-1 to the level of L-5. With such a spread, the phenol can destroy the entire sympathetic nerve supply to the limb below the knee. A 0.5-mL bolus of air or saline is then injected through each needle before it is removed—to prevent spilling of the small amount of neurolytic agent in the needle onto a somatic nerve during needle withdrawal, thus minimizing the risk of postinjection neuralgia.

Patients are kept on their side for 10 to 15 minutes to prevent spread of the solution laterally toward the genitofemoral nerve or posteriorly through the aponeurotic arcades or spaces in the origin of the psoas muscle and its fascia along the fibrous tunnel occupied by the rami communicantes, which connect the sympathetic chain with the lumbar spinal (somatic) nerves.

Because this entire procedure requires the patient to stay in the same position for 90 to 120 minutes, frequent reassurance throughout the procedure is essential. Moreover, if the patient manifests apprehension or anxiety or complains of discomfort, it might be necessary to give an additional dose of a sedative, opioid, or both, especially if the discomfort develops early in the procedure and is likely to persist.

After the 10-minute waiting period, the patient is turned supine but is instructed not to raise the head for 1 hour, during which time observations of skin temperature, blood pressure, and pulse are made at frequent intervals. If blood pressure remains stable after this period, the patient is allowed to sit for 45 minutes and resume oral intake. Patients with unstable cardiovascular disease should be observed and their vital signs monitored for at least 24 hours after the block.

In patients in whom the chemical sympathectomy is being done for relief of CRPS type I or II, or following an above-the-knee amputation, more extensive blocks may be indicated. It might be necessary to block the lowermost thoracic portions of the sympathetic chain to eliminate all sympathetic function to the entire limb and provide complete relief of pain. Because such extensive sympathectomy in men can produce sexual impotence, especially if done bilaterally, it should be considered only when severe pain is present and patients are informed about the complications and agree to proceed.

Results Three sets of results of the use of lumbar chemical sympathectomy are summarized in Table 104-9.

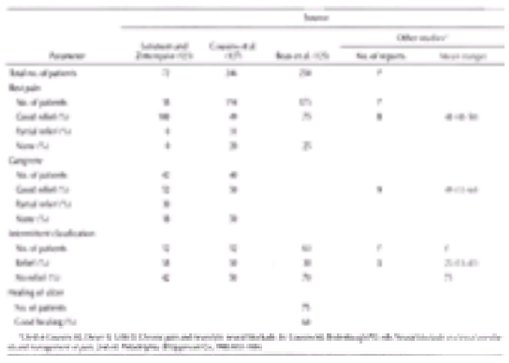

TABLE 104-9. Comparison of results of lumbar chemical sympathectomy for pain due to occlusive peripheral vascular disease

Löfstrom and Zetterquist (123) and Löfstrom and Cousins (126) treated patients with occlusive peripheral arterial disease by continuous lumbar sympathetic block with a local anesthetic. They then proceeded to carry out a block with phenol in those who were only temporarily relieved of their symptoms. The local anesthetic block produced prolonged pain relief in 28 of 55 patients (51%) with arteriosclerotic gangrene, 14 of 28 patients (50%) with pain caused by diabetes, five of 23 patients (22%) with severe rest pain, and one of 16 patients (6%) with intermittent claudication.

In a series of 250 percutaneous chemical sympathectomies done by Boas (125), 70% of patients had rest pain; 30% had trophic changes with ulcerations, gangrenous changes, or both; and 25% had intermittent claudication. Long-term results included relief of rest pain in 75% of patients (better than that achieved with surgical sympathectomy), healing of the ischemic lesions in 60%, but improvement of claudication in only 30% of patients with this complaint. Subsequently, Boas (119) mentioned that his group had obtained similar results with phenol block on more than 500 patients with arteriosclerotic symptoms and signs.

In the series reported by Cousins and associates (127), relief from rest pain was complete in 49% of patients and partial in 31%. In those without preexisting gangrenous changes, 84% of patients derived partial or complete relief as compared to 56% of those with a gangrenous lesion. The onset of pain relief coincided with the onset of sympathetic block and with increases in skin blood flow and temperature. The mean duration of pain relief was 5.9 + 0.6 months, which was similar to the mean duration of sweat modification (6.0 + 0 months). Two years after the blockade, 35% of patients were alive and the skin was intact, without evidence of ulcer or gangrene; 15% had undergone reconstructive surgery; and 25% required either local debridement or major amputation within an average of 10 months after the block. Only 10% of patients required a repeat block on the same side within a period of 3 to 12 months. Pain relief after the second block was always at least equal to that obtained with the first block. Cousins and colleagues (127) also noted that another, often neglected, benefit of sympathectomy is that it shortens the time to a clear demarcation area of the amputation level and improves the vascular supply to the stump. Moreover, because early sympathectomy is beneficial in treating some types of phantom limb pains, sympathectomy for pain relief performed 1 month before amputation can prevent postamputation pain, as suggested by the fact that none of their patients who underwent amputation developed severe phantom limb pain.

Cousins et al. (127) used prognostic blocks of the lumbar sympathetic chain with 0.5% bupivacaine in most of their patients. They believed that unless this is carried out, some patients who manifest the steal phenomenon because of the response of healthy vessels and the lack of response of diseased vessels might not be identified. Moreover, Cousins and coworkers (127), as well as Boas and associates (125), excluded patients whose primary complaint was intermittent claudication on the premise that such patients are best treated with reconstructive surgery. In a review of 14 studies, Löfstrom and Cousins (126) cited the percentage of patients with occlusive vascular disease who responded to lumbar sympathetic block in regard to such parameters as rest pain, skin lesion, and intermittent claudication: Rest pain was relieved in a mean of 48% of patients (range, 48% to 80%).

Complications In addition to the complications mentioned in Chapter 102 associated with the use of lumbar sympathetic block with local anesthetics, the most serious complication with chemical sympathectomy is genitofemoral neuralgia, which occurs in 5% to 7% of patients. It is presumably caused by the diffusion of the alcohol to the genitofemoral nerve as it lies on the anterior surface of the psoas major muscle, not too far from the lumbar sympathetic chain. This same complication follows surgical sympathectomy, suggesting that the nerve is damaged during the course of the operation. The condition is characterized by the usual burning and aching pain; allodynia may be present. It sometimes can be relieved by transcutaneous electrical nerve stimulation. In many patients, this condition is transient. Although some authors have claimed that the incidence of this complication is much higher with alcohol, this was not Bonica's experience in the more than 50 patients in whom chemical sympathectomy was done with 50% alcohol.

Neurolytic Block of Somatic Spinal Nerves

Based on his early experience with neurolytic block of somatic spinal nerves, Bonica continued to insist that, except in patients with severe terminal cancer pain not amenable to any other procedure, neurolytic block of somatic nerves should not be used. The primary rationale for this approach is that, during nerve regeneration, patients experience severe neuralgia in the nerves supplying the limb or trunk. Although some authorities (3) have suggested that the neuralgia is related to the fact that the nerve damage is caused by imprecise needle placement and incomplete neurolysis, this condition occurs in patients in whom the neurolytic agent was injected intraneurally, with complete destruction of the nerve.

Transsacral nerve block with a neurolytic agent is useful in individuals with severe unremitting perineal pain caused by inoperable cancer of the rectum or after abdominoperineal resection when that pain is not relieved by subarachnoid neurolysis. Because the S-4 segment provides predominant sensory innervation to the perineum, transsacral block of this segment with 2 mL of 6% aqueous phenol has been used to provide prolonged pain relief. Robertson (128) reported the use of this technique in nine patients with cancer of the rectum. Eight had undergone abdominoperineal resection, and one had an inoperable lesion and a defunctioning colostomy. The pain was asymmetric in all nine patients, more pronounced on one side of the perineum than the other, and was of such severity to be considered an indication for intrathecal neurolysis. All patients received a prognostic block with 2.5 mL of 0.5% bupivacaine, and an equal volume of 6% aqueous phenol was injected 24 hours later. The first injection provided pain relief of less than 1 week's duration in six patients, of 10 days' duration in one patient, of 202 days' duration in one patient, and of 414 days' duration each in one patient. A second injection produced pain relief lasting from 18 to 122 days, and three patients received a third block. Treatment was carried out on an outpatient basis, with no disturbances of bladder or motor function and with sensory changes limited to the perineum.

Neurolytic Somatic Block for the Relief of Chronic Nonmalignant Pain

Brief mention is made here of several indications for the use of neurolytic block in patients with nonmalignant chronic pain, including transsacral block for severe bladder pain and spasticity, abdominal nerve entrapment syndrome, coccyodynia, and the injection of small neuromas consequent to surgery.

Cystitis Simon and associates (129) reported on a prospective study to evaluate the results of the injection of 2 mL of 6% aqueous phenol at S-3 in 15 patients with severe pain caused by interstitial or hemorrhagic cystitis and in one patient who had a neurogenic spastic bladder. Following a diagnostic block with 0.5% bupivacaine, 2 mL of 6% aqueous phenol was injected through the right S-3 foramen. Of these patients, ten who received bupivacaine subsequently received phenol and, of these, seven reported significant long-lasting pain relief, one had pain relief for 1 week, and two received no benefit. The average follow-up period was 24 months, and the duration of response in those with persistent pain was at least as long. No patients suffered urinary or rectal incontinence.

Abdominal Nerve Entrapment Syndrome The abdominal nerve entrapment syndrome is a source of significant discomfort that can be disabling. It presents as intermittent pain in the region of the rectus abdominis muscle or a segmental neuralgia. It is provoked by increased intraabdominal pressure and twisting the trunk. It is relieved by focal injections of local anesthetic. The condition is usually treated with repeated injections of a long-lasting local anesthetic. McGrady and Marks (130) reported on a series of 76 patients treated with 1 mL of 6% aqueous phenol using a nerve stimulator to locate the optimal point of injection. Of those in the group of 44 patients whose diagnosis had been definitively made, 95% derived complete or partial relief of symptoms at follow-up lasting from 6 months to 4 years. In a group of 32 patients who had other symptoms that made the diagnosis less certain, 48% gained partial relief and 8% obtained complete relief.

Cryoanalgesia

The term *cryoanalgesia* was coined by Lloyd and colleagues (131) to describe the destruction of peripheral nerves by extreme cold to achieve pain relief. The

histologic effects of cryoanalgesia on nerves are summarized under Basic Information, earlier in this chapter. The procedure produces a small ice crystal that causes a second-degree nerve injury consisting of wallerian degeneration with axonal disintegration and breakup of the myelin sheath but with minimal disruption of the endoneurium and the basal lamina. Cryolesions are claimed to produce less fibrous tissue reaction than other forms of destruction (132). Since its introduction in 1976, this method has had limited clinical application, and the number of published reports is small (133,134,135 and 136).

Indications Cryoanalgesia has been used for local destruction of brain tissue and to block cranial and spinal nerves to relieve such problems as intractable facial pain, postthoracotomy pain, posttraumatic chest pain, and cancer pain. Because the duration of pain relief averages 2 weeks (range, 2 days to 7 months), the most fruitful uses are relief of postoperative and posttraumatic chest pain and relief of medium duration in patients with various chronic pain syndromes.

Technique Cryoanalgesia is done with a 15-gauge cryoneedle. Blockade is based on the principle of the Joule-Thompson effect, with nitrous oxide being used as the refrigerant gas (137). The Joule-Thompson effect occurs when gas at approximately 700 psi is injected through a nozzle; as it expands, it cools to approximately –75°C. The cooled gas impinges on the inner surface of the needle tip and absorbs heat from the surrounding tissue, and the warm gas is exhausted back up the needle and vented through the scavenger system. The Spembley-Lloyd cryoneedle uses a thermocouple to confirm the temperature achieved at the tip, and an electrical connection at the tip of the probe is connected to a peripheral nerve stimulator for precise location of the nerve. The probe is connected by a 6-foot piece of flexible tubing (Fig. 104-37) to a console that has a gas pressure regulator switch, a nerve stimulator socket, and dials for displaying gas pressure and probe tip temperature.

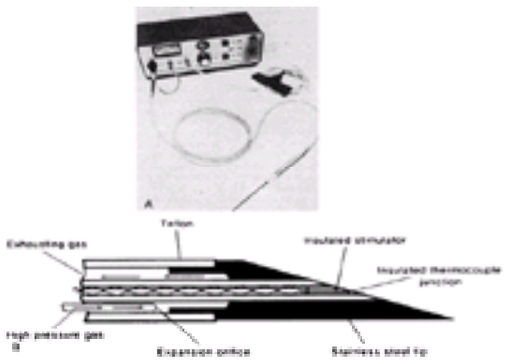

Figure 104-37. **A:** Spembley-Lloyd cryoanalgesia apparatus. The unit incorporates a cryosurgical system coupled to a nerve stimulator for accurate positioning of the probe. The probe is connected by 6 feet of flexible tubing to a console that has a gas pressure regulator switch, a nerve stimulator socket, and dials to display gas pressure and probe tip temperature. **B:** Details of the cryoprobe tip. A chrome-constantan thermocouple is fitted to the tip of the probe to monitor the temperature. The probe is 10 cm long and is constructed from a 15-gauge stainless steel hypodermic tube with an 18-degree, short-beveled point. An electrical connection is made to the tip of the probe from the nerve stimulator, and all parts of the probe are insulated from the patient and operator by a Teflon coating. (**B** from Lloyd JW, Barnard JD, Glynn CJ. Cryoanalgesia: a new approach to pain relief. *Lancet* 1976;2:932–934, with permission.)

Results Lloyd and colleagues (131) reported on the use of cryoanalgesia in 64 patients, of whom 52 obtained good relief of pain that lasted for a median period of 11 days, up to 7 months. Best results were obtained in providing pain relief to 15 of 17 patients (88%) with intercostal nerve pain, to all of six patients with facial neuralgia who underwent infraorbital or mental nerve block, and to eight of nine patients (89%) who had cancer (four of these had intercostal blocks, and five had the cryoprobe introduced through the sacral hiatus to produce caudal analgesia). Subsequently, the same group (133) reported on 29 patients who received intercostal block with cryoprobe under direct vision prior to closure of the thoracotomy. They compared postoperative opioid requirements with those of a control group of 29 patients who were matched for sex, age, and diagnosis and managed with intramuscular opioids (133). Those patients in the cryoanalgesia group derived more effective relief and required significantly fewer opioid injections for less time as compared to those in the control group. Barnard and colleagues (134) used cryoanalgesia in the management of chronic facial pain in 43 patients who received 85 cryogenic blocks of branches of the trigeminal nerve for the relief of the pain of tic douloureux, postoperative neuralgia, postherpetic neuralgia, and other types of facial pains. In 67% of patients with nonherpetic neuralgia, the pain relief persisted for a median of 93 days. Of 26 patients with postherpetic neuralgia, only 11 (42%) derived relief, which lasted 6 weeks. None of those in the three groups of patients treated by Lloyd et al. (131), Glynn et al. (133), and Barnard et al. (134) developed neuralgia subsequent to treatment, and no other serious complications have been reported.

Katz and associates (135) reported good relief of postthoracotomy pain following intercostal cryoanalgesia carried out under direct vision. Katz also stated (*personal communication,* 1988) that he and coworkers have used cryoanalgesia in nearly 150 patients, with good pain relief achieved in over 85% of patients. Jones and Murrin (136) reported results with the use of percutaneous cryotherapy of intercostal nerves in patients with various chronic chest pain syndromes who had had pain for 6 months to 2 years. Of 32 patients with postthoracotomy scar pain, 13 (40%) derived good relief, 10 (30%) had partial relief, and nine (30%) had little or no relief. Among 15 patients with postherpetic neuralgia, 11 (74%) derived good relief, two (13%) had partial relief, and two (13%) had little or no relief. The duration of pain relief for those in the latter group was less than 7 days in 79% of patients, whereas for those in the former group relief lasted considerably longer (136).

Neuroadenolysis of the Pituitary

Neuroadenolysis of the pituitary involves transnasal placement of a trochar tapped through intervening structures with a metal mallet to reach the pituitary fossa. Following verification of position, 0.5 to 6.0 mL of absolute alcohol was injected to destroy the pituitary gland. Complex hormonal and neurochemical responses were invoked to explain the sometimes dramatic pain relief that followed this procedure. There have not been further reports of its use or efficacy since the 1980s; its use appears to have languished with the advent of other advancements in the treatment of cancer pain. It was felt to be appropriate in severe pain from advanced cancer such as of the breast or prostate with widespread metastases. Several authors [Moricca (138), Lipton (139), Katz (141), Waldman (140), Levin (142)] reported on the procedure undertaken with the aid of fluoroscopy or stereotactic equipment in lightly anesthetized patients. Table 104-10 shows pain relief varying between 27% and 87% in over 1,500 patients. More details on the technique and outcomes are in the references. It has never been performed in our institution, and therefore we cannot comment directly on the procedure; from the absence of recent reports, it appears to be waning in popularity.

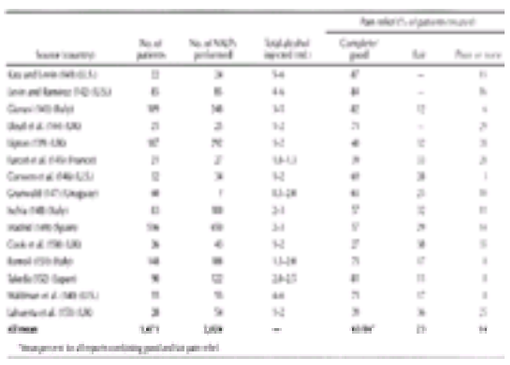

TABLE 104-10. Comparison of results with neuroadenolysis of the pituitary (NALP) for cancer pain

Neurolytic Blocks for Control of Spasticity

Indications

Although neurolytic nerve blocks are usually used for the control of chronic pain, they are also important for the treatment of spasticity consequent to injuries to the

central nervous system (e.g., stroke, cerebral palsy, and spinal cord damage secondary to trauma or disease, such as multiple sclerosis). Such patients often develop spasticity that is uncontrolled and often produce sporadic spontaneous and uncontrolled flexor or extensor movements that can severely compromise the patients' ability to sit in a wheelchair. Sometimes such spasms can be so violent that patients are catapulted out of their wheelchairs. Many patients with spinal cord injury develop spasms of the adductor muscles of the thigh, which in addition to the painful spasm affect the ability to perform perineal toilet and to carry out other aspects of nursing care.

Reduction of such profound skeletal muscle spasm by neurolytic block has been helpful in these patients (154,155,156,157,158,159,160 and 161). Less commonly, such blocks can be used to treat muscle spasms in the trunk or in the upper extremity associated with quadriplegia (154).

Some special indications for producing reversible spasms in such individuals also exist. Many patients use the muscle spasms as an integral part of their support for sitting and functioning both during recreation and at work. It is sometimes necessary, however, to reduce such spasms temporarily. For example, a patient might need to be nursed in the prone position for some length of time (e.g., during and after placement of a skin graft for a gluteal bed sore). Therefore, prolonged and complete elimination of flexion spasms would not be indicated because such spasms are useful to the individual during normal activities. In such cases, prolonged reversible therapy for the spasms is needed.

With the introduction of baclofen and the use of implantable intrathecal catheter and pump systems (162,163 and 164), the control of spastic problems has been revolutionized, and in our clinic population, there is very little call for neurolytic blockade. In the past, the majority of neurolytic procedures done in the clinic were for spasticity, but comparing the results with those from the use of baclofen pumps, it is apparent that the new method is far more user-friendly. Adjustment of dose to titrate to effect was not possible previously but is a routine part of the new technology.

Neurolytic procedures are still useful for the small minority of individuals who do not respond to intrathecal or oral baclofen.

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CHAPTER 105

Lesions of Primary Afferents and Sympathetic Efferents as Treatments for Pain

Parag G. Patil and James N. Campbell

In this chapter, we consider ablative operations of the peripheral nervous system for pain. Ablative procedures interrupt signal flow between pain generators in the periphery and the brain, or they remove neural structures that contribute to pain generation. As an example of the former, transection of a peripheral nerve prevents the transmission of pain-encoding signals from a painful region to the spinal cord. As an example of the latter, ablation of paraspinal sympathetic ganglia can eliminate the distal release of norepinephrine, which triggers nociceptor activity in the periphery.

Two fundamental approaches exist to address the problem of intractable pain: attempts to palliate and attempts to eliminate pain definitively. Ablative procedures have the capacity to eliminate pain and, therefore, have great appeal. However, ablative procedures are notorious for achieving only short-term benefits, a reputation that undermines their appeal. In support of such skepticism, animal research suggests that axotomy alone may be sufficient to induce pain (1). However, regardless of the perception that inappropriate patient selection may lead to considerable morbidity, the experience of some clinicians remains that ablative procedures have the capacity to relieve pain enduringly and that ablative procedures are useful therapeutic ventures in properly selected patients.

This chapter is divided according to the three major categories of ablative operations involving the peripheral nervous system: peripheral neurectomy, dorsal rhizotomy and ganglionectomy, and sympathectomy. The surgical treatment of trigeminal neuralgia, which is one of the most common of the diseases that are successfully treated by ablative procedures, is presented in Chapter 107. Ablative procedures aimed at the spinal cord, such as the DREZ operation for treatment of avulsion injury of the brachial plexus or cordotomy, used in pain due to malignant disease are presented in Chapter 106.

PERIPHERAL NEURECTOMY

Basic Considerations

There are two reasons a nerve may be cut to eliminate pain. One purpose is to denervate a pain-producing structure. For example, facet rhizotomy denervates the facet joints of the spine as a treatment of axial spine pain. A second purpose of nerve ablation is the interruption of pain signals from an injured nerve. Yet, there is some irony in this use of neurectomy. In mice, rats, and monkeys, transection of a somatic nerve may cause pain. To understand then how ablation may relieve pain, we must consider some aspects of the pathophysiology of neuropathic pain.

Pathophysiology of Neuropathic Pain

When sensory nerve fibers are severed, the proximal axons, which are still in continuity with cell bodies in the dorsal root ganglion, sprout and seek Schwann-cell guides. If the perineurium of the injured nerve has remained intact, such as in cases of crush or certain thermal injuries, the sprouts successfully reinnervate the target tissue. Successful regeneration may also occur when the transected ends of the nerve are surgically reapproximated (neurorrhaphy). However, when continuity with Schwann-cell guides is not present, the axon sprouts fail to reach the target tissue and randomly double-back on themselves, ultimately forming a densely packed cluster of nerve sprouts known as a *neuroma*.

Removal of a neuroma as a treatment of nerve injury pain is conceptually flawed. Cutting the nerve at a location that is proximal to the site of nerve injury, to remove the neuroma, results in the formation of a new neuroma. Surgery in which neuromas are removed should therefore be labeled *neuroma relocation surgery.* Relocating a neuroma in a non–pressure-sensitive area may alleviate pain in some patients.

Though nontraumatic neuropathies may induce pain in a variety of ways, pain from a single nerve lesion offers perhaps the clearest model for considering the mechanisms of neuropathic pain. Weir Mitchell brought attention to the problem of painful nerve injury after caring for injured soldiers during the American Civil War. A century later, Denny-Brown and Kirk (2) presented one of the first studies demonstrating that axotomy may induce behavioral signs of pain in an animal model. More recent studies have corroborated the observation that axotomy of a major nerve, by itself, may induce hyperalgesia in animals (see Chapter 3).

An important generator of neuropathic pain must be located at the site of nerve injury. This is demonstrated by the common finding that placement of local anesthetic at the site of the injury can dramatically relieve pain. Clearly, neural activity that arises from the nerve lesion site somehow produces pain. Four pathophysiologic mechanisms seem likely to play a role:

- *Ectopic generation of action potentials.* Though normally silent, nociceptive afferents may become spontaneously active following nerve injury, producing action-potential activity in the absence of any stimulus (3). This activity without a stimulus could be experienced as spontaneous pain.
- *Ectopic excitability.* Uninjured nerve trunks are minimally sensitive to stimuli. Following injury, these fibers may respond to normally nonpainful stimuli at ectopic, normally insensitive sites. For example, application of a mechanical stimulus may result in neural activity in an injured fiber, while having no effect on an uninjured fiber. Such ectopic mechanical excitability gives rise to Tinel's sign, an electrical sensation in the nerve's original target distribution, elicited by mechanical stimulation at the location of regenerating axons. As a second example, injured nociceptive axons may become abnormally sensitive to catecholamines, leading to pain when norepinephrine is released from local sympathetic terminals. This condition is termed *sympathetically maintained pain* (SMP) (4).
- *Nervi nervorum.* Nerves themselves appear to be innervated by nociceptive fibers. These nervi nervorum fibers may become sensitized to mechanical stimuli following nerve injury. Such a mechanism may explain, for example, the local tenderness and mechanical hyperalgesia of the ulnar nerve when it is entrapped at the elbow. Similarly, activation of the nervi nervorum may explain the local tenderness of nerves that are entrapped by scar tissue.
- *Ephaptic conduction.* Under normal physiologic conditions, signals in adjacent afferent fibers are insulated from each other. Activity in an injured nerve fiber may evoke activity in a nearby fiber, through a direct electrical connection between the two. During such ephaptic transmission, or *cross talk*, nonnoxious sensory stimuli may evoke activity in nociceptive fibers and may thereby cause pain.

Some of the mechanisms of ectopic generation of action potentials and ectopic excitability are now understood. Sodium ion channels that are sensitive to natural stimuli (mechanical, thermal, and chemical stimuli) are normally present in the membranes of sensory terminals. When an axon is severed, axonal transport of these channels from the cell body to the sensory terminal is interrupted. As a result, the channels are expressed ectopically in the neuroma formed at the injury site. Nociceptive fibers in the neuroma thereby become sensitive to natural, normally nonpainful stimuli, producing pain when these stimuli are present (5,6). The mechanisms of spontaneous activity in a neuroma are not as well understood, but both potassium and sodium channels may play a role.

In addition to neural activity arising at the site of injury, there are other mechanisms of neuropathic pain. Evidence supports what may be termed the *wallerian*

degeneration hypothesis. According to this hypothesis, uninjured nociceptors that are adjacent to nerves undergoing wallerian degeneration may become spontaneously active and may develop sensitivity to catecholamines, resulting in spontaneous pain and SMP. For example, injury to the L-6 nerve root in monkeys induces these changes in the nociceptive afferents of adjacent roots serving the same region of skin (7). To the extent that neuropathic pain results from this mechanism, peripheral neurectomy might be expected to worsen pain, since the nerve undergoes wallerian degeneration distal to the site of neurectomy. By contrast, such pain may be improved by topical application of capsaicin or by sympathectomy, since these therapies do not involve degeneration of the distal axon.

Rationale for Neuroma Relocation Surgery

Neuromas arise from nerve fibers, proximal to a region of transection or severe injury, which remain in continuity with their cell bodies in the dorsal root ganglia. Hence, the idea of *removing* a neuroma is conceptually flawed, since a new neuroma always will form at the freshly severed end of the nerve. Moreover, not all neuromas are painful. The use of peripheral neurectomy as a treatment for painful neuromas is therefore predicated on the hope that *relocation* of the neuroma may convert it from a painful to a painless one.

Why should neuroma relocation surgery ever work? Here, the basic sciences take their cues from the clinic. Clinical experience demonstrates that neuroma relocation surgery does work in some situations. The tissue milieu surrounding the nerve may determine whether a neuroma becomes painful or remains painless. Ectopic excitability and sensitivity of injured nociceptive fibers and of the nervi nervorum may provide a dominant mechanism of pain production. Furthermore, neuromas tend to be painful in locations where the severed nerves are subjected to excessive mechanical forces. Relocation of the neuroma may move it into a milieu that is shielded from mechanical stimuli. However, to the extent that there is location-independent, ectopic generation of action potentials in the neuroma, relocation surgery will fail.

Some investigators have argued that central mechanisms may account for pain in many situations of nerve injury and that neuroma relocation surgery may fail because of this. For cases in which anesthetic blockade of the injured nerve fails to relieve pain, an important trigger for pain may reside central to the neuroma. However, our observations as well as those of other experienced clinicians suggest that, in the great majority of patients with nerve injury pain, anesthetic block of the injured nerve strikingly relieves pain. In these latter cases, discharge in the peripheral nerve is required for the pain to be experienced. Thus, efforts to relieve pain by addressing the neural impulses that arise from the region of injury have some theoretical support. Central nervous system changes after peripheral nerve injury may also contribute to chronic pain.

Clinical Considerations

Preoperative Evaluation

Neurectomy is used in a variety of clinical scenarios that can be broadly divided into two groups: neuropathic pain resulting from nerve injury and nociceptive pain from a diseased tissue other than nerve. To decide that pain comes from nerve injury, the clinician needs to establish first that there has been an injury. The history is helpful. Something should have happened to the patient that would cause nerve injury. A patient with pain in the stump of an amputated limb probably has nerve injury pain. In fact, nerve injury pain frequently arises as a complication of previous surgery. In addition, the character of the pain may be helpful. For example, burning pain connotes neuropathic pain. On examination, the clinician should search for appropriate sensory/motor deficits. Often, a neuroma sign will be prominent at the site of nerve injury; if the nerve is undergoing regeneration, there may be both Tinel's sign at the advancing region of axon regeneration and a neuroma sign at the injury site where some axons have been irreversibly transected.

A prerequisite for the diagnosis of nerve injury pain is an anesthetic block. If blockade of the putative, pain-generating neuroma fails to relieve the pain nearly in its entirety, the rationale for neuroma relocation surgery is precarious. In addition, findings associated with complex regional pain syndrome, such as edema, hyperalgesia, and trophic changes, suggest that neurectomy will not help the patient. In such cases, however, there typically is no clear relief of pain following peripheral nerve blockade. Patients should be assessed for hyperalgesia to cooling stimuli. This finding is suggestive of SMP, discussed under Sympathetically Maintained Pain, later in this chapter. Finally, local tenderness in combination with a neuroma sign suggests entrapment-induced nerve injury. In this instance, nerve decompression would be indicated rather than neurectomy. It is important to note that even subtle entrapments without significant motor or sensory loss may induce severe pain.

After one has identified a specific nerve as a pain generator, the second step is to decide what to do with the nerve. Neuroma relocation is not the only option. If the injury is relatively recent and the nerve is relatively unimportant, a wait-and-see recommendation may be most appropriate. In some cases, there may be only a partial nerve injury. If this is the case, neurectomy may sacrifice function without assurance that the new neuroma will be less painful than the old one. Thus, nerve repair should be considered before performing a neurectomy.

Nerve repair has the potential to eliminate the neuroma with the bonus of restoring neurologic function. The clinician sometimes faces the ironic situation that, to repair an injured nerve, a normal nerve (e.g., sural nerve) may need to be sacrificed to provide donor grafts. Thus nerve repair is, in a sense, a neuroma relocation operation: The neuroma is relocated to the donor nerve. For conceptual reasons, repair of an injured nerve, when feasible, is preferable to permanent transection.

Other options may be considered for the treatment of neuropathic pain, including implantation of peripheral nerve stimulators, spinal cord stimulation, and medical therapy (opiates, anticonvulsants, membrane stabilizers, and tricyclic antidepressants). Prudent decision making is based on an analysis of risk versus benefit. Of note, if a nerve has already been completely severed, the risk of relocating that neuroma to a new location is low. Thus, in a case of a well-defined neuroma, when an anesthetic block relieves pain, surgical neurectomy may be the preferred *first* line of therapy when medications have failed.

Careful analysis may lead to rewarding outcomes. The following case presents the history, preoperative evaluation, and treatment of a patient with neuropathic pain:

> A 44-year-old woman presented with a chief complaint of right vaginal pain. This problem had been present for 3 years and originated with an excisional biopsy of a right-sided vaginal ulcer near the introitus. The pain was always present but especially disturbing were lightning attacks of pain that occurred unpredictably several times a day. Examination disclosed a subtle sensory loss in the right vulvar area. Medication trials were minimally helpful. An anesthetic block of the right pudendal nerve led to 50% pain relief. A combined ilioinguinal and genitofemoral nerve block also led to 50% pain relief. A local anesthetic block of all three nerves together led to 100% pain relief. As treatment, the right pudendal nerve was severed near the ischium through a perivulvar approach, and the patient, predictably, had 50% pain relief. At a separate setting, the right ilioinguinal and genitofemoral nerves were severed through a retroperitoneal approach. At 3-year follow-up, the patient had complete relief. There were no adverse sequelae.

In this case, both lumbosacral neural segments provided innervation to the painful neuromas. Failure to appreciate this would have led to a less than satisfactory result. This case underscores the need for complete blockade of pain during the application of local anesthetic to ensure that all involved nerves are identified.

Evaluation of patients with nociceptive pain in diseased tissue follows a similar strategy. The anatomy of sensory nerves in the damaged region must be defined. Once candidate nerves are identified, direct local anesthetic blocks indicate the level of benefit that could be obtained following nerve ablation. A successfully applied block should induce complete anesthesia in the distribution of each target nerve, but not beyond, to avoid issues of deficient test specificity and sensitivity. Remote blocks with different agents may enhance specificity by identifying problems due to nonspecific responses. As stated in Chapter 102, a surgical decision should never be made on the response to a single nerve block.

Operative Technique

Given that abatement of neuroma pain is the object of treatment, the primary surgical issue is where to relocate the neuroma. Troublesome neuromas typically are in areas near joints, scars, and structures with wide excursion. The implied mechanism is that mechanically tethered neuromas produce pain when subjected to mechanical stress. The idea of surgery is to relocate the neuroma to a location where this does not happen (8). Nerves may be cut back to locations such that the ends can be placed in healthy, well-vascularized muscle. Some have advocated that neuromas be placed in holes in bone. Placement of the nerve in these environments does not change the fact that the cut ends of the nerve will sprout and that a neuroma will form. However, with placement of the nerve into muscle or bone, the chances are reduced that the nerve will be subject to tension and shearing forces likely to play a role in pain generation.

Alternatives to neuroma relocation exist. The nerves may be cauterized, frozen, burned, or injected with toxic chemicals. These options have been reported to be successful, but their advantage over surgical neurectomy has never been demonstrated. However, a surgical procedure where the neurectomy is done sharply, with limited damage to the surrounding environment of the nerve, is the gold standard. Damage to the surrounding tissues, such as necrosis due to phenol injection, may

set up a new focus for pain generation (9).

Treatment of Neuropathic Pain

Indications. Division of major nerves can cause significant motor deficits, sensory deficits, or pain. Ablation of such nerves as a treatment of pain should ordinarily be considered only if the nerve is already divided. Nerve graft repair must always be considered prior to repeat transection. Neurectomy of minor nerves is more commonly performed than neurectomy of major nerves due to the relative loss of function. The following conditions may respond to neurectomy for pain treatment. In many of these conditions, the origin of the problem is entrapment of the nerve. In these instances, it is better to preserve the nerve when it can be decompressed. Neurectomy should be reserved for those situations in which decompression is unlikely to provide a satisfactory result and nerve repair is not possible.

Amputation Stump Pain. Amputation of a limb is necessarily associated with considerable nerve injury. Some amputations are associated with enduring pain for reasons that are not at all clear (10). In particular, amputees with neuromas in weight-bearing regions or regions of scar are more likely to experience stump pain. Surgical relocation of neuromas to more proximal or protected locations may provide benefit.

Intercostal and Intercostobrachial Pain. Chest trauma or thoracotomy may damage intercostal nerves. Shoulder trauma and axillary node dissection may damage the intercostobrachial nerve. Motor deficits associated with intercostal and intercostobrachial neurectomy are clinically insignificant; neurectomy is usually without significant drawbacks.

Perineal and Inguinal Pain. Injuries to the pudendal, ilioinguinal, iliohypogastric, and genitofemoral nerves occasionally result in severe pain. These injuries are often due to abdominal and pelvic surgery, episiotomy, hernia repair, entrapment, or blunt trauma. Stulz and Pfeiffer (11) reported relief of pain with neurectomy in 70% (16 of 23) of patients with ilioinguinal and iliohypogastric neuralgia as a complication of prior surgery. Starling and Harms (12) reported similar rates of success: 89% (17 of 19) for ilioinguinal neuralgia and 71% (12 of 17) for genitofemoral neuralgia. Others have not found such uniformly high success rates, and pain clinics often are referred patients who have failed to respond to multiple neurectomies.

Meralgia Paresthetica. Entrapment or injury of the lateral femoral cutaneous nerve may result in pain and dysesthesia in the anterolateral thigh, called *meralgia paresthetica*. Section of the nerve usually relieves pain (13). However, nerve decompression procedures may achieve the same benefit with the added advantage of restoring sensation. Nonsurgical treatments should always be undertaken prior to referral for surgery.

Saphenous Neuralgia. Spontaneous entrapment of the saphenous nerve in the subsartorial canal (14) or damage to the saphenous nerve during surgery (15) may lead to pain along the anterior and medial leg and the dorsum of the foot. Luerssen et al. (14) reported 50% (three of six patients) success following nerve decompression and 100% (three of three patients) success following saphenous neurotomy in patients with spontaneous saphenous neuralgia.

Morton's Neuroma. Formation of neuromas along an interdigital plantar nerve produces sharp, burning pain along the plantar surface of the foot with radiation into the toes (see Chapter 80). Such neuromas are associated with thickening of the epineurium and perineurium of the nerve, suggestive of chronic trauma. Johnson et al. (16) reported relief of pain in 67% (22 of 33) of patients, with 6 years' average follow-up, following excision of the plantar interdigital neuroma.

Results. What are the predicted results of neurectomy for nerve injury pain? The question is difficult to answer because the patients subjected to this treatment are heterogeneous. In addition, measurement of patient outcome varies greatly among studies with regard to methodologic rigor and technique. As suggested by the studies cited above, success rates vary from modest to high.

Burchiel and colleagues (17) have taken a systematic approach to the treatment of nerve injury pain, moving the field toward a definition of the indications for neuroma surgery. Forty-two patients with nerve injury pain were divided into four treatment groups:

1. Patients with distal sensory neuromas treated by excision of the neuroma and implantation of the proximal nerve into muscle or bone marrow.
2. Patients with *suspected* distal sensory neuromas in which the involved nerve was sectioned proximal to the injury site and implanted.
3. Patients with proximal neuromas-in-continuity of major sensorimotor nerves treated by external neurolysis. (*Neurolysis* is a term is a term used by surgeons to mean freeing a nerve from adjacent tissue; anesthesiologists sometimes use the term to mean destruction of the nerve; the former meaning applies here.)
4. Patients with nerve injuries at points of anatomic entrapment treated by external neurolysis and transposition.

Surgical success (rated as a greater than 50% subjective improvement in pain levels, subjectively rated pain relief as “good” or “excellent,” and no postoperative narcotic usage) varied between the groups. In the 40 patients who received postoperative follow- up care over 2 to 32 months (average, 11 months), 16 (40%) met these criteria. By group, successful pain relief was accomplished in 44% (eight of 18) of group 1, 40% (four of ten) of group 2, 0% (zero of five) of group 3, and 57% (four of seven) of group 4.

After obtaining these results, Burchiel and colleagues (17) attempted to determine retrospectively the extent to which indicators of nerve injury predicted surgical success. Such indicators included Tinel's sign, hyperalgesia, a “discrete nerve syndrome,” litigation, and prior procedures. Some predictors showed promise. For example, a *discrete nerve syndrome*, defined as a condition in which a single nerve could account for all the neurologic findings and pain distribution, tended to predict success. However, none of the relationships between preoperative diagnostic variables and treatment success achieved statistical significance.

One can only speculate as to why the results of this series differ substantially from those of other series. Perhaps patient selection accounts for differences, yet Burchiel et al. (17) appeared to discriminate the patients at high risk of failure. Surgical technique could play a role, but there is no evidence on which to base such a statement. In some cases, neuromas are innervated by more than one nerve. For example, proximal resection of the superficial radial nerve to treat dorsoradial wrist neuromas often relieves pain only temporarily. Further inspection reveals that the lateral antebrachial cutaneous nerve also innervates these neuromas, and thus success may require section of this nerve as well (18).

Another reason for failure in neuroma relocation surgery may relate to the discovery that the *distal* side of a severed nerve may also form a neuroma at the site of injury. Plexus formation distal to the neurectomy may allow intact nerve fibers from other nerves to sprout in retrograde fashion to innervate this distal site. This retrograde sprouting may create a potentially painful neuroma on the “wrong” side (19). Neuroma relocation surgery should perhaps therefore attend to neuroma formation on both sides of a severed nerve.

Indications and Results for the Treatment of Nociceptive Pain

Neurectomy may be performed to interrupt the flow of pain signals from a diseased tissue to the spinal cord. In these cases, a balance is sought between elimination of input from the pain-generating tissue and the potential formation of painful neuromas. Following neurectomy, regrowth of the transected nerve and invasion of the diseased tissue by surrounding nerves may result in a return of pain. In addition, progression of the disease process may enlarge the injured region, producing pain beyond the region of surgery. In the following disease processes, neurectomy may be an effective treatment of nociceptive pain:

Axial Spine Pain. The medial branches of dorsal rami innervate the paraspinal muscles, the interspinous ligament, and the zygapophyseal (facet) joints. Pain associated with movement of the lower back, which is relieved by rest and is not attributable to other spine pathology, may be relieved through bilateral, percutaneous radiofrequency or chemical ablation of these branches in the lumbar spine (20,21). In addition, neck pain associated with whiplash injury may benefit from a similar procedure in the cervical spine (22). The mechanism of pain relief is thought to relate to denervation of the facet joint. Since the dorsal ramus innervates several structures, other mechanisms are possible. Diagnostic anesthetic blocks of the facets should precede any denervation procedure. Only patients whose axial pain is not associated with radicular symptoms and who get dramatic pain relief from nerve blocks should be considered candidates for this denervation procedure. Most often, the procedure is performed percutaneously with radiofrequency heat lesions. The advantages of this procedure are that it can be done on an outpatient basis and morbidity is low. The disadvantage is that the procedure often confers only temporary relief or often no relief at all, regardless of the temporary effects of the diagnostic facet blocks. In patients with no prior spine surgery, these procedures have been reported to provide initial relief for 60% to 70% of patients (22,23 and 24). Rates are reported to be considerably lower, 20% to 50%, for patients with prior spine surgery (23,25,26). Our view is that this is a low-morbidity procedure that helps a modest number of patients with axial spine pain. Properly conducted clinical trials have not been reported.

Extremity Joint Pain. Denervation procedures aim to eliminate pain arising from degenerative processes in the joint, while preserving functions that may be lost after other forms of joint surgery. Buck-Gramcko (27) reported retention of wrist mobility with substantial reduction of pain in 69% of patients (135 of 195) following wrist

denervation surgery. Wilhelm reported success in 90% of patients with tennis elbow treated by denervation (28). Dellon et al. reported satisfaction in 86% (60 of 70) of patients following partial denervation surgery for persistent, postoperative knee pain (29).

Pelvic Pain. Neurectomy of the superior hypogastric (presacral) plexus has been advocated as a treatment for medically refractory pelvic pain. In 1948, Ingersoll and Meigs (30) reported complete relief of primary dysmenorrhea in 81% (72 of 89) of women treated with neurectomy. More recently, with the development of more effective analgesics, ablative approaches to pelvic pain have been largely limited to patients with secondary dysmenorrhea associated with endometriosis. Nezhat et al. (31) reported at least 50% relief from pain in 70% to 85% of patients with various stages of endometriosis, with 1-year follow-up, following presacral neurectomy combined with excision and vaporization of endometriotic lesions. The debate over the proper role of presacral neurectomy has been ongoing for well over 50 years; the introduction of the biopsychosocial model of chronic pain has spared many women unnecessary surgery (see Chapter 72).

Pain of Neoplastic Origin. Peripheral neurectomy is infrequently used in the treatment of pain due to cancer. This is due to the availability of alternative strategies with low morbidity and higher success rates, such as spinal opiates. Transecting a peripheral nerve may fail to relieve pain because of overlapping receptive fields of adjacent nerves or central plasticity. Sectioning most peripheral nerves results in not only numbness but also unacceptable motor loss. Peripheral neurectomies are rarely indicated in the extremities. However, localized chest or abdominal wall pain can successfully be treated with intercostal neurectomies; alcohol injection, cryoprobe, or radiofrequency lesions may be just as successful as an open surgical procedure and have less morbidity.

DORSAL RHIZOTOMY AND GANGLIONECTOMY

Rationale for Dorsal Root Surgery

The law of Bell and Magendie states that the dorsal root comprises solely primary afferent fibers while the ventral root comprises efferent fibers. Based on this, dorsal rhizotomy has immediate appeal as a way to block the inflow of nociceptive signals to the spinal cord. Injury to motor fibers in the ventral root is avoided (Fig. 105-1). No neuroma forms at the cut ends of the rootlets, as nerve fibers that enter the spinal cord are deprived of their cell body and hence degenerate (32).

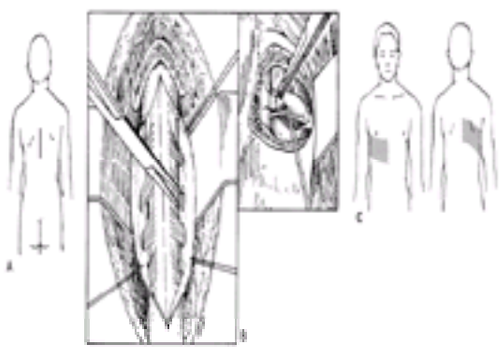

Figure 105-1. Dorsal rhizotomy. **A:** Location of midline dorsal incision for T-4 to T-7 dorsal rhizotomy. **B:** Intradural dorsal rhizotomy with application of metal clip on the rootlets of a root already transected above and being applied to the rootlets of a root below just prior to sectioning them. Inset on the right depicts extradural dorsal rhizotomy showing division of the dorsal root central to the ganglion prior to extirpation of the ganglion by a lesion that will be made just distal to the ganglion. **C:** Expected area of sensory loss following right T-4 to T-7 dorsal rhizotomy.

Traditionally an appealing treatment option for pain, rhizotomy in practice often fails to confer the lasting benefit that one might expect. Early surgeons performed dorsal rhizotomy for a broad range of conditions including stump pain, intercostal neuralgia, angina, visceral pain, and spastic hemiplegia. After comparing operative results for pain with those for spasticity in 1911, Groves (33) remarked, “Strangely enough, the division of the posterior spinal roots has given the least satisfactory results in those very cases where we should have expected it to be the most efficient … the relief of pain.”

An important problem with rhizotomy is that the sensory afferents that arise from a region of the body may provide contributions to multiple spinal nerves. Conversely, fibers from a single spinal nerve may innervate multiple segments of the spinal cord. As a result, sensory dermatomes overlap considerably, so that ablation of a single dorsal root produces little sensory deficit (34). The earliest studies (35,36) of the dermatomes appreciated this complexity, and early surgeons performed rhizotomy at multiple levels to achieve pain control (33). More recently, extensive remodeling of sensory dermatomes, attributed to intraspinal sprouting of dorsal root axons (37), functional reorganization of existing sensory pathways (38), and other mechanisms, has been described. Thus, the finding that patients often fail to derive sustained benefit from dorsal rhizotomy is no longer surprising.

A second problem involves the presence of afferent fibers in the ventral roots. In 1894, Sherrington (39) noted degeneration of fibers on the cord side of a transected ventral root (40). He suggested that these fibers, which he presumed would double back and reenter the cord through the dorsal root, might provide a physiologic basis for the observation that stimulation of the ventral root results in pain. Microscopy has demonstrated that some fibers do in fact enter the cord through ventral roots, cross the ventral horn, and synapse within the dorsal horn or enter the dorsal columns (41). Thus, dorsal rhizotomy may fail ultimately because of the presence of afferents that reach the spinal cord via the ventral root.

To obviate this problem, consideration may be given to performance of a sensory ganglionectomy. The cell body for all primary afferents is believed to reside in the dorsal root ganglion regardless of whether the fibers reach the spinal cord via the dorsal or ventral roots. One report cites a patient with recurrent pain following dorsal rhizotomy that experienced enduring pain relief following removal of the dorsal root ganglia at the same level, providing further evidence that afferents concerned with pain may enter the spinal cord through ventral roots (42). However, including ganglionectomy in a dorsal rhizotomy has not been demonstrated to yield better long-term results.

Clinical Considerations

Preoperative Evaluation

Identification of spinal levels appropriate for ablative lesions of nerve roots is accomplished through paravertebral local anesthetic nerve blocks. To predict most accurately the expected improvement with rhizotomy or ganglionectomy, local anesthetic blocks should be performed with placebo controls and at multiple levels.

Although rhizotomies are now done infrequently for pain, some patients in fact have enduring pain relief from rhizotomy or ganglionectomy, with acceptable morbidity. The challenge clinically is to pick the patients. Feasibility dictates selection of procedures to some extent. If the clinical problem is limited to one root, ganglionectomy has appeal in order to avoid the problem of ventral root afferents. Unfortunately, surgical ganglionectomy involves destruction of a substantial portion of the facet and therefore may not be practical if two or more roots are involved. Rhizotomy may be considered in this instance. However, the problem of pain recurrence may be higher. No clinical studies really compare rhizotomy and ganglionectomy. Thus, differences in outcome between the two procedures are not well understood.

Dorsal rhizotomy and sensory ganglionectomy spare motor efferents and do not lead to the formation of neuromas. However, careful attention must be given to the potential complications of dorsal root surgery. Ablations of the dorsal roots attenuate not only pain but also vibratory, temperature, and proprioceptive inputs. Loss of these sensory functions may be troublesome, particularly in the extremities. In addition, with the ablation of the highly vascularized dorsal roots, the blood supply to the spinal cord can be jeopardized. Ablation of more than six dorsal roots increases this risk considerably (34). Finally, dorsal rhizotomy and ganglionectomy, if unsuccessful, preclude the use of dorsal column stimulation as a means of pain treatment, because the primary afferents, on which the stimulator acts, undergo wallerian degeneration.

The following case presents the evaluation and treatment of a patient with neuropathic pain, in an ideal setting for performance of a ganglionectomy:

> A 42-year-old woman underwent an anterior cervical diskectomy and fusion with harvesting of a bone graft from the left iliac crest. An anterior abdominal

wall hernia developed at the site at which the bone was harvested. This defect was repaired with mesh, and the patient developed severe pain at the repair site. Eventually the repair site was explored, and injury to the subcostal nerve (T-12) was noted. The neuroma was resected back and relocated to a healthy muscular bed away from scar. Pain was relieved for several weeks and then returned. An additional attempt at neuroma relocation surgery met with the same fate. Opioid treatments as well as other pharmacologic approaches failed to provide satisfactory relief. Nerve root blocks of T- 12 but not of T-11 or L-1 led to complete pain relief. A ganglionectomy was performed at T-12, and the patient had sustained pain relief.

In this case, pain was limited to a single, clearly defined spinal level. The return of pain following neurectomy demonstrated the high likelihood of reformation of a painful neuroma. A single ganglionectomy both eliminated the pain and precluded the reformation of a painful neuroma.

Indications and Results for Rhizotomy in Cancer Pain

Indications for dorsal rhizotomy may be broadly divided into procedures for cancer and noncancer pain (43). Barrash and Leavens (44) reported success in 70% (50 of 71) of patients with cancer, with 10.5-month average follow-up. By contrast, Onofrio and Campa (45) reported an overall success rate of 41% (46 of 112) in patients with localized idiopathic pain. The differences in success rate between cancer and noncancer pain may result from earlier mortality among patients with cancer-related pain. Average results as derived from the literature are contained in Table 105-1.

Disease	Approximate no. of reported cases	Approximate long-term relief (% of total cases)
Occipital neuralgia	60	50
Cervicothoracic lumbar neuralgias	120	60
Postherpetic neuralgia	20	25
Failed lumbar disk	200	33[a]
Coccygodynia	70	60
Cancer	600	50

[a]Range: 10% to 86%.

TABLE 105-1. Average results reported with dorsal rhizotomy

Cranial and Cervical Pain. Rhizotomy of C-1 to C-4 in combination with cranial nerves V, IX, and X may provide effective pain relief from extensive head and neck cancers (46). In considering such a procedure, one would have to consider the morbidity of such an extensive operation in terms of sensory loss. In some cancer victims, however, sensory loss is already extensive. Dorsal cervical rhizotomy may also be combined with trigeminal tractotomy. Cancers of the lung or breast with brachial plexus involvement, with loss of function in the upper limb, may also benefit from cervical rhizotomy.

Thoracic Pain. Pain associated with cancers of the lung and breast with extension into the chest wall may benefit from dorsal rhizotomy. Arbit et al. (47) reported complete pain relief in 64% (nine of 14) and 50% to 100% pain relief in an additional 29% (four of 14) of patients with cancer pain, with 22-month median follow-up, following thoracic dorsal and ventral rhizotomy.

Sacral Pain. Cancers of the colon, rectum, urinary tract, cervix, and prostate may result in pain attributable to sacral roots. Ablation of the second and third sacral roots may affect bladder, sphincter, and sexual function. Saris et al. (48) reported success in 47% (7 of 15) of patients with colorectal cancer presenting with perianal pain, with 1-year median follow-up, following bilateral S-3 to S-5 rhizotomy. Felsoory and Crue (49) reported satisfactory results in 69% (20 of 29) of patients with colorectal (17), cervical (five), anal (three), and other (three) cancers, with unstated follow-up duration, following transection of the cauda equina at L-5/S-1. Sacral root division in cases where patients have already lost bladder and bowel function is a simple procedure that may confer striking benefit. The surgical anatomy is depicted in Figure 105-2.

Figure 105-2. Technique of extradural sacral rhizotomy. An S-1 laminectomy is performed, and thecal sac is dissected out circumferentially between S-2 and S-3, doubly ligated, and divided. (From Burchiel KJ. Neurosurgical procedures of the peripheral nerves. In: North RB, Levy RM, eds. *Neurosurgical management of pain.* New York: Springer-Verlag, 1997:148, with permission.)

Indications and Results for Rhizotomy in Noncancer Pain

Occipital Neuralgia. The greater occipital nerve, formed by the posterior primary ramus of C-2, and the lesser occipital nerve, formed by the C-2 and C-3 roots in the cervical plexus, jointly innervate the occipital region of the scalp. Occipital neuralgia is headache, characterized by severe paroxysmal lancinating or continuous pain, localized to this innervated region (50). Occipital neuralgia may be due to migraine, compression of the C-2 root, entrapment of the greater occipital nerve at the superior nuchal line, or nerve injury (51). Onofrio and Campa (45) reported relief from occipital neuralgia in 64% (nine of 14) immediately and 50% (seven of 14) after months to years following ablation of one to three cervical roots. Dubuisson (52) reported success in 71% (ten of 14) of patients, with 33-month average follow-up, following partial posterior rhizotomy at C-1 to C-3.

Extremity Pain. There are few indications for use of rhizotomy and/or ganglionectomy for the treatment of extremity pain, except possibly for monoradiculopathies as noted below. The fact that multiple roots may be involved, the morbidity of sensory loss, and the problem of frequent pain recurrence mean that these procedures are infrequently used for extremity pain. The choice of rhizotomy or ganglionectomy for the treatment of extremity pain requires a balance between (a) compromise of function due to elimination of sensation and (b) the elimination of pain. For the upper extremity, White and Kjellberg (34) reported successful treatment of diffuse upper extremity pain in 50% (seven of 14) of patients, with 3-year median follow-up, following rhizotomy at various levels. Following the procedure, none of the patients complained of unpleasant numbness or clumsiness of the hand, perhaps reflecting the seriousness of the preoperative condition. In the lower extremity, White and Kjellberg (34) reported successful treatment of lateral femoral cutaneous neuralgia in 67% (four of six) of patients, with 3-year median follow-up, following L-2 to L-3 rhizotomy.

Postsurgical Truncal Pain. Persistent pain following thoracotomy or laparotomy may be responsive to dorsal rhizotomy. White and Kjellberg (34) reported successful treatment of intercostal neuralgia in 75% (three of four) of patients, with 8-month median follow-up, following thoracic rhizotomy. Loeser (43) reported success in 33% (one of three) of patients at more than 3 months. By contrast, Onofrio and Campa (45) reported on 18 patients with postthoracotomy pain and five patients with postlaparotomy pain, none of whom obtained benefit. White and Kjellberg (34) also reported successful treatment of postherniorrhaphy neuralgia in 75% (three of

four) of patients, with 2-year median follow-up, following thoracolumbar rhizotomy. There is no large series of patients on which to base a useful discussion.

Visceral Pain. Though rarely used today, due to the advent of other techniques, dorsal rhizotomy has been reported to be highly effective in controlling visceral pain. White and Kjellberg (34) reported successful treatment of medically intractable angina in 75% (three of four) of patients, with 14-month median follow-up, following T-1 to T-4 rhizotomy. Success was 50% (three of six) for treatment of other forms of visceral pain (34).

Low Back Pain. Local and radicular pain due to lumbar spine disease is largely unresponsive, in the longer term, to dorsal rhizotomy. Loeser (43) reported success in 75% (12 of 16) at up to 3 months but only 14% (two of 14) at more than 3 months for patients with disk disease. Onofrio and Campa (45) reported improvement in 17% (11 of 64) of patients with lumbosacral pain following rhizotomy, with unstated follow-up. Wetzel et al. (53) reported success in 55% (28 of 51) at up to 6 months and 19% (seven of 37) at 2 years for patients with lumbar radiculopathy after lumbar surgery.

Postherpetic Neuralgia. Dermatomal pain following herpetic infection responds poorly to dorsal rhizotomy. Loeser (43) reported failure in two of two patients. Onofrio and Campa (45) reported success in only 20% (one of five) of patients, with 5-year follow up, following unilateral rhizotomy. The treatment of postherpetic neuralgia is discussed in Chapter 22.

Indications and Results for Ganglionectomy

Several series consider the efficacy of ganglionectomy and are worth noting. Stechison and Mullin (54) reported success in 100% (four of four) of patients with idiopathic greater occipital neuralgia, with 2-year average follow-up. Lozano et al. (55) reported that patients with occipital neuropathic pain due to trauma are more likely to experience significant pain reduction, following C-2 ganglionectomy, than other patient groups with occipital pain. Smith (56) reported success in 100% (ten of ten) of patients with intercostal pain due to thoracotomy (seven), herpes zoster (two), and cancer (one), following thoracic ganglionectomy. North et al. (57) reported greater than 50% relief from failed back surgery syndrome in none of the 13 patients they studied, with 5.5-year average follow-up. By contrast, Taub et al. (58) reported success in 59% (36 of 61) of patients with intractable monoradicular sciatica following dorsal root ganglionectomy, with 5 to 9 years' median follow-up. This unusually high rate of success likely reflects very careful patient selection.

Conclusions

There is little evidence in favor of ganglionectomy over dorsal rhizotomy and a wide variation in reported outcomes with either procedure for any diagnosis. Some patients do obtain long-term benefits, but prediction of outcome has been perilous.

SYMPATHECTOMY

Basic Considerations

Sympathetic efferents reach their target structures in two steps (see Chapter 8). Preganglionic sympathetic efferents arise in the intermediolateral cell column of the spinal cord at T-1 to L-3. Thinly myelinated fibers emerge in the ventral roots and transit briefly through the spinal nerve before exiting to form the white rami communicantes, leading to the paravertebral sympathetic ganglia. Some preganglionic fibers form synapses in the sympathetic chain with postganglionic neurons, from which unmyelinated fibers return to the spinal nerves, forming the gray rami communicantes. These postganglionic efferents provide sympathetic innervation to blood vessels, sweat glands, and other structures. Other preganglionic fibers pass through the paravertebral sympathetic chain without forming synapses and continue to the prevertebral ganglia. In the prevertebral ganglia, these efferents synapse with postganglionic effector neurons. From the prevertebral ganglia, unmyelinated fibers innervate the abdominal and pelvic viscera. Sympathectomy has been used in the treatment of pain from the limbs, the heart, and abdominal viscera. Presacral neurectomy and thoracic sympathectomy for cardiac pain are discussed earlier in this chapter and are not further addressed here.

There are three distinct mechanisms through which ablation of sympathetic nerves or ganglia may lead to pain relief:

- The sympathetic efferents in T-1 to L-3 that pass through the paravertebral sympathetic ganglia to the abdominal and pelvic viscera do not travel alone. They are accompanied by afferents, with cell bodies in the dorsal root ganglia of T-1 to L-3, which convey sensory information about distension and inflammation of visceral organs to the central nervous system. As a result of this colocalization, ablation of the prevertebral ganglia (or the nerves originating from them) interrupts the flow of nociceptive signals from visceral structures to the brain, thereby producing pain relief. Hence, as a treatment of visceral pain, sympathectomy is a form of sensory neurectomy.
- Sympathectomy may improve pain associated with ischemia. Sympathetic efferents maintain arterial tone. In vasospastic and vasoocclusive conditions, the vasodilation consequent to sympathectomy may ameliorate ischemia, thereby decreasing pain (59).
- Finally, sympathectomy may eliminate norepinephrine-mediated activation of nociceptors and thereby relieve SMP. In this section, we concentrate on this latter mechanism and extremity pain related to complex regional pain syndromes in which a component of pain has been demonstrated to be sympathetically maintained.

Sympathetically Maintained Pain

In some patients with chronic pain syndromes, the pain depends on the activity of sympathetic efferents in the painful area. This pain, termed *sympathetically maintained pain* (SMP), is defined as that aspect of pain that is relieved by blockade of sympathetic efferents (60). Pain that is unaffected by the activity of sympathetic efferents is termed *sympathetically independent pain*. The diagnosis of SMP is empiric. In any pain syndrome, a portion may be sympathetically maintained, while another part is sympathetically independent. Most notably, complex regional pain syndrome (Chapter 20) and other neuropathic conditions may or may not be associated with SMP.

SMP cannot be diagnosed purely from the history and the physical examination of the patient (61). However, a number of clinical features are helpful: (a) In general, SMP does not occur in places other than the extremities or the face. As a rule, the likelihood of developing SMP parallels the density of sympathetic innervation of the skin. Hence, truncal pain is far less likely to be due to SMP than is extremity pain. (b) Signs that may be inferred to represent increased sympathetic activity in the painful area do not denote the presence of SMP (62). For example, limbs associated with SMP may be warmer, cooler, or the same temperature as unaffected limbs. Similarly, differences in sweating, nail growth, and muscle tone do not contribute to the diagnosis of SMP (3). We have found that among patients with traumatic nerve or soft tissue injury with touch-evoked pain, all patients with SMP and 50% of patients with sympathetically independent pain have striking sensitivity to mild cooling stimuli (63,64).

In recent years, understanding of the pathophysiologic mechanisms underlying SMP has advanced significantly. By definition, SMP is eliminated by blockade of sympathetic efferent innervation of the painful area. Thus, an anesthetic block of the relevant sympathetic ganglia relieves pain in patients with SMP. Walker and Nulson (65) and White and Sweet (10) observed that stimulation of the sympathetic chain evokes pain in patients with SMP but not in those without SMP. Moreover, Walker and Nulson (65) noted that stimulation of the severed distal end of the sympathetic chain evokes pain in those diagnosed with SMP but not in other patients. Thus, the central connections of sympathetic efferent fibers are not required for stimulation of the sympathetic system to evoke pain. These observations establish that efferent sympathetic fibers, rather than afferent sensory fibers that may travel with the sympathetic fibers, account for SMP.

Three independent lines of evidence suggest that norepinephrine released from sympathetic fibers is critical in SMP. First, the regional infusion of guanethidine relieves pain in patients with SMP (66). Guanethidine is thought to act by depleting norepinephrine from sympathetic terminals. Second, in patients whose pain had been relieved by either sympathetic block or sympathectomy, an intracutaneous injection of norepinephrine into the previously painful area rekindles the pain and hyperalgesia. However, norepinephrine injected intracutaneously into normal subjects induces less pain and less hyperalgesia (67,68). Finally, administration of sympathetic a-adrenergic antagonists, such as prazosin (69), phenoxybenzamine (70), or phentolamine (71,72), relieves SMP.

Following nerve injury, the neuromas that form may acquire sensitivity to norepinephrine. As evidence in support of this hypothesis, injection of pH-balanced norepinephrine solution into normal subcutaneous tissues causes little pain. However, injection of norepinephrine onto painful neuromas does induce pain (73). Thus, nerve injury may be associated with SMP.

These observations suggest that an abnormal increase in the amount of norepinephrine released from sympathetic terminals is not likely the mechanism of SMP. Rather, it is the response to norepinephrine that appears to be critical in SMP. Whether this change is due to an upregulation of a-adrenergic receptors or increased

receptor sensitivity is unknown.

Clinical Considerations

Preoperative Evaluation

The most likely cause of poor pain relief after surgical sympathectomy is inadequate patient selection. Thus, preoperative evaluation is of great importance.

Quantitative Sensory Testing. Patients with SMP have hyperalgesia to a mild cooling stimulus, such as a drop of acetone placed on the skin. Our group and others have found that essentially all patients with SMP have cooling hyperalgesia (61,63,64). In fact, patients with SMP often spontaneously volunteer that the one stimulus that they most dread is cooling of the painful area. Cooling hyperalgesia occurs less frequently in patients with sympathetically independent pain. This suggests that cooling hyperalgesia is a highly sensitive, though not specific, indicator of SMP.

Local Anesthetic Sympathetic Ganglion Blocks. The traditional procedure to diagnose SMP is percutaneous injection of local anesthetic onto the sympathetic ganglia serving the painful region. In local anesthetic sympathetic ganglion blocks (LASB), ganglia are localized through anatomic landmarks, ideally under fluoroscopic guidance, and local anesthetic is injected into the region. The presence of local anesthetic at the ganglia prevents norepinephrine from being released into the peripheral tissues. Though frequently used to diagnose SMP, LASB results must be interpreted with care: (1) Incomplete block of individual ganglia may falsely underestimate the contribution of SMP to a painful condition. The extent of sympathetic block must be evaluated by assaying for the effects of sympathetic block, such as changes in skin temperature. (2) Spread of local anesthetic onto somatic afferents in the nerve roots, or blockade of sensory afferents that accompany sympathetic efferents, may induce pain relief by way of somatic block rather than sympathetic block. A careful sensory examination must be performed to ensure that somatic afferents are not affected by the injection of local anesthetic. (3) LASB may evoke a placebo response, causing overestimation of pain relief. In addition to these interpretive issues, LASB has some risk. Complications that have been reported with LASB include pneumothorax, phrenic and laryngeal nerve block, cardiac arrhythmia, kidney injury, hemorrhage, and inadvertent intravascular or epidural injections (see Chapter 102).

Systemic Phentolamine Infusion. An alternative strategy to assess the potential efficacy of sympathectomy involves the intravenous infusion of phentolamine, a short-acting antagonist of a-adrenergic receptors (71,72). There is good correlation between pain relief with LASB and that with systemic phentolamine infusion (SPI) (61,71). As a systemic infusion, phentolamine does not provide any information about anatomic localization, as is available with LASB. However, SPI has a number of advantages over LASB: (1) The test is painless in that the phentolamine is delivered systemically and does not require fluoroscopy or needles to be placed in the paravertebral space. (2) With SPI, a significant observation period can be used prior to the administration of the drug, and the patient can be blinded to the time of drug administration, allowing a placebo-control period in every trial. (3) SPI appears to be safer than LASB, with only nasal stuffiness and peripheral vasodilation reported as side effects (61,74). Furthermore, because the activity of nearby sensory afferents is preserved, SPI appears to be a more specific diagnostic test for SMP (61,71).

Intravenous Regional Block (IRB). A third method to detect SMP involves regional intravenous infusion of an agent that impedes peripheral release of norepinephrine (66). Such agents include bretylium, reserpine, and guanethidine (64). To avoid systemic circulation of the sympatholytic agent, a tourniquet is applied to the limb during the test. The central advantage of intravenous regional block (IRB) is localization of sympathetic block to the limb of interest. However, there are shortcomings: (1) Certain patients poorly tolerate the required tourniquet application. (2) The dramatic release of sympathetic neurotransmitter accompanying infusion of guanethidine in SMP patients may be severely painful. (3) The blocking agent may leak beyond the tourniquet, in some instances, with significant hemodynamic effects. (4) The need for a tourniquet makes IRB difficult to perform either in the trunk or in the lower extremity. (5) It is difficult to evaluate placebo responses with IRB. Though frequently mentioned as a means to diagnose and treat SMP, we believe that IRB has few advantages. The same degree of a-receptor blockade can be achieved with systemic phentolamine.

Medical Treatment of Sympathetically Maintained Pain

Once the diagnosis of SMP is made, the mainstay of treatment is operative or medical sympatholysis. A remarkable feature of SMP is that extended sympathetic blockade may lead to long-term or permanent relief from the disorder. When the goal of blockade is diagnosis, the diagnostic technique should be specific to the sympathetic nervous system. By contrast, when the goal is treatment, there need not be specificity. There are several medical and interventional means by which to achieve sympatholysis. The choice of technique should be based on considerations of safety, comfort, and efficacy. Multiple sympathetic ganglion blocks with local anesthetics have, in the past, served as the gold standard treatment. However, local anesthetic treatment of peripheral nerves may work as well, by inducing similar blockade of the distal sympathetic fibers. For example, SMP in the upper extremity could be treated either by LASB of the thoracic sympathetic ganglia or by local anesthetic application to the appropriate nerves. Alternatively, while epidural administration of anesthetic may lack specificity as a means to diagnose SMP, it may provide an effective treatment regimen. SPI has been used successfully to treat SMP in a patient with pain in all extremities due to Sjogren's associated polyneuropathy (75). When episodic treatments fail to provide adequate relief, chronic treatment with oral sympatholytics may reduce SMP. Both phenoxybenzamine and prazosin have been used in this regard (69,70). However, the systemic hypotension that frequently accompanies the use of these agents may preclude adequate sympathetic blockade. Finally, topical clonidine, which is likely to inhibit local norepinephrine release, may be a low-morbidity treatment of SMP in some patients (67). If well tolerated, this and other medical techniques could substantially reduce the need for surgical sympathectomy.

Operative Techniques

To achieve sympathectomy of the upper extremity it is necessary to resect the T-2 and the T-3 and T-4 sympathetic ganglia. Removal of less than all three ganglia risks inadequate sympathectomy for pain. One of our patients required extension of the sympathectomy to T-5. This is best achieved through a thoracoendoscopic technique, although all of the data on this operation have been acquired through open supraclavicular transaxillary or posterior costotransversectomy approaches. By contrast, the lumbar sympathetic chain is generally accessed through an anterolateral retroperitoneal surgical approach. Percutaneous approaches have been suggested, but these procedures often do not achieve enduring results. In addition, the addition of scarring by these approaches makes later surgical treatment more difficult.

Many clinicians have reported limited success in the treatment of pain with surgical sympathectomy (76,77). Failures of sympathectomy may reflect inadequacies either of the preoperative evaluation, as discussed above, or of the extent of the sympathectomy. For example, sympathetic outflow to the arm derives predominantly from the T-2 and T-3 ganglia and not from the stellate ganglion. Failure to remove the T-2 ganglion, at a minimum, will result in continued sympathetic innervation of the hand. An important feature in the lower extremity is that sympathetic innervation is often bilateral. Bilateral lumbar sympathectomy of L-2 to L-4 is typically necessary (Fig. 105-3). A typical history is that a patient will have impressive relief of pain that will last several weeks, following an ipsilateral lumbar sympathectomy. The pain then returns, and now this pain is relieved by a contralateral block of the lumbar sympathetic ganglia. Patients will typically have enduring relief of pain following contralateral lumbar sympathectomy (78,79). As in the upper extremity, complete sympathectomy is required for pain relief; the partial denervation that is successful for vascular diseases is not adequate as a treatment for pain.

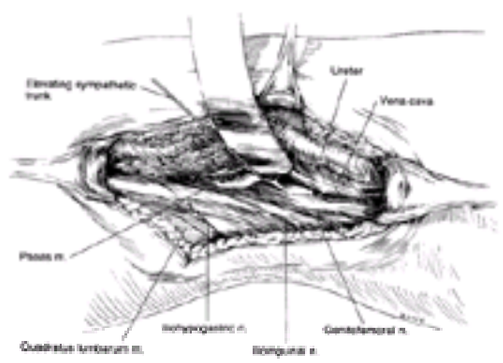

Figure 105-3. Open lumbar sympathectomy is done through retroperitoneal exposure of the sympathetic chain. (From Wilkinson HA. Neurosurgical procedures of the sympathetic nervous system. In: North RB, Levy RM, eds. *Neurosurgical management of pain.* New York: Springer-Verlag, 1997:170, with permission.)

Results of Sympathectomy for the Treatment of Pain

Ulmer and Mayfield (80) reported successful treatment of 96% (67 of 70) of soldiers with burning pain due to nerve injury by surgical sympathectomy of appropriate ganglia. In studies of a civilian population, Manart et al. (81) reported a “good” response to thoracic sympathectomy in 59% (13 of 22) of patients with burning posttraumatic pain, even when diagnostic blockades were not typically performed. For patients selected for preoperative diagnostic sympathetic block, Mockus et al. (82) reported improvement in 94% (29 of 31) of patients, with 3.4 years' average follow-up. Thompson (83) reported successful surgical treatment in 46% (55 of 120) of patients with SMP following minor trauma who were unresponsive to medical therapy.

As noted, results of sympathectomy largely depend on how carefully patients are selected (70). Our experience has been that patients do exceedingly well if the pain responds dramatically to sympathetic ganglion block and systemic infusion of phentolamine and there is provocation of pain with injection of norepinephrine when the patient is under the influence of an LASB. Though our conclusions are preliminary, it appears that if one or more of these elements is missing, the patient does less well. The modest response rates to sympathectomy in other series may reflect improper patient selection and inadequate sympathectomy (e.g., bilateral sympathectomy required for lower extremity pain) or more extensive unilateral ganglionectomy for total denervation of an extremity.

Postoperative Complications

Surgical sympathectomy may be associated occasionally with idiosyncratic complications. The most frequent complication, affecting 20% to 50% of patients, is postsympathectomy pain (or postsympathectomy neuralgia) (82,84,85). This condition is characterized by the sudden onset, a few weeks after the procedure, of superficial burning pain, deep aching pain, and cutaneous hyperalgesia (86). The pain arises in the *proximal* regions of limbs and the trunk, despite surgical ablation of sympathetic innervation to the *distal* limbs. Fortunately for most patients, postsympathectomy pain resolves spontaneously in several weeks to a few months and no further surgical intervention is warranted (84).

Ablation of sympathetic input to a region of skin results in sudomotor paralysis. In the upper extremity, the resultant dryness can be uncomfortable. In the lower extremity, dryness is better tolerated. Postural hypotension also can be a transient problem. However, even in patients with sympathectomy of all four extremities, this problem is usually not enduring.

Two additional complications of sympathectomy include paradoxical vasoconstriction and ileus. Sympathetic fibers arising from the celiac and mesenteric ganglia modulate gastrointestinal motility. Both complications are generally transient.

CONCLUSIONS

Ablative surgical procedures have a significant role in the treatment of a variety of painful conditions. Like many surgical procedures, enthusiasm for these techniques must be tempered by a keen appreciation of the potential complications. Nerve transection may induce pain, for example, and may dramatically relieve pain. This leaves to the clinician the sometimes daunting task of deciding if, when, and how to perform neurectomy. Each patient must be carefully evaluated. In the case of minor nerves previously transected, the clinician should not labor over the decision to relocate the neuroma to a protected, unscarred site. In this instance there is little to lose. Dorsal rhizotomy is seldom used in modern practice, but a survey of the existing literature reveals that patients certainly exist in whom rhizotomy conferred long-term benefit. Today's pain clinician does well to keep this option in mind in properly selected cases. Ganglionectomy has certain theoretical advantages over rhizotomy and neurectomy and is still another technique that should be considered in certain cases. Sympathectomy is helpful in patients with persistent SMP who are refractory to medical management. The key to success with this procedure, as with most surgery, is meticulous patient selection and proper execution of the operation.

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CHAPTER 106

Neurosurgical Operations on the Spinal Cord

Jason E. Garber and Samuel J. Hassenbusch

This chapter discusses various neurosurgical operations carried out on the spinal cord for the relief of chronic pain. Three major procedures are presented: anterolateral cordotomy, myelotomy, and dorsal root entry zone (DREZ) lesions. These ablative spinal procedures, as expected, occupy roles that are intermediates between the intracranial brainstem ablations and peripheral nerve lesions. The risks of the spinal procedures for pain are generally lower than with intracranial procedures, but they have a more restricted pattern of anatomic coverage. Peripheral denervations are technically easier to perform but often affect only a very limited anatomic area and have a higher chance of pain recurrence. Each procedure is discussed in terms of indications and contraindications, but the actual selection of an operation for a specific patient should be based on the type of pain (e.g., nociceptive, neuropathic, or visceral), the location of the pain, and the cause of the pain (e.g., cancer vs. noncancer).

The role of these intraspinal procedures is at the bottom of a long treatment continuum that includes (a) systemic treatments, such as various medications or physical therapy; (b) direct operations, such as spinal stabilization or surgical decompression; (c) thorough psychological evaluation and treatment as appropriate; (d) chemotherapy and/or radiotherapy (for cancer patients); and (e) regional anesthetics and opioids.

ANTEROLATERAL CORDOTOMY

Anterolateral cordotomy is an operative procedure in which the spinal anterolateral ascending system for the transmission of nociception, known as the *spinothalamic tract*, is interrupted for the relief of pain. Both percutaneous and open surgical techniques are available; the anatomic goal is the same, and results differ only with respect to the risks of each approach and to long-term results. Cordotomy is an example of an older procedure that has found increased use because of the development of a percutaneous technique. Computed tomographic (CT) guidance has led to even greater safety and efficacy.

The concept of relieving pain by section of the pain-conducting pathways in the anterolateral quadrant of the spinal cord was first proposed by Schuller (1) in 1910 based on observed deficits from spinal cord lesions in the anterolateral quadrant. It was not until 2 years later, however, that Martin (2), at the urging of Spiller, performed the initial thoracic cordotomy in a patient with pain from a tuberculoma. Stookey (3) was the first to report successful high cervical unilateral and bilateral cordotomy for severe pain. Foerster and Gagel (4) reported similar unilateral procedures a year later.

To avoid or minimize the risks of open surgery, a percutaneous stereotaxic procedure was advanced by Mullan and associates (5,6). This percutaneous method could be accomplished under local anesthesia simply, easily, and with a low morbidity rate in patients who otherwise might not be suitable for a major open operation.

The initial method for percutaneous cordotomy used a radiostrontium-tipped needle that was inserted into the spine at the C-1 to C-2 interspace laterally and came to lie anterolaterally in the subarachnoid space adjacent to the ventral quadrant of the spinal cord. The next approach introduced a wire electrode into the parenchyma of the spinal cord so that anodal current could be used to create the lesion in the ventral quadrant. In 1965, Rosomoff and associates (7) proposed a technique using a radiofrequency (RF) current to produce the lesion, which allowed rapid and solid lesion-making. Electrophysiologic monitoring of electrode position by electrical impedance and electrical stimulation were described by Gildenberg and associates (8) and by Hitchcock and Tsukamoto (9) and Tasker and Organ (10), respectively. The technique has become standard with the use of myelography to confirm spinal cord and dentate ligament position (11). CT guidance has added another level of accuracy to this procedure (12) (Table 106-1). Two other approaches (low anterior cervical “through-the-disk” and occipital to C-1 dorsal cervical) have also been described but have never been widely used (13,17). After discussing the percutaneous technique, including CT-guided electrode placement, the open operation is briefly considered.

Source	Technique	Comments or modifications
Mullan et al. (5)	Isotope needle; lateral cervical	Unpredictable, radiation risk, complex to prepare
Mullan et al. (6)	Unipolar electrode; lateral cervical	Erratic lesion, prolonged current time, unpredictable
Rosomoff et al. (7)	Radiofrequency current; bilateral or unilateral cervical	Rapid, solid lesion, portable, predictable
Crue et al. (13)	Radiofrequency; high cervical	Posterior approach, traverses spinal cord, higher levels (?)
Fox (14)	Radiofrequency	Current related to lesion size
Gildenberg et al. (15,16); Lin et al. (17)	Radiofrequency; low cervical, transdiskal	Anterior approach, decrease respiratory complications (?), more difficult technically, impedance measurements, increased safety
Hitchcock (18)	Radiofrequency; high cervical	Posterior approach, traverses spinal cord, higher levels (?)
Tasker et al. (19); Tasker and Organ (20)	Radiofrequency; lateral cervical	Physiologic identification of target site
Todd et al. (21)	Radiofrequency; high cervical, medulla	Posterior approach, useful for somatic and facial pain
Mullan (22)	Radiofrequency; lateral cervical	Electrical stimulation to identify tract, increased safety
Kanpolat et al. (23)	Radiofrequency; lateral cervical	Computed tomographic guidance for trajectory, min trials

TABLE 106-1. Developments in percutaneous cordotomy

Basic Considerations

The anatomy and physiology of the spinothalamic and other important ascending tracts in the anterolateral quadrant of the spinal cord that transmit nociceptive information are discussed in detail in Chapter 4. Important additional insights into the mechanism of action for this procedure have suggested that it interrupts more than just C fibers since pain relief correlates best with lessened sensation of cutaneous pinching and skin cooling (24). A diminished blood flow in the contralateral thalamus but not in cerebral cortex has also been demonstrated after cordotomy by positron emission tomography (25).

Indications

The optimal candidate for this operation should have unilateral severe pain, not adequately treated by other less invasive methods. As for neuropathic pain, cordotomy appears to be more effective in the treatment of intermittent shooting pain and evoked pain (i.e., allodynia and hyperpathia) rather than distressing dysesthesias, such as steady, burning, prickling, aching, or crawling (26). The former is mediated by the lateral spinothalamic tract, and ventrolateral cordotomy alleviates pain in more than 85% of patients. The latter is not transmitted entirely through the ventral quadrant, and these discomforts are relieved imperfectly or not at

all. Tabetic or pseudotabetic pain, although it has a dysesthetic quality, seems to respond well to cordotomy.

Anatomically, the procedure is indicated for pain in C-5 or lower dermatomes, preferably unilateral. It is almost entirely used for patients with pain from cancer, including those who previously could not be subjected to the major operation of laminectomy and spinothalamic section because of debilitation or a preterminal state. It is increasingly rare to use cordotomy to treat painful conditions that are intractable and nonmalignant in nature, although some argument can be made for use in the treatment of nociceptive pain, albeit of noncancer origin (27). When bilateral cordotomy is required, the contralateral procedure can be performed as a second stage no less than 1 week after the first.

Contraindications

Severe pulmonary dysfunction is the major contraindication to either percutaneous or open surgical cordotomy. The absence of a lung, *per se*, does not interdict the procedure, provided remaining pulmonary function is satisfactory. The site of concern is the reticulospinal tract, located near the spinothalamic tract and critical for automatic or unconscious breathing. Prior loss or significant decrease in this automatic breathing on the opposite side (e.g., from prior contralateral cordotomy or Pancoast syndrome) can lead to a total loss of unconscious respiration (Ondine's curse).

Recently incurred neurologic deficits, such as paresis or rectal or bladder disturbance, can be aggravated or recovery delayed by the superimposition of cordotomy; if this is the case, the effect is usually temporary. Midline pain is a relative contraindication, even with bilateral cordotomy. General medical contraindications such as a severe bleeding diathesis, unstable cardiac function, and untreated severe systemic infection should also be observed.

Clinical Considerations

Technique

The patient is placed in the supine position with the upper cervical spine horizontal (Fig. 106-1). The patient is given light intravenous sedation during the time of the needle placement prior to physiologic testing for the actual electrode placement. Using local infiltration anesthesia between the first and second cervical vertebrae, a lumbar puncture-cordotomy combination needle is introduced in the side of the neck on the contralateral side to the pain. An image intensifier is used to define the point of dural puncture, just anterior to the point halfway between the posterior and anterior bony margins of the spinal canal.

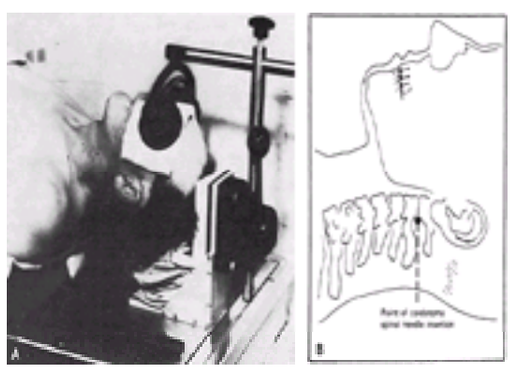

Figure 106-1. **A:** Position of patient for percutaneous C-1 to C-2 cordotomy. **B:** Site of insertion of needle for percutaneous C-1 to C-2 cordotomy.

Once the needle has been introduced into the subarachnoid space of the spinal canal, hyperbaric (heavier than water) contrast medium is injected to visualize the dentate ligament. A special insulated electrode (2-mm exposed metal tip) is inserted through the needle. Using physiologic monitoring (impedance readings), the electrode is directed so that the bare metal tip enters the parenchyma of the spinal cord (Fig. 106-2).

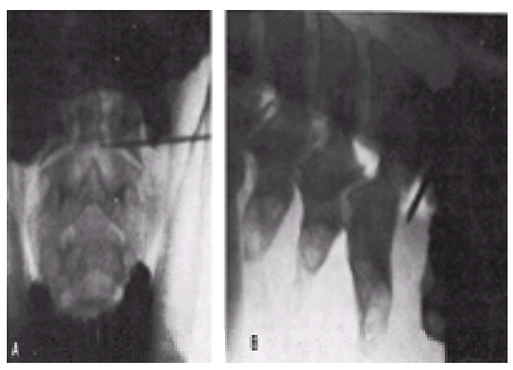

Figure 106-2. Position of needle electrode for percutaneous C-1 to C-2 cordotomy as seen on anteroposterior **(A)** and lateral **(B)** radiographs.

The cable of an RF generator is attached to the electrode, and the electrode tip is stimulated with 2-Hz and 100-Hz current. The patient is closely questioned about sensory changes and motor twitching during each stimulation. Ideally, at 2-Hz, there will be contractions in the ipsilateral neck or upper limb and, at 100-Hz, a sensory experience of contralateral warmth or occasionally cold or paresthesias in the target dermatomes. Spinothalamic evoked potentials have been used to aid in electrode localization (28). In this testing, stimulation is applied to the spinothalamic tract via the cordotomy electrode and recordings are made in the scalp area. Although the recordings correlate with the extent of the lesion, their clinical usefulness remains unclear.

A thermocouple-monitored temperature lesion is made, starting at 50°C and increasing by 5°C to 10°C increments (Fig. 106-3). The patient is tested carefully after each increment, both for the level of analgesia and for the possibility of complications—in particular, ipsilateral hemiparesis. Disturbances in temperature sensation are usually seen as a result of the cordotomy lesions. The location of the loss of temperature sensation, however, can vary significantly from that of the analgesia (29). It is even possible to perform a successful cordotomy without any alteration in temperature sensation.

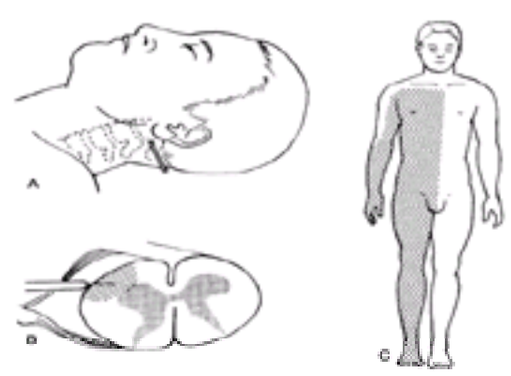

Figure 106-3. **A:** Site of percutaneous C-1 to C-2 cordotomy. **B:** Lesion produced by percutaneous C-1 to C-2 cordotomy. **C:** Extent of analgesia produced by left C-1

to C-2 percutaneous cordotomy.

Postoperative care consists of observation for ipsilateral leg weakness, bladder control changes, significantly lower analgesic requirements, and possible respiratory depression. Because of the degree and rapidity of pain relief, patients should be watched for possible narcotic withdrawal if systemic analgesics are lowered too quickly.

The CT-guided cordotomy technique is similar to the traditional percutaneous method except that the cordotomy electrode needle is inserted with the patient in a CT machine (23). CT images (512 × 512 matrix) with 2-mm slice thickness are used. A special electrode system (KCTE Kit, Radionics Inc., Burlington, MA) is also used to diminish the metallic artifact interference in the CT image (30).

An anterior approach for percutaneous cordotomy has also been described (31). An uninsulated 18-gauge spinal needle is inserted medial to the carotid sheath and lateral to the tracheoesophageal complex until it enters the disk. Using CT axial plane guidance, the needle is directed to the contralateral anterolateral spinal cord quadrant. Once the needle enters the spinal canal, water- soluble contrast dye is injected to delineate the spinal cord. An insulated RF electrode is inserted through the spinal needle and advanced into the spinal cord. The remainder of the procedure is similar to that described above.

Results

In most series, almost all cordotomies have been performed for pain from cancer, often lung or gastrointestinal cancer. Rarely, the procedure has been used in the treatment of lumbar radiculopathy or peripheral neuropathy (32). The target sites are the lower body as opposed to upper body in about two-thirds of patients.

In the hands of experienced surgeons, the spinothalamic tract can be located in 95% to 99% of patients, although the surgeon should not be hesitant to perform an early reoperation if appropriate analgesic levels are not obtained for technical reasons in the first cordotomy (27). “Adequate” levels of pain relief are found in as high as 95% of patients on discharge from the hospital. At last follow-up, however, the success rate can drop to 84% (Table 106-2) (27). Review of other published series suggests long-term success rates of 50% to 75% (Table 106-3). Rosomoff and colleagues (32) have reported that the satisfactory analgesia rates gradually drop over time since the operation: 84% at 3 months, 43% at 1 to 5 years, and then 37% at 5 to 10 years (see Table 106-2). It should be noted, however, that this refers to absolute pain relief. It is estimated that more than 50% of these patients felt they had received major help, could return to routine activities, and did not have problems of drug usage or distress severe enough to undergo repeat cordotomy.

Duration of follow-up	No. of operations	Results (successful)	
		No.	%
3 mo	599	495	84
3 mo to 1 yr	304	185	61
1-5 yr	299	127	43
5–10 yr	86	32	37

TABLE 106-2. Results of percutaneous cordotomy

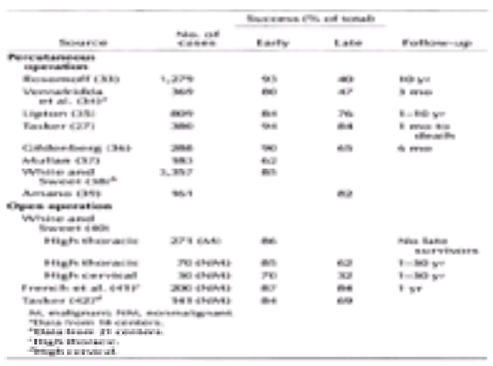

TABLE 106-3. Comparison of results of percutaneous and open cordotomy

Repeat cordotomies can be necessary in 10% to 20% of patients and, despite the prior cordotomy, can usually achieve levels of analgesia to acute testing pain. It appears that true pain relief, however, is captured in only about one-half of these patients undergoing a repeat cordotomy (27,32).

Four major groups account for the vast majority of patients with persistent pain after cordotomy (27). As many as 40% represent untreated neuropathic pain, either unmasked by the operation or as a component of a preoperative mixed nociceptive-neuropathic syndrome. This emphasizes proper patient selection and recognition that the procedure is more effective, in general, for nociceptive rather than neuropathic pain. Where there is apparent failure of pain relief for nociceptive pain, almost one-half are unexplained, but the rest represent inadequate levels of analgesia and early reoperation should be considered. The third group is a very small group (1% to 2%) with new nociceptive pain above the level of analgesia and might represent progression of disease. The last group is a relatively large group (40%) with development of “mirror pain.” This apparently new-onset pain is located ipsilateral to the side of the lesion and has classically been thought to be an “unmasking” of preoperative pain that was eclipsed by the more severe pain on the opposite side. There is other evidence, however, suggesting that ongoing stimuli in the area of the treated, contralateral pain might now trigger pain on the opposite side via some form of new synaptic sprouting in the spinal cord (43). In either event, this mirror pain is generally mild and controlled with significantly lower amounts of analgesics than those used prior to the cordotomy (44).

In the series of Rosomoff and associates (32), almost one-third of patients underwent bilateral cordotomies for pain relief. These were staged operations, at least 1 week apart. Of all patients with malignant disease, 35% required bilateral intervention. Only 30% of those with benign disease required bilateral intervention. The success of the second side appears to be similar to the first side—the major issue here is the complications that are specific to bilateral cordotomies.

Complications

A comprehensive summary of complications from unilateral cordotomy indicates that, in general, the complication rate is low (27) (Table 106-4). The mortality rate can vary between 0.6% and 6.0%, almost always related to respiratory problems. Bowel incontinence and mild worsening of micturition can be seen in up to 2% to 10% of patients—both should be transient. Significant, permanent worsening of bladder function, however, can be seen in 2% to 10% of patients. Although information relative to sexual function is difficult to obtain, it appears that about 4% of men note decreased sensation about the genitals on the analgesic side; true impotence appears to be very rare, even with bilateral cordotomies.

Type of complaint	Temporary		Permanent	
	No.	%	No.	%
Paresis	63	5	34	3
Ataxia	252	20	44	3
Urinary	123	10	29	2
Sexual			54	4
Postcordotomy dysesthetic syndrome			10	1
Respiratory				
Minor	36	3		
Major	23	2	12	1*
Dysesthesias			199	16

*Includes one death.

TABLE 106-4. Complications of 1,279 percutaneous cordotomies

Although a postoperative Horner's syndrome is frequently seen (as often as 75% of patients), it is essentially unavoidable but transient. Many patients complain of transient neck pain, often described as burning or dysesthetic, from the area of the needle puncture. Transient hypotension can also be seen (2% to 8%).

Of more concern is significant permanent weakness or ataxia, usually ipsilateral to the side of the cordotomy (2% to 10%). Ipsilateral weakness/ataxia, which is described as mild or transient, is reported in 3% to as many as 70% of patients. Contralateral limb weakness, presumably from lesioning too deep into the spinal cord, can also occur (1% to 6%).

Respiratory problems after unilateral cordotomy are rare and mild or transient (1% to 5% of patients). Severe respiratory failure can occur in 0.5% to 1.0% of patients but is more often seen as sleep-induced apnea (Ondine's curse) after bilateral cordotomies. The mechanism is related to an ascending system that contributes to the control of ventilation and is mediated through the upper cervical spinal cord (45). It may be delayed in onset, but its presence can be predicted by testing the patient's response to breathing carbon dioxide (46). Ablation of the response, which is normally a two- to threefold increase in minute volume, predicts the appearance of the syndrome, but not all patients go on to apnea. The process is usually self-limiting, lasting a few days to 3 weeks.

Postcordotomy dysesthetic syndromes—that is, burning distress throughout the entire area that was made analgesic—can occur in 1% to 10% of patients. Its pathophysiologic mechanism is unknown. Dysesthesias, in 16%, are noted separately. These sensations (e.g., tingling, burning, prickling in the area of pathologic implication) are not complications *per se*. They are uncomfortable feelings that were usually present preoperatively but were not conspicuous because of overriding pain. Once the pain has been eliminated by the cordotomy, the dysesthesias become discernible and prominent, although they usually take time to develop.

Open Surgical Cordotomy

Since the last edition of this text, the open surgical technique has become mainly of historical interest. The open technique might still be used in some rare circumstances such as in facilities in which percutaneous cordotomy equipment is not available or the surgeon performs it so infrequently as to lose skill in the procedure. However, thoracic cordotomy can be performed for lumbar and sacral pains without jeopardizing upper extremity or respiratory function; thus, it may have more utility than open upper cervical cordotomy. When the patient is unable to tolerate any procedure while awake, a percutaneous cordotomy can be performed under general anesthesia in a manner similar to above except that, of course, sensory testing with 100-Hz stimulation cannot be performed. The indications for the open technique are the same as the percutaneous counterpart.

Technique

Open surgical cordotomy is almost always performed under local anesthesia. High cervical cordotomy is done if levels of analgesia above C-8 are required. It is carried out with the patient in either the sitting or prone position. A lower-level cervical cordotomy can be carried out through an anterior approach with the patient in the supine position.

Thoracic cordotomy and a posterior cordotomy are carried out with the patient in the prone or lateral position (Fig. 106-4). After a midline incision is made, a laminectomy is carried out, which is extended to the facet on the side of the spinal cord to be incised. The dura and the arachnoid are opened, and the dentate ligament is identified. The anterolateral surface of the spinal cord is viewed, and an avascular area is found for the incision. A down-cutting cordotomy knife tip, projecting 6 mm in the cervical area and 4 to 5 mm in the thoracic area, is inserted just ventral to the dentate ligament, pulling the spinal cord onto the knife blade so as to penetrate cleanly. The blade cuts ventrally to transect the ventral quadrant down through the exit of the motor rootlets but spares the medial funiculus. In the thoracic area, if a bilateral cordotomy is required, the second side is sectioned one or two segments below the first cut at the same sitting.

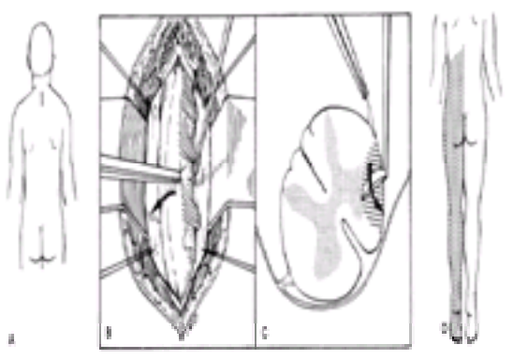

Figure 106-4. **A:** Site of open thoracic cordotomy. **B, C:** Method of performing open thoracic cordotomy. **B:** After T-1 to T-2 laminectomy, the dura is opened and the dentate ligaments sectioned. The linea alba is grasped in a hemostat and the spinal cord is rotated 45 degrees. **C:** A special cordotomy knife is used to section the anterolateral quadrant. **D:** Extent of analgesia on dorsal surface produced by right T-1 to T-2 open cordotomy.

Results and Complications

After open cordotomy, immediate relief was reported in 70% to 90% of patients who had undergone unilateral procedures and in 40% to 78% of those with bilateral procedures. A comparison of results from a sample of the larger series is presented in Table 106-3.

Mortality rates for open cordotomy ranged from 3% for the unilateral procedure to 20% for bilateral procedures. Paresis and urinary complications were high (10% to 20%), especially after bilateral procedures. Respiratory complications were the most common cause of death, but the exact numbers were not listed. Postcordotomy dysesthetic syndromes can occur in 11% of patients. Open surgical cordotomy seems to be less effective and certainly has a higher risk of complication than the percutaneous techniques.

Conclusions

Percutaneous cordotomy is simpler and better tolerated than open surgical techniques. Because the anatomic and physiologic bases for pain relief are the same for all cordotomies, true differences in long-term results might not be discernible. However, such advantages as the ease of performance, significant reduction of risk, and

the literally infinite repeatability make percutaneous cordotomy the procedure of choice.

Percutaneous cordotomy is a valuable procedure for the treatment of severe pain syndromes, especially if they are located in one limb and are nociceptive in quality. With the addition of CT guidance, the technique has become more facile. The risks of the procedure are significant but acceptable for this group of patients, especially those with limited expected survival times from cancer. The benefits, in terms of almost immediate pain relief and limited need for outpatient follow-up, are both cost-effective and gratifying.

MYELOTOMY

Commissural myelotomy at the thoracolumbar level for the treatment of pain was first described by Armour in 1927 (47) for a patient with tabetic abdominal pain. Putnam (48) was apparently unaware of this report when he claimed to have performed the first myelotomy in 1934. Since then, the popularity of this operation has waxed and waned. It seems quite logical that neurosurgeons would aim at producing bilateral pain relief with a single low-risk procedure that has little risk of damage to the important spinal axonal systems. Unfortunately, this apparently attractive operation has not been as effective as predicted on theoretical grounds. After the initial attempts on a few patients, commissural myelotomy was applied on a relatively large scale by French and German neurosurgeons in the 1940s and 1950s (49,50 and 51), subsequently becoming relatively obsolete for several years. At the end of the 1960s, Sourek (52,53 and 54) published encouraging results and once more aroused the interest of neurosurgeons in this technique. In the last 15 years, the topic has recurred sporadically in the neurosurgical literature, with various results reported (55,56,57,58,59,60,61,62,63,64,65,66,67,68 and 69). Approximately 425 myelotomies have been reported in the neurosurgical literature.

Basic Considerations

The original aim of commissural myelotomy was the interruption of all the decussating second-order spinothalamic fibers subserving pain perception on both sides of the body as they travel in the anterior commissure of the spinal cord. Theoretically, bilateral symmetric analgesia should have been achieved, with pain relief restricted to the segments where sensation had been altered. The length of the myelotomy incision should have been proportional to the extent of pain. What was seen, however, even after extensive longitudinal splitting of the spinal cord over several centimeters, was that a girdle of analgesia was present in the expected area but that pain relief extended caudally into regions that had no demonstrable sensory changes. Hence, the role of the spinothalamic fibers in pain relief after myelotomy is not clear.

Various hypotheses have been proposed to explain this antalgic but not analgesic effect of myelotomy. Sourek (52,53 and 54) theorized that the spinal commissurotomy interrupts two systems that conduct pain information: the slow-conducting anterolateral system and the fast-conducting mediodorsal system. The latter was believed to have a somatotopic arrangement and is contained in the medial portion of the posterior columns.

Sunder-Plassmann and Grunert (55) have reported their experiences with 56 midline myelotomies and described only bilateral segmental analgesia appropriate to the level of the myelotomy. In contrast, Hitchcock (56,57) and Schvarcz (58,69) carried out cervical stereotaxic myelotomies and reported extensive areas of pain relief without sensory changes. They thought that their procedure specifically interrupted an extralemniscal centrospinal multisynaptic pathway, with Schvarcz referring to “extralemniscal tractotomy (58).”

From an anatomic standpoint, Kerr and Lippman (70) have reported that the projections to the periaqueductal gray matter seen in cordotomy are topographically different from those seen in myelotomy. The gray matter around the central canal has been shown to have anatomic connections to brainstem areas involved in nociception (71). In patients who have had an open myelotomy, disorders attributable to damage to the posterior columns are frequently observed for several weeks after surgery.

A midline afferent pathway has been hypothesized that is a multisynaptic chain of short tracts (72). This operation would not only affect the crossing spinothalamic fibers but also the spinoreticular tracts (73). Finally, there is evidence for a tract in the anterior part of the medial borders of the posterior columns mediating visceral pain, both for pelvic pain and for more proximal epigastric visceral pain (74,75,76 and 77). This pathway synapses in the nucleus gracilis and activates neurons in the ventral posterior lateral nucleus of the thalamus.

Clinical Considerations

Technique

The two basic strategies for midline myelotomy are (a) open, requiring a laminectomy, opening of the dura, and making a lesion under direct vision, and (b) closed, making a lesion through a needle that has been passed through the skin, between adjacent laminae, and into the spinal cord.

The open operation requires a midline dorsal incision that is usually performed in the low thoracic and upper lumbar area. The upper end of the myelotomy is placed at least three cord segments above the highest level of the patient's pain. A laminectomy is performed, and the dura is opened widely. Retention sutures are used to hold the dura open, and the spinal cord is visualized. The arachnoid is incised, and the dorsal midline of the spinal cord is identified. The incision in the spinal cord is made in the exact midline between the two gracilis tracts and carried down ventrally until the ventral pia has been divided. The spinal cord is therefore totally transected so that the right and left sides no longer communicate. The central gray matter is destroyed, as are the decussating fibers that go on to form the spinothalamic tract (Fig. 106-5).

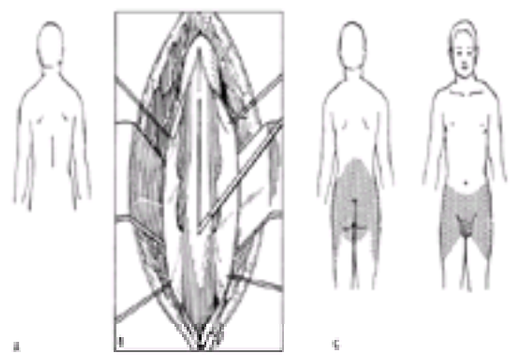

Figure 106-5. **A:** Site of thoracolumbar midline myelotomy. **B:** Method of performing midline myelotomy in thoracolumbar region. After a laminectomy of T-9 to L-1, the dura is opened and the dorsal midline of the spinal cord identified. A microknife is used to make a midline incision to the ventral pial surface. **C:** Extent of analgesia produced by thoracolumbar midline myelotomy.

Different techniques have been described over several decades. It is obvious that spinal commissurotomy or midline myelotomy is by no means a standardized procedure. Similar results have been obtained with quite different operations: The level, length, and depth of the spinal lesions vary extensively. For example, some neurosurgeons have reported limited myelotomies or even single stereotaxic RF lesions; others have used complete longitudinal splitting of the spinal cord over multiple segments from 100 to 110 mm long. It appears that no reliable or widely accepted criteria exist as to how long or how deep the incision should be to interrupt all fibers subserving a given painful area. Complete division of the anterior and posterior commissures appears to be the most effective method. Second, postoperative sensory changes are too variable to allow any physiologic appraisal of the effect of myelotomy; consequently, correlations between lesion size and site and outcome are impossible. Finally, the mechanism of pain relief after myelotomy is not understood.

Open myelotomy is a major surgical procedure that should be considered with caution. Patients in poor condition who have a short life expectancy are not often suitable. On the other hand, even the most extensive myelotomies have not guaranteed long- lasting pain relief. A CT-guided technique has also been described in the creation of lesions in the same area (78).

Percutaneous myelotomy has been described by only four surgeons; the procedure has probably been performed in about 150 patients, although pain relief in large regions of the body has been reported in as many as 79% of patients with cancer. Hitchcock (56,57) Schvarcz (58), and Gildenberg and Hirshberg (59) have described making a lesion at C-1, and Sourek (52,53 and 54) made lesions both at C-1 and at T-8 to T-10. Coagulation of the high spinal central gray matter produces dramatic changes in sensation and pain relief over variable but widespread regions of the trunk and extremities. In this technique, only a single lesion is made in the center of the spinal cord, at a segment just above the highest level of the painful areas. A single lesion is made at the thoracolumbar junction of the spinal cord (so-called punctate midline myelotomy) for the most common use of this procedure—pelvic visceral pain from rectal or uterine cancer (79). Follow-up times and areas of sensory loss have been variable, and the duration of pain relief is not clear.

Results

Despite the well-documented shortcomings, rewarding clinical results, mostly in cancer patients with pain in the pelvis, perineum, and/ or both lower extremities, have been reported in the literature (Table 106-5). Good pain relief without significant analgesia is also occasionally seen (80). In combined series, total relief of pain or total cessation of analgesics was initially reported in 92% of patients (161 of 175), most of whom had cancer pain. This rate, however, dropped to 59% (103 of 175) at last follow-up or death in the cancer pain patients. There has been great variance in these results, however, between different series, possibly because of differences in technique, especially the depth of the sectioning.

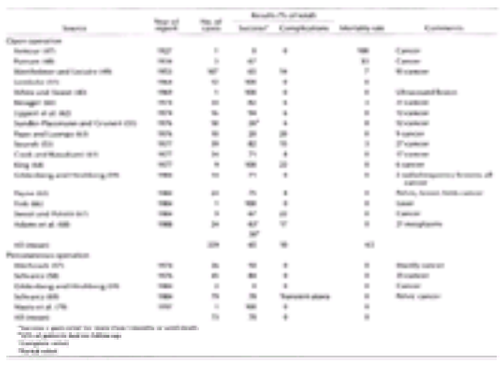

TABLE 106-5. Results of commissural myelotomy

Wertheimer and Lecuire (49), who applied myelotomy on a large scale more than 40 years ago, initially stated that myelotomy provided satisfactory pain relief in most patients with bilateral pain in the lower half of the body. The same clinical material was subsequently reanalyzed by Dargent and colleagues (50), who concluded that myelotomy was effective only for the management of vaginal and visceral pain, whereas rectal and lower limb pain were not significantly influenced. Later, Sourek (52,53 and 54) and Broager (60) reported good results for the relief of lower limb pain, whereas Cook and Kawakami (61) and Lippert and associates (62) did not succeed in relieving lower limb or spinal pain. As for the pain located in the upper part of the body, Lembcke (51) and Cook and Kawakami (61) reported satisfactory results, whereas Sourek's (52,53 and 54) experience was disappointing.

With stereotaxic cervical procedures, Hitchcock (56,57) and Schvarcz (58) succeeded in most patients irrespective of the location of pain. Between these two series, 100 patients were treated. Follow-up until death or for up to 5 years indicated that approximately 70% of patients had satisfactory pain relief. Papo and Luongo (63), however, obtained only short-lasting relief with a cervical procedure (superficial splitting and deep coagulation) regardless of the type and location of pain, which always recurred in patients who survived more than 2 to 3 months.

Sunder-Plassmann and Grunert (55) claimed that 91% of their patients were pain-free after midline myelotomy; 26% remained pain-free until their deaths or for the duration of follow-up, which lasted up to 4 years. Others feel that late pain recurrence as a result of a falling sensory level is rare (81). Myelotomy is a procedure confined to selected patients (82). All the published series have contained small numbers of patients.

Complications have been reported in 5% to 10% of the reported cases. Most surgeons agree that the typical open longitudinal midline myelotomy produces only a temporary loss of pain and temperature sensation in a girdle area that corresponds to the region of the cord incision. How long this unexplained sensory loss persists is unclear. Postoperative mortality has been low (up to 3%) in most recent series. Rarely, a dysesthetic or radicular pain of mild severity might occur at the top end of the area of pain relief (81). Other side effects include hyperesthesia, diminished proprioception, paresis, incoordination of gait, and motor and sphincter disturbances (80).

Conclusions

Although myelotomy remains a useful procedure, caution should be exercised when recommending myelotomy as the initial procedure for the relief of cancer pain. This procedure can be useful for the relief of bilateral pelvic and perineal pain because the other surgical alternative is bilateral cordotomy, which carries increased risk of bladder dysfunction. Epidural and intrathecal narcotics have unquestionably greatly reduced the numbers of patients who need ablative surgery for cancer pain. For the management of noncancer pain, open myelotomy is difficult to accept. So few surgeons have reported on C-1 RF myelotomy that it is impossible to adequately evaluate this variant, which can have a different anatomic substrate from the low thoracic myelotomy. Using the present understanding of the anatomy and physiology of mesial spinal cord systems, myelotomy techniques can be chosen but should be coupled with objective assessments of side effects and effects on different aspects of the pain (83). Present data strongly suggest that this is an effective procedure, albeit for a limited subset of cancer patients with intractable pain that is either bilateral or midline, especially located in the pelvis.

DORSAL ROOT ENTRY ZONE LESIONS

The DREZ operation entails making a series of lesions aimed at the substantia gelatinosa Rolandi and the surrounding fiber tracts. This operation was conceived and first used by Nashold and coworkers (84) in 1976 in a patient with severe pain secondary to brachial plexus avulsion. That patient has been reported to be free of pain ever since. By 1989, the Nashold group had done a total of 550 operations for various conditions (*personal communication* to Bonica, 1989). Almost 500 additional operations have been reported by other authors. Although Nashold and associates have the most extensive experience with this operation, many other neurosurgeons are performing this ablative procedure. The data published to date permit us to make reasonable inferences regarding its efficacy.

Basic Considerations

The DREZ operation involves the destruction of dorsal horn neurons and perhaps of the axons traveling in juxtaposition to the gray matter, particularly those segments that correspond to the patient's reported area of pain. The detailed anatomy of the human dorsal horn is discussed in Chapter 3 and Chapter 4; this chapter contains only a brief anatomic review relevant to this operation. The dorsal horn can be segmented on a cytoarchitectonic basis into six laminae (Rexed laminae). The five most superficial are clearly involved in the transmission of nociceptive information from the periphery and can play an essential role in some deafferentation or central pain states.

Not only are the synaptic connections from peripheral nociceptors localized in laminae I through V, but studies have demonstrated major concentrations of opiate receptors, substance P, and other biologically active peptides in these regions (85). Indeed, many believe that the “gate,” as described by Wall and Melzack (85), resides in this region of the spinal cord. The combination of classic neurophysiology and modern pharmacology points to this region as being critical in the processing of sensory information. In 1967, Loeser and Ward (86) reported that neurons in the dorsal horn became hyperactive when deafferentated. Nashold and coworkers (84) subsequently designed an operation to destroy the dorsal horn in patients with deafferentating lesions and severe pain. Initial successes have led to increasing use of this procedure; it has been almost exclusively used for pain states characterized by an injury to the nervous system referred to in this book as *deafferentation pain* and thought to have a peripheral-central pain mechanism; others have used the term *central pain*.

Few, if any, traditional surgical procedures have a significant chance of alleviating the pain that follows deafferentation (87). Certainly, rhizotomy, cordotomy, myelotomy, or sympathectomy is unlikely to produce long-term pain relief. DREZ lesions appear to be remarkably effective in brachial plexus avulsion and are reasonably effective for the relief of some types of postparaplegic pain, postamputation pain, postherpetic neuralgia, and for a small number of miscellaneous neuropathies and myelopathies.

The following chronic pain states are diagnoses that have been considered most appropriate for treatment by DREZ lesions: brachial plexus avulsion, other brachial plexus destructive lesions, sacral root avulsion, and postparaplegic pain. The procedure has also been used, although with a lower success rate, in the treatment of phantom limb pain, stump pain, postthoracotomy pain, postherpetic neuralgia, peripheral mononeuropathy, spinal cord tumor, multiple sclerosis, causalgia, and postrhizotomy pain. Specific predictive factors to indicate a favorable outcome are being developed.

Indications

The indications for DREZ lesions for the treatment of chronic pain include an established diagnosis and failure of medical-pharmacologic management. In addition, it is important that the patient have an understanding of alternative strategies, risks, and potential benefits. As previously mentioned, the diagnoses listed above are those that have thus far been considered to be appropriate for DREZ lesions. The number of patients treated, however, is currently limited in some of these diagnostic groups.

Contraindications

Contraindications relate to the patient's general health and ability to withstand a major surgical procedure, including such factors as infection, resistance to wound healing, blood and coagulation problems, and poor cardiopulmonary status. Patients who have a significant emotional component to their pain are rarely good surgical candidates, although the ravages of chronic pain can alter patients' judgment and emotions.

Clinical Considerations

Technique

DREZ lesions are performed under general anesthesia and require a laminectomy over each segment to be lesioned. For brachial plexus avulsion involving C-5 to T-1 dorsal roots, it is necessary to do a C-4 through T-1 laminectomy (Fig. 106-6). In the sacral segments, the anatomy of the conus permits extensive lesioning with a more limited laminectomy. The dura is opened, and the spinal cord is visualized. The dorsolateral sulcus is identified; the operating microscope is an important adjunct. Some neurosurgeons section the dentate ligaments so that the spinal cord can be rotated to orient the dorsal horn vertically. When the dorsal roots have been avulsed, the dorsolateral sulcus has a series of microcysts and gliosis. It is essential to see the intact dorsal roots rostral and caudal to the avulsion to identify the dorsolateral sulcus positively. Injury to nerves in the periphery or herpes zoster often leads to atrophic dorsal roots.

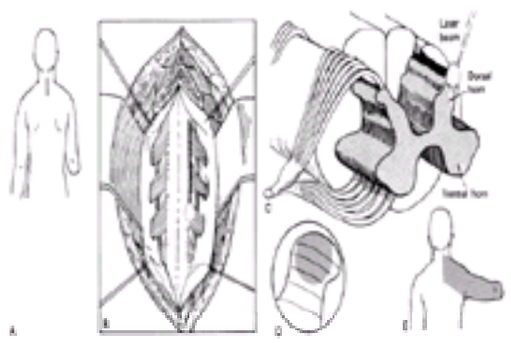

Figure 106-6. **A:** Site of C-5 to T-1 dorsal root entry zone (DREZ) lesions. **B,C:** Production of DREZ lesion using CO_2 laser. **B:** After a laminectomy of C-5 to T-1, the dura is opened and the dorsolateral sulcus is identified. The pial vessels are coagulated and a continuous lesion made in the dorsolateral sulcus to destroy the DREZ. **C:** After the laser is used, a microprobe is inserted into the dorsal horn to verify its destruction. **D:** Extent of lesion in dorsal horn. **E:** Analgesia produced by right C-5 to T-1 DREZ lesions.

Nashold and coworkers' (84,88) careful studies of this operative procedure should be required reading for any surgeon who wants to use DREZ lesions. His original RF electrode made too large a lesion and was apparently responsible for the high incidence of postoperative dorsal column and pyramidal tract dysfunction. The neurologic complication rate has fallen dramatically since Nashold shifted to a smaller thermistor-controlled electrode, which is 0.25 mm in diameter and 2 mm long for DREZ lesions in the spinal cord (88). Each lesion is made at 75°C for 15 seconds, and a series of lesions is done at 1-mm intervals; the longest series in one patient extending over a 5-cm length of the spinal cord. Using these parameters, each lesion in the spinal cord will measure 2.0 × 1.5 mm, which is adequate to destroy laminae I through V of the dorsal horn (88).

Sweet and Poletti (89) have described the deliberate use of a larger lesion in a small number of cases, and others have used variations of lesion making. The advent of the laser as a surgical tool has led to the use of both C_2 and argon lasers to lesion the DREZ (90,91). In research on cats regarding DREZ procedure (92), the lesions in dorsal horn produced by the RF probe were compared with those produced by CO_2 laser. Histologic examination revealed that depths of the laser and RF lesions were similar but the RF lesions showed more lateral spread. Laser lesions comprised 4.4% ± 1.6% of the cross-sectional area of the spinal cord, whereas the RF lesions occupied 22.8% ± 4%, demonstrating that the CO_2 laser produces smaller lesions than the RF electrode. Although the laser technique seems to be less traumatic to the spinal cord, it has not gained widespread use. This lower use might be a result of the possibility that the smaller lesions might not be as effective and/or the use of laser equipment is more cumbersome as compared to RF equipment. Another surgical technique is to coagulate the pia and vessels over the dorsolateral sulcus and to use a sickle knife to incise into the dorsal horn, followed by a ball dissection to destroy the dorsal horn under microscopic control. The dura is then closed in a watertight fashion, and the muscular and soft tissues are closed in the standard manner.

The postoperative course is usually benign; many patients have transient dorsal column or pyramidal tract dysfunction, but few have permanent deficits. It is presently unclear which method of destroying the dorsal horn is safest and most effective.

It is also unclear why lesions in the dorsal horn stop deafferentation pain states. Two or three autopsy reports published showed that DREZ lesions made at 450 mA for 5 to 15 seconds destroyed laminae I through IV of the dorsal horn and some of the white matter medial and lateral to the dorsal horn (89,93). In the third patient, who died on the twenty-eighth postoperative day and in whom the DREZ lesions were done according to the parameters mentioned above, the lesions involving the dorsal horn extended halfway into lamina VI, but there was minimal impingement on the white matter (94). These findings suggest that the technique described above accomplishes the objective and that additional neurologic deficits in either the posterior column or pyramidal tract functions are not required for effective pain relief.

A major concern with regard to the placement of DREZ lesions is proper localization for placement of these lesions. The dorsolateral sulcus is varyingly discernible; when the dorsal roots have been avulsed, the dorsolateral region can be densely adherent to the arachnoid or to the dura. The dorsal horn is obliquely oriented and the electrode, knife, or laser beam must be angled or the spinal cord rotated to create the desired lesion and avoid damage to the pyramidal tract or the dorsal column. When roots have been avulsed or the spinal cord damaged, it is helpful to expose the levels rostral and, when feasible, caudal to the proposed operative area so that normal dorsal roots can be visualized and the dorsolateral sulcus can be identified. Evoked potentials can also be used to localize the superficial tracts in the spinal cord and assist in the placement of lesions (94).

Results

Brachial Plexus Avulsion. The most common and most successful application of DREZ lesions is for the relief of the pain of brachial plexus avulsion. This traumatic disaster is most common in young men who ride motorcycles. Nashold's first patient suffered from this injury. An overall 83% success rate has been reported with many follow-ups of longer than 5 years (84,90,95,96,97,98,99,100,101,102,103,104 and 105). A few patients with sacral root avulsions have been included in these series. No other diagnosis has as high a likelihood of success, and no other operation is as likely to relieve this type of deafferentation pain. Table 106-6 summarizes the results obtained to date.

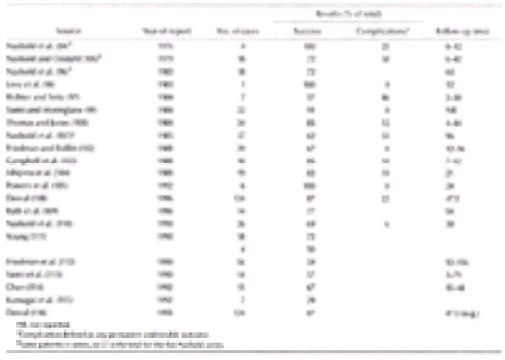

TABLE 106-6. Results of dorsal root entry zone operation for brachial plexus avulsion

Postparaplegic or Postquadriplegic Pain. Postparaplegic or postquadriplegic pain has also been relieved by DREZ lesions, particularly pain occurring at the transition between normal and anesthetic skin (90,91,96,97,99,105,117). The long-term success rate is 54%, but the duration of follow-up has been variable (Table 106-7). Some of the reported patients had drainage of posttraumatic syringomyelia at the same time; it is unclear whether DREZ lesions alone are responsible for their pain relief. It is puzzling that distal spinal cordectomy does not often relieve this type of pain but that DREZ lesions are sometimes effective. It should be recognized that this is not radicular pain, nor is it the pain associated with osseous instability that can occur with traumatic injury to the vertebral column. Although cordotomy is sometimes effective for this type of pain, the long-term results do not approach those obtained with DREZ lesions.

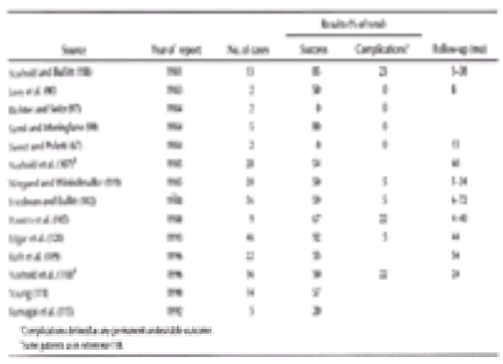

TABLE 106-7. Results of dorsal root entry zone operation for paraplegic pain

Postamputation Pain. Another type of central pain that has responded to DREZ lesions is postamputation pain (96,99,100,104,105,107,121) (Table 106-8). Hidden in this category are two different types of pain syndromes: stump pain and phantom limb pain (121,122). The overall results for postamputation pain are 39% success (11 patients) in a group of 28 patients. In Saris and associates' series (121), phantom limb pain is highly likely to respond (six of nine patients), whereas stump pain was never relieved (none of six patients). When phantom limb pain and stump pain were both present, good results were noted in two of seven patients, but only the phantom pain responded regularly. None of the other reports clearly discriminated between phantom limb pain and stump pain. Because of the aforementioned failures, DREZ lesion is not highly recommended for stump pain.

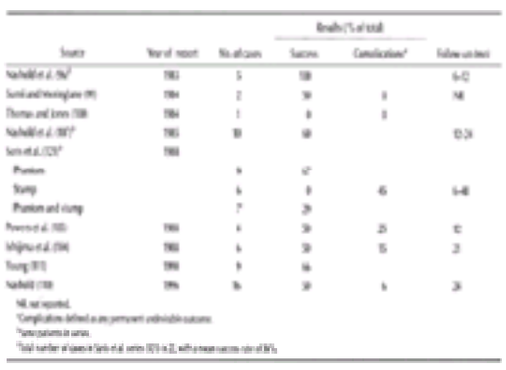

TABLE 106-8. Results of dorsal root entry zone operation for postamputation pain

Postherpetic Neuralgia and Other Disorders. In the earlier reports on the use of the DREZ lesion for postherpetic neuralgia, Nashold and associates (107) and Friedman and Nashold (117,123) reported that ten of 17 patients (59%) had good pain relief accompanied by a complication rate of 35%. In patients who had postherpetic pain for 6 months to 11 years and were followed 6 months to 6 years postoperatively, 29 of 32 (91%) had immediate relief. At 6 months, however, the figure dropped to 17 (53%), and at 18 months and thereafter only eight (25%) had persistent relief of postherpetic neuralgia involving the spinal nerves (Table 106-9) (102). Thirty-one patients with various myelopathies and neuropathies have also been treated with DREZ lesions (87,88,94,124). Approximately two-thirds had good results, with follow-ups of 6 to 19 months and a complication rate of 10% to 20%. The results are summarized in Table 106-10.

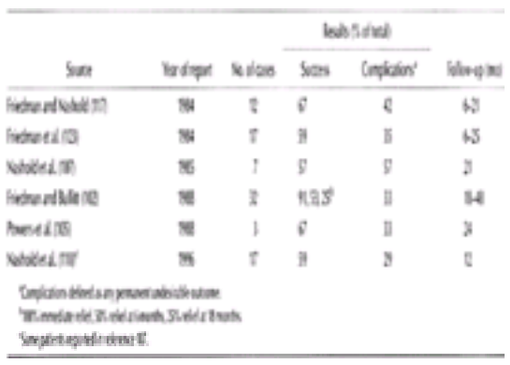

TABLE 106-9. Results of dorsal root entry zone operation for postherpetic neuralgia

Source	Year of report	No. of cases	Results (% of total)		
			Success	Complications*	Follow-up (mo)
Sunio and Waninglore (99)	1984	11	73	0	NR
Thomas and Jones (88)	1984	4	50	12	NR
Nashold et al. (107)	1985	7	86	NR	6–12
Ishijima et al. (204)	1988	6	50	33	12
Powers et al. (155)	1988	18	39	22	48
All		46	57	18	

NR, not reported.
*Complications defined as any permanent undesirable outcome.

TABLE 106-10. Results of dorsal root entry zone operation for other neuropathies and myelopathies

Subnucleus Caudalis Dorsal Root Entry Zone Lesions. Nashold and Brophy (125) and Bernard and associates (126) reported on the use of DREZ lesions on the subnucleus caudalis for the treatment of severe postherpetic neuralgia and other severe intractable facial pain. Following laminectomy of the C-1 to C-3 vertebrae and a small suboccipital craniectomy, the lesion is made to extend from the upper dorsal rootlet of C-2 to the tuberculum cinereum, slightly rostral to the level of the obex and the fourth ventricle. Production of DREZ lesions in the subnucleus caudalis also entails destruction of the descending trigeminal tract; the anatomic correlate of pain relief is unclear (121,125).

Since 1989, there have been at least 46 reported operations for facial pain using a two-electrode technique for subnucleus caudalis DREZ lesions. The overall pain relief was noted as “excellent” in 34% of patients and good in another 40%. The best results were obtained in patients with postherpetic pain involving one or more divisions of the trigeminal nerve (127). Pain resulting from facial trauma or dental surgery was not improved. In general, deafferentation pain responds to lesioning, but pain of a peripheral origin does not.

Comments and Conclusions

As more reports continue to be published regarding DREZ lesions, clear indications become more apparent for DREZ lesions in the management of chronic pain. The DREZ lesion is the only operation that was specifically designed to treat central and deafferentation pain. It is widely recognized that all standard ablative neurosurgical procedures are much more effective against pain associated with nociception (especially cancer pain) than they are against peripheral-central pain states. It remains unclear whether DREZ lesions are useful in patients with cancer pain; dorsal rhizotomy seems to be a less formidable operation for denervation of the painful area. The results of rhizotomy are variable, however, and it remains unclear whether the addition of ganglionectomy can improve them. Perhaps DREZ lesions will be effective in this type of pain.

More than any other ablative procedure, use of DREZ lesions can achieve variable results because of differences in lesion placement. It is not known how many segments above or below the level of injury the lesions should be made. Patients who have failed to obtain good pain relief might continue to suffer because the lesions did not extend far enough rostrally or caudally, yet the failure to relieve pain is ascribed to a deficiency of the operation itself. The poor results that sometimes follow DREZ lesions could be caused by failure of the surgeon to destroy the necessary amount of tissue, or could be a result of inherent shortcomings in the operation as a concept (95).

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CHAPTER 107

Surgical Treatment of Trigeminal Neuralgia

Deon F. Louw and Kim J. Burchiel

HISTORY

The trigeminal nerve was initially described in the sixteenth century by Fallopius (1). The eponymous designations of the Gasserian ganglion and Meckel's cave are derived from Gasser and, of course, Meckel more than a century later. In 1829, Charles Bell determined that the nerve had both a motor and a sensory root and that severance of the infraorbital nerve provoked loss of sensation without paralysis (2). He differentiated between the sensory function of the fifth nerve and the motor function of the seventh nerve, thus sparing patients misdirected surgical interventions. Trigeminal neuralgia is discussed in detail in Chapter 47. Stookey and Ransohoff have beautifully presented the history of the treatment of this disease (3).

The indication for surgery in the treatment of trigeminal neuralgia (tic douloureux) is the failure of medical management. This occurs either because of the lack of a response or the inability to tolerate medication side effects. No patient should be offered a surgical procedure in the absence of an adequate trial of medication management. On the other hand, surgery should not be withheld from the patient who suffers from this terrible affliction. The choice of surgical procedure is governed by the patient's age, medical condition, and preferences as well as the surgeon's available resources. The history of attempts to control the pain of tic douloureux with surgery is long, dating back to the sixteenth century. With the advent of anesthesia in the end of the nineteenth century, the development of new surgical techniques rapidly progressed (Table 107-1).

Neurectomy	Maréchal (1756)
Gasserian ganglion resection	Krause (1892)
Retrogasserian rhizotomy	Horsley et al. (1891)
	Spiller and Frazier (1901)
Report of 298 consecutive Gasserian ganglionectomies without mortality	Cushing (1920)
Partial section of V roots at the pons	Dandy (1929)
Electrocoagulation of Gasserian ganglion	Kirschner (1931)
Decompression of the trigeminal root	Taarnhøj (1952)
Compression of the trigeminal root	Shelden et al. (1955)
Vascular decompression	Gardner and Miklos (1959)
Temperature-controlled coagulation of Gasserian ganglion and rootlets	Sweet (1968)
Stereotactic radiosurgery of V root	Leksell (1971)
Microvascular decompression	Jannetta (1976)
Retrogasserian glycerol injection	Håkanson (1981)
Percutaneous compression of Gasserian ganglion	Mullan and Lichtor (1983)

TABLE 107-1. The history of surgical treatments for tic douloureux

NEURECTOMY

History

Maréchal, surgeon to Louis XIV, performed peripheral sectioning of the trigeminal nerve branches (3). These procedures were attempts at sectioning the infraorbital

nerve by making a generous intraoral incision. Andre's report of 1756 claimed superior results by destroying the same nerve with caustics (3). In the nineteenth century, Wood, Fowler, and Wagner published on the efficacy of neurectomy (3,4 and 5). As more direct attacks on the ganglion and root became feasible, neurectomy has been relegated to a secondary or palliative procedure.

Advantages

The procedures are readily and rapidly accomplished, with very low risk of complication. They can be performed under local or general anesthesia. Neurectomy results in complete anesthesia in the nerve distribution, and functional regeneration usually does not occur with wide separation of the two nerve ends (6).

Disadvantages

Relief, although very likely, is temporary. Most patients have a recurrence within 2 years. Substantial loss of sensation is initially evident in the territory of the sectioned nerve, and this may be followed by denervation hypersensitivity (anesthesia dolorosa) (6). Furthermore, neuromas occur at the site of transection and may be exquisitely sensitive.

Indications

Neurectomy is useful as a palliative procedure, particularly in debilitated patients. Loeser et al. suggest that appropriate candidates are those individuals who have failed gangliolysis and cannot withstand open intracranial procedures (6). The mandibular, infraorbital, and supraorbital nerves may be sectioned in patients with refractory trigeminal neuralgia, and attention may be directed either at the zone of referred pain or the trigger locus. It is important to avoid neurectomy in patients with atypical facial pain (see Chapter 47).

Technique

The skin incision for the supraorbital nerve is made within the unshaven eyebrow. The nerve is isolated distal to its foramen or notch. A hemostat is used to wind the nerve from its proximal portion, whereupon a second, more proximal hemostat is applied and rotated. This twisting action allows the nerve to be torn as close as possible to the ganglion (3). Stookey and Ransohoff maintained that the duration of relief is directly related to the extent of ganglion cell injury. The nerve is then also sectioned as distal as is feasible.

The infraorbital nerve is exposed through a sublabial incision. The mucosa is incised approximately 1.5 cm above the alveolar border (3) and the periosteum elevated. The infraorbital foramen and nerve are identified in the plane of the upper canine, and the nerve is resected as above.

The lateral approach to the mandibular nerve is the preferred route for neurosurgeons, whereas oral surgeons favor transoral exposure (7). A 3-cm curvilinear incision is based on the angle of the mandible, allowing the masseter fibers to be splayed concentrically. A burr hole is performed over the angle of the ramus, exposing the nerve. The nerve is transected in the usual manner and hemostasis ensured.

Results

Grantham and Segerberg reported an average relief of 33.2 months, ranging from 5 months to 8 years (8). Stookey and Ransohoff noted maximal duration of pain relief as 6 years for supraorbital nerve avulsion, and 2 years for the infraorbital (3). Rasmussen obtained good initial, but only modest 2-year, success rates (9).

PERCUTANEOUS RADIOFREQUENCY TRIGEMINAL GANGLIOLYSIS

History

Wright is credited with the first chemical Gasserian gangliolysis, injecting osmic acid after operative exposure of the ganglion (10). Harris was able to perform percutaneous alcohol injections into the ganglion in 1910, obtaining significant relief for his patients (11). In 1914 Härtel reported his still currently used extraoral technique for cannulating the foramen ovale and delivering alcohol into the ganglion (12). Other investigators tried boiling water and phenol, all with varying degrees of success.

Kirschner introduced electrocoagulation of the ganglion in 1932, using x-ray and stereotactic guidance (13). Progress in technique was reported by Sweet and Wepsic in 1974, who developed the use of radiofrequency current for gangliolysis (14). They also introduced electrical stimulation for localization and temperature monitoring to enhance modulation of lesion size. Many variations in technique have subsequently been reported.

Anatomy

Soeira et al.'s measurements of the Gasserian ganglion determined a mean length of 17 mm and a thickness of 4 mm (15). During ontogenesis, dura and arachnoid evaginate from the posterior fossa to cover the ganglion. The trigeminal cistern is the retroganglionic (retrogasserian) pocket of dura and arachnoid. It contains cerebrospinal fluid (CSF) and communicates with the basal cisterns through the trigeminal porus. The ganglion and cistern occupy Meckel's cave. The cell bodies are somatotopically oriented: ophthalmic anteromedial, mandibular posterolateral, and maxillary interposed (Fig. 107-1).

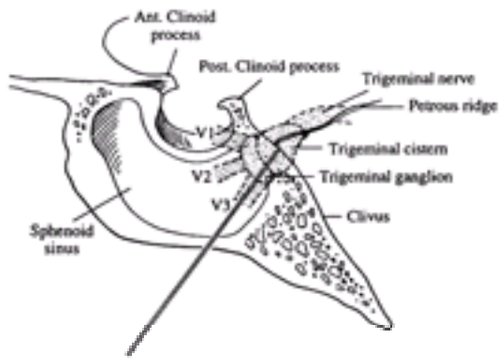

Figure 107-1. Lateral view of the region of the trigeminal ganglion. For trigeminal gangliolysis/rhizolysis, a needle (radiofrequency electrode, or spinal needle) is directed through the foramen ovale, through the third division (mandibular nerve), through the ganglion and into the trigeminal cistern. Note that the cistern is in communication with the posterior fossa and that agents injected into the cistern (i.e., radiocontrast agents or glycerol) will run directly into the posterior fossa unless the patient is sitting up with the head horizontal (see Fig. 107-4). (Ant., anterior; Post., posterior.)

Figure 107-4. Patient in a sitting position undergoing injection of glycerol into the cistern of Meckel's cave (the trigeminal cistern). The initial injection is of radiocontrast, which confirms location in the cistern. The contrast is then allowed to run back out of the needle, and the anhydrous glycerol (typically 0.3 mL) is injected. The patient remains in the sitting position for 2 hours to prevent loss of the glycerol into the posterior fossa and to maximize the neurolytic effect.

Advantages

Percutaneous radiofrequency trigeminal gangliolysis (PRTG) is rapid and well tolerated by the elderly or the debilitated. It is an outpatient procedure and carries very few major complications in experienced hands. Through awake stimulation the lesion can be accurately localized to encompass the pain or trigger zone. The technique can be safely repeated on multiple occasions should the pain return.

Disadvantages

PRTG is clearly not curative, and in many cases the neuralgia recurs. The average time to pain recurrence is approximately 3 years (16). Another disadvantage is that a minimum degree of sensory loss must accompany each gangliolysis. It is difficult to predict how disagreeable this may be to the individual patient, and, of course, anesthesia or analgesia dolorosa may occur in 5% to 10% of cases.

Indications

Strict clinical criteria (as outlined above) for typical trigeminal neuralgia constitute the best predictor of outcome. Patients offered surgery have developed either tolerance to or side effects from anticonvulsants. Many patients have experienced recurrent attacks of increasing severity, commonly complaining of severe suffering for a decade or more. Patients who are either unsuitable for or unwilling to undergo microvascular decompression (MVD) should be offered radiofrequency gangliolysis. Advanced age is not a contraindication, but coagulopathy or tenuous pulmonary or cardiovascular status may be.

Technique

We perform percutaneous radiofrequency gangliolysis in the operating room, although excellent results may be obtained (in experienced hands) in the fluoroscopy suite. The administration of glycopyrrolate will block a vagal response when the ganglion is cannulated. The face is prepped and an entry point chosen 2.5 cm lateral to the angle of the mouth and 1 cm inferior to the occlusal plane, if the V-3 fibers are targeted. A steeper trajectory, and hence an even lower and more lateral entry point, facilitates penetration of V-1 fibers. The patient's neck is placed in extension, and submental vertex fluoroscopy is used to identify foramen ovale. This orientation provides bilateral visualization of foramen ovale and foramen spinosum and is particularly useful in the older, osteoporotic patient. The anesthesiologist administers sufficient propofol (Diprivan) to rapidly achieve a surgical plane of anesthesia. The contralateral nare is cannulated with a nasal airway, through which the patient may be ventilated should respiratory arrest occur. The evanescent half-life of this agent has proven to be of great benefit in this procedure. Once the eye-blink reflex is lost, a stab incision is made in the skin and the 20-gauge cannula and stylet advanced toward the foramen ovale under continuous fluoroscopic control (Fig. 107-2). This trajectory is initially based on Hartel's points and subsequently on fluoroscopy. For third-division pain, the geometric center of the foramen ovale is perforated. For second- or first-division pain, the needle is directed into the more medial parts of the foramen. Foraminal entry is accompanied by a jaw jerk, at which point fluoroscopy is moved to the lateral plane. The cannula is then carefully advanced in relation to the petroclival angle, ensuring that overpenetration does not occur. Advancement more than 7 mm beyond the clival plane may result in abducens nerve injury (17). V-3 fibers are most likely encountered 5 mm proximal to the clival profile. The needle is advanced in 5-mm increments to impale V-2 and V-1 fibers, respectively (17). The stylet is removed and CSF frequently encountered. A straight or curved electrode is inserted. The patient is allowed to wake up, and 50 Hz of stimulation at fractions of a volt are used to confirm electrode positioning. Patients identify the division in which the needle is positioned by confirming the distribution of paresthesias produced by threshold stimulation, usually less than 0.2 to 0.3 V (1-millisecond pulse width). The patient is reanesthetized and thermal lesions created for 90 seconds, commencing at 75°C in previously untreated patients. The patient is reawakened and tested for sensory loss. The patient should not be able to discriminate sharp (pinprick) sensation from dull contact but should have preserved touch sensation. If further lesions are necessary to achieve adequate sensory loss, the patient is reanesthetized, and lesions are created in graduated fashion at 5° increments up to 95°C, with the patient reawakened and retested for sensory loss at each step. Reoperated cases are commenced at higher temperatures. The patients are observed in the recovery room and discharged the same day if stable.

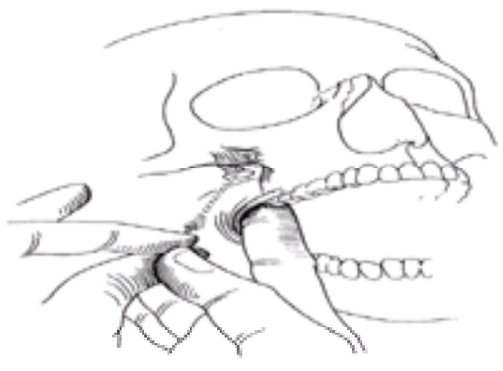

Figure 107-2. Hartel's technique of passing a needle through the foramen ovale via lateral puncture of the cheek. The needle is directed through the foramen under fluoroscopic control and does not pass intraorally.

Results

Initial relief is rated at 83% in Burchiel et al.'s series and as high as 99% in the report by Tew et al. (16,18). Long-term (more than 4 years) studies report recurrence rates as low as 14% and as high as 80% (14,16,17,18,19,20,21,22,23 and 24). The reported incidence of uncomfortable paresthesias ranged from 2% to 93%. Anesthesia dolorosa has been reported in 0.8% to 13.0% of patients.

Complications

Sweet has assiduously recorded data on surgical complications for percutaneous radiofrequency rhizotomies (25). Postoperative deaths were reported in 27 patients, largely from intracranial hemorrhage. Myocardial infarction, intracranial abscess, intracranial hemorrhage, and meningitis have also occurred (26,27 and 28).

Sweet reports 10 cases of major bradycardia, including two that progressed to asystole (29). These events are particularly common in balloon compression (see later). Dysesthesia is a distressing and common complication in radiofrequency gangliolysis. It occurs most often in fully anesthetic areas but may be experienced in

analgesic and even hypalgesic zones. We recommend avoiding profound analgesia in the trigger zones, and Sweet suggests scrupulous testing of the awake patient's tolerance of new numbness. This can be accomplished more readily by performing the final lesions with the patient alert. Corneal anesthesia, a common accompaniment to V-1 lesions, is readily managed with lateral eye shields, artificial tears, and frequent eye inspections. Neuroparalytic keratitis is distinctly uncommon with PRTG involving the first division, even after elimination of the corneal reflex. Acute visual loss has occurred for various reasons. Subhyaloid hemorrhage has been reported, as has central retinal artery occlusion. Complete blindness, along with total ophthalmoplegia, has also resulted, likely a consequence of electrode penetration of the inferior orbital fissure. The relatively minor (but frequent) complication of motor root weakness may become severely disabling if bilateral. Sweet recommends identification of the motor fibers by 2-Hz stimulation, followed by rotation of the Tew curved electrode to a sensory-specific site before lesioning (25). Using this technique, Tobler et al. reports an incidence of masticator paralysis of 1 in 150 cases (30). Although many complications have been anecdotally reported, the rate of complications in large series is less than 1%.

PERCUTANEOUS TRIGEMINAL GANGLION COMPRESSION

History

Mullan introduced percutaneous trigeminal ganglion compression (PTGC) in 1978 and initially published his results in 1983 (31). He recognized the need for developing a simple percutaneous compressive technique after studying the procedures of Täarnhøj and Sheldon. Sheldon initially performed an open decompression of the trigeminal peripheral branches, eventually realizing that the pain relief was a result of ganglial manipulation. He then proceeded to deliberately compress the posterior root fibers with a blunt dissector and obtained greater duration of pain relief compared with decompression alone (32).

Technique

Indications for PTGC are as for other percutaneous procedures. However, it carries a very low risk for corneal anesthesia and thus is particularly suitable for V-1 distribution pain. Patients are administered a general anesthetic. Using the same principles as in PRTG, a 14-gauge needle-cannula is inserted into the foramen ovale (see Fig. 107-1). The cannula has been modified by Gerber, who developed a blunt tip to prevent balloon laceration (33). A No. 4 French Fogarty embolectomy catheter is advanced 15 to 20 mm into the needle and inflated with 0.5 to 2.0 mL of water-soluble nonionic contrast medium. Initial inflation times were up to 10 minutes, but Mullan has now reduced this to 1 minute. This allows continued good results but with a significantly lowered dysesthesia rate. Fluoroscopy is used to confirm contouring of the balloon to a pear shape (Fig. 107-3). Continuous pulse and pressure monitoring is performed, as severe bradycardia and hypotension may occur. Intravenous atropine or glycopyrrolate and external pacing should be available.

Figure 107-3. Percutaneous trigeminal ganglion compression using the Hartel technique. The balloon is inflated with radiocontrast in the trigeminal cistern to produce a pear shape on fluoroscopic imaging.

Results

Immediate pain relief is reported from 89.9% to 100% (34). The longest recorded follow-up is that of 10 years for Mullan and Lichtor (35), who reported an 80% successful outcome at 5 years and 70% at 10 years. Average recurrence times have also been documented from 42 to 65 months by Meglio et al. (36,37). Rates of recurrence have been variously reported as 30%, 55%, and 77.4% (34). These relapses may respond to carbamazepine, even if the patient was refractory to the agent preoperatively. Most recurrences occur within 4 years but have been noted to occur up to 9 years after surgery (35). The 5-year reoperation rate (13%) is superior to PRTG (21% to 28%) and MVD (17% to 26%). However, 15% of patients surviving 10 years or longer undergo further, more invasive intracranial surgery.

PERCUTANEOUS RETROGASSERIAN GLYCEROL RHIZOLYSIS

History

Håkanson fortuitously discovered that intracisternal instillation of glycerol produced lasting pain relief with modest sensory loss (38). The mechanism of glycerol neurolysis is likely a nonspecific conduction blockade of small and large fibers (39). Spontaneous firing in large, damaged axons is also exquisitely sensitive to the application of glycerol. It has been postulated that these injured myelinated axons may rate the pain in trigeminal neuralgia (40).

Technique

The procedure is outpatient, and the set-up and monitoring as for PRTG. Under propofol anesthesia, the foramen ovale is penetrated with a 20-gauge, 3.5-inch spinal needle, as previously described. The foramen is penetrated slightly anterior to its midpoint, ensuring cisternal placement of the needle. After ensuring free flow of CSF, the patient is awakened and placed in the sitting position (Fig. 107-4). Isovue, 300 mg per L, is injected under fluoroscopic control, usually outlining the cistern with 0.15 mL and filling it with 0.35 mL (see Fig. 107-1). The contrast is allowed to drain from the needle, and approximately 0.3 mL of anhydrous glycerol instilled. Preferential neurolysis of the ophthalmic and maxillary divisions may be attempted by altering head tilt. It is mandatory for the patient to remain seated in a slightly flexed position for approximately 2 hours after surgery.

Results

Pain relief is rarely immediate, although approximately 50% are pain free within 24 hours. Resolution of pain occurs over the ensuing days to weeks in the remainder. Complete relief of pain has been reported to occur in 72% to 99% of those treated (41). Rates of recurrence range from 18.5% to 72% for both short- and long-term follow-up. Burchiel noted a higher recidivism rate for multiple sclerosis patients and those with technically unsatisfactory injections (41). Importantly, he detected an 80% recurrence of pain in the short term if the procedure failed to produce some sensory loss. Generic complications for needle trauma may accompany percutaneous retrogasserian glycerol rhizolysis. Glycerol may also provoke anesthesia dolorosa, dysesthesia, corneal anesthesia, oculomotor palsy, and aseptic meningeal reaction (42). In summary, the three methods of performing gangliolysis have similar success and complication rates. Balloon and glycerol techniques do not require patient communication and are better suited for those patients with whom the surgeon cannot communicate effectively due to language barriers or the patient's inability to cooperate. These procedures are quite safe, are relatively low cost, and do not require hospitalization but probably average about an 80% 1-year and 60% 5-year success rate.

RADIOSURGERY FOR TRIGEMINAL NEURALGIA

Bloodless brain surgery is inherently appealing under any circumstances but perhaps even more so in the chronic pain patient. Although there has been a recent flurry of interest in radiosurgery for trigeminal neuralgia, it in fact was first performed by Lars Leksell in 1951 (43). The target he chose was the trigeminal ganglion, and he reported excellent results on two patients in 1971 (44). Subsequently, Lindquist reported on the same procedure in 46 patients but with disappointing long-term results (45). Rand et al., noting a lack of response in some patients, suggested that the Gasserian ganglion was a suboptimal target (46). Kondziolka et al.'s

multicenter study hence reported on stereotactic radiosurgery targeting the proximal nerve and root entry zone (47). They postulated that inclusion of radiation-sensitive oligodendrocytes would enhance the radiobiological effect of the gamma knife (47). Additionally, the proximal nerve is more easily identifiable on magnetic resonance imaging than the ganglion, facilitating accurate target placement. Using doses varying from 60 to 90 Gy, they were able to report absence of pain in 58%, good control (50% to 90% relief) in 36%, and failure in 6%. Median follow-up was 18 months, during which time an additional 6% of cases recurred. The median time to pain reduction was 1 month, and there was a tendency to a better outcome in patients who had not had prior surgery. More recently, Young et al. noted pain relief in 95.5% of patients with classic tic symptoms who had not undergone prior surgery, with a recidivism rate of 3.3% in the follow- up period (mean 19.8 months) (48). Stereotactic radiosurgery appears to be low risk, and there are no reported cases of anesthesia dolorosa. A small number of patients have developed facial paresthesia or hypesthesia, but the overwhelming majority have intact sensation. Unfortunately, the delayed onset of pain relief may not appeal to the more desperate tic patients. It is also not feasible to tailor a target to the anatomic divisions of the trigeminal nerve. Larger cohorts and longer follow-ups should provide critically important information on what is potentially a useful addition to the surgical treatment of tic douloureux.

MICROVASCULAR DECOMPRESSION

History

Dandy's seminal surgical investigation of trigeminal neuralgia led him to write in 1945 that “in many instances the nerve is grooved or bent by the artery. This I believe is the cause of tic douloureux.” He also believed that on occasion tumors in the cerebellopontine angle could cause tic douloureux (49). Dandy, however, championed the suboccipital approach for trigeminal rhizotomy and did not advocate MVD. Gardner and Miklos recognized similar anatomic relationships and reported mobilization of an offending vessel from the nerve root (50). Jannetta's large series of decompressions brought general acceptance of the procedure to the neurosurgical community (51,52). He and Rand introduced the microscope to the procedure, initially favoring the transtentorial, subtemporal route (53). They later preferred the retromastoid approach, which has become standard throughout the world.

Anatomy

Jannetta et al. suggested that a looped superior cerebellar artery was the cause of 80% of trigeminal neuralgia (V-3) cases (54), noting a correlation of vascular compression (VC) site and pain distribution. V-2 pain was believed to be a consequence of lateral compression, the offending vessel usually an aberrant trigeminal vein communicating with the dura mater around Meckel's cave. V-1 pain was thought to result from caudal compression usually by the anterior inferior cerebellar artery. The incidence of trigeminal neuralgia increases with age, and this may result from associated brain “sag” and vascular tortuosity. Chronic nerve compression [particularly at the root entry zone (REZ)] could conceivably cause demyelination and provoke ectopic impulse generation or ephaptic conduction, leading to pain. Surgical displacement of the offending vessel should thus be “curative.”

Adams, however, contested this hypothesis. He contended that the episodic and usually unilateral characteristics of tic douloureux are incompatible with the Dandy model (55). In addition, asymptomatic nerve compression has been noted to occur in cadavers (56). Pagura et al. stated that VC is unlikely to explain trigeminal neuralgia in young patients without atherosclerosis and wondered about the mechanism of venous compression (57). Most neurosurgeons accept the VC hypothesis at this time.

Indications

Candidates for MVD are those with typical or atypical trigeminal neuralgia refractory to or intolerant of medical therapy. MVD is probably the procedure of choice in young patients, as it generally avoids sensory loss. It is therefore particularly appealing for V-1 distribution trigeminal neuralgia, avoiding the risk of corneal anesthesia. With modern neuroanesthetic techniques, advanced age has become less of a contraindication, but medically unstable patients should most likely be offered percutaneous procedures. It is unlikely that MVD would benefit anesthesia dolorosa or MS patients.

Technique

Patients undergo routine preoperative testing as well as baseline brainstem auditory-evoked responses (BAERs). General endotracheal anesthesia is administered and the patient positioned supine with an ipsilateral shoulder roll. The head is secured with pins, flexed, and contraversively rotated. The lateral decubitus and park bench position are also popular, as is the sitting position. The latter carries a higher risk of air embolism and sciatic stretch injury.

A vertical 4- to 6-cm incision is placed within 1 cm of the asterion. A “quarter-sized” craniectomy is performed and the dura mater incised parallel to the transverse and sigmoid sinuses. CSF is aspirated, and, using the operative microscope, the trigeminal nerve exposed in the cerebellopontine angle. Gentle cerebellar retraction may be needed, and ongoing BAER monitoring reduces the risk of acoustic nerve injury. Under microscopic control, compressive arterial loops are mobilized from the REZ and restrained with shredded Teflon felt. Large compressing veins may be similarly dealt with, or more likely, require coagulation and division. The dura is closed in watertight fashion and titanium mesh secured to the cranium for cosmetic purposes and to prevent muscle adherence to the dura.

Results

Reported outcomes vary, some studies having longer follow-ups than others. The patient pool is also heterogeneous in terms of gender, age, and prior treatments. Nevertheless, many groups report excellent short-term results, ranging from 69% to 94% (16,19,58,59,60,61,62 and 63). Jannetta et al. stated that 82% to 85% of patients experienced complete relief of pain, without numbness, and that an additional 10% have modest pain that is readily controlled on oral medication (54). Piatt and Wilkins' study noted 78% satisfactory and 22% poor results in patients with arterial VC, as opposed to 54% satisfactory outcomes in those without (64). The subgroup of patients with VC in the pontine-REZ angle did particularly well. Hamlyn and King detected a recurrence rate of 17% for arterial VC and 75% for venous VC, and 60% if they coexisted (65). Patients with typical, exclusively episodic pain respond far better than those with relentless, superimposed background pain (66). Bederson and Wilson reported better results for males, presumably a consequence of their greater incidence of root distortion (67). Barba and Alksne determined that a prior destructive procedure resulted in a recurrence rate of 50%, in contrast with 7% undergoing primary MVD (68). The outcomes reported above do not represent cures, average recurrence time (12% of cases) approximating 2 years (67,69). There is an annual recurrence rate of 2% following this: The 50% success rate occurs at 15 years postoperatively.

Complications

Mortality, although rare, may occur. Jannetta has reported four deaths and Apfelbaum three (70,71). Infarction and hemorrhage are the mainstay of mortality. Sweet noted that published data present a mortality of less than 1% and permanent disability of approximately 1%, which he believed to be considerably lower than the results of his private poll of 200 neurosurgeons (72). Morbidity can include brainstem or cerebellar stroke. CSF leaks may occur with or without meningitis. Cranial nerve palsies have been reported at a 4% to 10% incidence, the facial and auditory nerves being most susceptible (64,66,73). Intraoperative BAERs have helped reduce the incidence of these injuries, however. More rarely, abducens or trochlear paresis may result.

In summary, retromastoid craniectomy with MVD offers an 80% 5-year success rate, a 50% 15-year success rate with a complication rate of 5%, and a mortality rate of 0.5% based on our own experience and a review of the published literature.

TRIGEMINAL RHIZOTOMY

History

The first published account of trigeminal rhizotomy was that of Horsley et al. in 1891 (74). His candid account of this subtemporal intradural approach referred to the death of this patient. Macewen performed a similar procedure at a similar time, but this remained unpublished. Hartley and Krause followed in short order with an extradural subtemporal technique, and the procedure was designated the Hartley-Krause method by Horsley (75,76). Hartley resected V-2 and V-3 at their foramina as well as beyond the ganglion (75). Cushing recommended complete ganglion excision as well as motor root section (77). Frazier is credited with refining the procedure, recognizing that selective division of “symptomatic” portions of the root reduced morbidity (78). He also advocated sparing the motor root. “Frazier's operation” became the standard open procedure for decades, despite Dandy's assertion of the advantages of his retromastoid rhizotomy. With the benefits of the

microscope and modern anesthesia, Dandy's approach today affords the option of rhizotomy in the setting of a negative exploration for microvascular compression.

Indications

Trigeminal rhizotomy is less frequently used as a primary procedure for trigeminal neuralgia today, although it is still recommended by Adams (79). It is most commonly performed as a “palliative” alternative to MVD should the surgeon fail to detect convincing VC. It continues to be used for orofacial cancer pain, as it can completely denervate the face. A retromastoid exposure allows concomitant interruption of the glossopharyngeal nerve or nervus intermedius, if required.

As with all open cranial procedures, rhizotomy should be avoided in the aged or medically infirm and in those with hemorrhagic diatheses. It also can produce the spectrum of sensory side effects from paresthesias to anesthesia dolorosa. The risk of the latter, although small, is increased if a total rhizotomy is performed.

Technique

The retromastoid approach for rhizotomy is as described for MVD. The REZ is exposed in identical manner and fibers subtending the topography of pain targeted. It is generally assumed that somatotopy dictates a caudal location for mandibular fibers, and rostral for ophthalmic. However, variable rotation of the REZ may occur and a more reliable indicator is that the ophthalmic fibers are those most closely applied to the portio minor, irrespective of its pontine entry angle.

The traditional Frazier procedure is conducted under general anesthesia in the sitting position. The scalp is vertically incised for 8 cm from the zygomatic root and a 4- to 6-cm craniectomy performed in the temporal squamosa and lateral sphenoid wing. Extradural dissection is performed, and the middle meningeal artery coagulated and divided. The foramen ovale and mandibular division are identified, followed by mobilization of the dura propria from the temporal lobe dura. The maxillary division, the ganglion, and the root are located without placing undue traction on the greater superficial petrosal nerve, as this may cause facial palsy. The dura propria is incised, and the lateral two-thirds of the retrogasserian rootlets are sectioned (Fig. 107-5). The motor root is of course spared. The dura, fascia, and scalp are closed in the usual fashion.

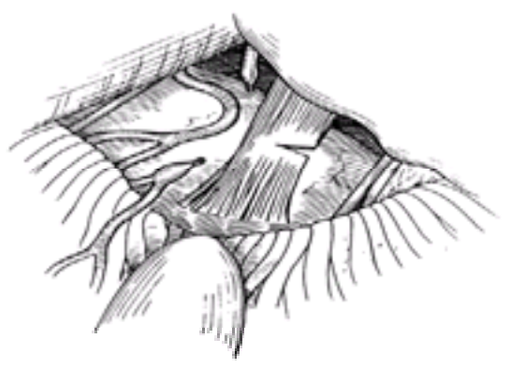

Figure 107-5. Depiction of a microscopic view of the right trigeminal nerve via a right retromastoid craniotomy. In this view, the petrous bone and the tentorium are located on the right and left sides of the upper part of the drawing, respectively. The fourth cranial nerve can be seen next to the tentorium, and the seventh and eighth cranial nerves are located to the right of the trigeminal nerve. The petrosal vein complex has been divided, and the cerebellum retracted in the lower part of the figure, exposing the trigeminal nerve. A lateral one-half rhizotomy of the main portion of the nerve (portio major) has been performed, sparing the more medial motor rootlets (portio minor).

Results

Recent statistics on the efficacy of rhizotomy are often combined with those on MVD. Nevertheless, extensive historical data exist, noting an initial success rate from 85% to 98% (80,81,82,83,84,85,86 and 87). Klun suggests that this diminishes to 50% at 5 years (87). The majority of recurrences occur in the first postoperative year and are related to the degree of sensory loss (88,89 and 90).

Complications

Mortality is reported to occur in 0.4% to 1.6% of cases (81,85), analogous to the incidence for MVD. General complications ranged from 5% to 25% (81,86). Specifically, paresthesias were noted in up to 55% of patients (81), whereas anesthesia dolorosa varied from 3.1% to 26.0% (85,87). Corneal anesthesia was detected in 0% to 4.6% of procedures (67,88). Cranial nerve injury may be seen in up to 10% of cases, although the majority are transient (64).

TRIGEMINAL TRACTOTOMY

History

In 1938 Olof Sjöqvist reported sectioning the descending tract of the fifth nerve at the inferior olivary level (91). He hypothesized that interrupting the tract before entering the nucleus caudalis might selectively section the pain fibers. White and Sweet noted hypalgesia in the distribution of the seventh, ninth, and tenth cranial nerves after trigeminal tractotomy (92). In 1965 Kunc reported selective tractotomy 12 mm above the second cervical root to alleviate glossopharyngeal neuralgia (93). Crue et al. and Hitchcock independently performed the first stereotactic percutaneous trigeminal tractotomies in 1967 and 1968 (94,95). Schvarcz targeted the nucleus caudalis oral pole, emphasizing the benefit of lesioning second-order neurons (96). He coined the term *trigeminal nucleotomy* for this procedure. In 1989 Kanpolat et al. pioneered computed tomography guidance for percutaneous trigeminal tractotomy-nucleotomy (97).

Anatomy

Pain and temperature fibers of the trigeminal nerve travel in the descending tract to the medulla and upper cervical cord, where they terminate in the spinal trigeminal nucleus. Pain fibers from the seventh, ninth, and tenth cranial nerves enter the medial aspect of the descending tract, which is then collectively called the *descending cranial nociceptive tract*. The spinal nucleus is divided rostrocaudally into the subnuclei oralis, interpolaris, and caudalis. The nucleus caudalis straddles the spinomedullary junction and represents the rostral extension of the substantia gelatinosa. It is a convergence zone for afferents from cranial nerves V, VII, IX, and X, as well as high cervical branches. The caudalis neurons are also prone to spontaneous activity if deafferented. This intersection of anatomy and pathophysiology provides a useful target in the surgical management of facial pain.

Technique

Percutaneous Tractotomy

Orofacial cancer pain and anesthesia dolorosa are the most common indications for percutaneous tractotomy. The patient is administered 8 to 10 mL of iohexol (240 mg per L) intrathecally and placed in Trendelenburg, approximately 15 minutes before the procedure (97). One-millimeter computed tomography slices are performed to confirm diffuse spread of contrast at the cervicomedullary junction. The still-awake patient is positioned prone on the computed tomography table, with the neck slightly flexed in the head support. Kanpolat's kit (Radionics) has 20- to 22-gauge needles and 2-mm thermocouple electrodes of 0.3 and 0.4 mm in diameter. Local anesthetic is administered 8 mm from the midline at the occiput–C-1 level. A 22-gauge needle (20-gauge for thick necks) is aimed toward the occipitocervical space on the lateral scanogram and on axial cuts. An ideal trajectory aims the electrode tip at the lateral third of the equator of the hemicord. A typical penetration is 3 mm deep and 6 mm lateral to the midline, at the level of the first cervical segment. Cord penetration is confirmed by an increase of impedance from 400 Ohm in CSF to usually greater than 1,000 Ohm in the spinal cord. Low- and high-frequency stimulation is used to confirm target acquisition. Initial lesions are performed for 20

seconds at 60°C and incrementally increased to 60 seconds at 70°C to 80°C while monitoring neurologic function.

Open Tractotomy

Patients are administered a general anesthetic and needle electrodes are applied to the ipsilateral supraorbital, infraorbital, and mental nerves at their foramina (34). A bipolar electrode is also applied over the median nerve. The patient is placed prone and the skull secured in a Mayfield clamp. A midline suboccipital incision and craniectomy is performed, as well as a C-1 laminectomy. Durotomy displays the cervicomedullary junction, which is then mapped with evoked potential responses to 500 milliseconds, 5 to 7 V, and 2- to 3-Hz pulses applied to the trigeminal and median nerve electrodes. Loss of median nerve–evoked potentials delineates the lateral boundary of the fasciculus cuneatus. Similarly, the vertical and horizontal borders of the descending tract are demarcated by trigeminal peripheral branch stimulation. The trigeminal divisions subtending the patient's pain are then ablated by a 3-mm deep radiofrequency electrode lesion (Fig. 107-6). Lesions are repeated until the appropriate evoked potentials are eradicated.

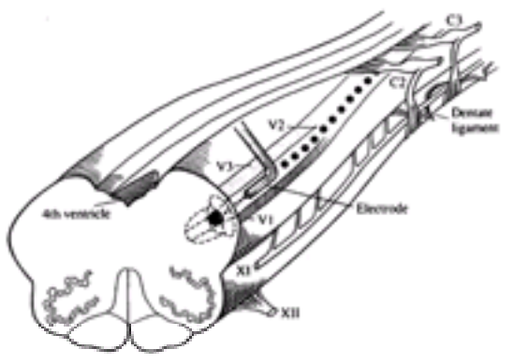

Figure 107-6. The caudalis dorsal root entry zone (tractotomy/nucleotomy) procedure. A suboccipital craniotomy is performed with C-1 laminectomy. The dura is opened, and the upper spinal cord and medulla just beyond the level of the obex of the fourth ventricle are exposed. A series of radiofrequency thermal lesions are then made in the nucleus caudalis and descending tract of the trigeminal system using a special radiofrequency needle electrode, insulated so as to spare the overlying dorsal spinocerebellar tract from thermal injury. Radiofrequency lesions are made from the obex to C-2.

Results

Kanpolat et al. reported a mean follow-up of 62 months on 30 cases of percutaneous tractotomy-nucleotomy, with complete or partial pain relief in 80%. He notes successful outcomes for all patients with glossopharyngeal and geniculate neuralgia, with good results for malignancy, atypical facial pain, and trigeminal neuralgia. The single case of anesthesia dolorosa did not respond (97).

Schvarcz reported on 100 cases, with a 57% good outcome for anesthesia dolorosa and 83.8% for cancer pain (98). Plangger et al. documented that 58% of open tractotomy procedures for trigeminal neuralgia accomplish complete, and 42% partial, pain relief (99). King reported a success rate of 75% to 85% for malignant pain (100). Clearly, long-term follow-up is more difficult in cancer patients. In addition, extensive malignancies may require sectioning of C-2 to C-4 dorsal roots to more completely denervate the skull base and upper neck.

Complications

The procedure has been aborted on two occasions by Kanpolat when electrode insertion/stimulation provoked unbearable pain (97). Ipsilateral limb ataxia can occur in at least 10% of patients, as the dorsal spinocerebellar tract and the external arcuate fibers overlie the descending trigeminal tract (101). Contralateral sensory loss is reported in 14% of cases as a result of injury to the spinothalamic tract. Hemiparesis, facial or masticatory paresis, and anesthesia dolorosa occur rarely (99). Complication incidence is related to lesion volume and can be minimized by physiologic mapping techniques.

CONCLUSIONS

Trigeminal neuralgia is unique among chronic pain conditions in that it reliably responds to both medical and surgical treatment. When patients become medically intractable, as discussed in Chapter 47, a large number of surgical procedures can be brought to bear on the problem. We believe younger patients in this group should have MVD of the nerve. For patients not wishing this degree of invasiveness and risk or in older patients who represent significant risk for a major neurosurgical procedure, including the risk of anesthesia, percutaneous rhizolysis is the best option. This can be performed by radiofrequency, glycerol, or balloon compression techniques, depending on the clinical situation and the experience of the neurosurgeon. Open rhizotomy is usually reserved for intractable cases or in patients in whom exploration for MVD proves negative for neurovascular compression. The role of tractotomy-nucleotomy, whether performed by open or percutaneous route, is still being defined; it is certainly not a primary procedure now, but should be reserved for the most difficult cases of refractory trigeminal neuralgia pain.

There is a loud debate in neurosurgical circles about the most appropriate neurosurgical operation for patients with tic douloureux. We have tabulated the published results of the common surgical treatments of tic douloureux (Table 107-2). Gybels and Sweet have written, “We conclude from available results that performance of a conservative percutaneous lesion represents the best tactic as the first invasive procedure” (102). Apfelbaum has advocated suboccipital craniectomy with MVD for patients younger than age 65 but gangliolysis for the elderly or medically infirm (or those with multiple sclerosis) (103). Jannetta et al. believe that suboccipital craniectomy with MVD “is indicated as a primary operative treatment” (54). Many other experienced neurosurgeons have published their viewpoints and the results on which they have based their conclusions. The introduction of stereotactic radiosurgery as yet another method of traumatizing the trigeminal nerve will certainly offer a third, less invasive strategy to provide pain relief to those who have failed medical management.

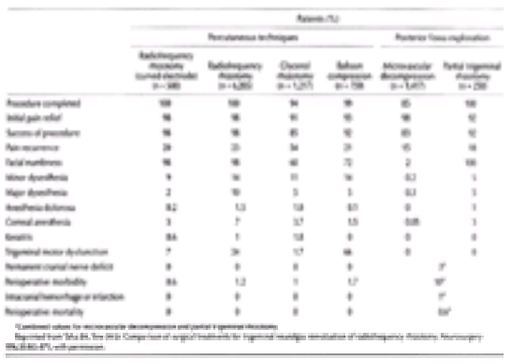

TABLE 107-2. Results of percutaneous techniques and posterior fossa exploration for patients treated for trigeminal neuralgia

Fortunately, most patients with trigeminal neuralgia can anticipate a good outcome from surgical management of the condition. The patient's choice of procedures should be based on a thorough discussion of the options, rationale, and risks with a neurosurgeon experienced in the management of trigeminal neuralgia.

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CHAPTER 108

Ablative Brain Operations for Chronic Pain

Ronald F. Young

The Melzack and Wall gate hypothesis of pain gave rise to a variety of electrical stimulation methods (e.g., peripheral nerve, spinal cord, deep brain) to treat pain; as a result, a decrease in the use of central ablative procedures ensued (1). Although the stimulation procedures are certainly useful, they produce satisfactory long-term relief of pain in a maximum of 50% of patients, and at least in the United States, neither deep brain stimulation nor trigeminal nerve stimulation is available due to lack of approval by the U.S. Food and Drug Administration (2,3,4,5 and 6). The increasing use of chronic intraspinal or intraventricular administration of analgesic agents also reduced interest in the use of central ablative neurosurgical operations to treat intractable pain. However, the long-term effectiveness of chronic intraspinal or intraventricular administration remains unproven and at best appears to be successful, even in the short-term, in no more than 50% of patients (7). Consequently, there has been a renewed interest in central ablative procedures as an important component of the surgical armamentarium available to treat chronic pain. This chapter reviews the author's approach to the use of central ablative procedures and their suitability for treatment of chronic pain, with emphasis on those procedures currently commonly in use. A few other procedures rarely used today are also discussed, mainly for the sake of history and completeness.

MEDULLARY AND PONTINEC SPINOTHALAMIC TRACTOTOMY

Those procedures that involve section of the lateral spinothalamic tract at either the medullary or pontine level were first executed in 1941 by Schwartz and O'Leary and by White (8,9). Their purported advantage over high cervical cordotomy is the ability to obtain a more rostral level of analgesia with medullary or pontine lesions, which may be useful in the treatment of pain in the shoulder or neck.

Basic Considerations

Anatomy

The lateral spinothalamic tract originates in nociceptors in the periphery that enter the spinal cord via A-d and C fibers that make synaptic connections in the spinal dorsal horn, cross to the contralateral side, and ascend in the spinal cord in the anterolateral quadrant (10,11,12 and 13). In addition, Jones and colleagues have demonstrated in cat and primate the existence of a dorsal spinothalamic tract, composed exclusively of fibers that originate in C nociceptors (14). This latter pathway travels in the dorsolateral funiculus of the spinal cord and projects widely to the medial and lateral thalamus as well as the suprageniculate areas and the pulvinar (15). Classically, the spinothalamic tract has been divided into two primary components: (a) the neospinothalamic tract, which conveys information concerning the spatial and temporal qualities of painful stimuli, and (b) the paleospinothalamic tract, which conveys information about the affective and motivational components of pain (see Chapter 4). In the ventral quadrant of the spinal cord, these two components are more or less homogeneously mixed, but at the medullary level, the paleospinothalamic component begins to diverge centrally and give off collaterals to the reticular formation (Fig. 108-1). This component then ascends in a multisynaptic reticulothalamic pathway to the medial nuclei of the thalamus and then to the limbic lobe. The neospinothalamic component, at the mesencephalic level, is composed of as few as 1,500 fibers, whereas the spinal component of the spinothalamic tract contains approximately 15,000 fibers (16). Unfortunately, a great deal of what we know about the spinothalamic tract was derived from experiments that used brief, acute, noxious stimuli, which are more easily studied electrophysiologically and behaviorally. More recent experiments, some of which have used chronic noxious stimuli, have elucidated many other components of the nervous system involved in pain perception. For instance, direct spinothalamic tract projections have been identified to the hypothalamus, to other limbic structures such as the amygdaloid nucleus, to the preoptic and septal areas, as well as to the basal ganglia (12,13). The presence of nociceptive afferents in the dorsal columns with projections to the gracile nuclei and to the thalamus has been demonstrated (12,13). Visceral pain afferents, particularly, may travel in the medial portion of the fasciculus gracilis bilaterally and also project via the gracile nuclei to the neutral posterolateral thalamic nuclei (12,13). Thus, it is not surprising that although section of the spinothalamic tract at the medullary or pontine levels may produce a more rostral level of “analgesia”—that is, loss of cutaneous pinprick and temperature sensation—effective, long-term relief of pathologic pain with these procedures is not common. This feature, combined with the complexity of the surgical operation required to perform the procedure, has led to its rarely being used today.

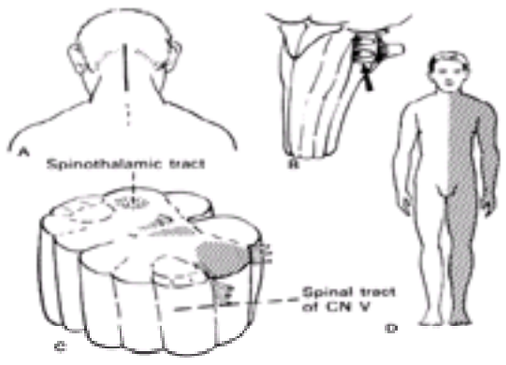


Figure 108-1. Medullary spinothalamic tractotomy. **A:** Site of skin incision. **B:** Dorsolateral view of medulla indicating site of incision in brainstem. **C:** Cross section of medulla indicating depth of incision into dorsolateral medulla. **D:** Extent of analgesia after right medullary spinothalamic tractotomy.

Indications

Ablative procedures that interrupt components of the neospinothalamic tract are generally used for the treatment of cancer pain because effective pain relief beyond 6 to 12 months is unusual, because the resulting sensory loss increases the risk of tissue injury (e.g., burns) of which the patient is unaware, and because a small but definite proportion of patients develop painful dysesthesias that are often more distressing than the original pain. These may be even more difficult to treat.

Most commonly, medullary or pontine spinothalamic tractotomy is considered for treatment of cancer-related pain in the shoulder or neck, such as lung cancers that produce Pancoast's syndrome or squamous cell cancers of the head and neck (17,18). Although purportedly more successful than high cervical cordotomy for relief of shoulder or neck pain, medullary tractotomy carries a similar risk of paralysis of the automatic phase of respiration, with resulting sleep apnea, and the same risk of death as with high cervical cordotomy. Interference with the automatic phase of respiration, although not fatal when a unilateral procedure is performed, may be fatal if the opposite hemidiaphragm is paralyzed due to a lung cancer (19). Finally, in spite of a high level of analgesia produced by medullary or pontine spinothalamic tractotomy, the deep aching, burning, and distressing pain that usually accompanies malignancies is frequently not relieved by these procedures. This is thought to occur because a significant proportion of the paleospinothalamic tract has already left the ventrolateral quadrant at the level of the surgical section. Alternatively, such sensations may be transmitted via the dorsal spinothalamic tract previously referred to (14,15). Patients who suffer from shoulder, neck, and arm pain due to involvement of the brachial plexus with cancer and who have lost functional use of the extremity may be effectively relieved of their pain by dorsal root entry zone (DREZ) lesions (20). If such patients continue to have use of the painful extremity, I prefer a medial thalamotomy, which, although perhaps slightly less effective than pontine or medullary tractotomy, carries a minimal risk of loss of extremity function (21). The loss of proprioception that accompanies DREZ lesions, in my experience, leads to a functionless extremity. I have not been able to produce the differential sparing of proprioception that Sindou describes with his micro- DREZotomy technique (22).

Results

Although success rates of 80% to 90% for relief of cancer pain were reported in the past, the virtual absence of any recent data casts doubt, in my opinion, on these figures (23,24,25 and 26). Furthermore, most of the reported patients survived for less than 6 months postoperatively. When one considers the current availability of multiple oral and parenteral opiates, the use of intraspinal opiates, and the availability of modern stereotactic techniques, it appears unlikely that patients with an expected survival of 6 months or less will be subjected to a major operation that requires a posterior fossa craniotomy to perform a medullary or pontine spinothalamic tractotomy. The reported 50% success rate and 14% complication rate for medullary or pontine tractotomy in the treatment of non-cancer pain also, in my opinion, makes this operation a poor choice *vis-à-vis* the other options (e.g., deep brain stimulation, medial thalamotomy). Although a stereotactic technique for pontine spinothalamic tractotomy has been described, only a handful of patients who have had the procedure performed have ever been reported. I am unaware of other surgeons who currently perform this procedure (27,28,29 and 30).

Clinical Considerations

Open medullary or pontine tractotomy is usually performed under general anesthesia, although combinations of regional or local anesthetic blockade combined with varying levels of intravenous sedation may also be used (23,24,25 and 26). I prefer the prone position for such operations, although the lateral decubitus position may be used as well. I do not recommend the sitting position because of the risk of air emboli. A small posterior fossa craniotomy and upper cervical laminectomy give adequate exposure. The use of an operating microscope is highly recommended. Although some authors recommend making the incision into the spinothalamic tract 2 to 10 mm below the level of the obex, lesions performed at these low levels are little more than high cervical cordotomies and could be more safely and easily performed using percutaneous techniques. Lesions performed well above the obex may damage the restiform body (inferior cerebellar peduncle) and lead to ipsilateral ataxia or lateropulsion or they may damage the ventrally located corticospinal tract, which, at this level (decussation of the pyramids), could lead to either contralateral or ipsilateral, or even bilateral, motor deficits.

Summary

Medullary or pontine tractotomy, although initially an appealing operation from the anatomic standpoint for the treatment of upper arm, shoulder, or neck pain, is, in reality, rarely used today. Its increased risk and marginal advantage over percutaneous high cervical cordotomy, as well as the frequent failure to relieve the deep, distressing pain of malignancies, generally make it a poor choice.

MEDULLARY TRIGEMINAL TRACTOTOMY

Rationale and History

Trigeminal tractotomy was first described by Sjöqvist and was based on the anatomic idea that all pain input from the orofacial structures is conducted via the descending trigeminal tract into the so-called nucleus caudalis, the most caudal of the three subdivisions of the spinal trigeminal nucleus (31) (Fig. 108-2). The nucleus caudalis is anatomically identical to the dorsal horn of the spinal cord, but the “trigeminal tract” is not a tract at all in the usual sense of that term. The term *tract* is usually applied to postsynaptic pathways within the spinal cord or brain (e.g., the spinothalamic tract) but the trigeminal tract is in reality a direct continuation of the primary afferent fibers in the trigeminal sensory root. The operation of medullary trigeminal tractotomy is, in reality, a partial rhizotomy of the trigeminal sensory root and nothing more. Its purported efficacy is based on the concept that all nociceptive trigeminal input in the trigeminal sensory root courses via the descending trigeminal tract into the nucleus caudalis and that nonnociceptive input enters the rostral portions of the spinal trigeminal nucleus (i.e., nucleus interpolaris and nucleus oralis) or into the principal sensory nucleus (31) (Fig. 108-3). Unfortunately, this is not the case. Studies have identified nociceptive input into more rostral components of the spinal trigeminal nucleus (i.e., the nucleus interpolaris and nucleus oralis). It is, in fact, input from the central portion of the face and intraoral structures that preferentially relays rostral to the nucleus caudalis (32,33 and 34). Nociceptive input in the seventh, ninth, and tenth cranial nerves also relays via the nucleus caudalis but does not travel via the descending trigeminal tract *per se*, but occupies a position on its medial edge (35). Our previously published experience confirms that trigeminal tractotomy at the level of the obex results in analgesia confined to the peripheral portion of the face, sparing virtually all intraoral structures (36) (Fig. 108-4). We suggested that the lesion at the medullary level be extended into the trigeminal nucleus to sever the intranuclear connections between the nucleus caudalis and the more rostral trigeminal subnuclei, which are also important in orofacial nociception (36). Certainly trigeminal tractotomy represents an advantage over complete section of the trigeminal sensory root; tractotomy spares many afferents responsible for tactile and proprioceptive sensation in the orofacial region. The corneal reflex is usually preserved after tractotomy and abolished after complete rhizotomy.

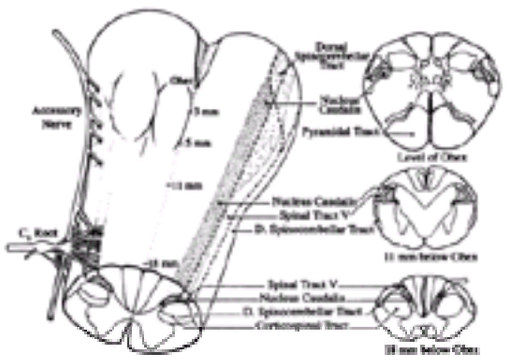


Figure 108-2. Anatomical arrangement of the spinal trigeminal complex shown longitudinally (left) and in cross sections (right) at the level of the obex and 11 and 18 mm caudal to the obex. (D, dorsal.) (Reprinted from Nashold BS, Abdul-Hak M, Ovelmen-Levitt J, et al. A new design of radiofrequency lesion electrodes for use in the caudalis nucleus DREZ operation. Technical note. *J Neurosurg* 1994; 80:1116–1120, with permission.)

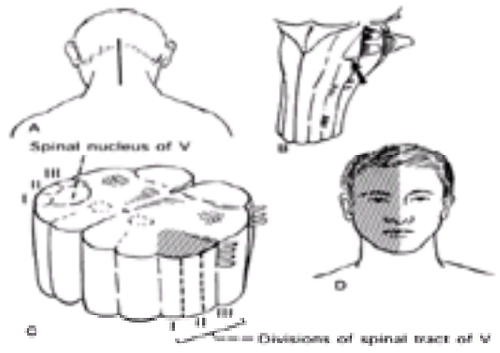


Figure 108-3. Medullary trigeminal tractotomy. **A:** Site of skin incision. **B:** Dorsolateral view of medulla indicating site of incision into brainstem. **C:** Cross section indicating depth of incision into dorsolateral medulla. **D:** Extent of analgesia after right medullary trigeminal tractotomy.

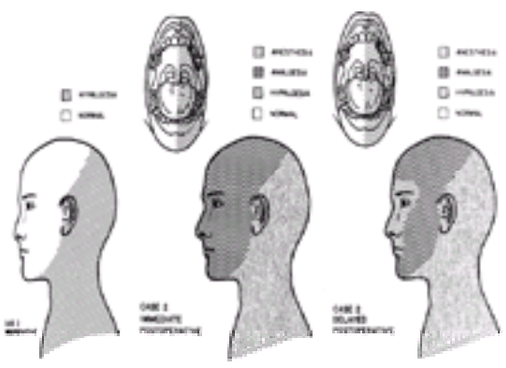


Figure 108-4. Changes in facial sensation before, immediately after, and several months after left trigeminal tractotomy performed at the level of the obex. (Reprinted from Young RF. Effect of trigeminal tractotomy on dental sensation in human. *J Neurosurg* 1982;56:812–818, with permission.)

Clinical Considerations

Indications

Medullary trigeminal tractotomy may be helpful for treatment of cancer-related pains of the face. This operation was, in the past, often combined with upper cervical rhizotomies for treatment of pain due to extensive head and neck cancers. It has also been described as effective for refractory cases of trigeminal neuralgia, but as previously described, medullary trigeminal tractotomy is anatomically little different from a partial rhizotomy of the trigeminal sensory root and is particularly ineffective if the pain originates, as it usually does, from central facial structures (e.g., lips) or intraoral structures (e.g., teeth) (37,38,39,40,41,42,43 and 44). Neuropathic orofacial pain (e.g., anesthesia dolorosa) is virtually never effectively treated by medullary trigeminal tractotomy because such pain is probably generated by spontaneously hyperactive neurons within the trigeminal nuclei, which are already disconnected from peripheral input (42). Neuropathic facial pain may be treated by trigeminal DREZ lesions, but my experience has been that trigeminal DREZ lesions are also often ineffective and the rate of complications is high (43) (see later discussion in this chapter). I prefer medial thalamotomy or deep brain stimulation for treatment of neuropathic facial pain (44,45,46 and 47).

Technique

Open trigeminal tractotomy is usually performed under general anesthesia with the patient in the prone position. A small posterior fossa craniotomy and upper cervical laminectomy are required for exposure. After dural opening, the operating microscope is used to identify the obex, the dorsolateral sulcus, and the emerging fibers of the accessory nerve, which mark the ventral extent of the incision into the tract. I prefer a deeper incision (at least 5 mm) than the 3-mm incision usually recommended because, as described earlier, I intend to section not only the trigeminal tract, but also the subjacent connections between the nucleus caudalis and the more rostral nuclei (36). I also prefer to make the incision as far rostral to the obex as possible in order to interrupt as much input from the central face and oral structures as possible. Unfortunately, the more rostral the incision is, the greater the likelihood of injury to the restiform body with ipsilateral arm ataxia and lateral pulsion (Fig. 108-5). If the lesion is extended dorsally and medially, there may be injury to the dorsal column nuclei with ipsilateral proprioceptive loss, and if the incision is too ventral, the spinothalamic tract may be injured with a contralateral loss of pain and temperature sensation in the extremities and trunk. Intraoperative electrophysiologic identification of the trigeminal tract and nucleus increases the efficacy and reduces the complications of the procedure (48).

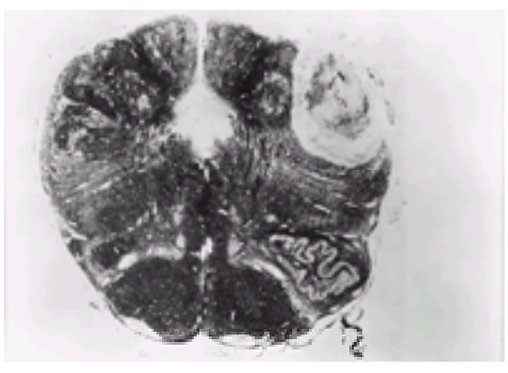


Figure 108-5. Autopsy specimen following left trigeminal tractotomy performed by the author at the level of the obex using an open radiofrequency technique. (Reprinted from King RB. Medullary tractotomy for pain relief. In: Wilkins R, Rengachary S, eds. *Neurosurgery*. New York: McGraw-Hill, 1983;2452–2454, with

permission.)

Stereotactic Trigeminal Tractotomy

The descending trigeminal tract in the medulla can be interrupted by a stereotactic technique (49,50,51,52,53,54 and 55). The procedure is done under local anesthesia with the patient in the prone or sitting position, depending on the type of stereotactic apparatus. One reason this procedure has not gained popularity is the difficulty in obtaining a satisfactory suboccipital approach with most types of stereotactic apparatus, but the Hitchcock apparatus is particularly suited for this approach (49,53). The electrode is angulated 30 degrees craniad and introduced 6 mm from the midline, where the trigeminal fibers lie 4 mm below the surface. A fine sharpened electrode is used because the pia is quite firm in this area. Verification of the electrode position can be obtained by electric stimulation at 50 Hz. With proper placement of the electrode, sensation is projected to the face at a low voltage. If the electrode is too deep or lateral in the spinothalamic tract, sensation can be projected elsewhere in the body. Stereotactic trigeminal tractotomy has been used both in cancer pain and as a secondary procedure for various noncancer chronic pains (49,50,51,52,53,54 and 55).

Hitchcock (49) reported pain relief in four out of five patients with head and neck pain caused by malignancy, in one out of two with neuralgialike facial pain, and in two out of three with postherpetic pain. Schvarcz (50) reported 25 patients, with a 94% success rate for various forms of neuralgia and a 100% success rate for relief of pain from various neoplasms (Table 108-1).

Source	Year of report	No. of cases	Indications	Results (% of total cases)				
				Success	Complications	Paresthesia	Anesthesia dolorosa	Death
Hitchcock (49)	1970	5	Cancer	80	0	0	0	0
Hitchcock (49)	1970	2	Neuralgia	50	0	0	0	0
Hitchcock and Schvarcz (50)	1972	3	Postherpetic neuralgia	100	33	0	0	0
Crue et al. (54)	1972	8	Cancer	75	0	0	0	0
Crue et al. (54)	1972	4	Neuralgia	50	25	0	0	0
Fox (55)	1973	4	Chronic pain	75	33	0	0	0
Fox (55)	1973	14	Cancer	100		0	0	0
Schvarcz (50)	1975	17	Neuralgia	94	–	–	–	–
		8	Cancer	100	–	–	–	–
Allmeyer		61		87.5	23.5	0	0	0

[a]Values are corrected analgesia at 6 mo.

TABLE 108-1. Results of percutaneous trigeminal tractotomy

Medullary trigeminal tractotomy can be helpful in selected patients with pain secondary to malignancy of the head and neck. Its role in the relief of other pain states has not been well established. A small number of neurosurgeons have used percutaneous trigeminal tractotomy for other pain states; results have been encouraging (49,50,51,52,53,54 and 55).

TRIGEMINAL DORSAL ROOT ENTRY ZONE LESIONS

Rationale and History

In the late 1970s and early 1980s, Sindou and Nashold described mechanical and radiofrequency (RF) techniques to ablate the so- called DREZ of the spinal cord (20,22). This method was based on the idea that many types of chronic pain are related to spontaneous neuronal hyperactivity in the DREZ and that ablation of these neurons may lead to pain relief (42). Later, Nashold and colleagues described an RF technique for ablation of the descending trigeminal tract and subjacent trigeminal nucleus caudalis, the trigeminal homologue of the spinal DREZ (56). The nucleus caudalis extends from about the level of the obex caudally to at least the second cervical spinal segment.

Clinical Considerations

Indications

Trigeminal DREZ lesions have been proposed for treatment of a wide variety of facial pain conditions, including postherpetic neuralgia, anesthesia dolorosa, poststroke facial pain, central facial pain in multiple sclerosis, posttraumatic facial pain, atypical facial pain, and migraine/cluster headache (57,58). Because the trigeminal DREZ operation is a major neurosurgical operation, it should be considered only after other less invasive methods have failed.

Technique

The procedure is usually performed under general anesthesia with the patient in either the prone or lateral decubitus position. A small posterior fossa craniotomy and upper cervical laminectomy are used to expose the medulla and upper cervical spinal cord as low as the second cervical nerve root (56,57 and 58). Using the operating microscope (see Fig. 108-2), the bulge that represents the trigeminal tract is identified just lateral to the fasciculus cuneatus of the dorsal columns. Tactile stimulation of the face or electrical stimulation of peripheral branches of the trigeminal nerve may be combined with microelectrode recording at the operational site to localize the trigeminal tract and underlying nucleus caudalis electrophysiologically. Nashold and colleagues have designed two special RF electrodes for the performance of trigeminal DREZ lesions (59) (Fig. 108-6). The electrodes are inserted sequentially into the trigeminal tract/nucleus from the obex to the C-2 nerve root, and a series of adjacent RF lesions is made over the entire extent of the nucleus caudalis.

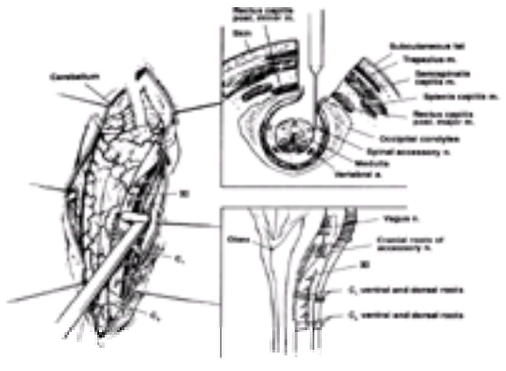


Figure 108-6. Techniques of trigeminal dorsal root entry zone procedure as described by Nashold using the electrode designed specifically for the trigeminal dorsal root entry zone procedure. (a, artery; m, muscle; n, nerve.) (Reprinted from Nashold BS, Abdul-Hak M, Ovelmen-Levitt J, et al. A new design of radiofrequency lesion electrodes for use in the caudalis nucleus DREZ operation. Technical note. *J Neurosurg* 1994;80:1116–1120, with permission.)

Results and Complications

In 1995, Gorecki et al. and Rawlings et al. reported on 101 trigeminal DREZ procedures performed at Duke University (57,58). Forty-six of these patients had the procedure performed with the newest electrodes. Overall, excellent pain relief was described in 34% and good pain relief in 40%. In postherpetic neuralgia, 71% obtained excellent or good pain relief. Eighteen patients (38%) described an improved quality of life. Complications in the form of ataxia were described in 54% of patients. My own experience and that of others with the trigeminal DREZ operation have been less rewarding (51). Only 30% to 40% of my patients have achieved satisfactory relief of pain. Other complications—for example, contralateral sensory loss due to injury to the spinothalamic tract and severe ataxia due to dorsal column injury—have led me to recommend trigeminal DREZ lesions only in desperate circumstances in which other procedures (e.g., trigeminal nerve stimulation, deep brain stimulation, thalamotomy, cingulotomy) have failed.

MESENCEPHALOTOMY

At the level of the mesencephalon, the spinothalamic tract is just below the pial surface and the so-called quintothalamic tract, which carries pain fibers from the face, is immediately subjacent. It was Walker who first suggested open surgical section at this level, but a high rate of complications led to the development of a stereotactic technique for mesencephalotomy (60).

Basic Considerations

The mesencephalon is an inviting target for a pain-relieving operation (61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77 and 78). The vast majority of pain input from the entire body and head are collected in three immediately adjacent pathways: the most superficial, the spinothalamic tract, the deeper, the quintothalamic tract, and the deepest, the spinoreticular tract (78). Not only do these pathways encompass the entire topography of the contralateral body, they also encompass the spatial and temporal qualities of pain, as well as the affective and motivational components. Theoretically, one would think that a correctly placed lesion in the mesencephalon could eliminate virtually any kind of pain. There are, however, some problems with this concept. First, with regard to neuropathic pain due to lesions of the nervous system, there is evidence that spontaneous neuronal hyperactivity at thalamic levels may be an independent generator of neuropathic pain (79). As thalamic pain generators are central to the level of a mesencephalic tractotomy, the later lesion would not be effective in relieving such pain. Also, because of the concentration of structures at the mesencephalic level, it is very difficult to make a lesion large enough to completely ablate the necessary pathways to relieve intractable pain without damaging important adjacent structures. The pathways for regulation of eye movements, particularly the medial longitudinal fasciculus and the oculomotor nucleus, are immediately adjacent to the pain pathways. Thus, disorders of ocular motility, such as diplopia and skew deviation, are very common if adequate-sized mesencephalic lesions are made (80).

Clinical Considerations

Indications

The major indication for stereotactic mesencephalic tractotomy is cancer pain in the head and neck, and/or the shoulder and arm. The procedure may be useful when unilateral diaphragm paralysis related to lung cancer would make high cervical cordotomy hazardous because of the risk of sleep-induced apnea, which does not occur with mesencephalic tractotomy. Neuropathic facial pains, such as anesthesia dolorosa or postherpetic neuralgia, may also respond to mesencephalic tractotomy. Neuropathic pains of the body, such as postcordotomy dysesthesias, phantom limb pain, brachial plexus, or lumbosacral plexus avulsion pain, may also respond to mesencephalotomy (61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77 and 78,80) (Table 108-2).

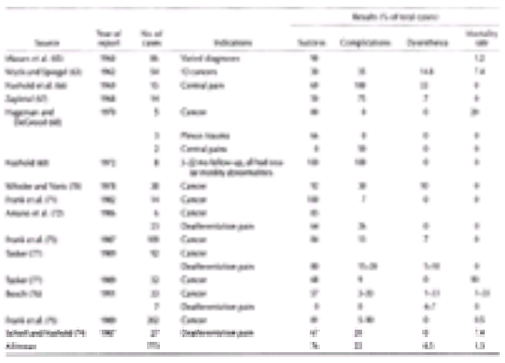


TABLE 108-2. Results of stereotactic mesencephalotomy

For nociceptive pain, relief can be expected in perhaps 60% to 70% of patients, whereas for neuropathic pain, long-term success may be anticipated in perhaps 40% to 50% (see Table 108-2).

Technique

The procedure is performed stereotactically using local anesthesia with minimal intravenous sedation. Stereotactic magnetic resonance imaging (MRI) may be used anatomically to localize the target but intraoperative electrophysiologic localization has been described as essential for final target localization. This information, however, derives from a time when ventriculography was used for anatomic localization. With the advent of stereotactic MRI localization very accurate lesion localization can be obtained, and whether this newer method will reduce or eliminate the need for physiological localization for the performance of mesencephalotomy is unclear.

The intended or best target for mesencephalotomy is also debatable. Lesions at the level of the superior colliculus are said to result in successful pain relief in up to 75% of patients but to result in defects in ocular motility in 87%. Lesions at the level of the inferior colliculus result in pain relief in less than 60% of patients, but the incidence of defects in ocular motility is reduced to approximately 17% (78,80).

Lesions are usually generated with an RF electrode, and emphasis has been placed on making small lesions using low temperatures and gradually enlarging the lesions while continuously assessing the patient's neurologic status, particularly extraocular movements and the strength and sensation of the face and extremities. It is well to emphasize that the size of the RF electrode and temperature are the primary controllable parameters that determine the size of RF lesions (81). The time of lesioning is a poor parameter for controlling the size of an RF lesion because the lesion gradually enlarges once the local temperature is above 48°C until it reaches its final size at approximately 30 seconds. The slope of the curve, which describes lesion enlargement, is relatively linear between 0 and 30 seconds, but even a few seconds' difference can significantly affect lesion size. To produce lesions of a consistent size that will yield reproducible results, only changes in electrode size and temperature should be used to alter the size of RF lesions, and the duration should be greater than 30 seconds.

The primary problem with stereotactic mesencephalotomy is its complications (78,80). The high rate of abnormalities of ocular motility has already been discussed. In addition, postmesencephalotomy dysesthesias, sensory loss due to injury to the lateral lemniscus, and motor complications due to injury to the extrapyramidal motor pathways in the ventral tegmentum make mesencephalotomy a high-risk procedure. These complications may be reduced by careful electrophysiologic localization, but the small size of the target and the multiple adjacent tightly packed structures to be avoided will continue to make mesencephalotomy a high-risk procedure.

THALAMOTOMY

Rationale and History

Virtually all pain-related information was thought to relay through one of several thalamic nuclei, and thus the thalamus was one of the early targets for stereotactic operations to relieve pain (82). As mentioned previously, however, direct relays from nociceptive neurons via the spinothalamic tract have been traced to several

limbic structures, and these targets are not ablated by thalamotomy (12,13). In general, thalamotomy has a high early success rate in pain relief, but in the past, frequent recurrences reduced the long-term effectiveness to perhaps 30% (83,84,85,86,87,88,89,90 and 91). Advances in understanding the role of the thalamus in chronic pain as well as advances in imaging and lesion making have, in my opinion, made thalamotomy a reasonable operation for dealing with particularly difficult patients with intractable pain (44,45).

Basic Considerations

Both the neospinothalamic and paleospinothalamic tracts, as well as the quintothalamic trigeminal tract, relay through the thalamus (82). The neospinothalamic tract terminates in the ventral posterolateral (VPL) thalamic nucleus, and the homologous fibers from the trigeminal system relay in the ventral posteromedial thalamic nucleus (Fig. 108-7). Likewise, the dorsal spinothalamic tract (at least in nonhuman primates) relays through these thalamic nuclei (15). Lesions placed in the VPL and ventral posteromedial nuclei are reasonably successful in relieving pain, but they are associated with loss of pain and temperature sensation contralateral to the lesion and are associated with a risk of producing a secondary pain syndrome akin to the so-called thalamic syndrome of Dejerine-Roussy. In addition to this role in the transmission of information concerning painful stimuli, studies have shown that neurons in the VPL thalamic nucleus may become independently or spontaneously hyperactive and potentially be independent generators of chronic pain (85,86). If this situation is truly the case, then the emphasis on pain transmission pathways as sites for lesioning, especially with neuropathic pain, may be misguided. Tasker and colleagues described groups of neurons in VPL that exhibited three different patterns of spontaneous bursting discharges (85,86). These neuronal discharge patterns were identified via microelectrode recordings in awake patients with neuropathic pain who were undergoing stereotactic operations. The neurons studied did not discharge in response to peripheral stimuli, and the firing patterns suggested cellular pathology similar to that seen in neurons injured by calcium influx after ischemia. It was postulated that such abnormal discharges may represent either a form of postsynaptic degeneration after injury or loss of presynaptic input.

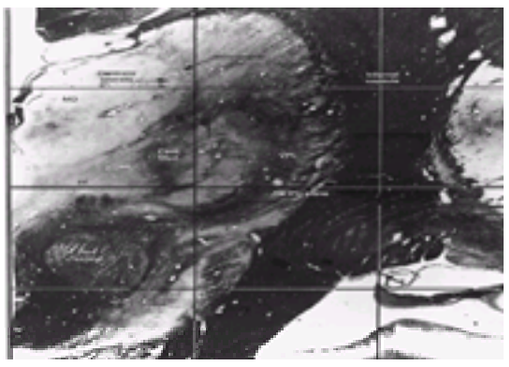


Figure 108-7. Coronal section of the brain 10 mm posterior to the mid-commissural point. See text for explanation. [AC-PC plane, plane of the AC (anterior commissure) and PC (posterior commissure); Cent. Med., centré median nucleus; MD, medial dorsal nucleus; PF, parafascicular nucleus; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus.] (Reprinted from Young RF. Stereotactic surgical ablation for pain relief. In: Rengachary SS, Wilkins RH, eds. *Neurosurgical operative atlas*. Baltimore: Williams & Wilkins, 1992;177–188, with permission.)

Our own microelectrode studies have identified neurons with similar discharge patterns in the medial thalamic nuclei of patients with both neuropathic and nociceptive pain (79) (Fig. 108-8). The medial thalamic nuclei—the intralaminar nuclei, the lateral portion of the medial dorsal nucleus, the parafascicular and center median nuclei—are the relay points for the paleospinothalamic tract and the dorsal spinothalamic tract and project widely to the association cortex of the cerebral hemispheres and to many of the nuclei of the basal ganglia (see Fig. 108-7). Lesions in the medial thalamus may result in relief of pain without detectable sensory loss and without the risk of producing a secondary neuropathic pain syndrome (44,45,87,89). Other projections from the multisynaptic spinoreticular system project to the dorsomedial and anterior thalamic nuclei and relay to the frontal cerebral cortex and to the limbic system. Lesions in these nuclei are thought to affect the suffering associated with chronic pain and may blunt the patient's overall response to stimuli in general, but not to the degree described with extensive prefrontal lobotomies.

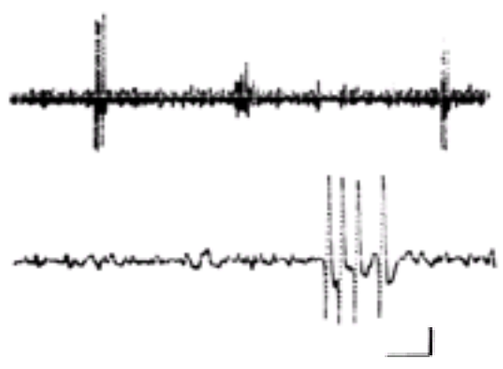


Figure 108-8. Single cell recording from the medial thalamus of a patient with chronic pain that demonstrates the spontaneous bursting pattern typical of deafferented neurons. (Reprinted from Young RF. Stereotactic surgical ablation for pain relief. In: Rengachary SS, Wilkins RH, eds. *Neurosurgical operative atlas*. Baltimore: Williams & Wilkins, 1992;177–188, with permission.)

Indications

In the past, cancer-related pain was the most frequent indication for thalamotomy (87,88). In the past 15 years, most cancer pain is treated by oral, parenteral, or intraspinal opiates, and few patients are now referred for thalamotomy to treat cancer pain. Thalamotomy, however, may be particularly useful for pain related to carcinomas of the head and neck or to shoulder and arm pain related to the Pancoast syndrome, neither of which responds well to opiates (86,87,88,89,90 and 91). Our own primary experience with medial thalamotomy has been in the treatment of non–cancer-related pain (44,45). As with most ablative procedures for the treatment of pain, nociceptive pain responds much better to thalamotomy than does neuropathic pain.

Results

For pain due to chronic spinal disorders (e.g., the failed laminectomy syndrome) or other types of nociceptive pain, approximately 70% of patients can be expected to report at least a 50% decrease in pain intensity, cessation of narcotic analgesics, and improvements in ability to function in daily living. For neuropathic pain (e.g., thalamic syndrome, anesthesia dolorosa, postherpetic neuralgia, phantom pain after amputations, and spinal cord injury pain) similar results are reported for approximately 50% of the patients in our experience. Many have reported an initial high success rate with thalamotomy but a marked decrease in efficacy within 6 to 12 months of the procedure. This observation has led to the recommendation that thalamotomy be performed only for patients with cancer-related pain with limited life expectancy. Our own experience has been that with lesions of proper size and location the results of thalamotomy are long lasting. It is for this reason that we continue to use the procedure for the treatment of other forms of noncancer pain where life expectancy is not limited. Several reviews of thalamotomy for treatment of chronic pain have been published as well (87,88,89,90 and 91).

Clinical Considerations

Thalamotomy is performed using stereotactic techniques and local anesthesia (44,45,87,88,89,90 and 91). Thus, the procedure is suitable for nearly all patients, and considerations that might contraindicate more extensive neurosurgical procedures performed under general anesthesia are not of concern when considering thalamotomy. The patient's head is held in a rigid fixation device, which serves both to immobilize the head and also to act as a stereotactic reference system to

identify the intended thalamic target radiographically. Classically, ventriculography was used to identify the anatomy of the third ventricle and certain reference points in the brain (e.g., the anterior and posterior commissures), from which the stereotactic coordinates of the intended target could be determined by reference to standard brain atlases. With the advent of first computed tomography and more recently MRI scanning, ventriculography is not required. Thus, the overall morbidity of thalamotomy has been reduced because seizures, hemorrhages, and infection, among other possible complications of ventriculography, are eliminated. Stereotactic MRI scanning provides more information than ventriculography, but in a noninvasive manner. Earlier concerns about the accuracy of MRI-guided stereotactic procedures have been overcome by recent advances in stereotactic MRI procedures (92,93). MRI also provides important details about thalamic size and location of important adjacent structures to be avoided (e.g., internal capsule) but currently MRI scanning is not sufficiently detailed to allow identification of individual thalamic nuclear groups. Thus, some dependence on stereotactic atlases is still required but advances in technique allow standard atlases to be adjusted using computer techniques to conform to the anatomy of individual patients' brains.

Intraoperative electrophysiologic recording has usually been used to provide detailed localization of thalamic nuclear targets and, in addition, to elucidate the somatotopic arrangement within certain thalamic nuclei (91). Within the medial thalamic nuclei, which is the primary target of thalamotomy to treat pain, there is no somatotopic arrangement and the area in which beneficial lesions may be placed for pain treatment is fairly large, so that the need for electrophysiologic target identification has been questioned. Our medial thalamotomy lesions performed with RF lesioning and with electrophysiologic guidance, based on identification of the neurons previously described with abnormal bursting and firing patterns, have been carefully studied as to their anatomic locations (79) (Fig. 108-9 and Fig. 108-10). The most effective lesions encompassed the lateral portion of the dorsomedial nucleus, the intralaminar zone, and the center median and parafascicular nuclei. Based on these observations, we have been able to target the same region based on stereotactic MRI scanning alone and create radiosurgical lesions in the same target area using the Leksell gamma knife radiosurgical system (94,95,96,97 and 98) (Fig. 108-11). This noninvasive technique allows thalamotomy lesions to be created in an identical location to those performed with RF lesioning but without the necessity to insert a lesioning probe through the brain, thus eliminating any risk of intracranial hemorrhage or infection. The RF and radiosurgical thalamotomy lesions are, in our experience, approximately equally successful with effective relief of nociceptive pain in nearly 70% of patients and relief of neuropathic pain in approximately 50%. One difference between RF and radiosurgical thalamotomies is the time course of onset of the effect. RF lesions are created virtually immediately, and the pain-relieving effect is also immediate. Radiosurgical lesions, however, develop over 2 to 3 months and reach maximal size approximately 6 months after the procedure. Pain relief with radiosurgical thalamotomy follows a similar time course, with gradual onset approximately 2 to 3 months after the procedure and a stable effect by 4 to 6 months. Thus, for patients with cancer pain, the RF method is probably more suitable, whereas with noncancer pain, the radiosurgical method may have some advantage in terms of safety when speed of onset of the pain-relieving effect is not as necessary. Leksell and colleagues first reported their experience with radiosurgical or so-called gamma thalamotomy in the 1970s for treatment of cancer-related pain (99,100). Our experience with radiosurgical thalamotomy has been almost exclusively in the treatment of noncancer pain, both nociceptive and neuropathic.

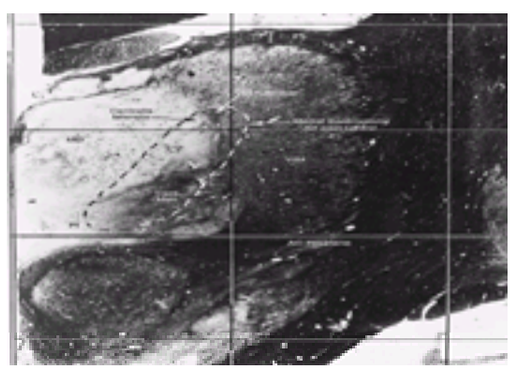


Figure 108-9. Coronal section of the brain 7 mm posterior to the mid-commissural point. The ideal location of a medial thalamic lesion to treat chronic pain is outlined by the dashed line. [AC-PC plane, plane of the AC (anterior commissure) and PC (posterior commissure); Cent. Med., centré median nucleus; MD, medial dorsal nucleus; PF, parafascicular nucleus; VIM, ventral intermediate nucleus.] (Reprinted from Young RF. Stereotactic surgical ablation for pain relief. In: Rengachary SS, Wilkins RH, eds. *Neurosurgical operative atlas*. Baltimore: Williams & Wilkins, 1992;177–188, with permission.)

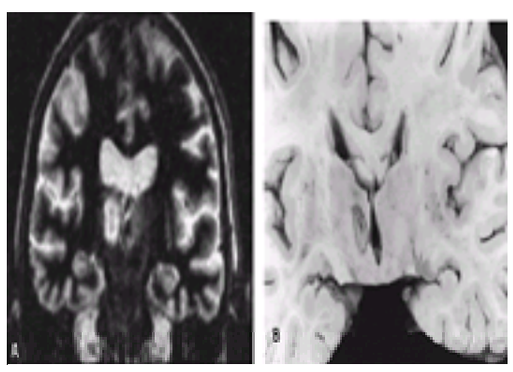


Figure 108-10. **A:** Coronal magnetic resonance imaging scan immediately after a right radiofrequency medial thalamotomy that resulted in complete relief of intractable shoulder and arm pain caused by lung cancer with brachial plexus invasion. The patient remains alive and free of pain 1.5 years after the procedure. **B:** Autopsy specimen demonstrating a right radiofrequency thalamotomy lesion that resulted in complete and lasting relief of postherpetic neuralgia that had failed to respond to deep brain stimulation. The patient died 1 year after the procedure of unrelated causes.

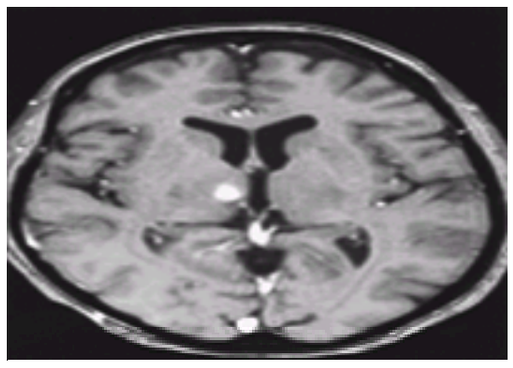


Figure 108-11. Axial magnetic resonance imaging scan that demonstrates a medial thalamotomy lesion made with the Leksell gamma knife that relieved intractable back and leg pain related to the failed lumbar laminectomy syndrome. The pain, which had not responded to either spinal cord stimulation or to intraspinal opiates, has been completely relieved for more than 3.5 years.

Other Thalamic Targets

Lesions have also been performed in other thalamic nuclei for treatment of intractable pain. These include the anterior nuclei and the pulvinar (101,102,103,104 and 105). The anterior nuclei have primary connections with the frontal lobes, and anterior nucleus thalamotomy is thought to alter mainly the affective and motivational components of chronic pain. Anterior thalamotomy is rarely performed today. The possible mechanism of pain relief by lesions in the pulvinar is unclear. Animal studies have shown involvement of the pulvinar as an indirect route for afferent stimuli with projections to the temporal lobe and thence to the sensory cortex of the

brain (77,78 and 79). Some relation of the pulvinar to pain perception has also been suggested (105,106). The exact target sites within the pulvinar are unclear and there is no electrophysiologic guide to targeting for pulvinotomy, which is currently usually based on MRI anatomic guidance alone. Both medial and lateral lesions in the pulvinar have been suggested and bilateral lesions appear more successful than unilateral lesions. Pulvinotomy has been used to treat both cancer-related and non–cancer-related pains (101,102,103,104 and 105). No sensory loss accompanies pulvinotomy and pain relief extending beyond 1 year after the procedure has been reported in approximately 25% of the patients.

Summary

Thalamotomy is a useful procedure for treatment of intractable pain, both cancer-related and non–cancer-related. Lesions in the medial thalamus, anterior thalamus, and pulvinar may relieve pain without altering normal sensory function and are the most desirable target areas. Technical advances, particularly stereotactic MRI target localization and noninvasive lesioning techniques using radiosurgery, have made thalamotomy safer and more accurate. The procedure is probably underused in the management of chronic pain even given the difficulty in interpreting the published results of thalamotomy due to differences in reporting methods and the limited length of follow-up periods in many reports.

HYPOTHALAMOTOMY

The procedure of making small stereotactic lesions in the posterior hypothalamus was introduced by Sano (107) in 1962 for the treatment of violent aggressive behavior, especially in those with epilepsy and mental retardation. Because of the theoretical consideration that painful stimulation always causes signs of sympathetic discharges, Sano and associates began to perform posteromedial hypothalamotomy for intractable pain (108,109). It was also reported by Fairman (110) at approximately the same time but has not become widely used.

Basic Considerations

Anatomy and Physiology

The anatomy of the area of the hypothalamus in which a lesion is made for pain relief does not correspond to a specific nucleus as defined by anatomic studies. It corresponds, however, to the area in which microelectrode recording demonstrates evoked activity at a latency of more than 100 milliseconds on stimulation of the contralateral superficial radial nerve, which has been shown to be a result of C-fiber stimulation transmitted along a multisynaptic pathway (108,111).

This area of the posteromedial hypothalamus has connections with the parafascicular nucleus and probably with the primary and secondary somatosensory cortex, as well as with the ipsilateral ventrocaudalis parvocellularis but not the dorsomedial nucleus (108,111,112). The physiologic basis of hypothalamotomy has been described as the normalization of ergotropic and trophotropic balance coordinated by that area (108), but the meaning of this concept is unclear.

Indications

Stereotactic posteromedial hypothalamotomy is used infrequently and is generally reserved for the patient with cancer pain, particularly if it involves the face and especially if the patient manifests a great deal of suffering, anxiety, or depression in addition to the pain (113). It has been used with mixed success for pain of postherpetic neuralgia involving the face (108,110). Hunter (112), Hassenbusch (103), and Gildenberg et al. (26) have reviewed this interesting procedure.

Results

Patients who obtain pain relief after hypothalamotomy behave differently from patients who obtain relief after frontal lobotomy. After lobotomy, cingulumotomy, or dorsomedial thalamotomy, patients might be relieved of suffering and no longer require pain medications but might indicate, when asked, that the pain is still perceived. After hypothalamotomy, the response is much more like that seen after an intralaminar thalamotomy: Patients report that they no longer perceive the pain. Satisfactory pain relief was obtained with hypothalamotomy for cancer pain in 70% of patients in one series (113) and in five of six patients in another series (108), but it must be recognized that this group of patients does not ordinarily require long-term follow-up. Partial relief has been reported in the use of hypothalamotomy for herpes zoster, causalgia, and thalamic pain (110). Two-thirds of patients with somatic pain, particularly after cancer, had relief from hypothalamotomy, but in general those patients with dysesthetic pain did poorly.

Clinical Considerations

Anesthesia

Hypothalamotomy is always done under local anesthesia because of the desirability of identifying electrode localization by stimulation or recording. Sedation must be carefully selected so as not to interfere with those activities (114).

Lesion Site

An electrode is introduced stereotaxically to a target 2 mm below the midpoint of the intercommissural line and 2 mm lateral to the lateral wall of the third ventricle. The operation can be done bilaterally in cases of widespread pain, but success can result from a unilateral lesion placed contralateral to the location of pain.

Electrode Localization by Stimulation

Recording of evoked activity on painful electrical stimulation of the contralateral radial or medial nerve can verify proper position of the electrode. In addition, application of pinpricks to the skin over wide areas of the body can produce evoked responses, with latencies of 300 to 2,000 milliseconds (108). Electrical stimulation causes signs of sympathetic discharge such as rise in blood pressure, tachycardia, pupillary dilation, or occasionally neck movement or ocular movement. Patients report a sensation of fear or horror during stimulation, but no sensation of pain.

Summary

More logical and potentially more successful procedures than hypothalamotomy currently exist for the treatment of pain. Few reports have been presented in the literature, and few neurosurgeons have found the procedure to be particularly helpful.

Hypothalamotomy is a surgical procedure that does not have a rational foundation in our understanding of the anatomy and physiology of the brain. Other stereotactic procedures have a clearer anatomic substrate and appear to have a higher likelihood of success. The indications for hypothalamotomy are not clear, nor is it clear that it offers any advantages over more commonly performed thalamotomies.

PRECENTRAL AND POSTCENTRAL GYRECTOMY

Excision of portions of the sensory cortex was first proposed by Leriche (115) and apparently was first performed by De Gutiérrez-Mahoney (116,117). Although the initial short-term results of excision of the postcentral gyrus were encouraging, the vast majority of patients who had this procedure have described recurrence of their pain.

Basic Considerations

Anatomy and Physiology

The postcentral gyrus, which includes Brodmann's areas 1 to 3 and part of area 5, is the principal cortical region for the integration and interpretation of sensory information. The precentral gyrus plays a similar role for motor activities; the precise localization of function varies from patient to patient. It has been known since the

turn of the century that lesions involving the human postcentral gyrus could dramatically alter sensation and could alter chronic pain states. Precise localization could be determined only by autopsy studies, and these were infrequent. The role of the cerebral cortex in the perception and response to pain is not clear and major disagreements remain as to the rational basis of cortical resection for relief of pain (see Chapter 5).

Indications

Certainly, gyrectomy is not a primary procedure for relief of pain. The development of stereotactic surgery and implanted electrodes for stimulation has probably played a role in the infrequent use of this surgical procedure. The lack of data makes it difficult to determine the possible advantages of gyrectomy.

Clinical Considerations

Technique

With the technology currently available, this operation is best performed under local anesthesia so that cortical mapping can be undertaken and the resection can be based on both physiologic and anatomic data. A large craniotomy is required to expose the central and precentral regions, similar to that used for cortical resection of an epileptic focus.

Results

In 1969 White and Sweet (118) summarized their review of 21 publications, which included data on 38 patients (Table 108-3). Of the 18 initial successes, only four were said to be relieved of their pain when assessed one or more years later. Even the much more extensive lesion used by Pool and Bridges (119), which undercut the parietal lobe for 7.5 cm posterior to the central sulcus, provided pain relief for only a little more than a year. Lende and coworkers (120) removed both the precentral and postcentral gyri of the face projection area to the upper border of the insula. This resection included both the primary and secondary sensory areas for the face as well as all of the precentral motor sensory cortex. Only mild contralateral facial weakness was noted, probably because of the bilateral cortical representation for the face. Data were reported on two patients. One had continuous unilateral burning facial pain secondary to a pontine stroke and was rendered pain-free until he died 20 months later from heart disease. The other had continuous facial pain after a retrogasserian rhizotomy for trigeminal neuralgia and was pain free for at least 17 years.

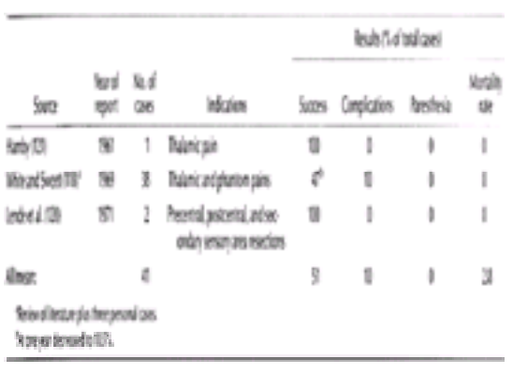


TABLE 108-3. Results of postcentral gyrectomy

It is possible that removal of the entire primary and secondary sensory areas along with the corresponding motor area can succeed where less extensive operations have failed (121). I am not aware of any reports of such operative procedures.

Complications

Cortical excisions do involve some risk of focal epilepsy, especially in the region of the central sulcus. Extensive cortical lesions can also result in contralateral sensory and motor loss.

FRONTAL LOBE OPERATIONS FOR PAIN

Prefrontal Leukotomy

Contemporary frontal lobe operations for pain evolved from prefrontal leukotomy, an operation originally devised for the treatment of severe intractable psychiatric disorders (122). No other class of surgical procedures has been subjected to the political and scientific scrutiny that has accompanied “psycho-surgery.” The abusive use of prefrontal leukotomy in the first 25 years of its widespread acceptance led to a rebound that, at least in the United States, makes it difficult to perform any psychosurgical procedure. Although prefrontal leukotomy probably has no contemporary application, its descendant, cingulumotomy, can be effective for the relief of pain in properly selected patients.

Basic Considerations

Anatomy and Physiology. The prefrontal leukotomy procedure was based on experimental observations in animals of calming effects after bilateral division of white matter fibers immediately anterior to the frontal horns of the lateral ventricles (123). These fibers project from the cingulate gyrus and dorsomedial thalamus to areas 9 through 14 of the frontal cortex. They are the rostral projection of the reticular-activating system and diffuse thalamic projection pathways. Subsequent reports indicated that some patients with complaints of pain as part of their mental illness lost their pain after prefrontal leukotomy (124,125). These reports stimulated the use of bilateral prefrontal lobotomy for the treatment of various chronic pain states (126,127,128,129,130 and 131). The operation, whether primarily for psychiatric disorders or chronic pain, was then refined, at first by restricting the bilateral leukotomy to medial frontal white matter (132).

Clinical Considerations

Techniques. Although prefrontal lobotomy is popularly regarded as a surgical procedure done by inserting an icepick through the orbital roof and blindly traumatizing the frontal lobes, most neurosurgeons have used a trephine hole placed anterior to the coronal suture, either laterally or superiorly. The dura is opened in a cruciate fashion and blood vessels on the cortical surface are coagulated. A ventricular needle is passed in the plane of the proposed leukotomy to ensure that it is anterior to the frontal horn of the lateral ventricles. A leukotome is then inserted to transect the bulk of the white matter. The operation is usually performed under local anesthesia.

Variations in the surgical technique include suction-coagulation under direct vision, injection of sclerosing solutions, and use of RF current to make lesions. Limited leukotomies have been performed by manually directing the lesion to the area of interest.

Results. The effectiveness and limitations of these procedures in the treatment of various pain states were well described by Elithorn and colleagues (133). They evaluated 25 patients managed with standard bilateral prefrontal leukotomy or with the more restricted bilateral section of only the medial frontal white matter. Evaluation, at a minimum of 6 months after operation (mean 24 months), was based on patients' and relatives' opinions and on a social functioning rating scale. All patients but one had chronic pain; the largest groups were five with postherpetic neuralgia, four with atypical facial pain, and three with painful torticollis.

These operations did not change the perception of acute pain or responses to it except for a suggestion of a more intense but briefer response to noxious stimulus. Two-thirds of the patients were considered to be improved, however, with six of 25 much improved based on the social function rating scale, although only one-third of

the patients or relatives thought there had been improvement. Patients with the most extensive operations had the best outcomes based on the evaluation by the patients and relatives, but not on the social function rating scale. Those with the most severe pain did least well by any measure. Older patients had better outcomes. Patients with large “standard” leukotomies all showed some personality change, which was considered severe in one-third. Eight of 13 patients with more limited medial frontal leukotomies demonstrated personality changes; these were severe in two.

Benefit in patients with severe organic pain usually required some personality change. Elithorn and associates (133) concluded that the major beneficial effect of these operations was to reduce depression and anxiety, with a more variable effect on obsessive behavior. In pain patients the typical postleukotomy picture was one in which patients still complained of severe pain but at the same time showed an inappropriately cheerful affect and the inability to sustain an attitude or mood. Unfortunately, only 13 of 25 patients returned to their preoperative level of intellectual and physical activities. Generally similar results were reported by others (134).

Unilateral Prefrontal Leukotomy

The value of unilateral prefrontal leukotomy in chronic pain of diverse causes were evaluated by Scarff (135,136) in 33 patients. He found that two-thirds of patients were improved without major personality changes. White and Sweet (137) disagreed with this conclusion, however, and stated that mental changes were always present when suffering had been alleviated, although unilateral prefrontal leukotomy was less likely to lead to the severe personality changes seen after bilateral lesions. White and Sweet (137) also indicated that suffering returned if patients survived more than 6 months after a unilateral prefrontal lobotomy. When psychological functioning returned to normal, patients were likely to suffer again.

Summary

In these reports, the major features of frontal lobe procedures for pain were evident: major effects on depression and anxiety, little or no effect on pain perception or on the patient's report of pain, but an apparent reduction in the impact of the pain on the patient's affect and functioning. These same features also apply to modern, more limited, frontal operations for pain, although these newer operations have no measurable effect on personality or intellectual performance. Prefrontal leukotomy is no longer considered to be a reasonable operation for pain relief because of its devastating effect on social activities and intellectual performance.

CINGULUMOTOMY

Basic Considerations

Cingulotomy or cingulumotomy is one of a number of operations that involve lesioning a part of the frontal lobes (Fig. 108-12). Early operations, such as extensive prefrontal lobotomies and resection of various portions of the frontal cortex, did not dissociate effects on reducing suffering from intractable pain and effects on more general aspects of emotional responses to nonpainful stimuli and intellectual function. Resection of the anterior cingulate gyrus (cingulectomy) was reported to relieve suffering without producing major effects on personality and intellect (138). With the advent of stereotactic methods, the idea of placing an RF lesion in the outflow path of the cingulate gyrus, the cingulum, was proposed, thus the term *cingulotomy* or *cingulumotomy*. Foltz and White described an experimental study in which morphine withdrawal was nearly abolished by cingulumotomy and then they reported pain relief in humans after stereotactic cingulumotomy guided by ventriculography (139,140). Other investigators reported that addiction to narcotics or alcohol could also be cured by cingulumotomy. Neuropsychological studies showed that these positive effects of cingulumotomy were not accompanied by adverse effects on personality or intellectual function (141,142). More recently, positron emission tomography scan studies have demonstrated increased metabolic activity in the cingulate gyrus elicited by the application of noxious stimuli, thus solidifying a role for this region in pain appreciation (143,144).

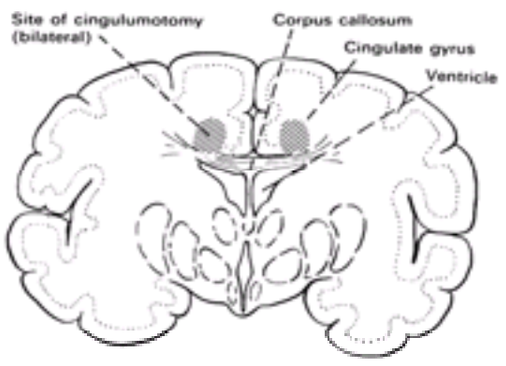
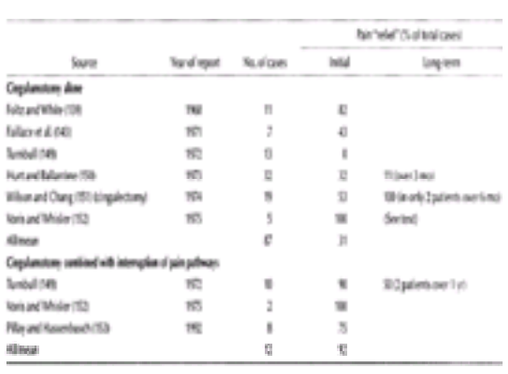


Figure 108-12. Coronal section of brain indicating sites of lesions for cingulumotomy.

Clinical Considerations

Indications

Cingulumotomy is indicated for intractable pain that has failed to respond to other less invasive forms of therapy. Both pain due to cancer and non–cancer-related pain may be alleviated with this procedure (145,146,147 and 148) (Table 108-4 and Table 108-5). Nociceptive and neuropathic pain may respond to cingulumotomy. There is no somatotopic representation within the cingulate region, and therefore cingulumotomy may be used for treatment of pain in any location within the body. It is important to know that cingulotomy is performed bilaterally; unilateral cingulotomy is of no demonstrated benefit for treatment of chronic pain. It has also been suggested that cingulotomy may be particularly indicated if anxiety or “suffering” and/or narcotics addiction are compounding problems because of the beneficial effect of cingulotomy on these two problems. Where cingulotomy should fit *vis-à-vis* other central ablative pain-relieving procedures such as thalamotomy has not been clarified.



Source	Year of report	No. of cases	Initial	Long-term
Cingulumotomy alone				
Foltz and White (138)	1968	11	82	
Wallace et al. (143)	1971	7	43	
Turnbull (149)	1972	13	8	
Hurt and Ballantine (150)	1973	12	32	11 (over 3 mo)
Wilson and Chang (151) (cingulectomy)	1974	19	53	100 (in only 2 patients over 6 mo)
Vorro and Whitaker (152)	1975	5	100	(See text)
All mean		67	71	
Cingulumotomy combined with interruption of pain pathways				
Turnbull (149)	1972	10	90	50 (2 patients over 1 yr)
Vorro and Whitaker (152)	1975	2	100	
Pillay and Hosenbaneh (153)	1990	8	75	
All mean		12	92	

TABLE 108-4. Results of cingulumotomy for cancer pain

Source	Year of report	No. of Cases	Pain "relief" (% of total cases)		
			Initial	Long-term	Comments
Foltz and White (139)	1968	29	67	42 (1 yr plus)	
Fulton et al. (140)	1971	2	50	50 (2 yr)	
Turnbull (141)	1972	7	57		Alone
Turnbull (141)	1972	6	50	17	With anterior capsulotomy
Hurt and Ballantine (153)	1973	36	22	22 (over 6 mo)	
Wilson and Chang (151)	1974	4	50	0 (over 1 yr)	
Vonn and Wikmäe (152)	1975	11	73	18 (over 1 yr)	Alone
Vonn and Wikmäe (152)	1975	7	71	0 (over 1 yr)	With anterior capsulotomy (3) or thalamotomy (2)
Brugger and Olivier (154)	1972	17		82 (over 6 mo)	
Corkin et al. (155)	1979	11	82	82 (over 1 yr)	
Pillay and Hoenerbach (153)	1992	3	50	50 (1 yr)	
All mean		125	59	38	

TABLE 108-5. Results of cingulumotomy for nonmalignant chronic pain

Technique

Cingulotomy is usually performed under local anesthesia but may be performed under general anesthesia as well because intraoperative electrophysiologic localization does not help in target location. Initially, cingulotomy was performed using ventriculography but more recently, a technique using MRI localization has been proposed that is superior to ventriculography and presumably safer (146,147). The target is located approximately 25 mm posterior to the tips of the frontal horns of the lateral ventricles as identified on axial, coronal, or sagittal MRI scans. The center of the proposed lesion is located in the center of each cingulate gyrus. We make the cingulotomy lesions using a 2-mm-diameter RF lesioning probe with 10-mm exposed tip and with a thermistor in order to measure the temperature (Fig. 108-13). The probe is introduced via a 6- to 8-mm scalp incision located just anterior to the coronal suture and 15 to 20 mm lateral to the midline. The stereotactic coordinates of the planned target are determined and set on the Leksell stereotactic frame. The twist drill opening is then made by passing the drill through the stereotactic guides, which ensures that the opening is oriented in the correct trajectory for introduction of the lesioning probe directly to the target. Using this technique, the procedure is minimally invasive and avoids some of the problems that may be associated with larger cranial openings such as dural bleeding and especially loss of cerebrospinal fluid, which may result in brain shifts that could move the intended target significantly from its preoperative location. Because electrophysiologic localization is not helpful, we do not recommend either electrical recordings or stimulation before lesioning. An early attempt by us to use electrical stimulation resulted in a grand mal seizure, presumably due to cortical spread of the stimulating current. The lesioning probe is introduced to the target and an RF lesion is created at 85°C for 60 seconds. The probe is removed and the procedure is repeated on the contralateral side. The entire procedure can be easily accomplished in 30 to 45 minutes. Some authors have recommended enlarging the lesions either superficially and/or deeper, but we have not usually done this (147,148). Also, some authors have recommended placing a second set of lesions just posterior to the first ones, but we have usually not done this either (147,148). We have performed an immediate postoperative MRI with contrast while the patient remains in the stereotactic frame in order to confirm the accuracy of lesion placement and to assess for possible postoperative hematoma. So far we have not identified intracranial hemorrhage after cingulotomy, but it is a risk of any stereotactic operation in which a probe is introduced into the brain.

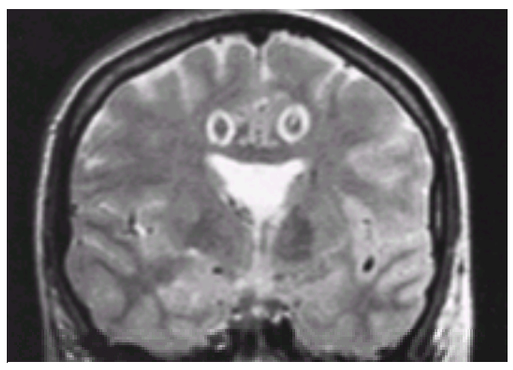


Figure 108-13. Coronal magnetic resonance imaging scan immediately after bilateral radiofrequency cingulotomy for treatment of facial anesthesia dolorosa. The pain had failed to respond to prior trigeminal dorsal root entry zone lesions and to medial thalamotomy but has been relieved for more than 1.5 years after the cingulotomy.

Results

The reported results of cingulotomy are encouraging, with approximately 50% of patients reporting significant decreases in pain. There were only minor differences in the success rates for cancer-related or non–cancer-related pains. Reported success rates do appear to decrease if follow-up time is extended so that overall the procedure may be slightly more effective for cancer pain. As is usual with most pain-relieving surgical procedures, neuropathic pain appears to respond less well to cingulotomy than nociceptive pain.

Complications of cingulotomy are few and primarily due to rare cases of intracranial hemorrhage. Otherwise, neurologic deficits do not occur and effects on neurocognitive behavior, even with large lesions, are minimal or nonexistent.

We have found cingulotomy to be useful in combination with medial thalamotomy where one or the other lesion was not successful alone. In most of our combined lesion patients, we have begun with a medial thalamotomy if the pain is unilateral and then proceeded to cingulotomy if the pain relief was unsatisfactory from thalamotomy alone. For more widespread or midline pain, we have begun with cingulotomy and then added unilateral or in some cases bilateral medial thalamotomy (usually in staged procedures 2 to 3 months apart) if cingulotomy alone is unsuccessful.

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CHAPTER 109

Multidisciplinary Pain Management

John D. Loeser and Dennis C. Turk

The differentiation of chronic pain from acute pain was a seminal development in both clinical medicine and basic research. It has led to new research strategies focusing on the changes that occur in tissues and the nervous system in response to injury. Another important change in the traditional approach to pain patients was the subdivision of chronic pain patients into those with cancer, those with injury to the nervous system, those with chronic diseases, and those whose complaints of pains could not be understood on the basis of observable pathology (see Chapter 2). Every patient's complaints are likely to be influenced by his or her attitudes, beliefs, expectancies, and current mood. Individuals express their pain verbally and nonverbally (i.e., by overt expressions of pain and distress), and these behaviors are largely under the influence of environmental parameters including responses from significant others (see Chapter 10). In this chapter, we focus on patients who have failed to respond to traditional medical treatment and for whom cognitive, affective, and environmental factors are particularly important in the maintenance of the pain and disability. This distinct subset of patients warrants identification by appropriate diagnostic evaluation and referral to and treatment at a multidisciplinary pain center (MPC) (see Chapter 18).

This is the last part of a three-chapter segment (see Chapter 11 and Chapter 18) addressing the conceptual basis and implementation of multidisciplinary pain management. The assessment of patients who are candidates for multidisciplinary pain management is presented in Chapter 18. Here, we discuss the design and implementation of multidisciplinary pain treatment and its reported outcomes. Multidisciplinary pain management originated in the 1950s because of Bonica's (1,2) emphasis on pain patients and gained momentum with the work of Fordyce in the 1960s and 1970s (3). Many other psychologists and physicians also have contributed to this rapidly developing field (4,5). For patients who do not respond to traditional medical and surgical strategies, it has become a common treatment strategy. Since this type of treatment of chronic pain patients engages the skills of many providers, much of the content of this textbook is relevant to multidisciplinary pain management. Many other chapters contain specific information on the building blocks of this treatment, especially Chapter 10, Chapter 12, Chapter 16, Chapter 24, Chapter 25, Chapter 26, Chapter 88, Chapter 89, Chapter 90, Chapter 91, Chapter 92, Chapter 93 and Chapter 94.

The epidemic of chronic pain complaints and the disability associated with them has afflicted all of the industrialized countries to some degree. As health care costs for those who suffer from chronic pain have grown, it has become apparent that the traditional biomedical model provides an inadequate foundation for the delivery of effective health care. Multidisciplinary pain management evolved because it has proven to be more effective and less costly than the traditional methods of addressing chronic pain (6,7). It employs a biopsychosocial model and relies heavily on the cognitive-behavioral approach (see Chapter 89).

For many chronic pain patients, the forces that have led the patient to report persistent pain remain obscure. Traditional diagnostic processes have failed to identify a remediable cause of pain. These patients require treatment because of the disruption of their life that they ascribe to pain. Indeed, their health care providers must feel comfortable abandoning the search for cure and, instead, accept palliation as a viable outcome. The goal, then, is to improve the patient's ability to function, not to cure the disease that has led to pain. Hence, the diagnostic process must identify the areas of functional impairment and disability, and treatment must address all of the factors that contribute to disability. In contrast to traditional medical therapy, patients cannot be passive recipients of the ministrations of providers. Such patients must accept responsibility and work to achieve the benefits of treatment.

A useful conceptualization of the problem of chronic pain without identifiable and treatable pathology is that “the patient is hurting more than he or she needs to.” Secondary effects of the pain, such as depression, physical deconditioning, social isolation, inappropriate medications, vocational dysfunction, and superstitious beliefs about the body may be the primary determinants of the patient's overall condition. It is the treatment of these and related issues that are the focal point of multidisciplinary pain management.

Vast numbers of people will, if asked, report that they have chronic pain problems of more than trivial severity (8). They may even take occasional medications or consult a physician or other health care provider. Infrequent sickness days may occur. However, these people remain functional and do not suffer from their pain or become disabled to any significant degree. They are not appropriate candidates for multidisciplinary pain management. Many other people have chronic pain and seek health care. They may have a diagnosable disease and receive appropriate therapy from their primary physician or a single specialist. As long as function returns and their pain complaints diminish, they have no need of multidisciplinary pain management.

Several epidemiologic studies (9,10) have compared the characteristics of people who have chronic pain in the community with those of patients treated at MPCs. The patients treated at the specialized pain centers are more likely to demonstrate higher levels of emotional distress, work-related injuries, use of the health care system, constant pain, use of opioid medication, prior surgeries, and functional impairments. Moreover, they have lower levels of education and were more likely to have negative attitudes about the future. Flor et al. (11) reported that patients treated at MPCs had a mean duration of pain of more than 7 years. Obviously, those referred to MPCs have long histories of severe pain intensity, are high health care users, and suffer from significant emotional distress. They are a particularly recalcitrant set of pain patients. As discussed in Chapter 18, only those patients who meet the criteria for multidisciplinary pain management should be enrolled in such a treatment program.

It has been our observation, however, that many patients are treated as if they had a clear-cut diagnosis and as if they were showing a good response to therapy, when, in fact, the diagnosis merely reflects what the provider does to earn a living and the patient has not benefited from the treatment. Interminable therapy often adds to the patient's disability and is not acceptable. Some patients are sent from one biomedically fixated physician to another, like billiard balls caroming across a table from cushion to cushion. Each provider does his or her thing and sends the patient on to another ineffective series of treatments. Timely referral to an MPC, not a parade of specialists, is required.

DESCRIPTION OF MULTIDISCIPLINARY PAIN PROGRAMS

Although there is no single format for multidisciplinary pain management, almost every treatment facility of this type has a generic concept and plan (Table 109-1). These treatment programs also share general features (Table 109-2). This is probably because of the pioneering and preeminent role of the University of Washington Multidisciplinary Pain Center and its faculty in training pain management specialists, lecturing throughout the world, and publishing scientific articles and numerous book chapters (12). The concept underlying this form of treatment is the biopsychosocial model, in contrast to the biomedical model that characterizes most of medicine. Figure 109-1 depicts the components of this concept and emphasizes that health care providers can only observe pain behaviors, not pain itself (13).

Reconceptualization of the patient's pain and associated problems from uncontrollable to manageable.
Overt or covert efforts are made to foster optimism and combat demoralization.
Flexibility is the norm with attempts to individualize some aspects of treatment to patient needs and unique physical and psychological characteristics.
Emphasize active patient participation and responsibility.
Provide education and training in the use of specific skills such as exercise, relaxation, and problem solving.
Encourage patient feelings of success, self-control, and self-efficacy.
Encourage patients to attribute success to their own role.

TABLE 109-1. Concepts of treatment at multidisciplinary pain clinics

Share a common conceptualization of chronic pain patients.
Synthesize the diverse sets of information based on their own evaluations, as well as those of outside consultants, into a differential diagnosis and treatment plan customized to meet the specific need of each patient.
Work together to formulate and implement a comprehensive rehabilitation plan based on available data.
Share a common philosophy of disability management.
Act as a functional unit whose members are willing to learn from each other and modify, when appropriate, their own opinions based on the combined observations and expertise of the entire group.

Adapted from Turk DC, Stieg RL. Chronic pain: the necessity of interdisciplinary communication. Clin J Pain 1985;1:163–167.

TABLE 109-2. General features of multidisciplinary pain treatment teams

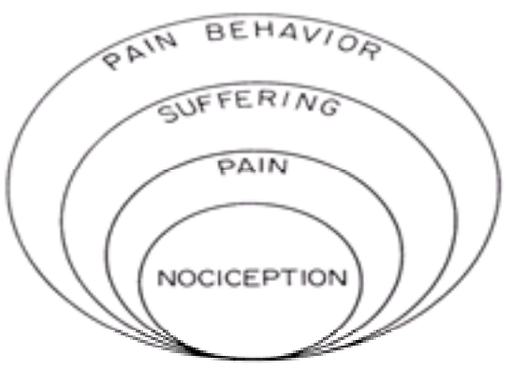

Figure 109-1. Loeser's model of the four components of pain. (From Loeser JD. Concepts of pain. In: Stanton-Hicks M, Boas R, eds. *Chronic low back pain.* New York: Raven Press, 1982:146, with permission.)

Nociception, pain, and suffering are personal, private, internal events whose existence can only be inferred by observing a patient's behavior. In the clinical setting it is impossible to measure any of these internal events; external observers can only quantify pain behaviors. The biopsychosocial model assumes that all human behavior, including the complaint of pain, reflects a combination of the events occurring within the patient's body, the recognition of these events, the appraisal of these events, the affective responses to these events, and the influence of the environment. The model calls for addressing all of these components at once and in a coordinated fashion, to present the patient with a single treatment program that encompasses all of the treatable issues.

In multidisciplinary pain treatment and rehabilitation programs, patients are usually treated in groups of five to 15. Patients work on at least four generic issues simultaneously: physical, pharmacologic, psychological, and vocational. Programs usually emphasize physical conditioning, medication management, acquisition of coping and vocational skills, and gaining knowledge about pain and how the body functions. Individual and group counseling addresses patient needs. In contrast to traditional Western health care, the emphasis is on what the patient accomplishes, not on what the providers accomplish. The providers see themselves as teachers, coaches, and sources of information and support.

Multidisciplinary pain management requires the collaborative efforts of many health care providers, including, but not limited to, physicians, nurses, psychologists, physical therapists, occupational therapists, vocational counselors, social workers, and support staff (Table 109-3). The health care providers must act as a team, with extensive interactions among the team members. In the current managed care environment in the United States, with occult rationing (managing costs, not care, is the true agenda), it is often difficult to arrange for funding of this type of health care, even though this model offers more outcome data than any other type of treatment of chronic pain. This is particularly true for low back pain. We review some of these results later in this chapter, but see also Turk and Okifuji (6,7).

Physicians
Psychologists
Nurses
Physical therapists
Occupational therapists
Vocational counselors
Social workers
Recreational therapists
Dieticians
Support staff
Patients
Significant others

TABLE 109-3. Participants in multidisciplinary pain programs

Facilities

The facilities for a multidisciplinary pain treatment program can exist within a large hospital or medical center or they can be completely free-standing. The evaluation of new patients and the follow-up of those who have graduated from the treatment program require dedicated space. Along with individual examination rooms there must be a conference room for group meetings with patients and their significant others. Other larger rooms must accommodate patient education groups, group psychotherapy sessions, relaxation sessions, and physical therapy activities. High-tech physical therapy equipment may impress patients and payers, but it is certainly not an essential aspect of this type of pain management. Adequate space to permit the simulation of aspects of occupational activities is highly desirable.

Support staff and space for their activities are essential.

Patient Treatment Strategies

Table 109-4 itemizes the goals of multidisciplinary pain management. Every patient has a different mixture of functional limitations, pain behaviors, affective disturbance, physical disability, and vocational dysfunction. Successful treatment addresses each of these general areas.

Identify and treat unresolved medical issues.
Eliminate inappropriate medications.
Institute desirable medications.
Improve aerobic conditioning, endurance, strength, and flexibility.
Eliminate excessive guarding behaviors that interfere with normal activities.
Improve coping skills and psychological well-being.
Alleviate depression.
Assess patient resources and identify vocational and recreational opportunities.
Educate the patient about pain, anatomy, physiology, psychology, and discriminating hurt from harm.
Educate the patient about prudent health care consumption.
Assist the patient in establishing realistic goals and maintaining treatment gains.

TABLE 109-4. Goals of multidisciplinary pain management

The original multidisciplinary pain management programs were all inpatient-based. It is now apparent that outpatient programs can be equally successful if they have adequate intensity and duration (14). There are no controlled studies to determine the optimal duration of treatment and hours per day; nor does the literature reveal which aspects of the various components are most important for a treatment program. It is clear that the effects of a multidisciplinary pain treatment program are greater than the sum of its parts, however. Common features of all programs include physical therapy, medication management, education about how the body functions, psychological treatments (e.g., coping skills learning, problem solving, communication skills training), vocational assessment, and therapies aimed at improving function and the likelihood of return to work. Programs usually have a standard daily and weekly format that providers can tailor to an individual patient's needs. The overall length of a program depends in part on unique patient requirements.

Typical programs operate 8 hours per day, 5 days per week, and last 3 to 4 weeks, although some programs meet less frequently and last for longer periods. The daily schedule used at the University of Washington Multidisciplinary Pain Center is shown in Table 109-5. All good programs include a prolonged follow-up period with options for brief interactions to help patients maintain their gains.

Monday through Friday	
8:00–8:25	Movement, stretch, body mechanics
8:35–10:35	Physical and occupational therapy, individual and group sessions
10:45–11:15	Skill building group (nursing)
11:15–11:45	Relaxation group/muscle reeducation (nursing)
12:00–12:30	Lunch
12:15–12:55	Rounds with treatment team
12:30–12:55	Individual sessions/muscle reeducation
1:00–1:50	MD didactic group
2:00–2:55	Physical and occupational therapy, individual and group sessions
3:00–3:50	Psychology didactic group
4:00–4:55	Physical therapy individual sessions
Saturday	
8:30–9:30	Physical therapy (group)
9:30–10:30	Occupational therapy (group)
10:30–11:00	Stretch class (group)

TABLE 109-5. Structured program patient schedule at University of Washington Pain Center

Each of the treatment team members makes a specific contribution to the overall program. The most difficult aspect of multidisciplinary pain management is identifying health care providers who can function as members of a treatment team.

Role of the Physician

The physician is responsible for the initial history and physical examination, review of outside records, and determination of the need for any further diagnostic tests. Detailed assessment of the patient's medication history is also a key physician contribution. The implementation of medication management, including drug tapering by means of a pain cocktail technique (see Chapter 88), is also the physician's responsibility. Another important task for the physician is to review the medical issues and the findings in diagnostic tests and imaging studies with the patient. The physician also plays an essential role in the education of the patient and in legitimizing all of the other components of the treatment program.

Role of the Psychologist

The psychologist conducts the initial psychological evaluation, monitors and implements the cognitive and behavioral treatment strategies, teaches the patient coping skills, and educates patients about the relationships among thoughts, feelings, behavior, and physiology. It is important to recognize that working with chronic pain patients requires appropriate education and training for the psychologist, just as it does for the physician. The psychologist leads both individual and group educational and counseling sessions for the patients. In addition, the psychologist plays a critical role in helping other members of the treatment team use sound behavioral principles in designing patient treatment activities (see Chapter 88).

Role of the Nurse

The nurse is a key part of the treatment program, playing a major role in patient education regarding such topics as medication, diet, sleep, hygiene, and sexual activity. Another nursing function is assisting patients in the practice of newly learned skills, assessing medication responses, and acting as the focal point of the communications that keep such a program operational. The roles of nurses vary with their skills and the interactions with other providers. Since the nurses tend to be with patients throughout their entire treatment course, they are a focal point for continuity in the treatment program.

Role of Physical and Occupational Therapists

Physical and occupational therapists provide assessment and active physical therapies for patients to improve their strength, endurance, and flexibility. They do not provide passive modalities of treatment. They assist the patient in developing proper body mechanics and strategies for coping with the physical demands of a job and everyday life. They function mainly as teachers and coaches.

The occupational therapists review the patient's work history, disabilities, and factors that may play a role in determining who goes back to work and who does not. They help in the establishment of work-hardening and training activities. Some programs heavily emphasize ergonomic issues and use high-tech in physical therapies; however, the need for this type of treatment is unclear.

Role of the Vocational Counselor

The vocational counselor plays a critical role in the treatment of an individual for whom return to work is a treatment goal. Initial assessment occurs as part of the screening process (see Chapter 18), but in-depth evaluation of interests, education, aptitude, physical capacities, learning capabilities, work experience, transferable skills, and vocational goals occurs on entry into the treatment program. The goals are to identify vocational opportunities and barriers to effective return to work. In addition to occupational counseling, counselors provide job-seeking skills training, placement counseling, job hardening, information about educational options, and liaison services. Information obtained by the vocational counselor is critical for other team members to establish realistic goals for the patient. In some organizations, rehabilitation nurses provide this service.

TREATMENT PRINCIPLES

The goals of multidisciplinary pain management are normally specific, definable, operationalizable, and realistic. Table 109-6 lists a set of goals commonly targeted in MPCs. As they have evolved, MPC treatments have become performance-based, goal- directed, and outcome driven. Integration of medical evidence related to patients' pain and physical impairment with information concerning what patients are doing or failing to do because of their pain, how these behaviors influence patients' physical capacity, how others respond to the patient, the influence of psychosocial factors that contribute directly and indirectly to patients' physical and emotional status, and the potential for rehabilitation (i.e., disability) is essential. The treatment team must build an alliance with patients to instill a willingness to accept the need for self-management.

Identification and treatment of unresolved medical problems
Elimination of inappropriate medication
Symptomatic improvement
Restoration of physical functioning
Restoration of social and occupational functioning—social reintegration, return to productive employment
Reduction in use of health care system
Improvement in coping and psychological functioning—foster independence

Adapted from Turk D, Stacey B. Multidisciplinary pain centers in the treatment of chronic pain. In: Frymoyer J, Ducker T, Hadler N, eds. *The adult spine: principles and practice*. New York: Raven, 1997:253–274.

TABLE 109-6. General goals of multidimensional pain centers

Physical therapy uses behavioral medicine principles (15) and engages few, if any, passive modalities. Biofeedback can be a useful adjunct because it teaches the patient that he or she can gain control over various bodily functions (see Chapter 90). The emphasis is on improving strength, endurance, and flexibility through the patient's physical activities. The therapists provide instruction, guidance, safety, and encouragement. Accomplishments, rather than pain behaviors, receive rewards. Patients maintain graphs of their daily activity and track their progress. As patients progress, they engage in more complex activities that simulate the workplace requirements.

Medications are given on a time-contingent basis, to uncouple the reinforcement of pain behaviors by medications. In general, patients in an MPC program do not derive adequate pain relief from analgesic medications, and thus, they are usually tapered by means of the pain cocktail technique. This technique is simply a method of converting all opioids to an equivalent dose of methadone and delivered with a masking vehicle. The dose is then tapered over the period of treatment, always with the full knowledge of the patient. Most medications are discontinued; the common exceptions are antidepressants, which often help chronic pain patients. Pain clinics discourage long-term use of other medications both because of their potential side effects and because their use undermines the philosophical concept that the patient must learn to control his or her pain and not depend on health care providers or their prescriptions.

Psychological strategies generally aim to alter behavior rather than change the patient's personality. Patients learn coping skills because this is frequently a deficiency that has led to the patient's many difficulties (Table 109-7). Couples therapy is sometimes appropriate. Issues that patients bring up receive attention in either the group format or in individual therapy, as needed. As depression is so often a component of the chronic pain problem, it warrants psychological as well as pharmacologic interventions. Psychologists provide relaxation and consolidation sessions that allow patients to work on newly acquired skills and explore educational topics and new psychological skills (Table 109-8).

Maintenance of gains	Program orientation
Making and using a coping plan	Purposes of group sessions
Relaxation training	Program goals
Physiology of stress	Goal setting
Quieting response	Focused breathing
Evaluation of use of coping plan	Hurt vs. harm
Preparing for new patients	Identifying gains
Time planning	Review of patient education materials

From Loeser JD, Egan KJ. Inpatient pain treatment program. In: Loeser JD, Egan KJ, eds. *Managing the chronic pain patient: theory and practice at the University of Washington Multidisciplinary Pain Center*. New York: Raven Press, 1989:41, with permission.

TABLE 109-7. Relaxation and consolidation topics

Pain mechanisms	Depression
Gate theory	Effects of exercise and inactivity
Headaches	Low back pain
Biomechanics	Role of surgery for pain
Drugs: use and abuse	Dealing with doctors
Workers' compensation	Program orientation
Former patient visit	Maintenance of gains
Acute versus chronic pain	Discharge planning
Healing and disuse	

From Loeser JD, Egan KJ. Inpatient pain treatment program. In: Loeser JD, Egan KJ, eds. *Managing the chronic pain patient: theory and practice at the University of Washington Multidisciplinary Pain Center*. New York: Raven Press, 1989:40, with permission.

TABLE 109-8. Patient education topics

Another important aspect of multidisciplinary pain management is education. This is an activity that is shared by physicians, psychologists, and nurses. Topics cover a wide array of the problems facing those who suffer from chronic pain. Subject selection and content is, to some degree, are functions of the needs of each group of

patients, but content always includes a core set of issues (Table 109-9).

Stress management	Assertiveness training
Relaxation training	Cognitive strategies
Coping skills	Communication skills
Anger management	Dealing with depression
Pain behaviors	Crisis management
Sleep disorders	Costs/meanings of pain
Physiology of stress	

From Loeser JD, Egan KJ. Inpatient pain treatment program. In: Loeser JD, Egan KJ, eds. *Managing the chronic pain patient: theory and practice at the University of Washington Multidisciplinary Pain Center*. New York: Raven Press, 1989:41, with permission.

TABLE 109-9. Topics for skills training

Team meetings occur daily to review any patient problems. Formal review of all patients takes place on a weekly basis. Communications with the patient's primary care providers, financial sponsors, compensation systems, and so forth are a major issue for such treatment programs and occupy a significant amount of professional time and effort. Numerous papers describe different treatment programs and their individual treatment strategies (12,16). The International Association for the Study of Pain, many national societies, and several medical specialties (17) have offered guidelines for multidisciplinary pain management facilities. These are all very general and do not specify any details of the components of a treatment program.

Variations around the themes described above continue to evolve, based on availability of resources, policies of major payers, theoretical constructs, and the preferences and biases of those who establish such treatment facilities. Our experiences at the University of Washington Multidisciplinary Pain Center and the University of Pittsburgh and observations made during our travels throughout the world suggest a set of broad principles, outlined in Table 109-10.

The single most important ingredient is the existence of health care providers who are willing to work together as a team. "The magic is in the interactions" has been an oft-repeated answer when I was asked to explain how we could successfully carry out such a treatment program.
The health care providers must care about chronic illness and not be totally locked into acute disease, as is fostered by the biomedical model.
The commitment of the provider to the patient is essential.
Patients must want to change their lives and must be willing to give the program a try.
They must recognize that in this type of treatment program, the patients do the therapeutic work.
The treatment is the start of a journey to reclaim one's life from the pain problem; long-term support is required to keep the patient on the road to recovery.
The attempt to treat the untreatable leads to demoralization of the treatment team. Patients must be properly selected.

TABLE 109-10. Principles of multidisciplinary pain management

An important issue is the maintenance of gains that have occurred during the treatment program. Surrounded by a team of supportive health care providers and other patients, most patients see some gains by the end of treatment. However, many are unable to maintain their gains when they return to their normal family and occupational activities. In the closing days of a treatment program, each patient must learn strategies for maintaining his or her gains in a less supportive environment. Most programs have established brief follow-up interactions to try to assist patients in keeping up their physical and psychological skills and preventing relapses.

Every year since the mid-1980s the University of Washington Multidisciplinary Pain Center and the University of Pittsburgh Pain Evaluation and Treatment Institute have received visits from health care professionals who wish to learn the “magic” of our treatment programs. They are certain that our providers know some tricks and have original techniques to cure pain patients. The “magic” that such programs possess, of course, is simply the interactions between providers and patients. All of the providers are of equal standing and earned respect for their activities in the pain treatment program. The team presents a unified front to each patient. Effective leadership, consistency of treatment philosophy and implementation, dedicated providers, and the realization that the whole is greater than the sum of its parts all contribute to our success (12,18).

OUTCOMES

Given constraints on health care resources, there is a growing interest in accountability and evidence-based treatment outcome data. All components of health care delivery are under scrutiny to determine whether they are not only clinically effective but also cost-effective. The effectiveness of pain treatment facilities and, in particular, multidisciplinary pain rehabilitation treatment has been debated and singled out by some third-party payers for special criticism (19). Often the debates have centered around anecdotal information and hearsay. Surprisingly, the dialogue largely ignores the growing body of outcomes research published over the past quarter century. Referring physicians and third-party payers tend to rely on salient cases, usually failures, treating them as representative and relying on them as the basis for criticizing pain centers. Conversely, pain centers often respond based on their clinical experience and the recall of particular successes that are viewed as representative of the outcomes from their facility, rather than systematically collected empirical data. The battles are taking place on the wrong fields.

To many third-party payers, the term *multidisciplinary pain center* is often synonymous with *expensive*. It is true that treatment at an MPC can be expensive. Involvement of multiple disciplines is labor intensive and costly, because each of the clinicians involved in treatment receives payment for the services provided. Based on a survey of pain treatment facilities conducted in 1995, Marketdata Enterprises (20) concluded that the average cost of treatment at an MPC was $8,100. Estimates tally over 3,300 pain treatment facilities and solo pain-treatment practitioners in the United States (20). The American Pain Society (21) has compiled detailed information on 352 MPCs. Based on the Marketdata survey, it appears that approximately 2.9 million Americans (0.11% of the population) are treated for chronic pain each year with only about 176,850 (6%) of these treated at MPCs. Over 60% of these treated patients had their backs as the primary location of their pain. Research indicates that an average back pain patient treated at an MPC has had 1.7 surgeries prior to treatment (11). Extrapolating from these numbers, 106,111 back pain patients (60% of the total) with 1.7 prior surgeries are treated at MPCs each year.

Several epidemiologic studies have examined the characteristics of patients treated at MPCs as compared to patients with chronic pain not treated at these facilities (9,10,22). The patients treated at MPCs had reports of constant pain, high levels of emotional distress, work- related injuries, significantly lower levels of education, high levels of health care utilization, and high levels of opioids, high levels of functional impairment, and negative attitudes about the future. Furthermore, the average duration of pain for patients treated at MPCs is over 7 years (11). Weir et al. (23) concluded that the “picture that emerges is one of a pain clinic patient who is isolated from meaningful relationships, whose pain interferes with all aspects of his life, who has lost his energy and determination, is unemployed, is in constant pain and experiences the threat, loss and harm of his pain problem” (p. 1413). Furthermore, these patients are refractory to other types of treatment regimens, including surgery. Given these characteristics, it seems reasonable to assume that chronic pain patients for whom MPCs provide services have the most recalcitrant problems and are resistant to improve. As we examine the question of the effectiveness of MPCs, it is important to keep these patient characteristics in mind.

Using the Marketdata Enterprises survey data (20), we can estimate that the cost of treating chronic pain patients at MPCs is over $1.5 billion per year (average cost of treatment $8,100 × 176,850 patients treated). This figure confirms that treatment at an MPC can be expensive. To put these costs in perspective, consider that the annual costs for treatment of chronic pain in general is very high. Frymoyer and Durett (24) estimated that back pain cost $33.6 billion for medical payments, $11 to $43 billion for disability compensation, $4.6 billion for lost productivity, and $5 billion in legal services. In one study, the average cost of nonsurgical health care in the

year prior to treatment of patients at MPCs was over $13,284 (25). We can again apply this average cost to the estimated 176,850 patients treated at MPCs (20) and estimate that the nonsurgical expenditures in health care for these patients would exceed $3 billion. Thus, total expenses for surgical and nonsurgical health care costs for a cohort of patients prior to their treatment at MPCs would be in excess of $4.5 billion. This figure omits inflationary increases in health care in the United States in the past 5 years.

Returning to the data cited regarding the primary location of pain (60% with back) and the number of surgeries (1.7), we suggest that patients treated at MPCs each year have had 106,111 operations on their backs. Assuming $15,000 per surgery (24), the cost of back operations for one cohort of patients treated at MPCs would be in excess of $1.6 billion. Consider that, when evaluating the effectiveness of treatment at MPCs, a substantial proportion of the patients are surgical failures.

The cost of multidisciplinary treatment compared with the alternatives merits attention. Approximately 250,000 lumbar surgeries are performed for pain each year at an estimated cost of $15,000 per operation. Using these figures, the cost of lumbar surgery for back pain alone is over $3.5 billion each year. Although there is no question that the cost of treatment for chronic pain is high, the cost of treatment at an MPC is comparatively low.

Asking whether MPCs are effective, however, may be an unsuitable way to phrase the question of whether they are worthwhile. It might be more appropriate to broaden the question to ask how effective are pain treatment facilities *compared to alternative treatments* and *on what outcome criteria*. That is, in the example of back pain, one might ask how effective are pain treatment facilities compared to alternatives such as surgery on measures such as reduction in pain, reduction in medication and health care utilization, increased physical activity, closure of disability claims, and return to work.

Numerous reviews and several metaanalyses on treatment outcome studies have evaluated the clinical and cost-effectiveness of MPCs (11,26,27). There is an array of outcomes reports for multidisciplinary pain treatment programs (28,29,30,31 and 32). Not all clinics have the same patient mix, and not all treatment programs are as potent as others. There are far too many publications about MPCs to review each one independently and to comment on its strengths and weaknesses. Despite the recalcitrance of the pain problems of the patients treated, they generally support the efficacy of MPCs on multiple outcome criteria (11,26,27,33).

Criteria of Treatment Success

Chronic pain conditions present not a single but multiple problem areas. Thus, the evaluation of treatment effectiveness must target several criteria. Among the most important criteria are (a) pain reduction, (b) iatrogenic complications, (c) reduction or elimination of inappropriate opioid medication, (d) health care utilization, (e) increase in activity, (f) return to work, and (g) closure of disability claims.

The importance of these criteria varies depending on who asks the question. For example, whether a patient resumes gainful employment may be the most significant outcome criterion for a workers' compensation carrier, and pain reduction may be of only limited consequence. A managed care organization may view use of the health care system as the most important outcome, caring less about patients' employment status. Referring physicians, in contrast to some patients, may be most concerned about reduction in opioid medication (34).

Pain Reduction

Pain reduction is perhaps the most common criterion measure of outcome in various treatment approaches for pain problems. Pain reduction following treatment at MPCs ranges from 20% to 40% (11). Studies investigating the long-term maintenance of pain reduction for MPCs have generally reported that pain reductions observed at discharge tend to be maintained at follow-up of up to 2 years (16).

On the other hand, pain reduction following conventional medical and surgical treatments is discouraging. For example, Dvorak and colleagues (35) studied 575 patients who were operated on for lumber disk herniation and concluded that 70% continued to complain of back pain 4 to 17 years after surgery. Lehmann et al. (36) showed similar results with follow-up of patients who had undergone spinal fusions for back pain, with 57% continuing to have back pain during the previous year. In another study, North et al. (37) noted that 66% of the patients who underwent repeated surgeries for back pain continued to experience pain symptoms 5 years after the surgeries.

Spinal surgery is not the only set of operative procedures that have been proven to be less than optimal in alleviating pain. Seres (38) noted that deep brain stimulation achieved some pain relief for only around 30% of chronic pain patients. In a direct comparison, Gallon (39) showed that only 17% of the surgical patients viewed themselves as improved compared to 38% of nonsurgically treated patients. Thus, the results for different surgical procedures seem at best comparable and at times not as good as the results for MPCs in reducing pain (11). However, when it comes to pain reduction, *per se*, the effectiveness of both surgery and treatment at an MPC is rather modest. Complete elimination of pain seems the exception rather than the rule for most treatments.

Iatrogenic Complications

In evaluating any treatment, the prevalence of iatrogenic complications is important because these can greatly increase costs as well as contribute to disability. Dzioba and Doxey (40) examined the outcome of 116 occupationally injured lumbar back surgery patients and found that over 43% had poor results. Surgical procedures themselves sometimes cause additional problems that may require repeat surgery. In a series of 78 surgical patients, Long et al. (41) observed that 11.6% developed serious complications from the procedure. Furthermore, of all the operations performed, 56% were necessary to correct a complication from a previous surgery. Gallon (39) reported that a significantly higher proportion of chronic low back pain patients who had surgery (58%) described themselves as worse on a measure of disability when compared to conventionally treated patients (30%). Repeated surgery, however, may not resolve the problem. The Workers' Compensation Board of Ontario, Canada, estimated that after a second back operation, 20% worsen, 60% stay the same, 20% improve, but no one is cured (42). In contrast to surgery, MPCs rarely report any significant iatrogenic problems following treatment.

Elimination or Reduction of Opioid Medication

A national survey of opioid prescribing practice suggests that the long-term use of opioid medications for chronic noncancer pain is relatively common (43). However, the appropriateness of such practice is embroiled in debate because adverse side effects, such as physical and psychological dependency, have been observed in up to 66% of chronic noncancer pain patients (migraine patients) treated with opioids (44). For a review of these studies, see reference 45. One trial of long-term opioids for geriatric pain patients was terminated early because of the significant side effects reported by patients (46).

Flor et al. (11) found that over 50% of patients treated at MPCs were taking opioid medication on admission. Yet despite taking opioids, these patients were referred for treatment at MPCs for their intractable pain. Because of potentially detrimental effects of opioids and attempts to encourage self-initiated pain management, elimination or reduction of opioid intake is an important part of most multidisciplinary treatment programs.

In general, MPCs appear to be effective in eliminating or greatly reducing opioid intake in chronic pain patients. Studies report that up to 100% of patients decrease opioid use by the time of treatment termination at MPCs (11). Maintaining opioid-free status after multidisciplinary treatment also seems promising: Over 65% of treated patients remain opioid-free at 1-year follow-up (32,38).

The figures on reduction of opioids are particularly impressive because they are concurrent with a statistically significant reduction of pain. In contrast, the prevalence of opioid intake seems to remain approximately at the same level when patients received conventional pain treatment (11). In one surgical study, Lehmann et al. (36) noted that 53% of patients who had spinal fusions to eliminate back pain continued to take analgesic medication after the procedure.

Utilization of the Health Care System

Utilization of the health care system is of particular interest because it demonstrates one of the major areas of economic impact of chronic pain problems. MPCs effectively reduce utilization of the health care system following treatment. In these studies (32,38), 62% to 90% of patients did not seek any additional treatment for their pain during a 3- to 12-month posttreatment period. Caudill et al. (28) reported that of 109 patients who were treated at an MPC conducted within the context of a health maintenance organization reduced their pain-related clinic visits by 36% during the first year after MPC treatment. Compared to conventionally treated patients (i.e., medication and/or surgery), MPCs consistently show superior rates of reduced health care utilization (6,7). Several studies directly compared the outcomes for MPCs and conventional treatments on the number of additional surgeries and hospitalizations (47,48,49 and 50). The findings seem consistently to demonstrate that

MPC treatment reduces subsequent health care utilization significantly more than conventional treatment for chronic pain (Fig. 109-2).

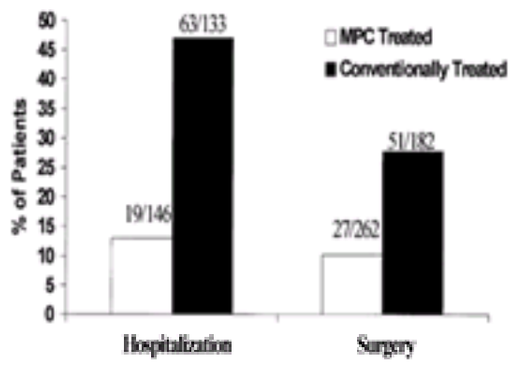

Figure 109-2. Frequency of patients receiving additional surgery and hospitalization following treatment: comparisons between multidisciplinary pain center (MPC) and conventional treatments.

On the other hand, invasive medical procedures may result in undesirable complications, thereby increasing the subsequent use of the health care system. Lehmann et al. (36) reported that 15% of patients who had undergone spinal fusion for back pain required repeated surgery. Earlier, we noted the Long et al. (41) observation that 56% of the surgeries performed were conducted to remedy complications from a previous surgery. Thus, in addition to the surgeries performed, over 50% of operated-on patients are likely to require yet another surgery.

Increase in Activity

Increase in activity and functional restoration are central goals of multidisciplinary pain treatment. According to the quantitative review of outcome studies (11), substantially greater increases in activity level occurred in patients treated at MPCs (65%) compared to conventionally treated patients (35%).

When studies have examined the effects of surgical treatment on patients' activity levels, the results are far from satisfactory. In general, most studies report no change in patients' ability to engage in functional activities such as ability to walk, go up stairs, sleep, or drive following surgery (37).

Return to Work

Although return to work is an important outcome as it has significant socioeconomic implications, several factors impede patients' return to work, aside from their pain. Return to gainful employment for chronic pain patients depends on factors such as local economy, job availability, and the aggressiveness of case managers. Most chronic pain patients have been off work for a substantial period. As noted, the average time off from work is over 7 years (11). Skills that were useful prior to the pain onset may be outdated, making patients less marketable. Some employers may be unwilling to hire someone with a history of back pain, especially if a job requires a significant amount of physical exertion and there is no way to make reasonable accommodations for the physical demands of the job. Denial of continuing disability may lead some patients to return to work even when they are significantly impaired.

Despite these constraints, multidisciplinary pain treatment returns a significant percentage of patients to gainful employment, as numerous studies show. The results of 11 studies with 259 conventionally treated and 435 MPC-treated patients indicate that the rate of returning to work among treated patients is substantially higher (67%) when compared to the rate among the untreated patients (24%) (16). Reviewing the literature, Flor et al. (11) and Cutler et al. (26) arrived at similar figures, suggesting that heterogeneous groups of patients treated at MPCs were twice as likely to return to work as conventionally treated patients.

Most of the published studies on return to work following treatment at MPCs have included patients with diverse pain syndromes. Chronic back pain is a particularly difficult problem to treat, with the odds of returning to work following a conventionally treated back injury of at least 3 months quite poor (51). In light of this statistic, such patients should be less likely to benefit from treatment at MPCs. Feuerstein et al. (52) specifically looked at return to work for chronic back pain patients treated at MPCs and, based on 11 published studies, reported that 71% of MPC-treated patients returned to work, compared to 44% of conventionally treated patients. Thus, even for the difficult problem of chronic back pain, MPCs appear to do remarkably well in returning people to work.

It is useful to compare the return-to-work rates for back pain patients between multidisciplinary and surgically treated patients. In an early study, Beals and Hickman (53) reported that only 36% of industrially injured patients receiving surgery for back pain returned to productive labor following surgery. Wiesel et al. (54) noted that approximately 50% of surgically treated patients returned to gainful employment following surgery. More recently, North et al. (37) reported that only 25% of patients who had spinal cord stimulators surgically implanted returned to work. Even more abysmal outcomes were reported in a study conducted in Belgium, in which only seven of 145 (5%) pain patients implanted with spinal cord stimulators had returned to work 1 year following the surgery (55).

The results of studies of back pain patients treated at MPCs suggest that these facilities return anywhere from 50% to 150% more patients to work than does surgery. These results are even more impressive when we note that the typical patient treated at an MPC has already undergone surgery (11); thus, patients treated at MPCs are often surgical nonresponders.

A word of caution is in order concerning the use of return to work as an outcome criterion. The figures presented do not account for recurrences in symptoms or disability after an initial return to work. Recurrence is a commonly observed phenomenon for those with musculoskeletal injuries. Bergquist-Ullman and Larsson (56) and Biering-Sorenson (57) reported 1-year recurrence rates of over 60% for back pain patients. More recently, Crook and Moldofsky (58) observed a 43% recurrence for a sample of workers' compensation patients with musculoskeletal injuries.

Closure of Disability Claims

Chronic pain is costly to society due to loss of productivity and disability payments to patients. A handful of studies examined the success in closure of disability claims. For example, Seres and Newman (31) reported that within 3 months after discharge, closure of the claims was recommended for 75% of the cases. Painter et al. (59) followed patients for a longer period and reported that the proportion of the patients receiving compensation declined from 70% at admission to 45% at 2-year follow-up. Focusing specifically on workers' compensation patients, Fey et al. (60) observed that at 2- to 3-year follow-up, 89% of the cases were closed. In one study of litigation status, it was reported that 86% of the litigation cases were resolved within 1 year after discharge (61).

Cost-Effectiveness of Multidisciplinary Pain Centers

Although the results reported for MPCs suggest that these facilities are clinically effective, one must also ask whether they are cost-effective. We can examine cost-effectiveness by considering data on savings in health care utilization and closure of disability claims and subtracting the cost of treatment at the pain facility.

Savings in Health Care Utilization

The impressive reductions in health care utilization reviewed above translate readily into monetary figures. Simmons et al. (25) reported a 62% reduction of medical costs as a result of treatment in an MPC. They noted that the costs for medical treatment of their patients in the year prior to treatment averaged $13,284 ($34,794 corrected for inflation) and in the year after MPC treatment averaged $5,596 ($15,303 corrected for inflation), resulting in a total savings of $123,000 ($299,485 corrected for inflation) in medical costs for 16 patients (savings of $18,718 per patient corrected for inflation). If we extrapolate the savings reported by Simmons et al. to the 2,318 patients successfully treated in MPCs reported in the Flor and associates' (11) metaanalysis, a savings of over $43 million in medical expenses accrue in the first year following treatment. If we further assume that the average cost of pain clinic treatment is $8,100, then treating the entire set of pain patients cited in Flor et al. (3,089) would cost approximately $25 million (correcting for inflation). This would result in a net saving in medical expenses alone during the first year of $18 million. These figures are only for the first year's medical expenses and do not consider savings in reduced disability payments, gains in productivity, and gains in

revenue from taxes paid by successfully treated patients.

Based on Simmons and associates' (25) data, we estimated a first year savings of $18,718 in medical expenditures. Subtracting the cost of the multidisciplinary treatment, $8,100, yields an average savings in medical expenditures of $10,618 per patient for the first year. Using the figure of 176,000 patients treated at MPCs (11), we estimate that the medical cost savings during the first year following treatment at an MPC of over $1.87 billion. The savings are likely to continue in subsequent years. Bell et al. (62) estimate the annual medical costs for failed back syndrome patients to be $12,900 (including hospitalization, physician visits, medications, alternative therapies, diagnostic procedures, rehabilitation, and other therapies). Note that this is only about one-half (inflation corrected) of that reported by Simmons et al. (25). Using the figure of 68% reduction in health care costs in the year following treatment at an MPC reported by Simmons et al., we estimate that the cost savings for health care expenditures in years subsequent to the first year following treatment at $8,772 per treated patient per year. Again using Marketdata Enterprises' (20) estimate of the number of treated patients at MPCs of 176,850, the annual savings in health care expenditures would be over $1.5 billion. The average age of patients treated at MPCs is 45 (11), and assuming a mean life expectancy of 75 we estimate $45 billion in savings in health care expenditures (without correcting for inflation rates during those 30 years).

Stieg and Turk (63) pointed out the impressive figure of $250,000 (over $350,000 in 1998 dollars) as the cost for each compensation-covered worker with a back injury on the job lost to permanent disability. In their metaanalysis, Flor et al. (11) reported that, of the 50% of patients treated at MPCs who were receiving financial compensation at admission, an average of 43% returned to work following treatment. Thus, a substantial percentage of patients with long-standing disability can return to work following treatment at an MPC.

Savings in Disability Compensation

We can extrapolate from the 3,089 patients included in the Flor et al. (11) metaanalysis. From this sample, 1,544 were off work and receiving disability compensation. Following treatment, 664 (43%) returned to work. If $350,000 was saved in disability for each of these patients, the net savings in disability would exceed $2 billion. Of course we could carry this extrapolation forward to the approximately 176,850 patients treated in rehabilitation programs at MPCs each year in the United States. In this example, the savings would amount to over *$13 trillion* (176,000/2 × 0.43 × $350,000) for a 1-year cohort of treated patients!

In the past, patients who have been referred to MPCs consisted of those who did not respond to conservative treatment measures and surgical interventions. Thus, the “easiest” problems had already been solved. This selection process results in the bias that those who are referred to MPCs have the most refractory problems. In addition to the pain syndrome, these patients have concomitant medication dependency problems, emotional disturbance, and general life disruptions. Moreover, the mean duration of pain in pain clinics is over 7 years. The cost-saving potential of MPCs, therefore, is quite telling.

Systematic comparisons of the cost-effectiveness across different modalities need a common index. The index of cost-effectiveness can be defined as:

$$\text{Cost-Effectiveness Index} = \frac{\text{Improvement}}{\text{Cost of Treatment}} \times 100$$

One can compare the cost-effectiveness of MPCs with alternative interventions when comparable outcome data are available. Turk and Stacey (16) reported that rate of return to work for MPC patients was 67% compared to 24% for conventionally treated patients. For surgically treated patients, the average of two studies is 43% (53,54). Treatment costs for MPC, conservative, and surgical treatments are estimated as $8,100 (20), $26,000 (64), and $15,000 (24), respectively. Using the return-to-work rate as the improvement score, we report the cost-effective index score for each treatment modality in Figure 109-3. The cost-effective index score of the multidisciplinary pain treatment far exceeds surgical and medical treatments. Indeed, based on the index scores, multidisciplinary treatment can be considered nine times as cost-effective as conservative treatment and 3.6 times as cost-effective as surgical treatment in helping patients return to work.

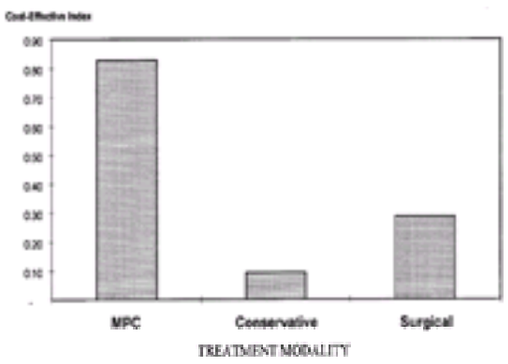

Figure 109-3. Cost-effective index by treatment modalities. (MPC, multidisciplinary pain center.) (From Turk DC, Okifuji A. Treatment of chronic pain patients: clinical outcomes, cost-effectiveness and cost-benefits of multidisciplinary pain centers. *Crit Rev Phys Med Rehabil* 1998;10:181– 208, with permission.)

Flor et al. (11) concluded that “[o]verall . . . multidisciplinary pain clinics are efficacious. Even at long-term follow-up, patients who are treated in such a setting are functioning better than 75% of a sample that is either untreated or that has been treated by conventional, unimodal treatment approaches” (p. 226). Based on calculations using published data, Turk and Okifuji (6,7) estimated that the cost of returning one patient to work following treatment at an MPC was approximately $15,000 compared to $320,000 to return one patient to work following lumbar surgery. Thus, multidisciplinary pain treatment programs are 21 times more effective than surgery in returning patients to gainful employment. Okifuji and colleagues (65) extrapolated from available data reported in the Flor et al. (11) metaanalysis of 3,089 patients and estimated a savings of $280 million from savings in medical and surgical expenditures and disability compensation for these patients. In this light, the success rate is very impressive.

CONCLUSIONS

The team approach to complex chronic pain patients as found in a multidisciplinary pain treatment facility has evolved with an underlying set of principles. These include the recognition that cartesian mind-body dualism is a curse on effective health care. Second, a biopsychosocial model is required to capture all of the relevant factors. Third, the treatment must address the pain itself and not just be a search for hidden causes and specific remedies for these causes. Fourth, the treatment must address the restoration of well- being and not just the alleviation of symptoms. Finally, the illness is not just chronic pain but is also the failure to work, often ascribed erroneously to the pain instead of the patient or the patient's circumstances.

Pain is not a monolithic entity such as a fracture or deficiency of some essential nutrient. Rather, pain is a concept used to focus and label a group of behaviors, thoughts, and emotions. Pain has many dimensions, including sensory and affective components, location, intensity, time course, and the memories, meaning, and anticipated consequences that it elicits. Since there are many facets to pain, no single outcome measure captures all of the relevant issues. Thus, outcomes assessment must look at a variety of criteria to adequately describe the effects of any treatment. Furthermore, the dissociation of specific effects of a treatment from nonspecific treatment effects or the natural history of the disease process requires prospective, randomized clinical trials (see Chapter 82). Such studies have examined patients who have chronic pain.

We suggest that simply asking whether MPCs are effective is not the appropriate question. Rather, we believe that it is important to focus on the results for a set of outcomes and to compare these results to alternative treatments. From our analysis, we believe we can answer the questions posed by stating that a substantial body of literature supports the assertion that multidisciplinary pain treatment is effective in reducing pain, the use of opioid medication, and the use of health care services; it increases activity, returns people to work, and aids in the closing of disability claims. Moreover, treatment at MPCs targets patients with the most recalcitrant problems, yet the benefits appear to exceed those for conventional treatments including surgery and, in contrast to surgery, there are no known iatrogenic complications of treatment at MPCs. Not only do MPCs appear to be clinically effective, they also appear to be cost-effective, with the potential to provide substantial savings in health care and disability payments.

Ironically, the best outcomes data in terms of clinical trials and the widest array of predictive variables occur with multidisciplinary pain management. It should become the gold standard against which all other treatments for chronic pain are measured. The treatment principles developed in MPCs should be applied much earlier in the career of chronic pain patients; prevention is always better than remediation. Even for patients who have been disabled for prolonged periods, multidisciplinary pain management can offer restoration to a normal lifestyle.

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CHAPTER 110

Building the Future

C. Richard Chapman, John D. Loeser, and Dennis C. Turk

Dr. John Bonica wrote the first edition of this book in the 1950s, when anesthesiology was a young specialty and very little organized knowledge existed on the subject of pain. Defining the scope of the book largely from clinical experience, he combed the limited literature of the day for evidence, opinions, and techniques. The end product of his work was a compendium of knowledge about pain—nearly everything that medicine knew about pain to that date. Although Bonica could not have foreseen the splendid progress that medical science would make in the second half of the twentieth century, he produced a book that became a milestone for progress in medicine. It defined pain as a field of scientific inquiry and clinical care, and thus changed the lives of countless patients around the world.

In the decades that followed publication of the first edition, neuroscientists uncovered nociceptors, nociceptive-specific pathways in the spinal cord, and the processes of peripheral and central sensitization. The gate-control theory introduced the idea of descending modulatory processes. Multiple discoveries uncovered new ideas of endogenous modulation: neuropeptides, stress- produced analgesia, stimulation-produced analgesia. The discovery of opioid receptors led to an understanding of how opioids mimic endogenous peptides in the central nervous system. Work on arachidonic acid and the prostaglandin pathway solved the long-standing mystery of how aspirin relieves pain and opened the door to new advances in the control of pain related to inflammation.

In the 1990s, research on functional brain imaging during the experience of pain demonstrated that what we call *pain* involves massive, distributed processing in limbic structures as well as somatosensory pathways. This work supported one of Bonica's basic principles: Pain is not a simple signal of tissue trauma traveling along specific pathways in the nervous system, but rather a complex sensory and emotional experience. Psychologists gained a basis for arguing that pain is a subjective phenomenon constructed within the brain and embedded in the context of ongoing cognitive activity and the social environment specific to the person.

Progress in the psychological study of pain showed that the experience of pain is not simply a primitive warning signal that the mind detects and appreciates. Awareness of injury and anguish both depend heavily on what people expect or think about themselves, the meaning of the symptom, the immediate situation, the treatment, and the implications for the future. Early on, psychologists introduced the important distinction between pain as a private experience and pain behavior. This helped physicians understand that the clinical presentation of pain is not necessarily an accurate rendering of nociceptive activity in the patient's nervous system. Further development of the psychology of pain has helped elucidate the powerful role that psychological factors play in the transition from acute to chronic pain, in the response to interventions aimed at relieving pain, in the disability associated with chronic pain, and in the success of rehabilitation in patients with chronic pain.

This edition of *Management of Pain* is a resource for a new century—a century in which the rate of technological progress in medicine and related fields almost certainly will be unprecedented and exponential. Advances in genetics, molecular biology, immunology, neuroscience, and many other technologically sophisticated areas are already staggering. As scientific achievement moves forward on multiple fronts, it will open opportunities for medicine that even the best science fiction writers of our time cannot imagine. What, if anything, will technological advances in genetics and other areas mean for the field of pain? What advances will occur in the field of pain itself? What control can we exert today on the kinds and quality of developments that will define the field of pain medicine in the years to come?

The purposes of this chapter are to (a) consider pain in light of ongoing evolution in medicine and related sciences, (b) examine the conceptual bases of the field that define how we assess patients with pain, (c) choose interventions and evaluate outcomes, and (d) forecast progress in both the scientific understanding of pain and clinical practice issues. Unlike the chapters that precede it, this chapter emphasizes time. Borrowing a distinction from Greek, we concern ourselves less with time as *chronos* than with time as *kairos*. *Chronos* is time as we measure it with watches and calendars; *kairos* refers to an opportune time, the right time, the time to act on an opportunity. *Kairos* is important because the values we emphasize today, the choices we make, the interventions we introduce or favor, and our vision of treatment outcomes all have long-range consequences. The roots of the future lie in the present. We should pay close attention to the future consequences of our current choices and actions. The dramatic impact that Bonica had on medicine in the last half of the twentieth century stemmed directly from the groundwork he laid in the first edition of this book. In this chapter, we explore the opportunities that our generation of pain clinicians and scientists has for shaping the future.

EVOLUTION IN MEDICAL SCIENCE AND PRACTICE

Scientists who gather facts would like to believe that accumulation of facts is synonymous with understanding and that scientific understanding is fundamental and immutable. Clinicians, similarly, like to think of medicine as practice based on a growing body of stable evidence. Unfortunately, humans are more complex and dynamic. Medicine is a part of society, and society evolves continuously. Continual changes in ethics and values, economics, technology, knowledge, and their interactions provide an ever- changing context for what we call *facts*. The ongoing processes of self-organization that govern all of nature affect medicine as well.

Ideally, scientific evidence should govern practice. Figure 110-1, however, illustrates some of the forces that shape the practice of medicine. When the acquired immunodeficiency syndrome emerged during the 1980s, it quickly became obvious that social issues can greatly affect the allocation of resources and priorities in medicine. During the 1990s in the United States, economic forces exerted enormous influence on the practice of medicine, imposing significant change and disruption in practice patterns. As the diagram in Figure 110-1 indicates, the factors that govern change in medical practice also influence one another. Day-to-day medical practice takes place in a complex and dynamic social context.

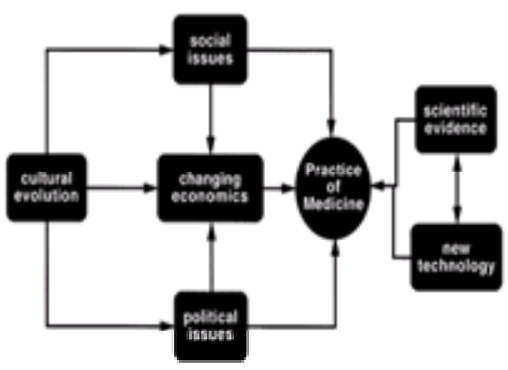

Figure 110-1. Forces that shape the practice of medicine.

The social evolution framework offers a useful perspective for considering the future of pain management in medicine. The principles of evolution apply as readily to social entities like pain management in medicine as they do to biological entities such as animals surviving in the wild. Darwinian theory indicates that the survival of an organism depends on successful adaptation, and social evolutionists find clear parallels in social and cultural entities. Dawkins (1) and others (2,3,4 and 5) have applied this reasoning to social constructions and ideas, like those that govern the practice of medicine. They have introduced the field of *memetics*: the study of ideas and concepts viewed as living organisms, capable of evolution and reproduction in the collective of social intelligence. Memetics is based on an evolutionary model of social information transmission. A *meme* (which rhymes with theme) is an information pattern, held in one person's memory, that can be copied to another person's memory. Put another way, a meme is a cognitive or behavioral pattern that one individual can transmit to another. In describing memes, Brodie (5) said

> Memes are to a human's behavior what our genes are to our bodies: internal representations of knowledge that result in outward effects upon the world. . . . Memes are hidden, internal representations of knowledge that result, again along with environmental influence, in external behavior and the production of cultural artifacts.

There are many ways to transmit a meme, including scientific publication (6), but the primary mechanism for such transmission is simple imitation, according to Blackmore (7). Her model seems to fit the memes that govern everyday medical practice. For example, the principles for when to prescribe and when to withhold opioid medication from a cancer patient constitute a meme. We strive to make this an evidence-based decision rule, but in everyday practice, it is something that young physicians generally learn by imitating older role models in day-to-day practice. The belief that surgery is the best treatment for low back pain is also a meme.

Late in the 1990s in the United States, a new meme emerged among pain physicians: off-label use of gabapentin to control neuropathic pain. Despite a paucity of scientific evidence, pain physicians began prescribing gabapentin for virtually every intractable pain on a trial-and-error basis. This pattern, which one can observe again and again in all areas of medicine, illustrates the spread of a meme by imitation. Carr and Cousins (6) recognized the potential importance of the memetics framework for pain management. Although they discussed scientific publication as a vehicle for memetic replication rather than imitation, they usefully described the replication of a new meme as occurring at an exponential rate, up to the maximum level that the environment will sustain. This produces the familiar S-shaped curve. The gabapentin fad nicely fits this pattern. Of course, rapid replication does not ensure survival of the meme, but it does affect the social climate of practice.

Memetics views ideas and practices as units of cultural information that fail or survive across generations in a Darwinian social environment. It parallels contemporary biology, which tends to view life as the propagation of genetic information: Evolution promotes the selective survival, generation after generation, of some part of that information. When an idea survives because people pass it on to other people, it qualifies as a meme. Memeticists emphasize that a meme resembles a gene rather than a message in that the transmission is a replication: The person who transmitted the meme continues to carry it. Memes are replicators: They are to society what genes are to biology. They are mechanisms of both social stability and adaptational social change.

Memetics, then, is a young theoretical and empirical approach to studying the replication, spread, and evolution of memes. It can account for the spread of ideas and practices, resistance to change, and causal influences in general. Clearly, the transmission of myths and values across generations through storytelling played an essential role in the survival and evolution of preliterate human societies. The transmission of memes is no less important today, but the ways in which we transmit memes and the strategies that memes seemingly employ to adapt and survive are much more complicated.

Just as evolutionary theorists can account for disease due to microbial organisms, memeticists can account for destructive social forces. Some writers have used memetics to introduce the concept of information disease. A meme can adapt and survive in human culture as a pathogen that threatens the survival of other memes just as microorganisms can cause biological disease (5). Misinformation, biases, and prejudices replicate and fight for survival just as effectively as ideas and beliefs based in scientific evidence. Memes that act against the good of society as a whole and the individuals who transmit them are pathogens that constitute thought contagion.

The emerging field of memetics has important implications for medicine, which, after all, is a form of social organization. We may wish to believe that ideas and practices survive in medicine because they are true (i.e., they have support in valid evidence), but the memeticist insists that memes will survive in any way that they can. Just as some organisms manage to evolve devious and seemingly ingenious ways of surviving in a hostile environment (e.g., deception, symbiosis), memes find surreptitious ways of adapting and propagating themselves within medicine. Having a body of supporting scientific evidence, as Carr and Cousins (6) describe, definitely confers an advantage on a meme for survival in medicine, but clever memes (including the pathogens) can find many other ways to survive.

Consider, for example, the belief that administering opioid drugs to cancer patients will cause addiction. Extensive evidence indicates that this is incorrect, and multiple policy statements speak against it (see Chapter 36 and Chapter 84). Yet this meme continues to thrive. One of its strategies is clever use of public media. Newspapers and television inform the public that some celebrity has become addicted to pain killers, occasionally celebrities make public statements about their addiction to pain killers, and now and again one of them dies from an overdose or an accident, again allegedly due to inadvertent addiction to pain medication. No expert ever validates such claims of addiction, and no one ever questions their validity: Such assertions are generally false or badly distorted. The impressions that such claims make on health care providers and patients alike is far more powerful than the evidence that science and sound policy accumulate. The memeticist would emphasize that the “pain medication causes addiction” pathogen will readily stoop to deceit or other tricks to ensure its survival. Its only natural enemy is evidence, and evidence lives only in the environment of science.

In this and other ways, memetics helps us to see the complexity of the challenges we face in our attempts to improve pain management. In the sections that follow, we apply memetics in an attempt to examine the present and the constraints that the past has imposed on it, and we use this framework to envision the future. We suggest that awareness and strategic use of memes may provide pain management specialists a way of exerting control in the social evolution that lies ahead.

CONCEPTUAL BASICS AND EVOLUTION IN PAIN MEDICINE

Our ability to advance the field effectively depends not only on discovery and the introduction and adaptation of new memes but also on our ability to identify and control meme pathogens, both new and old. In this section we consider three basic memes: mind-body medicine, the concept of pain, and the concept of interdisciplinary management. The notion of mind-body interactions has achieved current popularity, but it derives from Cartesian dualism and it is the Cartesian meme in thin disguise. As the contributions to this volume indicate in multiple areas, the constraints of dualism are a major threat to progress in pain management. In contrast, the concept of pain is a meme that must continually adapt to a changing base of evidence in neuroscience, behavioral science, cognitive science, and other areas. Failure to evolve the concept and to integrate it with progress elsewhere in medicine and science will retard the field's future growth and compromise its viability. Finally, the relatively new concept of interdisciplinary pain management has benefited patients and medicine alike, but whether it can survive in a harsh economic climate is far from certain. We discuss these three concerns within the memetic framework.

Mind-Body Medicine

Books and journal articles too numerous to count proclaim the importance of mind-body awareness in medical practice [see, e.g., the journal *Advances in Mind-Body Medicine* published by Harcourt Health Sciences, Chopra (8), or the nonprofit foundation, *The Center for Mind-Body Medicine*, located in Washington, D.C.]. Continuing medical education programs celebrate this theme, and the National Institutes of Health in the United States offer program grants based on the mind-body relationship. That the mind can affect the body in astonishing ways seems to be a truth that medicine regularly rediscovers. Dualism, which nearly everyone rejects on a conceptual basis, survives and thrives for many reasons. Perhaps the chief reason is that it offers a very convenient conceptual basis for describing experiences such as pain.

The distinction between mind and body originated with the ancient Greeks, but it took root in Western medicine because of Descartes' early theories (see Chapter 1). For Descartes, the body functioned as a machine, and the mind, an essentially independent entity, resided and presided in the brain. The Cartesian homunculus experienced pain as the delivery of injury signals from a mechanical and otherwise passive nervous system. As an independent entity, it decided what to make of those signals. Dennett (9) described the Descartes' mind as the “Cartesian theatre.”

Today we know that the brain is the organ of awareness and of behavior. There is no homunculus or other brain center of awareness and executive control that houses an independent mind. The so-called mind is an emergent property of the brain and its intrinsic properties of self-organization. The uniquely human sense of past and future and the sense of self stem not from soul but from the frontal lobes. What we call the *mind* is the functioning of the brain. Moreover, as Freeman (10) has usefully pointed out, human brains exist in relationship to other brains. Our brains have evolved to make adaptive, complex social relationships possible. Culture, society, human values, and other abstract constructs are products of the social human brain and not the stuff of a separate mind. As Turner (11) put it, the human

person consists of “patterns of dynamic activity in a human brain that has evolved to serve the human body of which it is a part. Culture, society, language, and the rest of human life are patterns in brains. Meaning is patterns in human brains.” And so is pain, whether or not it corresponds in the expected way to observable tissue pathology.

One of the ongoing challenges in pain medicine is the poor fit between observable tissue trauma and the anguish and disability that the patient manifests. The pain control requirements of multiple patients with identical trauma vary widely, with some suffering severe pain and others little or none. Many chronic pain patients have pathology insufficient to account for their debilitating pain and, in some cases, no pathology at all. Conversely, in about one-third of patients, imaging of body areas for reasons unrelated to a pain complaint reveals structural or other pathologies that should be causing pain and pain-related dysfunction in an apparently pain-free individual (12). Responses to interventions vary as widely as the presentations of pain themselves due to nonspecific treatment effects, as Chapter 81 explains. We do not have, as yet, good scientific explanations for the wide range of individual differences that we see.

Physicians perplexed, and sometimes frustrated, by the poor fit of patient complaint to scientific accounts of pain mechanisms have tended to invoke popular psychology for explanations and guidance. Popular psychology is a folk wisdom rooted in mentalism that has little or nothing to do with the extensive field of psychology, which is well-grounded in scientific method. Popular psychology would have us believe that a patient's back pain might be all in his mind, that a woman's inexplicable pelvic pain is psychogenic, or that a painful phantom limb is a mental phenomenon. When patients gain pain relief unexpectedly, as with a placebo, we sometimes attribute this to the power of the mind. In these and many other ways, popular psychology would separate the mental from the physical: emotions, fatigue, mood disorders, and medication seeking are all mental phenomena. Medicine is obliged to cope with these nuisances, but its business is to treat the body. The implicit dualism meme, symbiotically aligned with popular psychology, all too often acts as a barrier that keeps the physician from seeing the patient as a complete entity. It also offers a quick and dirty explanation for phenomena that should challenge further study. Slowly but surely, neuroscience is revealing that many of the seeming mysteries of pain are due not to mentalism but to the plasticity of the nervous system.

One of the challenges we face for the future, then, is that of escorting the dualism meme to the end of its natural life, at least in pain medicine. We need to introduce competitive conceptual frameworks that work better and more naturally in daily practice. Perhaps one avenue to achieving this goal will be to integrate psychological services more fully within everyday pain management practice. Except in the case of the anesthetized patient, no patient is free of psychological characteristics. Often the most important parts of the evaluation and the outcome indicators are inherently psychological measures (see Chapter 12, Chapter 13, Chapter 14, Chapter 15, Chapter 16, Chapter 17 and Chapter 18). The purposes of psychologist participation in a case are not the conducting of mental measurement and documentation of outcomes in the realm of subjective reality. Psychological services complete the description of the patient as a whole person, and they embed both the pain problem and the projected impact of an intervention in that larger framework.

Patients with chronic pain often fear and sometimes resent seeing a psychologist. This represents to them the invocation of a pathogen meme: “Let's see if it's all in his or her head.” They fear that psychological evaluation is an attempt to invalidate the pain, to relegate it to the realm of mentalism. Sadly, in some settings they are correct. Some physicians still work on the basis of old memes: “If a pain exists without an evident cause, it must be psychological (mental).” This meme plays to the extreme in some settings. In psychiatric long-term care facilities, for example, the staff often tends to invalidate pain complaints by ascribing them to hallucinogenic or reinforcement mechanisms. A clear need exists for a new meme—a model of pain that recognizes pain as a complex pattern of brain activity of variable origin that interacts with the person's ongoing social environment and experiences. Both medical practitioners and the lay public as a whole need to receive and embrace this meme.

Concept of Pain

There is no reason to assume that the fundamental experience of pain has changed much as the human race has progressed. For the cave dweller who struck his or her head on the cave roof in the dark, the feeling of anger-tinged pain was probably rather like the experience of a contemporary human who bumps his or her head in an unfamiliar building in the dark. Our concept of what pain is, however, continues to evolve. We have no idea what primitive humans thought about pain. The ancient Greeks, like Aristotle, spoke of pain as a passion of the soul. Through the early to mid-twentieth century, medicine viewed pain primarily as a primitive sensory modality. Today, we formally construe it as a subjective experience, negative in hedonic tone, that has both sensory and emotional features, and it bears cognitive associations to tissue injury.

Informally, pain means very different things to different people in the health sciences. To the sensory neurophysiologist, it is still primarily a sensory messaging system designed to accurately render injurious change in bodily tissues. The neurologist addressing neuropathic pain may think of it as pathologic or dysfunctional sensory signaling. The psychologist may see pain as a complex perceptual experience with sensory, emotional, and cognitive dimensions, constructed within the brain and constrained by immediate context and individual past history. The pain meme clearly evolves, spinning off many variations. What will tomorrow bring?

In the memetic framework, of course, the question becomes “What will survive?” The notion of pain as a primitive sensory signaling system has survived well throughout medicine and in related disciplines, albeit not in the multidisciplinary world of pain itself. It works well enough for the ophthalmologist who sees a patient with pain secondary to glaucoma or the emergency room physician who sees pain related to a minor burn. It fails, however, for the physician who encounters a complex regional pain syndrome or a painful phantom limb. It has in some chronic pain cases led to needless and ultimately harmful surgical invasion, ill- advised amputations, inappropriate prescribing of strong medications, and extensive trial-and-error invasive procedures. In many respects, the satisfyingly simple notion of pain as a primitive sensory signaling system has become a memetic pathogen.

We need to develop and introduce a concept of pain that integrates explanations of mechanisms from nociceptors and peripheral neuropathic conditions to subjective awareness of tissue damage. The emerging field of consciousness research should prove helpful. Consciousness researchers regard the emergence of phenomenal reality from the activity of a physical brain as “the hard problem” (13). This explanatory gap, between brain activity and subjective awareness, stymies pain researchers as well. As functional brain imaging and consciousness theory evolve, our ability to conceptualize the complexity and dynamic nature of pain will grow. Continuously updating our definition and understanding of pain should rank among our highest priorities.

Concept of Interdisciplinary Management

Early in his experiences with chronic pain, Dr. Bonica envisioned the advantages that multiple and varied specialists could confer for the assessment and treatment of chronic pain. In founding the University of Washington Multidisciplinary Pain Clinic, he brought clinical psychologists, pharmacists, and other nonphysician providers to the conference table with anesthesiologists, neurologists, physiatrists, neurosurgeons, orthopedic surgeons, psychiatrists, and others. This blend of perspectives kept each specialist from exercising specialty-specific tunnel vision, and in conferences a group understanding often emerged that greatly exceeded the understanding that the record would yield after a series of serial consultations. Experience of this sort, gathered in many settings, shows that complex, chronic problems have optimal, multifaceted solutions.

Unfortunately, standard practice patterns are barriers to such solutions. Current economic forces seek to optimize short-term clinical efficiency at the cost of benefits such as rehabilitation and return to work, despite the evidence of the cost-effectiveness of multidisciplinary rehabilitation (see Chapter 109). The meme Bonica introduced—that of interdisciplinary management of chronic pain— must struggle to survive. Unfortunately, the short-term cost to a health care organization for chronic pain is not the same as the long- term cost of that patient to society. Moreover, the emphasis on traditional invasive treatments to the exclusion of rehabilitation will have financial consequences for third-party payers. The cost-effectiveness of surgery has proven poor for some of the common chronic pain syndromes (see Chapter 109). Worse yet, this is not a win-win situation for the patient and the health care organization: The benefits to the organization exceed those to the patient. Economic memes are proving to be dangerous pathogens.

Because the meme of interdisciplinary management of chronic pain is of potentially lasting value, it is important that we take steps to ensure its successful adaptation to climatic change and hardship. Adaptation, survival, and reproduction (we would like to see this meme spread) would benefit from three steps: (a) economic adaptation, (b) evolution and improvement, and (c) a symbiotic relationship to public opinion and the media.

The economic adaptation of a clinical service is straightforward. It must save money, not add to costs. Fortunately, technological progress is on our side and can help in minimizing costs. Electronic technology and developments in informatics have made it increasingly easy to obtain extensive interview and testing data from patients with minimal staff time, to summarize such data and make them immediately available in electronic form to the various specialties, and to add each specialist's findings to the record in a timely fashion. List servers provide an alternative to face-to-face conferencing when necessary. Teleconferencing minimizes the inconvenience of working together across multiple sites. Thus, it should be possible for an innovative clinic to minimize the cost of interdisciplinary collaboration.

The long-range financial benefits of interdisciplinary management, compared to standard unidisciplinary management are already clear, as Chapter 109 indicates. A steady growth of evidence that unequivocally demonstrates the long-range economic benefits of interdisciplinary management should eventually carry the day, because health care organizations are maturing and improvements in their long-range planning will eventually make good use of such evidence.

Finally, the interdisciplinary management of chronic pain needs public opinion on its side. Pain specialists have not transmitted the meme of interdisciplinary management of chronic pain to the lay public. Worse yet, some obstreperous patient groups are promulgating a memetic pathogen on the World Wide Web and elsewhere. They contend that physicians can cure pain surgically, but they are evading their responsibilities by insisting on multidisciplinary evaluation and rehabilitation. “Know your enemy” is their slogan. Paradoxically, this meme draws indirect support from various physician groups who have financially vested interests in one or another invasive procedure. As Figure 110-1 indicates, public opinion is a major force that helps shape the practice of medicine. Interdisciplinary management needs to marshal public opinion to its side. This requires aggressive efforts to diffuse the meme for interdisciplinary management of chronic pain into the public arena. Millions of people suffer from conditions in which pain is a major symptom. To date, this segment of the public has exerted little or no organized influence on public policy.

SCIENCE AND PAIN

Neuroscience, behavioral science, cognitive science, and social science all contribute to pain research and treatment. Each is its own world with its own subculture and associated memes; indeed, some of these areas comprise multiple competing paradigms. The scientific aspects of pain, therefore, are complex. The challenge for the future is not simply to pursue neuroscience and thereby further explicate the basic nature of pain. It will require integration of knowledge and cooperation across these areas. For the early part of the twenty-first century, four scientific themes are likely to prove important for clinical practice: (a) role of emotion in pain mechanisms; (b) physiologic consequences of nociception; (c) assessment of people in pain; and (d) individual differences in pain and its expression.

Emotion and Pain Mechanisms

The field of emotion research is growing rapidly, with many levels of scientific inquiry advancing in parallel (14). Investigations into emotion's basic mechanisms, theory about its evolutionary origins and purposes, and study of its expression and communication all bear on pain. As Chapter 24 indicates, pain has emotional features, and for the patient an experience of pain is more like an intense negative emotion than a burden of sensory information about location, quality, and intensity.

For most of the twentieth century, pursuit of the mechanisms of pain targeted sensory pathways and the central mechanism of sensory processing. The introduction of functional brain imaging to the pain field revealed substantial distributed processing in the brain during pain with several limbic foci (see Chapter 24 for a review). In parallel, neurophysiologic studies revealed spinohypothalamic and spinoreticular pathways for nociceptive traffic in the central nervous system. The fate of the nociceptive signals in these areas is uncertain and perplexing because they appear to initiate complex limbic and arousal processes rather than lead to a succinct destination such as somatosensory cortex. Still, the unfolding evidence seems to indicate that pain, as evolution formed it, involves an integration of sensory information with adaptive negative emotional arousal. As Chapter 24 indicates, sensory processes provide basic information about tissue trauma to the brain; emotional processes represent the biological threat (meaning) that the tissue trauma has for the organism at a given moment in a given setting. Put simply, negative emotion is not a response to pain but rather a part of pain. It is an adaptive response to tissue trauma.

Because pain has diagnostic value for acute disorders such as appendicitis or herpes zoster, physicians tend to ask patients only for pain's sensory features. From the patient's perspective, however, the affliction of pain is the anguish that it brings, not its sensory qualities. Patients seek relief from the unpleasantness and negative emotional features of pain.

Future research on the mechanisms of pain will need to explicate the complementary nature of sensory and emotional processes. The mechanisms of the emotional aspect of pain have received too little attention and remain comparatively ill defined. Preceding negative emotional states such as fear and apprehension can worsen the emotional severity of a painful condition such as postoperative pain (15), and emotional preparation can minimize the severity and distress of pain (16). Although it is always better to prevent nociception from the outset, it is important to consider the emotional features of pain and to include them as targets in pain relief interventions. The knowledge base necessary for assessing and addressing the emotional dimension of pain is only now beginning to emerge.

Physiologic Consequences of Nociception

Preoccupation with pain as a subjective experience has caused researchers to place heavy emphasis on tracing sensory transmission. However, as Chapter 3 indicates, most of the neural traffic occasioned in the dorsal horn of the spinal cord by an injurious event serves purposes other than sensory signaling. There is ongoing bidirectional communication at an unconscious level between the brain and other parts of the body, and through this the central nervous system takes care of basic housekeeping tasks necessary for life. Nociceptive signaling plays an important role in pattern of communication. Postural changes, overuse of joints and muscles, the development of inflammation, exposure to temperature extremes or other dangerous environmental factors, and other adjustments go on constantly, beneath the threshold of awareness. This signaling activity is nociception, but it is not pain because it is not conscious. It represents the monitoring of tissue to detect and prevent impending trauma rather than a response to trauma.

When frank trauma occurs, the consequent nociception induces largely unconscious reflex responses at the segmental level. These are both motor and sympathetic. Motor reflex responses include reflex withdrawal, as when a person touches a hot object, and sometimes they induce skeletal muscle tension that provides bracing in the area of a wound. Severe motor reflex responses can cause muscle spasm that becomes a secondary source of nociception. Sympathetic reflexes constrain peripheral blood flow and thus protect against blood loss at the site of an injury. Prolonged changes in microcirculation can affect the chemical environment of nociceptors in and around a wound, affecting function and sometimes contributing to tissue sensitization. In persons who are not otherwise healthy at the time of injury, sympathetic reflexes can contribute to cardiovascular morbidity.

Nociceptive stimulation of the hypothalamus can produce a complex array of consequences (see Chapter 24), including excitation of the paraventricular nucleus. The paraventricular nucleus can activate the hypothalamic-pituitary-adrenocortical (HPA) axis, introducing various peptides and increasing cortisol in the systemic circulation. HPA activation mounts a stress response that readies the individual to meet an emergency. The short-term benefits of HPA axis arousal are largely positive, but the consequences of long-term arousal are deleterious, fostering sleep disturbance, circadian dysrhythmia, myalgia, and fatigue (17).

Finally, recent work is showing that the central nervous system demonstrates substantial plasticity (18). The classical Cartesian assumption of a mechanistic nervous system faithfully transmitting signals of injury to the mind is clearly erroneous. Studies of changes in brain representation related to amputation indicate that major changes begin within hours of deafferentation. Our understanding of how prolonged nociception or neuropathic signaling affects the brain and its representation of body areas is still primitive, but all indications are that prolonged nociception can create lasting changes in both function and structure.

Clearly, a need exists for more research on the physiologic consequences of nociception, with attention to the implication of special patient populations. Institutionalized patients who cannot speak or who are confused or demented may experience pain that they cannot express. Often, the only behavioral evidence is diffuse distress and social withdrawal. The consequences of untreated nociception on the overall health of the patient are never positive and may lead to further morbidity and increased costs of care (see Chapter 45).

Future research on nociception is likely to call into question the standard definition of pain. Medically, the consequences of nociception are important, and nociception is not necessarily conscious. Indeed, pain as a conscious event is but one of many products of nociceptive activity.

Measurement of Pain

Current tools for measuring pain in clinical situations are crude. More fundamentally, the assumption behind pain measurement is primitive and somewhat misguided. Health care providers often believe that they should measure the pain *per se*. That is, one should quantify the various features of pain. In fact, the challenge is to measure the person in the role of patient with regard to a particular feature that interferes with normal living. That feature is pain, and it is multidimensional in nature. Pain measurement is about measuring people; it is not an exercise in mentalism.

Normally, the clinician simply asks the patient in one way or another to report features of the pain such as its intensity and location. Moreover, conventional pain measurement tools focus predominantly, and in most settings entirely, on the sensory features of the pain. As noted above, this is of some diagnostic value to the

health care provider, but it is the affective features of the pain that distress the patient. One major problem is that such methods effectively exclude several important populations such as preverbal infants and cognitively compromised patients, including some populations that require institutional care. We also have problems in assessing therapeutic outcome following interventions for pain, particularly chronic pain, as Chapter 82 indicates. This problem area has important economic implications because, if we restrict pain measurement to subjective report, we cannot demonstrate convincingly that interdisciplinary intervention for chronic pain is efficacious and cost-effective.

Chapter 15 reviews the tools available for measuring pain and its relief. We emphasize here that measurement approaches depend on the formal definition of pain and the memes associated with it. Pain measurement does not take place in a vacuum: Major cultural and historical influences constrain how we think and our ability to proceed innovatively in pain measurement.

Our methods for clinical pain measurement rest on the assumption (yet another meme) that introspection is the only valid method. Pain is a conscious state or at least a conscious experience, and therefore the only access we have to it is through direct first- person examination of the contents of consciousness. This is a bold approach because there is little or no justification for assuming that untrained, nonobjective patients can examine themselves and report in an accurate, unbiased way what they feel. Most pain management anesthesiologists have seen chronic pain patients who, immediately after a well-executed nerve block, simply cannot say whether a pain of many years' duration has gone away.

Beneath the surface of our current measurement practices lurk several memetic pathogens. The Cartesian dualism meme is the most egregious. We assume implicitly that the patient has a separate and objective mind that can examine what is going on in the mechanical body and provide a faithful report. In fact, the same brain is simultaneously producing, experiencing, and reporting the pain. The act of reporting affects attention and thereby changes the producing and experiencing.

The “pain as a primitive sensory experience” pathogen is also at work in such measurement efforts. It seems appropriate to put a simple number on a patient's pain to gauge its intensity and then to intervene in hopes of lowering that number. Unfortunately, the sensory intensity of a pain is but one of its features, and its subjective reality depends on context. The constant intensity of a patient's aching shoulder, for example, may seem a mild annoyance during a day filled with activity and yet become a major source of distress and a barrier to restful sleep at night when the environment is quiet.

Yet another memetic pathogen is that the report of chronic pain always stems from a continuous awareness of one or more foci of marked nociceptive activation in the periphery or of neuropathy. This pathogen thrives because it is sometimes true, but the overwhelming majority of exceptions defeats the rule.

Finally, when a patient is noncompliant during pain measurement, the physician often invokes the mentalism meme—“it's all in his or her head.” As if to collude, some patients, when asked to rate pain on a scale of one to ten, report pain of 15 or 20, with a subtle or sometimes obvious disdain for the assessment process. Because of this meme, it is easy to assume that the problem is psychological because the patient exaggerates. It is hard to consider that the patient may have a need to communicate the emotional intensity of the pain experience rather than the sensory intensity and to feel that the care providers understand the anguish and intend to address it. In these and other ways, our current pain assessment practices serve us poorly.

Quantifying outcomes after chronic pain relief intervention is another vexing conundrum. Mentalism demands that we measure the conscious experience of the patient, but payers and health care institutions are loath to spend substantial sums of money for nothing more than a change on a subjective numeric rating scale. The obvious answer is that the goal of the intervention must be to improve function, and this we can quantify in many ways (e.g., range of motion, endurance, return to work). That such measures correlate poorly with subjective ratings of pain intensity seems to challenge the validity of the pain. The meme that pain as a conscious entity impairs function and ultimately causes disability exerts a heavy influence, and it, too, may be a pathogen.

Chronic pain is a complex state, and progress in pain measurement will depend in part on progress in causal modeling. We need a better understanding, not only of the causes of pain, but also of the factors that produce disability and chronicity. In cases in which patients have ongoing nociception or neuropathy, it is reasonable to predict a causal relationship between what the patient can do and what his or her nervous system is doing. In other cases, where there is little or no evidence of cause for noxious signaling in the nervous system, the very concept of having uncontrollable chronic pain and the integration of that concept with the sense of self may have a causal influence in perpetuating disability. In some cases, both of these factors causally influence ability to work or function normally. Unfortunately, a numeric rating of pain intensity measures neither of them. We need tools that measure the person comprehensively, with regard to pain, function, beliefs, and resilience. Progress in outcomes measurement may well require multivariate causal modeling grounded in theory more advanced than we can presently produce.

Broadly speaking, meaningful progress in pain measurement cannot take place until a favorable memetic climate emerges. Dualism and the mentalism that it fosters are major barriers. We need to resolve the question of whether deleterious nociceptive traffic in the nervous system that is unperceived should qualify as pain. If so, then we cannot relegate pain to the realm of mentalism. In addition, we need to further develop our understanding of the importance of the affective component in clinical pain states. Our current approaches do not quantify this in a satisfactory manner. Again, the scientific community that studies emotion would not relegate emotion to the realm of mentalism: Affect has physiologic mechanisms and physiologic manifestations. The affective aspect of pain should be no different. These considerations point to future objectification in pain measurement.

CONCLUSIONS

As clinicians and scientists we wish to believe that we make independent choices, that we see things as they are. Social evolutionists challenge this. They assert that medicine and science, like everything else produced by humans, take place in a cultural context governed by unseen forces. The memeticist approach to social evolution, an analogue of Dawkin's radical notion of the selfish gene (1), offers a provocative perspective. Dawkins argued that genes are active agents of their own replication and survival and the organisms that they express (including humans) are but tools produced to meet these ends. As genes are to biology, so are memes to culture. The memeticist contends that a meme is an idea that takes on its own life. It seeks to survive and replicate itself. Whether its survival strategy supports the good of humankind or the destruction of those who embrace it and transmit it is immaterial to the meme. Humans are mere agents of memes; they are never the masters.

Since Dawkins first introduced these ideas in 1976, humans have begun to take control of genes. The Human Genome Project is well under way, and the first experiments in cloning are behind us. Genetic engineering has become a major focus of scientific and technical development. It would seem that Dawkins must now acknowledge that humans have gained the upper hand and are not now solely the instruments of their genetic code.

In the memeticist framework, we face the parallel dilemma. We can be instruments of the memes that govern our behavior, or we can assert ourselves and take charge of them. Just as geneticists need to map the human genome, so pain medicine needs to map the memes that govern its practice. When we fully understand what makes us what we are, we are free to eradicate pathogens, shape evolution, and introduce new memes compatible with science and compassionate care.

A new century invites new visions, new beginnings. It is a moment of *kairos*. If pain management is going to survive and thrive into the future, then we must begin now to examine the beliefs and assumptions on which we base our reasoning and our action. The future is ours to define.

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